TNFα INHIBITOR TREATMENT TRAJECTORIES

LEARNINGS ON BIOSIMILARS FROM CLINICAL PRACTICE

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TNFα inhibitor treatment trajectories

learnings on biosimilars from clinical practice

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TNFα inhibitor treatment trajectories: learnings on biosimilars from clinical practice
PhD thesis, Utrecht University, The Netherlands

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(met een samenvatting in het Nederlands)

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CHAPTER 1

General Introduction

Patients with immune-mediated inflammatory diseases (IMIDs), such as rheumatoid arthritis (RA) and inflammatory bowel disease (IBD), often require drug treatment. Many drugs that act on the immune system through different mechanisms are available for the treatment of IMIDs in general; these drugs include immunomodulators and corticosteroids as well as disease-specific drugs, for example mesalazine for the treatment of IBD. All drugs have their own specific properties that determine in which phase of the disease and/or for which patients they are more or less useful. For example, corticosteroids are effective in swiftly suppressing disease flares, but their adverse events (e.g. adrenal insufficiency, increased risk of diabetes mellitus and osteoporosis[1]) make them less desirable for long-term treatment. Immunomodulators, such as methotrexate or azathioprine, can slow disease progression in a more fundamental way; however, they can take up to several months to produce beneficial effects. Hence, all drugs, with their specific mechanisms of action, have both advantages and disadvantages. In addition, multiple individual drugs with similar mechanisms of action are available in several instances, all with slight differences in effectiveness, frequency, types of adverse events, available formulations, route of administration and approved indications. Responses to these drugs (efficacy and adverse events) vary between patients and within patients over time, even for compounds with the same mechanism of action.

For an individual patient, it can be quite difficult to choose which drug should be used as first-line treatment (and in which dosage and formulation) and as second- or third-line treatment in case of unsatisfactory responses. Physicians are supported in these decisions by clinical guidelines that provide multiple options; however, these guidelines are based on evidence at the population level and are not tailored to individual patients. For the individual patient, finding a drug regimen that is effective, easy to use and without (unacceptable) adverse events can present a puzzle. In addition, treatment might involve dose changes over time, switching from one drug to another or even stopping drug treatment. As a result, differences exist among individual patients throughout the trajectories of their drug treatment for their IMID.

Over the last decades, treatment strategies for IMIDs have evolved. For example, treatment of patients suffering from RA used to begin with non-steroidal anti-inflammatory drugs and would step up to immunomodulatory drugs if the disease remained active or joints were damaged (the so-called step-up strategy).[2,3] This pattern has changed over the years, and current practice is to begin with immunomodulators as soon as possible after the patient has been diagnosed and combine these with high-dose corticosteroids for a short term (step-down strategy). This strategy aims to control disease progression rapidly at early stages and to prevent joint damage.[4]

TNFα inhibitors and their biosimilars

The treatment options for IMIDs expanded several decades ago with the regulatory approval of biologicals. In contrast to most small-molecule drugs, biologicals directly target the molecules or molecular pathways involved in the inflammatory processes of IMIDs.[5,6] Within the class of biologicals, TNFα inhibitors are currently often used as first-line biological therapy, and these agents have become the standard of care for the treatment of IMIDs. TNFα inhibitors have revolutionized the treatment of patients with IMIDs; however, as with all drugs used to treat IMIDs, responses vary among patients. The one-year drug persistence is reported to be between 45% and 67% (depending on the IMID indication), and 13% to 20% of patients must switch to another TNFα inhibitor, a biological with a different mode of action or to a Janus kinase (JAK) inhibitor due to lack or loss of effect or unacceptable adverse events.[7,8] Therefore, similar to small-molecule treatment, finding the correct TNFα inhibitor (or other biological or JAK inhibitor) that provides effective treatment without (unacceptable) adverse events can be challenging.

The introduction of biologicals has posed a challenge to society, as their high price has had a considerable impact on healthcare budgets.[7] When the market exclusivity of the TNFα inhibitors infliximab, etanercept and adalimumab expired, similar versions of the original active substances, called biosimilars, were introduced in clinical care. A biosimilar is defined by the European Medicines Agency (EMA) as 'a biological medicinal product that contains a version of the active substance of an already authorised original biological medicinal product (originator) in the European Economic Area'.[8] Biosimilars must fulfil several stringent criteria to ensure similarity to their originator, including demonstration of no relevant differences in physiochemical and biological properties in a large number of analytical tests and in-vitro studies. Furthermore, makers of biosimilars need to demonstrate that the compounds are similar to their originator in terms of pharmacokinetics and -dynamics, efficacy and safety. These properties are demonstrated by conducting equivalence trials, preferably in patients with the most sensitive indication for which the originator has been approved. Based on thorough scientific consideration, similarity confirmed in that indication can then be extrapolated to (all) other indications for which the originator has been approved.[8]

With the introduction of biosimilars, financial competition has reduced the price of TNFα inhibitor treatment and improved patient access to these therapies. To reduce treatment costs, many patients already under treatment with the originator have been transitioned to the biosimilar. The efficacy and safety of transitioning from an originator TNFα inhibitor to a biosimilar has been extensively studied in double-blinded, randomised, controlled trials (RCT) in which patients were randomised

between continuing with an originator and transitioning to a biosimilar. For example, in the NOR-SWITCH study, in which patients were transitioned from an infliximab originator to a biosimilar, 30% experienced disease progression compared with 26% of patients who had continued with the originator. This result fell within the prespecified 15% noninferiority margin, and the authors thus concluded that transitioning had not affected efficacy and safety.[9] In addition, for etanercept and adalimumab, double-blinded transitioning studies have demonstrated that transitioning to the biosimilar has no effect on efficacy, safety or immunogenicity.[10,11] Transitioning from the originator to a biosimilar has also been recently supported by the EMA; originators and biosimilars are considered interchangeable and clinically equivalent.[12]

Policies and guidelines for the use of biosimilars have been introduced to guide physicians and pharmacists regarding for which patients, and under which conditions, it is appropriate to prescribe or dispense a biosimilar. Thus, in addition to clinical considerations regarding which drug to prescribe for IMID patients, local, regional and national financial factors must also be considered when choosing a treatment.

Treatment trajectories of IMID patients

In (pharmaco)epidemiological research, the study of drug use patterns and determinants thereof (i.e. drug utilisation) as well as studies concerning the relationship between exposure to a drug and an outcome, for example treatment effect or adverse events, are the key focus. Observational studies of the use of TNFα inhibitors in daily clinical practice can provide important knowledge, for example regarding treatment effect and/or adverse events. Current treatment guidelines provide little direction to clinicians related to which TNFα inhibitor (or biological with another mode of action) might be most favourable for an individual IMID patient and in which treatment line.[13–15] Results from observational studies might support clinicians (and patients) in this decision-making. Moreover, especially during the first years after the introduction of the initial biosimilars, there was a call for more research regarding biosimilars.[16] (Further) RCTs are sometimes unfeasible or unnecessary, but observational studies can address this call for more research.

For high-quality epidemiological studies, it is essential to have a valid assessment of the exposure status of the patient.[17] The exposure status can be obtained from prescription and dispensing records that are primarily used for clinical and administrative purposes. Every time a patient has drugs prescribed or dispensed, data (name of the drug, strength, dosing regimen, number of syringes, date of prescribing or dispensing) are added.[18] By compiling prescription or dispensing records, these data can be summarized in treatment episodes[19] and events in a patient's treatment, such as initiation or

discontinuation of a drug, treatment switches or dose adjustments, can be derived. A treatment episode depicts the time a patient has been exposed to a certain drug, starting with initiation and ending when the drug is discontinued, as depicted in Figure 1, and may contain information regarding dosage and treatment interruptions.

As patients with IMID often experience multiple changes in treatment, multiple treatment episodes should be considered to gain complete insight into the longitudinal course of these patients' treatments. The sum of all treatment episodes from a patient, which is often defined as the treatment trajectory, provides a clear presentation of the entire course of a patient's treatment. A treatment trajectory begins when the patient initiates the first drug of interest and ends when the last drug of interest is finished (Figure 1).[20]

Individual treatment trajectories of IMID patients can be driven by both medically related and non-medically related changes. In general, medically related changes are driven by an unwanted treatment response, mainly a non-response or the occurrence of an adverse event, or achievement of sustained remission in the patient. Unwanted response or achievement of sustained remission could be derived from the treatment trajectory, for example as a switch to another drug (and to which one), a drug dosage increase, a drug taper or the discontinuation of a drug. These events provide information regarding the patient's health, the course of the disease and the disease prognosis. Non-medically related changes would be, for example, financially driven transitions from an originator to a biosimilar. As the therapy duration often spans many years and includes many possible treatment switches and adjustments, treatment trajectories of individual IMID patients can vary significantly and provide unique and valuable data for (observational) research.

Example treatment trajectory

To illustrate the value of treatment trajectories in IMID patients for pharmaco-epidemiological research, a fictional treatment trajectory is presented in the next paragraphs. This example is the treatment trajectory of a (fictional) patient (male, 55 years old), who was diagnosed with RA and for whom drug treatment was initiated. At the start of treatment, the treatment target (treat-to-target strategy) was selected; this target is usually remission (28-joint Disease Activity Score [DAS28] below 2.6) or low disease activity (DAS28 between 2.6 and 3.2).[21,22] The following 'prescription events' related to TNFα inhibitor use are illustrated: treatment initiation, treatment switch, transitioning from an originator to a biosimilar and retransitioning to the originator.

Initiation of TNFα inhibitor treatment

After the patient had undergone six months of methotrexate (MTX) treatment, the target of treatment had not been reached; therefore, a TNFα inhibitor was added by the treating physician. Such decisions can be based on several factors, such as the type and severity of the disease, timing, and the presence or absence of contra-indications.[23,24] After the physician and the patient decided to begin TNFα inhibitor treatment, they first needed to decide which TNFα inhibitor to start. This decision depends on several factors, most importantly the indication, as not all TNFα inhibitors are approved for every IMID, as well as patient preference, for example self-administration of a subcutaneous injection at home or intravenous administration at the hospital ward by a nurse. Other factors that influence the choice of initial TNFα inhibitor are costs as well as guidelines and policies on hospital, national or international levels. Our patient and his treating physician choose to add adalimumab (Humira®) to the treatment. The prescription was created and filled, resulting in a prescription and a dispensing record in the healthcare data. With these data, the treatment episode for adalimumab was defined as started.

Up to this point, our patient had experienced a current treatment episode for MTX, a completed treatment episode for prednisolone and a newly initiated treatment episode for adalimumab (Figure 1).

Switching biological treatment

Due to loss of response, the patient discontinued adalimumab after having used the drug for some time (Figure 1), and the patient was classified as a secondary non-responder. The disease process in secondary non-responders is most likely TNFα-mediated, as they previously did respond to a TNFα inhibitor. It is known that patients can lose response to a TNFα inhibitor due to the formation of antibodies that either neutralise the initial TNFα inhibitor or increase its clearing. However, these antibodies are specific to the TNFα inhibitor, and patients can thus safely switch to another type of TNFα inhibitor.[25,26] In the case of this patient, a switch was made to etanercept, and thus a treatment episode for etanercept was added to the patient's treatment trajectory (Figure 1).

The success of a second biological can be predicted based on the reason for switching; remission rates in patients who have switched because of adverse events are higher compared to remission rates in patients who have switched due to primary or secondary non-responses (61% vs. 30–45% in IBD).[27] If the second-line biological fails, patients can switch to a third-line treatment, although the rates of success decrease with every subsequent line of (biological) treatment.[28]

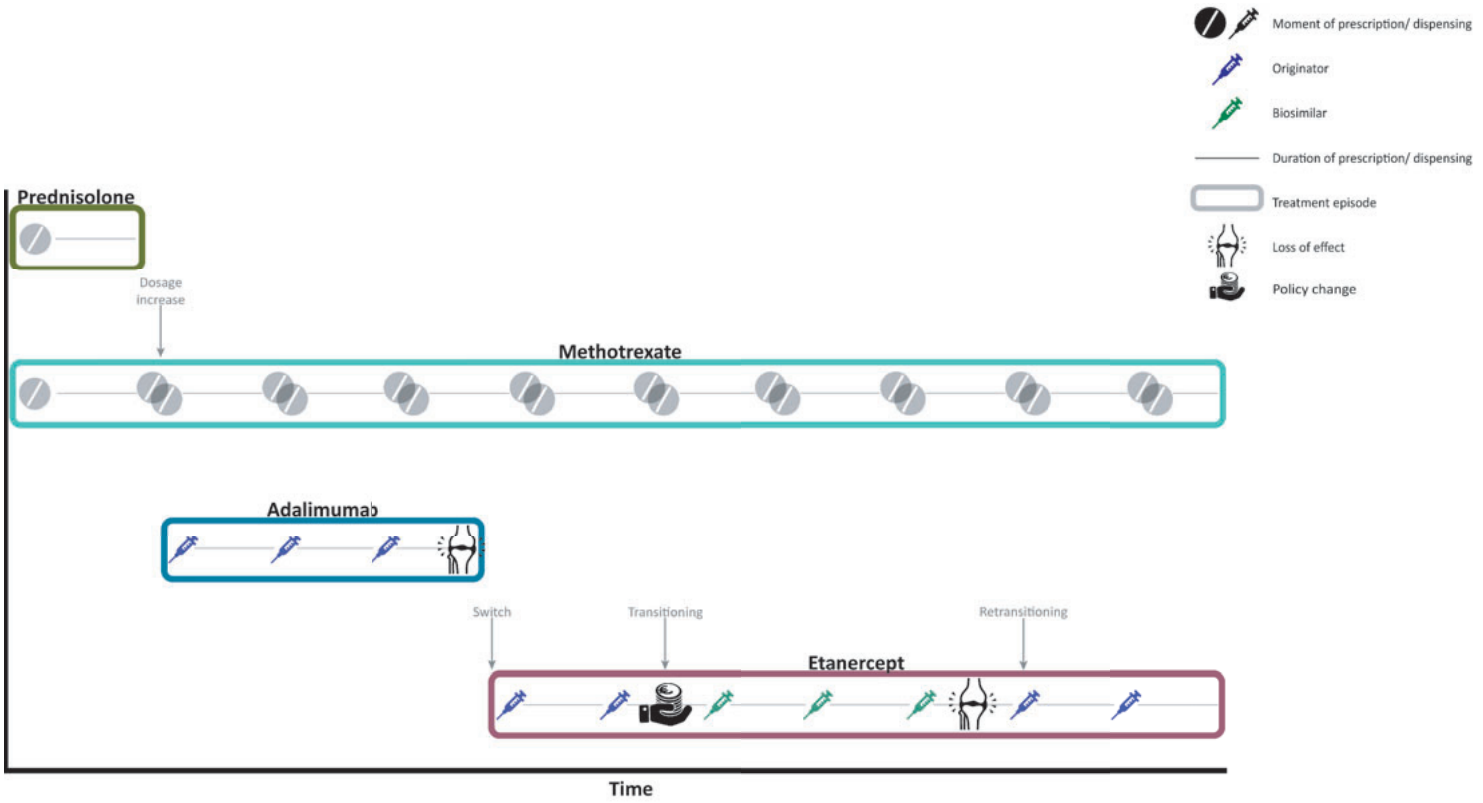

Figure 1: Compiling prescription and/or dispensing records into treatment episodes and the depiction of the treatment trajectory of the example patient.

Transitioning from originator to biosimilar

Up to this point, the described treatment episodes had been based on the active substance of the drug. However, treatment trajectories could also be constructed for a single substance and thus on the level of the drug product. This is of particular interest when patients transition from an originator TNFα inhibitor to a corresponding biosimilar, thus continuing treatment with the same active substance but under another brand name. Based on the proven similarity, no efficacy and/or safety issues are expected when patients transition to a biosimilar. Nevertheless, some physicians are concerned regarding the efficacy, safety, quality and immunogenicity of biosimilars and/or on the extrapolation of approved indications. These concerns can result in hesitation to start new patients on biosimilar treatment or to transition patients from originators to biosimilars.[29–31] However, to support physicians in confidently prescribing biosimilars in both situations, national regulatory authorities from most European countries have provided educational information directed to physicians regarding biosimilars and transitioning.[32] Moreover, international medical societies such as the European League Against Rheumatism, the American College of Rheumatology for RA patients, the European Crohn's and Colitis Organisation (ECCO) and the American Gastroenterological Association for IBD patients have published position statements explaining whether and under which conditions they consider transitioning patients appropriate, for example in transitioning only patients with a stable disease.[33–36] Furthermore, guidelines from national medical societies can also provide direction regarding biosimilar transitioning to physicians.

During etanercept treatment of the example patient, etanercept biosimilars had been introduced on the market. The treating hospital of the patient decided to transition patients who had been under treatment with the originator etanercept to the corresponding biosimilar, as depicted in the treatment trajectory of the patient in Figure 1. To inform patients of the upcoming transition, groups such as regulatory authorities, medical associations and patient organisations have developed educational material directed at patients, aiming to improve patient knowledge regarding biosimilars.[37] Despite these efforts, studies have shown that patients remain concerned about the quality, efficacy and safety of biosimilars and the possible recurrence of disease flares.[38,39]

These concerns may be reflected in the findings of observational studies of transitioning as part of routine clinical care, which have reported conflicting results. Many observational studies have reported no differences in terms of efficacy and safety between continuing treatment on an originator and transitioning to a biosimilar, in line with results from RCTs. However, other studies have reported higher discontinuation

rates in patients who have transitioned from an originator to a biosimilar as compared with patients who have continued with the originator.[40]

Treatment trajectories after transitioning

After the patient was transitioned to a biosimilar, the options for the course of his treatment trajectory were similar to those described previously. If a patient responds well, treatment with the biosimilar is continued, and no further change in the patient's treatment trajectory is necessary. Over time, the patient could even transition from the first biosimilar to a second (known as cross-transitioning, which is beyond the scope of this thesis). However, if a patient develops an unwanted response, which could be either a secondary non-response or an adverse event, they have the option to switch to another biological (other active substance, which could be either an originator or a biosimilar) or a JAK inhibitor, irrespective of having transitioned to a biosimilar. This switch would alter the course of the patient's treatment trajectory similarly to the pathway described earlier.

Retransitioning

Our patient lost treatment effect during treatment with the etanercept biosimilar and developed more disease complaints. As the patient had been satisfactorily treated with the originator etanercept before the introduction of the biosimilar, he wished to return to the originator (i.e. retransitioning), as depicted in the treatment trajectory in Figure 1. Retransitioning is inconsistent with the principle of similarity between the originator and the biosimilar and is not mentioned or even discouraged by the clinical guidelines as a treatment option.[13,34] Nevertheless, our patient was not unique in retransitioning, as studies have reported that of patients who had transitioned from originator to biosimilar, 2.6–25.8% subsequently retransitioned.[41,42] Retransitioning could be considered as a potential unsatisfactory treatment response to the biosimilar, as the reasons for retransitioning often reported are a sudden loss of effect and/or adverse events after transitioning to the biosimilar. For most patients, the loss of effect or the appearance of adverse events in these studies was not clinically verifiable (objectively) by a physician and could be considered as having been subjective.[40,43] This could be attributed to the 'nocebo effect' (i.e., patients' negative expectations that lead to the experience of adverse events or the perception of a decrease in response).[43,44] However, the nocebo effect is difficult to confirm. A previous study reported that 87% of patients had regained effect after retransitioning,[45] suggesting a psychological component to the complaints. However, in general, retransitioning could also be based on factors not related to a nocebo effect, such as allergy to the excipients used in the formulation of the biosimilar.[46]

Objectives of this thesis

Construction of drug treatment trajectories has been extensively studied in pharmacoepidemiology, as these trajectories are crucial for generating knowledge regarding longitudinal effects of treatment. However, introduction of new types of drugs for which administration diverges from the traditional daily regimen and for which delivery can be distributed over different types of clinical settings face specific challenges that have not been fully addressed. An example of such classes of drugs are the TNFα inhibitors, which have long and sometimes changing dosing intervals and for which retrieving complete patient drug data, especially at the drug product level, can be challenging.

Moreover, TNFα inhibitor treatment trajectories have been studied in relation to patient transitioning from an originator TNFα inhibitor to a biosimilar. However, previous studies have mainly focused on transitioning from a TNFα inhibitor originator to a biosimilar as a single event, and the effect of transitioning on the longitudinal drug treatment trajectory of patients with IMIDs has remained understudied. An example is the knowledge gap regarding the incidence of retransitioning and the characteristics of patients most at risk for retransitioning. This knowledge could support clinicians in responding to patients with unwanted responses after transitioning to biosimilars.

Therefore, the objectives of this thesis are to provide insight into the TNFα inhibitor treatment trajectories of patients with IMIDs. We further aim to provide quantitative and qualitative insight into the frequency and determinants of transitioning from an originator TNFα inhibitor to a biosimilar, on retransitioning to the originator and on strategies for biosimilar implementation. Lessons related to biosimilar implementation for clinical care might be distilled from these studies.

Thesis outline

In **Chapter 2**, we provide insights into the switching patterns of IMID patients who initiated treatment with a TNFα inhibitor but switched to another biological. We map patterns of multiple switches and look for determinants for switching. This study provides an overview of the switching of biologicals in clinical care in general without specifically focusing on biosimilars.

In **Chapter 3**, clinical guidelines for transitioning from an originator TNFα inhibitor to a biosimilar for IBD patients are studied. Recommendations on biosimilar use are described in the European ECCO guidelines and country's national guidelines. In this chapter, the presence and content of guidance from European gastroenterology associations for TNFα inhibitor biosimilar use are mapped for 26 European countries.

One of the recommendations in the guidelines described in Chapter 3 relates to retransitioning. Retransitioning is further analysed in **Chapter 4.** In this chapter, knowledge regarding the incidence of retransitioning and which patients, diseases, treatments and implementation strategy factors might be related to retransitioning are studied.

In **Chapter 5,** the incidence of retransitioning in one indication and one specific TNFα inhibitor and determinants for retransitioning are studied. Patients who had retransitioned were qualitatively interviewed; **Chapter 6** presents their perspectives on transitioning and retransitioning.

In **Chapter 7**, the risk of infliximab discontinuation in IBD patients who had retransitioned from an infliximab biosimilar to the originator is compared to that for patients who had remained on a biosimilar. Reasons for discontinuation are also compared.

Finally, in **Chapter 8**, the general discussion, the results of the preceding chapters are discussed in a broader perspective, including our recommendations for the implementation of future biosimilars in clinical practice.

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CHAPTER 2

Switching TNFα inhibitors: patterns and determinants

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Abstract

The aim of this study was to assess switching patterns and determinants for switching in patients initiating TNFα inhibitor (TNFα-i) treatment. Patients were included who started TNFα-i treatment between July 1, 2012 and December 31, 2017, from three Dutch hospitals, and were diagnosed with rheumatic diseases (RD), inflammatory bowel disease (IBD), or psoriasis. Outcomes were switching, defined as initiating another biological; switching patterns including multiple switches until the end of follow-up; determinants for first switch, assessed using multivariate logistic regression. A total of 2228 patients were included (median age 43.3 years, 57% female), of which 52% (n = 1155) received TNFα-i for RD, 43% (n = 967) for IBD, and 5% (n = 106) for psoriasis. About 16.6% of RD patients, 14.5% of IBD patients, and 16.0% of psoriasis patients switched at least once, mainly to another TNFα-i. TNFα-i dose escalation (OR 13.78, 95% CI 1.40-135.0) and high-dose corticosteroids initiation (OR 3.62, 95% CI 1.10-12.15) were determinants for switching in RD patients. TNFα-i dose escalation (OR 8.22, 95% CI 3.76-17.93), immunomodulator initiation/dose escalation (OR 2.13, 95% CI 1.04-4.34), high-dose corticosteroids initiation (OR 6.91, 95% CI 2.81-17.01) and serum concentration measurement (OR 5.44, 95% CI 2.74-10.79) were determinants for switching in IBD patients. Switching biological treatment occurred in about one in six patients. RD patients with TNFα-i dose escalation and/or high-dose corticosteroids initiation were more likely to switch. IBD patients with TNFα-i or immunomodulator initiation/dose escalation, high-dose corticosteroids initiation or serum concentration measurement were more likely to switch. These findings might help clinicians anticipating switching in TNFα-i treatment.

Introduction

Tumor necrosis factor (TNF) α inhibitors have revolutionized the treatment of several immune-mediated inflammatory diseases (IMID), such as rheumatic diseases (RD), inflammatory bowel disease (IBD) and psoriasis. Five TNFα inhibitors are currently available for patient care in Europe: adalimumab and infliximab are, among others, approved for RD, IBD, and psoriasis, etanercept and certolizumab pegol are approved for RD and psoriasis and golimumab is approved for RD and IBD.[1–5]

TNFα inhibitors are advised as first-line biological treatment in IMID when conventional immunomodulator treatment, such as methotrexate or azathioprine, does not achieve sufficient clinical benefit. TNFα inhibitors may improve clinical signs and symptoms and make low disease activity and remission realistic objectives for patients suffering from IMIDs.[6–10] However, although many patients benefit from TNFα inhibitor treatment, several patients experience a lack of efficacy or bothersome side effects.[11,12] For those patients, switching to another biological drug, or to a Janus Kinase (JAK) inhibitor, is recommended. The choice for switching to a second TNFα inhibitor or to a biological drug belonging to another mechanistic class depends on the indication of use and on the reason for switching. For example, the IBD guideline advices on switching based on response to the TNFα inhibitor, drug concentrations and presence of antibodies,[6] whereas the rheumatoid arthritis (RA) guideline does not provide a strategy in choosing between another TNFα inhibitor or to a biological drug belonging to another mechanistic class.[7]

In clinical practice, switching to another biological treatment frequently occurs. A previous study in RD patients showed that 67% of the patients remained persistent users (percentage of patients on the same biological drug after 12 months of initiation)[13] of their first TNFα inhibitor, 13% had switched to another biological drug (other TNFα inhibitor or biological belonging to another mechanistic class) and 20% had discontinued biological treatment.[13] A study in IBD patients reported a 1-year persistence of TNFα inhibitors of 48.5% for CD and 44.8% for UC. Switching to another biological drug occurred in 19.4% of CD and 20.3% of UC patients.[15] One-year persistence was higher in psoriasis patients; 77.4% of patients were persistent users, 17.5% had switched to another biological drug and 5.1% had discontinued biological treatment.[16]

Several determinants for TNFα inhibitor treatment discontinuation in IMID have been identified. For example, women are at a 1.3 to 1.8 times higher risk for discontinuation than men.[17–19] Concomitant use of methotrexate decreases the risk of discontinuation in RD patients by 22%,[21] and in psoriasis patients by 66.2%.[20] The risk of TNFα inhibitor

treatment discontinuation additionally increases by 1.4–6.0% per year with increasing age.[19,20]

The aforementioned studies mainly focused on biological treatment discontinuation and determinants thereof, or only on the first biological treatment switch, in a single indication. However, little has been studied on the patterns of multiple switches of biological treatment across multiple indications and on determinants specifically for switching biological treatment. Data on switching patterns, including information on the type of biological drug, and more knowledge on determinants for switching may support more efficient treatment with biological drugs.

The aim of this study was to assess switching patterns and determinants associated with switching in patients who initiated TNFα inhibitor treatment for IMID between 2012 and 2017.

Materials and Methods

Design and setting

This cohort study included patients from three large hospitals in the Netherlands: the Spaarne Gasthuis, the Medisch Spectrum Twente (MST) and the University Medical Center Utrecht (UMC Utrecht). The Spaarne Gasthuis and the MST are both large teaching hospitals; the UMC Utrecht is an academic teaching hospital.

Dispensing data from the outpatient pharmacy from the Spaarne Gasthuis, the MST and the UMC Utrecht were obtained from CompuGroup Medical (CGM). Hospital and laboratory data from the Spaarne Gasthuis and the MST were obtained directly from the hospital and pharmacy information systems, that is, through Epic (Spaarne Gasthuis) and Vipharma and GLIMS (MST).

Hospital and laboratory data from the UMC Utrecht were obtained from the Utrecht Patient Oriented Database (UPOD). UPOD is an infrastructure of relational databases comprising data on patient characteristics, hospital discharge diagnoses, medical procedures, medication orders, and laboratory tests for all patients treated at the UMC Utrecht since 2004. UPOD data acquisition and management was in accordance with current regulations concerning privacy and ethics. The structure and content of UPOD are described in more detail elsewhere.[21]

Since January 1 2012, all outpatient-administered biological drugs have been exclusively dispensed by the outpatient pharmacy of the hospital where a patient is treated due to reimbursement regulations in the Netherlands. Consequently, the outpatient

pharmacy contains a complete overview of all biological drugs used in the home setting.[22]

Study population

All new users of TNFα inhibitors (etanercept, infliximab, adalimumab, certolizumab and golimumab), treated for RD, IBD, or psoriasis, between July 1, 2012, and December 31 2017 (Spaarne Gasthuis and MST) or between January 1, 2013, and December 31, 2017 (UMC Utrecht) were included in the cohort. New users were defined as patients who had no use of any biological drug for RD, IBD, or psoriasis for at least 6 months prior to the date of inclusion. The date of the start of the first TNFα inhibitor within the study period was assigned as the patient's index date.

For all patients included, date of birth, gender, treatment indication defined as RD, IBD, or psoriasis (derived from the specialism of the prescriber of the TNFα inhibitor), type of biological drug, dose and dosing regimen, dispensing date (outpatient biological drugs) or administration date (biological drugs administered at the hospital ward), having TNFα inhibitor serum concentration or anti-drug antibodies measured, use of immunomodulators and high-dose corticosteroids were collected.

Switching Patterns

For each patient treatment episodes were constructed, defined as the duration of use of a single type of biological drug over time. For outpatient biological drugs, this was the time between the first dispensing of that biological drug until the end of the duration of the last dispensing. For biological drugs administered at the hospital ward, this was the time between the first administration of that biological drug until the last administration plus the standard dosing interval. A maximum permissible gap of 90 days (outpatient biological drugs) or twice the length of the standard dosing interval (biological drugs administered at the hospital ward) was allowed to correct for potential temporary treatment interruptions (e.g. due to surgery or infections).

From these treatment episodes, switching patients were identified, defined as starting a treatment episode of another biological drug (or a JAK inhibitor) within the maximum permissible gap of the previous one. In addition, patients who did not switch were identified as persistent users (one treatment episode for the index TNFα inhibitor from the index date until the end of follow-up or censoring) or discontinuers of biological treatment (no dispensing of the index TNFα inhibitor, without switching).

For the analysis of switching patterns, all biological (and JAK-inhibitor) treatment switches were studied, including multiple treatment switches. Sankey diagrams

were constructed to present switching patterns, stratified by indication (RD, IBD or psoriasis). The number of patients who switched and median time until the switch were added to the diagram.

The following biological drugs were included in the analysis: abatacept, anakinra, belimumab, brodalumab, canakinumab, guselkumab, ixekizumab, rituximab, sarilumab, secukinumab, ustekinumab, vedolizumab (biological drugs), and baricitinib and tofacitinib (JAK inhibitors).

Determinants for switching

Determinants for switching from the first TNFα inhibitor to another biological drug (or JAK inhibitor) were explored in a nested casecontrol analysis. Cases were defined as patients who switched at least once during follow-up. Patients who did not switch were included as controls. Up to four controls were randomly selected for each case by using incidence density sampling. Cases and controls were matched by the type of TNFα inhibitor at the index date, treatment in the same hospital and the date of initiation of treatment (± 3 months). Controls could be selected more than once, and patients who became cases could be selected as controls at earlier time points.

The following determinants for switching were explored: age at index date (continuous, years); gender (categorical); dose escalation of TNFα inhibitor within 60 days before the switch (yes or no); initiation or dose escalation of treatment with immunomodulator within 60 days before the switch (yes or no); initiation of treatment with high-dose corticosteroids within 60 days before the switch (yes or no); and TNFα inhibitor serum concentration measurement (or anti-drug antibodies for the specific TNFα inhibitor) within 60 days before the switch (yes or no).

Dose escalation of outpatient-administered TNFα inhibitors was defined as having any increase in dose or shortening of dosing interval of the index TNFα inhibitor in the 60-day period before the switch. For infliximab, dose escalations were defined as either a minimum 25% increase[23] in dose in the 60-day period before the switch or an increase in dosing interval of a minimum of 8 days to overcome rounding up and dose increases due to an increased weight of the patient or logistic issues.

The following immunomodulators were included: sulfazalazine, mesalazine, mercaptopurine, tioguanine, mycophenolic acid, leflunomide, ciclosporin, azathioprine, methotrexate and hydroxychloroquine.

Data analysis

Descriptive statistics were used to present the baseline characteristics of the patients. Treatment patterns were presented in a Kaplan Meier curve for persistent use of index TNFα inhibitor. Switch to another biological drug or JAK inhibitor and discontinuation of index TNFα inhibitor without switching were presented in cumulative incidence curves.

Determinants for switching were analyzed with conditional logistic regression, stratified per indication. All possible determinants were first analyzed univariately, and determinants with a p-value of <.1 in the univariate analysis were analyzed using multivariate conditional logistic regression.

In a sensitivity analysis, the impact of changing the definition of new users was assessed by only including patients who did not use any biological drug for RD, IBD or psoriasis 12 months prior to the date of inclusion. This was done to discriminate prevalent users of TNFα inhibitor from new users.

Data were analyzed using R version 3.6.1 (R Foundation for Statistical Computing).

Results

A total of 2228 patients were included, with a median age of 43.3 years, 56.6% of the patients being female (Table 1). Of the included patients, 1155 (51.8%) were diagnosed with RD, 967 (43.4%) with IBD and 106 (4.8%) with psoriasis. Adalimumab was the most frequently (40.9%) used TNFα inhibitor for the total study population, but etanercept was the most used TNFα inhibitor in RD patients (47.5%), infliximab in IBD patients (62.4%). At baseline, 49.6% of the patients additionally used an immunomodulator. This differed between indications; with concomitant use in 58.1% of RD patients, 43.1% of IBD patients, and 16.0% of psoriasis patients.

Switching patterns

Approximately 16% of patients switched from the initial TNFα inhibitor to another biological drug, which was comparable across indications, as shown in Figure 1. About 44.5% of patients discontinued their initial TNFα inhibitor without switching to another biological drug, this was comparable between the indications as well. One year after the index date, 62.4% of RD patients, 63.4% of IBD patients, and 58.7% of psoriasis patients were still using their index TNFα inhibitor. The median duration of use was 1.9 years in RD patients, 2.1 years in IBD patients and 1.6 years in psoriasis patients.

Table 1: Patient characteristics of the cohort at baseline

	Total n= 2228	RD n= 1155	IBD n= 967	Psoriasis n= 106
Females (%)	1261 (56.6%)	705 (61.0%)	515 (53.3%)	41 (38.7%)
Median age (IQR)	43.3 (26.8–57.2)	49.1 (33.3–70.0)	34.4 (22.5–51.2)	50.6 (34.4–60.4)
Etanercept	573 (25.7%)	549 (47.5%)	-	24 (22.7%)
Infliximab	654 (29.3%)	41 (3.6%)	603 (62.4%)	10 (9.4%)
Adalimumab	911 (40.9%)	488 (42.3%)	351 (36.3%)	72 (67.9%)
Certolizumab	13 (0.6%)	13 (1.1%)	-	-
Golimumab	77 (3.5%)	64 (5.5%)	13 (1.3%)	-
Baseline use of immunomodulator	1105 (49.6%)	671 (58.1%)	417 (43.1%)	17 (16.0%)
Median follow-up (IQR) (years)	3.4 (2.1–5.0)	3.6 (2.2–5.2)	3.3 (2.0–4.8)	3.2 (2.1–4.5)

IQR: interquartile range

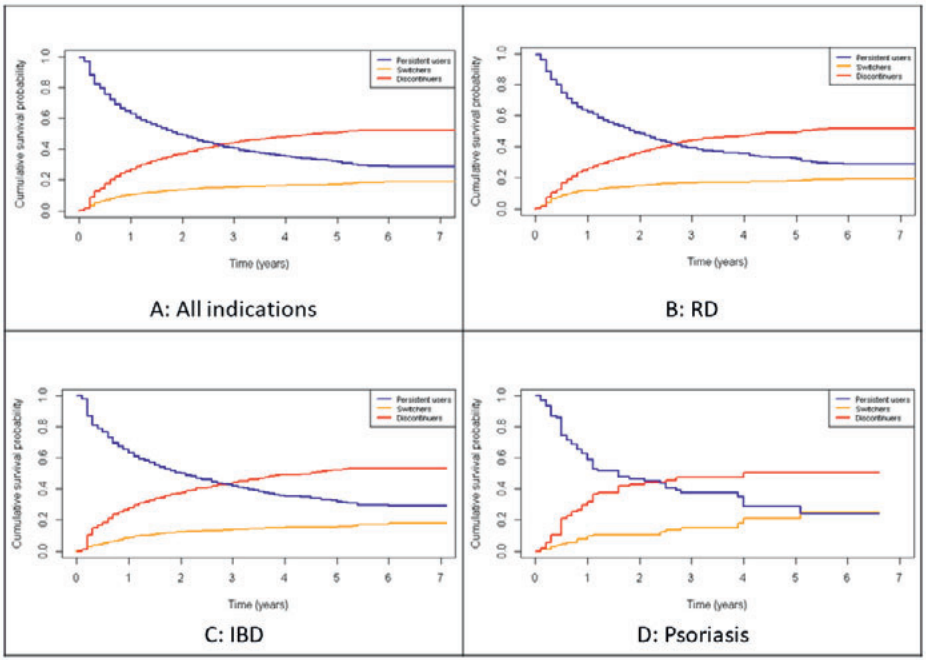


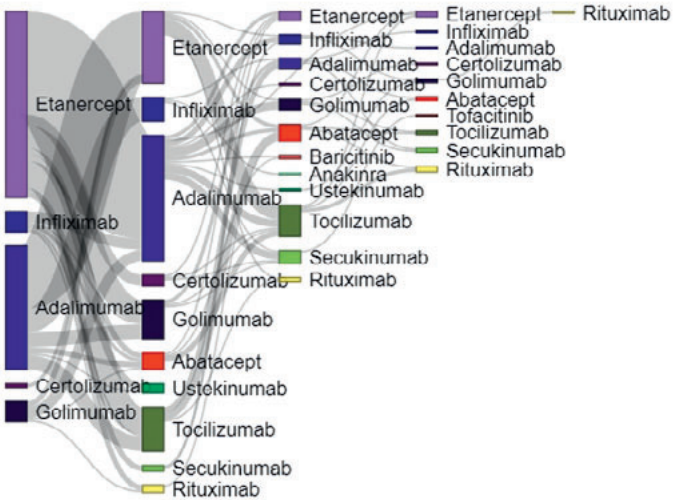
Figure 1: Kaplan–Meier curve of time of persistent use of initial TNFα inhibitor; time until switch to another biological; time until discontinuation TNFα inhibitor without switching for all indications (A), RD (B), IBD (C) and psoriasis (D).

The majority of RD and IBD patients switched from their index TNFα inhibitor to a second TNFα inhibitor (76.6% and 74.3%); most psoriasis patients switched to ustekinumab (64.7%), as shown in Figure 2A-C. About 33% of RD patients, 20% of IBD patients, and 12% of psoriasis patients switched a second time; some patients to a third TNFα inhibitor (36.5% for RD and 37.0% for IBD), some to an interleukin inhibitor (41.3% for RD and 8.1% for IBD) and some to a selective immunosuppressant (19.0% for RD and 51.9% for IBD), except for psoriasis, these patients switched all to a TNFα inhibitor. Switching three times or more occurred in 8.9% of RD, 2.1% of IBD, and 5.9% of psoriasis patients. The median time until switch was comparable between patients with RD, IBD and psoriasis (Figure 2A-C).

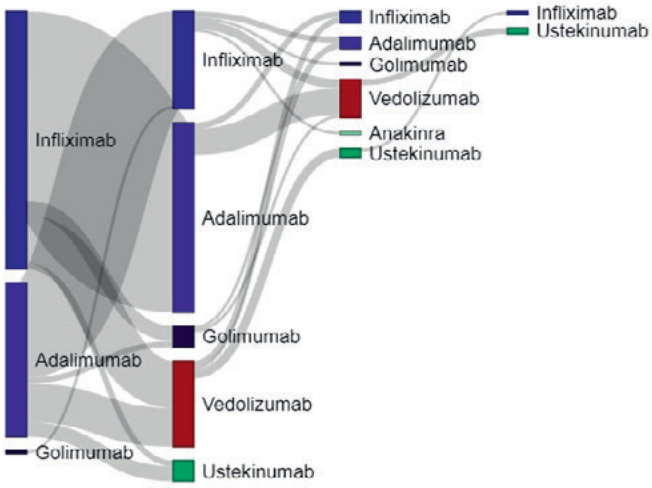
Determinants for switching

The assessment of determinants showed that patients suffering from RD who had a dose escalation of their TNFα inhibitor (OR 13.78, 95%CI 1.40 - 135.0) or initiated high-dose corticosteroid treatment (OR 3.62, 95% CI 1.10 - 12.15) were more likely to switch biological treatment (Table 2).

(A)



(B)



(C)

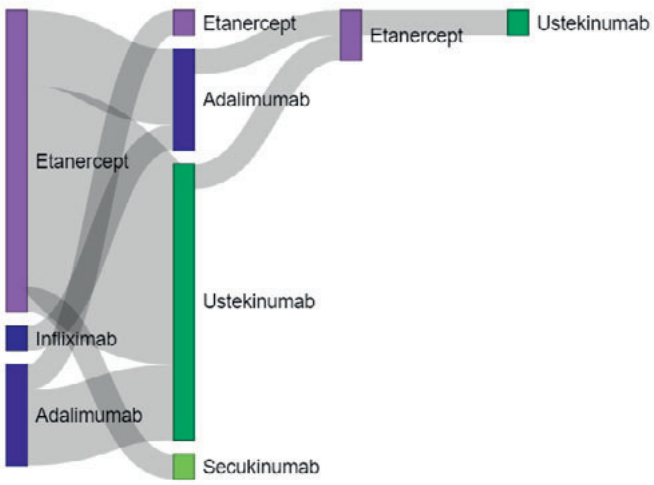


Figure 2 (A) Switching patterns of RD patients with median time (IQR) until switch. TNFα inhibitors (etanercept, infliximab, adalimumab, certolizumab, golimumab) were colored purple, selective immunosuppressants (abatacept, tofacitinib, baricitinib) were colored red, interleukin inhibitors (anakinra, ustekinumab, tocilizumab, secukinumab) were colored green and rituximab was colored yellow. (B) Switching patterns of IBD patients with median time until switch. TNFα inhibitors (infliximab, adalimumab, golimumab) were colored purple, selective immunosuppressants (vedolizumab) were colored red and interleukin inhibitors (anakinra, ustekinumab) were colored green. (C) Switching patterns of psoriasis patients with median time until switch. TNFα inhibitors (etanercept, infliximab, adalimumab) were colored purple and interleukin inhibitors (ustekinumab, secukinumab) were colored green.

Table 2: Determinants for the first switch to a second biological for RD patients

	No. cases n= 171	No. controls n= 627	OR (univariate) 95% CI	OR (multivariate) 95% CI
Median (IQR) age at index date	47.4 (29.5)	48.2 (26.3)	0.99 (0.98-1.00)	-
Gender				
Males	61 (35.7%)	241 (38.4%)	Ref	
Females	110 (64.3%)	386 (61.6%)	0.88 (0.81-1.60)	-
TNFα dose escalation				
No	168 (98.2%)	626 (99.8%)	Ref	
Yes	3 (1.8%)	1 (0.2%)	12 (1.25-115.4)*	13.78 (1.40-135.0)
Initiation/ dose escalation immunomodulator				
No	143 (83.6%)	547 (87.2%)	Ref	
Yes	28 (16.4%)	80 (12.8%)	1.43 (0.85-2.42)	-
High-dose corticosteroid				
No	166 (97.1%)	621 (99.0%)	Ref	
Yes	5 (2.9%)	6 (1.0%)	3.24 (0.99-10.65)*	3.62 (1.10-12.15)
Serum concentration measurement				
No	170 (99.4%)	627 (100%)		
Yes	1 (0.6%)	0 (0%)	NA	-

*p-value <.1

IBD patients who had a dose escalation of their TNFα inhibitor (OR 8.22, 95% CI 3.76 - 17.93), initiated or intensified immunomodulator treatment (OR 2.13, 95% CI 1.04 - 4.34), initiated high-dose corticosteroid treatment (OR 6.91, 95% CI 2.81 - 17.01) or had a serum concentration measurement (OR 5.44, 95% CI 2.74 - 10.79) were more likely to switch as well (Table 3).

