Regulatory Safety Learning Driven by the Mechanism of Action: The Case of TNF-α Inhibitors

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The summary of product characteristics (SmPCs) is an important information source that includes the adverse drug reactions (ADRs) associated with the drug. Drugs with the same mechanism of action are expected to have a similar ADR profile and thus a substantial overlap of the described ADRs in the SmPC. The objective of this study is to assess this overlap. We extracted all ADRs (excluding hypersensitivity and administration site reactions) that were described in the first and all subsequent versions of the SmPCs of all approved TNF-α inhibitors in the European Union. The Medical Dictionary for Regulatory Activities was used to characterize the ADRs. At the end of follow-up, 293 unique ADRs (at high level term level) were described in the SmPCs of the 5 TNF-α inhibitors. There was substantial variation in the number of ADRs described in the SmPC among the TNF-α inhibitors. Of the 293 ADRs, 133 (45%) were described in the SmPC of one TNF-α inhibitor and 39 (13%) in the SmPCs of all 5 TNF-α inhibitors. Serious ADRs and ADRs classified as important risks were described approximately four times more often in a second SmPC than ADRs not classified as such. In conclusion, the ADRs described in the SmPCs of the TNF-α inhibitors differ considerably in number and type. In order to adequately inform prescribers and patients, acquired knowledge of the safety profile of drugs with the same mechanism of action should increasingly be taken into account in the assessment of all drugs within the class.

Study Highlights

WHAT IS THE CURRENT KNOWLEDGE ON THE TOPIC?

☑ Although previous studies evaluated whether safety information was taken into account as part of the regulatory assessment for drugs with the same mechanism of action, a complete picture of the dynamics is lacking.

WHAT QUESTION DID THIS STUDY ADDRESS?

☑ What is the overlap adverse drug reactions (ADRs) described in the summary of product characteristics (SmPC) of drugs with the same mechanism of action (i.e., TNF-α inhibitors) during the life-cycle of the product and which factors influence the overlap?

WHAT DOES THIS STUDY ADD TO OUR KNOWLEDGE?

☑ The overlap in ADRs described in the SmPCs of different TNF-α inhibitors is limited. However, serious ADRs, ADRs classified as important risks by the regulators, and ADRs first described in the first-in-class TNF-α inhibitor were significantly more often described in the SmPC of at least two TNF-α inhibitors.

HOW MIGHT THIS CHANGE CLINICAL PHARMACOLOGY OR TRANSLATIONAL SCIENCE?

☑ Acquired knowledge of the safety profile of drugs with the same mechanism of action should increasingly be taken into account for all drugs within the class. For this, a critical appraisal of the underlying mechanism leading to an ADR's occurrence should be performed.

At the time of regulatory approval, the efficacy and safety of a new drug will have been studied in a population of limited size (on average, ~ 1,700 individuals) during a relatively short period of time.[1,2] In addition, the types of patients included in clinical studies can differ considerably from the types of patients using the drug in daily clinical practice, as these clinical studies often exclude patients with

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multiple diseases and specific populations, such as pregnant women and the elderly.[3] Therefore, infrequently occurring adverse drug reactions (ADRs), ADRs that only occur after a long duration of exposure, and ADRs occurring in special populations are usually detected after approval, when the drug is used in daily clinical practice. Regulatory authorities therefore require companies to further characterize their drug's safety profile when it is used in daily clinical practice. This is achieved through collecting and evaluating ADRs and performing postauthorization safety studies. When additional information becomes available, this can result in different regulatory actions. For example, the benefit–risk balance of the drug can become negative due to new information that is collected in clinical practice. This could result in restricting the indication to the patient group for which the benefit–risk balance remains positive or even in revoking the market authorization. A less far-reaching but frequently applied regulatory action is the incorporation of the newly identified safety data in the product information. Annually, hundreds of such safety-related changes in the product information (summary of product characteristics (SmPCs) in the European Union) are approved by the regulatory authorities.[4,5]

The occurrence of many ADRs is a direct consequence of the mechanism of action of a drug. Such ADRs are likely to also occur in users of another drug with the same mechanism of action. For example, artery dissections and aneurysms were found to be associated with the use of vascular endothelial growth factor inhibitors (VEGF-inhibitors).[6,7] These ADRs are applicable to all VEGF-inhibitors, as VEGF inhibition impairs the vascular wall integrity. Moreover, tuberculosis infections associated with infliximab use were detected during the postmarketing phase and are considered a class effect of the TNF-α inhibitors.[8,9] TNF-α is a pro-inflammatory cytokine that plays a central role in the immune response against tuberculosis infection.[8,9] Treatment with TNF-α inhibitors can therefore reactivate latent tuberculosis infections.

In order to adequately inform prescribers and patients about the safety profile of the drug, ADRs that are linked to the mechanism of action are expected to be described in the product information of all drugs with the same mechanism of action. Previous studies showed a variability in to what extent safety information is presented as part of the regulatory assessment for drugs within the same class. For example, Stefansdottir *et al*. showed that only 40% of the ADRs that were identified in the product information of two drugs within the same class (based on indication, mechanism of action, and structure of the drug) were described in the product information of both drugs.[10] Another study showed that serious safety issues identified prior to the approval of HIV drugs were taken into account in the approval process of other drugs within the same class.[11] These studies focused either on serious safety events or on a selection of drugs within the same class and therefore did not reflect the complete picture of the dynamics of incorporating class effects in the product information.

