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ORIGINAL RESEARCH

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

Rosanne W Meijboom[a,b], Liese Barbier[c], Louise C Druedahl[d], Kati Sarnola[e], Hanna M Tolonen[f,g], Helga Gardarsdottir[b,h,i], Toine C G Egberts[b,h] and Thijs J Giezen[a,b,j]

[a]Pharmacy Foundation of Haarlem Hospitals, Haarlem, The Netherlands; [b]Division of Pharmacoepidemiology and Clinical Pharmacology, Utrecht Institute for Pharmaceutical Sciences, Utrecht, The Netherlands; [c]Department of Pharmaceutical and Pharmacological Sciences, KU Leuven, Leuven, Belgium; [d]Centre for Advanced Studies in Biomedical Innovation Law (CeBIL), Faculty of Law, University of Copenhagen, Copenhagen, Denmark; [e]Research at Kela, Social Insurance Institution of Finland (Kela), Helsinki, Finland; [f]HUS Pharmacy, HUS Helsinki University Hospital, and University of Helsinki, Helsinki, Finland; [g]Clinical Pharmacy Group, Division of Pharmacology and Pharmacotherapy, Faculty of Pharmacy, University of Helsinki, Helsinki, Finland; [h]Department of Clinical Pharmacy, University Medical Centre Utrecht, Utrecht, The Netherlands; [i]Department of Pharmaceutical Sciences, University of Iceland, Reykjavík, Iceland; [j]Department of Clinical Pharmacy, Spaarne Gasthuis, Haarlem and Hoofddorp, The Netherlands

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 Organization (ECCO) were collected. Treatment guidelines and biosimilar position papers from 2010 to 2022 were included. Data were extracted using a template.

Results: 26 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.

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Biosimilar; gastroenterology; guidelines; inflammatory bowel disease; infliximab; switching; tumor necrosis factor inhibitors

1. 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) [2]. TNFα inhibitors neutralize TNF and consequently reduce inflammation [3]. 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 [4]. This allowed the introduction of biosimilars as lower-cost versions of these medicines [4]. 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)' [5]. 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 [6]. Until October 2022, four biosimilars for infliximab and 11 for adalimumab had been approved for IBD in

CONTACT Thijs J Giezen tgiezen@sahz.nl Department of Clinical Pharmacy, Spaarne Gasthuis, Haarlem and Hoofddorp, Boerhaavelaan 24, 2035 RC, Haarlem, The Netherlands

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the EU [7]. 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 [8].

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 Organization (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 [9]. 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 [10].

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.

2. Patients and methods

2.1. 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 A1) [11,12]. 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 e-mail 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 e-mail (and two reminder e-mails) 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 [13]. If no guidelines were found on the association's website, and the association did not respond to the e-mails, the guidelines could not be retrieved and were excluded or were considered nonexistent.

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.

2.2. 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 [10] 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 Table A2 for the template and a more detailed description.

Data was extracted from the guidelines by RWM in a standardized form in Microsoft Excel. The coauthors (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 A3). 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.

2.3. 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.

3. Results

3.1. 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.

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.