Table 3: Determinants for the first switch to a second biological for IBD patients

	No. cases n= 136	No. controls n= 459	OR (univariate) 95% CI	OR (multivariate) 95% CI
Median (IQR) age at index date	38.6 (31.8)	32.7 (31.9)	1.01 (0.99-1.02)	-
Gender				
Males	61 (44.9%)	204 (44.4%)	Ref	
Females	75 (55.1%)	255 (55.6%)	0.97 (0.66-1.43)	-
TNFα dose escalation				
No	91 (66.9%)	424 (92.4%)	Ref	
Yes	45 (33.1%)	35 (7.6%)	10.83 (5.51-21.26)*	8.22 (3.76-17.93)

Table 3: Continued.

	No. cases n= 136	No. controls n= 459	OR (univariate) 95% CI	OR (multivariate) 95% CI
Initiation/ dose escalation immunomodulator				
No	95 (69.9%)	415 (90.4%)	Ref	
Yes	41 (30.1%)	44 (9.6%)	4.45 (2.65-7.89)*	2.13 (1.04-4.34)
High-dose corticosteroid				
No	109 (80.2%)	440 (95.9%)	Ref	
Yes	27 (19.8%)	19 (4.1%)	8.12 (3.74-17.62)*	6.91 (2.81-17.01)
Serum concentration measurement				
No	86 (63.2%)	405 (88.2%)	Ref	
Yes	50 (36.8%)	54 (11.8%)	6.55 (3.65-11.77)*	5.44 (2.74-10.79)

*p-value <.1

The study did not include a sufficient number of cases with psoriasis to allow for a case-control analysis in this group of patients.

The sensitivity analysis produced similar results both for the treatment patterns and determinants analysis as the main analysis (Table S1 - S3).

Discussion

In this study, we investigated switching patterns and determinants for switching in patients with RD, IBD, or psoriasis initiating treatment with TNFα inhibitors in the Netherlands between July 2012 and December 2017. Our study demonstrated that about 16% of patients switched biological treatment, mainly to another type of TNFα inhibitor. A limited number of patients (5.5% of the RD patients, 2.3% of the IBD patients and 1.9% of the psoriasis patients) switched twice during follow up. TNFα inhibitor dose escalation and initiation of high-dose corticosteroid were associated with switching in RD patients while dose escalation of the TNFα inhibitor or immunomodulator, initiation of high-dose corticosteroid treatment, and TNFα inhibitor serum concentration measurement were associated with switching in IBD patients.

Our study demonstrated that 16.6% of RD patients, 14.5% of IBD patients and 16.0% of psoriasis patients switched biological treatment after a median of 0.52 - 1.96 years of use. Other studies with similar duration of follow-up published similar percentages of switchers, ranging from 12.9% in RD and psoriasis patients to 14.6% in IBD patients.[14,24] A study in psoriasis patients reported higher percentage of switching (54.9%), which in

part could be explained by the longer follow-up of 12 years and inclusion of a biological drug that was withdrawn from the market.[25] The majority of RD and IBD patients in our study switched to another type of TNFα inhibitor, which was in line with previous studies in these indications.[15,26]

About 33% of RD patients, 19% of IBD patients, and 12% of psoriasis patients who switched once, additionally switched a second time during follow up. A similar switching rate to third-line biological treatment of 20% in RD patients was found.[27] In RD and IBD, no clear preference regarding the type of biological used for the second switch during follow-up was seen. Surprisingly, 25 patients in our study sequentially used three different types of TNFα inhibitors, which is not in accordance with guidelines of the American College of Rheumatology and the European Crohn´s and Colitis Organisation.[28,29] However, until recently, particularly in IBD, limited options were available after the failure of treatment with TNFα inhibitors.

Our study showed that TNFα inhibitor dose escalation and initiation of high-dose corticosteroid treatment was associated with an increased likelihood of switching to a second biological in both RD and IBD patients. Initiation or dose escalation of an immunomodulator and TNFα inhibitor serum concentration measurement were associated with switching as well in IBD patients. These factors are possible markers for disease worsening and, consequently, switching. In RD and IBD patients, disease flares are often treated by initiating high-dose corticosteroids or immunomodulators.[28,30] However, in contrast to RD, if an IBD patient experiences a flare, measuring serum drug concentrations (and anti-drug antibodies), and intensifying the dose are also commonly used strategies.[29] Thus, in both indications, these determinants, together with the finding that switching occurred after a median of more than 6 months, might indicate that loss of effect of the index TNFα inhibitor, experienced as flaring of the disease was the most important reason for switching biological treatment. There is also some coherence between these actions as for a patient experienced a flare, a clinician could, for example, measure the TNFα inhibitor serum concentration and simultaneously initiate high-dose corticosteroids to instantly treat the flare.

A study in IBD patients demonstrated that initiation of high-dose corticosteroids and serum concentration measurement were predictors of switching.[15] However, contradictory to our findings, dose escalation of the TNFα inhibitor was found to decrease the likelihood of switching. This discrepancy could be attributed to the authors' more stringent definition of dose escalation compared to our study. We assessed dose escalation within a 60 day time frame prior to switch while Chen et al. defined a dose escalation as a dose that was higher than the standard dose without

using a specific timeframe. For example, if a patients was using etanercept once per 2 weeks, but increased the dose to once per 10 days in the 60-day period prior to switching, we considered this a dose escalation.

Our study was, to the best of our knowledge, unique in mapping longitudinal switching patterns, including multiple switches, across the three major indications for TNFα inhibitor treatment and explored determinants for switching across multiple indications. Another strength of this study was the large number of included patients, which reflects the general patient population. Moreover, as patients were included from two large hospitals and one university hospital, this study provides an ideal reflection of switching patterns across various hospitals.

One of the three included hospitals had stringent guidelines for the first- and second-line biological treatment for each indication; which possibly affected switching patterns. However, switching patterns for patients treated for RD and IBD at this hospital were similar to the other two hospitals who did not have stringent guidelines or restrictions. The local policies in one included hospital advised psoriasis patients not to initiate treatment with a TNFα inhibitor but with an interleukin inhibitor. Thus, we were only able to include a limited number of psoriasis patients from this hospital.

It is important to consider that patients might use the outpatient-administered TNFα inhibitor differently from what is indicated on the dosing label. This could result in an overestimation of the number of discontinued patients. However, we applied a broad permissible gap of 90 days between dispensings to overcome this. Same applies to misclassification of first use, which we defined minimum biological-free period of 6 months before the initiation. However, prolonging this period to 12 months did not impact our results.

We additionally did not have information on the reason for switching to another biological drug or the discontinuation of biological treatment. As the reason for switching treatment influences the choice of second-line biological drug, this information might add to the understanding of the switching patterns seen.

Finally, as the indication for TNFα inhibitor treatment was derived from the specialism of the prescriber, we were unable to make distinctions between the individual RD, such as RA, AS, psoriatic arthritis and juvenile idiopathic arthritis. RA and AS are the most prevalent rheumatic diseases,[31] we believe that these are also the most prevalent types of RD in our cohort. As the biological treatment strategies in RA and AS are

comparable and there are no differences in reimbursement regulations between these indications, we believe that aggregating all types of RD has little impact on our results.

In conclusion, this large study of real-life data on biological use demonstrated specific switching patterns of patients who initiated TNFα inhibitor treatment. Approximately 16% of patients switched biological treatment, this was comparable between the three indications. Most RD and IBD patients switched to another TNFα inhibitor. A minority of the patients switched a second time, but in these patients, there was no clear preference for TNFα inhibitors or biological drugs belonging to another mechanistic class.

TNFα inhibitor dose escalation and the initiation of high-dose corticosteroid treatment were determinants for switching in RD patients. TNFα inhibitor dose escalation, immunomodulator dose escalation, the initiation of high-dose corticosteroid treatment and the measurement of TNFα inhibitor serum concentration were determinants for switching in IBD patients. These findings might help clinicians to anticipate on switching of TNFα inhibitor treatment in these patients.

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Supplementary files

Table S1: Number of switched and discontinued patients – sensitivity analysis

	Total (n=2010)	RD (n=1027)	IBD (n=883)	Psoriasis (n=100)
No. switched patients (%)	306 (15.2%)	161 (15.7%)	129 (14.6%)	16 (16%)
No. discontinued patients (%)	879 (43.7%)	440 (42.8%)	393 (44.5%)	46 (46%)

Table S2: Patients on index TNFα inhibitor after one year and median duration of use – sensitivity analysis

	Total (n=2010)	RD (n=1027)	IBD (n=883)	Psoriasis (n=100)
No. patients on index TNFα inhibitor after one year (%)	1255 (62.4%)	626 (61.8%)	571 (63.6%)	56 (57.2%)
Median duration of use (year)	1.9	1.9	2.0	1.6

Table S3a: Determinants for the first switch to a second biological for RD patients – Sensitivity analysis

	No. cases n= 153	No. controls n= 533	OR (univariate) 95% CI	OR (multivariate) 95% CI
Median (IQR) age at index date	46.5 (29.1)	48.8 (28)	0.99 (0.98-1.01)	-
Gender				
Males	56 (36.7%)	225 (42.2%)	Ref	
Females	97 (63.3%)	308 (57.8%)	0.79 (0.88-1.84)	-
TNFα dose escalation				
No	149 (97.4%)	532 (99.8%)	Ref	
Yes	4 (2.6%)	1 (0.2%)	13 (1.43-121.7)*	-
Initiation/ dose escalation immunomodulator				
No	131 (85.6%)	480 (90.1%)	Ref	
Yes	22 (14.4%)	53 (9.9%)	1.56 (0.90-2.72)	-
High-dose corticosteroid				
No	151 (98.7%)	529 (99.2%)	Ref	
Yes	2 (1.3%)	4 (0.8%)	1.9 (0.35-10.4)	
Serum concentration measurement				
No	152 (99.3%)	532 (99.8%)	Ref	
Yes	1 (0.7%)	1 (0.2%)	4 (0.25-63.96)	-

*p-value <.1

Table S3b: Determinants for the first switch to a second biological for IBD patients – Sensitivity analysis

	No. cases n= 125	No. controls n= 426	OR (univariate) 95% CI	OR (multivariate) 95% CI
Median (IQR) age at index date	38.8 (31.4)	33.8 (32.9)	1.00 (0.99-1.02)	-
Gender				
Males	60 (48.0%)	198 (46.5%)	Ref	
Females	65 (52.0%)	228 (53.5%)	0.95 (0.64-1.42)	-
TNFα dose escalation				
No	99 (79.2%)	402 (94.4%)	Ref	
Yes	26 (20.8%)	24 (5.6%)	11.1 (4.45-27.55)*	13.66 (4.73-39.43)
Initiation/ dose escalation immunomodulator	86 (68.8%)	382 (89.7%)	Ref	
No	39 (31.2%)	44 (10.3%)	4.70 (2.69-8.23)*	4.04 (2.02-8.06)
Yes				
High-dose corticosteroid	27 (21.6%)	406 (95.3%)	Ref	
No	98 (78.4%)	20 (4.7%)	9.59 (4.08-22.52)*	10.68 (4.73-39.43)
Yes				
Serum concentration measurement				
No	76 (60.8%)	373 (87.6%)	Ref	
Yes	49 (39.5%)	53 (12.4%)	6.65 (3.66-12.09)*	5.03 (2.56-9.12)

*p-value <.1

CHAPTER 3

Recommendations on TNFα inhibitor biosimilar use in clinical practice: a comparison of European gastroenterology IBD guidance

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Expert Opin Biol Ther. 2023;23:1-17.

Abstract

Background

Professional associations publish guidance advising gastroenterologists on prescribing biosimilars; however, guidelines differ between countries and change over time. This study aimed to map the presence and content of guidance from European gastroenterology associations on TNFα inhibitor biosimilar use and its development over time.

Research design and methods

Guidelines on biosimilar prescribing from national gastroenterology associations in the European Economic Area (EEA) partnered with the European Crohn's and Colitis Organisation (ECCO) were collected. Treatment guidelines and biosimilar position papers from 2010 to 2022 were included. Data were extracted using a template.

Results

Twenty-six of 30 EEA countries have an ECCO-partnered gastroenterology association, of which 14 (53.8%) had national guidelines addressing biosimilars, four (15.4%) followed ECCO's position, and three (11.6%) had treatment guidelines without mentioning biosimilars. From five countries (19.2%) no guidelines were retrieved. Among 18 countries with guidance, 14 (77.8%) associations endorsed initiating biological treatment with biosimilars, and 13 (72.2%) endorsed transitioning from originator to biosimilar. Nine associations published multiple guidelines over time addressing biosimilars; overall, their positions became more encouraging.

Conclusions

The majority of gastroenterology associations endorsed biosimilar use. The lack of (up-to-date) guidelines for some associations indicates an area of improvement to support biosimilar use in clinical practice.

Introduction

Tumor Necrosis Factor (TNF)α inhibitors have significantly improved the pharmacological treatment of inflammatory bowel disease (IBD), including Crohn's Disease (CD) and ulcerative colitis (UC). These agents make clinical and endoscopic remission realistic targets for patients who do not respond sufficiently to first-line conventional therapy, such as aminosalicylates or immunomodulators, sometimes combined with (short-term) corticosteroids.[1] TNF is a central cytokine in the pathogenesis of IBD, causing inflammation located in the gut (UC), or affecting the whole gastrointestinal tract (CD).[1] TNFα inhibitors neutralize TNF and consequently reduce inflammation.[2] However, TNFα inhibitors, like most biological medicines, were substantially more expensive than conventional small-molecule medicines, which has stressed healthcare budgets[4] and sometimes limited patients' access to these treatments.

The patent and regulatory exclusivities expired several years ago for the infliximab (Remicade) and adalimumab (Humira) brand products, the two most used TNFα inhibitors in IBD.[3] This allowed the introduction of biosimilars as lower-cost versions of these medicines.[3] A biosimilar is defined by the European Medicines Agency (EMA) as 'a biological medicinal product that contains a similar version of the active substance of an already authorized biological medicinal product (also called the reference product or originator)'.[4] For a biosimilar to be authorized in the European Union (EU), it undergoes an extensive comparability exercise with the originator biological to assess its biosimilarity, both in vitro and in vivo.[5] Until October 2022, four biosimilars for infliximab and 11 for adalimumab had been approved for IBD in the EU.[6] Introducing these biosimilars in many countries has led to price competition, resulting in lower healthcare costs and, in some cases, improved patient access to biological therapy.[7]

With the introduction of biosimilars, it became possible to start new patients with a biosimilar instead of an originator and to switch patients currently under treatment with an originator to the biosimilar. The latter process is also referred to as 'transitioning'. The use and clinical acceptance of biosimilars have been heavily debated among physicians, with positions changing over time. For example, in their 2013 position paper on biosimilars, the European Crohn's and Colitis Organisation (ECCO) stated that more research, specifically in IBD patients, was needed to ensure that biosimilars are effective and safe before prescribing them. Furthermore, the 2013 guideline did not mention transitioning.[8] However, ECCO's updated position in 2017 was much more supportive of biosimilar use; it stated that both starting new patients on a biosimilar and transitioning patients from originator to biosimilar are acceptable as they do not affect efficacy or safety.[9]

Clear guidance on implementing biosimilars in clinical practice is essential to support gastroenterologists in prescribing biosimilars with confidence. In general, gastroenterologists have two important sources for guidance on prescribing biosimilars: guidelines issued by ECCO and guidelines issued by their national gastroenterology association. The availability and content of these national gastroenterology guidelines might differ between countries, so comparing guidelines highlights the similarities and differences in the national positions by gastroenterologists on biosimilars. Currently, an overview of clinical guidelines regarding the use of biosimilars in clinical practice is not available for EEA countries. Therefore, little is known about the resemblance or divergence between clinical guidelines from gastroenterology associations on biosimilar use on the European level.

This study aimed to map the presence and content of guidance from gastroenterology associations in countries of the EEA on the use of biosimilars in clinical practice, including the development of guidance on biosimilar prescribing over time.

Patients and methods

Systematic search and inclusion of guidelines

Guidelines were retrieved from national gastroenterology associations of EEA member countries (hence the 27 EU Member States, plus Norway, Liechtenstein, and Iceland) and countries listed as partners of ECCO (n=26) (Table S1).[10,11] Inclusion was limited to those countries within the EEA, since biosimilars in these countries are subject to the regulations for biosimilar regulatory approval of the EMA. The list of ECCO partner organizations was verified to be up to date by email contact with ECCO.[12]

Guidelines were manually searched from the websites of the national gastroenterology associations and from PubMed between February 2022 and May 2022. To validate the manual search, each national gastroenterology association was contacted via email (and two reminder emails) and asked to provide their guidelines. If no response was received, guidelines found on the gastroenterology associations' website were eligible for inclusion. Guidelines were included if they addressed the treatment of Crohn's disease, ulcerative colitis, or IBD in general or the treatment of IBD with biologicals because these potentially contain guidance on biosimilars. Position papers specifically addressing biosimilars were also included. Guidelines published between 2010 and May 2022 were included because the EMA authorized the first biosimilar with a gastroenterological indication in 2013.[12] If no guidelines were found on the association's website, and the association did not respond to the emails, the guidelines could not be retrieved and were excluded or were considered non-existent.

If no guidelines were available, but the national gastroenterology association explicitly referred to a guideline from another medical association, either on the website or in response to the emailed request from the authors, that guideline was included in this study. For example, a guideline from an overarching non-disease-specific association for medical specialists would be included. Only guidelines from medical associations were included; thus, guidelines from regulatory authorities were excluded.

If national associations had published multiple versions of their guidelines over the study period, all versions were included from 2010 until May 2022 to review the evolving landscape of biosimilar guidance over time. In case a gastroenterology association had published multiple guidelines, all were included, and discrepancies between the guidelines were analyzed and reported. If the national gastroenterology association that was listed as a partner of ECCO had no guidelines available, and ECCO's website had another gastroenterology association from that country listed (as 'other organization'), that association was checked for guidelines, which were included if present.

Data extraction

The primary outcome of this study was to assess gastroenterology associations' guidelines for recommendations on starting new patients on a biosimilar and on transitioning patients from an originator to a biosimilar. In addition, guidance related to transitioning, such as informing and monitoring patients, was also assessed. Information on these outcomes was extracted from the included guidelines.

First, a standardized data collection template was designed, discussed among the authors, and adjusted until a consensus was reached. The standardized template contained detailed questions on the guidelines for prescribing biosimilars. The template was based on the 2017 ECCO guideline on biosimilars[9] and the authors' expertise. The template included characteristics of the guidelines themselves, such as the type of document, the year the guidelines were published, recommendations on starting treatment with a biosimilar, transitioning patients from originator to biosimilar, which patients were eligible for biosimilar treatment (for starting or transitioning), recommendations on informing and monitoring patients during transitioning, and recommendations on cross-transitioning (biosimilar to biosimilar) and retransitioning (biosimilar to originator). See S2 for the template and a more detailed description.

Data was extracted from the guidelines by RWM in a standardized form in Microsoft Excel. The co-authors (LB, LCD, KS, and HMT) validated data extraction from the guidelines by cross-checking for eight countries if they had guidelines available, and

crosschecking data extraction from the guidelines from all countries that had national guidelines available and from the ECCO position paper on biosimilars (Table S3). Data were discussed in a group meeting, and discrepancies or disagreements were discussed until a consensus was reached. Data extraction was done as much as possible in the original language of the guideline, but if the understanding of the original language was insufficient, Google translate was used for translation to English.

For the national gastroenterology associations with multiple versions of guidelines, including biosimilars, data was extracted from each guideline document and compared to identify potential development over time.

Data analysis

The availability of guidelines was visually depicted. Baseline characteristics (type of document and year of publication) and recommendations on starting and transitioning were summarized by country and listed as the number of associations, and the percentage from the total number of national gastroenterology associations with guidance available was provided. The development of guidance over time was graphically presented and separated into a chart that lists the recommendations for starting patients on a biosimilar and transitioning patients from originator to biosimilar.

Results

Baseline characteristics

Of the 30 EEA countries, four countries were excluded because they did not have a gastroenterology association partnered with ECCO. Of the remaining 26 countries, gastroenterology associations from 14 countries (53.8%) had a national guideline that addressed biosimilars, gastroenterology associations from four countries (15.4%) followed the position of ECCO, associations from three countries (11.6%) had guidelines that did not mention biosimilars, and, from five associations (19.2%), no guidelines were retrieved (Figure 1). In total, 40 guidelines (including guidelines without mention of biosimilars and guidelines with multiple versions) were retrieved. One guideline version was retrieved from six national gastroenterology associations, and a further four national associations and ECCO's position paper on biosimilars yielded two versions. Four associations yielded three versions and tree associations yielded four.

In total, 18 countries, including 28 guidelines, had guidance on biosimilars. National gastroenterology associations from nine countries had multiple versions of their guidelines available that included biosimilars. All included guidelines were publicly available on the national gastroenterology association's website or via Pubmed.

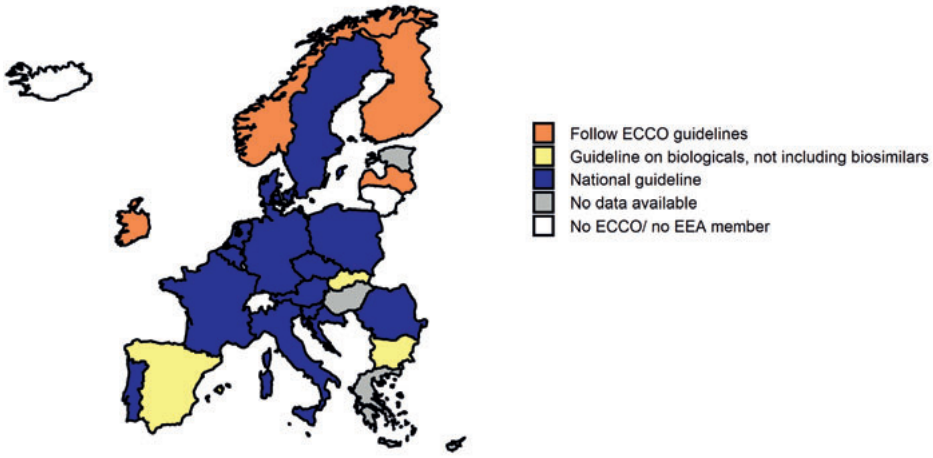

Figure 1: Availability of guidelines on the use of biosimilars in clinical practice from national gastroenterology associations (n countries included=30).

As depicted in Table 1, 18 national gastroenterology associations had their own guidelines that included recommendations on biosimilars or followed ECCO guidelines. Of these, 13 (72.2%) were a position paper specifically on biosimilars. Four (22.2%) were a section or paragraph on biosimilars in another type of guideline, such as a guideline on the use of biologicals in IBD, and Germany (5.6%) had both a position document on biosimilars and a section in their clinical treatment guidelines for Crohn's disease and ulcerative colitis. The most recent versions of the guidelines were published between 2014 and 2022, with the majority published between 2017 and 2019.

Initiating TNFα inhibitor treatment with a biosimilar

Table 1 summarizes recommendations from gastroenterology associations' most recent guidelines regarding initiating TNFα inhibitor treatment using biosimilars. For the majority of the 18 national gastroenterology associations (n=14 [10 with national guidelines and 4 that follow ECCO], 77.8%), no extra recommendations were provided when initiating treatment with a biosimilar in treatment-naïve patients compared with starting TNFα inhibitor treatment with the originator (Figure 2a). National gastroenterology associations from Croatia and Slovenia (11.1%) did not accept initiating treatment with a biosimilar because they did not support the concept of extrapolation of indications. The association from Romania did not include guidance on initiating patients on biosimilars but only transitioning from originator to biosimilar. The guideline from the Danish gastroenterology association does not distinguish between biosimilar medicines as they are considered equivalent and substitutable, without further explicit recommendations on the use of biosimilars.

Most national gastroenterology associations (n=12, 66.7%) reported no extra recommendations regarding which patients could initiate TNFα inhibitor treatment with a biosimilar. The gastroenterology associations from Austria and Croatia restricted starting a biosimilar only to patients with indications in which the biosimilar was tested; the other countries did not mention which patients can initiate biosimilar treatment.

Transitioning patients from TNFα inhibitor originator to biosimilar

The majority (n=13, 72.2%) of the national gastroenterology associations accepted transitioning patients from originator to biosimilar (Table 1, Figure 2b) in the most recent version of their guidelines. These associations were approximately the same as the associations that endorsed treatment-naïve patients to initiate TNFα inhibitor treatment with a biosimilar, except for the Austrian association that only allowed naïve patients to initiate biosimilar treatment. Transitioning to a biosimilar was not acceptable for gastroenterology associations from Austria, Romania, Croatia and Slovenia (22.2%). The latter two associations also did not endorse naïve patients initiating TNFα inhibitor treatment with a biosimilar. Gastroenterology associations from Romania and Croatia did not endorse transitioning patients from an originator to a biosimilar, but retrieving informed consent was recommended for the patients who were transitioned. The guideline from the Danish association made no recommendations, but only stated that they do not distinguish between biosimilars as they are considered equivalent and substitutable.

Out of the 13 associations that endorsed transitioning to a biosimilar, seven reported that all patients are eligible for transitioning, Belgium restricted eligibility to patients in remission, and Portugal to patients treated with originator for a specific time. The type of patients eligible for transitioning was not specified by four national gastroenterology associations that endorsed transitioning.

Fourteen national associations recommended informing patients about transitioning, with six countries additionally stating that patients should consent to transitioning, and Belgium stating that patients should be informed to mitigate from the nocebo effect.

National gastroenterology associations of eight countries had recommendations on monitoring patients after transitioning. The recommendations were diverse. The French and Dutch associations' guidelines recommended extra monitoring of clinical parameters, the Belgian associations' guideline mentioned monitoring for pharmacovigilance (without further specifying what is meant), and the Croatian

and Slovenian mentioned monitoring for adverse events. The Polish guideline recommended monitoring of immunogenicity. The associations from Portugal and Sweden mentioned that patients could be monitored in routine clinical care.

Cross-transitioning and retransitioning

Recommendations on cross-transitioning (i.e., transitioning from one biosimilar to another biosimilar of the same originator) varied. The gastroenterology association from the Netherlands found it acceptable to transition patients once, either from originator to biosimilar, or from biosimilar to another biosimilar, and the association from Sweden recommended cross-transitioning in a study context. However, gastroenterology associations from eight countries, including the four associations following the ECCO guidelines, did explicitly not support cross-transitioning. For seven associations, specific guidance on cross-transitioning was not provided, or a stance on cross-transitioning was not applicable because the association did not endorse transitioning. The different guidelines from Germany varied on cross-transitioning; cross-transitioning was not endorsed by the German clinical guidelines, as they noted that data on this topic was scarce. However, the German position paper found cross-transitioning acceptable.

Retransitioning (i.e., transitioning from biosimilar back to the originator, after an initial transition from originator to biosimilar) was explicitly not accepted by the four associations following the ECCO guidelines because, according to the ECCO guideline, evidence of effectiveness and/ or safety is lacking (Table 1); retransitioning was not mentioned in the other guidelines. The German clinical guidelines did not endorse retransitioning, but this was not mentioned in the German position paper.

Development of guidance over time

Fourteen national gastroenterology associations had multiple versions over time of their guidelines available (Table 2 and Figure 2a and Figure 2b). Guidelines published between 2010 and 2013 did not include recommendations on the use of biosimilars (Figure 2a and Figure 2b). Guidelines published in 2013 and 2014 did not accept initiating TNFα inhibitor treatment with a biosimilar and transitioning patients from originator TNFα inhibitor to a biosimilar. In 2015, this pattern first changed with guidelines that accepted initiating TNFα inhibitor treatment with a biosimilar until, eventually, all national gastroenterology associations that had updated their guidelines indicated acceptance of transitioning from originator to biosimilar (Table 2).

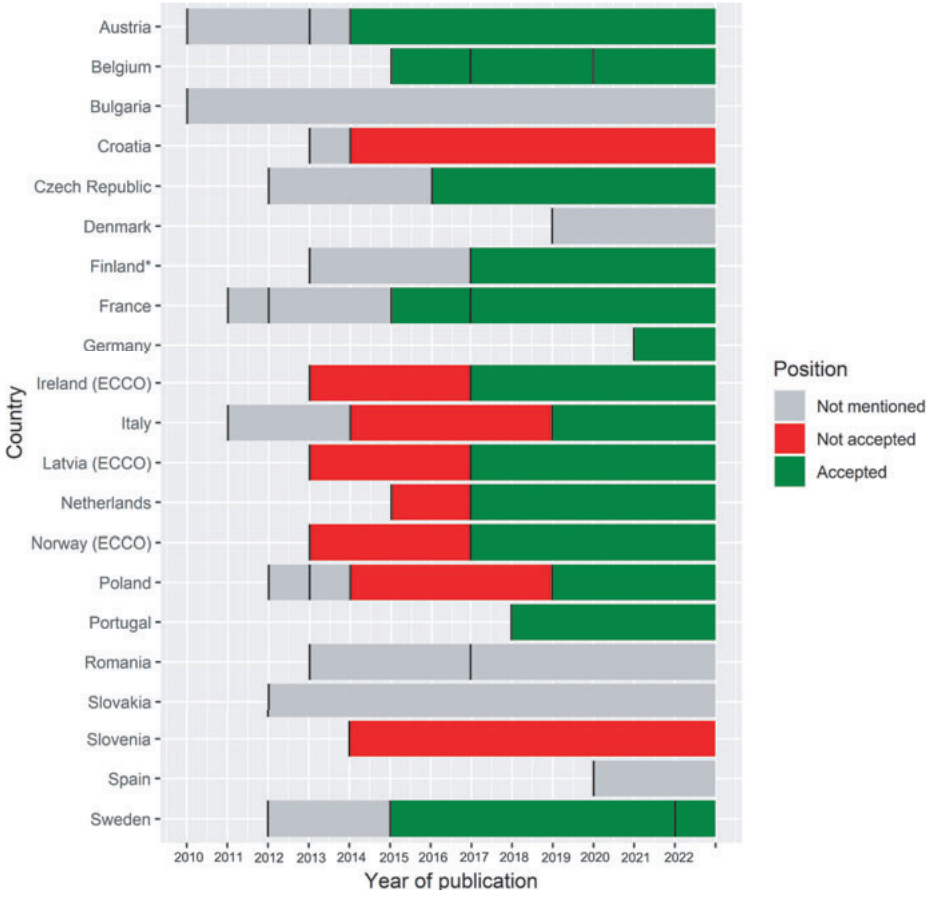

Figure 2a: Development on guidance on starting TNFα inhibitor treatment with a biosimilar over time. The black line indicates a new guideline version (end of follow-up May 2022).
*Finland had national guidelines in 2013, but changed to following ECCO's guidance in 2017

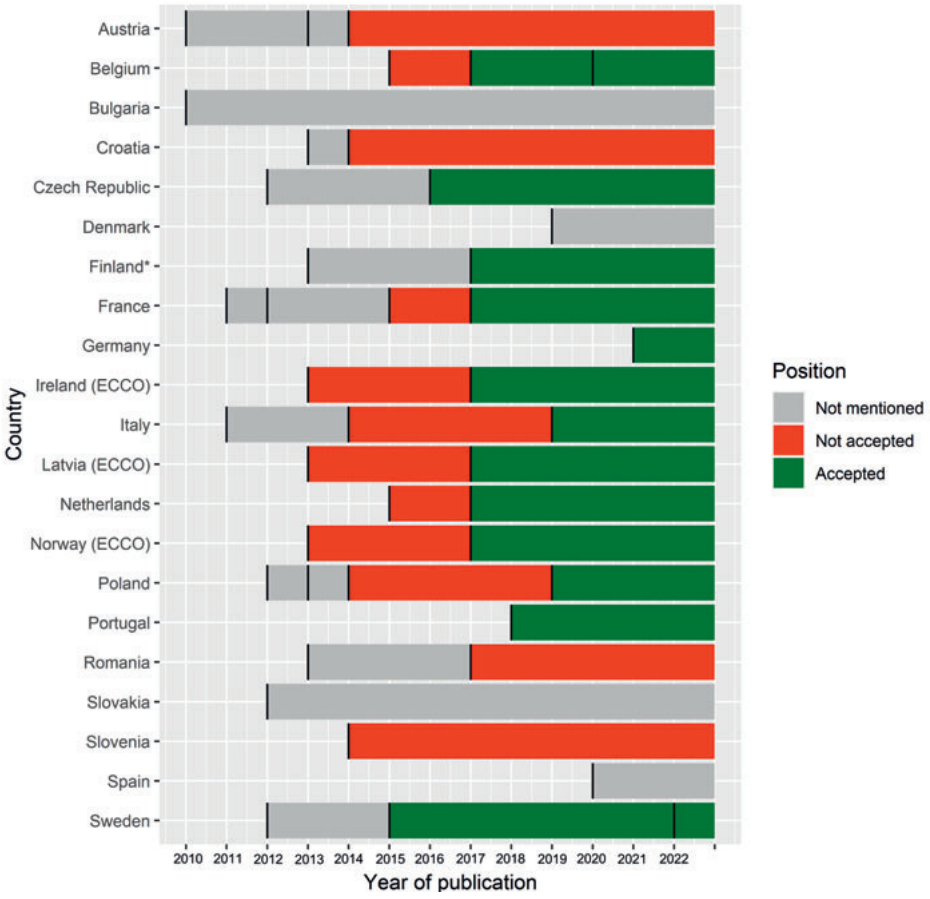

Figure 2b: Development on guidance on transitioning patients from an originator TNFα inhibitor to a biosimilar over time. The black line indicates a new guideline version (end of follow-up May 2022).
*Finland had national guidelines in 2013, but changed to following ECCO's guidance in 2017

Discussion

This study aimed to provide an overview of guidance from gastroenterology associations on starting IBD patients on a biosimilar and transitioning IBD patients to a biosimilar in EEA countries. In most countries (n=18 of 26 included EEA countries, 69.2%), gastroenterology associations had guidance available on prescribing biosimilars in the form of a national guideline, position paper, or statement referring to an ECCO guideline. From the gastroenterology associations of eight countries (30.8%) no guidelines on biosimilar use were retrieved.

The majority of the associations from the 18 countries endorsed initiating TNFα inhibitor treatment with a biosimilar (n=14) and transitioning current patients from originator to biosimilar (n=13). However, there was varied guidance on the presence and content of recommendations regarding informing and monitoring patients while transitioning, cross-transitioning, and retransitioning. The gastroenterology associations of nine countries had multiple versions of their guidelines available that indicated the development of their positions on biosimilars over time, specifically showing a development towards broader support of biosimilars.

In this study, eight of the 26 countries with an ECCO-partnered gastroenterology association had no guidance regarding the use of biosimilars in clinical practice available, either because no guidelines were retrieved (Cyprus, Estonia, Greece, Hungary and Malta), or because the national guidelines did not include recommendations on biosimilars (Bulgaria, Slovakia and Spain). Professional guidelines, such as guidelines from their association, are an essential source of information on biosimilars for gastroenterologists.[13] Gastroenterologists, as well as other physicians, have typically had reservations about biosimilars. A recent systematic literature review showed that around three out of four European gastroenterologists were reluctant regarding the practice of transitioning patients from originator to biosimilars due to insufficient knowledge of biosimilars.[13] Moreover, other factors, such as the paucity of a structured transitioning strategy, limit physicians from transitioning their patients.[14] A previous study demonstrated that incentive policies, such as guidelines on biosimilar use, are positively associated with biosimilar uptake.[15] Although many other factors contribute to a countries biosimilar uptake, for countries that had no guidance, the uptake of biosimilars was low. For example Slovakia, that did not include any mentioning of biosimilars in their clinical guidelines, has a biosimilar market share of 12%, which is well below the EU average of 41%.[7] Moreover, in Spain, the prescriber initiates transitioning patients from the originator TNFα inhibitor to a biosimilar. However, recommendations on the use of biosimilars in treatment guidelines are lacking in the gastroenterology field, which could temper gastroenterologists in prescribing biosimilars.[16] Thus, clinical

guidelines are vital to facilitate evidence based use of biosimilars in clinical practice, and countries that had no gastroenterology guideline on biosimilars available, are urged to construct guidelines and/ or to make them (publicly) accessible.

The most recent version of national gastroenterology guidelines from seven countries, and those from ECCO, were published at least five years ago. In three countries, the timespan between guideline versions was five years or longer, a lengthy period considering the increased knowledge of and experience with biosimilars. This gap in time could delay the adoption of revised gastroenterology guidelines that utilize new knowledge of biosimilars and may postpone clinicians and patients benefitting from this knowledge.[17]

In almost all guidelines that include recommendations on biosimilars, the position on the use of biosimilars in clinical practice (yes or no) was evident. The most recent versions of the guidelines that included explicit recommendations on biosimilars (n=17) indicated their positions on the use of biosimilars in clinical practice. Many also provided physicians with recommendations for transitioning patients from an originator to a biosimilar. Three quarters of guidelines (n=14) indicated that patients should be informed regarding transitioning to a biosimilar. This recommendation aligns with studies on patients' wishes during transitioning from an originator to a biosimilar; patients have expressed the need for quality information to make them comfortable with transitioning to a biosimilar.[18,19]

Additionally, one-third of the guidelines provided recommendations on extra monitoring of patients during transitioning. However, the type of parameters to monitor varied significantly between guidelines (e.g. monitoring of adverse events, clinical parameters, or for pharmacovigilance). However, details on what to monitor and when were lacking. Moreover, based on the principle of similarity between the biosimilar and the originator, monitoring patients in routine clinical care could be sufficient.

Cross-transitioning and retransitioning are generally not endorsed (including by ECCO) and might not be addressed sufficiently in current guidance for clinicians to navigate these situations. More biosimilars for an originator are becoming available in clinical practice, and cross-transitioning is increasingly studied.[20–22] These developments could potentially decrease healthcare spending, similar to originator-to-biosimilar transitioning. Retransitioning is reported to occur in about 7% of IBD patients who transitioned from originator to biosimilar and is caused by a (perceived) loss of effect or experience of adverse events.[23] As this occasionally occurs, despite not

being endorsed in guidelines, recommendations on this topic are important to inform and support clinicians with retransitioning patients. Although retransitioning might not be in line with current scientific evidence, from the perspective of patients who experienced (perceived) unwanted effects after transitioning (i.e., the nocebo effect), retransitioning might be desirable.[24]

While this study focused on the availability, similarities, and differences between national gastroenterology associations' positions on biosimilar use, earlier studies have mapped the guidance and positions on the use of biosimilars provided by health authorities, such as regulatory agencies, health technology assessment (HTA) bodies or ministries of health across Europe. Of the 19 countries included in this study and studies on health authorities' positions on the use of biosimilars, positions were aligned between gastroenterology associations and health authorities in most countries (Belgium, Croatia, Czech, Finland, France, Germany, Italy, Latvia, the Netherlands, Norway, Portugal, and Slovakia).[25–28]

However, positions differed between gastroenterology associations and their national health authorities in Austria, Ireland, and Romania. Austrian health insurance policies endorse prescribing the most economical medicine and thus may endorse transitioning from originator to biosimilar; conversely, the country's gastroenterology association discourages transitioning.[26,27] The Irish gastroenterology association and the governmental prescribing guidelines differ regarding which patients are eligible for transitioning. The gastroenterology association follows ECCO's recommendation that all patients are eligible. In contrast, the governmental prescribing guidelines advised transitioning only stable, well-supervised patients.[27] The Romanian gastroenterology association discouraged transitioning from originator to biosimilar. However, the insurance coverage of the originator is restricted, which could lead to financial uncertainty for patients.[26] To a lesser extent, the Swedish gastroenterology association had a more favorable position on the cross-transitioning of patients compared to their regulatory authority.[25] Furthermore, Spanish gastroenterology guidelines do not guide biosimilar use, but Spanish health authorities recommend transitioning patients from originator to biosimilar.[27]

Gastroenterologists probably have to prioritize adhering to governmental policies or laws, or the outcomes of (national or regional) price negotiations over their associations' recommendations, in case of discrepancies, which limits the impact of gastroenterology associations' guidance. For countries in which recommendations and regulations on biosimilars are not aligned, guidance could be improved by collaborating to harmonize them across gastroenterology associations, health authorities other

involved parties within the country. Of note, some health authorities might receive direct financial benefits from patients transitioning from originator to biosimilar, whereas the direct incentives for gastroenterology associations are often limited.

Besides national regulatory agencies' positions, EMA and the Heads of Medicines Agencies (HMA) recently published a joint position on biosimilar interchangeability, stating that biosimilars approved in the EU are interchangeable. In other words, a biosimilar can be used instead of its originator (or vice versa) or another biosimilar corresponding to the same originator, and the clinical effect will be the same.[29] This statement aligns with ECCO's statement on transitioning patients from originator to biosimilar, but, in contrast to ECCO's position, it also facilitates cross-transitioning from one biosimilar to another of the same originator.

The national gastroenterology associations with multiple versions of guidance all showed a trend of becoming more encouraging towards using biosimilars in clinical practice. This pattern is similar to the evolution of ECCO's position, which was primarily motivated by the results of the NOR-SWITCH trial.[9] The NOR-SWITCH study demonstrated no difference in disease worsening between patients who remained on originator infliximab compared with patients who transitioned from originator infliximab to a biosimilar.[30] The NOR-SWITCH study's results and the subsequent changes to ECCO's position on biosimilars might explain the development of gastroenterology guidance towards more supportive recommendations regarding biosimilars at the national level of EEA countries.

It could be hypothesized that favorable guidance from national gastroenterology associations on biosimilar use is associated with higher usage of TNFα inhibitor biosimilars. However, many more factors influence the use of biosimilars. This finding is evidenced by the Romanian and Slovenian associations' restrictive guidelines on prescribing biosimilars in gastroenterology, while the TNFα inhibitor biosimilar market share is 28% in Romania but 49% in Slovenia. By contrast, in Belgium, guidelines encourage biosimilar use in gastroenterology, but the biosimilar market share for TNFα inhibitors is 'only' 33%.[7] These numbers underline that clinical guidelines on prescribing biosimilars are only one of several factors that contribute to the uptake of biosimilars.

Furthermore, countries differ in terms of regulating the use of biosimilars. For example, Denmark and Norway have a national tendering systems, thus the use of biosimilars for multiple indications is decided on a national level. The transition from originator to biosimilar in Denmark was mandatory, both for patients and for clinicians. Thus gastroenterology associations' recommendations on the uptake of biosimilars would

contribute little to their, almost total, biosimilar uptake.[31,32] In Belgium, the decision to prescribe a biosimilar differs based on the active substance. For infliximab, the decision is determined by the tender outcomes, but for adalimumab, it depends generally on the individual gastroenterologist.[33] Since TNFα inhibitor biosimilars are also prescribed for indications other than for IBD, other guidelines on biosimilars may affect biosimilar uptake. The goal of biosimilars is to create price competition between the originator and the corresponding biosimilars, which also can result in a lower-priced originator. Therefore, countries should not strive to achieve the highest uptake of biosimilars, but for the usage of the best-value biologicals, which can either be the originator or a biosimilar.[34]

Strengths and limitations

The present study provides a comprehensive overview of the positions of the national gastroenterology associations in the EEA countries of biosimilar use. A significant strength of this study includes the substantial efforts to ensure comprehensive data collection, including a manual search of guidelines from all national gastroenterology associations that are ECCO members and contacting these associations to obtain their guidelines and validation purposes. Further, the data extraction process was validated via cross-checks on seventeen countries, including all national guidelines and group discussions to overcome differences in interpretation of recommendations.

However, the present study also contains some limitations. First, despite a thorough search and three emails to each national gastroenterology association, no treatment guidelines were found for five countries. This could mean that no national guidelines exist in these countries, or that these guidelines were not retrieved in this study. Twelve associations responded to the e-mail requests for guidelines (Table S1), thus possibly some guidelines that were not publicly available were not retrieved.

Second, gastroenterologists might adhere to guidelines for prescribing biosimilars other than those from national gastroenterology associations, such as regional, or hospital guidelines, but those types of guidance documents were not included in this study. In general, adherence to guidelines was not studied; thus if gastroenterologists prescribe according to the guidelines and the actual impact of guidelines on prescribing behaviors are unknown.

Third, gastroenterology associations from several countries had guidelines available in their national language, including some languages not (sufficiently) understood by the authors. Automatic translation by Google Translate was used in these cases. However, some information might be difficult to interpret with automatic translation.

Moreover, despite of limitations in language, the authors had various interpretations of some recommendations, possibly indicating that clinicians might have multiple interpretations of these recommendations as well.

Conclusions

Almost three-quarters of national gastroenterology associations in EEA countries with an ECCO affiliation had guidance on biosimilar prescribing, either in the form of a national association guideline, a position paper, or an endorsement of ECCO guidelines. Associations in most countries endorsed initiating TNFα inhibitor treatment with a biosimilar (n=14) and transitioning from an originator to a biosimilar (n=13). In general, positions became more supportive of biosimilar use over time. Guidance on how to monitor patients and on multiple transitions was scarcer and more varied between countries. There are still countries where the national gastroenterology association lacks guidelines, possesses outdated guidelines, or utilizes guidelines that are inconsistent with current best practices; accordingly, there is room to improve guidance on biosimilar prescribing by medical associations. Clear guidance can support gastroenterologists in confidently prescribing biosimilars to treatment-naïve patients and to patients transitioning from an originator to a biosimilar.