For biological medicinal drugs, the occurrence of ADRs is often related to the mechanism of action. Furthermore, biologicals are of specific interest, as over the last decade the share that biologicals comprise of newly launched active substances worldwide has increased and is expected to increase further.[12] Therefore, we performed a case study on TNF-α inhibitors, as these represent an important drug class within the group of biologicals because TNF-α inhibitors are considered to be key treatment options for multiple types of autoimmune disease. Furthermore, the first TNF-α inhibitor was approved in the European Union in 1999; therefore, extensive experience has been gained with the safety profile of TNF-α inhibitors, allowing early as well as long-term safety aspects to be studied.

The aims of this study are to assess the overlap in ADRs described in the product information of drugs with the same mechanism of action (i.e., TNF-α inhibitors), during the life-cycle of the product, to assess the lag time from the identification of new ADRs to the description of the same ADR in the product information of another TNF-α inhibitor, and to identify factors associated with the description of such ADRs in the product information of multiple TNF-α inhibitors.

METHODS

Extraction, classification, and selection of the ADRs

In this study, we included all ADRs described in the first and all subsequent versions of the SmPCs of the TNF-α inhibitors that had been approved by the European Commission as of December 31, 2019. We excluded the SmPCs of biosimilars because, according to the EU legislation, the SmPCs of biosimilars are the same as the SmPCs of the reference product.[13] Although, in the European Union, the product information consists of both the SmPC and the patient information leaflet, we focused on the SmPC because the content of the patient information leaflet is directly based on the SmPC. All versions of the SmPCs were retrieved through the Union Register of medicinal products maintained by the European Commission. During the life-cycle of a drug, new information on the efficacy and safety becomes available, which can result in an update to and therefore a new version of the SmPC. Both companies and regulatory authorities can initiate an update of the SmPC. However, irrespective of who initiates an update, it is always assessed by the regulatory authorities. A new version of the SmPC is available in the Union Register when, after the regulatory authorities' recommendation of approval, a positive decision is issued by the European Commission.

All ADRs were extracted using a text-mining method from all versions of the selected SmPCs. The extraction was limited to the specific section of the SmPC that describes the ADRs that are associated with the drug (SmPC section 4.8: "Undesirable effects"). The text-mining method was validated through multiple sources. First, we compared the extracted ADRs with the ADRs available in the PROTECT ADR database. This database was created by the European Medicines Agency (EMA) and partners as part of an Innovative Medicines Initiative funded project (PROTECT Work Package 3) and includes all ADRs described in section 4.8 of all versions of the SmPC up to June 30, 2017 (for more details, see http://www.imi-protect.eu/adverseDrugReactions.shtml). We manually compared the ADRs within the PROTECT database and our extracted ADRs with the ADRs in the SmPC available in the community register of medicinal products of the European Commission. Second, through the text-mining method, it was determined in which version of the SmPC an ADR was first described, which we checked manually for all ADRs.

The ADRs were classified using the Medical Dictionary for Regulatory Activities (MedDRA).[14] MedDRA provides validated standardized terminology, which is, among others, used to describe ADRs in the SmPC. MedDRA has a hierarchical structure. The ADRs in SmPC section 4.8 are usually described at the preferred term level. Preferred terms are grouped into high-level terms (HLTs), which are one level higher in the structure of MedDRA. For example, the preferred terms "cutaneous tuberculosis" and "pulmonary tuberculosis" fall within the HLT "tuberculous infections." For this study, we assessed the overlap in ADRs described in the SmPCs of the different products at the HLT level, as we considered that this reflects clinical practice most accurately.

We excluded hypersensitivity reactions and administration site reactions, as these are related to the molecule and/or route of administration. Hypersensitivity reactions and administration site reactions were defined as all ADRs included in the standard MedDRA query "hypersensitivity" or within the high-level group term (HLGT) "administration site reactions." These include, for example, anaphylactic reactions, administration-related reactions, and Stevens-Johnson syndrome. For the remaining ADRs, we did not specifically assess whether these were considered to be related to the mechanism of action. However, we assumed that these are applicable to all TNF-α inhibitors.

Overlap in the ADRs described in the SmPCs of the different TNF-α inhibitors

The overlap in the ADRs (at the HLT level) described in the SmPCs of the different TNF-α inhibitors was assessed in three ways.

1. *Overlap at initial approval:* At the time of approval of non-first-in-class TNF-α inhibitors, experience will have been gained with the ADRs associated with previously approved TNF-α inhibitors. We assessed for each TNF-α inhibitor (besides the first-in-class) whether ADRs described in the SmPC of previously authorized TNF-α inhibitors were incorporated in the SmPC at the moment of regulatory approval. For example, for the third approved TNF-α inhibitor, we assessed the number of unique ADRs that overlapped with those described in the SmPCs of the first and second approved TNF-α inhibitors. For this, we took into account the latest version of the SmPC of the first and second TNF-α inhibitor before approval of the third TNF-α inhibitor. We then assessed whether these ADRs were described in the SmPC at the time of approval of the third TNF-α inhibitor.
2. *Overlap at the end of follow-up:* Extensive experience has been gained of the ADRs associated with the TNF-α inhibitors, given that these have been used in clinical practice for many years. To assess the overlap in ADRs when the safety profile is considered to be mature, we assessed whether an ADR was described in one, two, three, four, or all five of the last versions of the SmPCs of the TNF-α inhibitors (i.e., at the end of follow-up: December 31, 2019).
3. *Lag time in overlap:* When new ADRs are identified for a TNF-α inhibitor, these are considered to be applicable to other TNF-α inhibitors. However, this process takes time. To estimate this lag time, we assessed the time between the first description of an ADR in the SmPC of any of the TNF-α inhibitors (index date) and the uptake of that ADR in the SmPC of another (i.e., a second) TNF-α inhibitor.

Determinants for overlap in the ADRs

The following determinants were assessed to study the overlap in the ADRs described in the SmPCs of the different TNF-α inhibitors.