3.2. 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

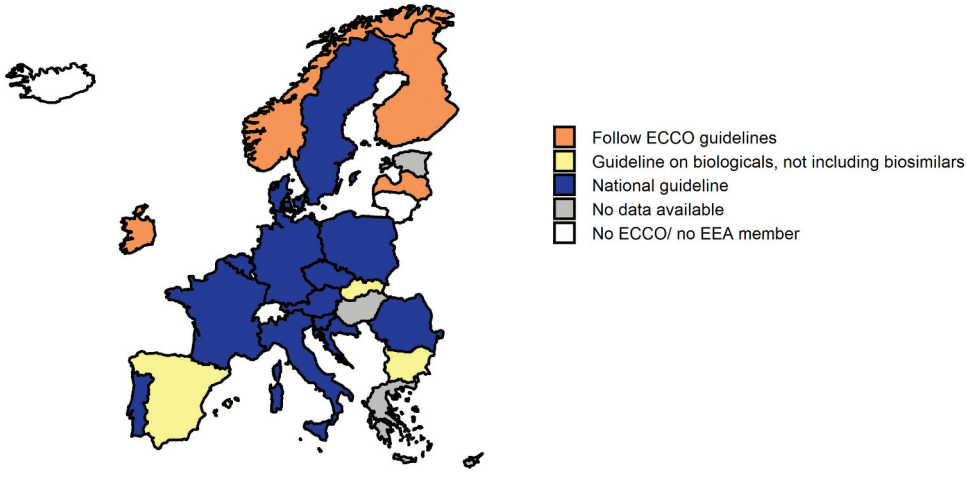

Figure 1. Availability of guidelines on the use of biosimilars in clinical practice from national gastroenterology associations (n countries included = 30).

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 pharmaco-vigilance, 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
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	✗	✗

(*Continued*)

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
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	✗	✗
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 treatment'
** 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
-: Not applicable

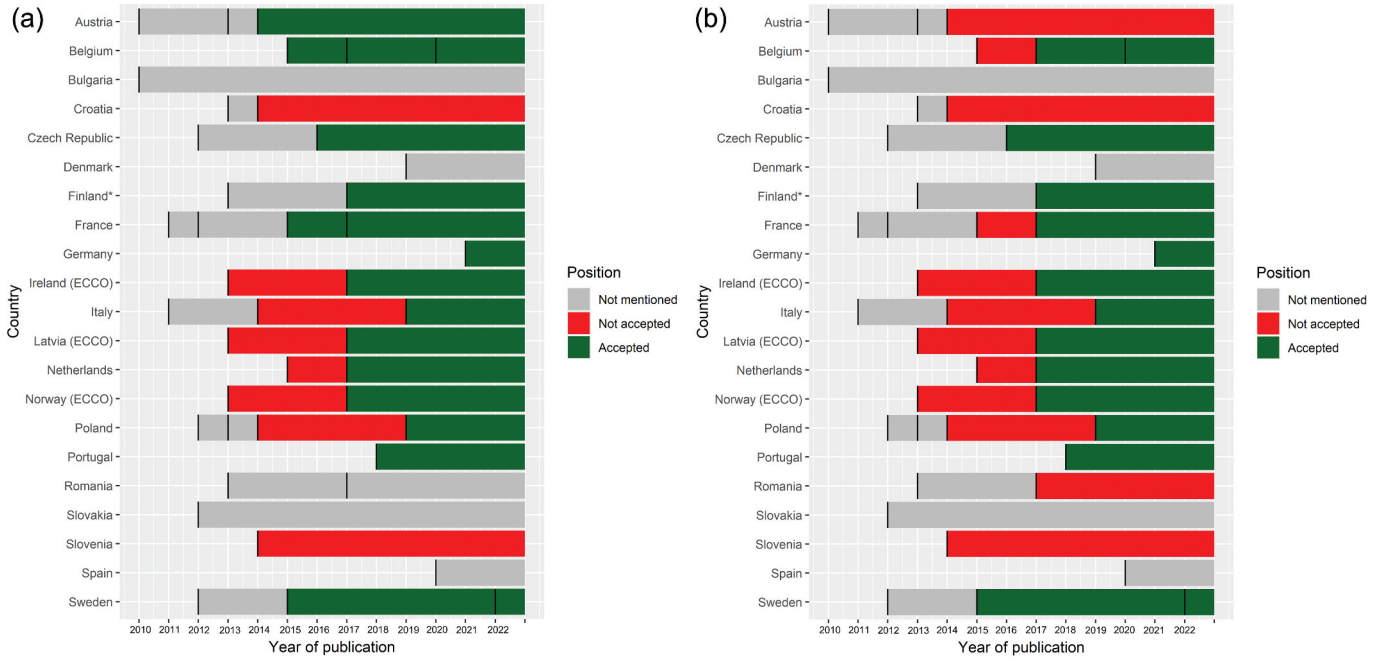

Figure 2. **(a)**. Development on guidance on starting TNFα inhibitor treatment with a biosimilar over time. The black line indicates a new guideline version (end of follow-up May 2022). ***Finland** had national guidelines in 2013, but changed to following ECCO's guidance in 2017. (**b**). Development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

(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.