Table 1: Guidelines on the use of biosimilars from national gastroenterology associations (only information on the most recent guideline is provided)

	Initiating biological treatment with a biosimilar		Transitioning from originator to biosimilar					
	Starting new patients on biosimilar	**Type of patients who can start with biosimilar**	**Transitioning from originator to biosimilar**	**Type of patients who can transition**	**Recommendation on informing patients**	**Recommendation on monitoring patients**	**Recommendation on cross-transitioning**	**Recommendation on retransitioning**
Austria (2014) Position paper	✓	Only patients from a specific population or with a specific indication in which the biosimilar is tested	✗	Not mentioned	Not mentioned	Not mentioned	Not mentioned	Not mentioned
Belgium (2020) Position paper	✓	All patients	✓	Patients in clinical remission	Patients should be informed on biosimilar, but also on nocebo effect	Patients should be followed for pharmacovigilance, not further specified	Not mentioned	Not mentioned
Croatia (2014) Position paper	✗ studies specific in IBD patients are needed	Only patients within the tested population, no extrapolation of indication is allowed	✗	Patients who gave consent and who had ineffectiveness and/ or side effects on the originator	Patients should be fully informed, and agree	Monitor adverse events in routine setting	Not mentioned	Not mentioned
Czech Republic (2016) Other clinical guideline	✓	Not mentioned	✓	Not mentioned	Not mentioned	Not mentioned	Not mentioned	Not mentioned
Denmark (2019) Other clinical guideline	*	Not mentioned	*	Not mentioned	Not mentioned	Not mentioned	Not mentioned	Not mentioned
Finland (2017) ECCO Position paper	✓	All patients	✓	All patients	Patients should be fully informed	Not mentioned	✗	✗
France (2017) Other clinical guideline	✓	All patients	✓ Under conditions**	Not mentioned	Patients should be fully informed, and agree	Appropriate clinical monitoring	✗	Not mentioned

Table 1: Continued.

	Initiating biological treatment with a biosimilar		Transitioning from originator to biosimilar					
	Starting new patients on biosimilar	**Type of patients who can start with biosimilar**	**Transitioning from originator to biosimilar**	**Type of patients who can transition**	**Recommendation on informing patients**	**Recommendation on monitoring patients**	**Recommendation on cross-transitioning**	**Recommendation on retransitioning**
Germany (2021) Position paper*** clinical guideline (2x)	✓	All patients	✓	Not mentioned	Patients should be fully informed	Not mentioned	Inconclusive; no consensus between different guidelines	Inconclusive; no consensus between different guidelines
Ireland (2017) ECCO Position paper	✓	All patients	✓	All patients	Patients should be fully informed	Not mentioned	✗	✗
Italy (2019) Position paper	✓	All patients	✓	Not mentioned	Patients should be fully informed, and agree	Not mentioned	✗	✗
Latvia (2017) ECCO Position paper	✓	All patients	✓	All patients	Patients should be fully informed	Not mentioned	✗	✗
Netherlands (2017) Position paper	✓	All patients	✓	All patients	Patients should be fully informed	Extra monitoring of clinical parameters	✓†	Not mentioned
Norway (2017) ECCO Position paper	✓	All patients	✓	All patients	Patients should be fully informed	Not mentioned	✗	✗
Poland (2019) Position paper	✓	All patients	✓	All patients	Patients should be fully informed††	Assessment and monitoring of immunogenicity	✗	✗

Table 1: Continued.

	Initiating biological treatment with a biosimilar		Transitioning from originator to biosimilar					
	Starting new patients on biosimilar	**Type of patients who can start with biosimilar**	**Transitioning from originator to biosimilar**	**Type of patients who can transition**	**Recommendation on informing patients**	**Recommendation on monitoring patients**	**Recommendation on cross-transitioning**	**Recommendation on retransitioning**
Portugal (2018) Position paper	✓	All patients	✓	Only patients >6 months on originator	Patients should be fully informed, and agree	Monitoring in routine clinical care, no extra monitoring during transitioning	✗	✗
Romania (2017) Position paper	Not mentioned	Not mentioned	✗ unless informed consent	Only patients who are informed and gave consent	Patients should be fully informed, and agree	Not mentioned	Not mentioned	✓
Slovenia (2014) Position paper	✗studies specific in IBD patients are needed	Not mentioned	✗†††	Not mentioned	Patients should agree	Monitor adverse events in children and adults	Not mentioned	Not mentioned
Sweden (2022) Other clinical guideline	✓	All patients	✓	All patients§	Not mentioned	Monitoring in routine clinical care	✓under monitoring, preferably in a study	Not mentioned

* "The guideline does not distinguish between different biosimilar medicines that are deemed to be equivalent and substitutable in terms of treament"
** At initiation of the prescriber, the patient should be informed and give consent, appropriate clinical monitoring and traceability of the biosimilar
*** Reaction on document from HTA body – HTA document also included
† One time transitioning is possible, this could also be transitioning from one biosimilar to another. Repeated transitioning should be avoided
†† No consensus was reached on this topic, however, 70% of experts participating in drawing the guidelines agreed on this statement
††† Unless a patient has a lack of response on the originator
§ Except in patients who had insufficient effect of the originator, or who had an allergic reaction to the originator

✓: Acceptable
✗: Not acceptable

Table 2: Development of guidance on biosimilars over time

	Initiating biological treatment with a biosimilar		Transitioning from originator to biosimilar					
	Starting new patients on biosimilar	**Type of patients who can start with biosimilar**	**Transitioning from originator to biosimilar**	**Type of patients who can transition**	**Recommendation on informing patients**	**Recommendation on monitoring patients**	**Recommendation on cross-transitioning**	**Recommendation on retransitioning**
Belgium								
2020	✓	All patients	✓	Patients in clinical remission	Patients should be informed on biosimilar, but also on nocebo effect	Patients should be followed for pharmaco-vigilance, not further specified	Not mentioned	Not mentioned
2018	✓	Not mentioned	✓	Patients in clinical remission	Patients should be fully informed	Not mentioned	Not mentioned	Not mentioned
2015	✓	Not mentioned	✗	Not mentioned	Not mentioned	Not mentioned	Not mentioned	Not mentioned
Finland ECCO position paper* 2017	✓	All patients	✓	All patients	Patients should be fully informed	Not mentioned	✗	✗
France								
2017	✓	All patients	✓Under conditions**	Not mentioned	Patients should be fully informed, and agree	Appropriate clinical monitoring	✗	Not mentioned
2015	✓	Not mentioned	Transitioning is not recommended but possible***	Not mentioned	Not mentioned	Not mentioned	Not mentioned	Not mentioned

Table 2: Continued.

	Initiating biological treatment with a biosimilar		Transitioning from originator to biosimilar					
	Starting new patients on biosimilar	**Type of patients who can start with biosimilar**	**Transitioning from originator to biosimilar**	**Type of patients who can transition**	**Recommendations on informing patients**	**Recommendation on monitoring patients**	**Recommendation on cross-transitioning**	**Recommendation on retransitioning**
Ireland								
ECCO position paper 2017	✓	All patients	✓	All patients	Patients should be fully informed	Not mentioned	✗	✗
2013	✗ studies specific in IBD patients are needed	Not mentioned	Not mentioned	Not mentioned	Patients should be fully informed	Not mentioned	Not mentioned	Not mentioned
Italy								
2019	✓	All patients	✓	Not mentioned	Not mentioned	Not mentioned	✗	✗
2014	✗	Not mentioned	✗	Not mentioned	Patients should give written informed consent	Not mentioned	Not mentioned	Not mentioned
Latvia								
ECCO position paper 2017	✓	All patients	✓	All patients	Patients should be fully informed	Not mentioned	✗	✗
2013	✗studies specific in IBD patients are needed	Not mentioned	Not mentioned	Not mentioned	Patients should be fully informed	Not mentioned	Not mentioned	Not mentioned

Table 2: Continued.

	Initiating biological treatment with a biosimilar		Transitioning from originator to biosimilar					
	Starting new patients on biosimilar	**Type of patients who can start with biosimilar**	**Transitioning from originator to biosimilar**	**Type of patients who can transition**	**Recommendations on informing patients**	**Recommendation on monitoring patients**	**Recommendation on cross-transitioning**	**Recommendation on retransitioning**
Netherlands								
2017	✓	All patients	✓	All patients	Patients should be fully informed	Extra monitoring of clinical parameters	✓†	Not mentioned
2015	Only start after explicitly informing the patient	Not mentioned	✗	Not mentioned	Not mentioned	Not mentioned	Not mentioned	Not mentioned
Norway								
ECCO position paper 2017	✓	All patients	✓	All patients	Patients should be fully informed	Not mentioned	✗	✗
2013	✗studies specific in IBD patients are needed	Not mentioned	Not mentioned	Not mentioned	Patients should be fully informed	Not mentioned	Not mentioned	Not mentioned
Poland								
2019	✓	All patients	✓	Not mentioned	Patients should be fully informed††	Assessment and monitoring of immunogenicity	✗	✗
2014	✗studies specific in IBD patients are needed	Patients who gave consent	✗	Patients who gave consent	Patients should be fully informed, and agree	Not mentioned	Not mentioned	Not mentioned

Table 2: Continued.

	Initiating biological treatment with a biosimilar		Transitioning from originator to biosimilar					
	Starting new patients on biosimilar	**Type of patients who can start with biosimilar**	**Transitioning from originator to biosimilar**	**Type of patients who can transition**	**Recommendations on informing patients**	**Recommendation on monitoring patients**	**Recommendation on cross-transitioning**	**Recommendation on retransitioning**
Sweden								
2022	✓	All patients	✓	All patients†††	Not mentioned	Monitoring in routine clinical care	✓ under monitoring, preferably in a study	Not mentioned
2015	✓	All patients	✓only in study context	Not mentioned	Not mentioned	Monitoring in routine clinical care	Not mentioned	Not mentioned
ECCO								
2017	✓	All patients	✓	All patients	Patients should be fully informed	Not mentioned	✗	✗
2013	✗studies specific in IBD patients are needed	Not mentioned	Not mentioned	Not mentioned	Patients should be fully informed	Not mentioned	Not mentioned	Not mentioned

* Finland had national guidelines in 2013 that did not include biosimilars, but changed to following ECCO's guidance in 2017
** At initiation of the prescriber, the patient should be informed and give consent, appropriate clinical monitoring and traceability of the biosimilar
*** Only at the initiative and responsibility of the prescriber
† One time transitioning is possible, this could also be transitioning from one biosimilar to another. Repeated transitioning should be avoided
†† No consensus was reached on this topic, however, 70% of experts participating in drawing the guidelines agreed on this statement
††† Except in patients who had insufficient effect of the originator, or who had an allergic reaction to the originator

✓: Acceptable
✗ : Not acceptable

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Supplementary Files

Table S1: Overview of the EEA member states [1] and the included gastroenterology association from that country and the reference to their guidelines

Country	National Gastroenterology society	Reference to guideline
Austria	ÖGGH - Österr. Gesellschaft für Gastroenterologie und Hepatologie†	Samonigg H, Fazekas F, Gastl G, et al. Biosimilars – aktueller stellenwert. 2014. http://www.oeggh.at/download/cs-biosimilars.pdf. Accessed 07/02/2022 Novacek G, Haas T, Knoflach P et al. Adalimumab in der Behandlung des adulten Morbus Crohn –Update eines Konsensus der Arbeitsgruppe Chronisch Entzündliche Darmerkrankungen der Österreichischen Gesellschaft für Gastroenterologie und Hepatologie. Z Gastroenterol 2013; 51: 1101–1109 Reinisch W, Dejaco C, Feichtenschlager T et al. Infliximab in der Therapie des Morbus Crohn – ein praktischer Leitfaden: aktualisierter ÖGGH-Konsensus der Arbeitsgruppe Chronisch-entzündliche Darmerkrankungen der ÖGGH. Z Gastroenterol 2011; 49: 534–542
Belgium	BIRD – Belgian Intestinal Research and Development	Somers M, Bossuyt P, Ferrante M, Peeters H, Baert F. Belgian IBD Research Group [BIRD] Position Statement 2019 on the Use of Adalimumab Biosimilars in Inflammatory Bowel Diseases. J Crohns Colitis. 2020 Jun 19;14(5):680-685. Franchimont D, Ferrante M, Louis E, De Vos M, Dewit O, Van Hootegem P, Moreels T, Liefferinckx C, Bossuyt P, Baert F, Rahier JF, Vermeire S. Belgian IBD research group (BIRD) position statement 2017 on the use of biosimilars in inflammatory bowel diseases (IBD). Acta Gastroenterol Belg. 2018 Jan-Mar;81(1):49-53. Vermeire S, Louis E, Dewit O, Franchimont D, Moreels T, Ferrante M, Rahier JF, Van Hootegem P, De Vos M, Mana F, Baert F; Belgian IBD Research & Development (BIRD). Clinical and scientific aspects related to biosimilars in inflammatory bowel diseases (IBD): position document of the Belgian IBD Research & Development Group (BIRD). Acta Gastroenterol Belg. 2015 Jan-Mar;78(1):26-9.
Bulgaria	Bulgarian Association for Inflammatory Bowel Diseases†	Български консенсус за IBD. 2010 http://ibd-bg.com/download/bg/24/BG%20Guidelines_%20UC,%20CD.pdf Accessed 06/05/2022
Croatia	HGD – Croatian Society of Gastroenterology†	Hrvatsko gastroenterološko društvo. Sekcija za upalne bolesti crijeva. Stav o primjeni biološki sličnih lijekova (biosimilara) u liječenju upalnih bolesti crijeva. 2014 http://hucuk.hr/wp-content/uploads/2014/04/images_brusura_HGD_biosimilari.pdf Accessed 06/05/2022 Vucelič B, Čucovic- Čavka S,Banič M et al. Hrvatski Konsenzus o Liječenju Upalnih Bolesti Crijeva Bioloskom Therapijom. Acta Med Croatica, 67 (2013) 75-87

Table S1: Continued.

Country	National Gastroenterology society	Reference to guideline
Cyprus	Cyprus Society of Gastroenterology†	No guidelines found
Czech Republic	Česká gastroenterologická společnost ČLS JEP†	M. Bortlík M, Ďuricová D, Kohout P et al. Doporučení pro podávání bio logické terapie u idiopatických střevních zánětů: třetí, aktualizované vydání. Gastoent Hepatol 2016;70 (1): 11-27 M. Bortlík M, Ďuricová D, Kohout P et al. Doporučení pro podávání biologické terapie u idiopatických střevních zánětů: 2. Vydání. Gastroent Hepatol 2012; 66(1): 12–22
Denmark	DSGH – Dansk Selskab for Gastroenterologi og Hepatologi	https://dsgh.dk/wp-content/uploads/2022/06/bioterapiibd.pdf Accessed 19/01/2023
Estonia	EGEÜ - Eesti Gastrointestinaalse Endoskoopia Ühing†	No guidelines found
Finland	SGY - Suomen Gastroenterologiayhdistys	Referred to ECCO
France	GETAID - Groupe d'étude therapéutique des Affections Inflammatoires du Tube Digestif† SNFGE - Société Nationale Française de Gastro-Entérologie†	Groupe d'Etude Therapeutique des Affections Inflammatoires du tube Digestif (GETAID). L'INFLIXIMAB : REMICADE®, INFLECTRA®, REMSIMA®, FLIXABI®.20/09/2017. https://www.getaid.org/fiches-medicament/linfliximab-remicade-inflectra-remsima-flixabi Accessed 04/03/2022 La Société Nationale Française de Gastro-Entérologie (SNFGE). Information sur les infliximab biosimilaires (Août 2017) https://www.snfge.org/download/file/fid/2784 Accessed 28/04/2022 La Société Nationale Française de Gastro-Entérologie (SNFGE). Information sur les infliximab biosimilaires. 15/04/2015. Accessed 28/04/2022 Groupe d'Etude Therapeutique des Affections Inflammatoires du tube Digestif (GETAID). Adalimumab - Humira® https://www.snfge.org/download/file/fid/316 Accessed 30/05/2022

Table S1: Continued.

Country	National Gastroenterology society	Reference to guideline
Germany	Kompetennetz Darmerkrankungen† Deutsche Gesellschaft fur Gastroenterologie, Verdauung- und Stoffwechselkrankheiten	Kucharzik T, Dignass A, Atreya R et al. Aktualisierte S3-Leitlinie Colitis ulcerosa – Living Guideline. Z Gastroenterol 2020; 58: 241–326 Sturm A, Atreya R, Bettenworth. Aktualisierte S3-Leitlinie „Diagnostik und Therapie des Morbus Crohn" der Deutschen Gesellschaft für Gastroenterologie, Verdauungs- und Stoffwechselkrankheiten (DGVS). Z Gastroenterol 2022; 60: 332–418 Deutsche Gesellschaft fur Gastroenterologie, Verdauung- und Stoffwechselkrankheiten. Stellungnahme zur Änderung der Arzneimittel-Richtlinie: Anlage VIIa (Biologika und Biosimilars) - Erstfassung. https://www.dgvs.de/wp-content/uploads/2021/08/Website_Bokemeyer_Siegmund_Gemeinsame-Stellungnahme-Arzneimittel-Richtlinie_Anlage-VIIa_12072021.pdfAccessed 30/05/2022 Gemeinsamer Bundesausschus. Biologika und Biosimilars: Austauschbarkeit von biotechnologisch hergestellten Arzneimitteln. https://www.g-ba.de/themen/arzneimittel/arzneimittel-richtlinie-anlagen/biologika-biosimilars/ Accessed 30/05/2022
Greece	EOMIFNE – Hellenic Group for the Study of IBD†	No guidelines found
Hungary	MGT - Magyar Gasztroenterológiai Társaság†	No guidelines found
Iceland	No gastroenterology association member of ECCO	NA
Ireland	ISGE – Irish Society of Gastroenterology	Referred to ECCO

Table S1: Continued.

Country	National Gastroenterology society	Reference to guideline
Italy	IG–IBD – Italian Group for the Study of IBD	Fiorino G, Caprioli F, Daperno M et al. Use of biosimilars in inflammatory bowel disease: A position update of the Italian Group for the Study of Inflammatory Bowel Disease (IG-IBD). Digestive and Liver Disease 51 (2019) 632–639 Annese V, Vecchi M on behalf of the Italian Group for the Study of IBD (IG-IBD). Use of biosimilars in inflammatory bowel disease: Statements of the Italian Group for Inflammatory Bowel Disease. Digestive and Liver Disease 46 (2014) 963–968 Fiorino G, Girolomoni G, Lapadula G et al. The use of biosimilars in immune-mediated disease: A joint Italian Society of Rheumatology (SIR), Italian Society of Dermatology (SIDeMaST), and Italian Group of Inflammatory Bowel Disease (IG-IBD) position paper. Autoimmunity Reviews 13 (2014) 751–755
Latvia	GEAB – Gastroenteroloģijas Atbalsta Biedrība	Referred to ECCO
Liechtenstein	No gastroenterology association member of ECCO	NA
Lithuania	LIBDA – Lithuanian IBD Association*	NA
Luxembourg	No gastroenterology association member of ECCO	NA
Malta	Malta Association of Physicians†	No guidelines found
Norway	NGF – Norsk Gastroenterologisk Forening	Referred to ECCO

Table S1: Continued.

Country	National Gastroenterology society	Reference to guideline
The Netherlands	NVMDL – Nederlandse Vereniging van Maag-Darm-Leverartsen	Federatie Medisch Specialisten. Standpunt Biosimilars Federatie Medisch Specialisten. 14/09/2017 https://demedischspecialist.nl/sites/default/files/Standpunt%20Biosimilars%20Federatie%20Medisch%20Specialisten.PDF Accessed 30/05/2022 Initiatief in Crohn en Colitis. Handleiding Behandeling IBD – 2014-2015. 10/06/2015 https://www.mdl.nl/sites/www.mdl.nl/files/richlijnen / Document_volledig_Handleiding_met_literatuur_def.pdf Accessed 30/05/2022
Poland	PSG - Societas Gastroenterologiae Polonia	Łodyga M, Eder P, Gawron-Kiska M et al.Guidelines for the management of patients with Crohn's disease. Recommendations of the Polish Society of Gastroenterology and the Polish National Consultant in Gastroenterology. Gastroenterology Rev 2021; 16 (4): 257–296 Jahnz-Różyk K, Brzosko M, Lech-Marańda E et al. The Polish Expert Group Position Statement on the Safety of Biological Treatments with Monoclonal Antibodies and Fusion Proteins: An Update jhpor, 2019, 1 DOI:10.7365/JHPOR.2019.1.3 Mularczyk A, Gonciarz M, Bartnik W et al.Biosimilar medicines - their use in the treatment of inflammatory bowel diseases. Position statement of the Working Group of the Polish National Consultant in Gastroenterology Prz Gastroenterol. 2014;9(1):1-3. doi: 10.5114/pg.2014.40842. Łodyga M, Eder P, Bartnik W. Wytyczne Grupy Roboczej Konsultanta Krajowego w dziedzinie Gastroenterologii i Polskiego Towarzystwa Gastroenterologii dotyczące postępowania z pacjentem z chorobą Leśniowskiego-Crohna. Prz Gastroenterol 2012; 7 (6): 317–338 DOI: 10.5114/pg.2012.33040
Portugal	GEDII – Grupo de Estudo da Doenca Inflammatória Intestinal†	GEDII – Grupo de Estudo da Doenca Inflammatória Intestinal. Posição conjuntaSubstituiçao Automática de Medicamentos Biotecnológicos. https://www.gedii.pt/_orientacoes_clinicas Accessed 30/05/2022
Romania	Clubul Roman pentru Boala Crohn si Colita Ulcerativa RCCC†	Societatea Romana de Gastroenterologie si Hepatologie. Document De Pozitie pe Tema Medicamentelor Biologice. http://srh.org.ro/wp-content/uploads/2017/05/17-03-08-Document-pozitie-Biologice-semnat_versiune-scurta.pdf Accessed 30/05/2022 Monitorul Oficial Al Romaniei. Anexa Nr. 13 Boala Cronica Inflmatorie Intestinala. Partea I, Nr. 525 bis/21.VIII.2013 https://rccc.ro/wp-content/uploads/2021/02/ordin-536.pdf Accessed 30/05/2022

Table S1: Continued.

Country	National Gastroenterology society	Reference to guideline
Slovakia	Slovak Society of Gastroenterology – IBD Working Group†	Kužela L, Zakuciová M. Štandardný diagnostický a terapeutický postup. 53. metodický list racionálnej farmakoterapie. Racionálna liečba chronických nešpecifických zápalov čreva. Ročník 15 júl 2012 Číslo 5-7
Slovenia	SZGH – Slovensko Zdruzenje za Gastroenterologijo in Hepatologijo	Slovensko združenje za gastroenterologijo in hepatologijo. Stališče Slovenskega združenja zagastroenterologijo in hepatologijo ozdravljenju bolnikov s kronično vnetnočrevesno boleznijo s podobnimibiološkimi zdravili. Gastroenterolog 2014; 1: 5–7
Spain	GETECCU – Grupo Español de Trabajo de Crohn y Colitis Ulcerosa	Sicilia B, Santiago A, López G et al. Tratiamento de la Colitis Ulcerosa. 2020 ISBN 978-84-09-26787-3
Sweden	SOIIBD – Svensk Organisation för IBD-Studier Svensk Gastroenterologisk Förening	Svensk Gastroenterologisk Förening. Behandlingsstrategier vid inflammatorisk tarmsjukdom – med inriktning på biologisk terapi. 09/03/2022 https://svenskgastroenterologi.se/wp-content/uploads/2022/03/2022-Behandlingsstrategier-vid-IBD.pdf Accessed 26/04/2022 Svensk Gastroenterologisk Förening. Användning av infliximab-biosimilarer vid inflammatorisk tarmsjukdom. 31/08/2015 https://svenskgastroenterologi.se/wp-content/uploads/2017/06/2015-Anv%C3%A4ndning-av-infliximab-biosimilarer-vid-IBD.pdf Accessed 23/04/2022 Svensk Gastroenterologisk Förening. Läkemedelsbehandling vid Crohns sjukdom. 2012 https://svenskgastroenterologi.se/wp-content/uploads/2017/06/2012-Lakemedelsbehandling-vid-Crohns-sjukdom-1.pdf 23/04/2022

* No website and functioning email address found, thus this association was excluded and classified as no ECCO member

† Did not respond to the e-mails requesting for guidelines

S2: Template for data extraction

The data collection template consisted of three parts. First, general information on presence of guidelines and, if applicable, characteristics of guideline itself were collected. The type of guideline was categorized into the clinical disease treatment guideline, other clinical treatment guidelines, e.g. guidelines on biologicals in IBD, or position papers (i.e. consensus statements, position documents, etc.)

Second, information on the content of the guideline was collected. This included guidance on starting naïve patients on a biosimilar; whether starting IBD patients on a biosimilar was accepted and which patients were eligible for starting with a biosimilar. And it included information on guidance on transitioning IBD patients from an originator to a biosimilar; data was collected on the acceptance of transitioning patients, which patients were eligible for transitioning, guidance on informing patients about the transition and if and how patients should be monitored during transitioning, and if cross-transitioning (biosimilar to biosimilar) and retransitioning (originator to biosimilar) was accepted.

Part 1: General information

Question	Answer
Country:	
Name of national gastroenterology society:	
Guideline available from national gastro-enterology society: If yes, link to guideline:	Yes/ No
Does the national gastroenterology society (also) refer to guideline outside own society?	[] No [] Yes, to ECCO guidelines []Yes, to other guideline/ document from other organization*
*Link to other guideline/ document	
*Type of guideline/ document:	[] Guideline from overarching/ other medical association [] Guideline from regulatory authority [] Guideline from other organization. *Please specify type of organization*
** Link to guideline:	
Type of guideline	[] Clinical treatment guideline Crohn's disease or ulcerative colitis [] Other clinical treatment guideline [] Position paper
Year guideline was published in:	
Date of information extraction:	

Part 2: Content of the guideline

Question	Answer
Starting new patients on biosimilar	
Does the guideline provide recommendations on starting new patients on a biosimilar?	Yes/ No
What does the guideline recommends on starting treatment with a biosimilar?	[] No extra recommendations compared with starting biological treatment in general [] Do not start treatment with a biosimilar, because studies specific in IBD patients are needed (no extrapolation of indication) [] Do not start treatment with a biosimilar, because of other reason. *Please specify* [] Not mentioned [] Other, *please specify*
Which patients are, according to the guideline, eligible for starting treatment with a biosimilar?	[] All patients [] Specific patients, *please specify which types of patients* [] Not mentioned [] Other, *please specify*
Transitioning current patients to biosimilar	
Does the guideline provide recommendations on transitioning patients to a biosimilar?	Yes/ No
What does the guideline recommends on transitioning patients to a biosimilar?	[] Transitioning patients to a biosimilar is acceptable [] Transitioning patients to a biosimilar is <u>not</u> acceptable. *If mentioned, please specify reason* [] Transitioning patients to a biosimilar is acceptable under certain conditions/ circumstances. *Please specify...* [] Not mentioned [] Other, *please specify*
Which patients are, according to the guideline, eligible for transitioning to a biosimilar?	[] All patients [] Patients with stable response to the originator [] Patients in clinical remission [] Not mentioned [] Other, *please specify*
What is the recommendation on informing patients on transitioning?	[] Patients should be fully informed [] Not mentioned [] Other, *please specify*
What is the recommendation on monitoring of patients? *Multiple options possible*	[] Monitoring in routine clinical care, no extra monitoring during transitioning [] Extra monitoring of medicine serum concentrations and/ or antibodies [] Extra monitoring of clinical parameters [] Extra monitoring of disease activity [] Not mentioned [] Other, *please specify*

What is the recommendation on cross-transitioning (biosimilar to biosimilar)?	[] Cross-transitioning is acceptable [] Cross-transitioning is not acceptable [] Cross-transitioning is acceptable in certain cases or under certain conditions, *please specify* [] Not mentioned [] Other, *please specify*
What is the recommendation on retransitioning (originator ▸ biosimilar ▸ originator)	[] Retransitioning is acceptable [] Retransitioning is not acceptable [] Retransitioning is acceptable in certain cases or under certain conditions, *please specify* [] Not mentioned [] Other, *please specify*

*Either guideline of European scientific medical association (ECCO), and/ or general medical guideline, non-disease specific guideline

Table S3: List of crosschecked country data

Author	Country
HMT	Czech Republic Finland Ireland Italy Romania Slovenia
LB	Belgium France Netherlands
LCD	Croatia Denmark Germany Sweden ECCO position statement on the use of biosimilars for Inflammatory Bowel Disease – An Update
KS	Austria Hungary Poland Portugal

CHAPTER 4

Patients retransitioning from biosimilar TNFα inhibitor to the corresponding originator after initial transitioning to the biosimilar: a systematic review

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Abstract

Background

Transitioning patients from an originator to a corresponding biosimilar has been extensively studied in both randomized controlled trials and observational studies. Although transitioning is considered well-tolerated, with no negative impacts on efficacy and/or safety, 2.6-25.8% of patients restart treatment with the originator (retransitioning). Retransitioning to the originator can be considered an indication of biosimilar treatment failure or dissatisfaction with biosimilar treatment. Increasing our knowledge of patients who retransition might help to reduce the number of patients retransitioning.

Objective

Our objective was to estimate the cumulative incidence of patients who retransitioned from a tumor necrosis factor (TNF)-α inhibitor biosimilar to originator and to explore potential patient, disease, and treatment and implementation strategy factors associated with retransitioning.

Method

We conducted a systematic literature search in the PubMed, EMBASE, and Cochrane Central Register of controlled trials databases until March 2021. Studies on TNFα inhibitors, biosimilar transitioning, and retransitioning were included. Transitioning was defined as switching from an originator to a biosimilar, and retransitioning was defined as switching from an originator to a biosimilar and back to the originator. Characteristics of the studies were descriptively analyzed. Studies were weighted by the number of patients transitioning, and the primary outcome was the median cumulative incidence of retransitioning. For each of the factors related to patient, disease, and treatment and implementation strategy, studies were stratified according to the categories of that factor. The weighted medians and interquartile ranges (IQRs) of the cumulative incidence of retransitioning in these studies were calculated and compared to explore whether a potential association existed between these factors and the cumulative incidence of retransitioning.

Results

Of 994 screened publications, 37 were included. The weighted median cumulative incidence of retransitioning was 7.6% (IQR 6.8-17.2). Studies that included only patients with inflammatory bowel disease (6.6 vs. 15.1-17.7% for other indications), included only patients with stable disease (7.0 vs. 13.7% for including all patients), and did not offer retransitioning at the introduction of the biosimilar (7.0 vs. 11.1% for studies that offered retransitioning) reported less retransitioning. In addition, the

incidence of retransitioning was lower when extra laboratory monitoring was part of the implementation strategy (1.6 vs. 6.1%) and when gainsharing (patients' healthcare directly benefits from financial savings from transitioning) (1.4 vs. 7.2% for studies without gainsharing) was applied.

Conclusions

In studies on transitioning patients from TNFα originator to biosimilar, 8% of patients retransitioned. Retransitioning appeared to be lower in studies that included only patients with stable disease and in studies that did not offer patients the option of retransitioning at the introduction of the biosimilar. In addition, retransitioning appeared to be lower in studies that implemented extra laboratory monitoring as part of the biosimilar implementation strategy. Clinicians should consider implementing these suggestions as they might reduce retransitioning rates and improve the introduction of biosimilars in clinical practice. PROSPERO registration ID: CRD42021226381.

Introduction

Tumour Necrosis Factor (TNF)-α inhibitors are currently the cornerstone treatment for several immune-mediated diseases such as rheumatoid arthritis and inflammatory bowel disease (IBD).[1-3] At the time they were introduced, these treatments were a very effective but costly treatment modality. The introduction of biosimilars ("a biological medicinal product that contains a version of the active substance of an already authorized biological medicinal product [originator]" [4]) several years ago lowered the price of TNFα inhibitor treatment and improved patient access to these treatments.[5] Biosimilars for three TNFα inhibitors are currently approved. The first infliximab biosimilar was approved in 2015 in Europe[6] and in 2016 in the USA[7], the first etanercept biosimilar was approved in 2016 in both Europe and the USA[7,8], and the first adalimumab biosimilar was approved in 2018 in Europe[9] and in 2016 in the USA.[7]

The similarity of biosimilars in terms of quality, efficacy, and safety, including immunogenicity, must be thoroughly demonstrated in an extensive comparability exercise in which physiochemical properties, biological activity, immunochemical properties, and in vivo pharmacological properties are compared between originator and biosimilar.[4] Similarity is confirmed in at least one randomized controlled trial (RCT) where TNFα inhibitor-naïve patients are randomized between the originator and the corresponding biosimilar.[10-12] Since biosimilars have properties similar to those of their originators, it is expected that patients already treated with the originator can transition to the biosimilar without any impact on the efficacy, safety and immunogenicity of their treatment. This has been confirmed in several RCTs, including the NOR-SWITCH study, in which 241 patients receiving originator infliximab were randomized to continuing originator or transitioning to the biosimilar. Disease worsening was reported in 26% of the patients who remained on originator and in 30% of patients who transitioned to the biosimilar, which was within the pre-specified 15% inferiority margin.[13] Other double-blinded RCTs involving TNFα inhibitors also demonstrated non-inferiority between remaining on originator and transitioning to a biosimilar.[14]

Transitioning from originator to biosimilar has also been extensively studied for different biologicals in several therapeutic indications in observational studies. Within these studies, infliximab was the most frequently studied biosimilar. Overall, these studies concluded that there were no major safety issues, including immunogenicity, after transitioning.[14] However, some studies, have shown that patients who transitioned to a biosimilar experienced loss of effect and/or adverse events (AEs), resulting in higher discontinuation rates than in patients who remained on the originator.[15-18] It has also been shown that, of all patients who transitioned from originator to biosimilar,

2.6-25.8% restarted treatment with the originator (retransitioning).[16,19] Retransitioning to the originator can be considered an indication of biosimilar treatment failure or dissatisfaction with biosimilar treatment.[20] Retransitioning in these studies was mainly driven by patient-reported outcomes, such as subjective AEs, with no differences in objective, clinical parameters. Thus, the authors attributed this to the nocebo effect (i.e., patients' negative expectations leading to AEs being experienced or a perceived decrease in response).[14,21]

However, the different percentages of retransitioning in these studies might also be related to factors other than the nocebo effect. For example, since RCTs apply extensive inclusion and exclusion criteria compared with observational studies performed as part of routine clinical care, outcomes in RCTs are often not achieved in clinical practice.[22] However, in observational studies, certain criteria can also be applied to select patients eligible for transitioning, such as transitioning only patients with clinically stable disease. These selection criteria might affect the incidence of patients retransitioning.

Moreover, the process or strategy used to implement a biosimilar can differ between studies. Some studies extensively inform patients about transitioning and monitor their transitioned patients frequently, whereas in other studies patients are transitioned as part of routine clinical care with limited information and no extra routine visits. These differences in biosimilar implementation strategies influence a patient's experience of the transition and affect the incidence of patients who retransition.[23]

Retransitioning is often a sign of treatment failure or discontent and could negatively influence the patient's treatment. In addition, retransitioning could potentially undo the financial benefits of biosimilars. Knowledge about how to introduce a biosimilar in clinical practice while minimizing the risk to patients retransitioning is therefore of value.

The aim of this systematic review was to estimate the cumulative incidence of patients who retransitioned from TNFα inhibitor biosimilar to originator and to explore potential patient, disease, and treatment and implementation strategy factors associated with retransitioning.

Methods

Systematic literature search

We conducted a systematic literature search in the PubMed, EMBASE, and Cochrane Central Register of controlled trials (CENTRAL) databases to identify all

published articles investigating or citing TNFα inhibitors, biosimilar transitioning, and retransitioning. The exact search terms and medical subject headings terms used are presented in Table S1 in the electronic supplementary material (ESM). As shown in Table S1, a broad search string was applied to prevent relevant articles being missed after which the studies found were manually checked. The systematic review was conducted according to the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) statement.[24] The review protocol is available at PROSPERO (registration ID CRD42021226381). The search string was first executed on 19 November 2020 and was repeated on 25 March 2021 to include relevant recently published articles.

Selection of studies

Studies found in the search strategy were merged in Rayyan QCRI and duplicates were removed. Only original research articles were included. Congress abstracts, reviews, editorials and other opinion articles were excluded. The reference lists of review articles were manually checked by RM for additional, potentially relevant articles not captured in the electronic search.

Titles, abstracts, and full-text publications of the identified records were screened by RM to select relevant articles and a 5% random sample was cross-checked by HG. In case of uncertainty or disagreement, articles were discussed until consensus was reached and, if necessary, a third reviewer (TG) was consulted. Articles were included if they met the following criteria: (1) study involved transitioning from a TNFα inhibitor (including etanercept, infliximab and adalimumab) originator to a biosimilar, (2) the number of patients who retransitioned was reported or could be calculated, (3) the article was an original research article published in a peer-reviewed journal, (4) the article included baseline characteristics of the patients who transitioned, (5) the article was written in English and (6) the full-text version of the article could be obtained. Transitioning was defined as patients in whom the biosimilar was introduced after the originator, without treatment with other drugs in between. Retransitioning was defined as restarting the originator directly after discontinuing a biosimilar, without treatment with other drugs in between. In summary, transitioning was defined as: switching from the originator to a biosimilar and retransitioning was defined as: switching from the originator to a biosimilar and back to the originator. Both transitioning and retransitioning involved changes with the same active biological substance.

Outcome

The main outcome of this study was to assess the cumulative incidence of patients treated with biosimilar adalimumab, etanercept or infliximab for any indication who retransitioned. In addition, the reasons why patients retransitioned (i.e., loss of effect, AEs, other) was collected when possible. Information about these outcomes were extracted from the publications included.

Factors associated with retransitioning

In this study, factors related to patient, disease, and treatment, and implementation strategy were explored.

Factors related to patient, disease, and treatment included the following: age restrictions (only adult patients or all age categories); the therapeutic indication for which TNFα inhibitor was used (rheumatic disease [RD], IBD, multiple indications or other indications); only patients with stable disease or all patients; the type of TNFα inhibitor (etanercept, infliximab, adalimumab, or multiple); only patients with a minimum duration of originator use or all patients.

RD included ankylosing spondylitis, chronic reactive arthritis, juvenile idiopathic arthritis, psoriatic arthritis, and rheumatoid arthritis; IBD included ulcerative colitis and Crohn's disease; and multiple indications included a combination of RD, IBD and/ or other indications for which TNFα inhibitors are indicated. Studies were considered to only include patients with stable disease if they mentioned stable disease, low disease activity, or remission as an inclusion criterion. Minimum duration originator use was defined as having any inclusion criterion on the duration of use of originator prior to transitioning—for example, at least 6 months use of originator— and was categorized as either only patients with a minimum duration use of originator or all patients.

Factors related to implementation strategy included the following: the manner in which information on transitioning to patients was provided (both written and verbal information from healthcare professional [HCP], only written information, only verbal information from HCP); training of HCPs (both educational and communication; only educational; only communicational—that is, motivational communication on transitioning); the type of consent given by patients (informed consent, opt in [patients need to grant permission to transition to a biosimilar but this is not as formal as informed consent, for example verbal permission], opt out [patients are transitioned to a biosimilar unless stated otherwise [including mandatory transitioning]); gainsharing (patients' healthcare directly benefits from financial savings from transitioning—yes or no); whether the HCP gave patients, at the time of transitioning, the option to

retransition (yes or no); extra control visits to the outpatient ward (yes or no); and extra laboratory monitoring (yes or no). Extra control visits and extra laboratory monitoring were classified as such if they were explicitly mentioned as not part of routine clinical care.

Other variables assessed included baseline characteristics of the study publications, including the following: type of funding (funded by industry or publicly funded); type of study (RCT, cohort study, case-control, case-series, other); geographical location of the study (continent: Europe, Asia, USA, other); the year in which patients in the study were transitioned (start of the study); duration of follow-up (months); randomization of patients (yes or no); blinded treatment (yes or no); and number of transitioned patients in the study. Baseline characteristics of the patients included in the studies included the following: age at transitioning (< 45, 45-55, > 55 years); percentage of included females; indication; type of TNFα inhibitor (active substance adalimumab, etanercept, infliximab, or multiple); years since first diagnosis of disease; duration of originator treatment prior to transitioning to the biosimilar.

All data extracted from the articles were entered in a standardized data collection format, created in Microsoft Excel. Data were entered by RM and cross checked by HG. In case of uncertainty or disagreement, data were discussed until consensus was reached; if necessary, a third reviewer (TG) was consulted.

Data analysis

Characteristics of the studies were descriptively analyzed. In the other analyses, studies were weighted by the number of patients transitioning in the study. The primary outcome—the cumulative incidence of patients retransitioning—was plotted against the study follow-up time in a weighted dot plot to explore whether the duration of the study and cumulative incidence of patients retransitioning were correlated. The weighted dot plot presents the percentage of patients retransitioning over time, and the size of the dot represents the number of patients who initially transitioned from originator to biosimilar.

For each of the factors related to patient, disease, and treatment and implementation strategy, studies were stratified according to the categories of that factor (e.g., extra laboratory monitoring—yes or no). The weighted median (based on the number of patients who initially transitioned from originator to biosimilar) and interquartile range (IQR) of the cumulative incidence of patients who retransitioned in these studies were calculated and compared to explore whether a potential association between these factors existed and the cumulative incidence of patients who retransitioned.

Results

The systematic literature search resulted in 994 unique studies. After screening, 149 studies were identified in which patients were transitioned (originator to biosimilar) from a TNFα inhibitor originator to a biosimilar. Of those studies, 112 were excluded: 109 did not report on retransitioning (originator to biosimilar and back to originator), two did not report any baseline characteristics of the transitioned patients, and one was not published in a peer-reviewed journal. The remaining 37 studies were included in this systematic review (Fig. 1). The included studies and the excluded review articles (*n* = 98) were manually checked for relevant studies that were not captured in the systematic literature search, but no additional studies were included. Data extracted from the individual studies are presented in Tables S2 and S3 in the Supplementary Files.

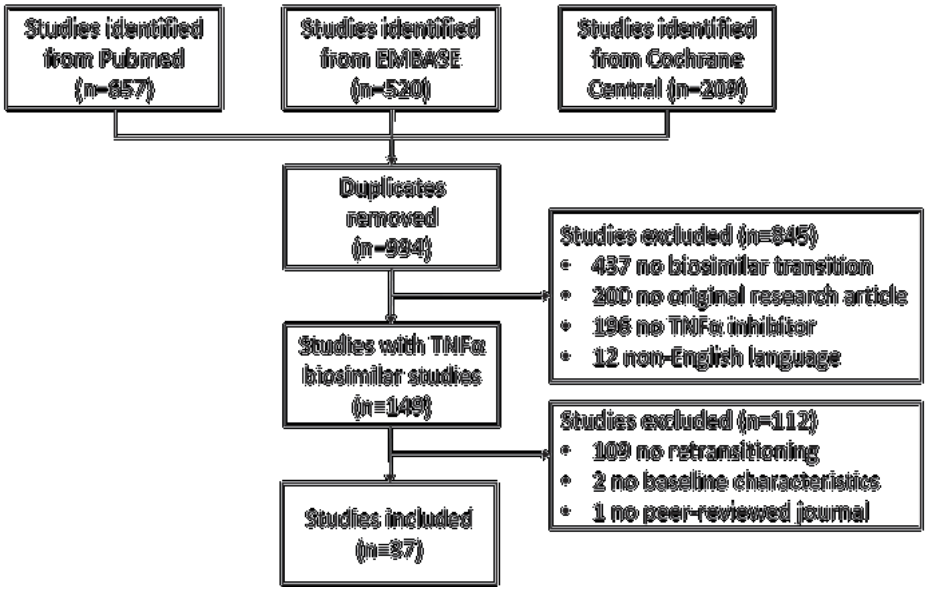

Figure 1: Flow chart of study selection.

Table 1 presents the characteristics of the included studies, in which patients were transitioned from a TNFα inhibitor originator to a biosimilar. The majority of included studies were publicly funded (78.4%), included a cohort study design (97.3%), and were performed in Europe (91.9%). In the majority of studies, patients were transitioned in 2015 (18.9%) or 2016 (35.1%). The median follow-up was 12 months. The 37 studies included a median of 94 (IQR 45–192) patients; more than half of the studies included patients with a RD (59.9%), and more than half of the studies involved patients receiving infliximab (62.2%).