- *Nature of the ADR:* The ADRs were characterized at the system organ class level, which is the highest level in the MedDRA hierarchy. We assessed whether the ADR was included in the system organ class infections and infestations.
- *Seriousness of the ADR*: We classified ADRs as being serious if they were included in the important medical events list of the EMA. This list includes the ADRs that result in death, are life-threatening, require hospitalization or prolong existing hospitalization, result in persistent or significant disability, or are birth defects.[15]
- *Regulatory importance of the ADR:* We categorized the ADR as regulatory important if these were included as such in the risk management plan (RMP) of any of the TNF-α inhibitors at marketing approval or during follow-up. Safety issues are included as important risks in the RMP by the regulators if these should be further characterized after marketing approval and are likely to have an impact on the benefit–risk balance.[16] The RMPs were retrieved from the internal database of the Medicines Evaluation Board.
- *First-in-class:* We assessed whether the ADR was described in the SmPC of the first TNF-α inhibitor to be approved within the class of TNF-α inhibitors.
- *Regulatory monitoring:* In the first 3 years after regulatory approval, the safety of a drug is more frequently evaluated than after this period. We therefore assessed whether ADRs included in the SmPC of, for example, the first and second TNF-α inhibitors were more frequently included in the SmPC of the third TNF-α inhibitor in the first 3 years after regulatory approval than in the period thereafter.

Within the EU regulatory system, the application assessment is led by different rapporteurs. For each product, we assessed the influence of having at least one rapporteur in common that is responsible for the regulatory assessment on the overlap in ADRs described in the SmPCs of the TNF-α inhibitors at the end of follow-up. Information on the rapporteurs that were responsible for the regulatory assessment of the different TNF-α inhibitors was retrieved from the European Public Assessment Reports published at the time of approval.

Data analysis

We used descriptive statistics to calculate the overlap in the ADRs (at the HLT level) described in the SmPCs of the different TNF-α inhibitors. To assess the overlap at the end of follow-up, we divided the number of ADRs that were described in one, two, three, four, or all five of the SmPCs of the different TNF-α inhibitors by the total number of unique ADRs described in the SmPCs at the end of follow-up (December 31, 2019). This analysis was also performed at the HLGT level, which is one level higher in the hierarchical structure of MedDRA. This sensitivity analysis was performed to assess whether comparable HLTs were described in the SmPCs of the TNF-α inhibitors. To assess the overlap at the time of approval, we calculated the number of unique ADRs described in the SmPCs of other TNF-α inhibitors before the approval of the new product. We then calculated the percentage of these ADRs that were described in the SmPC at the time of approval of the product.

Kaplan–Meier analysis was performed to assess the time from the first description of an ADR in the SmPC of any of the TNF-α inhibitors to the time when this ADR was described in the SmPC of another TNF-α inhibitor. As this time cannot be estimated for products that had not been approved at the time when an ADR was first described in an SmPC, we included only the TNF-α inhibitors that had been approved at the time when the ADR was first described.

Hazard ratios (HRs) with corresponding 95% confidence intervals (CIs) were calculated using univariate Cox regression analysis to assess the association among the determinants "nature of the ADR," "seriousness of the ADR," "regulatory importance of the ADR," "first-in-class," and the ADR being described in the SmPC of at least two of the TNF-α inhibitors.

To determine the influence of the more intensive regulatory monitoring in the first 3 years after approval on the overlap, we divided, for each

product, the follow-up period in the period after the first 3 years after approval and the period > 3 years after approval. For each product, we assessed the number of ADRs that was first described in the SmPC of the other approved TNF-α inhibitors in both periods (≤ 3 years after approval and > 3 years after approval). We then assessed for each product whether the ADRs that were first described in the SmPC of other TNF-α inhibitors are described in the SmPC of the product in question. This number was then divided by the total number of ADRs identified in the period within and after 3 years following approval.

To assess the influence of sharing at least one rapporteur responsible for the regulatory assessment, we grouped the TNF-α inhibitors that have at least one rapporteur in common and determined whether, for these TNF-α inhibitors, the overlap in describing the ADRs in the SmPC is different from that for the TNF-α inhibitors that do not share at least one rapporteur.

We performed the data analysis using R statistical software version 3.6.0.

RESULTS

As of December 31, 2019, a total of 5 TNF-α inhibitors (excluding biosimilars) had been approved in the European Union. The first-in-class TNF-α inhibitor (infliximab) was approved in 1999, followed by etanercept, approved in 2000, and adalimumab, approved in 2003. The last 2 (certolizumab and golimumab) were approved in 2009. None of the drugs was taken off the market during follow-up.

After initial approval, of the five drugs' SmPCs, the SmPC of infliximab was changed the most often (n = 25) to describe new ADRs (at the HLT level, excluding hypersensitivity and administration site reactions), whereas the SmPC of certolizumab was updated three times during follow-up. As shown in **Figure 1**, there was substantial variation in the number of ADRs described in the SmPCs. At initial approval, a total of 66 ADRs were described in the infliximab SmPC, 41 in the etanercept SmPC, 90 in the adalimumab SmPC, 134 in the certolizumab SmPC, and 73 in the golimumab SmPC. At the end of follow-up, in the adalimumab SmPC the most ADRs were described (n = 200). In the SmPCs of certolizumab, infliximab, etanercept, and golimumab, respectively, 142, 131, 103, and 80 ADRs were described at the end of follow-up. For adalimumab, 110 ADRs were added to the SmPC after regulatory approval whereas, for certolizumab, 8 ADRs were added to the SmPC after regulatory approval.