3.3. 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.

3.4. 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; crosstransitioning 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 was not mentioned in the German position paper.

3.5. Development of guidance over time

Fourteen national gastroenterology associations had multiple versions over time of their guidelines available (Table 2 and Figures 2a and Figure 2b). Guidelines published between 2010 and 2013 did not include recommendations on the use of biosimilars (Figures 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).

4. 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 toward 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 [14]. 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 [14]. Moreover, other factors, such as the paucity of a structured transitioning strategy, limit physicians from transitioning their patients [15]. A previous study demonstrated that incentive policies, such as guidelines on biosimilar use, are positively associated with biosimilar uptake [16]. Although many other factors contribute to a country's 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% [8]. 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 [17]. 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 [18].

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)

Table 2. Development of guidance on biosimilars over time.

		Initiating biological treatment with a biosimilar		Transitioning from originator to biosimilar					
Country	Guidelines	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
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
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

(*Continued*)

Table 2. (Continued).

Country	Guidelines	Initiating biological treatment with a biosimilar: Starting new patients on biosimilar	Initiating biological treatment with a biosimilar: Type of patients who can start with biosimilar	Transitioning from originator to biosimilar: Transitioning from originator to biosimilar	Transitioning from originator to biosimilar: Type of patients who can transition	Transitioning from originator to biosimilar: Recommendation on informing patients	Transitioning from originator to biosimilar: Recommendation on monitoring patients	Transitioning from originator to biosimilar: Recommendation on cross-transitioning	Transitioning from originator to biosimilar: 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

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 [19,20].

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 [21–23]. 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 [24]. 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 [25].

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) [26–29].

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 [27,28]. 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 [28]. 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 [27]. To a lesser extent, the Swedish gastroenterology association had a more favorable position on the cross-transitioning of patients compared to their regulatory authority [26]. Furthermore, Spanish gastroenterology guidelines do not guide biosimilar use, but Spanish health authorities recommend transitioning patients from originator to biosimilar [28].

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 [30]. 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 toward 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 [10]. 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 [31]. The NOR-SWITCH study's results and the subsequent changes to ECCO's position on biosimilars might explain the development of gastroenterology guidance toward 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% [8]. 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 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 [32,33]. 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 [34]. 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 [35] .

4.1. 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 e-mails 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 A1), 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.

5. 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.

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Declaration of interest

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Author contributions

RW Meijboom, L Barbier, LC Druedahl, K Sarnola, HM Tolonen, H Gardarsdottir, ACG Egberts, TJ Giezen contributed to the study design. RW Meijboom, L Barbier, LC Druedahl, K Sarnola, HM Tolonen contributed to the data collection and analysis. RW Meijboom wrote the first draft of the manuscript. All authors critically revised the manuscript. All authors approved the final version of the manuscript.

Data availability statement

Data are available upon request.

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Appendix

Table A1. Overview of the EEA member states [12] 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 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. 19 June 2020;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
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/linflximab-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
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

(*Continued*)

Table A1. (Continued).

Country	National Gastroenterology society	Reference to guideline
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
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
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
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 978–84-09-26,787-3

(*Continued*)

Table A1. (Continued).

Country	National Gastroenterology society	Reference to guideline
Sweden	SOIIBD – Svensk Organization för IBD-StudierSvensk 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 e-mail address found, thus this association was excluded and classified as no ECCO member† Did not respond to the e-mails requesting for guidelines

Table A2. 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:	Yes/ No
If yes, link to guideline:	
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 not 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 A3. 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