Table 1: Characteristics of the included studies, in which patients were transitioned from TNFα inhibitor originator to the corresponding biosimilar

Characteristic	Publications (n=37)
Publication characteristics	
Funding	
Industry	8 (21.6%)
Public	29 (78.4%)
Study design characteristics	
Type of study	
Cohort	36 (97.3%)
Case series	1 (2.7%)
Case-control	-
Other	-
Geographical location of study	
Europe	34 (91.9%)
North-America (USA)	2 (5.4%)
Asia	1 (2.7%)
Year of start transitioning	
2012	1 (2.7%)
2013	-
2014	3 (8.1%)
2015	7 (18.9%)
2016	13 (35.1%)
2017	5 (13.5%)
2018	4 (10.8%)
NR	4 (10.8%)
Duration of follow-up, months, median (IQR)	12.0 (6.0-15.1)
Randomization of patients	
Yes	1 (2.7%)
Treatment blinded for patients	
Yes	-
No. included patients median (IQR)	94 (45–192)
Study population characteristics	
Age	
<45 years	12 (32.4%)
45-55 years	15 (40.5%)
>55 years	9 (24.3%)
Not reported	1 (2.7%)
% Females mean (SD)	53.6 (13.0)
Indication	
Rheumatic Disease	22 (59.5%)
Inflammatory Bowel Disease	7 (18.9%)
Multiple indications	4 (10.8%)
Other	4 (10.8%)

Table 1: Continued.

Characteristic	Publications (n=37)
Type of TNFα inhibitor	
Etanercept	11 (29.7%)
Infliximab	23 (62.2%)
Adalimumab	2 (5.4%)
Multiple	1 (2.7%)
Years since first diagnosis	
<10 years	7 (18.9%)
10-15 years	10 (27.0%)
>15 years	6 (16.2%)
Not reported	14 (37.8%)
Duration of originator treatment prior to transitioning to a biosimilar	
<5 years	14 (37.8%)
5-10 years	14 (37.8%)
>10 years	1 (2.7%)
Not reported	8 (21.6%)

IQR: interquartile range; SD: standard deviation

The overall weighted median cumulative incidence of patients who retransitioned (originator to biosimilar and back to originator) was 7.6% (IQR 6.8–17.2), and the incidence did not increase with increasing follow-up time (Fig. 2). Two studies reported a much higher cumulative incidence (50.0% [25] and 71.7% [26]) than all other studies.

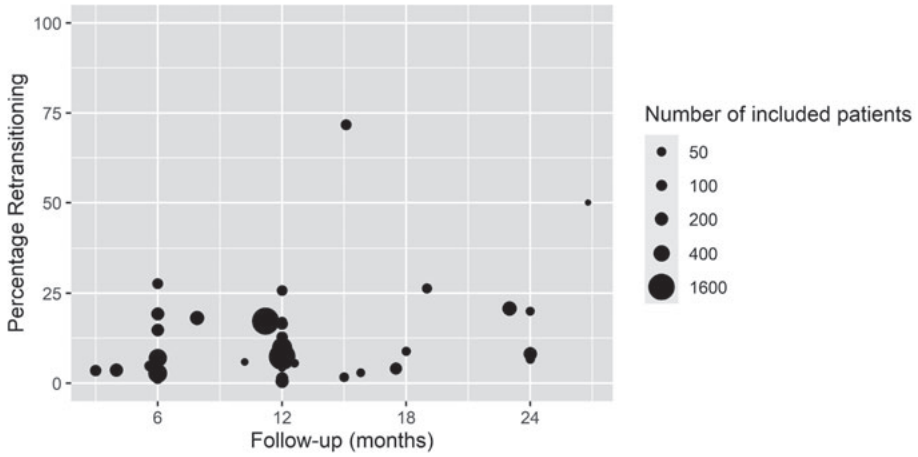

Figure 2: Weighted scatterplot of the cumulative incidence of patients who retransitioned per study.

As depicted in Table 2, studies that were performed in 2014, 2015, and 2016 reported the highest cumulative incidence of patients who retransitioned (21.4%, 7.8% and

17.8%, respectively). In studies performed later in time, the incidence decreased to 6.2% in 2017 and 4.1% in 2018.

The reason for retransitioning was reported in 26 studies (70.3%), which included a total of 4813 patients. Reasons for retransitioning were mainly due to loss of efficacy (50.2% of patients), adverse events (AE; 45.8% of patients) or both (3.5% of patients). The types of AEs reported varied; infections were mentioned, as were AEs such as fatigue, headache, and malaise.

Table 2: Year of transitioning and the weighted median cumulative incidence of patients retransitioning

Year of transitioning	No. studies (n=37)	No. patients (n=8555)	Median cumulative incidence of patients retransitioning, IQR (weighted)
2012	1	36	5.6% (NA)
2014	3	149	21.4% (3.4-46.6)
2015	7	1752	7.8% (3.5-18.8)
2016	13	4869	17.8% (11.7-19.1)
2017	5	790	6.2% (4.8-7.6)
2018	4	370	4.1% (2.5-6.8)
Not Reported	4	589	12.8% (8.7-15.7)

Factors associated with retransitioning

Patient, disease and treatment factors

Factors related to patient, disease, and treatment are depicted in Table 3. Studies that limited inclusion to only adult patients reported a weighted median of 6.6% of patients who retransitioning, compared with 8.9% in studies that included all age groups.

Two disease-related factors were evaluated in this review: the indication for which patients were treated and whether studies included only patients with stable disease or all patients. The incidence of patients who retransitioned was lowest in studies in patients with IBD compared studies in the other indications (6.6% for IBD versus 15.1–17.7%). Studies that only included patients with stable disease reported a weighted median incidence for retransitioning of 7.0% compared with 13.7% in studies that included all patients.

Studies in patients receiving adalimumab reported less retransitioning than studies with other TNFα inhibitors (3.1 vs. 4.1–6.7%). However, adalimumab was only evaluated in two studies, which included a limited number of patients. Studies that only included patients who had a minimum duration of use of the originator before transitioning reported a weighted median incidence of 18.3% of patients retransitioning compared with 15.1% in studies with no restrictions on duration of originator use.

Table 3: Patient, disease and treatment factors and the weighted median cumulative incidence of patients retransitioning

Characteristic	No. studies (n=37)	No. patients (n=8555)	Median cumulative incidence of patients retransitioning, IQR (weighted)
Patient factors			
Age			
Only adult patients	22	7324	6.6% (5.7-9.1)
All age categories	15	1231	8.9% (6.9-22.8)
Disease factors			
Indication			
Rheumatic Disease	22	4573	15.1% (5.4-16.0)
Inflammatory Bowel Disease	7	1556	6.6% (0.9-8.3)
Multiple indications	4	2330	16.2% (13.7-18.8)
Other	4	96	17.7% (7.2-33.1)
Disease stability			
Only stable patients	15	2085	7.0% (1.5-7.1)
All patients	22	6470	13.7% (8.0-21.4)
Treatment factors			
Type of TNFα inhibitor			
Etanercept	11	3705	6.5% (3.7-8.0)
Infliximab	23	4525	6.7% (6.7-14.2)
Adalimumab	2	180	3.1% (1.2-5.1)
Multiple	1	145	4.1% (NA)
Minimum duration use originator			
Only patients with minimum duration of use	13	3525	18.3% (7.4-19.2)
All patients	24	5030	15.1% (13.2-16.9)

Implementation strategy-related factors

Several factors regarding how patients were informed on transitioning to the biosimilar were studied, as depicted in Table 4. Studies in which patients were informed about transitioning using both written information and (the option of) verbal information from their HCP reported a median incidence of retransitioning of 19.4%, which is higher than that found with either one of the options (9.9% for only written information; 4.7% for only verbal information from the HCP); however, studies that asked for informed consent to transition reported lower incidences of patients retransitioning than did studies that asked for consent in a less formal way.

The type of training to HCPs was reported in only seven studies (18.9%), with a total of 1074 patients included. There was no clear association between the type of training and the incidence of patients who retransitioned; the weighted median was 2.7% in studies that reported both educational and communication training, 6.8% in studies

with only educational training, 25.8% in the study with only communication training, and 7.1% in studies that did not report on training to HCPs.

Studies in which patients' healthcare directly benefited from the financial gains of transitioning to a biosimilar (gainsharing) reported less retransitioning (1.4%) than did studies that did not report gainsharing (7.2%), although gainsharing was reported in only two studies. A higher incidence of patients who retransitioned was reported in studies that, during transitioning, offered patients the option of retransitioning if the biosimilar was not satisfying (11.1 vs. 7.0%).

Extra laboratory monitoring of patients after transitioning seemed to result in fewer patients retransitioning than when no extra laboratory monitoring was part of the biosimilar implementation strategy (1.6 vs. 6.1%, respectively). Additional control visits did not appear to be associated with an effect on the numberof patients who retransitioned.

Table 4: Implementation strategy factors and the weighted median cumulative incidence of patients retransitioning

Characteristic	No. studies (n=37)	No. patients (n=8555)	Median cumulative incidence of patients retransitioning, IQR (weighted)
Manner of providing information			
Both written information and verbal information from HCP	13	1918	19.4% (6.7-19.7)
Written information	1	758	9.9% (NA)
Verbal information from HCP	6	590	4.7% (0.5-25.7)
Not Reported	17	5289	7.4% (3.6-15.2)
Training of HCPs			
Both educational and communication	2	670	2.7% (2.7-2.9)
Educational	4	315	6.8% (1.4-33.4)
Communication	1	89	25.8% (NA)
Not Reported	30	7481	7.1% (5.2-10.1)
Type of consent			
Informed consent	13	2189	1.6% (1.4-7.6)
Opt-in	9	2030	9.0% (3.4-24.3)
Opt-out	3	1838	9.7% (5.0-13.1)
Not Reported	12	2498	7.4% (5.3-16.0)
Gainsharing			
Yes	2	256	1.4% (1.4-1.5)
No	0	0	-
Not Reported	35	8299	7.2% (5.4-17.2)

Table 4: Continued.

Characteristic	No. studies (n=37)	No. patients (n=8555)	Median cumulative incidence of patients retransitioning, IQR (weighted)
Option offered to retransition			
Yes	5	463	11.1% (4.1-20.0)
No	0	0	-
Not Reported	32	8092	7.0% (5.3-7.8)
Extra control visits			
Yes	14	1473	5.4% (1.6-17.5)
No	16	4690	7.1% (6.8-27.8)
Not Reported	7	2392	18.3% (9.4-26.0)
Extra laboratory monitoring			
Yes	15	2460	1.6% (2.0-2.7)
No	12	3320	6.1% (4.8-7.0)
Not Reported	10	2775	5.8% (3.8-13.7)

Discussion

This systematic review studied the cumulative incidence of patients who retransitioned and the association between patient, disease, and treatment, and implementation strategy-related factors and retransitioning. The overall median cumulative incidence of retransitioning was 7.6%. Retransitioning occurred to a lesser degree in patients with IBD than in those with other indications and in patients with stable disease at the start of the biosimilar. Actively offering the option to retransition resulted in more patients retransitioning then when this was not offered or reported. Extra laboratory monitoring as part of the implementation strategy resulted in fewer patients retransitioning and gainsharing might also result in fewer patients retransitioning although the number of studies reporting on gainsharing was very limited.

Of the studies included in this review, the vast majority (91.9%) were performed in Europe, and only 5.4% of the studies were performed in the USA. Fewer biosimilars are registered in the USA than in Europe, and the use of biosimilars is also lower,[27] which translates in clinical practice to limited experience and knowledge with biosimilars among prescribers and reluctance to prescribe a biosimilar.[28] This finding might also be explained by different regulations: In the USA, marketing authorization holders of a biosimilar can apply for approval of their biosimilar as interchangeable with the originator by demonstrating interchangeability, and such a biosimilar can be substituted at the pharmacy level.[30] However, only one biosimilar insulin is currently approved as an interchangeable biosimilar,[30] which could make practitioners reluctant to transition patients in clinical practice, thereby hampering the uptake of biosimilars. The European Medicines Agency (EMA) defines interchangeability as the possibility

of exchanging one medicine for another that has the same therapeutic effect, e.g., originator to biosimilar or vice versa. The EMA does not require additional studies to show interchangeability and decisions on interchangeability are left to the individual member states. A previous paper by EU regulators concluded that biosimilars licensed under the stringent regulatory requirements in the EU are interchangeable with their originator.[31,32]

We found a median cumulative incidence of retransitioning of 7.6% (IQR 6.8–17.2). The cumulative incidence of retransitioning did not increase with increasing follow-up time, implying that retransitioning occurred mainly in the first months after transitioning to the biosimilar. As the time of follow-up does not seem to be related to the cumulative incidence calculated we consider it appropriate to present an overall cumulative incidence for all studies together. Two studies reported a much higher cumulative incidence of patients retransitioning than the other studies included in this review. In the study by Riller et al.,[25] half of the patients retransitioned. However, this study included only eight patients, diagnosed with neurosarcoidosis. Xue et al.[33] also reported failure of infliximab biosimilar in patients with neurosarcoidosis, with effect regained after retransitioning. The authors attributed this finding by variations in afucosylation between the originator and biosimilars, which might be associated with differences in biological activity specifically in sarcoidosis.[33] However, the effect of afucosylation variations in sarcoidosis has not been extensively studied. In the study by Yazici et al.,[34] performed in Turkey, 72% of patients retransitioned. According to the authors, the incentives for the use of biosimilars are minimal in Turkey, since both originators and biosimilars are fully reimbursed.[34] However, as other countries also reimburse both originators and biosimilars, this cannot fully explain their large cumulative incidence of retransitioning. However, political factors such as the availability of the originator, regional/national policies, and pricing and reimbursement of originators and biosimilars are, however, likely to affect the number of patients who retransition. Within the present study, we were not able to study the impact of political factors on the number of patients retransitioning. However, as the included studies covered a variety of settings with different policies on implementation of biosimilars, we expect the cumulative incidence found to be representative.

We found that several factors related to patients, their disease, and their treatment could play a role in the incidence of patients who retransitioned. First, fewer patients with IBD retransitioned than those with other indications. This was a striking result: In the first years that biosimilars were available, gastroenterologists were hesitant to transition patients from originators to biosimilars.[38] However, in a qualitative study performed in Europe a few years later, gastroenterologists seemed more confident

than rheumatologists in transitioning patients to biosimilars;[39] therefore, the lower numbers of retransitioning patients with IBD might be explained by the more positive opinions of gastroenterologists. This is reflected in the larger uptake of biosimilars in patients with IBD than in those with RD.[40] There were no differences between studies in patients with IBD and other indications in terms of the year the study was performed, the type of TNFα inhibitor, or the inclusion of only patients with stable disease; consequently, these factors did not explain the lower incidence of retransitioning in patients with IBD. Unfortunately, none of the included studies specifically studied patients with psoriasis, which is also an important indication of TNFα inhibitors.

Second, including only patients with stable disease appeared to be associated with less retransitioning, which might be due to attribution effects (allocating preexisting or unrelated symptoms to the change in treatment).[41] Patients in this review who had not (yet) achieved disease stability might misattribute flares in their disease to the transition to biosimilar instead of to the natural course of their disease. In addition, only transitioning patients with stable disease from originator to biosimilar is not in line with the principle of the biosimilar being similar to the originator.[42,43]

Finally, less retransitioning was reported in studies in which patients received adalimumab than in studies of other TNFα inhibitors. Adalimumab was the last biosimilar to be introduced in clinical care, which could mean that the introduction of adalimumab biosimilars benefited from knowledge gained from and experience with the introduction of previous biosimilars for clinicians, pharmacists and patients. This is supported by our finding that studies performed after 2016 reported less retransitioning.

In this review, we also studied biosimilar implementation factors. Several factors concerned issues on how patients were informed about transitioning to a biosimilar. We found that the incidence of retransitioning appeared to be increased in studies in which patients were most informed about biosimilar transitioning but decreased in studies in which patients were asked for informed consent. This seems contradictory, since informing patients well is part of obtaining informed consent. Studies in patients with IBD or RD reported that patients wished to be informed with positive and structured information on transitioning from originator to biosimilar and wanted to be actively involved in this decision.[44,45] However, our results demonstrate that providing more information to patients did not result in fewer patients retransitioning, which contradicts the recommendations in previous reviews.[21,46]

The two studies applying gainsharing reported a smaller incidence of retransitioning than did studies that did not report on gainsharing. In the studies that reported on gainsharing, the financial savings from transitioning to the biosimilar were used for a "long-term appointment of a switch pharmacist"[47] (not further specified) and for the appointment of IBD nurses and pharmacists for a "nurse-led IBD biologicals service for improving IBD patient safety and quality of care".[48] Patients might be more positive about biosimilars when they directly benefit from the financial savings, but the number of studies was too limited for final conclusions. Providing patients with the option of retransitioning at the introduction of the biosimilar—if the patient is not satisfied with the biosimilar—increased the incidence of retransitioning. This finding seems logical and was also previously described.[20] In addition, the possibility of implementing gainsharing as part of transitioning patients from originators to biosimilars depends on the political situation regarding the reimbursement of biologicals.

Increased laboratory monitoring of patients after transitioning appeared to be related to fewer patients retransitioning. However, extra laboratory monitoring after transitioning did not seem to reflect the scientific principles of the biosimilar being similar to the originator.[49] The European Alliance of Associations for Rheumatology specifically states that measuring antidrug antibodies is not needed, since they do not expect an increase in antibodies after transitioning to a biosimilar.[42] However, although extra laboratory monitoring may not be justified, it could make patients feel safer and more confident in transitioning to the biosimilar and therefore prevent them from retransitioning.

This systematic review aimed to provide a complete overview of studies in which patients retransitioned to an originator after being transitioned from a TNFα inhibitor originator to a corresponding biosimilar. To our knowledge, this is the first review to study the incidence of retranisitioning and to explore whether the number of patients retransitioning could be related to patient, disease, and treatment and implementation strategy factors. However, the present study contains some limitations. We extracted patient, disease, and treatment and implementation strategy factors from the included studies and categorized them as "yes" or "no". This categorization was subjective, so could have been subject to interpretation errors. However, cross checking of data extraction by an independent second reviewer, which revealed no discrepancies suggesting robust data collection.

The extensiveness of reporting factors investigated in this review varied substantially in the included studies. If a factor was implemented but not reported in the study article, it was not included in this review. Some factors were only seldomly reported.

In particular, implementation strategy factors were often missing. Therefore, we were unable to statistically test associations or draw any causal conclusions. To overcome this, we explanatorily analyzed associations between patient, disease, treatment, and implementation strategy factors and the cumulative incidence of retransitioning.

The results of this study present several leads in optimizing the introduction of a biosimilar TNFα inhibitor in clinical practice and reducing the incidence of patients retransitioning. First, as less retransitioning was seen in studies that included only patients with stable disease, clinicians might consider transitioning only such patients. Retransitioning in patients with unstable disease is probably more related to the psychological distress of transitioning than to properties of the biosimilar. Waiting until disease is stable might solve this. Even though these patients are treated with the originator for a longer time, which is costly, it might still be beneficial in the long term, with fewer patients retransitioning.

Second, to optimize biosimilar implementation strategies, informing patients about transitioning and asking for their consent to do so might improve a patient's willingness to transition. However, as this did not reduce retransitioning in the included studies, it should not be expected in clinical practice. Actively providing the option of retransitioning when commencing treatment with the biosimilar seemed to result in more patients retransitioning, so this is also not recommended. Although the reporting of gainsharing was limited, the incidence of retransitioning was substantially lower in studies that applied gainsharing, so further study of this factor could be valuable. Extra laboratory monitoring of patients seemed to result in fewer patients retransitioning. However, this seems counterintuitive from the similarity perspective and is not recommended in the treatment guidelines.

Despite these recommendations of factors that may reduce the incidence of patients retransitioning, any thought of completely preventing retransitioning might be overly optimistic. The nocebo effect is often mentioned as the underlying reason for retransitioning,[14,21] and this is related to patients' lack of awareness of and misperceptions and attitudes about treatment.[51,52] Patients' behavior and their attitudes towards treatment are influenced by their capabilities, opportunities, and motivations, as described in the COM-B (capabilities, opportunities, motivation, behavior).[53,54] To further reduce patient retransitioning, the components that define patients' behavior should be directed into a more positive attitude towards biosimilars.

Conclusion

In studies on transitioning patients from TNFα originator to biosimilars with a median 12 months of follow up, 8% of patients retransitioned. Retransitioning appeared to be lower in studies that included only patients with stable disease, in studies that did not offer patients the option of retransitioning at the introduction of the biosimilar, and in studies that applied extra laboratory monitoring as part of the implementation strategy. Clinicians could consider implementing these factors to reduce the number of patients retransitioning to the originator and improve the introduction of biosimilars in clinical practice.

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Supplementary information

Table S1: Search string used

Source	Search string
Pubmed	("biosimilar*"[Title/Abstract] OR "follow on biologic*"[Title/Abstract] OR "subsequent entry biologic*"[Title/Abstract] OR "Biosimilar Pharmaceuticals"[MeSH Terms]) AND ("drug substitution*"[Title/Abstract] OR "switch*"[Title/Abstract] OR "transition*"[Title/Abstract] OR "Drug Substitution"[MeSH Terms])
EMBASE	(Biosimilar*:ti,ab,kw OR Follow-on biologic*:ti,ab,kw OR Subsequent entry biologic*:ti,ab,kw OR ('biosimilar agent'/exp) AND (drug substitution*:ti,ab,kw OR switch*:ti,ab,kw OR transition*:ti,ab,kw OR 'drug substitution'/exp)
Cochrane Central	"follow on biologic*" OR biosimilar* OR "subsequent entry biologic*" AND "drug substitution*" OR switch* OR transition*

Table S2: Characteristics of included studies

Study	Funding	Type of study	Location	Year of start	Duration follow-up (months)	Rando-mization	Blinded treatment	No. patients	Median/ mean age (y)	Females	Indication	Type TNFα inhibitor	Disease duration (y)	Duration originator treatment (y)
Abdalla et al.[54]	Public	Cohort	Europe	2014	15.8	No	No	34	45-55	50%	RD	Infliximab	10-15	<5
Al Tabaa et al.[55]	Public	Cohort	Europe	2016	6	No	No	94	45-55	54%	RD	Etanercept	>15	NR
Avouac et al.[56]	Public	Cohort	Europe	2015	7.9	No	No	260	45-55	55%	Multiple	Infliximab	10-15	5-10
Binkhorst et al.[57]	Public	Cohort	Europe	NR	4	No	No	197	<45	51%	IBD	Infliximab	NR	NR
Boone et al.[58]	Public	Cohort	Europe	2016	12	No	No	125	45-55	55.2%	Multiple	Infliximab	NR	<5
Bruni et al.[59]	Public	Cohort	Europe	NR	24	No	No	220	>55	64.5%	RD	Etanercept	10-15	5-10
Bruni et al.[60]	Public	Cohort	Europe	2018	6	No	No	82	45-55	54.8%	RD	Adalimumab	10-15	5-10
Chan et al.[61]	Public	Cohort	Europe	2016	3	No	No	113	NR	NR	RD	Etanercept	NR	NR
Deaner et al.[62]	Public	Case series	USA	2017	10.2	No	No	17	<45	76.5%	Other	Infliximab	NR	<5
Ditto et al.[63]	Public	Cohort	Europe	2017	12	No	No	87	>55	57.5%	RD	Etanercept	>15	5-10
Evripidis et al.[64]	Public	Cohort	Europe	2017	18	Yes	No	45	<45	13.3%	RD	Infliximab	<10	5-10
Felis-Giemza et al.[65]	Public	Cohort	Europe	2016	6	No	No	162	45-55	54.3%	RD	Etanercept	NR	NR
Fitzgerald et al.[66]	Industry	Cohort	USA	2016	11.2	No	No	1680	>55	65.7%	Multiple	Infliximab	NR	NR
Glintborg et al.[35]	Industry	Cohort	Europe	2016	12	No	No	1621	>55	59.5%	RD	Etanercept	NR	5-10
Park et al.[67]	Public	Cohort	Asia	2012	12.6	No	No	36	<45	30.5%	IBD	Infliximab	NR	NR
Kiltz et al.[68]	Industry	Cohort	Europe	2017	5.6	No	No	84	45-55	52.4%	RD	Etanercept	<10	<5
Kumar et al.[69]	Public	Cohort	Europe	2014	12	No	No	23	<45	91.7%	Other	Infliximab	<10	<5
Lauret et al.[70]	Public	Cohort	Europe	2015	23	No	No	265	45-55	45%	Multiple	Infliximab	10-15	5-10
Layegh et al.[71]	Public	Cohort	Europe	2015	24	No	No	45	>55	71%	RD	Infliximab	>15	>10
Madenidou et al.[72]	Public	Cohort	Europe	2016	19	No	No	72	>55	55.6%	RD	Etanercept	>15	<5
Mahmmod et al.[73]	Public	Cohort	Europe	2015	12	No	No	758	<45	53.8%	IBD	Infliximab	<10	<5
Müskens et al.[74]	Public	Cohort	Europe	2016	12	No	No	70	>55	51%	RD	Etanercept	10-15	5-10

Table S2: Continued.

Study	Funding	Type of study	Location	Year of start	Duration follow-up (months)	Rando-mization	Blinded treatment	No. patients	Median/ mean age (y)	Females	Indication	Type TNFα inhibitor	Disease duration (y)	Duration originator treatment (y)
Nikiphorou et al.[75]	Industry	Cohort	Europe	NR	11	No	No	39	45-55	56%	RD	Infliximab	NR	<5
Petit et al.[76]	Public	Cohort	Europe	2018	12.3	No	No	45	45-55	55%	RD	Infliximab	NR	5-10
Provenzano et al.[77]	Public	Cohort	Europe	2018	17.5	No	No	145	45-55	57.9%	RD	Multiple	10-15	5-10
Ratnakumaran et al.[36]	Public	Cohort	Europe	2016	12	No	No	191	<45	45.5%	IBD	Infliximab	10-15	<5
Razanskaite et al.[48]	Industry	Cohort	Europe	2015	12	No	No	143	<45	56.6%	IBD	Infliximab	<10	NR
Riller et al.[25]	Public	Cohort	Europe	2016	26.8	No	No	8	<45	62.5%	Other	Infliximab	NR	<5
Scherlinger et al.[78]	Public	Cohort	Europe	2015	12	No	No	89	45-55	43%	RD	Infliximab	>15	NR
Schmitz et al.[79]	Public	Cohort	Europe	NR	12	No	No	133	<45	55.6%	IBD	Infliximab	NR	<5
Selmi et al.[80]	Industry	Cohort	Europe	2017	6	No	No	557	>55	57.1%	RD	Etanercept	10-15	5-10
Tapete et al.[37]	Public	Cohort	Europe	2018	6	No	No	98	<45	35.7%	IBD	Adalimumab	<10	NR
Tweehuysen et al.[81]	Public	Cohort	Europe	2015	6	No	No	192	>55	52%	RD	Infliximab	10-15	5-10
Tweehuysen et al.[16]	Industry	Cohort	Europe	2016	6	No	No	625	>55	55%	RD	Etanercept	<10	<5
Valido et al.[82]	Public	Cohort	Europe	2016	15	No	No	60	45-55	35%	RD	Infliximab	>15	5-10
Xue et al.[33]	Public	Cohort	Europe	2016	24	No	No	48	45-55	50%	Other	Infliximab	10-15	<5
Yazici et al.[26]	Industry	Cohort	Europe	2014	15.1	No	No	92	<45	52.2%	RD	Infliximab	NR	<5

*NR: Not reported; IBD: inflammatory bowel disease; RD: rheumatic disease; USA: United States of America

Table S3: Incidence of retransitioning, patient, disease, treatment and implementation strategy related factors per study

Study	Retransitioning	Inclusion: only adults	Inclusion: only stable disease	Inclusion: minimum duration use originator	Manner providing information	Training HCPs	Type of consent	Gainsharing	Option offered to retransition	Extra control visits	Extra laboratory monitoring
Abdalla et al.[54]	2.9%	No	No	No	NR	NR	Opt-in	NR	NR	No	No
Al Tabaa et al.[55]	27.7%	No	Yes	Yes	NR	Educational	NR	NR	NR	NR	Yes
Avouac et al.[56]	18.1%	Yes	No	Yes	NR	NR	Informed consent	NR	NR	Yes	NR
Binkhorst et al.[57]	3.6%	Yes	No	No	Verbal information from HCP	NR	Informed consent	NR	NR	Yes	Yes
Boone et al.[58]	12.8%	Yes	No	No	Both WI and VI	NR	Informed consent	NR	NR	No	Yes
Bruni et al.[59]	8.2%	Yes	Yes	Yes	Both WI and VI	NR	Informed consent	NR	NR	NR	NR
Bruni et al.[60]	1.2%	Yes	Yes	Yes	NR	NR	Informed consent	NR	NR	Yes	Yes
Chan et al.[61]	3.5%	NR	NR	NR	Both WI and VI	NR	NR	Yes	NR	Yes	NR
Deaner et al.[62]	5.9%	No	No	Yes	NR	NR	NR	NR	NR	No	No
Ditto et al.[63]	5.7%	Yes	Yes	No	Both WI and VI	NR	Informed consent	NR	Yes	Yes	NR
Evripidis et al.[64]	8.9%	No	Yes	Yes	Verbal information from HCP	NR	NR	NR	NR	Yes	Yes
Felis-Giemza et al.[65]	14.8%	No	No	No	NR	NR	NR	NR	NR	Yes	Yes
Fitzgerald et al.[66]	17.3%	Yes	No	Yes	NR	NR	NR	NR	NR	NR	NR
Glintborg et al.[35]	7.4%	Yes	No	No	NR	NR	Opt-out	NR	NR	No	No

Table S3: Continued.

Study	Retransitioning	Inclusion: only adults	Inclusion: only stable disease	Inclusion: minimum duration use originator	Manner providing information	Training HCPs	Type of consent	Gainsharing	Option offered to retransition	Extra control visits	Extra laboratory monitoring
Park et al.[67]	5.6%	Yes	No	No	NR	NR	NR	NR	NR	No	No
Kiltz et al.[68]	4.8%	Yes	No	No	NR	NR	Opt-out	NR	NR	No	No
Kumar et al.[69]	4.3%	Yes	No	No	NR	NR	NR	NR	NR	Yes	No
Lauret et al.[70]	20.8%	Yes	Yes	Yes	NR	NR	Informed consent	NR	NR	Yes	Yes
Layegh et al.[71]	6.7%	Yes	No	No	Both WI and VI	NR	Opt-in	NR	NR	No	No
Madenidou et al.[72]	26.4%	No	No	No	Both WI and VI	NR	Opt-in	NR	Yes	NR	NR
Mahmmod et al.[73]	9.9%	Yes	No	No	Written information	NR	Opt-in	NR	NR	No	No
Müskens et al.[74]	17.1%	No	Yes	No	Both WI and VI	Educational	Opt-in	NR	Yes	No	No
Nikiphorou et al.[75]	15.4%	No	Yes	No	NR	NR	Informed consent	NR	NR	No	No
Petit et al.[76]	6.7%	No	No	No	Both WI and VI	Both educ. and comm.	NR	NR	NR	No	No
Provenzano et al.[77]	4.1%	No	Yes	Yes	NR	NR	Opt-in	NR	Yes	NR	NR
Ratnakumaran et al.[36]	0.5%	No	No	No	Verbal information from HCP	NR	Informed consent	NR	NR	No	Yes
Razanskaite et al.[48]	1.4%	Yes	No	No	Both WI and VI	Educational	NR	Yes	NR	Yes	Yes
Riller et al.[25]	50.0%	No	No	No	Verbal information from HCP	Educational	Informed consent	NR	NR	No	No

Table S3: Continued.

Study	Retransitioning	Inclusion: only adults	Inclusion: only stable disease	Inclusion: minimum duration use originator	Manner providing information	Training HCPs	Type of consent	Gainsharing	Option offered to retransition	Extra control visits	Extra laboratory monitoring
Scherlinger et al.[78]	25.8%	No	Yes	Yes	Verbal information from HCP	Communication	Opt-in	NR	Yes	NR	NR
Schmitz et al.[79]	16.5%	Yes	No	No	Both WI and VI	NR	Opt-out	NR	NR	Yes	Yes
Selmi et al.[80]	7.0%	Yes	Yes	Yes	NR	NR	Informed consent	NR	NR	No	No
Tapete et al.[37]	7.1%	No	Yes	No	NR	NR	Informed consent	NR	NR	Yes	Yes
Tweehuysen et al.[81]	19.3%	Yes	No	No	Both WI and VI	NR	Opt-in	NR	NR	No	Yes
Tweehuysen et al.[16]	2.7%	Yes	No	No	Both WI and VI	Both educ. and comm.	Opt-in	NR	NR	No	Yes
Valido et al.[82]	1.7%	Yes	Yes	No	Verbal information from HCP	NR	Informed consent	NR	NR	Yes	Yes
Xue et al.[33]	20.0%	No	Yes	Yes	Both WI and VI	NR	NR	NR	NR	Yes	Yes
Yazici et al.[26]	71.7%	Yes	No	No	NR	NR	NR	NR	NR	NR	NR

*Both WI and VI: Both written information and verbal information from HCP; NR: Not reported; HCP: health care professional

CHAPTER 5

Incidence of and reasons and determinants associated with retransitioning from biosimilar etanercept to originator etanercept

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Abstract

Background

Patients in clinical practice are transitioned from originator etanercept (OR-ETA) to biosimilar etanercept (BS-ETA), but some subsequently retransition. Insights into the incidence of and reasons for retransitioning and the characteristics of these patients could help clinicians successfully introduce biosimilars.

Objective

Our objective was to assess the incidence of and reasons for retransitioning from BS-ETA to OR-ETA in patients with a rheumatic disease (RD) and to explore the determinants thereof.

Methods

This cohort study included all patients with RD who had transitioned from OR-ETA to BS-ETA in a large hospital in the Netherlands in 2016. The incidence of retransitioning to OR-ETA and the 1-year persistence with BS-ETA were assessed using the Kaplan–Meier estimator. Reasons for retransitioning were classified as related to (1) efficacy, (2) adverse events, (3) the administration device, and (4) other. Determinants for retransitioning, including baseline and treatment characteristics, were assessed in a nested case–control study using conditional logistic regression.

Results

We included 342 patients (median age 57.8 years; 53.5% females). At 1 year after transitioning, 9.4% of patients had retransitioned to OR-ETA and 69.7% were persistent with BS-ETA. At the end of follow-up (median 4.4 years), 47 patients (13.7%) had retransitioned to OR-ETA. The median time until retransitioning was 0.55 years (interquartile range 0.2–1.3). Most patients (n = 34 [72.3%]) retransitioned because of a (perceived) loss of effect, followed by adverse events (23.4%). In total 3.8% of patients switched to another biological treatment or a Janus kinase inhibitor; 17.1% of patients discontinued BS-ETA without retransitioning or switching within the first year. Univariate determinants for retransitioning included initiating corticosteroids or intensifying immunomodulator treatment (odds ratio [OR] 2.37; 95% confidence interval [CI] 1.03–5.45) and the number of visits to the rheumatology department (OR 2.06; 95% CI 1.55–2.74). In the multivariate analysis, only the number of visits to the rheumatology department remained significantly associated with retransitioning (OR 2.19; 95% CI 1.60–3.01).

Conclusion

When introducing a biosimilar in clinical care, clinicians should anticipate that one in seven patients will retransition to the originator. A (perceived) loss of effect was the most frequently reported reason for retransitioning. Patients who visited the rheumatology department more frequently had an increased risk of retransitioning, which is likely to be related to patients reporting a loss of effect and to adverse events resulting in more visits to the rheumatology department.

Introduction

Several tumor necrosis factor (TNF)-α inhibitor biosimilars have been available in Europe and the USA for several years. The market exclusivity right for originator etanercept expired in Europe in January 2016, and the first etanercept biosimilar was introduced in clinical practice soon thereafter. A biosimilar is defined as a "biological medicinal product that contains a version of the active substance of an already authorized biological medicinal product (originator)".[1] The similarity of the biosimilar etanercept to the originator was demonstrated by an extensive comparability exercise comparing physiochemical properties, biological activity, immunochemical properties, and in vivo pharmacological properties.[2] Finally, efficacy and safety were studied and similarity confirmed in three premarketing clinical studies, which randomly assigned TNFα inhibitor-naïve patients with rheumatoid arthritis to originator etanercept or to the biosimilar.[3-5]

The market entry of the etanercept biosimilar, as with all biosimilars, has led to competition, reduced prices and reduced financial burdens for healthcare budgets. Therefore, many patients in clinical practice are currently transitioned from originator etanercept to the biosimilar. A phase III randomized clinical trial (RCT) study in which patients were blindly transitioned from originator etanercept to a biosimilar confirmed that transitioning to etanercept biosimilar did not impact efficacy, safety and immunogenicity.[6]

However, the results of RCTs in which patients transitioned from originator etanercept to the biosimilar have not been reflected in observational studies. Patients who transitioned from originator etanercept to the biosimilar identified from the DANBIO registry in Denmark remained stable in their disease activity but had a significantly lower 1-year persistence of 82% (95% confidence interval [CI] 79–83) compared with 88% (95% CI 87–90) in the historic cohort of originator etanercept users.[7] Similar results were reported in the Dutch BIOSPAN study, where patients who transitioned from originator etanercept to the biosimilar had a higher relative risk (hazard ratio [HR] 1.57; 95% CI 1.05–2.36) of treatment discontinuation. Patients who transitioned also experienced more subjective adverse events than did users of the originator (84 vs. 40%).[8]

Moreover, in the aforementioned observational studies and others, 2.7–17.2% of patients who transitioned from originator etanercept to the etanercept biosimilar retransitioned to originator etanercept within 6–12 months.[7-10] The most important reasons for retransitioning were adverse events caused by the etanercept biosimilar, including subjective adverse events such as arthralgia and fatigue, or (perceived) loss of

effect. According to the authors of these studies, the higher rate of subjective adverse events after transitioning to the etanercept biosimilar could have been caused by the nocebo effect (where negative perceptions of transitioning to a biosimilar result in unwanted effects[9]); however, this has not been explicitly studied.

Current studies have not provided insight into which types of patients are more likely to retransition to originator etanercept. An important consideration for clinicians is whether a successful transition from the originator to the biosimilar can be achieved with a limited burden on the patient. Insights into the incidence of and reasons for retransitioning and the characteristics of patients who are most likely to retransition could help clinicians ensure the successful introduction of biosimilars.

The aims of this study were to assess the incidence of and reasons for retransitioning from biosimilar etanercept to originator etanercept in patients with a rheumatic disease (RD) and to explore the determinants of retransitioning.

Methods

Setting and study population

This cohort study was conducted at the Spaarne Gasthuis, a large teaching hospital in Haarlem and Hoofddorp, the Netherlands. In line with current Dutch reimbursement regulations, all biologicals used for the treatment of RDs in the outpatient setting have been exclusively dispensed by the outpatient pharmacy of the treating hospital since 2012.[11]

Patients treated with etanercept for RD and who transitioned from originator etanercept to biosimilar etanercept between June 2016 and December 2016 were included. The date at which a patient first received biosimilar etanercept was assigned as that patient's index date. Patients were followed from the index date until retransitioning to originator etanercept, switching to another biological or Janus kinase (JAK) inhibitor, discontinuing biological treatment, being lost to follow-up, or death or reaching the end of data collection (18 April 2021), whichever came first.

In the Netherlands, the decision to transition patients to a biosimilar is made by individual hospitals; transitioning is directed by treating physicians and hospital pharmacists. All patients in this study received a letter to inform them about the introduction of biosimilar etanercept and an additional information package about the biosimilar. Patients received their usual care during the transition. However, patients had the option of consulting their rheumatology nurse or rheumatologist if they had questions or concerns about transitioning to biosimilar etanercept or if they

required extra training by the rheumatology nurse on using the biosimilar etanercept autoinjector. The information and communication on transitioning was consistent throughout the whole period (June–December 2016).

Retransitioning

For each included patient, treatment episodes for the biosimilar etanercept were constructed. These episodes were defined as the time between the first dispensing of biosimilar etanercept until the end of the duration of the final dispensing within the treatment episode, calculated based on the number of syringes dispensed and the dosing frequency. The information required to construct the episodes (dose and dosing regimen, specialism of the prescriber, and dispensing date) was collected from CompuGroup Medical (Echt, the Netherlands), an outpatient pharmacy system. A maximum permissible gap of 90 days was allowed to elapse between the theoretical end date of a dispensing and the subsequent dispensing date. The 90-day limit was based on the 90-day standard dispensing period in the Netherlands, which is applicable to clinical practice at the Spaarne Gasthuis.

Retransitioning was defined as restarting originator etanercept within the maximum permissible gap of 90 days from the theoretical end date of biosimilar etanercept dispensing. The date of retransitioning was assigned as the patient's event date. The reason for retransitioning was extracted from the electronic patient dossier EPIC (Madison, WI, USA) and classified as related to (1) efficacy, (2) an adverse event, (3) the autoinjector through which the biosimilar was administered, or (4) other.

We also assessed persistence on biosimilar etanercept, the incidence of switching from biosimilar etanercept to another biological or JAK inhibitor, and the incidence of discontinuing etanercept treatment without switching. Persistence (continuous use) was assessed at 6 months, 1 year, and end of follow-up. Switching was defined as dispensing of another biological or JAK inhibitor (listed in the Supplementary File S1) registered for RD within the maximum permissible gap after the theoretical end date of the final dispensing of biosimilar etanercept. Discontinuing biosimilar etanercept without switching was defined as no dispensing of biosimilar etanercept within the maximum permissible gap without retransitioning or switching.

Patient- and treatment-related characteristics associated with retransitioning

To explore the patient- and treatment-related characteristics associated with retransitioning, we performed a nested case–control study. Cases were defined as patients who retransitioned from biosimilar etanercept to originator etanercept. Up to

four controls were randomly selected for each case using incidence density sampling. Cases and controls were matched by index date (index date between June and August 2016 or between September and December 2016) to correct for potential seasonal influences during transitioning.

The following characteristics were explored: age at index date (continuous, years); sex (male or female); biosimilar etanercept dosing interval at index date (7 days[12] or more than 7 days); use of other biologicals registered for RD prior to originator etanercept (yes or no); duration of originator etanercept treatment before index date (longer or shorter than the median duration of originator etanercept treatment); initiation of corticosteroids or intensification of immunomodulator treatment in the 60-day period before the event (yes or no); hospitalizations, defined as having been hospitalized (yes or no) within 6 months before the event, included as a representation of the general health condition of the patient; and number of outpatient visits to the rheumatology department, defined as the sum of the number of outpatient visits and phone consultations with the rheumatology department in the 60-day period before the event (continuous).

The included immunomodulators and corticosteroids are listed in S2.

Data analysis

Descriptive statistics were used to present the characteristics of the patients and the reasons for retransitioning. Time on biosimilar etanercept was presented with a Kaplan–Meier curve. The cumulative incidence of retransitioning, switching, or discontinuing was presented in cumulative incidence curves. Patient and treatment characteristics associated with retransitioning were explored using conditional logistic regression and expressed as odds ratios (ORs) with corresponding 95% CIs. All characteristics were included in the multivariate model.

Data were analyzed using R version 3.6.1.

Results

In total, 342 patients transitioned to biosimilar etanercept during the study period and were thus included in our cohort. An overview of the included patients is presented in Fig. 1. The median age of the patients was 57.8 years, and 53.5% were female. For a majority of patients (93.0%), originator etanercept was the first biological treatment, and the median duration of originator etanercept treatment prior to the index date was 4.3 years. At the index date, the median dosing interval was 7 days, which is in line with the approved dosing interval (Table 1).