Overlap in the ADRs described in the SmPCs of the different TNF-α inhibitors

Overlap at initial approval. Prior to the approval of etanercept (second-in-class), experience had been gained with the ADRs associated with infliximab (first-in-class). At the time of the approval of etanercept, a total of 66 unique ADRs were described in the SmPC of infliximab. Of these 66 ADRs, 21 (32%) were described in the initial SmPC of etanercept (**Figure 2**). Prior to the approval of adalimumab, a total of 90 unique ADRs were described in the SmPCs of infliximab and etanercept. Of these 90 ADRs, 53 (59%) were described in the initial SmPC of adalimumab. Of the 238 unique ADRs that were described in the SmPCs of infliximab, etanercept, and adalimumab prior to the approval of certolizumab and golimumab, 94 ADRs (39%) were described in the initial SmPC of certolizumab whereas 62 (26%) were described in the initial SmPC of golimumab.

Overlap at the end of follow-up. At the end of follow-up, a total of 318 different ADRs (at the HLT level) were described

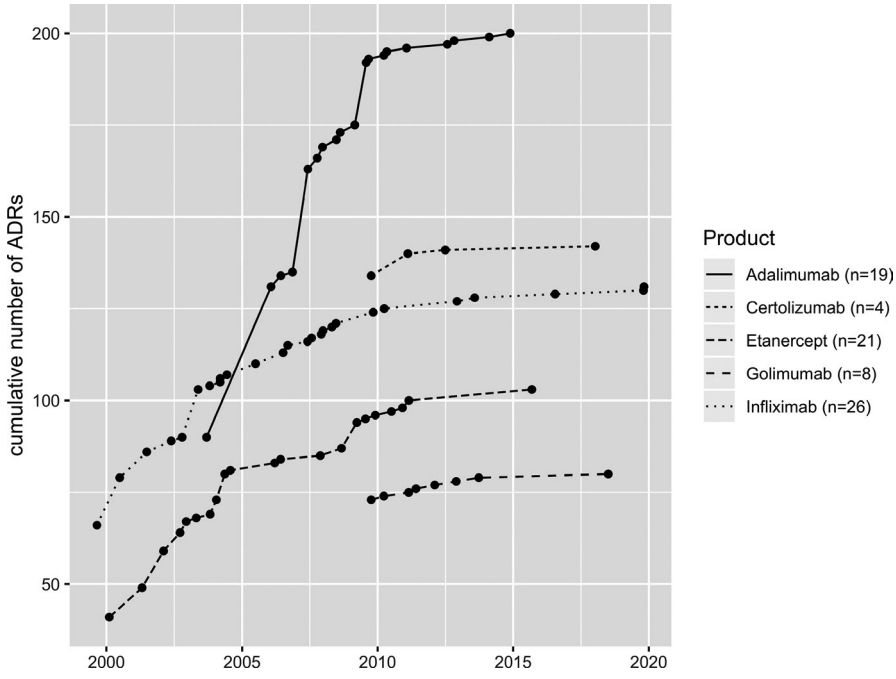

Figure 1 Changes to the SmPCs of the TNF-α inhibitors over time to include new ADRs (at the HLT level, excluding hypersensitivity and administration site reactions); n = number of different versions of the SmPC. ADRs, adverse drug reactions; HLT, high-level term; SmPCs, summary of product characteristics.

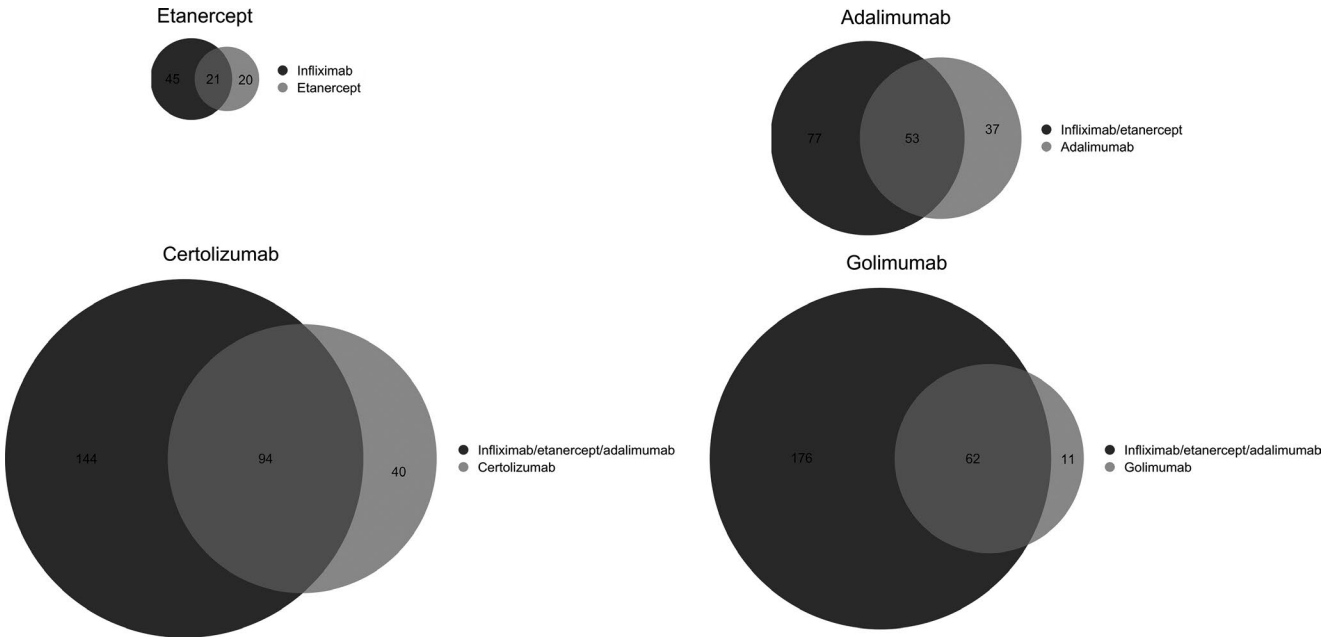

Figure 2 Venn diagrams showing the overlap in the ADRs described in the initial SmPC of etanercept, adalimumab, certolizumab, and golimumab and of the ADRs identified prior to the approval of these drugs. ADRs, adverse drug reactions; SmPCs, summary of product characteristics.