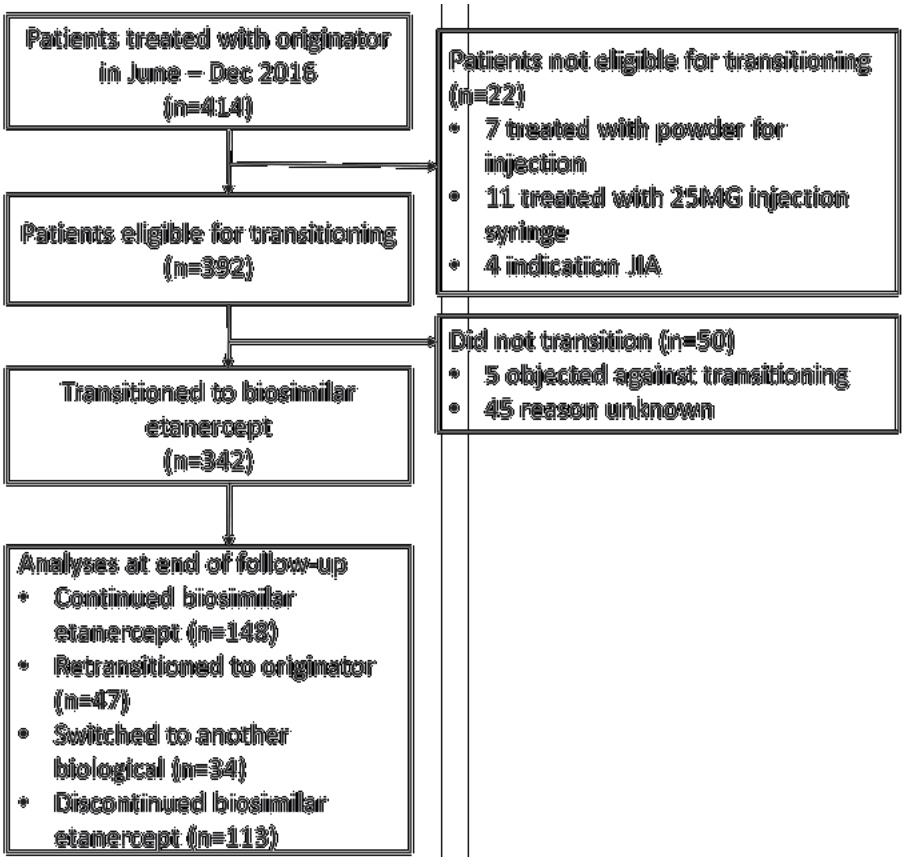

Figure 1: Flow chart of included patients. JAK: Janus kinase; JIA: juvenile idiopathic arthritis.

In total, 9.4% of the patients had retransitioned to originator etanercept 1 year after the index date and 47 patients (13.7%) had retransitioned at the end of follow-up (median 4.4 years). The median time until retransitioning was 0.55 years (interquartile range [IQR] 0.2–1.3) (Fig. 2). (Perceived) loss of effect after the introduction of the biosimilar was the most frequently reported reason for retransitioning (n = 34 [72.3%]). Patients reported, among other symptoms, an increase in pain, swelling of joints, and (morning) stiff- ness, and 11 (23.4%) patients reported one or more adverse event resulting in retransitioning to originator etanercept. The type of adverse events reported varied, but the most frequently reported was an itching skin reaction (four patients). No patients retransitioned because of the autoinjector through which biosimilar etanercept was administered. Two patients (4.2%) retransitioned for other reasons.

Aside from retransitioning, the persistence with biosimilar etanercept was 82.4% at 6 months and 69.7% at 1 year. In total, 3.8% of patients switched to another biological treatment or a JAK inhibitor; 17.1% of patients discontinued biosimilar etanercept without retransitioning or switching within the first year.

Patients who retransitioned remained treated with the originator for a median of 2.0 years (IQR 0.8–4.0). Eight of the 47 retransitioned patients (17.0%) switched to another biological within a median of 1.0 years (IQR 0.5–1.5) after retransitioning. These patients switched to adalimumab (n=2), baricitinib (n=1), secukinumab (n=2), rituximab (n=1), tocilizumab (n=1), or ustekinumab (n=1).

Table 1: Baseline characteristics of the study cohort (n = 342)

Patient and treatment characteristics	**n = 342**
Females	183 (53.5%)
Age at index date (median, IQR), years	57.8 (47.6-67.7)
Dosing interval at index date (median, IQR), days	7 (7-10)
No. biologicals used prior to index date	
0	318 (93.0%)
1	16 (4.7%)
2	7 (2.0%)
>2	1 (0.3%)
Duration of originator etanercept treatment (median, IQR), years	4.3 (2.8-4.6)*
Follow-up time from index date (median, IQR), years	4.4 (4.1-4.6)

Data presented as n (%) unless otherwise specified
IQR: interquartile range
*Information on treatment with originator etanercept was available from January 2012; patients could have been treated for a longer period.

As depicted in Fig. 2, at the end of follow-up, 33.0% of the patients (n=113) had discontinued biosimilar etanercept treatment without retransitioning or switching. Of these discontinued patients, 78.8% (n=89) restarted biosimilar etanercept within a median of 3.8 months (IQR 3.3–5.6). Three patients (2.7%) restarted treatment with infliximab, golimumab, or adalimumab within a median of 22.7 months (IQR 15.0–35.8) after discontinuing biosimilar etanercept. The characteristics for retransitioning were explored in the nested case–control study and are presented in Table 2. Of the 11 patients in the retransitioning cohort (cases) initiating corticosteroids or intensifying immunomodulator treatment, five intensified immunomodulator treatment, five initiated corticosteroid treatment, and one did both. Within the control group, 11 patients intensified immunomodulator treatment, 12 initiated corticosteroid treatment, and one did both. None of the patients initiated immunomodulator treatment.

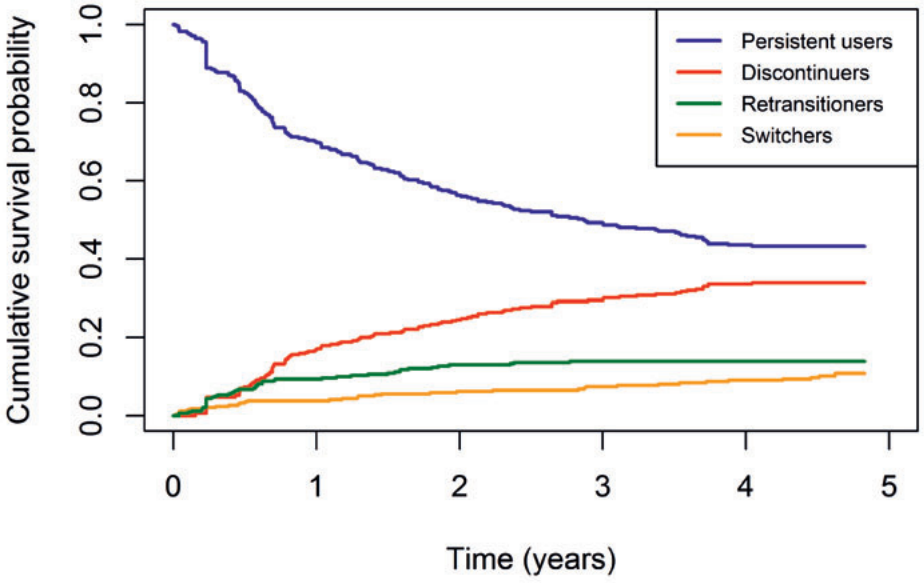

Figure 2: Kaplan–Meier curve of time on biosimilar etanercept and time until retransitioning; time until switch to another biological and time until discontinuation of biological treatment.

From the univariate analysis, initiating corticosteroids or intensifying immunomodulator treatment increased the odds of retransitioning by 2.37 (95% CI 1.03–5.45) compared with patients without changes in corticosteroid or immunomodulator treatment. The frequency of outpatient visits to the rheumatology department in the 60-day period before retransitioning was associated with a significantly increased risk of retransitioning, where the odds increased by 2.06 (95% CI 1.55–2.74) for every additional visit. No other determinants studied were associated with retransitioning. The multivariate analysis revealed that, for each outpatient visit to the rheumatology department, the odds of retransitioning increased by 2.19 (95% CI 1.60–3.01).

Table 2: Association between different patient and treatment characteristics and retransitioning (cases) from biosimilar etanercept to originator etanercept

	Cases n= 47	**Controls n= 188**	**OR (univariate model)* 95% CI**	**OR (multivariate model) 95% CI**
Age, years (mean, SD)	58.0 (14.5)	57.3 (13.9)	1.00 (0.98–1.03)	1.00 (0.97-1.03)
Gender				
Male	15 (31.9%)	90 (47.8%)	Ref	Ref
Female	32 (68.1%)	98 (52.1%)	1.95 (0.99–3.83)	1.36 (0.61–3.05)

Table 2: Continued.

	Cases n= 47	Controls n= 188	OR (univariate model)* 95% CI	OR (multivariate model) 95% CI
Biosimilar etanercept dosing interval at index date				
7 days	35 (74.5%)	122 (64.9%)	Ref	Ref
>7 days	12 (25.5%)	66 (35.1%)	0.61 (0.29-1.29)	0.63 (0.27-1.48)
Previous use of other biological				
No	44 (93.6%)	178 (94.7%)	Ref	Ref
Yes	3 (6.3%)	10 (5.3%)	1.00 (0.27–3.74)	1.42(0.30-6.67)
Duration of originator etanercept treatment				
More than 4.3 years	24 (51.1%)	93 (48.9%)	Ref	Ref
Less than 4.3 years	23 (48.9%)	96 (51.1%)	0.91 (0.48–1.75)	0.72 (0.32-1.64)
Initiating corticosteroids or intensifying immune-modulator treatment				
No	36 (76.6%)	166 (88.3%)	Ref	Ref
Yes	11 (23.4%)	22 (11.7%)	**2.37 (1.03–5.45)**	2.12 (0.80–5.64)
Hospitalization				
No	42 (89.4%)	168 (89.4%)	Ref	Ref
Yes	5 (10.6%)	20 (10.6%)	1.00 (0.36–2.76)	0.44 (0.12-1.53)
Number of visits to the rheumatology department				
(mean, sd)	2.2 (1.7)	0.8 (1.1)	**2.06 (1.55–2.74)**	**2.19 (1.60–3.01)**

SD: standard deviation.
*Crude estimates are matched by design on index date (index date between June and August 2016 or index date between September and December 2016). Data presented as n (%) unless otherwise specified. Signifcant results are presented in bold.

Discussion

In this study, we investigated the incidence of and reasons for retransitioning to originator etanercept in a cohort of patients with RD who transitioned from originator etanercept to biosimilar etanercept over a median time of 4.4 years. We also explored the determinants for retransitioning. We demonstrated that approximately one in seven patients retransitioned, and most did so within 1 year of transitioning to the biosimilar. The most frequently reported reason for retransitioning was a (perceived) loss of effect after the introduction of the biosimilar. Patients who initiated corticosteroids or intensified immunomodulator treatment, as well as patients who had frequent visits to the rheumatology department, had an increased risk of retransitioning. However, in

the multivariate model, only the frequency of visits to the rheumatology department seemed to be associated with retransitioning.

This study demonstrated that 9.4% of patients had retransitioned to originator etanercept 1 year after the introduction of the biosimilar, which increased to 13.7% after 4.4 years of follow-up. This finding was in line with those of previous studies in which patients were transitioned in 2016 or 2017, reporting that 2.7–13.3% of their patients retransitioned within 6–12 months.[7-9]

In the present study, the majority of patients (82.4%) continued to use biosimilar etanercept 6 months after transitioning from originator etanercept to biosimilar etanercept; this proportion decreased to 69.7% at 1 year after transitioning. Previous studies on transitioning to biosimilar etanercept in patients with RD, also performed in 2016, reported higher rates of persistence, varying from a 6-month persistence of 90%[8,13] to a 1-year persistence of 73–83%.[7,10] Political factors such as the availability of the originator, regional/ national policies, and pricing and reimbursement of the originator and the biosimilar are likely to affect the persistent use of the biosimilar and therefore the proportion of patients retransitioning. In our study, originator etanercept was still available, which might (partly) explain the differences found. We acknowledge that retransitioning will not occur if the originator is no longer available or reimbursed. A structured positive framing strategy toward biosimilars has been demonstrated to positively affect patients' opinions regarding biosimilars.[14] Although the letter patients received within our study contained factual information about biosimilars, patients were given the opportunity to discuss their concerns with the rheumatologist and/ or rheumatology nurse. However, positive framing direct from the beginning of the implementation strategy might have contributed to higher persistence.

Patients who did not retransition to originator etanercept and who were not persistent with biosimilar etanercept were subdivided into patients who switched to another biological treatment (or to a JAK inhibitor) and patients who discontinued without switching. At 6 months after transitioning, 3.5% of patients had switched and 7.4% had discontinued. This was higher than the 3.0% who discontinued within 6 months after transitioning in the study by Tweehuysen et al.[8] However, in that study, patients who discontinued because of remission were censored and not counted as discontinued, which explains the lower percentage of discontinued patients found.[8]

Three-quarters of the patients who were classified as biosimilar etanercept discontinuers at the end of follow-up restarted treatment with biosimilar etanercept within a few months. This could be because they initially discontinued treatment

because they experienced sustained remission[15] but then experienced a flare and restarted treatment.[16] Another explanation for this finding might be that patients who continuously used biosimilar etanercept, but prolonged the dosing interval without informing the outpatient pharmacy, were misclassified as discontinued. To minimize the number of misclassified patients, we used a broad permissible gap of 90 days. However, if the dosing interval more than doubled, patients could still have been misclassified as discontinuers.

Previous studies reported that approximately one-half of patients were not persistent with biosimilar etanercept because of either objective clinical worsening or subjective health complaints,[7,8,10] which could be classified as the nocebo effect. The present study demonstrated that the majority of patients retransitioned because of (perceived) loss of effect when treated with the biosimilar. Although retransitioned patients remained treated with the originator etanercept for a median of 2.0 years, which might suggest that patients regained treatment effect, the nocebo effect might have played a role. By contrast, patients in a previous study remained treated with originator etanercept for 0.65 years, but the follow-up was shorter.[7] For the patient, a (perceived) loss of effect, regardless of whether it is classified as a nocebo effect, is a burden and might negatively impact treatment outcome. No patient retransitioned because of the autoinjector used to administer the biosimilar etanercept. This finding is supported by a previous study that examined patient perceptions of the autoinjector of the biosimilar etanercept and the originator etanercept and reported a preference for the biosimilar's autoinjector.[17] Although the biosimilar device was not reported as a reason for retransitioning in the present study, it should be taken into consideration during the introduction and implementation strategy for biosimilars.

In the current study, initiating corticosteroids or intensifying immunomodulator treatment in the 60-day period before the event, as well as the number of visits to the rheumatology department in the 60-day period before the event, increased the odds of retransitioning. However, when other patient- and treatment-related factors were accounted for, only the number of visits to the rheumatology department was associated with retransitioning: each visit in the 60-day period before the event increased the odds of retransitioning by 2.19. The patients in our study who wished to retransition were extensively contacted by the treating rheumatologist or the rheumatology nurse to discuss their concerns with the biosimilar before the decision on retransitioning was made. This might (partly) explain the association. Initiating corticosteroids or intensifying immunomodulator treatment was also not significantly associated with retransitioning in the multivariate (full) model. Although no formal correlation existed between the initiation of corticosteroid treatment or

intensification of immunomodulatory treatment and the number of visits to the rheumatology department, some coherence between these determinants is possible. Although transitioning to biosimilar etanercept does not increase disease activity,[6] patients might experience a loss of effect, resulting in more complaints, which might be treated by initiating or intensifying corticosteroids or immunomodulator treatment and simultaneously retransitioning to originator etanercept.

For clinical practice, these results highlight that, when patients transition from originator etanercept to the biosimilar, clinicians should anticipate one in seven patients not persisting with biosimilar treatment and retransitioning to the originator. In addition, clinicians should be aware that retransitioning occurs not only in the first few months after transitioning but also later.

This study provides insight into transitioning from originator etanercept to biosimilar in patients with RD using real-world clinical data. As such, it provides a reflection of daily clinical practice and contributes to the limited knowledge regarding retransitioning. We included a heterogeneous patient population in terms of treatment duration and biological treatment history, and we did not restrict inclusion to a certain type of RD or to patients whose diseases were clinically stable.

Moreover, we assessed the incidence of retransitioning over a longer period of time than did previous studies. Our results indicate that retransitioning was not limited to the first months after transitioning, suggesting that studies with a shorter follow-up might have underestimated the incidence of retransitioning.

Several limitations of this study must be addressed. First, the indication for etanercept treatment for the included patients was not known. However, as retransitioning to the originator is not recommended for any RD, we consider it unlikely that this information could have influenced our results and main conclusions. Furthermore, we commenced our data collection in 2016, and experience with biosimilars has increased since then. However, a recent study demonstrated that a gap in healthcare professionals' knowledge about biosimilars still exists.[18] Therefore, studies on patients transitioning from originator to biosimilar are required to increase knowledge about and improve the introduction of future biosimilars in clinical practice. Moreover, by starting data collection in 2016, we were able to follow patients over a longer period of time than did previous studies. Finally, this study was performed in one hospital, which might compromise its generalizability to other settings. However, because our results complement those of similar previous studies, we believe that the information provided by our study is further applicable to other hospitals. As previously discussed,

political factors such as the availability of the originator, regional/national policies, and pricing and reimbursement of the originator and the biosimilar are likely to affect the proportion of patients who retransition. Within the present study, the originator was available and reimbursed throughout the study period. This might have an effect on the generalizability of our results.

Conclusion

The results of this study demonstrate that, despite an extensive implementation strategy, when introducing a biosimilar in clinical care, clinicians should anticipate several patients retransitioning to the originator. The most frequent reason for retransitioning was a perceived loss of effect, followed by adverse events after the introduction of the biosimilar. Patients who visited the outpatient rheumatology department more frequently had an increased risk of retransitioning, which probably reflects patients reporting loss of effect and adverse events, resulting in more visits to the rheumatology department as part of the implementation strategy chosen. The provision of information specifically aimed at the concerns of these patients might prevent them from retransitioning. Therefore, more qualitative studies are required to obtain more detailed information on the underlying reasons for retransitioning from both patients and physicians to improve the introduction of biosimilars in clinical care.

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Supplementary files

S1: Overview of included biologicals and JAK inhibitors for switching
Abatacept, anakinra, baricitinib, canakinumab, ixekizumab, rituximab, sarilumab, secukinumab, tofacitinib, tocilizumab and ustekinumab

S2: Overview of included immunomodulators and corticosteroids
Immunomodulators: sulfasalazine, mycophenolic acid, leflunomide, ciclosporin, azathioprine, methotrexate and hydroxychloroquine. Treatment with corticosteroids was defined as the use of at least 10 mg of prednisolone, to distinguish this from low-dose maintenance corticosteroid treatment, or a local injection with methylprednisolone or triamcinolone in the 60-day period before the event.[13]

CHAPTER 6

Patients' perspectives on transitioning from a TNFα inhibitor originator to a biosimilar and retransitioning to the originator

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Preliminary results

Abstract

Background

Many patients with rheumatic diseases have transitioned from TNFα inhibitor originator to a biosimilar alternative for cost-containment reasons. Some of these patients retransition (i.e., restarted originator treatment). Little is known about these patients' in-depth perspectives on transitioning and retransitioning to biosimilar drugs. Better knowledge on patients' perspectives could improve the introduction and acceptance of biosimilars.

Aim

The aim of this study is to analyse patients' perspectives on transitioning to a TNFα inhibitor biosimilar and retransitioning to the corresponding originator.

Methods

We recruited Dutch patients with rheumatic diseases who transitioned from etanercept or adalimumab originator to a corresponding biosimilar and then retransitioned to the originator between 2016 and 2022. We conducted in-depth, semi-structured interviews focussing on patients' opinions on and experiences with transitioning to a biosimilar, the biosimilar product and retransitioning. The interviews were transcribed and analysed in NVivo using thematic analysis.

Results

Eight patients participated in this study and were included in this interim analysis. Perceptions were grouped into eight themes, centered around three actors: The healthcare institute (HCI), the healthcare professional and the patient. The HCI developed a transitioning policy, and patients expressed that transitioning negatively affected their relationship with the HCI. Patients reported trust in their HCP. They found that the HCP had little say in the decision of transitioning to the biosimilar, but was responsible for decisions on retransitioning. Also, patients reported on various needs regarding information and counselling on biosimilars from their HCP. Patients reported a lack of autonomy in decision-making. All patients reported to have negative experiences with the biosimilar, resulting in the wish to retransition. However, the reported treatment effect of the originator after retransitioning varied. The impact of transitioning varied; for some, it had a severe negative impact on their lives, whereas others described it only as inconvenient.

Conclusions

Patients reported to lack autonomy in decisions on transitioning. They blamed this on the HCI which they considered prioritising finances over patients' health.

Patients considered their relationship with their rheumatologists to be strong. They acknowledged that their complaints during biosimilar treatment were adequately addressed by retransitioning them to their originator. To improve the implementation of biosimilars in clinical practice, policy makers could consider implementing a financial gain sharing model, increase trust in biosimilars and generic medicines in general, and increase patient involvement in decisions on transitioning to a biosimilar.

Introduction

Tumour Necrosis Factor (TNF)α inhibitors have revolutionised the treatment of, among others, rheumatoid arthritis for patients insufficiently responding to conventional disease-modifying antirheumatic medicines.[1] Eighteen biosimilars for TNFα inhibitors have been introduced in clinical rheumatology care[2] and more are expected in the future. In line with what is stated in most clinical guidelines, the European Medicines Agency (EMA), consider biosimilars as clinically equivalent to originators in terms of efficacy, safety and quality. These can, therefore, be considered interchangeable, meaning that patients can transition from originator to biosimilar without expecting a negative impact on efficacy and/ or safety.[3] This policy is based on the totality of the evidence, including data on the product quality attributes and findings from RCTs and observational studies, which showed no relevant differences in efficacy and safety among patients who transitioned to the biosimilar compared to patients who remained on the originator TNFα inhibitor.[4,5] Today, transitioning patients to a biosimilar is increasingly being implemented in clinical practice.[6] As biosimilars are often considerably cheaper than their originators, transitioning patients to a biosimilar is considered to contribute to health cost containment.

The perspectives of patients themselves on transitioning from an originator to a biosimilar have been studied previously. Studies conducted in Belgium and France showed that the majority of patients (55%-68%) would be willing to transition to a biosimilar if prescribed by their physician, despite having concerns regarding the quality, efficacy and safety of the biosimilar and the recurrence of disease flares.[7,8] Among the 44 patients who had already experienced the transition to a biosimilar, 66% felt that they were insufficiently informed about biosimilars and that being adequately informed was a prerequisite for accepting the transition and being compliant with the biosimilar.[8]

The hesitancy of some patients to transition to a biosimilar might contribute, to some extent, to patients retransitioning (i.e., discontinuing biosimilar and restarting the originator treatment) at a later stage. Research from our group showed that 14% of patients who transitioned from etanercept originator to the corresponding biosimilar subsequently retransitioned. Most patients who retransitioned reported that they experienced loss of effect and/or adverse events during biosimilar treatment,[9] which might indicate that retransitioning is more related to the patient (and the disease) than to the biosimilar product.

Since the biosimilar is considered similar to the originator in terms of quality, efficacy and safety, it is unlikely that loss of effect or adverse events during treatment with

the biosimilar will be solved when retransitioning the patient to the originator. In clinical treatment guidelines, such as the guideline on management of rheumatoid arthritis from the European League Against Rheumatism (EULAR), retransitioning is not recommended.[6] However, it has been reported that patients might perceive positive treatment outcomes from retransitioning, especially in patients who might have experienced a nocebo effect.[10] A nocebo effect is defined as an unexplained, unfavourable therapeutic effect subsequent to a non-medical switch from originator to biosimilar accompanied by the regaining of beneficial effects after reinitiating the originator.[11] Other factors that can be considered as reasons for retransitioning include preference for the originator when it concerns excipients and the type of auto-injection devices or injection volume used.[12,13]

Only a few studies have reported on patients' reasons for retransitioning. However, these studies do not provide enough in-depth detail to allow for a sufficient understanding of patients' motivations for retransitioning. The experiences and perspectives towards biosimilars of patients who retransitioned from a biosimilar to an originator could provide valuable insights for improving the introduction and acceptance of biosimilars in clinical practice.

The aim of this study is to study patients' perspectives on transitioning from a TNFα inhibitor originator to a corresponding biosimilar and retransitioning to the originator in the Netherlands. This was studied among patients with a rheumatic disease who transitioned from a subcutaneous TNFα inhibitor originator to a biosimilar and subsequently retransitioned to the originator.

Method

Study design

This was a qualitative study using semi-structured interviews with patients with a rheumatic disease. Interviews were conducted between May 2022 and November 2022. A semi-structured interview style was chosen to ensure that all interviews were conducted in a comparable way while also allowing for in-depth identification of perspectives through a thorough discussion.

This study was conducted in line with the Consolidated Criteria for Reporting Qualitative Research (COREQ) guidelines.[14]

Setting and study population

In the Netherlands, TNFα inhibitors can be dispensed in two different settings depending on the type. There are TNFα inhibitors that are dispensed by the outpatient

hospital pharmacy and subcutaneously (s.c.) administered by the patient themselves in the home setting. But also TNFα inhibitors that are prepared and dispensed by the in-hospital pharmacy and intravenously (i.v.) administered by a nurse in the hospital. This study was limited to patients treated with s.c. administered TNFα inhibitors in the home setting (i.e., etanercept and adalimumab).

Adult patients (18 years and older) who were treated with an s.c. administered TNFα inhibitor for a rheumatic disease and who transitioned from TNFα inhibitor originator to a corresponding biosimilar and subsequently retransitioned to the originator were eligible for participation in this study. Retransitioning was defined as discontinuing a biosimilar and restarting the corresponding originator between 2016 and 2022. Enbrel (etanercept) and Humira (adalimumab) were included as originators, Benepali and Erelzi were included as biosimilars for Enbrel, and Amgevita, Hyrimoz, Idacio and Imraldi were included as biosimilars for Humira.

Two strategies were used for patient recruitment, namely, recruitment through patient organisations and recruitment through one hospital. Four patient organisations (Patient Partners, Reuma Nederland, Reumapatiëntenvereniging Utrecht, Reuma Patiënten Vereniging Arnhem)[15–18] placed a recruitment text on their websites and/or in their newsletters. In addition, they sent out a message (S1 in the Supplementary Files) to their members with a description of the study and a call for participation. The recruitment text was also published in a newsletter and a magazine for rheumatology patients (Reuma Magazine). Patients who were interested in participating were asked to contact the researchers directly.

In addition, patients eligible for participation were selected from the outpatient pharmacy of the Spaarne Gasthuis in collaboration with the Department of Rheumatology of the Spaarne Gasthuis. The patients received a letter (S1 in the Supplementary Files, tailored to the type of TNFα inhibitor used by the patient) asking them to contact the researcher in case they wanted to participate.

Prior to the interview, participants interested in participating received a participant information letter, including a brief description of the topics that were to be discussed (S2 in the Supplementary Files, tailored to the type of TNFα inhibitor used by the patient). In the patient information letter, a link to the digital informed consent form (S3 in the Supplementary Files) was included.

The aim was to include at least 10 – 12 patients in the study or until data saturation was reached. Data saturation was defined as the absence of new themes on transitioning or retransitioning in an interview.

Data collection

Data was collected in a single one-to-one interview, held face-to-face or by (video) calls. All interviews were conducted by a researcher (RWM, a female PhD candidate who has received training in qualitative research) with no relation to the participants.

A semi-structured interview guide was created to explore patients' perspectives on biosimilar transitioning and retransitioning. In order to capture relevant perspectives on transitioning and retransitioning, the interview was subdivided into topics derived from previous studies on patients' perspectives on biosimilars[7,19,20] and from discussions with experts involved in treating and transitioning patients to biosimilars ([hospital] pharmacists). Topics included:

- Experience with the biosimilar
- Experience with and perception of transitioning to a biosimilar
- Experience with and perception of retransitioning from the biosimilar to the originator

The first draft of the interview guide was reviewed by two experts on qualitative research, piloted with a professional patient and adjusted according to the outcomes of the review and the pilot. The final interview guide is listed in S4 in the Supplementary Files.

The following demographic information was collected from all participants: year of birth, gender, indication for which the TNFα inhibitor is used, year of diagnosis (duration of disease), brand names of the originator and biosimilar TNFα inhibitors used, and names of other medication used for treatment of the rheumatoid disease.

Data analysis

All interviews were recorded using a voice recorder. The recorded audio files were transcribed verbatim manually or by using Amberscript with manual checking. Transcripts were coded using NVivo version 20 (QSR International).

Thematic analysis was used to analyse the data. Interviews were first inductively analysed without preconceived categories, thus allowing the categories to arise from the codes by searching for recurrent themes. The six stages of thematic analysis were

applied: familiarisation with the data, generation of initial codes, searching for themes, reviewing themes, defining and naming themes and producing the report.[21]

The coded transcripts of the first two interviews were used to create a first set of main categories and subcategories by clustering the codes (the codebook). These were discussed by two researchers (RWM and HG). After coding all the interviews, the main categories and subcategories were discussed and adjusted by RWM and HG. The transcripts of the interviews were coded by RWM.

Ethical approval

The Institutional Review Board of the Division of Pharmacoepidemiology and Clinical Pharmacology, Utrecht University (reference number UPF2205) and the Institutional Review Board of the Spaarne Gasthuis (reference number 2022.0028) approved the protocol of this study. All patients gave informed consent prior to participation.

Results

A total of eight patients participated in this study and were included in this interim analysis. Four patients were interviewed via videocalls, and four were interviewed face-to-face, of which three took place in their homes and one at the hospital. The median duration of the interviews was 37 minutes (range of 25 – 52 minutes). Patients had a median age of 60.5 years, and 75% were female. Six patients (75%) were treated with etanercept and two (25%) with adalimumab (Table 1). As patients were recruited via the websites and newsletters of several patient organisations and or through a healthcare institute, the actual number of approached patients and the response rate could not be assessed.

Table 1: Patients' characteristics

	n=8
Female gender, n (%)	6 (75.0%)
Age, median (interquartile range) years	60.5 (53.3-71.8)
Indication	
Rheumatoid Arthritis	3 (37.5%)
Axial Spondylarthritis	3 (37.5%)
Arthritis Psoriatica	2 (25.0%)
Course of treatment	
Etanercept	6 (75.0%)
Enbrel – Benepali - Enbrel	4
Enbrel – Benepali – Erelzi – Enbrel	2
Adalimumab	2 (25.0%)
Humira – Imraldi – Humira	1
Humira – Imraldi – Amgevita – Humira	1

Three patients were treated with two biosimilars. Two patients treated with etanercept transitioned from the originator to the first biosimilar prior to transitioning and several years later cross-transitioned to the second etanercept biosimilar due to cost-containment reasons. One patient treated with adalimumab was transitioned from the originator to the first biosimilar due to cost-containment reasons. However, the patient was cross-transitioned to the second biosimilar due to unwanted response to the first biosimilar, which was in line with the policy of the treating healthcare institute.

Eight themes emerged from the interviews that were related to three different actors within the healthcare chain, including the healthcare institute (HCI), the healthcare professional (HCP) and the patient themselves (Figure 1). These are discussed below and illustrated by anonymous patient quotations.

The healthcare institute

The patients included in this study were treated at a tertiary hospital specialising in rheumatology and a general secondary, large teaching hospital.

Institutional policy

All patients reported that the decision to transition from their originator to the biosimilar was based on the policy of their treating HCI. The biosimilar transitioning policy was considered to be financially driven due to the lower cost of biosimilars. Patients' opinions on this policy differed. Some agreed and acknowledged the need for cost containment in healthcare, whereas others felt that medical decisions should not be financially driven.

> *"There was probably a financial aspect involved [with transitioning], and I believe that this aspect does not belong in the medical community. I understand prices are currently astronomically high, thus we have to seek ways to make it more affordable." (P101)*

Moreover, some patients doubted the financial gains from transitioning to a biosimilar. Some had compared pricing based on publicly accessible information on the internet and found that the price of the biosimilar was identical to that of the originator. As a result, they were not convinced of the financial gains. They also considered that other healthcare costs increased after they transitioned, for example, due to increased use of emergency care, which might outweigh the financial benefits of biosimilars. In addition, one patient was frustrated about transition to a biosimilar for

cost-containment while other expensive medicines that were no longer needed had to be disposed of, which felt like wasting money.

> *"I had three syringes of an interleukin-17 inhibitor left, and they could be thrown away because they [the rheumatology ward, red] don't use returned medicines. Why are all these medicines thrown away? There is so much opportunity for cost savings, which was the reason I stopped being treated with the originator [TNFα inhibitor, red]. Maybe they did not throw away those medicines, I could still be treated with the originator." (P202)*

Patient – HCI relationship

For some patients, the HCIs' financially driven decision to transition them to the biosimilar affected their relationship with the HCI, as they felt that money was more important than their personal wellbeing.

> *"Money was more important than the patient." (P001)*

Furthermore, two patients were cross-transitioned from the first etanercept biosimilar to the second, but retransitioned to the etanercept originator and not to the first biosimilar. The policy of the first biosimilar not being available for financial reasons made these patients question transparency on financial matters.

> *"What I don't understand is that I'm being told I have to transition from the originator to the biosimilar for financial reasons (...) I don't understand why now [after an unwanted response to the second biosimilar, red] the originator has been prescribed, while the first biosimilar was cheaper (...) Or has the pharmaceutical company made a special offer to the rheumatologist that was more favourable?" (P102)*

However, one patient pointed out another aspect of the relationship between the patient and the HCI, namely, their duty of care.

> *"The hospital has the obligation to offer you a decent medicine. Thus, it [originator, red] was available again." (P201)*

The healthcare professional

Patients reported that the rheumatologist was the healthcare professional (HCP) responsible for their rheumatologic treatment and the main HCP involved in transitioning them from originator to biosimilar. Patients only scarcely mentioned

other HCPs possibly involved in transitioning from originator to biosimilars, such as rheumatology nurses or pharmacists.

The patient-rheumatologist relationship

Most patients were positive about their relationship with their treating rheumatologist. They had trust in their rheumatologist, felt supported by them and were confident that the rheumatologist was acting in their best interest. When the rheumatologist decided to retransition patients to the originator, patients felt that the rheumatologist addressed their complaints well and tailored treatment to their needs. One patient stated that their positive relationship with their rheumatologist was dependent on her agreement in decision-making. If the rheumatologist had not cooperated with the patient's wish to retransition, this would have negatively impacted the relationship. Some patients changed rheumatologists over the years due to practical reasons. However, switching to another rheumatologist in case of disagreement about treatment (such as transitioning to the biosimilar) was only mentioned as a hypothetical option.

> *"I visit the doctor because I hope she can solve my complaints. So, you must have some confidence in them. Otherwise, it does not work. I am confident that the rheumatologist, in this case, acts in your best interest." (P201)*

Patients expressed that they were dependent on the rheumatologist for treating their disease and that they had to maintain a good relationship. Patients also mentioned that they felt insufficiently educated to make treatment decisions, such as transitioning to a biosimilar, and as a result, depended on the knowledge of the rheumatologist.

Influence of the HCP

Patients believed that it was not within the remit of the rheumatologist to decide if patients should be transitioned to the biosimilar but that they were bound by the institutional policies. As a result, patients did not think the rheumatologist could have prevented the transition and was therefore not to blame when the patients were transitioned to the biosimilar.

> *"My rheumatologist was more or less, according to my perspective, forced to prescribe her patients a biosimilar." (P101)*

Figure 1: Graphical representation of the three actors (grey) and eight themes (white) identified from the interviews.

The absence of influence of the rheumatologist on transitioning contrasts with how patients perceived the role of the rheumatologist when they were retransitioned. For that decision, the rheumatologist was considered to have the autonomy to make a clinically based medical treatment change. Some patients felt positive about this decision, as the rheumatologist attempted to address their unwanted response to the biosimilar and their wish to return to their "normal" treatment. However, the retransition process was confusing or even frustrating for some patients.

> *"So when the biosimilar did not give the proper response, the doctor was able to treat me with the originator and said: 'I will make an exemption for you'. But then I thought, why didn't you keep treating me with the originator? Then I would not have to go through all of this." (P202)*

Information and counselling

Patients reported various experiences with receiving information and counselling on transitioning to the biosimilar. Most patients recalled receiving verbal information from their rheumatologist in advance regarding the transition from originator TNFα inhibitor to the biosimilar, but not the exact wording. Some patients also recalled receiving a letter from the pharmacy informing them of the upcoming transition to the biosimilar. One patient recalled finding the written information impersonal, but this was not mentioned by other patients. A few patients reported having consulted other sources for information about biosimilars, such as the website of their patient organisation.

When the biosimilar was prescribed for the first time, some patients received instructions on how to use the new auto-injection device, while others did not recall any special attention when they started using the biosimilar.

> *"They tell you that from now on, you will get a different injection with a different name and a different package. I received no instructions on how to use it. You are sent home with a new package, and you just have to figure it out yourself." (P104)*

Some patients had little need for medication counselling as they found that they already knew how to inject themselves and that injecting the biosimilar was more or less similar to injecting the originator or felt that they were responsible for reading the injection manual. However, a few patients described more injection discomfort with the biosimilar due to differences in the injection device, such as increased injection speed. Medication counselling during retransitioning was not needed, as they had used the originator before. Medication counselling at the start of their originator TNFα

inhibitor was considered far more important, as using a TNFα inhibitor impacts daily health management, for example, when patients have an infection.

Most patients had no extra routine visits scheduled after being transitioned. However, as they all developed complaints after transitioning, they had more frequent contact with their rheumatologist after starting treatment with the biosimilar. Patients valued that they could quickly and easily get an appointment with their rheumatologist and that the rheumatologist was easily accessible for questions. One patient expressed that she missed scheduled follow-up right after transitioning from the originator to the biosimilar and that this follow-up would have helped her feel more guided in transitioning, and that her disease flare would have been noticed earlier.

> *"If they [complaints after transitioning, red.] were better monitored, changes would be noticed. But that didn't happen in my opinion [...] If they were better monitored, my ankle, for example, would not have been damaged." (P001)*

The patient

Patients in this study had various perspectives on their experience of transitioning from originator to biosimilar and retransitioning to the biosimilar. All patients felt that transitioning (and retransitioning) affected their sense of autonomy, their treatment and themselves.

Autonomy

Patients expressed that they felt little autonomy in the choice to transition from originator to biosimilar and that this was imposed on them by the HCI. This contributed to the negative relationship with the HCI described earlier. Some patients stated that if they disagreed with a treatment change, their only option was to change to another HCI. However, this was only stated as a hypothetical option.

> *"You barely have anything to say about that [transtioning to the biosimilar, red]. So yes, you have to. Well, nothing is forced, but of course, you will agree because if you don't, then what will be your next step? Another hospital? In the hope you will get the originator there? That will take, I don't know how many weeks!" (P201)*

Treatment

Patients' beliefs regarding the efficacy and safety of the biosimilar and their individual response to the biosimilar varied. Some patients had a high level of trust in biosimilars, which was built on the positive experiences of other patients, the information provided by the rheumatologist and/or research on biosimilars. These patients expected no

difference in treatment with their originator and the biosimilar. Patients' opinions on transitioning to biosimilars were aligned with their views on switching from brand names to generic medicines in general. If they accepted generic switching, they were also open to transitioning to biosimilars. Some patients even hoped that the biosimilar was better than the originator.

> *"Why would it have no effect or less effect? The active substance is the same, so that is present. I do not care about the brand name, as long as it works." (P201)*

> *"I was a little sceptical regarding the effectiveness [of the biosimilar, red]. Is this as good? Does it perform similarly to the originator, and will it not cause unwanted effects? Those are the two questions I have. And then you start injecting and testing. You are aware of everything that happens, in terms of pain or inflammation or whatever. But, that does not necessarily have to be related to the biosimilar." (P104)*

Patients experienced various negative clinical effects when they started using the biosimilar. This included a lack of effectiveness resulting in disease-related complaints such as pain, loss of strength, inflammation and fatigue, or adverse events such as psoriasis and blood count abnormalities. These disease flare-ups and/or adverse events made them want to retransition to the originator. One patient reported a more positive reaction to the biosimilar than to the originator, experiencing fewer adverse events and fewer injection site reactions. However, when this patient cross-transitioned to a second etanercept biosimilar treatment, the effect was lost, and the patient wished to retransition. Some patients experienced injection discomfort, but for them, this was not unacceptable and not their reason for retransitioning.

Most patients felt relieved when they heard that they would be retransitioned to the originator. Prior to retransitioning, patients expected that the originator would yield the same clinical effect as they experienced before the biosimilar was introduced. However, some patients were also concerned that effects would not be regained with the originator, for example, due to the development of drug antibodies.

After retransitioning, most patients reported to regain treatment effect to the same level as prior to transitioning or even better effects. However, some did not recover from the complaints with the biosimilar; one patient remained treated with the originator despite adverse events and one patient switched to other biologicals, but without regaining full treatment effect.

Impact

For some patients, loss of control over the disease after transitioning had a severe impact on their daily lives. Some patients reported to slowly lose control over the disease while not immediately linking it to the use of the biosimilar. They instead blamed themselves for doing too many physical activities and limited themselves in daily physical activities to spare energy.

> *"They think I did too much of this or I did too much of that. So, you are searching for the cause within yourself. You have overexerted yourself. I started doing less, as I had less energy, a lot of pain and disabilities." (P001)*

Loss of control over the disease also had an emotional impact on patients. Patients expressed disappointment at not experiencing the expected treatment effect from the biosimilar. Moreover, one patient felt angry towards the HCI for the impact that the transitioning policy had on her life, which was severely negatively affected by losing disease control after transitioning.

As stated before, most patients reported regaining treatment effects (or not experiencing adverse effects anymore) after retransitioning. They reported a positive effect on their general wellbeing and increased ability to be active. However, one patient's blood count abnormalities did not disappear after retransitioning, which caused him to remain concerned about his health in general and about the effects on his upcoming surgery.

All patients connected the complaints after transitioning directly with the biosimilar, but their perceptions of the effect of these complaints on their lives varied. Some patients remained upset about the experience, while others looked back on the transition and retransition period as merely inconvenient. Patients who regained effect after retransitioning were less concerned about the period of transitioning to the biosimilar and retransitioning to the originator compared with patients who continued to experience unwanted effects.

Some patients pointed out that having disease flare-ups also had a financial impact on society. Aside from the direct increased healthcare costs described earlier, other disease-related costs, such as orthopaedic shoes, also increased. Moreover, one patient stated that she lost the ability to work, which is a financial burden for society.

> *"In the end, transitioning to the biosimilar was more expensive for the healthcare insurer due to spendings on orthopaedic shoes and an upcoming surgery." (P001)*

Discussion

This qualitative study focussed on patients' perspectives on transitioning from a TNFα inhibitor originator to a biosimilar and retransitioning to the originator. Patient perspectives were centred around the role of the HCI, the role of the HCP(s) and their own experiences as patients in transitioning to a biosimilar. This study adds to our understanding of patients' experiences with biosimilars in patients who retransitioned after being transitioned to a biosimilar.

Trust in biosimilars

We found ambiguity in the trust patients had in biosimilars at their introduction. Trust was gained through reassurance from or general trust in their rheumatologist, whereas other patients were less trusting. These various levels of trust were aligned with findings from a Canadian qualitative study in which some patients anticipated lesser effects or more adverse events after transitioning to a biosimilar, whereas other patients expected no impact on their treatment.[22]

The patients in this study who had limited trust in the biosimilar were mainly concerned about the effect of the biosimilar on their individual disease and wellbeing. However, they did not explicitly express concerns with the quality of biosimilars in general. This finding is in contrast to what has been reported in previous studies from Belgium and France on trust in the efficacy and safety of biosimilars in general, as well as beliefs that biosimilars are of inferior quality compared with their originators.[7,8] However, these studies mainly included patients that had never been treated with biosimilars and/or had not heard of biosimilars, whereas the patients in our study all were familiar with and had experiences with biosimilars, which might explain the differences in general beliefs.

Some patients in this study had trust in biosimilars and expected similar treatment effects as with the originator. However, after transitioning, these patients developed complaints that they attributed to the biosimilar. In previous studies, increasing patients' trust in biosimilars was presented as a solution for preventing unexplained, unwanted effects from the biosimilar (sometimes classified as the nocebo effect).[23,24] The patients in our study contradict the idea that building trust in biosimilars completely prevents unwanted effects resulting in retransitioning. Thus, while increasing trust may contribute to a reduction in the number of patients retransitioning, it cannot be fully prevented. Thus, providers should accept that some patients will retransition or switch to another active substance.

Similarities with perspectives on generic medicines

The patients who expressed negative opinions on biosimilars also expressed similar opinions on brand to generic substitution with small-molecule medicines. This was also reported in an Australian study that found an association between refusing generic medicines and refusing biosimilars.[25] The introduction of biosimilars seems to have some similarities with the introduction of generic medicines several decades ago. Studies from that time on patients' perspectives on generic medicines reported similar concerns about the generic medicines being as safe and effective as the branded medicines.[26–28]

However, experience with generic medicine use in clinical practice has resulted in increased trust over the years[29] and substituting branded medicines has increasingly become common practice in Europe.[30] Biosimilars have been on the market for 17 years,[2] which is a relatively short period of time compared to generic medicines. It can be expected that the discussions on transitioning patients from originator to biosimilars will follow the same patterns as with generics; thus, transitioning to biosimilars will become more and more accepted over time. This is partly visible through declining numbers of patients retransitioning during the past years,[31] indicating increasing acceptance of biosimilars. However, as with generic medicines, expecting full acceptance of biosimilars and no patients retransitioning over time might be too optimistic.