in the SmPCs of the TNF-α inhibitors. Of these 318 ADRs, 25 (8%) were classified as hypersensitivity reactions and/or administration site reactions and were therefore disregarded, resulting in a total of 293 ADRs that were included in the analysis. Of these 293 ADRs, 133 (45%) were described in the SmPC of one TNF-α inhibitor, 58 (20%) in the SmPC of 2 TNF-α inhibitors, 40 (14%) in the SmPC of 3 TNF-α inhibitors, 23 (8%) in the SmPC of 4 TNF-α inhibitors, and 39 (13%) in the SmPC of all 5 TNF-α inhibitors. The 39 ADRs that were included in all SmPCs included tuberculous infections, lower respiratory tract and lung infections, skin melanomas (excluding ocular), and nausea and vomiting symptoms (**Table S1**).

The sensitivity analysis, performed at one level higher in the hierarchical structure of MedDRA (HLGT level), showed that, at the end of follow-up, a total of 138 ADRs (HLGTs) were described in the SmPCs. Of these 138 ADRs, 37 (27%) were described in the SmPC of one TNF-α inhibitor, 30 (22%) in the SmPC of 2 TNF-α inhibitors, 21 (15%) in the SmPC of 3 TNF-α inhibitors, 20 (14%) in the SmPC of 4 TNF-α inhibitors, and 30 (22%) in the SmPC of all 5 TNF-α inhibitors. The 30 ADRs (HLGT level) that were included in all SmPCs included terms such as mycobacterial infectious disorders, general system disorders (not elsewhere classified), and gastrointestinal signs and symptoms (**Table S2**).

Lag time overlap. One year after the first description of an ADR in the SmPC of any of the TNF-α inhibitors, ~ 7% of these ADRs were described in the SmPC of another TNF-α inhibitor. This percentage increased to ~ 19% after 5 years. The median lag time between first description of an ADR in an SmPC to uptake of this ADR in another SmPC was ~ 3 years and ranged from 0 to 15 years (**Figure 3**).

Determinants for overlap in the ADRs

As shown in **Table 1**, serious ADRs and ADRs that were classified as important risks by the regulators were described approximately four times more often in the SmPC of at least two TNF-α inhibitors compared with ADRs not classified as such (HR = 4.5, 95% CI: 1.8–10.8; HR = 4.6, 95% CI: 2.0–10.5, respectively). In addition, when the ADR was first described in the SmPC of infliximab (first-in-class), it was described almost three times more often in the SmPC of at least one other TNF-α inhibitors (HR = 2.8, 95% CI: 1.4–5.6) compared with ADRs that were first described in the SmPC of non-first-in-class products. Although ADRs classified as infections and infestations were described more often in a second SmPC compared with other ADRs (HR = 2.1, 95% CI: 1.0–4.5), this difference was not significant.

In the first 3 years after approval of the individual TNF-α inhibitors, a total of 71 ADRs were first described in the SmPCs of the other TNF-α inhibitors, whereas in the period thereafter a total of 380 ADRs were first described in the SmPCs of other TNF-α inhibitors. Of the 71 ADRs, 31 (44%) were described in the SmPCs of the individual TNF-α inhibitors in the first 3 years after approval, whereas of the 380 ADRs first described in the SmPCs of the other TNF-α inhibitors > 3 years after approval, 25 (7%) were described in the SmPC of the individual TNF-α inhibitors.

Four of the five TNF-α inhibitors shared at least one rapporteur that is responsible for the regulatory assessment. Therefore, the influence of having at least one rapporteur in common on the overlap in ADRs could not be studied.

DISCUSSION

This study showed that the overlap in ADRs (at the HLT level) described in the SmPCs of TNF-α inhibitors is limited; 45% of

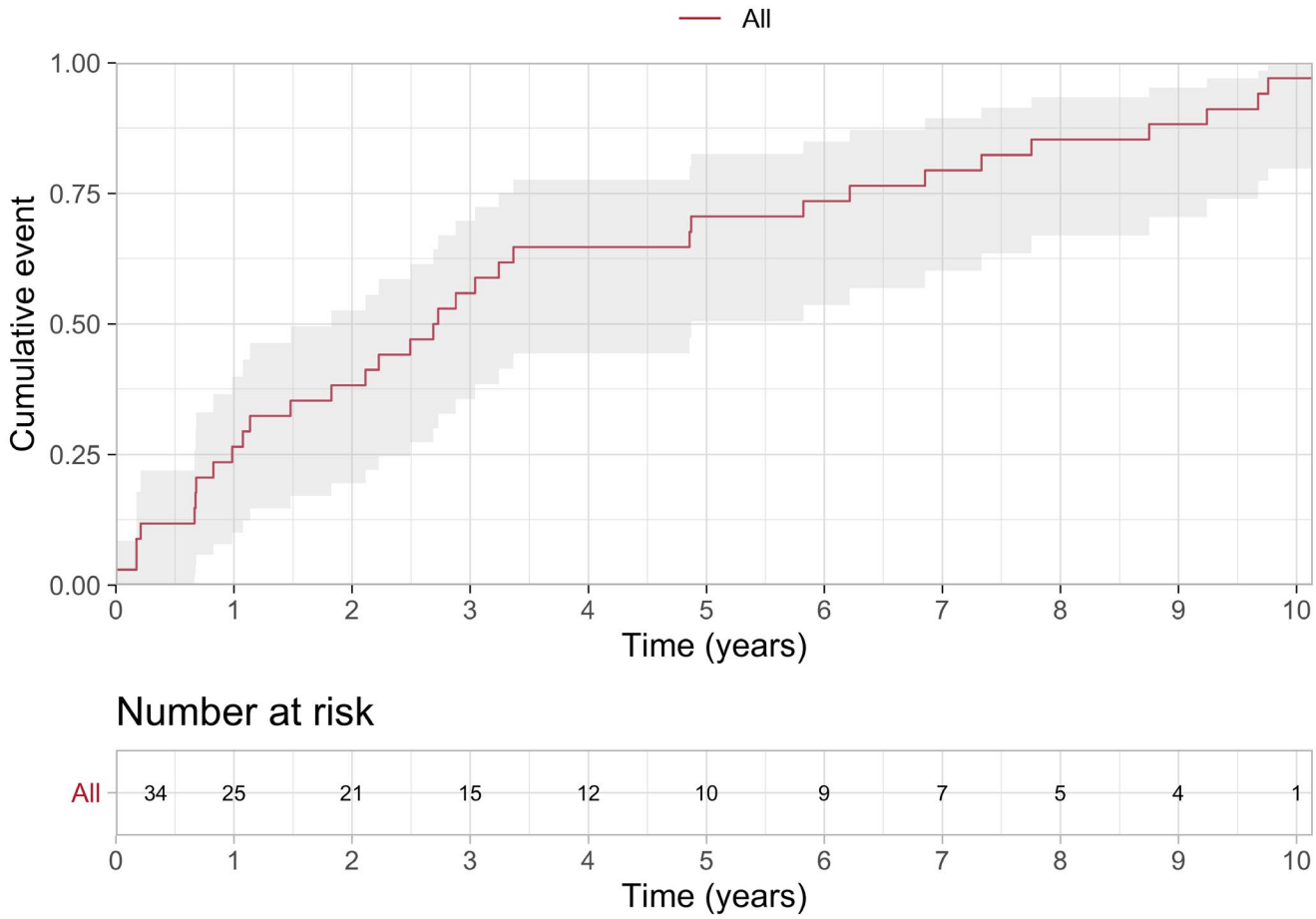

Figure 3 Time from the first description of an ADR in the SmPC of any of the TNF-α inhibitors to the first description of the same ADR in the SmPC of a second TNF-α inhibitor. ADR, adverse drug reactions; SmPC, summary of product characteristic. [Colour figure can be viewed at wileyonlinelibrary.com]

the ADRs were described in the SmPC of only one TNF-α inhibitor. Moreover, prior knowledge of the ADRs associated with previously approved TNF-α inhibitors is not fully transferred to non-first-in-class TNF-α inhibitors; only 39% of the ADRs that were identified prior to the approval of non-first-in-class TNF-α inhibitors were described in the SmPC at the approval of the non-first-in-class TNF-α inhibitor. If an ADR was described in at least two SmPCs, the median lag time to uptake of the ADR

Table 1 Univariate Cox regression analysis studying the determinants associated with the description of the ADR in the SmPC of at least two TNF-α inhibitors

	# of ADRs in second SmPC (%)	HR (95% CI)
Nature of the ADR		
Infections and infestations (*n* = 20)	9 (45)	2.1 (1.0–4.5)
Other (*n* = 115)	25 (22)	Reference
Seriousness		
Nonserious ADR (*n* = 61)	6 (10)	Reference
Serious ADR (*n* = 74)	28 (38)	4.5 (1.8–10.8)
Regulatory importance		
ADR not classified as important risk (*n* = 67)	7 (10)	Reference
ADR classified as important risk (*n* = 68)	27 (40)	4.6 (2.0–10.5)
First-in-class		
ADR first described in follow-on drug (*n* = 97)	17 (18)	Reference
ADR first described in first-in-class drug (*n* = 38)	17 (45)	2.8 (1.4–5.6)

ADRs, adverse drug reactions; CI, confidence interval; HR, hazard ratio; SmPCs, summary of product characteristics.

in a second SmPC was ~ 3 years. Specific characteristics of the ADRs ("seriousness," "regulatory importance," and "first-in-class") were shown to be associated with the description of the ADR in at least two SmPCs. As four of the five TNF-α inhibitors shared at least one rapporteur that was responsible for the regulatory assessment, we could not formally study the influence of having a rapporteur responsible for the regulatory assessment in common. However, it can be concluded that although four of the five TNF-α inhibitors shared at least one rapporteur, the overlap of ADRs included in the SmPC of the different TNF-α inhibitors is considered limited. Finally, in the first period after approval, when the regulatory monitoring is more intensive, the percentage of ADRs that was identified and subsequently described in the SmPC was higher than in the period thereafter.

The results of our study are in line with those of other studies that showed that the comparability of the product information of drugs within the same class is limited. Previous studies have shown that the product information differs among regulatory authorities (e.g., the US Food and Drug Administration (FDA) in the United States and the EMA in the European Union), despite being based on the same information.[17,18] Even between generic drugs that have been proven to be bioequivalent, differences in the product information are present.[19] Stefansdottir *et al*. showed that ~ 40% of ADRs (at the HLGT level) were described in the product information of both the first-in-class and second-in-class drugs.[10] Our study showed that ~ 55% of the ADRs at the HLT level and 73% of the ADRs at the HLGT level were described in the product information of at least 2 TNF-α inhibitors, which is substantially higher. This may be explained by the number of products included, as in our study we included all TNF-α inhibitors whereas Stefansdottir *et al*. included the only first-in-class and second-in-class products. We assumed that small differences in the exact mechanism of action did not result in major differences in the safety profile. However, we did not specifically assess whether all ADRs included in our analysis were related to the mechanism of action. For example, ADRs, such as headache and nausea, are not necessarily related to the mechanism of action but occur generally in patients treated with drugs.