Lack of autonomy in transitioning

Patients experienced the decision to transition to a biosimilar as dictated by the HCI, and most felt they lacked autonomy and involvement in this decision. This aligns with previous findings reporting that patients want to be involved in the decision to transition from an originator to a biosimilar[19] or from brand name to generic medicines.[26,27] Similar to what some patients in our study indicated, patients in a Canadian study expressed similar frustrations towards decision-makers.[22] Other have reported on patients' willingness to transition to a biosimilar if initiated by their rheumatologist,[7] however, this opinion was not shared by all patients in our study. Moreover, these patients strongly expressed their need for information on biosimilars and training with the new injection device as important prerequisites for transitioning, whereas this was less emphasised by the patients in our study.

Patients felt a lack of autonomy and considered that the HCI prioritised financial matters over their health. Some patients stated that cost containment is not sufficient justification for treatment change, which has also been reported in studies on generic substitution[34] as well as on biosimilar transitioning.[32] By contrast, patients in another

qualitative study accepted a financially driven transition solely benefitting the general healthcare system.[33] However, these patients were sampled from a voluntary transition trial; thus, transition was not mandatory for them.

In the Dutch healthcare system, decisions lowering healthcare expenses result in cost-containment for HCIs but not (directly) for patients. As such, there are no obvious incentives for patients to transition to a biosimilar. For patients, it was clear that their originator treatment was expensive and that the biosimilar was cheaper. However, they expressed no details on the benefits and possibilities of financial savings. This highlights the importance of accounting for the context of the healthcare system in which the transition is made. In some healthcare systems, such as the Canadian healthcare system, patients were motivated to transition to a biosimilar since it would reduce their out-of-pocket payments.[22] In other healthcare systems, such as in Denmark, biosimilars are implemented at the national level, with very limited options for HCPs to prescribe the originator.[35]

As suggested in earlier studies, biosimilar acceptance could be improved with transparency on the amount and allocation of these savings, for example, on hospital facilities or staff.[19,36] Moreover, specifically allocating biosimilar savings to the patients (i.e. gainsharing[37]), for example, by appointing an extra rheumatology nurse, provides patients with a tangible incentive for transitioning that might also contribute to increased biosimilar acceptance.

Role of and relationship with the HCI and the rheumatologist

Patients in this study perceived the HCI and the rheumatologist as two separate actors, which became clear in their perspective of responsibilities and decision-making. The HCI was responsible for the policy of transitioning them from the originator TNFα inhibitor to the biosimilar, and the rheumatologist had to comply with this policy. However, when the patients developed complaints, the rheumatologist was considered in charge of clinical decision-making, and role of the HCI in retransitioning was not explicitly mentioned.

These different roles of the HCI and the rheumatologist affected the relationship patients had with those actors. Patients expressed positive feelings towards their rheumatologist in terms of trust and believed that they acted in the patients' best interests. By contrast, patients felt that the HCI was not acting in their best interest but focussed more on financial interests, as stated earlier. Patients included from the Spaarne Gasthuis should have received information regarding the obligation of the HCI to transition their patients to a biosimilar. This was due to the reduced reimbursement

for TNFα inhibitors which was insufficient to cover the price of the originator. This was not mentioned by the patients in this study. The distinction between the HCI and the rheumatologist was striking, as patients did not mention the involvement of the rheumatologist in the decision of biosimilar implementation in the clinic. However, the lack of involvement of rheumatologists in decisions on transitioning was also mentioned by HCPs in a study on HCPs' perceptions of biosimilars.[38]

Retransitioning to originator treatment

Most patients were satisfied with their originator treatment prior to transitioning, and considered their treatment as important for them in terms of functioning and wellbeing. All experienced unwanted effects during biosimilar treatment, and due to these unwanted effects, they wished to retransition. They perceived retransitioning as going "back to normal". Therefore, all patients were pleased when the rheumatologist decided to retransition them. This illustrates the complicated position of biosimilars and a deep wish for the originator treatment in some patients. The option of retransitioning as a condition for biosimilar transitioning was of major importance to patients. This condition has also been confirmed in other studies from Denmark, Canada and the United Kingdom.[19,22,32] Thus, to improve the acceptance of biosimilars, offering patients the option of retransitioning might be considered in the biosimilar implementation strategy.

Cross-transitioning

In recent years, multiple biosimilars corresponding to the same originator have become available on the European market.[2] Therefore, patients who transitioned from originator TNFα inhibitor to a biosimilar might cross-transition to another biosimilar for cost-containment reasons. Two patients treated with etanercept cross-transitioned, and reported a positive experience with their first biosimilar but not their second. Some studies have found cross-transitioning to be safe and effective.[39] However, others report that patients had reservations about cross-transitioning, citing a lack of experience and evidence, the potential for confusion, and limited cost savings.[36] These concerns have also been voiced for (multiple) generic substitutions.[40] The two patients in this study did not disapprove of cross-transitioning itself, but of the perceived negative effects of the treatment with the second biosimilar. As only two patients experienced this transition, more research is needed regarding patients' perceptions and needs in cross-transitioning. Notably, one patient cross-transitioned from the first adalimumab biosimilar to the second biosimilar prior to retransitioning. This was due to the specific hospital policy for adalimumab that patients who were not satisfied with the first adalimumab biosimilar should try the second biosimilar prior to retransitioning.

Implications

When choosing a strategy for implementing biosimilars in clinical practice, clinicians should balance voluntary transitions with HCI mandates (which are obliged by payers), actively providing the option to retransition in cases of patient dissatisfaction with the biosimilar. For future biosimilar implementation strategies, a number of factors can be considered. Firstly, one of the options could be to implement a gainsharing model (i.e., the savings from transitioning to a biosimilar are directly or partially allocated to patient care, such as appointing an extra nurse). Previous research from our group showed that in studies where gainsharing was applied, a lower incidence of patients retransitioning than was reported by studies that did not.[31] A gainsharing model provides an incentive for patients to transition but also increases financial transparency, which some patients in this study lacked.

Secondly, efforts could be made to increase trust in biosimilars and generic medicines in general. This involves (continued) efforts by HCPs, such as rheumatologists and pharmacists, to improve patients' understanding of generics or, for example, regulation of the appearance of generics to decrease patients' confusion. And lastly, more patient involvement in decision making on transitioning could increase perceived autonomy and improve biosimilar acceptance.

Most patients expressed a high level of trust in and satisfaction with their treating rheumatologist. This positive finding is valuable for future biosimilar implementations. Patients did not mention the involvement of the pharmacy in transitioning, or only in a logistical sense. As pharmacists are considered to have the highest level of knowledge on biosimilars[41], by being more involved, they could help to improve the implementation of biosimilars. For example, as some patients experienced little medication counselling and little follow-up, pharmacists could fill this space.

Generalizability

This study focussed on patients treated with s.c. TNFα inhibitors. Transitioning from an s.c. TNFα inhibitor originator to a biosimilar could be accompanied by a change in device, which makes transitioning a very explicit change for patients. By contrast, for patients receiving i.v. administered TNFα inhibitors (i.e. infliximab), transitioning is not always noticeable, for example, as the infusion bag could be labelled with solely 'infliximab', without the brand name. Therefore, we believe that the introduction of an s.c. TNFα inhibitor in clinical practice could differ considerably from the introduction of a biosimilar of an i.v. administered originator. Our findings are therefore limitedly generalisable to the introduction of i.v. administered biosimilars. As the perspectives of our patients are not specific for TNFα inhibitors, we believe that our results are

generalisable to the introduction of biosimilars for other biologicals purposed for long-term use as well.

Strengths and limitations

This study was, to our knowledge, the first study that studied patients' perceptions of biosimilars in a population that retransitioned from biosimilar treatment to the originator. The topic of retransitioning is not well-studied yet; thus, our study adds knowledge from a new perspective. As retransitioned patients generally retransition due to dissatisfaction with the biosimilar, this population is worth studying in order to improve the introduction of biosimilars in clinical care.

The present study also has some limitations. First, this interim analysis included only eight patients. As data saturation was not reached, we might have missed important themes. In order to draw final conclusions, more patients will be included in this ongoing study. Second, as patients were not randomly selected for this study, selection bias might have occurred, and the opinions expressed by the included patients might not represent the opinions of all retransitioned patients. Third, most (n=7, 87.5%) patients were treated at the same hospital and same department. Perceptions from the patients treated at another HCI differed considerably from the patients from the Spaarne Gasthuis, for example, regarding the biosimilar implementation strategy, indicating that the generalizability of our study results might be limited. Moreover, as countries differ in their policies and regulations on biosimilars, our results might not be generalisable to other healthcare systems. Finally, as the introduction of the etanercept biosimilar took place in 2016 and that of adalimumab in 2018, some patients were unable to recall the details of the introduction. For example, all patients from the Spaarne Gasthuis received a letter from the rheumatology department and the pharmacy and were invited for an extra appointment at the outpatient clinic with the rheumatologist and/ or the rheumatology nurse to inform them of the upcoming transition to the biosimilar. However, the letter and the extra appointment were scarcely mentioned by patients. This indicates potential recall bias.

Conclusions

Patients who retransition from a biosimilar to originator report amongst the positive perceptions a strong patient relationship with their rheumatologist and acknowledgement of feeling heard when they expressed complaints during biosimilar treatment. However, a number of negative perceptions were voiced including lack of autonomy in the decision to transition which was considered mainly driven by cost containment considerations of health care institutions. To improve the implementation of biosimilars in clinical care, policy makers could consider implementing a financial

gain sharing model, increase trust in biosimilars and generic medicines in general, and increase patient involvement in decisions on transitioning to a biosimilar.

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Supplementary Files

S1: Example letter to patients

Patients treated with adalimumab received a letter in which etanercept and the brand names were replaced with adalimumab and the corresponding brand names. For the patients recruited via patient organisations a neutral letter containing no substance or brand names was composed.

Experiences with transitioning from a biosimilar to an original biological (Ervaringen met het wisselen van een Biosimilar nAaR een oRigineel bIologisch mEdicijn [BARRIE studie])

Researchers from Spaarne Gasthuis, the Foundation Pharmacy of Haarlem Hospitals (SAHZ), and Utrecht University are looking for people who have transitioned from etanercept under the brand name Enbrel® to etanercept under the brand name Benepali®, and then retransitioned to Enbrel®. The researchers want to understand the reasons people had for retransitioning from Benepali® to Enbrel®. They also want to know what people think about transitioning between different brand names of biologicals in general.

We would like to learn more about experiences regarding transitioning from Enbrel to Benepali and what your opinion is regarding transitioning in general. We will use this information to improve the transitioning process between different brand names in clinical practice. Everything you say will be treated confidentially and will not be shared with your doctor or the pharmacy personnel. Participating in this research will not affect your treatment. This research project has been approved by the Local Feasibility Advice Committee (ACLU) of Spaarne Gasthuis and the Institutional Review Board (IRB) of Utrecht University.

<u>What does your participation entail?</u>
Participants in the study will have a conversation with the researcher. This will be a one-time conversation lasting approximately 45-60 minutes. The researcher will ask you various questions about your opinions and experiences regarding retransitioning from Benepali® to Enbrel® and your opinions and experiences with Benepali®. Prior to the conversation, you will receive more information to help you prepare. The conversation can take place via (video) call or at a location of your preference. You can choose how and where you would like to have the conversation.

Want to know more?

If you would like more information and/or are interested in participating in this research, please feel free to contact Rosanne Meijboom on 06-xxxxxxxx or send an email to rmeijboom@spaarnegasthuis.nl.

S2: Example of a participant information letter

Patients treated with adalimumab received a letter in which etanercept and the brand names were replaced with adalimumab and the corresponding brand names. For the patients recruited via patient organisations a neutral letter containing no substance or brand names was composed.

Experiences with transitioning from a biosimilar to an original biological (Ervaringen met het wisselen van een Biosimilar nAaR een oRigineel bIologisch mEdicijn [BARRIE studie])

Information for participants

Dear Sir/ Madam,

With this information letter, we would like to ask if you would like to participate in a scientific study. Participation is voluntary. You are receiving this letter because you have been diagnosed with rheumatism for which you are treated and you have transitioned from etanercept under the brand name Enbrel® to etanercept under the brand name Benepali®, and then retransitioned to Enbrel®.

Participating in the study involves a one-time conversation with a researcher. In this letter, you will find more information about the study and your rights. Please read this information carefully. You may take your time to think before making a decision.

Questions and contact

If you have any questions, please feel free to contact the researcher. The researcher can be reached by phone or email:

Name: Rosanne Meijboom
Phone number: 06 xx xxx xxx
Email: rmeijboom@spaarnegasthuis.nl

About the study

This study is conducted by Spaarne Gasthuis, the Foundation Pharmacy of Haarlem Hospitals (SAHZ), and Utrecht University (Department of Pharmaceutical Sciences). The research has been reviewed and approved by the Local Feasibility Advice Committee (ACLU) of the Spaarne Gasthuis and the Institutional Review Board (IRB) of Utrecht University.

Why are we conducting this study?

We would like to learn more about the opinion and experiences of people who retransitioned from Benepali® to Enbrel®. We also want to learn about what they find important when it comes to transitioning. With your help, we hope to improve the transition process between different brand names in the future.

If you are unsure whether you are suitable to participate, you can always call or email the researcher for clarification.

What does participating in this study mean?

Participation in this study is voluntary. In total, we will include approximately 10-12 participants in the study.

If you choose to participate, you will be invited for a one-time conversation (lasting approximately 45-60 minutes). The conversation will be with a researcher who is a pharmacist and conducts research on transitioning between different brand names. The conversation will be conducted in Dutch.

The transition from Enbrel® to Benepali® and retransition to Enbrel® will be discussed. We will ask why you retransitioned and what your experience with retransitioning was. We will also ask about your opinion of treatment with Benepali® itself and your thoughts on the transitioning process.

We would like to learn more about your experiences, what went well, and what you would have preferred differently. There are no right or wrong answers; we simply want to hear your opinion.

The conversation can be conducted via (video) call, or at a location of your choice where you feel comfortable. You can choose how and where you would like to have the conversation. You can have this conversation with the researcher alone, but if you prefer to have others present, for example your partner or caregiver, that is also allowed.

Important to know

With this study, we hope to improve the transitioning process between different brand names in the future. You will not directly benefit from participating in this research, but it may help other people who will transition in the future.

We will not inform your doctor or pharmacy personnel that you are participating in this study. Everything you say during the conversation will not affect your treatment.

The conversations will be recorded for documentation purposes. This helps the researchers when analysing the conversation. All recordings will be transcribed into text. Only the researchers will have access to these recordings. Once the research is completed, the recordings will be destroyed. The transcriptions of the conversations will be securely stored for 10 years and then also destroyed.

The researchers will write a scientific article about the research results, which may include statements made by participants in our research. These statements could include something you said during the conversation. We will pseudonymize the data, meaning that your name will not be mentioned.

Your information

For the purpose of the study, we need the following information

- The type of rheumatism you have (for example rheumatoid arthritis, psoriatic arthritis axial spondyloarthritis, juvenile idiopathic arthritis, or another form of rheumatism)
- The year in which your rheumatism was diagnosed
- The names of the medication you are currently using

To schedule the conversation, we also need

- Your email address

- Your phone number
- Your place of residence (if you do not wish to have the conversation via video call

The information we collect from you will be assigned a code. The key to the code will be stored securely within the SAHZ. When processing your data, we will only use this code, ensuring that nobody can identify you. We will keep your data for 10 years.

If you would like to know more about how we handle your data, please ask the researcher. If you have a complaint about the handling of your data, you can also contact the Data Protection Officer of Spaarne Gasthuis (email: fg@spaarnegasthuis.nl).

YES, I want to participate in this study
If you would like to participate, please digitally sign the consent form.
The final deadline for registration is October 1, 2022.

No, I do not want to participate in this study
Participation is voluntary. If you do not wish to participate, you do not need to take any action.

Will I receive information about the results?
Once the study is completed, you can receive a summary of the outcomes through the researchers.

Complaints
If you have a complaint, please discuss it with the researchers. If you prefer not to do so, you can contact the Complaints Officer of the Spaarne Gasthuis.
Phone number: 023 – 224 2130
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S3: Informed consent form

Experiences with transitioning from a biosimilar to an original biological

(Ervaringen met het wisselen van een Biosimilar nAaR een oRigineel bIologisch mEdicijn [BARRIE studie])

Dear participant

In this form, you give your consent to participate in the BARRIE study. Please read the form carefully so that you know what you are committing to.

I want to participate in this study.

- I hereby give permission to the researchers from Utrecht University to use the information I provided during the conversation for this research.
- I have received information from the researchers about the study.
- Any questions I had have been adequately answered.
- I am aware that participation is completely voluntary. I know that I can decide not to participate at any time, without having to provide a reason.
- My data will only be used for this study.
- My data will be processed under a study number so that they cannot be easily traced back to my person.
- I am aware that recordings will be made during the conversation, and that these recordings will only be accessible to the researchers to accurately analyze the conversation. Once the study is completed, the recordings will be destroyed.
- The transcribed information from the conversation will be securely stored for 10 years after the completion of the study and then destroyed.
- This consent form will be kept completely separate from the collected study data.

Consent

O Yes, I give my consent

Your information

Name:

Place:

Date:

Signature:

Location of the conversation
I would like the conversation to take place:
o Via video call
o In person at the location:

This is the end of the consent form. Thank you for filling it out.
The researcher will contact you to schedule an appointment.

S4: Interview guide

(Full written version)

Welcome, thank you for coming here.

Before we start: some introductions and some general information about the research.

- Introduce myself
- Explain the study objective: In this study, we aim to understand the experiences of individuals who have retransitioned from biosimilars to original biological medicines. Ultimately, we hope to learn how to improve the transitioning process between original biological medicines and biosimilars in the future.
- We will conduct interviews with individuals who have undergone such a transition, including yourself. I would like to hear your opinions and experiences. There are no right or wrong answers.
- Everything you say will be treated confidentially. Data will be processed only in coded form, without your name and will not be traceable back to you.
- Participating in this research will not affect your treatment, and the information will not be shared with your doctor or pharmacy staff.
- You can withdraw from the study at any time without providing a reason.
- The conversation will be recorded for the purpose of converting the conversation into text. Recordings will be destroyed after the research is completed.
- The interview will last approximately 45-60 minutes, with a possible break in between.
- Once the study is finished, we will publish the findings in a scientific journal. This will take some time, however, you can receive a summary earlier (also through patient associations).
- Do you have any questions before we start?
- If not, I would like to start the recording device now.

Do you have any questions before we begin?
If not, I would like to start the recording device now.

Before starting the interview:
Introduction: This study is about retransitioning to the original biological medicine (Enbrel or Humira). You were treated with Enbrel/Humira, then transitioned to the biosimilar (same active substance but different name), and then retransitioned to the original biological medicine. So:

Original biological ▸ medicine	Biosimilar ▸	Original biological medicine
Enbrel	*Benepali*	*Enbrel*
Humira	*Amgevita, Imraldi*	*Humira*

Introduction question (if not yet known):

1. Which original biological medicine were you treated with, and which biosimilar did you transition to?

I would like to first discuss the retransitioning process, and then talk about when you started using the biosimilar.

Topic retransitioning

1. You retransitioned from the biosimilar to Enbrel/Humira. How did you feel about the retransitioning?
2. What was the reason or trigger for you retransitioning? Why did you retransition to the original biological medicine instead of trying another type of medication?
3. What were your expectations of you retransitioning?
4. Whose initiative was it to retransition? Whose idea was it to retransition?
   What kind of guidance and information did you receive at the time of retransitioning?
5. What did you notice when you retransitioned to the original biological medicine?
   What is your experience with your current treatment? (if still using it)

Going back in time to when the biosimilar was introduced

At the beginning of our conversation, we discussed retransitioning first and I also explained that we would like to discuss when you originally transitioned from Enbrel/Humira to the biosimilar. Now, I would like to talk to you some more about this moment. So, we're taking a step back in time to when you were still using Enbrel/Humira and decided to transition to the biosimilar.

Topic experience with switching from the original biological medicine to the biosimilar

1. What information was provided to you about the biosimilar before you made the transition?
   Who provided you with that information?
   Who decided that you would switch from Enbrel/Humira to the biosimilar?

2. What were your own preferences when switching from Enbrel/Humira to the biosimilar? What did you think of that information?
3. What were your expectations of the biosimilar before you started using it?
4. What kind of guidance did you receive when you started using the biosimilar for the first time?

Now, let's talk about your experience with using the biosimilar.

Topic experience with the biosimilar itself (the product)

1. What was your experience with regards to the effect of the biosimilar? If there were differences in effects/side effects, when did you notice them? What did you do?
2. What was your experience with using the new injection pen?
3. Did you notice any other effects when you started using the biosimilar?

Now, I have posed all my questions and we have come to the end of this conversation.

Would you like to add anything that hasn't been discussed?

I would also like to know some general information about you:

<u>Demographic information</u>
Year of birth
Gender
Diagnosis (rheumatoid arthritis, psoriatic arthritis, axial spondyloarthritis, juvenile idiopathic arthritis, or another form of rheumatism)
Year of diagnosis
Other medications currently being used

That concludes our conversation.

Conclusion

1. Do you have any further questions?
2. Mention my contact information: email or phone number.
3. When the research is complete, would you like to receive a summary? If yes, what is your email address?

I want to sincerely thank you for your participation!

CHAPTER 7

Discontinuation of infliximab treatment in patients with inflammatory bowel disease who retransitioned to originator and those who remained on biosimilar

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Accepted for publication

Abstract

Background and aims

Many patients with inflammatory bowel disease (IBD) have transitioned from infliximab originator to biosimilar. However, some patients retransition to originator (i.e. stop biosimilar and reinitiate originator). Whether this sign of potential unsatisfactory treatment response is related to the product or the patient/ disease is unclear. We aimed to compare the risk of and reasons for infliximab discontinuation between retransitioned patients and those remaining on biosimilar.

Methods

IBD patients who transitioned from infliximab originator to biosimilar between January 2015 and September 2019 in two Dutch hospitals were eligible for this study. Retransitioned patients (retransitioning cohort) were matched with patients remaining on biosimilar (biosimilar remainder cohort). Reasons for discontinuation were categorised as unwanted response or remission. Risk of unwanted discontinuation was compared using a Cox proportional hazards model.

Results

Patients in the retransitioning cohort (n=44) were younger (median age 39.9 versus 44.0 years), more often female (65.9% versus 48.9%) and had shorter dosing intervals (median 48.5 vs 56.0 days) than in the biosimilar remainder cohort (n=127). Infliximab discontinuation due to unwanted response was 22.7% in the retransitioning and 13.4% in the biosimilar remainder cohort, and due to remission was 2.3% and 9.4%, respectively. Retransitioned patients are at increased risk of discontinuing due to unwanted response compared with biosimilar remainder patients (adjusted HR 3.7, 95%CI 1.0-13.9).

Conclusions

Retransitioned patients are at increased risk of infliximab discontinuation due to unwanted response. Retransitioning appeared related to the patient/ disease and not the product. Clinicians might switch patients opting for retransitioning to other treatment regimens.

Introduction

Tumour necrosis factor (TNF)α inhibitors have enriched the treatment of patients with inflammatory bowel disease (IBD). These agents made clinical and endoscopic remission realistic treatment targets.[1,2] However, the drawback of treatment with TNFα inhibitors used to be their high price compared with conventional treatment, such as thiopurines, and this has placed a financial burden on health care systems and limited patients' access. Several years ago, the loss of market exclusivity for some of these blockbusters resulted in the introduction of biosimilars and thus in lower prices with improved patient access. A biosimilar is a 'biological medicinal product that contains a version of the active substance of an already authorised biological medicinal product (originator)'.[3] Biosimilars approved by the European Medicines Agency (EMA) have proven to be as safe and effective as the originators, and are considered interchangeable with their corresponding originators, meaning that a biosimilar can be used instead of its originator.[4]

In 2014, the first infliximab biosimilar entered the European market.[5] Since then, many patients treated with originator infliximab in clinical practice have transitioned to the biosimilar, mainly because the biosimilar was lower-priced.[6,7] When transitioning from originator to biosimilar, patients are still treated with the molecule infliximab. Thus, transitioning differs from switching to another biological (with another active substance), for example when patients have an inadequate response to infliximab.

Transitioning has been proven effective and safe in double-blind studies, such as the NOR-SWITCH study. This study compared disease worsening, defined as a Harvey–Bradshaw Index increase of 4 points or more from baseline and a score of 7 or higher (Crohn's disease; CD), or a Partial Mayo Index increase of 3 points or more from baseline and a score of 5 or higher (ulcerative colitis; UC), between patients with IBD who transitioned from infliximab originator to biosimilar with patients who remained on originator. The NOR-SWITCH study reported that the incidence of disease worsening in the transitioned patients (36.5% for CD and 11.9% for UC) was more frequent, but within the predefined absolute margin set for non-inferiority of 15% to the incidence in patients who remained on originator (21.2% for CD and 9.1% for UC).[8]

Despite the fact that many patients in clinical practice successfully transition from infliximab originator to biosimilar, studies have demonstrated that on average 7% of patients with IBD who transitioned subsequently retransitioned to originator infliximab (i.e. they stopped the biosimilar and reinitiated the originator).[9] Retransitioning is mainly due to either a perceived or objective increase in disease activity or the occurrence of (subjective) adverse events after transitioning to the biosimilar.[10–12]

However, no clear pharmacotherapeutic rationale exists for retransitioning, and furthermore, it is not recommended in clinical guidelines.[13]

After retransitioning to the originator, patients could regain efficacy or adverse events could resolve, which might indicate that they have experienced the nocebo effect. The nocebo effect refers to 'an unexplained, unfavourable therapeutic effect subsequent to a non-medical switch from originator infliximab to biosimilar infliximab with regaining of the beneficial effects after reinitiating the originator'.[14] Retransitioning could also be related to a general lack of confidence in biosimilars by patients and/or prescribers.[15,16] Thus, it is unclear if retransitioning is related to the drug product or to the patient and his/her disease.

The aim of this study was to compare the risk of and reasons for infliximab discontinuation between patients who retransitioned to originator and those who remained on biosimilar in a study base of patients with IBD who had transitioned from infliximab originator to the corresponding biosimilar.

Methods

Setting

This study was conducted at two large teaching hospitals in the Netherlands: Spaarne Gasthuis (SG; Haarlem and Hoofddorp, the Netherlands), which has 601 beds and 34,000 clinical hospitalisations annually, and Medisch Spectrum Twente (MST; Enschede, the Netherlands), which has 547 beds and 30,000 clinical hospitalisations annually.

On the 1st of January 2012, reimbursement regulations were implemented in the Netherlands that required all outpatient-administered biologicals registered for IBD to be exclusively dispensed by the outpatient pharmacies of the hospitals where the patients are treated. All in-hospital administered biologicals are dispensed by the hospital pharmacy and administered at the day-care clinic. Consequently, the hospital pharmacy has a complete overview of all biologicals used by a patient with IBD.[17]

Dispensing data (brand name, ATC code, dose, dosing interval, and dispensing date) from the outpatient pharmacy (outpatient used medication) from SG and MST were obtained from the outpatient pharmacy system CompuGroup Medical (CGM; Echt, the Netherlands). Dispensing data (brand name, ATC code, dose, administration date, and prescriber) and patient information (gender and date of birth) from SG hospital pharmacy (in-hospital administered medication) were obtained from the pharmacy information system Centrasys (Nexus, Vianen, the Netherlands). Prescription data

(brand name, ATC code, dose, administration date, and prescriber) and patient information (gender and date of birth) from MST were obtained from Vipharma (HI Systems, Oosterhout, the Netherlands), the hospital's electronic prescription system (in-hospital administered medication). Reasons for retransitioning to infliximab originator and discontinuing infliximab treatment were obtained by manually searching electronic patient files from Epic (Epic, Verona, WI) (SG) and Hix (ChipSoft, Amsterdam, the Netherlands) (MST). Outpatient and in-hospital data were linked using patients' social security number (SG) or unique patient identification number (MST).

Ethical approval

The protocol of this study was approved by the Institutional Review Board of the SG (reference number: 2020 0116) and the Institutional Review Board of the MST (reference number: KH22-15).

Study design and patients

This was a matched cohort study in a study base of patients with IBD (diagnosis derived from the specialism of the prescriber) who had transitioned from infliximab originator (Remicade) to infliximab biosimilar (including Remsima, Inflectra, and Flixabi) between 1 January 2015 and 30 September 2019. In the Netherlands, transitioning patients from infliximab originator to biosimilar is controlled by the individual hospitals, and transitioning is directed by treating physicians and hospital pharmacists. Patients were informed on the transition by the treating gastroenterologist or the IBD nurse. In principle, all patients with IBD treated with infliximab were eligible for transitioning. Transitioning was strongly encouraged, but not mandatory. Patients could object to transitioning and then remained treated with originator infliximab. The latter group was not included in this study. The date of transitioning was assigned as the patient's transition date. Patients with less than 1 year of follow-up from the transition date were excluded.

From this study base, all patients who retransitioned during the study period to originator were identified and included in the retransitioning cohort. Retransitioning from infliximab biosimilar to originator was defined as having at least one dispensing of the originator following transitioning, thus after having at least one dispensing of the biosimilar. To ensure retransitioning was intended, and not due to, for example, an accidental prescription error, the electronic health record (EHR) file notes of the patients were checked. If retransitioning was also mentioned in the file notes, patients were considered to be retransitioned. If there was not any mentioning, patients were considered as solely transitioned. For the patients in the retransitioning cohort, the date of retransitioning was assigned as their index date.

Reasons for retransitioning were extracted from the EHR file notes and were classified as loss of effect, adverse events, remission, other or unknown. Loss of effect included increased calprotectin, gastrointestinal complaints including abdominal pains, changes in defaecation (frequency and/ or composition), and intestinal complaints and loss of effect in general. Adverse events were further subdivided into skin complaints including redness, eczema, psoriasis, itching and hives; joint complaints including joint pains and stiffness, fatigue or other adverse events.

Retransitioned patients were matched with up to 3 patients[18] from the study base who had transitioned from originator to biosimilar and not retransitioned. These patients formed the biosimilar remainder cohort. Patients in the biosimilar remainder cohort could only be matched once to a patient in the retransitioning cohort.[19] Retransitioned patients who could not be matched were excluded. Matching was performed based on the following criteria: (i) treatment in the same hospital, as treatment policies may differ between hospitals; (ii) transition date in the same 6-month calendar period, accounting for changes in treatment policies and treatment options over time; and (iii) duration of biosimilar use from transition date: patients were matched on the duration of biosimilar use[20], defined as the time from transition date until the match date, as depicted in Figure 1 where patient 2 is matched with patient 1. Patient 1 received infliximab on the index date, thus the patient cannot discontinue infliximab for the next 8 weeks (standard infliximab dosing interval[21]). To account for this in the biosimilar remainder cohort, their index date was set on their infliximab administration date closest prior to the match date.

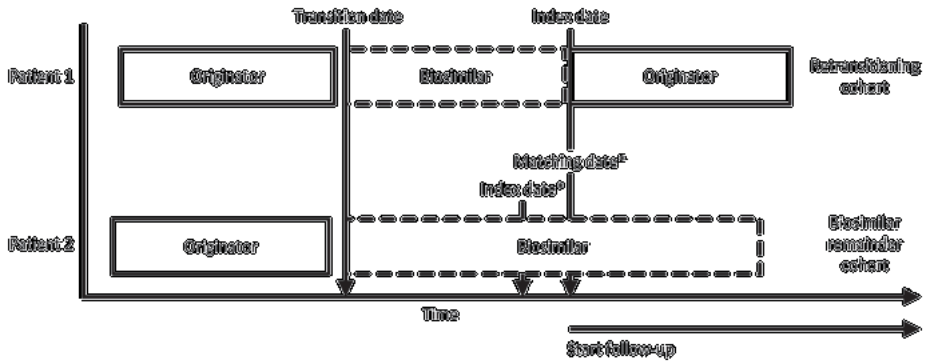

Figure 1: Matching of patients.
*For patients in the biosimilar remainder cohort, the infliximab biosimilar administration date closest prior to the matching date was assigned as their index date

Patients were followed from their index date until discontinuation of biological treatment, censoring, death, loss to follow-up, or the end of data collection (30

September 2020), whichever came first. In case retransitioned patients were accidentally re-introduced on the biosimilar without any mentioning of this change in their EHR file notes, this was considered a prescription error and these patients were still considered retransitioned and continuing their infliximab originator treatment.

Outcomes

The primary outcome of this study was infliximab treatment discontinuation. To identify discontinuation, treatment episodes of infliximab treatment were first constructed for each patient. A treatment episode was defined as the time between the first infliximab administration until the last administration. A maximum gap of 8 weeks between the theoretical end date of the previous administration and the next one was permitted to account for small adjustments in dosing schedules for non-medical reasons (e.g. holidays). Patients were considered to have discontinued infliximab treatment if they did not receive an infliximab administration within the maximum permissible gap (total of 16 weeks after the date of the last administration, considering a standard dosing interval of 8 weeks[21]).

Reasons for discontinuing were extracted from the EHR file notes and were classified according to the same classification as for reasons for retransitioning described earlier.

Potential confounders

Age, gender, duration of use of infliximab originator prior to transitioning (1 year or less, or more than 1 year[22]), and the number of other biologicals that a patient used before initiating treatment with infliximab were assessed as potential confounders.[22,23]

Data analysis

The baseline characteristics of the patients were descriptively analysed. Reasons for retransitioning from biosimilar to originator infliximab were plotted in pie charts and reasons for discontinuing infliximab treatment were plotted in stacked bar charts. Reasons for discontinuing were classified as either due to due to remission or due to unwanted response, including loss of effect, adverse events and other unwanted response. In the following analysis, discontinuing due to unwanted response was analysed, thus patients discontinuing due to remission were censored at the time of discontinuation. Kaplan–Meier curves were used to present the risk of infliximab treatment discontinuation for both cohorts. The hazard ratio (HR) of infliximab discontinuation was calculated using unadjusted and adjusted conditional Cox proportional hazards models. The model was adjusted for the aforementioned potential confounders summarizing these in a propensity score and including this in

the analysis. The data were analysed using R version 3.6.3 (R Foundation for Statistical Computing, Vienna, Austria).

Results

In total, 198 patients who had at least one year of follow-up transitioned from infliximab originator to the biosimilar. These patients had a median age of 39.9 years and 53.0% were female. Of the 198 patients who transitioned, 49 patients (24.7%) retransitioned to originator infliximab during follow-up. Retransitioning occurred after a median (interquartile range; IQR) of 8.6 (3.7-14.0) months after transitioning. There were no major differences between the two included hospitals.

After matching, the retransitioning cohort comprised 44 patients and the biosimilar remainder cohort comprised 127 patients; 2 patients from the retransitioning cohort could only be matched with 1 patient, while 1 patient from the retransitioning cohort could only be matched with 2 patients. Five retransitioned patients could not be matched with any patient; therefore, these patients were excluded from the retransitioning cohort. These patients were transitioned in calendar periods with an insufficient amount of biosimilar remainder patients to match all retransitioned patients.

The retransitioning and biosimilar remainder cohorts had some differences in baseline characteristics; patients in the retransitioning cohort were younger (median 39.9 years versus 44.0 years in the biosimilar remainder cohort), were more often female (65.9% versus 48.9%), and had a shorter median dosing interval than patients in the biosimilar remainder cohort (48.5 days [IQR 42-56] days vs 56 days [IQR 45-56]), as depicted in Table 1.

Table 1: Baseline characteristics of the retransitioning cohort and the biosimilar remainder cohort

	Retransitioning cohort n= 44	**Biosimilar remainder cohort n= 127**
Median (IQR) age at transitioning (years)	39.9 (28.4-52.8)	44.0 (31.8-57.7)
Females (%)	29 (65.9%)	62 (48.9%)
Median (IQR) duration of infliximab originator prior to transitioning (years)	4.6 (2.3-4.9)	3.7 (2.5-4.8)
Median (IQR) dose at index date (mg)	400 (300-500)	400 (350-500)
Median (IQR) dosing interval at index date (days)	48.5 (42-56)	56 (45-56)

Table 1: Continued.

	Retransitioning cohort n= 44	Biosimilar remainder cohort n= 127
No. of biologicals prior to transitioning		
0 (only Infliximab)	34 (77.3%)	114 (89.8%)
1	9 (20.4%)	10 (7.9%)
2	1 (2.3%)	3 (2.3%)
Median (IQR) follow-up (years)	2.8 (2.4-3.2)	2.9 (2.4-3.2)

The main reasons for patients to retransition were loss of effect (36.4%), adverse events (29.5%) or both loss of effect and adverse events (22.7%) (Figure 2). One patient (2.3%) was retransitioned due to lack of trust in the biosimilar, this was classified as 'other'. For the other patients (9.1%), the reason for retransitioning was not explicitly specified in their EHR file notes. The most reported adverse events were fatigue (reported by 12 patients), skin complaints (8 patients) and joint complaints (7 patients).

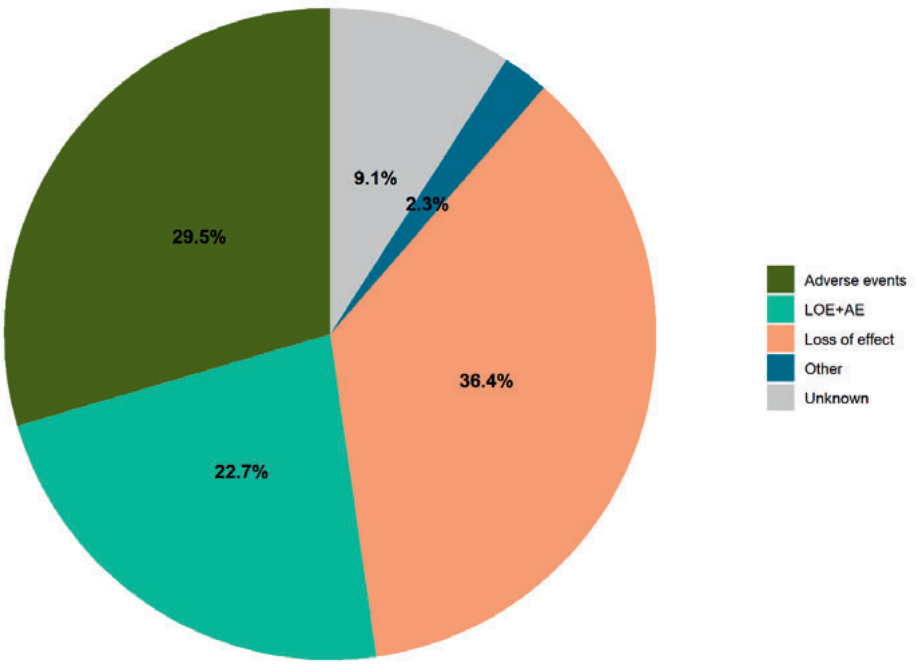

Figure 2: Reasons for retransitioning from infliximab biosimilar to originator (n=44).
LOE: Loss of effect; AE: Adverse events

Six months after the index date, none of the patients in the retransitioning cohort discontinued their infliximab treatment compared with 9.4% in the biosimilar remainder cohort, which increased to 9.1% in the retransitioning cohort and 11.8% in the biosimilar remainder cohort after one year, and to 25.0% in the retransitioning cohort and 22.8% in the biosimilar remainder cohort at the end of follow up (Table 2).

Table 2: Proportion of infliximab discontinuation of the retransitioning cohort and the biosimilar remainder cohort

	No. patients	6 months n (%)	1 year n (%)	End of follow up n (%)
Overall Infliximab discontinuation				
Retransitioning cohort	44	0 (0%)	4 (9.1%)	11 (25.0%)
Biosimilar remainder cohort	127	12 (9.4%)	15 (11.8%)	29 (22.8%)
Discontinuation due to remission				
Retransitioning cohort	44	0 (0%)	0 (0%)	1 (2.3%)
Biosimilar remainder cohort	127	6 (4.7%)	6 (4.7%)	12 (9.4%)
Discontinuation due to unwanted response				
Retransitioning cohort	44	0 (0%)	4 (9.1%)	10 (22.7%)
Biosimilar remainder cohort	127	6 (4.7%)	9 (7.1%)	17 (13.4%)

At the end of follow-up, 11 and 29 of all patients in the retransitioning cohort and the biosimilar remainder cohort, respectively, had discontinued their infliximab treatment, due to remission and unwanted response (Table 2). Their reasons for discontinuing were compared between the two cohorts (Figure 3). Patients in both cohorts discontinued mainly due to loss of effect and adverse events (36.4% and 27.3% in the retransitioning cohort, 34.5% and 13.8% in the biosimilar remainder cohort, respectively). In total, 3 patients in the retransitioning cohort discontinued due to adverse events, mainly due to skin complaints (reported twice), and 4 patients in the biosimilar remainder cohort, categorised as other (depression, dyspnoea), skin complaints, and unknown adverse event (both reported once). Patients in the biosimilar remainder cohort discontinued more often due to remission (41.4% versus 9.1%).

In total, 10 patients who retransitioned (22.7%) and 17 patients (13.4%) who remained on biosimilar discontinued infliximab due to unwanted response (Table 2). Of these discontinued patients, 5 (50.0%) out of the retransition cohort switched to another biological for their IBD treatment (adalimumab, golimumab, vedolizumab, or ustekinumab) and 5 (50.0%) discontinued without switching to another biological. In the biosimilar remainder cohort, 3 (17.6%) of the patients who discontinued switched to another biological and 14 (82.4%) discontinued without switching.

The cumulative incidence of discontinuation of infliximab due to unwanted response was also compared between the cohorts in a Kaplan Meier curve (Figure 4). As the lines of the cumulative incidence curves crossed, hazard ratios (HR) were calculated for the period prior to the lines crossing (at 11.2 months, Figure 4) and after. In both the unadjusted and adjusted Cox proportional hazard models up to 11.2 months of follow up, patients in the retransitioning cohort had a similar risk of overall infliximab discontinuation due to an unwanted response compared with patients in the biosimilar remainder cohort (unadjusted HR 1.1, 95% CI 0.3-4.3; adjusted HR 1.0, 95% CI 0.3-4.2). After 11.2 months, patients in the retransitioning cohort were at increased risk for overall infliximab discontinuation (unadjusted HR 2.1, 95% CI 0.7-6.2; adjusted HR 3.7, 95% CI 1.0-13.9).

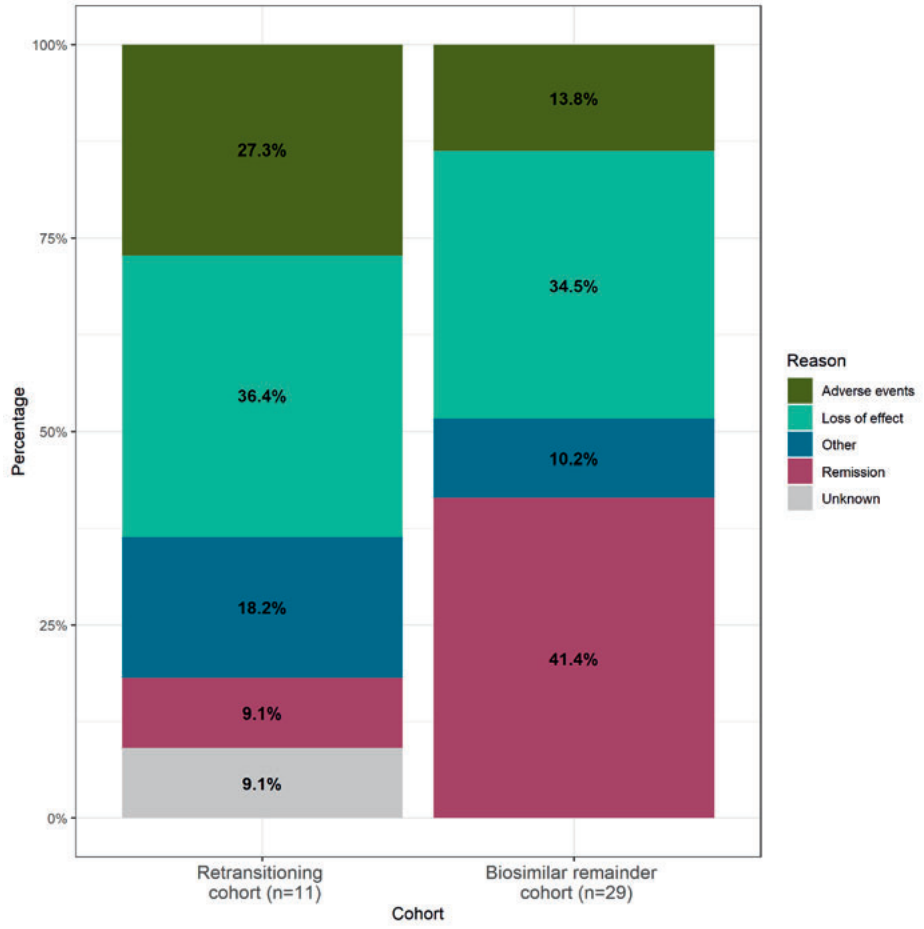

Figure 3: Reasons for discontinuing infliximab per cohort.