Within the European regulatory system, safety issues are in general assessed on the product level. However, procedures (i.e., signal or referral procedures) are in place in which specific safety issues are evaluated for the group of drugs with the same mechanism of action as a whole. When the regulatory authorities conclude that an ADR is considered to be a class effect, the ADR should be included in the SmPCs of all drugs involved in the procedure. For example, a signal of lichenoid skin reactions was identified for adalimumab following a scientific publication, and the regulatory authorities concluded that this ADR should be added to adalimumab's SmPC.[20] This assessment initiated the evaluation of lichenoid skin reactions as a potential class effect following a literature review, leading to the addition of this ADR in the SmPCs of the other TNF-α inhibitors. In addition, a signal of Kaposi's sarcoma was initially only identified for infliximab based on several reported cases.[21] However, based on the data, it was decided that the scope should be extended to all TNF-α inhibitors. These signal and referral procedures are part of the European pharmacovigilance system and can be considered for safety issues identified in the postmarketing setting. However, as illustrated by the results of our study, previous knowledge on the safety profile is not fully taken into account at the time of approval. Therefore, also at the time of approval and as part of extension of indication procedures (potential), class effects should be considered.

The challenge of evaluating ADRs as class effects includes the tradeoff between the level of uncertainty about the causal association and the precaution of adding ADRs to the SmPC that have not (yet) been observed for the specific product. This balance may shift for specific ADRs, as illustrated by the results of our study that serious ADRs and ADRs classified as important risks were significantly more often described in a second SmPC. To facilitate the assessment of class effects, we argue that specific attention should be given to the assessment of the underlying mechanism by constructing adverse outcome pathways. This could follow an integrated approach for which pharmacovigilance data as well as information from clinical and preclinical studies should be taken into account. In addition, automated tools are being developed using input from, for example, spontaneous reporting databases and the product information of drugs with the same mechanism of action in order to facilitate the identification of ADRs.[22]

Given the nature of the challenge of evaluating ADRs as class effects, this challenge is not limited to the European regulatory system. This is, for example, illustrated by a study performed using data from the FDA showing that major safety issues described in the black box warnings differed among drugs with the same mechanism of action.[23] The lag time observed in our study may, however, be different in the United States as compared with the European Union setting. In the United States, ADRs with limited impact on the benefit-risk balance can be submitted to the FDA 30 days before distribution of the new product information, whereas updating the SmPC to include new ADRs in the European Union typically takes several months.[24,25] In addition, the presentation of safety information in the product information differs between the United States and the Eurpean Union. For example, in the US product information, the incidence of the ADRs observed in the clinical studies is reported for both the experimental and comparator arm, whereas in the European Union only the incidence of ADRs in the experimental arm is described. Providing information from both arms, may give further context for healthcare professionals to the occurrence of the ADRs.

We illustrated the overlap of ADRs described in the SmPCs of drugs with the same mechanism of action on the basis of only one class of drugs. However, considering the earlier-described characteristics of the regulatory system, the results are expected to be applicable to other classes of drug. The European pharmacovigilance system, however, has evolved over time as result of the implementation of the EU pharmacovigilance legislation that came into force in 2012. The greater part of this study took place before this legal change. Currently, each product is assigned to a team of (co)rapporteurs from the Pharmacovigilance Risk Assessment Committee. We expect that this procedure, together with EMA oversight, has resulted in more harmonized SmPCs of recently authorized products compared with those

we have studied here. In addition, we did not account for differences in indications of the TNF-α inhibitors. Although all TNF-α inhibitors are indicated for rheumatoid arthritis, additional indications differ among the products. The relationship between the number of different indications and the number of ADRs described in the SmPC, however, does not show a consistent pattern. For example, at the initial approval of golimumab and certolizumab, the indication of golimumab was broader than that of certolizumab, whereas ~ 45% more ADRs were described in the certolizumab SmPC compared with the golimumab SmPC.[26,27] In addition, the indications of certolizumab and golimumab were extended several times, which did not result in the addition of multiple ADRs, whereas for adalimumab, as part of an extension of indication procedures, multiple ADRs were added to the SmPC.

CONCLUSION

Existing as well as new knowledge of ADRs for drugs with the same mechanism of action is not in its entirety described in the safety information of all drugs. In addition, when knowledge of ADRs is transferred from one drug to another, this takes considerable time. In order to inform healthcare professionals and patients about the complete picture of the safety profile, knowledge of the safety profile of drugs with the same mechanism of action should increasingly be taken into account for all drugs within the class.

SUPPORTING INFORMATION

Supplementary information accompanies this paper on the *Clinical Pharmacology & Therapeutics* website (www.cpt-journal.com).

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CONFLICT OF INTEREST

All authors declared no competing interests for this work.

AUTHOR CONTRIBUTIONS

L.A.M., T.G., J.H., T.C.G.E., H.G.M.L., and H.G. wrote the manuscript. L.A.M., T.G., J.H., T.C.G.E., H.G.M.L., and H.G. designed the research. L.A.M., T.G., J.H., T.C.G.E., H.G.M.L., and H.G. performed the research. L.A.M. and H.G. analyzed the data. J.H. contributed new reagents/analytical tools.