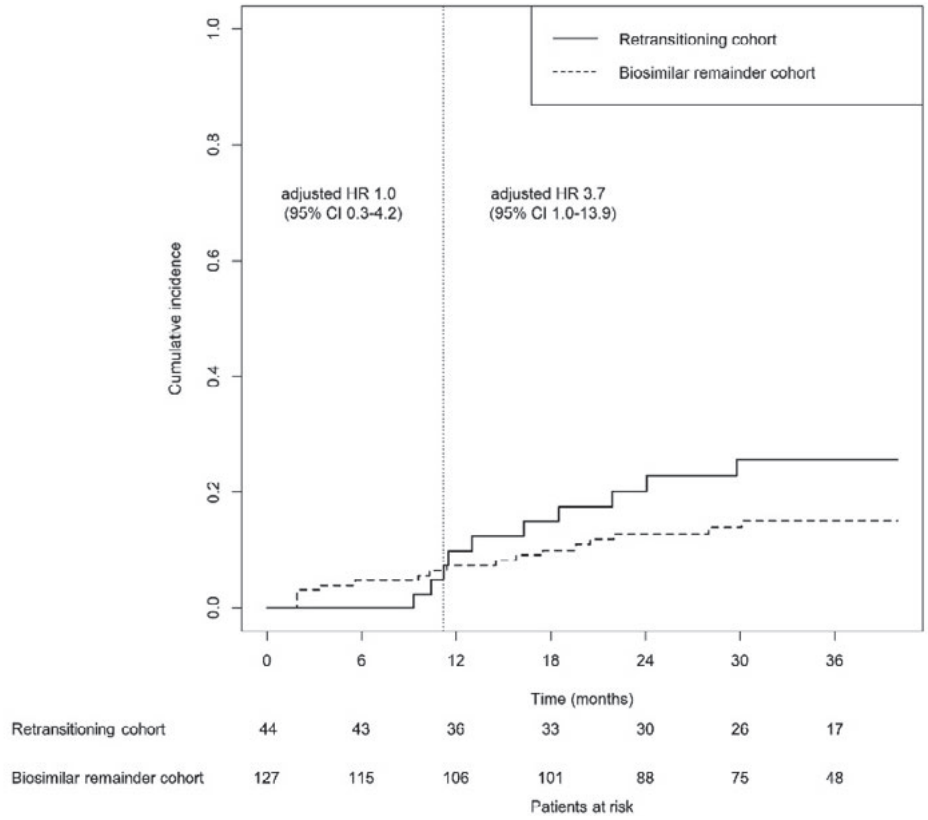

Figure 4: Cumulative incidence of infliximab discontinuation due to unwanted response, the dashed vertical line at 11.2 months indicates the moment of lines crossing.

Discussion

In this study, we found a similar overall proportion of patients who discontinue infliximab between patients who retransitioned compared with patients who remained on biosimilars. However, patients who retransitioned discontinue infliximab treatment more often due to unwanted response compared with patients who remained on biosimilar (22.7% vs 13.4%), whereas patients who remained on biosimilar discontinue infliximab more often due to remission (9.4 vs 2.3%). Patients who retransitioned have after 11.2 months of treatment over a three-fold increased risk for discontinuing infliximab due to unwanted response compared with patients who remained on biosimilar (adjusted HR 3.7 ,95% CI 1.0-13.9). This was in contrast with the similar risk of discontinuation between the two cohorts in the first 11.2 months of treatment (adjusted HR 1.0, 95% CI 0.3-4.2). This aligned with our finding that the proportion of patients who discontinued infliximab due to unwanted response within one year

was moderately increased in the retransitioning cohort compared with the biosimilar remainder cohort (9.1% vs 7.1%), but this further diverged at the end of follow-up (22.7% in the retransitioning cohort versus 13.4% in the biosimilar remainder cohort).

In total, 24.7% of patients in our study who initially transitioned from originator to biosimilar subsequently retransitioned, which is much higher than the 7% reported in an earlier systematic review.[9] Studies included in the systematic review had a median follow-up of 12 months. However, as patients in our study retransitioned after a median of 8.6 (3.7-14.0) months, the long follow-up time of our study (median 3.6 years from transitioning) allowed for more patients to retransition, which shows that retransitioning might also occur after a longer period of time.

A previous study reported similar infliximab discontinuation rates between patients who retransitioned and patients who remained on biosimilar, which was under 10% in both cohorts after one year follow up.[24] In this previous study, both patients who remained on biosimilar and those who retransitioned were followed from the moment of transitioning to the infliximab biosimilar. Following the latter cohort from transitioning onwards might induce immortal time bias, as these patients are not yet exposed to the originator and thus cannot discontinue originator treatment from the moment follow-up started, whereas patients who remained on the biosimilar could discontinue directly after transitioning. In our analysis, patients who retransitioned were followed from the moment of retransitioning to overcome this bias. Therefore, we believe that the method used in our study provides a less biased comparison between patients who retransitioned and patients who remained on biosimilar treatment.

Other previous studies, including between 74 and 260 patients, have described the effect of retransitioning anecdotally and with conflicting outcomes. Some studies have reported that patients who retransitioned were treated successfully with at least 2 to 4 administrations of infliximab originator,[14,25] whereas another study have reported patients discontinuing infliximab originator shortly after retransitioning.[11] The findings in our study demonstrate that the risk for discontinuing infliximab in patients who retransitioned compared with patients who remained on biosimilar appeared to increase over time. Retransitioning is done due to complaints on the biosimilar, such as loss of effect and adverse events, intending to regain effects and/ or dispose adverse events. Thus, patients and clinicians might first try a few administrations to wait for the effect of the reintroduced originator. However, as the infliximab biosimilar is similar to the originator in terms of efficacy and safety, it is expected that these patients did not benefit from retransitioning to originator and discontinued infliximab treatment.

This is supported by the finding that patients in the retransitioning cohort had used more other biologicals prior to infliximab initiation and had a shorter infliximab dosing interval, which puts them at higher risk of switching to another biological[26] and might indicate that these patients already had more disease complaints.[27] Moreover, less patients in the retransitioning cohort discontinued infliximab treatment due to remission, which also suggests less treatment benefit.

However, a subset of patients who retransitioned persisted treatment with the originator infliximab, which suggested that these patients benefitted from retransitioning. These patients might have attributed their complaints to the biosimilar; for example, they could coincidentally have experienced disease worsening at the time of transitioning. This is supported by the finding that three patients who retransitioned also increased their infliximab dose, which could (partly) explain the regained effect.

Five patients (all from the same hospital) who retransitioned received alternately both infliximab originator and biosimilar, and since this was not mentioned in their EHR file notes, this could have been due to prescribing errors. When these patients were consciously transitioned to infliximab biosimilar, they experienced complaints such as fatigue, abdominal pains and changes in defaecation. However, when they were unconsciously alternating originator and biosimilar, no complaints were mentioned in their dossiers, indicating that these patients alternated between infliximab originator and biosimilar without any reported issues. Despite the number of these patients is low, this finding might indicate that consciously transitioning from originator to biosimilar induces complaints in certain patients.

As the route of administration and excipients of Remicade and infliximab biosimilar are identical[21,28–31] (except for Zessly, which was not used in this study), contrary to subcutaneously administered TNFα inhibitors, issues such as allergy for excipients and difficulties with administration devices should not contribute to retransitioning for infliximab.

Retransitioning from biosimilar to originator has similarities with generic to brand retransitioning in small-molecule treatment, which has been extensively studied for antiepileptic brand to generic transitioning. Such studies have demonstrated that patients who retransitioned from generic to brand were at an increased risk of hospitalisation or of a dose increase of their antiepileptics; furthermore, they had more comorbidities compared with patients who remained on their generic antiepileptics.[32–34] This finding was not related to differences in the pharmacokinetic properties of generics,[35] but rather it reflects patients' attitudes towards generics and their anxiety

regarding disease flares.[36] Similar to small-molecule treatment, retransitioning from biosimilar to originator appears to be more related to the patient and his/her disease than to the product itself.

For clinicians, patients who wish to retransition can be troublesome, as doing so is not recommended in the IBD treatment guidelines[1,2,37] and no pharmacotherapeutic rationale exists for retransitioning to infliximab originator. Our results demonstrated that patients who retransition might have an increased risk of discontinuing infliximab due to loss of effect or adverse events, which could indicate that retransitioning is mainly related to the patient and/or to problems with his/her disease, and that it is less likely related to the infliximab biosimilar itself. As patients do not seem to benefit from retransitioning, clinicians might – after a thorough investigation to confirm active disease – consider switching patients who opt for retransitioning to another treatment regimen.

The strengths of our study include its comprehensive strategy for matching patients and its data analysis. By matching patients who retransitioned with patients who remained on biosimilar by calendar time and hospital, patients were similar in terms of treatment policies and the availability of options for switching treatment. Moreover, by matching them on the time of biosimilar treatment, patients were followed from the same moment in their treatment trajectory. Our thorough matching strategy allowed for a fair comparison of the two cohorts.

However, this study also had some limitations. As the number of included patients was small, it was not feasible to perform subgroup analyses, for example stratification on indication (Crohn's disease or ulcerative colitis). Moreover, this study was performed in patients with IBD only. However, as both the nocebo effect and the attribution effect, which are both possibly the main drivers of retransitioning, are patient-related but not indication-related, we believe that our results are generalisable to other indications as well. Furthermore, biosimilars for other biologicals for long-term use are and will become available. We believe that the results from this study will be applicable to those biosimilars as well.

In conclusion, our study demonstrated that patients who retransitioned discontinued infliximab treatment more often due to unwanted response compared with patients who remained on biosimilar, whereas patients who remained on biosimilar discontinued infliximab more often due to remission. Patients who retransitioned have, over time, over a three-fold increased risk for discontinuing infliximab due to unwanted response compared with patients who remained on biosimilar. These findings indicate that

retransitioning is mainly related to the patient and problems with his/her disease and less likely related to the infliximab biosimilar. Clinicians could consider patients who opt for retransitioning to another treatment option.

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CHAPTER 8

General Discussion

Introduction

For decades, conventional, small-molecule immunomodulator drugs were the cornerstone of pharmacological treatment for patients with immune-mediated inflammatory diseases (IMIDs), such as rheumatoid arthritis (RA) and inflammatory bowel disease (IBD).[1] However, treatment options have expanded since biologicals were introduced on the market in 1999.[2] Within the class of biologicals, TNFα inhibitors are currently often used as first-line biological therapy, and these agents have become the standard of care for the treatment of IMIDs.[3–5] However, the therapeutic response to TNFα inhibitors, as to all (biological) drugs, varies between patients and within a patient over time.

At the time of introduction, TNFα inhibitors were a costly treatment modality, which posed a challenge due to their impact on healthcare budgets. The introduction of biosimilars ("a biological medicinal product that contains a version of the active substance of an already authorised biological medicinal product [originator]" several years ago led to competition, resulting in lower prices for TNFα inhibitor treatment and improved patient access to these treatments.[6]

The varying response to TNFα inhibitors and the introduction of biosimilars resulted in changes in the course of pharmacological treatments of individual patients with IMIDs. This thesis aimed to provide insight into the TNFα inhibitor treatment trajectories for patients with IMIDs. We further aimed to provide quantitative and qualitative insight into the frequency and determinants of transitioning from an originator TNFα inhibitor to a biosimilar, on retransitioning to the originator, and on biosimilar implementation strategies. From these studies, lessons on biosimilar implementation for clinical care are distilled.

A drug treatment trajectory contains an overview of medicines used by a (group of) patient(s), starting from the moment a patient initiates a medicine of interest and ending when the last drug within this trajectory has been eliminated from the body. This treatment trajectory often contains multiple drug treatment episodes that depict treatment with one (or multiple) drugs. Treatment episodes are constructed from a patient's prescription or dispensing records obtained from healthcare databases, which contain healthcare activities in daily clinical care, such as initiation of a drug or a dose change.

Drug treatment trajectories provide a clear outline of an IMID patient's drug treatment, and these can also reflect information on a patient's wellbeing and the course of their disease. For example, if a patient is treated with a TNFα inhibitor and has reached low

disease activity or remission, they are likely to continue treatment with that TNFα inhibitor. When the patient has reached sustained remission, the TNFα inhibitor might be tapered. On the other hand, if a patient is treated with a TNFα inhibitor but is not doing well or experiences a disease flare, therapy can be augmented with comedication such as corticosteroids, or, in some cases, the TNFα inhibitor dosage can be increased. If the patient experiences lack or loss of effect of the TNFα inhibitor or a (severe) adverse event, the decision can be made to switch to another TNFα inhibitor, a biological with another mode of action, or a JAK inhibitor.

In addition to providing information on the clinical course of a disease, drug treatment trajectories also provide information on the course of the treatment, including transitioning to a biosimilar. As biosimilars and originators are similar products, transitioning from an originator to a biosimilar in daily clinical care should, in principle, not affect the course of a patient's treatment. Depending on the implementation strategy, patients are informed about biosimilars by their health care professional (HCP), nurse and/or pharmacist, and might receive informational material. However, some patients remain concerned about the quality, efficacy, and safety of the biosimilar and the recurrence of flares of their disease.

These concerns might be reflected in the findings of observational studies on transitioning as part of routine clinical care, which reported conflicting results. Some patients report no major differences in efficacy and/or safety between continuing treatment with the originator or transitioning to biosimilars, while others report increased discontinuation rates (indicating treatment failure) of the patients who transitioned to biosimilar.[7]

Strikingly, in some observational studies, a subset of patients (2.6-25.8%) who were transitioned from an originator to a biosimilar subsequently retransitioned (i.e., restarted originator treatment), mainly due to (perceived) loss of effect and/or adverse events.[8,9] Based on the comparability between an originator and its biosimilar, the pharmacological rationale for retransitioning is unclear and is not expected to regain effect. However, it might be, from a patient's perspective, a logical response to their unexplained but existing problems with biosimilar treatment.

Previous research provided various snapshots into the drug treatment trajectory for IMID patients, for example, when starting TNFα inhibitor treatment, moving from first-line to second-line biological treatment, and transitioning from a (TNFα inhibitor) originator to biosimilar.[10–12] However, insight into long-course treatment trajectories, including multiple events, is scarce. Furthermore, despite a subset of

patients retransitioned in their drug treatment trajectory, little is known about the reasons for retransitioning, patients' perceptions on retransitioning, and potential factors that limit the risk of retransitioning.

There are specific (pharmacoepidemiologic) challenges involved in the study of treatment trajectories of TNFα inhibitors. TNFα inhibitors are dispensed in both the hospital and the outpatient or community pharmacy setting, which can make complete data retrieval challenging. TNFα inhibitors have long (one-to-eight-week[2,13]) standard dosing intervals, which are often adjusted to the individual patient depending on the course of the disease and, for example, the occurrence of an infection. This complicates exposure assessment and the construction of drug treatment trajectories when healthcare databases are used. Furthermore, when including biosimilars in the drug treatment trajectories, identifiability (identification which specific product the patient received) is of major importance. However, in clinical care, (intended) transitions from an originator to a biosimilar (and sometimes vice versa) are sometimes poorly documented. Therefore, tackling these challenges is important for constructing valid drug treatment trajectories.

In this thesis, insight into the TNFα inhibitor treatment trajectories of patients with IMIDs was provided. Quantitative and qualitative insight into the frequency and determinants of transitioning from an originator TNFα inhibitor to a biosimilar, on retransitioning to the originator, and on biosimilar implementation strategies were also provided. Within this general discussion, two aspects of the findings in previous chapters will be put into a broader perspective by discussing 1) the challenges in creating drug treatment trajectories and 2) the introduction of biosimilars in clinical practice, followed by recommendations for future research and clinical care.

1. Challenges in creating drug treatment trajectories

Constructing drug treatment trajectories is essential in pharmacoepidemiology to depict a patient's exposure to one or more drugs over time. Transforming healthcare data registered in the routine clinical care setting into drug treatment trajectories has several challenges. These include turning irregular patterns of prescriptions and/or fills into clinically logical patterns of patient drug use and defining the maximum permissible gap between subsequent prescriptions or fills, after which the patient is defined as discontinued.[14] Performing this transformation for the use of biologicals in the treatment of IMIDs can bring about some additional challenges, most importantly in a) assessing the patient's exposure status in a valid way and b) interpreting the patient's disease status based on the drug treatment trajectories. These challenges will be discussed in detail below.

a. Drug treatment trajectories as a valid tool for depicting exposure status

Assessing TNFα inhibitor treatment trajectories necessitates access to the specific type of data that can be used to construct these treatment trajectories. Similar to constructing drug treatment trajectories in general, at minimum, the type of TNFα inhibitor (active substance), the moment of administration, and the administered dose are required. In the field of pharmacoepidemiology, these data are often derived from prescription data, pharmacy dispensing data, hospital administration data, or claims data. The prescription or dispensing date usually serves as a proxy for the start date of administration and the actual administration. Using the dosing regimen and the number of units dispensed (and optionally pharmacokinetic and -dynamic properties), the length of the expected exposure for the specific drug can be calculated.

In this thesis, dispensing data and, in some cases, prescription data have been used to assess exposure to TNFα inhibitors. TNFα inhibitors can be dispensed in primary and secondary care. Four types of TNFα inhibitors (etanercept, adalimumab, certolizumab pegol, and golimumab[13,15–17]) are administered as a subcutaneous (s.c.) injection and, thus, usually administered by the patient themselves in their preferred setting, often at home. These subcutaneously administered TNFα inhibitors can be dispensed via the hospital outpatient pharmacy, such as is custom in the Netherlands, or via the community pharmacy, as is the case in, among others, Nordic countries. In the past, infliximab was only dispensed and administered as an intravenous infusion in a clinical setting (such as a [outpatient] hospital ward). However, since 2019, it has also become available as an s.c. injection.

Creating TNFα inhibitor treatment trajectories requires that data from both settings are available, including the possibility of linking the data from these two settings at the level of the individual patient. After obtaining data on TNFα inhibitor use, transforming these data into drug treatment trajectories requires great care, as there are several potential opportunities for misclassification of the exposure. The main sources of exposure misclassification are misclassification of the drug product, misclassification due to the TNFα inhibitors' dosing regimen, and immortal time bias.

(Mis)classification of the drug product

Challenges in the classification of the drug product when creating drug treatment trajectories can occur when it is unclear which specific drug product was used by the patient. The data sources often used in pharmacoepidemiological studies to create drug treatment trajectories may contain different levels of detail regarding the drug product. In this thesis, the active substance level was used to construct TNFα inhibitor

treatment trajectories, such as in *Chapter 2*, which analysed switching from one active substance to another. In *Chapter 5* and *Chapter 7*, drug treatment trajectories were constructed at the brand name level, as these chapters studied transitioning to a biosimilar. Creating drug treatment trajectories on the brand name level requires data on the drug product to which the patient was exposed. However, this is not captured in every data source by default. This is the case when products are, due to prescribing systems and/or prescribing policies, prescribed at the level of the active substance, such as was the case in one of the three hospitals included in *Chapter 2*. In this case, the level of the active substance was sufficient. However, we were unable to use the data of this specific hospital in, for example, *Chapter 7*. In other data sources, for example, claims databases, brand names are often available, but other variables, such as dosing regimens, might not be. This illustrates the issue that not all data sources contain all data required to identify which brand name a patient was exposed to.

Moreover, for large (international) databases, which can be used to create TNFα inhibitor treatment trajectories, identifying the specific brand name (biosimilar or originator) can be challenging. In the European Union, both the international non-proprietary name (INN) and the brand name from the specific manufacturer are used, with only the brand name differentiating between products with the same active substance (e.g., Inflectra, an infliximab biosimilar). The United States, however, applies a different system, adding a four-letter suffix to the active substance's INN to distinguish between biosimilars and originators at the INN level (e.g., infliximab-dyyb (Inflectra)).[18,19] Both the EU's system for brand names and the US system, which uses the four-letter suffix, are suitable for constructing drug treatment trajectories at the product level since individual brand names can be identified in both systems.

Moreover, when constructing drug treatment trajectories, one might encounter unexpected patterns that are methodologically well constructed from a pharmacoepidemiological perspective but are less logical from a clinical perspective. This is not truly a misclassification of the drug product in a formal sense, but it might affect the drug treatment trajectories. To correctly assess these drug treatment trajectories, researchers often need to combine multiple data sources and/or consulting clinicians to obtain information on which originator or specific biosimilar the patient was exposed to.

In *Chapter 7*, some patients appeared to transition from an originator infliximab to a biosimilar and vice versa multiple times, which is unexpected from a clinical perspective. We suspected that these unexpected trajectories were due to (accidental) prescribing errors. In order to overcome this, every patient's electronic health record

(EHR) file notes were checked to see if retransitioning was explicitly mentioned by the HCP. If retransitioning was not mentioned, we assumed that it was a prescription error. After checking the patients' EHR file notes, the patients' drug treatment trajectories were much more logical from a clinical perspective, as many transitions turned out to be accidental errors. Thus, researchers need to exclude potential misclassification due to prescription errors and, if applicable, describe how they minimise this form of misclassification in their study protocols.

Misclassification due to the dosing regimen of TNFα inhibitors

When patients initiate TNFα inhibitor treatment, they usually, after receiving a loading dose schedule, follow standard dosing regimens as described in the specific TNFα inhibitor product information. TNFα inhibitors (similar to other biologicals registered for IMID) have standard dosing intervals ranging from once weekly to once every eight weeks.[2,13,16,17,20] This dosing interval is based on the pharmacokinetic and pharmacodynamic properties of TNFα inhibitors; they have a half-life of approximately 3-14 days, and their pharmacodynamic effects last for months.[21]

These pharmacokinetic and pharmacodynamic properties and long dosing intervals create specific challenges for assessing exposure status and, thus, for creating drug treatment trajectories. In assessing exposure status to drugs that are administered daily, the exposure usually ends at the theoretical end date of the last prescription, thus (in theory) when the patient took the last tablet.[22] However, in assessing exposure to TNFα inhibitors, depending on the TNFα inhibitor, the long dosing intervals mean that exposure might end several weeks after the last administration. This should be taken into account when constructing treatment trajectories for TNFα inhibitors but also for other (biological) drugs with similar properties.

Throughout a patient's drug treatment trajectory, various factors could change their individual dosing regimen, and these changes can be intended or unintended. Intended dosing regimen changes include prolonged dosing intervals (e.g., from weekly etanercept administrations to every two weeks) when the disease is well-controlled but also shortened dosing intervals when the disease is less controlled.[23] Data in the hospital setting captures information on the dispensed and/or administered dose. However, for s.c. TNFα inhibitors administered in the home setting, changes in a patient's individual dosing schedule are often not fully captured. TNFα inhibitors are usually dispensed for several months, in this thesis, usually for three months. When assessing exposure based on pharmacy dispensing records, the duration of the prescription is based on the dose that is captured at the moment of dispensing and the number of syringes dispensed. If the dosing regimen was changed during the duration

of the prescription without informing the pharmacy, the actual exposure would be prolonged or shortened (depending on the dosing regimen change) compared to the calculated exposure, leading to misclassification of exposure. In addition to the control or lack of control over the disease, dosing regimens could also incidentally change by skipping a TNFα inhibitor administration when the patient is recovering from an infection or due to logistic reasons, for example, a holiday.

In *Chapters 2 and 5*, data from pharmacy dispensing records were used to assess the drug treatment trajectories of (among others) s.c. TNFα inhibitors administered in the home setting. Some of these records had a variable dosing regimen, for example, "once every 3 - 4 weeks, depending on disease state", without further information on the patients' exact regimens. In these chapters, we used the longest regimen within the patients' variable dosing regimens to avoid misclassifying patients as discontinued. Thus, the example dosing regimen was assessed as once every four weeks. However, this potentially leads to overestimating the duration of the patient´s exposure.

Dosing regimen changes can also be unintended, due to medication non-adherence, for example. For TNFα inhibitors, non-adherence (defined as a <80% medication possession ratio) is reported to be between 25% and 29%,[24,25] which is similar to non-adherence to methotrexate in RA (26%)[26] and thiopurines in IBD (29.5%).[27] Notably, in these studies, the standard dosing regimen,[24] or the dosing regimen as captured in pharmacy records[25] was used. Thus, these studies did not account for intended dosing regimen changes. Non-adherence to TNFα inhibitors is associated with loss of response,[25] as it can increase the risk for the formation of antibodies, for example.[28] Thus, in studies on the effect of TNFα inhibitors, results might be differentially biased due to non-adherence, as non-adherence affects both the exposure and the outcome of the study. In *Chapters 2 and 5*, we had no information on medication non-adherence, which was a significant limitation in both chapters.

Due to these (uncaptured) changes in dosing regimens, the estimated exposure was incorrect, time gaps arose between subsequent prescriptions or dispensings, and ultimately, these time gaps exceeded the maximum permissible gap, and the patient was misclassified as discontinued. The underlying reasons for misclassifying the exposure are related to the clinical effect of the TNFα inhibitor (prolonged dosing interval: effective treatment; shortened dosing interval: ineffective treatment; administrations skipped: infections, possible adverse event). This leads to bias in the exposure-outcome assessment and the clinical interpretation of the patient's health status.

The previous paragraphs highlights the importance of researchers carefully considering handling these uncertainties in dosing regimens and choosing the length of the maximum permissible gap between prescriptions and/or fills. These choices affect their exposure definition, and, in case treatment discontinuation is the study outcome, their outcomes. Therefore, the transparency of these choices in the study protocol or methodology section of related research papers should be encouraged. In the ENCePP checklist for study protocols,[29] operational details for defining exposure are required, although not on the detailed level of handling dosing regimens and maximum permissible gaps. Adhering to the ENCePP checklist would be a valuable first step to encouraging transparency, and extending the checklist should be considered.

Another way to overcome the discrepancy between the dosing regimen captured in the data source and the patient's actual dosing regimen is by directly obtaining information on the actual dosing regimen with which the patient is complying. For infliximab administered in the hospital setting, this could be done by obtaining medication administration data. For TNFα inhibitors administered in the home setting, an (automatic) registration of administering the dose would be ideal. This could either be done by the patient, in, for example, the patient's EHR patient portal, or automatically using the device or the needle container.[30] The latter solutions also capture patients' medication non-adherence and are used in, for example, assessing medication non-adherence in clinical trials.[31]

Immortal time bias

When designing studies in which drug treatment trajectories of patients who transitioned from TNFα inhibitor originators to biosimilars are compared with patients remaining on originators, the follow-up period needs to be carefully defined to avoid immortal time bias. Immortal time bias is the bias that occurs when there is a time lapse between the start of a patient follow-up and the start of the actual exposure. During this time, the patient is considered "immortal".[32] This can be illustrated by a cohort of patients transitioning from an originator to a biosimilar. Before the biosimilar was initiated, the patients had used the originator for some time. If follow-up for these patients starts at the initiation of the originator, they are not exposed to the biosimilar, as treatment with the originator is a prerequisite to be included in the study. During the time these patients are still treated with the originator and not exposed to the biosimilar, they cannot develop the outcome (for example, drug discontinuation). Thus, they are considered immortal to the outcome.

We encountered a similar issue in *Chapter 7*, in which we compared the risk of infliximab discontinuation between patients who retransitioned from infliximab

biosimilar to the originator and patients who remained on an infliximab biosimilar. Both cohorts of patients were initially treated with the biosimilar before some patients retransitioned to the originator. We overcame this potential bias by starting follow-ups for patients who retransitioned from the moment they re-initiated the infliximab originator. However, as the comparator group was already on biosimilar treatment, starting their follow-up from the moment they initiated biosimilar treatment would lead to biased results, as they are in an earlier phase of their drug treatment trajectory, and discontinuation risks change over time. In order to overcome this, patients were matched based on the duration of biosimilar treatment time, meaning that patients who remained on biosimilar were matched to a patient in the retransitioned cohort with a similar duration of biosimilar treatment time. This is illustrated as the matching date in Figure 1.

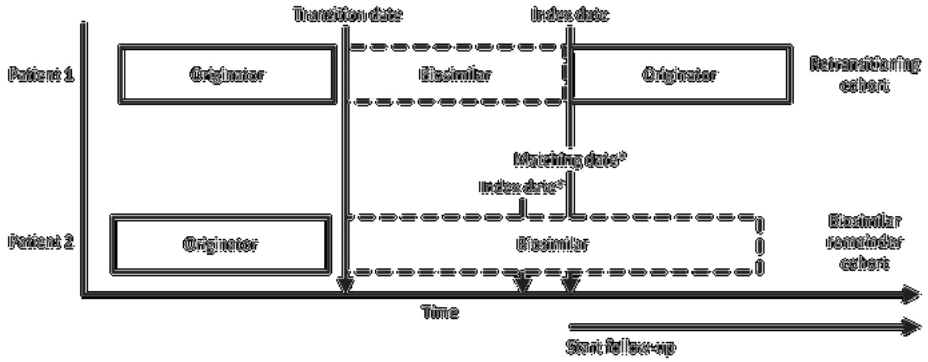

Figure 1: Matching of patients in *Chapter 7*. For patients in the biosimilar remainder cohort, the infliximab biosimilar administration date closest prior to the matching date was assigned as their index date.

How follow-up time is defined in studies that assess outcomes after (re)transitioning is important and has an impact on the study's conclusions. This is illustrated when comparing the results from our study in *Chapter 7* with the previous study by Mahmmod et al.[33] This previous study also studied infliximab discontinuation between patients who retransitioned and patients who remained on biosimilar. In this study, follow-up started for all patients at the moment they transitioned to a biosimilar. The authors found no difference in discontinuation rates between the retransitioned patients and the patients continuing biosimilar treatment. [33] However, as retransitioned patients were not yet exposed to the originator at the start of follow-up, the time they were treated with the biosimilar could be considered as an immortal time bias, leading to underestimating discontinuation rates among the retransitioned patients.

In our study, a larger proportion of patients who retransitioned discontinued infliximab treatment compared with patients remaining on biosimilar, whereas Mahmmod et al.

found similar proportions of patients discontinuing infliximab. The matching strategy and start of follow-up in *Chapter 7* are in line with recommendations on designing comparative studies between patients continuing originator treatment versus patients transitioning from originator to biosimilar.[34] However, this is not standard practice in all papers comparing originator and biosimilar treatments, leading to questionable outcomes.[35] Thus, adherence to these recommendations should be improved to avoid immortal time bias.

Furthermore, in the case of long-acting biologicals such as infliximab, patients cannot discontinue treatment for several weeks or even months after they (re)transition due to the long standard dosing interval of eight weeks. If this is not taken into account in the analysis, this might also create immortal time bias. For patients in the retransitioned cohort in *Chapter 7*, follow-up started from the exact moment of an infliximab administration. To account for this, we started the comparator cohort's (biosimilar remainder cohort) follow-up from the closest administration before the matching moment, as shown as the index date for the biosimilar remainder cohort in Figure 1. However, as this source of immortal time bias is not mentioned in the recommendations, these should be extended.

Conclusion

Transforming routinely collected healthcare data on the use of TNFα inhibitors into drug treatment trajectories has specific challenges, mainly in correctly classifying the drug product, taking the long and sometimes changing dosing regimens into account, and avoiding immortal time bias. These challenges are applicable not only to constructing treatment trajectories for TNFα inhibitors but also to other biologicals.

b. Drug treatment trajectories as a reflection of the patient's disease status

The TNFα inhibitor treatment trajectories above are constructed with information on the active substance or the brand name of the drug product, dosing regimen, date of dispensing or administration, and the number of units dispensed or administered. From these data, alterations in the TNFα inhibitor treatment are visible. These include, for example, a switch to another TNFα inhibitor or to another biological with a different mode of action (or a JAK inhibitor), a change in dosing regimen that is captured in the data, as described above, or discontinuation of the TNFα inhibitor. These alterations in treatment are often clinically motivated and can indicate the patients' well-being and the course of the disease, which reflects treatment effects and is, therefore, valuable information for clinical practice and for research.

Switch to another biological

In *Chapter 2*, we demonstrated that the incidence of switching from the initiated TNFα inhibitor to another biological (other TNFα inhibitor or biological with another mode of action) was similar across IMID indications. We found that approximately 16% of patients who initiated TNFα inhibitor treatment switched treatment after a median treatment duration of more than six months. A switch to another biological can indicate many different aspects of a patient's well-being, depending on the timing of the switch and to which product. In general, switching is recommended in clinical guidelines when patients experience lack of effect, loss of effect, and/or adverse events from their TNFα inhibitor. Guidelines recommend switching patients who never had treatment effect within a few months to a biological with another mode of action and recommend switching patients who initially had a positive treatment effect but lost the effect to either another TNFα inhibitor or a biological with another mode of action. Patients with adverse events could either switch to another TNFα inhibitor or biological with another mode of action, depending on the type and severity of the adverse event.[4,5] Thus, the type of treatment a patient switches to gives some information on the reason for switching. However, based solely on an individual patient's drug treatment trajectory constructed with health care data, switches due to loss of effect cannot be distinguished from switches due to adverse events, which makes interpreting the clinical reasons for switching treatment challenging. Moreover, clinicians might, for the individual patient, make treatment decisions that are not fully in line with the guidelines, or clinicians might adhere to national or regional guidelines or formularies with other recommendations on switching.

To further interpret the clinical reasons for switching, we used additional data on (disease-specific) comedication and laboratory data to untangle the most obvious reason for switching, which seemed to be loss of effect. Nevertheless, by assessing the clinical reasons for switching based on proxies for disease worsening in *Chapter 2*, we were unable to assess if patients (also) had adverse events or other reasons for switching.

Discontinuing treatment without switching

If disease control is not reached after trying several biological treatments and/or JAK inhibitors, a patient may also discontinue biological treatment and receive non-pharmacological interventions, such as surgery for IBD.[36] IBD patients who underwent a resection and do not have risk factors (e.g., smoking) are eligible for discontinuing treatment until disease symptoms return.[37] However, observing treatment discontinuation in a patient's drug treatment trajectory could also be due to sustained remission. In *Chapter 7*, 7.6% of included patients discontinued their

infliximab treatment because they had reached sustained remission, and in a previous study, 21% of patients were able to discontinue infliximab, as they were in sustained remission.[38] This indicates that interpreting treatment discontinuation in a patient's drug treatment trajectory is also challenging, as it could be interpreted as both treatment failure or treatment success.

Transitioning to a biosimilar and retransitioning to the originator

Non-medically driven changes can also impact a patient's drug treatment trajectory, most importantly, a transition from an originator TNFα inhibitor to a biosimilar or between different biosimilars with the same active substance. These transitions are often brought about due to policy changes with underlying financial drivers. The decision to implement a biosimilar in clinical practice could be made on a national (e.g., Denmark[39]), regional (e.g., Italy[40]) or hospital level (e.g., the Netherlands [*Chapter 7*]), depending on the health system. Moreover, the decision of which patients are transitioned to the biosimilar also depends on national or local decision-making. In our review in *Chapter 4*, patient- and disease-related factors associated with the incidence of retransitioning in the included studies were explored. We found that in some of the included studies, all patients were transitioned from an originator to a corresponding biosimilar, but in others, only a selection of patients were transitioned, for example, those with stable disease or after a minimum duration of originator use. When studying transitions from an originator to a biosimilar, it is important to know at the patient level in settings with mandatory transitioning of all patients, such as Denmark[41], why a certain patient was not transitioned, as patients who transitioned might differ from patients who did not, potentially resulting in channelling bias.[42]

For patients who retransitioned from a biosimilar to the originator, it is often also not clear from data such as the patients' comedication or laboratory values what the reason for retransitioning was. For example, if a patient retransitioned to the originator due to experiencing an adverse event on the biosimilar, this can often not be derived from comedication or laboratory values. However, the reason for retransitioning is valuable information for understanding a patient's drug treatment trajectory.

Gaining insights on clinical reasons for treatment change

As described above, conclusive information on the reason for treatment alterations is needed for interpreting alterations in the drug treatment trajectories. In *Chapters 5* and *7*, we were able to extract information on changes in individual patients' drug treatment trajectories from their EHR file notes, including patients' reasons for retransitioning from biosimilar to originator treatment and reasons for treatment discontinuation. However, manually searching individual EHR file notes is time-

consuming and laborious and thus only feasible in studies with small sample sizes. In order to overcome this issue, future research should improve natural language processing and data mining techniques for extracting information from unstructured text, such as free-text EHR file notes. Advancements in techniques for extracting structured information are already under development but are not yet sufficient for unstructured text.[43] Unstructured text is less suitable for automatic information extraction; thus, it requires advanced methods and machine learning techniques for reliable extraction.[44] Moreover, they should be tailored to the specific terminology and characteristics of IMID patients, for example, to the large variety of descriptions of disease recurrence or adverse events.

Noting clinical data in a structured format is frequently used in disease registries, such as the Danish DANBIO registry, which captures disease and treatment information from all Danish patients with a rheumatic disease and includes information collected from their HCP but also from the patients themselves.[45] Registries often cover a specific indication or a specific drug and are thus not always useful, for example, for studying multiple diseases or drugs. Nonetheless, they demonstrate the possibility of capturing data in a structured way. This is also shown in the Dutch 'Medicatieproces 9',[46] a standard (language) of medication use data to improve information exchange between health care settings, which is also a form of structured data notation and might also be useful for research purposes. To improve the quality of structured data notation for research purposes, clinicians in the UK and the Netherlands already receive feedback on the quality of their recordings.[47] However, they still need training to improve the quality of their coding.[48] This should be embedded in clinicians' prescription training and facilitated by the EHR.

In *Chapter 5*, we studied patients who transitioned from the originator etanercept to the corresponding biosimilar. A subset of these patients retransitioned to the originator. We manually extracted their reasons for retransitioning from their EHR file notes. In *Chapter 6*, we interviewed patients directly on (among others) their perceptions of retransitioning. Comparing the reasons extracted in *Chapter 5* and the perceptions in *Chapter 6* yielded the insight that patients have a much broader reasoning for retransitioning from the biosimilar than we extracted from the EHRs. These included, for example, detailed descriptions of the development of multiple patient complaints, including a timeline that is summarised in the EHR file notes as "increased disease activity". Therefore, information directly extracted from patients is a valuable addition, and patients should be used as a source of information more often. This could be carried out such as in the previously mentioned DANBIO registry, in which patients register information on their disease status and well-being.[45] This would

enable researchers to gather information directly from patients themselves without the interference and interpretation of their HCP. The Dutch IB-DREAM register also allows patients to directly report adverse events.[49] However, both examples are still limited to one group of diseases and, especially in the case of the IB-DREAM, limited patient input. Thus, there is still room for expanding the options of capturing information directly from the patient.

Conclusion

In conclusion, drug treatment trajectories are a valuable source for studying clinically oriented research questions. However, for detailed clinical interpretation of drug treatment trajectories, additional data on patients' disease status and well-being are necessary.

2. Introducing a biosimilar in clinical practice

The primary focus of this thesis was the transition from a TNFα inhibitor originator to a biosimilar. After transitioning, most patients (70% in *Chapter 5*) remained on their biosimilar treatment, indicating that, for most patients, transitioning to a biosimilar was successful. However, as we showed in *Chapters 4, 5, 6, and 7*, a number of patients retransitioned from the biosimilar back to the originator. This indicates sub-optimal treatment with the biosimilar, related to patients experiencing loss of effect, adverse events with the biosimilar, and/or not feeling confident with the biosimilar. Factors related to retransitioning were also explored and included patient, disease- and treatment-related factors, and factors related to the implementation strategy (*Chapters 4 and 5*). As already discussed, studies in this thesis of patients who transitioned and a subset of those who retransitioned yielded many methodological insights on creating drug treatment trajectories. However, they also yielded several insights and recommendations on the introduction of biosimilars and on retransitioning for clinical practice.

Selecting a biosimilar for clinical care

For all TNFα inhibitors that lost market exclusivity up to 2022, multiple biosimilars have become available.[50] Thus, healthcare systems not only benefit from competition between originators and biosimilars but also from competition among the different biosimilars.

Selecting the lowest-priced biosimilar allows for the greatest financial benefits from transitioning to a biosimilar. However, despite proof of biosimilarity for the drug substance (the active substance), the originator and the individual biosimilars may vary in terms of the drug product. Biosimilars do not include the same excipients by

default, and, in the case of s.c.-administered TNFα inhibitors, the same injection device as their corresponding originator. As these differences affect patients' experience of the biosimilar, these are relevant characteristics when selecting which biosimilar will be introduced.

In the past, issues with drug devices have been reported when substituting brand drugs for generics, for example, with inhalation drugs, where an increase in the number of reports of diminished therapeutic effect was observed among patients who were substituted from brand to generic inhalation drugs.[51,52] This may be explained by the problems patients encountered with substituting one device for the other, which could lead to more asthma exacerbations.[53,54]

For TNFα inhibitor biosimilars, several differences between the originators and biosimilars related to the device have been mentioned, which could be disadvantageous. However, some patients prefer the biosimilar. For example, the adalimumab biosimilar Amgevita has a thicker needle than the adalimumab biosimilar Imraldi,[55] which is related to more injection site pain.[56] In addition, the adalimumab biosimilar Amgevita's prefilled pen contains latex in the needle cover, a substance that may cause allergic reactions.[20] In our study (*Chapter 6*), two patients reported more injection discomfort with Imraldi than with Humira due to differences in needle injection speed, which is in line with findings in a previous study on patients' experiences with injecting Imraldi and Humira.[57] Despite reporting this discomfort, they did not indicate that this was their main reason for retransitioning to Humira.

However, in the case of the etanercept biosimilar, most patients (74%) preferred the Benepali autoinjector over that of Enbrel, as it was easier to use.[58] Moreover, fewer injection site reactions were reported for Benepali compared with Enbrel in both our study (*Chapter 6*) and previous research.[59] Thus, in terms of the drug product, transitioning to a biosimilar could also have advantages for patients.

The most-debated difference in terms of excipients for TNFα inhibitors is the citric acid buffer that used to be in Humira but was removed in 2016.[60] Patients reported less injection pain with the citrate-free formula compared with the citrate-containing formula.[61] However, some adalimumab biosimilars, such as Imraldi, contain citrate to improve the stability of the product at room temperature.[15]

For professionals in charge of selecting a biosimilar for clinical practice, factors like the drug formulation and injection device should be considered when selecting a biosimilar. Despite the active substance being similar, differences between the

drug products might exist. These can be relevant for patients' satisfaction with the biosimilar compared with the originator (or the 'old' biosimilar in the case of cross-transitioning). Therefore, (hospital) pharmacists are advised to consider not only cost but also all of the aforementioned factors when selecting the most suitable biosimilar for their patients.

Acceptance of biosimilars: analogy with brand-to-generic substitution

Patients who do not accept brand-to-generic substitution are also more likely not to accept transitioning from an originator to a biosimilar. This was mentioned by some patients in *Chapter 6*, who were interviewed on their perceptions on biosimilars and has also been reported in previous research. [62,63] Substituting a brand drug for a generic has been performed for many decades and is current clinical practice. From a regulatory perspective, the generic drug needs to demonstrate bioequivalence to obtain market authorisation. Thus, from a pharmacological perspective, no changes in response to the generic drug compared to the brand drug are expected. Despite the proven bioequivalence, as showed in an Irish study, almost one in five patients stated an explicit belief that the brand drug is better than the generic and one in 10 patients opposed brand-to-generic substitution.[64] A study from New Zealand conducted in 2015 showed that several patients still have concerns about the efficacy (36%), quality (25%) and safety (18%) of generic drugs.[65]

Due to the similarities in opinions on brand-to-generic substitution with originator-to-biosimilar transitioning, it is likely that some patients will continue to question biosimilars, as is still the case for generics. Moreover, biosimilars have more complex terminology. Small-molecule generics are often referred to as identical copies of the brand molecule. However, biosimilars are, due to clinically irrelevant heterogeneity of the molecules produced in biotech processes, considered similar to their originators. For some patients, it might be complex to understand that similarity in biosimilars is just as ensuring as identicality in generics. This makes it even more unlikely to expect all patients to accept biosimilars. Regarding generics, in the Netherlands, it is accepted that a subset of patients who switched from a brand to a generic drug will be retransitioned to the brand drug or not switched at all. The same could be considered for biosimilars. The decision of which patients retransition should be made on an individual basis between the HCPs (medical specialist and [hospital] pharmacist). In *Chapter 4*, we saw that the incidence of retransitioning varied between 0.5% and 72% across the included studies, indicating that the incidence varies greatly across settings and strategies and that one overall expected incidence of retransitioning for all settings cannot be provided. Clinical guidelines could support HCPs in decisions

on retransitioning. However, as shown in *Chapter 3*, retransitioning is included in only a subset of guidelines on biosimilars. Thus, medical associations are encouraged to include retransitioning in their biosimilar guidelines.

Communication with and guidance for transitioning patients

Previous studies have recommended increasing patients' knowledge and thereby managing their expectations of biosimilars with the intention of reducing unexplained, unwanted effects when IMID patients transition from an originator to a biosimilar. [66–68] Thus, building the HCP confidence in biosimilars is key and can be achieved through educating the HCPs on biosimilars. The HCPs are then expected to transfer this information and confidence in biosimilars to their patients. The HCP may tailor the content and level of information to the individual patient or use positive framing.[66,68] According to those studies, to streamline the transitioning process, a structured strategy should be used with standardised communication from all HCPs to patients, minimising the risk of divergent opinions being expressed.[66,69]

In *Chapter 6*, patients reflected on their trust in biosimilars and the information they received from their HCPs prior to first use of the biosimilar. Despite the fact that all patients included in this study had retransitioned to the originator, several patients mentioned that they did have trust in biosimilars. This trust was gained after receiving reassuring information from their HCP and other patients' experiences with biosimilars. Some patients responded well to their initial biosimilar but lost effect when they cross-transitioned to the second biosimilar. These findings contradict the idea that building trust in biosimilars will eliminate these unexplained and unwanted responses finally resulting in retransitioning.

Furthermore, as stated earlier, patients' opinions on biosimilars are often not independent but are a reflection of their opinions on generic drugs in general. Solely focussing on positive and unified communication strategies regarding one biosimilar transition will not address patients' concerns regarding generics in general. Therefore, patients should also become more familiar and comfortable with generic drugs in general. Other studies suggest that communication on generics might improve generic acceptance.[70]

Informing patients about biosimilars is important for practical reasons, such as a change in injection device, for example. However, informing patients in order to build their trust in biosimilars will not fully prevent unwanted responses after transitioning. Therefore, when introducing biosimilars in clinical care, HCPs should not over-rely on communication strategies to prevent unwanted responses.

Unwanted responses after transitioning to biosimilars

Several observational studies reported higher discontinuation rates among patients who transitioned from TNFα inhibitor originator to biosimilar compared with patients who remained on originator treatment.[71–76] Their explanation for this finding was that patients who transitioned had more subjective complaints (such as fatigue, in contrast to objective complaints, like increased faecal calprotectin in IBD) after transitioning, which could be linked to the nocebo effect.[77] The nocebo effect is defined as a negative effect of a (pharmacological or non-pharmacological) treatment induced by the patient's negative expectations of the treatment and not related to the physiological action of the treatment, and is the negative counterpart of the placebo effect. These negative expectations can be influenced by many different factors, such as the HCP's verbal (e.g., informing on possible adverse events) and non-verbal communication, observing other patients experiencing symptoms, or media attention.[68]

A previous study added to the definition of the nocebo effect that patients should regain benefits after retransitioning.[81] Following this definition, of the 342 patients included in *Chapter 5*, 38 (11.1%) retransitioned, mainly due to loss of effect and continued treatment with the originator for a median of 2.0 years, suggesting a positive effect of retransitioning and supporting that the nocebo effect played a role. However, actually confirming that the loss of effect was a nocebo effect is difficult, as it also fits within the expected course of the disease and/or treatment. The course of IMIDs is often capricious, with subsequent cycles of low and high disease activity. Disease control is negatively affected by various patient-related factors unrelated to their TNFα inhibitor use, such as stress, overexertion, smoking, cold weather (RD), use of NSAIDs or antibiotics (IBD), and many others.[82–85] Moreover, in general, IMIDs progress over time, and treatment responses also decrease over time. This is illustrated by the finding in *Chapter 2* that about 50% of IMID patients who initiated TNFα inhibitor treatment discontinued treatment within two years, probably due to lack or loss of effect or immunogenicity.

Thus, irrespective of transitioning to biosimilars, disease flares might be triggered by various factors, and response to TNFα inhibitor treatment decreases over time. Although in controlled studies, such as the NOR-SWITCH study, this is ruled out by the control group[86], individual patients might have attributed a losing effect or the experience of adverse effects to the biosimilar. This was illustrated by some patients in *Chapter 6*, who experienced loss of effect and/or various adverse events after transitioning to their biosimilar, attributing these unwanted effects to the biosimilar.

Some patients in *Chapter 6* pointed out that this loss of treatment effect can have a severe impact on patients' daily lives and, therefore, should be treated adequately regardless of the nocebo effect playing a role in these complaints. Thus, authors of (observational) studies on the clinical effects of transitioning patients to biosimilar are encouraged to think beyond categorising (subjective) complaints as a nocebo effect since this does not benefit clinical care for these patients. The next paragraphs will further elaborate on this topic, including recommendations for clinical practice.

Follow-up after transitioning

As the biosimilar is similar to the originator in terms of efficacy, safety, and immunogenicity, it is expected that the course of treatment will not change compared to if the originator was continued. Thus, extra follow-up for transitioned patients, in addition to routine follow-ups outside transitioning, are, from a pharmacological perspective, not necessary.

However, patients experience the transition as a major change in their treatment or, despite all scientific evidence, worry about the efficacy and safety of the biosimilar. Moreover, patients in *Chapter 6* stated that they felt dependent on their TNFα inhibitor originator for pursuing a normal life and were worried about loss of effect having a severe impact on their lives.

To address patients' concerns, extra follow-up for patients after transitioning could be of value. The findings from the systematic review in *Chapter 4* suggest that extra follow-up with laboratory measurements and/or extra visits to the outpatient ward is associated with a lower retransitioning rate. Based on the similarity principle between biosimilars and originators, this is probably not because the biosimilar needs extra monitoring but because it might reassure patients that they are being looked after. Some patients that participated in our qualitative study on retransitioning (*Chapter 6*) stated that they lacked monitoring of the course of their disease right after transitioning. One patient stated that she felt that her disease flaring might have been detected earlier if she had been monitored after transitioning. A previous study on substituting brand antiepileptics for generics also found that more frequent contact with the nurse made participants more secure and comfortable, which explained their low switchback rates to brand antiepileptics.[87]

This aspect of patients' need for follow-up is currently not fully reflected in European clinical guidelines. In *Chapter 3,* we showed that while the national gastroenterology associations endorse biosimilar transitioning in their guidelines, only half recommended monitoring patients after transitioning. Further, we saw that the recommendations on

monitoring were diverse and unspecific. For example, monitoring for pharmacovigilance was recommended but without further specifying what it meant or when to monitor.

As most patients retransition due to loss of effect or adverse events, the most logical parameters to monitor are disease activity, adverse events, and general well-being. There are several possibilities for monitoring, for example, with extra visits, telephone calls, or monitoring in a digital patient portal. The most efficient and feasible way to perform this follow-up should be developed in further research. However, extra patient follow-up requires additional use of healthcare and thus will increase costs. This should be taken into account when developing a follow-up strategy. Furthermore, without extra patient follow-up, there is already an increased use of healthcare services directly after a patient transitions from an originator to a biosimilar.[88]

Conclusion

Despite many patients having successfully transitioned from their originator TNFα inhibitor to a biosimilar, the introduction of biosimilars in clinical practice can still be improved, for example, by providing extra follow-up to transitioned patients. However, the expectation of complete acceptance of biosimilars and thereby the total prevention of patients from retransitioning is too optimistic. Therefore, HCPs and policymakers should adjust their expectations and policies, analogue with brand-to-generic substitution and switchbacks and accept that a minor population of patients will retransition.

Recommendations for future research

TNFα inhibitor treatment trajectories, including the introduction of biosimilars was a central topic of this thesis. Findings from creating treatment trajectories for TNFα inhibitors are also applicable to other (long-term) biological treatments and for other indications, as they deal with similar challenges. Throughout this research, the following (more methodologically focused) recommendations and directions for future research arose:

- Researchers are encouraged to critically assess their considerations when creating drug treatment trajectories and describe these in their protocols and publications. These considerations include:

    - Handling dosing regimen changes not captured in traditional data sources such as prescription or dispensing data.

  - Carefully selecting the length of the maximum permissible gap between prescriptions and/or dispensings, including taking the pharmacokinetic and dynamic properties into account.

  - In studies in which patients are (re)transitioned between an originator and a biosimilar, verifying that transitions were intentional and not accidental (when possible).

- Despite immortal time bias being widely known and not specific to biosimilars, studies that focus on (re)transitioning to a biosimilar are at risk for this bias. Researchers could adhere to existing guidelines and recommendations specific to biosimilars and the general pharmacoepidemiologic guidelines to avoid this bias. This might require (additional) education in (pharmaco)epidemiologic principles.

- When studying transitions from an originator to a biosimilar, researchers should be acquainted with the clinical and policy context in which it is decided that patients will transition, as this could affect treatment outcomes by potentially channelling of biosimilar treatment to certain patients.

- To interpret clinical reasons for patients switching treatment, discontinuing treatment, and retransitioning from biosimilar to originator, researchers should seize additional data, as solely a patients' drug treatment trajectories are insufficient for understanding clinical reasons. EHR file notes can be a useful source of additional information but also directly asking the patient.

- Researchers should develop methods for capturing information on patients' actual medication use. This could be done, for example, using digital patient portals of the EHR or with smart devices that automatically capture medication administrations.

- As more biosimilars of one originator have become available, biosimilar-to-biosimilar transitioning (cross-transitioning) will be performed more often in clinical practice. In *Chapter 3*, we found that only a few associations had guidance on cross-transitioning. In *Chapter 6*, some patients experienced unwanted effects after cross-transitioning, which illustrates that cross-transitioning does not naturally go hassle-free. In order to improve cross-transitioning, research regarding patients' (and possibly HCPs') cross-transitioning needs should be carried out, and guidelines should incorporate a position on cross-transitioning.

Recommendations for clinical practice

Within this thesis, patients transitioning from a TNFα inhibitor to a biosimilar were studied in various contexts and stages of their drug treatment trajectories. In addition to methodologic recommendations, this also yielded several recommendations for implementing biosimilars in clinical practice:

- When selecting a biosimilar to introduce in their clinical practice, (hospital) pharmacists should, together with prescribers, nurses, and patients, consider multiple assets of the product and not only base their decision on the lowest-priced biosimilar.

- It appears that patients' lack of trust in biosimilars is associated with a lack of trust in generic drugs in general. Trust in generics and biosimilars should be increased by educating patients on generics, emphasising their efficacy and safety.

- However, HCPs should be aware that patients who do have trust in biosimilars can still experience unwanted, unexplained effects after transitioning to a biosimilar. Thus, they should be aware that building trust will not completely prevent all patients from retransitioning.

- Policymakers (and HCPs and pharmacists [and payers]) should accept that a certain amount of patients will not transition to a biosimilar and a certain amount will retransition. Thus, they should tailor their policies and guidelines to some patients not transitioning or some retransitioning.

- Patients who have transitioned from a TNFα originator to a biosimilar should receive follow-up care to address their possible concerns after transitioning. This follow-up should be tailored to patients' needs, as probably not all patients will need extra follow-up. The practical recommendations for follow-up should be developed in further research.

Conclusion

In conclusion, in this thesis, the TNFα inhibitor treatment trajectories of IMID patients were mapped and analysed, which provided insight into the trajectories themselves. By addressing the transition from an originator TNFα inhibitor to a biosimilar, the thesis provided insights into the impact of biosimilar transitioning on TNFα inhibitor treatment trajectories. Moreover, retransitioning from a biosimilar to an originator was studied from several angles. From these insights, recommendations were provided for the improvement of constructing drug treatment trajectories and the introduction of biosimilars in clinical care.

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CHAPTER 9

Summary & Samenvatting

9.1 Summary

Introduction

For patients with immune-mediated inflammatory diseases (IMIDs), treatment options have expanded from conventional, small-molecule immunomodulator drugs to biologicals. Within the class of biologicals, Tumour Necrosis Factor (TNF) α inhibitors are commonly used as first-line biological therapy, and these agents have become the standard of care for the treatment of IMIDs. However, the therapeutic response to TNFα inhibitors, as to all (biological) drugs, varies between patients and within a patient over time.

At the time of introduction on the market, TNFα inhibitors were costly, which posed a challenge due to their impact on healthcare budgets. The introduction of biosimilars ("a biological medicinal product that contains a version of the active substance of an already authorised biological medicinal product [originator]") several years ago led to competition, resulting in lower prices for TNFα inhibitor treatment and improved patient access to these treatments. IMID patients treated with an originator TNFα inhibitor in clinical practice were transitioned to the biosimilar for cost-containment reasons. As biosimilars and originators are similar products concerning quality characteristics, efficacy and safety, transitioning from an originator to a biosimilar in daily clinical care should, in principle, not affect the course of a patient's treatment. However, in some observational studies, a subset of patients subsequently retransitioned (i.e., restarted originator treatment), mainly due to (perceived) loss of effect and/or adverse events. Based on the comparability between an originator and its biosimilar, the pharmacological rationale for retransitioning is unclear and is not expected to regain effect. However, it might be, from a patient's perspective, a logical response to their unexplained but existing problems with biosimilar treatment.

As described in *Chapter 1*, an IMIDs patient's (TNFα inhibitor) treatment over time can be captured in treatment trajectories. A drug treatment trajectory is the period of time during which the patient is exposed to one or more drugs of interest and depicts the longitudinal treatment course of one or multiple patients. These trajectories capture both medically related, such as unwanted response or remission and non-medically related changes, such as transitioning to a biosimilar. As the therapy duration often spans many years and includes many possible treatment adjustments such as switches and dose changes, treatment trajectories of individual IMID patients can vary significantly and provide unique and valuable data for (observational) research.

In this thesis, insight into the TNFα inhibitor treatment trajectories of patients with IMIDs was provided. Quantitative and qualitative insight into the frequency and

determinants of transitioning from an originator TNFα inhibitor to a biosimilar, on retransitioning to the originator, and on biosimilar implementation strategies were also provided. From these insights, learnings on implementing a biosimilar in clinical practice were distilled.

Switching TNFα inhibitor treatment

In *Chapter 2*, we assessed switching (i.e. shifting from one active substance to another) patterns and determinants for switching in patients initiating TNFα inhibitor treatment. We demonstrated that about 17% of patients with a rheumatic disease (RD), 14.5% of patients with inflammatory bowel disease (IBD) and 16% of patients with psoriasis switched at least once during their treatment trajectory, mainly to another TNFα inhibitor. TNFα inhibitor dose escalation (OR 13.78, 95% CI 1.40-135.0) and high-dose corticosteroids initiation (OR 3.62, 95% CI 1.10-12.15) were determinants for switching in RD patients. TNFα inhibitor dose escalation (OR 8.22, 95% CI 3.76-17.93), immunomodulator initiation or dose escalation (OR 2.13, 95% CI 1.04-4.34), high-dose corticosteroids initiation (OR 6.91, 95% CI 2.81-17.01) and serum concentration measurement (OR 5.44, 95% CI 2.74-10.79) were determinants for switching in IBD patients. The determinants for switching might indicate disease worsening, lack of response after initiating a TNFα inhibitor and/ or diminished effect of the TNFα inhibitor over time. These findings might help clinicians anticipating switching in TNFα inhibitor treatment.

Transitioning from a TNFα inhibitor originator to a biosimilar

In *Chapter 3*, clinical guidelines for transitioning (i.e. shifting from originator product to another brand name containing the same active substance) IBD patients from an originator TNFα inhibitor to a biosimilar were studied. We mapped the presence and content of guidance for TNFα inhibitor biosimilar use from European gastroenterology associations partnered with the European Crohn's and Colitis Organisation (ECCO). We found that 26 out of 30 countries in the European Economic Area have an ECCO-partnered gastroenterology association, of which 14 (53.8%) had national guidelines addressing treatment with biosimilars, four (15.4%) followed ECCO's position, and three (11.6%) had treatment guidelines without mentioning biosimilars. From five countries (19.2%) no guidelines were retrieved. Among 18 countries with guidance, 14 (77.8%) associations endorsed initiating biological treatment with biosimilars, and 13 (72.2%) endorsed transitioning from originator to biosimilar. Retransitioning was explicitly not endorsed by the associations following ECCO's position, but was not mentioned in any other guideline. Nine associations published multiple guidelines over time addressing biosimilars; overall, their positions became more positive towards use of biosimilars. Thus, the majority of gastroenterology associations endorsed biosimilar

use. The lack of (up-to-date) guidelines for some associations indicates an area of improvement to support biosimilar use in clinical practice.

One of the recommendations in the guidelines analysed in *Chapter 3* relates to retransitioning (i.e. discontinued use of the biosimilar and reinitiated treatment with the originator). Retransitioning is further studied in *Chapter 4*. Retransitioning from the biosimilar to the originator can be considered an indication of biosimilar treatment failure or dissatisfaction with biosimilar treatment. We estimated the cumulative incidence of patients who retransitioned from a TNFα inhibitor biosimilar to originator between 2012 and 2018 and to explore potential patient, disease, and treatment and implementation strategy factors associated with retransitioning. We found that in studies in which patients were transitioned from TNFα originator to biosimilar about 8% of patients retransitioned. Retransitioning appeared lower in studies that included only patients with stable disease, in studies that did not, at the introduction of the biosimilar, offered the option of retransitioning and in studies that applied extra laboratory monitoring and/or gainsharing (patients' healthcare directly benefits from financial savings from transitioning) as part of the implementation strategy.

Chapter 5 focussed on the incidence of retransitioning and determinants thereof solely in RD patients who transitioned from etanercept originator to the biosimilar in a large teaching hospital. Of the 342 patients included, 47 (13.7%) had retransitioned to originator at the end of follow-up (median 4.4 years). Most patients (n = 34 [72.3%]) retransitioned because of a (perceived) loss of effect, followed by adverse events (23.4%). Patients who visited the rheumatology department more frequently had an increased risk of retransitioning, which is likely to be related to patients reporting a loss of effect and/ or adverse events resulting in more visits to the rheumatology department.

Patients who had retransitioned were interviewed about their perspectives on transitioning and retransitioning; data from the first eight patients included in this ongoing study are presented in *Chapter 6*. Patients reported to lack autonomy in decisions on transitioning. They blamed this on their health care institute which they considered prioritising finances over patients' health. Patients considered their relationship with their rheumatologists to be strong. They acknowledged that their complaints during biosimilar treatment were adequately addressed by retransitioning them to their originator. To improve the implementation of biosimilars in clinical practice, policy makers could consider implementing a financial gain sharing model, increase trust in biosimilars and generic medicines in general, and increase patient involvement in decisions on transitioning to a biosimilar.

In *Chapter 7*, we compared the risk of and reasons for infliximab discontinuation between patients who retransitioned to originator and those who remained on biosimilar in a cohort of patients who transitioned from the infliximab originator to the biosimilar. Patients who retransitioned were matched to patients who remained treated with biosimilar infliximab. We found that 22.7% of patients in the retransitioning cohort vs 13.4% in the biosimilar remainder cohort discontinued infliximab due to an unwanted response, and 2.3% vs 9.4% of patients, respectively, discontinued due to remission. Retransitioned patients have a more than threefold increased risk of discontinuing due to an unwanted response compared with patients remaining on the biosimilar. Retransitioning in patients treated with infliximab appears to be mainly patient- or disease-related and less likely to be product-related. Clinicians might switch patients opting for retransitioning to other treatment regimens.

Discussion

Chapter 8 puts the findings of the studies presented in this thesis into a broader perspective. First, we described the challenges when creating drug treatment trajectories. Several challenges are met when using drug treatment trajectories as a valid tool for depicting exposure status. Creating drug treatment trajectories for TNFα inhibitors sometimes requires data from multiple settings, such as prescription and/ or dispensing data from the inhospital and the outpatient pharmacy, including the possibility of linking the data from these settings at the level of the individual patient. Furthermore, there is a potential for misclassification of the drug product, as not all data from these settings contain information on the brand name, which is required to differentiate between the originator and a biosimilar TNFα inhibitor. Next, TNFα inhibitors have long standard dosing intervals, and the dosing intervals could be personalized to the individual patient, often not fully captured in health care databases, resulting in misclassification of exposure status. Moreover, studies in which drug treatment trajectories of patients who transitioned from TNFα inhibitor originators to biosimilars are compared with patients remaining on originators, there is a potential for immortal time bias.

Using drug treatment trajectories to reflect the patients' disease also contains several challenges. The underlying reasons for events in the trajectories, such as switching treatment and discontinuing treatment without switching could be difficult to interpret, as they can indicate many different aspects of a patient's well-being, both negatively (e.g. loss of treatment effect, adverse events), but also positively (e.g. discontinuing treatment due to sustained remission). In addition, for patients retransitioning from a biosimilar to the corresponding originator, the reasons are often unclear from their treatment trajectories. To overcome these challenges in interpreting

a patients' treatment trajectory, additional information on the patients' disease status and well-being are needed, for example from individual electronic health records file notes.

Second, we gave several insights and recommendations on the introduction of biosimilars and on retransitioning from biosimilar to originator for clinical practice. We advise in selecting a biosimilar for clinical care not to consider only the cost of the biosimilar, but also the properties of its injection device and its excipients, as these can be be relevant for patients' satisfaction with the biosimilar. Furthermore, we described the analogy between the acceptance of brand-to-generic substitution and transitioning to biosimilars. Based on this analogy, we need to accept that a subset of patients who transition from originator to biosimilar will retransition to the originator, and include this in medical associations' biosimilar guidelines.

Moreover, we described the limited role of communication strategies in building trust in biosimilars in patients with the aim of preventing retransitioning. We stated that informing patients on transitioning to a biosimilar is important for practical reasons, such as a change of injection device. However, when introducing biosimilars in clinical care, health care professionals should not over-rely on communication strategies to prevent unwanted responses. Patients' perceptions on biosimilars can reflect their perceptions on generic drugs in general, thus efforts are needed to help them become more familiar and comfortable with generic drugs in general.

In addition, we gave insights in potential reasons for patients experiencing unwanted treatment response after transitioning to a biosimilar. In previous studies this is often classified as due to a nocebo effect. However, confirming the nocebo effect is difficult and the unwanted response could also be due to other factors, such as disease progression. Disease progression could fit into the natural course of the disease, or can be caused by general loss of treatment effect. However, it can be falsely attributed to transitioning to the biosimilar. It is therefore important to follow up patients after they transitioned to a biosimilar.

Last, we provided suggestions for future research and for improving the implementation of biosimilars in clinical practice. We made several recommendations to improve constructing drug treatment trajectories, e.g. critically assess important considerations in creating drug treatment trajectories, avoiding immortal time bias and including clinical and policy context to be aware of potential channelling of biosimilars to certain patients. We further recommended including additional data for interpreting events in drug treatment trajectories. Moreover, we yielded recommendations aiming to

improve the implementation of biosimilars in clinical practice, in terms of selecting a biosimilar, increasing trust, accepting a certain amount of patients retransitioning from biosimilar to originator and providing follow-up care to patients who transitioned from originator to biosimilar.

9.2 Samenvatting

Patiënten met immuun-gemedieerde ontstekingsziekten (IMID's), bijvoorbeeld reuma of de ziekte van Crohn worden vaak behandeld met biologische geneesmiddelen, ook wel biologicals genoemd. Binnen de groep van biologicals worden Tumor Necrosis Factor (TNF) α-remmers het meest gebruikt, en deze middelen zijn nu de standaardbehandeling voor IMID's. Het effect van TNFα-remmers kan echter verschillen tussen patiënten en binnen een patiënt in de loop van de tijd.

Toen de TNFα-remmers ongeveer 25 jaar geleden op de markt kwamen waren deze duur, en dat zorgde voor extra druk op het gezondheidszorgbudget en daarmee op de zorgverzekeringspremie. Door de komst van biosimilars (geneesmiddel met dezelfde werkzame stof, maar met een andere merknaam) werd de behandeling met TNFα-remmers goedkoper omdat er concurrentie ontstond. Veel IMID-patiënten die tot dan toe behandeld werden met de originele TNFα-remmer, werden gewisseld naar een biosimilar vanwege kostenbesparingen. Originele TNFα-remmers en biosimilars zijn qua kwaliteit, effectiviteit en veiligheid vergelijkbaar. Daarom zou wisselen van een originele TNFα-remmer naar een biosimilar geen effect moeten hebben op het beloop van de behandeling van een patiënt. Echter, in sommige eerdere onderzoeken bleek dat een deel van de patiënten die gewisseld waren van originele TNFα-remmer naar een biosimilar, vervolgens weer terug wisselde naar het origineel. Patiënten deden dat voornamelijk omdat zij het idee hadden dat de biosimilar minder goed werkte dan het origineel, of meer bijwerkingen gaf. Aangezien de originele TNFα-remmers en biosimilars even effectief en veilig zijn, is het onwaarschijnlijk dat patiënten meer effect of minder bijwerkingen ervaren als ze terug wisselen naar het origineel. Vanuit het perspectief van de patiënt kan dit echter wel een logische verklaring zijn voor de ontstane problemen tijdens het gebruik van een biosimilar.

In *Hoofdstuk 1* van dit proefschrift hebben we beschreven dat de behandeling van een IMID-patiënt met een TNFα-remmer vastgelegd kan worden in behandelpatronen. Een medicatie behandelpatroon is de periode waarin de patiënt blootgesteld wordt aan één of meerdere geneesmiddelen en geeft het beloop van de behandeling van één of meer patiënten weer. Deze behandelpatronen bevatten zowel veranderingen in de gezondheid van de patiënt, zoals ongewenste reacties of remissie, als niet-medische veranderingen, zoals wisselen naar een biosimilar. Omdat IMID-patiënten vaak jarenlang behandeld worden met geneesmiddelen, soms switchen van geneesmiddelen of de dosis van hun geneesmiddel aanpassen, verschillen de behandelpatronen van individuele IMID-patiënten veel van elkaar. Dit geeft veel waardevolle en unieke gegevens voor onderzoek.

In dit proefschrift hebben we inzicht gegeven in de behandelpatronen met TNFα-remmers van patiënten met IMID's. We hebben zowel kwantitatief als kwalitatief inzicht geboden in de frequentie van en factoren die een rol spelen bij de overstap van een originele TNFα-remmer naar een biosimilar, het teruggaan naar het originele geneesmiddel en de strategieën voor de implementatie van biosimilars. Op basis van deze inzichten hebben we aanbevelingen gegeven met betrekking tot de implementatie van een biosimilar in de klinische praktijk.

Switchen van TNFα-remmers

In *Hoofdstuk 2* hebben we de patronen van het switchen (het overstappen van de ene werkzame stof naar de andere) en mogelijke risicofactoren voor switchen bij patiënten die startten met het gebruik van een TNFα-remmer onderzocht. We hebben aangetoond dat ongeveer 17% van de patiënten met een reumatische aandoening (RD), 14,5% van de patiënten met inflammatoire darmziekte (IBD) en 16% van de patiënten met psoriasis ten minste één keer zijn geswitcht tijdens hun behandeltraject, meestal naar een andere TNFα-remmer. We vonden een sterk verhoogd risico op switchen bij RD-patiënten bij wie de dosis van de TNFα-remmer verhoogd was (ongeveer 13 keer zo hoog) en/of gestart waren met hoge doses corticosteroïden (ongeveer drie keer zo hoog). Ook vonden we een sterk verhoogd risico op switchen bij IBD-patiënten bij wie de dosis van de TNFα-remmer verhoogd was (ongeveer 8 keer zo hoog), gestart waren met een immunomodulator geneesmiddel of de dosis verhoogd hadden van het immunomodulator geneesmiddel (ongeveer twee keer zo hoog), gestart waren met hoge doses corticosteroïden (bijna 7 keer zo hoog) en/ of een meting hebben gehad van de TNFα-remmer-bloedspiegel (ongeveer 5 keer zo hoog). Al deze factoren kunnen erop wijzen dat de ziekte verslechterde, te weinig effect na het starten van een TNFα-remmer en/of vermindering van effect van de TNFα-remmer in de loop van de tijd. Deze bevindingen kunnen artsen helpen bij het anticiperen op patiënten die een TNFα-remmer gebruiken en mogelijk gaan switchen.

Wisselen van een originele TNFα-remmer naar een biosimilar

In het bovenstaande hoofdstuk werd gekeken naar switchen van de ene werkzame stof naar de ander. In de volgende hoofdstukken wordt ingegaan op wisselen van een originele TNFα remmer naar een biosimilar. Beide bevatten dezelfde werkzame stof, maar hebben een andere merknaam. In *Hoofdstuk 3* werden de nationale behandelrichtlijnen van diverse Europese landen voor het wisselen van IBD-patiënten van een originele TNFα-remmer naar een biosimilar bestudeerd. We hebben de aanwezigheid en inhoud van richtlijnen voor het gebruik van TNFα-remmer biosimilars in kaart gebracht van Europese verenigingen voor maagdarmlever (MDL)-artsen die samenwerken met de European Crohn's and Colitis Organisation (ECCO). We

ontdekten dat 26 van de 30 landen in de Europese Economische Gemeenschap een MDL-vereniging hebben die gelieerd is aan ECCO, waarvan 14 nationale richtlijnen hadden over biosimilars, vier de richtlijnen van ECCO zelf volgden, en drie behandelrichtlijnen hadden zonder vermelding van biosimilars. Van vijf landen werden geen richtlijnen gevonden. Van de 18 landen met richtlijnen, keurden 14 verenigingen het starten van biologische behandeling met biosimilars goed, en 13 (72,2%) keurden de wissel van origineel naar biosimilar goed. Terug wisselen naar het originele geneesmiddel werd door de verenigingen die het standpunt van ECCO volgden afgekeurd, maar werd niet genoemd in de andere richtlijnen. Negen verenigingen publiceerden in de loop van de tijd meerdere richtlijnen over biosimilars; over het algemeen werden hun standpunten positiever over de acceptatie van biosimilars. De meerderheid van de MDL-verenigingen steunde dus het gebruik van biosimilars. Het gebruik van biosimilars kan verbeterd worden door het ontwikkelen van actuele richtlijnen over biosimilars door MDL-verenigingen die deze nu nog niet hebben.

Eén van de aanbevelingen in de in *Hoofdstuk 3* bestudeerde richtlijnen gaat over terug wisselen van de biosimilar naar de originele TNFα-remmer (d.w.z. stoppen met de biosimilar en het origineel opnieuw starten). Terug wisselen naar de originele TNFα-remmer wordt verder onderzocht in *Hoofdstuk 4*. Terug wisselen van de biosimilar naar de originele TNFα-remmer kan wijzen op falen van de behandeling met de biosimilar of dat de patiënt ontevreden is over de biosimilar. We hebben bepaald welk deel van de patiënten die tussen 2012 en 2018 zijn terug gewisseld van een TNFα-remmer biosimilar naar de originele TNFα-remmer. We hebben ook factoren van de patiënt, de ziekte, de behandeling en de implementatiestrategie onderzocht die mogelijk verband houden met terug wisselen. We ontdekten dat in studies waarin patiënten werden gewisseld van een originele TNFα-remmer naar een biosimilar ongeveer 8% van de patiënten terug wisselden. Er leken minder patiënten terug te wisselen in studies waar alleen patiënten die stabiel waren in hun ziekte meededen, in studies waar bij de introductie van de biosimilar de mogelijkheid van teruggaan naar de originele TNFα-remmer niet werd aangeboden, en in studies die extra laboratoriummonitoring aanboden en/of waarin patiënten direct voordeel hadden bij wisselen naar de biosimilar.

Hoofdstuk 5 richtte zich op hoe vaak terug wisselen voorkomt en mogelijke risicofactoren hiervoor bij RD-patiënten die wisselden van het originele etanercept (een soort TNFα-remmer) naar de biosimilar. Van de 342 patiënten waren er 47 aan het einde van de studie gedurende een gebruiksperiode van gemiddeld ruim vier jaar terug gewisseld naar het originele etanercept. De meeste patiënten (ongeveer driekwart) gaven aan dat ze waren terug gewisseld vanwege een (waargenomen) verlies van effect, en ongeveer een kwart vanwege bijwerkingen. Patiënten die de polikliniek

reumatologie vaker bezochten, hadden een verhoogd risico op terug wisselen, wat waarschijnlijk komt doordat patiënten die een verlies van effect en/of bijwerkingen ervaren de polikliniek reumatologie vaker bezoeken.

Patiënten die waren terug gewisseld werden kwalitatief geïnterviewd over hun perspectieven op wisselen en het terug wisselen; gegevens van de eerste acht patiënten van dit lopende onderzoek zijn beschreven in *Hoofdstuk 6*. Patiënten meldden dat ze geen autonomie hadden bij beslissingen over wisselen van een originele TNFα-remmer naar een biosimilar. Ze gaven de schuld aan hun ziekenhuis, want ze hadden het idee dat het ziekenhuis kostenbesparingen prioriteerden boven de gezondheid van de patiënten. Patiënten vonden wel dat ze een goede relatie hadden met hun reumatoloog. Ze vonden ook dat hun reumatoloog hun klachten tijdens de behandeling met de biosimilar adequaat aanpakte door hen terug te laten wisselen naar hun originele TNFα-remmer. Om de implementatie van biosimilars in de klinische praktijk te verbeteren, zouden beleidsmakers kunnen overwegen om patiënten direct voordeel te geven van kostenbesparingen, het vertrouwen in biosimilars en generieke geneesmiddelen in het algemeen te vergroten, en patiënten meer te betrekken bij beslissingen over wisselen van een originele TNFα-remmer naar een biosimilar.

In *Hoofdstuk 7* hebben we het risico op en de redenen voor het stoppen met infliximab (een soort TNFα-remmer) vergeleken tussen patiënten die terug wisselden naar het originele infliximab en degenen die op de biosimilar bleven. Deze patiënten waren eerder allemaal gewisseld van het originele infliximab naar de biosimilar. Patiënten die terug wisselden werden gematcht aan patiënten die behandeld bleven worden met de biosimilar infliximab. We hebben gevonden dat bijna een kwart van de patiënten die terug wisselden stopte met infliximab door een ongewenste reactie, zoals verlies van effect of bijwerkingen, vergeleken met ongeveer een zevende van de patiënten die op biosimilar bleven. Ook stopten vier keer minder patiënten die terug wisselden omdat hun ziekte onderdrukt (in 'remissie') was. Terug gewisselde patiënten hebben meer dan drie keer zoveel risico om te stoppen met infliximab door een ongewenste reactie vergeleken met patiënten die op de biosimilar bleven. Terug wisselen van patiënten behandeld met infliximab lijkt voornamelijk gerelateerd te zijn aan de patiënt en/of zijn of haar ziekte en minder aan de biosimilar. Artsen zouden patiënten die willen terug wisselen van de biosimilar naar het originele kunnen switchen naar andere geneesmiddelen.

Discussie

In *Hoofdstuk 8* heb ik de bevindingen van de studies in dit proefschrift in een breder perspectief geplaatst. Ten eerste heb ik de uitdagingen bij het creëren van

geneesmiddel behandelpatronen beschreven. Behandelpatronen voor TNFα-remmers vereisen gegevens uit meerdere instellingen, zoals voorschrijf- en/of aflevergegevens van de ziekenhuis- en de poliklinische apotheek, en de mogelijkheid om die gegevens te koppelen op het niveau van de individuele patiënt. Bovendien bestaat er een gevaar voor verkeerde classificatie van het geneesmiddelproduct, omdat niet alle data informatie bevat over de merknaam, die informatie is wel nodig om onderscheid te maken tussen een originele TNFα-remmer en een biosimilar. Daarnaast hebben TNFα-remmers lange doseerintervallen, bijvoorbeeld elke acht weken een infuus. Deze doseerintervallen worden in de praktijk soms aangepast aan de gezondheid van de patiënt. Maar de dosisaanpassing wordt niet altijd vastgelegd in databases. Dit kan leiden tot verkeerde classificatie of een patiënt een geneesmiddel wel of niet gebruikt. Bovendien bestaat er een risico op *immortal time bias* in studies waarin behandelpatronen van patiënten die zijn gewisseld van originele TNFα-remmers naar biosimilars worden vergeleken met patiënten die bleven op een originele TNFα-remmer.

Het gebruik van medicatie behandelpatronen brengt echter ook uitdagingen met zich mee om inzicht te krijgen in de ziekte van de patiënt. Onderliggende redenen voor gebeurtenissen in de behandeling, zoals switchen naar een ander geneesmiddel, of stoppen met een geneesmiddel zonder te switchen zijn soms moeilijk te interpreteren. Ze kunnen duiden op negatieve effecten in de behandeling, bijvoorbeeld verlies van effect of bijwerkingen, maar ook positieve effecten zoals onderdrukking van de ziekte ('remissie') en daarom stoppen met geneesmiddelen. Bovendien zijn ook de redenen voor het terug wisselen van een biosimilar naar de originele TNFα-remmer vaak onduidelijk op basis van alleen de behandelpatronen. Om deze redenen toch te kunnen achterhalen en de behandelpatronen van een patiënt goed te kunnen interpreteren, is extra informatie nodig over de ziekte en het welzijn van de patiënt, bijvoorbeeld uit de notities van de arts of verpleegkundige in het elektronisch patiëntendossier van de patiënt in het ziekenhuis.

Ten tweede hebben we verschillende inzichten en aanbevelingen gegeven voor de introductie van biosimilars en het teruggaan van biosimilars naar originele TNFα-remmers. We adviseren artsen en (ziekenhuis)apothekers niet alleen te kijken naar de kosten van de biosimilar, maar ook naar de eigenschappen van de injectiepen en de hulpstoffen. Deze eigenschappen kunnen een rol spelen in de tevredenheid van patiënten met de biosimilar.

We hebben beschreven dat er veel overeenkomsten zijn tussen wat patiënten vinden van substitutie van merk geneesmiddelen naar generieke geneesmiddelen en van

wisselen naar een biosimilar. Daarom raden we aan om te accepteren dat een deel van de patiënten die wisselen van originele TNFα-remmer naar biosimilar weer terug wisselt naar het origineel, en om dit op te nemen in de richtlijnen voor biosimilars van medische verenigingen.

Ook hebben we beschreven dat terug wisselen voorkomen door het vergroten van vertrouwen in biosimilars m.b.v. een communicatiestrategie beperkt werkt. We hebben gesteld dat het informeren van patiënten over de wisseling naar een biosimilar belangrijk is om praktische redenen, zoals een verandering van injectiepen. Echter, bij de introductie van biosimilars in de kliniek moeten zorgprofessionals niet overmatig veel vertrouwen op communicatiestrategieën. Aangezien de perceptie van patiënten over biosimilars overeen kan komen met hun perceptie over generieke geneesmiddelen in het algemeen, zouden patiënten ook meer vertrouwd en comfortabel moeten worden met generieke geneesmiddelen in het algemeen.

Daarnaast hebben we inzicht gegeven in mogelijke redenen waarom patiënten een ongewenste reactie ervaren na de overstap naar een biosimilar. In eerdere studies wordt dit vaak geduid als een nocebo-effect. Dit is een negatief verwachtingseffect, en het omgekeerde van het placebo-effect. Het is echter moeilijk vast te stellen dat een ongewenste reactie op een geneesmiddel, zoals verlies van effect van het geneesmiddel of een bijwerking zeker komt door het nocebo-effect. De ongewenste reactie kan ook te wijten zijn aan andere factoren, zoals ziekteprogressie. Ziekteprogressie kan passen in het natuurlijke beloop van de ziekte of komen door een algemeen verlies van behandeleffect, maar kan (ten onrechte) worden toegeschreven aan de wissel naar de biosimilar. Daarom hebben we aanbevelingen gegeven voor de follow-up van patiënten nadat ze zijn gewisseld naar een biosimilar.

Tot slot hebben we aanbevelingen gedaan voor toekomstig onderzoek en voor de implementatie van biosimilars in de klinische praktijk. We deden verschillende aanbevelingen om het creëren van behandelpatronen te verbeteren, bijvoorbeeld kritisch zijn op belangrijke keuzes, het vermijden van *immortal time bias* en het opnemen van klinische en beleidscontext om bewust te zijn van mogelijke *channeling* van biosimilars naar bepaalde patiënten. We hebben ook aanbevolen om aanvullende gegevens op te nemen voor de interpretatie van gebeurtenissen in behandelpatronen. Bovendien hebben we aanbevelingen gedaan om de implementatie van biosimilars in de klinische praktijk te verbeteren, wat betreft de keuze van een biosimilar, het vergroten van het vertrouwen, het accepteren van een bepaald aantal patiënten dat terug wisselt van biosimilar naar origineel en het bieden van follow-upzorg aan patiënten die zijn overgestapt van origineel naar biosimilar.

CHAPTER 10

Appendices

10.1 Dankwoord

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10.3 List of publications

Meijboom RW, Barbier L, Druedahl LC, Sarnola K, Tolonen HM, Gardarsdottir H, Egberts TCG, Giezen TJ. Recommendations on TNFα inhibitor biosimilar use in clinical practice: a comparison of European gastroenterology IBD guidance. Expert Opin Biol Ther. 2023 Mar 23;1-17.

Meijboom RW, Gardarsdottir H, Egberts TCG, Giezen TJ. Patients Retransitioning from Biosimilar TNFα Inhibitor to the Corresponding Originator After Initial Transitioning to the Biosimilar: A Systematic Review. BioDrugs. 2022 Jan;36(1):27-39

Meijboom RW, Gardarsdottir H, Becker ML, Ten Wolde S, Egberts TCG, Giezen TJ. Incidence of and Reasons and Determinants Associated with Retransitioning from Biosimilar Etanercept to Originator Etanercept. BioDrugs. 2021 Nov;35(6):765-772

Meijboom RW, Gardarsdottir H, Becker ML, de Groot MCH, Movig KLL, Kuijvenhoven J, Egberts TCG, Leufkens HGM, Giezen TJ. Switching TNFα inhibitors: Patterns and determinants. Pharmacol Res Perspect. 2021 Aug;9(4):e00843

10.4 Author's contribution

Chapter 1 General Introduction

RWM wrote the general introduction. Her PhD supervisory team reviewed various versions of the general introduction. RWM implemented their feedback, and her PhD supervisory team approved the final version.

Chapter 2 Switching TNFα inhibitors: patterns and determinants

RWM designed the study, collected and analysed the data and wrote the draft manuscripts. All co-authors provided significant contributions to these aspects. RWM implemented their feedback up to the final publication.

Chapter 3 Recommendations on TNFα inhibitor biosimilar use in clinical practice: a comparison of European gastroenterology IBD guidance

RWM designed the study, collected and analysed the data and wrote the draft manuscripts. All co-authors provided significant contributions to these aspects. RWM implemented their feedback up to the final publication.

Chapter 4 Patients retransitioning from biosimilar TNFα Inhibitor to the corresponding originator after initial transitioning to the biosimilar: a systematic review

RWM designed the study, collected and analysed the data and wrote the draft manuscripts. All co-authors provided significant contributions to these aspects. RWM implemented their feedback up to the final publication.

Chapter 5 Incidence of and reasons and determinants associated with retransitioning from biosimilar etanercept to originator etanercept

RWM designed the study, collected and analysed the data and wrote the draft manuscripts. All co-authors provided significant contributions to these aspects. RWM implemented their feedback up to the final publication.

Chapter 6 Patients' perspectives on transitioning from a TNFα inhibitor originator to a biosimilar and retransitioning to the originator

RWM designed the study, collected and analysed the data and wrote the draft manuscripts. All co-authors provided significant contributions to these aspects. RWM implemented their feedback up to the final publication.

Chapter 7 Discontinuation of infliximab treatment in patients with inflammatory bowel disease who retransitioned to originator and those who remained on biosimilar

RWM designed the study, collected and analysed the data and wrote the draft manuscripts. All co-authors provided significant contributions to these aspects. RWM implemented their feedback up to the final publication.

Chapter 8 General Discussion

RWM wrote the general discussion. Her PhD supervisory team reviewed various versions of the general discussion. RWM implemented their feedback, and her PhD supervisory team approved the final version.

10.5 About the author

Rosanne Meijboom was born in 1989 in Rheden. She obtained her Bachelor of Science in Pharmacy at the Rijksuniversiteit Groningen in 2012 and her Master of Science in Pharmacy in 2014. After her graduation, Rosanne worked as a pharmacist in several hospital pharmacies where she performed routine clinical care and was involved in several projects related to medication safety.

In 2018, she started her PhD project at the Pharmacy Foundation of Haarlem Hospitals and the Division of Pharmacoepidemiology and Clinical Pharmacology of Utrecht University. The research was conducted under the supervision of prof. dr. Toine Egberts, dr. Thijs Giezen and dr. Helga Gardarsdottir. During her PhD training, Rosanne presented her research at national and international conferences As part of her doctoral education, she followed a training programme which included the Master's programme in Epidemiology (Master's degree obtained in 2022) and courses on general research skills and academic competencies. Moreover, she contributed to educational activities of the Pharmacy curriculum of the Utrecht University, including teaching in the Pharmacy Master's course "Therapy of Oncological Diseases" and the Master's course "Pharmacy in Practice". She was also a member of the 2019 cohort of the Future Medicine Fellows, with which she organised a Summer School on Cell and Gene Therapy.

From August 2023 onwards, Rosanne will start a new journey as a clinical assessor at the Dutch Medicines Evaluation Board.