1. Duijnhoven, R.G., Straus, S.M., Raine, J.M., de Boer, A., Hoes, A.W. & De Bruin, M.L. Number of patients studied prior to approval of new medicines: a database analysis. *PLoS Med.* **10**, e1001407 (2013).
2. Pregelj, L., Verreynne, M.L. & Hine, D. Changes in clinical trial length. *Nat. Rev. Drug Discov.* **14**, 307–308 (2015).
3. Rothwell, P.M. External validity of randomised controlled trials: "to whom do the results of this trial apply?" *Lancet* **365**, 82–93 (2005).
4. Lester, J., Neyarapally, G.A., Lipowski, E., Graham, C.F., Hall, M. & Dal Pan, G. Evaluation of FDA safety-related drug label changes in 2010. *Pharmacoepidemiol. Drug Saf.* **22**, 302–305 (2013).
5. Ebbers, H.C., Al-Temimi, E., Moors, E.H., Mantel-Teeuwisse, A.K., Schellekens, H. & Leufkens, H.G. Differences between post-authorization adverse drug reactions of biopharmaceuticals and small molecules. *BioDrugs* **27**, 167–174 (2013).
6. Hatem, R., Bebawi, E. & Schampaert, E. Potential sunitinib-induced coronary artery and aortic dissections. *Can. J. Cardiol.* **33**, 830.e17-830.e18 (2017).
7. European Medicines Agency. PRAC recommendation on signals: adopted at the 8–11 July 2019 PRAC meeting <https://www.ema.europa.eu/en/documents/prac-recommendation/prac-recommendations-signals-adopted-8-11-july-2019-prac-meeting_en.pdf> (2019). Accessed March 3, 2020.
8. Gardam, M.A. *et al*. Anti-tumour necrosis factor agents and tuberculosis risk: mechanisms of action and clinical management. *Lancet Infect. Dis.* **3**, 148–155 (2003).
9. Keane, J. *et al*. Tuberculosis associated with infliximab, a tumor necrosis factor alpha-neutralizing agent. *N. Engl. J. Med.* **345**, 1098–1104 (2001).
10. Stefansdottir, G. *et al*. Safety learning from drugs of the same class: room for improvement. *Clin. Pharmacol. Ther.* **91**, 872–880 (2012).
11. Arnardottir, A.H., Haaijer-Ruskamp, F.M., Straus, S.M., de Graeff, P.A. & Mol, P.G. Effect of safety issues with HIV drugs on the approval process of other drugs in the same class: an analysis of European Public Assessment Reports. *Drug Saf.* **34**, 1101–1114 (2011).
12. IQVIA Institute for Human Data Science. The Global Use of Medicine in 2019 and Outlook to 2023 (2019).
13. European Medicines Agency. QRD general principles regarding the SmPC information for a generic/hybrid/biosimilar product (2018).
14. MedDRA Maintenance and Support Services Organization. Medical Dictionary for Regulatory Activities <https://www.meddra.org/>.
15. European Medicines Agency. Inclusion/exclusion criteria for the "Important Medical Events" list <https://www.ema.europa.eu/en/documents/other/eudravigilance-inclusion/exclusion-criteria-important-medical-events-list_en.pdf> (2020). Accessed April 5, 2020.
16. European Medicines Agency. Guideline on good pharmacovigilance practices: Module V – Risk management systems (Rev. 2) <https://www.ema.europa.eu/en/documents/scientific-guideline/guideline-good-pharmacovigilance-practices-module-v-risk-management-systems-rev-2_en.pdf> (2017).
17. Kesselheim, A.S., Franklin, J.M., Avorn, J. & Duke, J.D. Speaking the same language? International variations in the safety information accompanying top-selling prescription drugs. *BMJ Qual. Saf.* **22**, 727–734 (2013).
18. Eriksson, R. *et al*. Discrepancies in listed adverse drug reactions in pharmaceutical product information supplied by the regulatory authorities in Denmark and the USA. *Pharmacol. Res. Perspect.* **2**, e00038 (2014).
19. Duke, J., Friedlin, J. & Li, X. Consistency in the safety labeling of bioequivalent medications. *Pharmacoepidemiol. Drug Saf.* **22**, 294–301 (2013).
20. European Medicines Agency. Pharmacovigilance Risk Assessment Committee (PRAC) Minutes of the meeting on 09-12 July 2018 <https://www.ema.europa.eu/en/documents/minutes/minutes-prac-meeting-9-12-july-2018_en.pdf> (2018).
21. European Medicines Agency. Pharmacovigilance Risk Assessment Committee (PRAC) Minutes of PRAC meeting on 28 – 31 October 2019 (2019).
22. Schotland, P. *et al*. Target adverse event profiles for predictive safety in the post-market setting. *Clin. Pharmacol. Ther.* https://doi.org/10.1002/cpt.2071
23. Panagiotou, O.A., Contopoulos-Ioannidis, D.G., Papanikolaou, P.N., Ntzani, E.E. & Ioannidis, J.P. Different black box warning labeling for same-class drugs. *J. Gen. Intern. Med.* **26**, 603–610 (2011).

24. European Commission. Commission Regulation (EU) No 712/2012 <https://ec.europa.eu/health//sites/health/files/files/eudralex/vol-1/reg_2012_712/reg_2012_712_en.pdf> (August 3, 2012).
25. Food and Drug Administration. Changes to an Approved NDA or ANDA revision 1 <https://www.fda.gov/files/drugs/published/Changes-to-an-Approved-NDA-or-ANDA.pdf> (April 2004). Accessed October 18, 2020.
26. European Medicines Agency. Simponi: EPAR - Public assessment report <https://www.ema.europa.eu/en/documents/smop-initial/committee-medicinal-products-human-use-summary-positive-opinion-simponi_en.pdf> (2009).
27. European Medicines Agency. Cimza: EPAR - Public assessment report <https://www.ema.europa.eu/en/documents/assessment-report/cimzia-epar-public-assessment-report_en.pdf> (2009).