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ORIGINAL RESEARCH ARTICLE

Real World Data on the Utilization Pattern and Safety Profile of Infliximab Originator Versus Biosimilars in Italy: A Multiregional Study

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Abstract

Background In recent years, several biosimilar drugs, including those of infliximab, have obtained marketing authorization from the European Medicines Agency (EMA). Given the peculiarity of the safety profile of biological medical products (originator and biosimilars), the evaluation of their tolerability represents an important component of pre-marketing and post-marketing clinical development. For example, infliximab products may cause adverse drug reactions (ADRs) including acute infusion reactions, delayed hypersensitivity reactions, and loss of efficacy, as a direct consequence of immunogenicity. Therefore, specific contraindications, special warnings and precautions have been introduced in the infliximab Summary of Product Characteristics (SPC).
Objective The aim was to assess the magnitude of preventable ADRs in individual case safety reports (ICSRs) having infliximab as a suspected drug across Italy (using the spontaneous reporting systems), and the probability of reporting infections, infusion reactions, lack of efficacy, and hypersensitivity for originator and biosimilars of infliximab.
Methods We analyzed ADRs reported across the 2015–2017 period in the databases of five Italian regions: Campania, Lombardy, Sicily, Tuscany, and Veneto. Preventability of ADRs was assessed using the P-method. To compare the probability of reporting infections, infusion reactions, lack of efficacy, and hypersensitivity as ADRs as opposed to other types of ADRs between originator and biosimilars of infliximab, we used the reporting odds ratio (ROR). For descriptive purposes, the number of ICSRs involving infliximab, the number of infliximab vials distributed in the aforementioned Italian regions and the relative reporting rate stratified by semester were reported.
Results From October 2015 to October 2017, 459 ICSRs reported infliximab as a suspected drug (222 ICSRs related to infliximab originator and 237 to infliximab biosimilars). In the same period, 81,906 vials of infliximab were distributed, resulting in a reporting rate of six ICSRs/1000 vials. Overall, 34 cases (7.41%) were categorized as preventable. The most frequently detected critical criteria were "documented hypersensitivity to administered drug or drug class," "inappropriate prescription for patient's underlying medical condition" and "incorrect dose." Biosimilars had, in adjusted analyses, an increased probability of being reported as suspected in ICSRs reporting infusion reactions (ROR 4.09; 95% confidence interval [CI] 1.26–13.32) when compared to Remicade®. On the contrary, they had a decreased probability of being reported as suspected in ICSRs reporting infections or lack of efficacy (ROR 0.33; 95% CI 0.12–0.89; ROR 0.35; 95% CI 0.20–0.61).
Conclusion Our study demonstrates that, along with a rapid increase in the utilization of infliximab biosimilars across Italy, there was also an increase in reporting ADRs induced by infliximab biosimilars. Of the reported ADRs, 7.4% were considered preventable. In adjusted analyses, infliximab biosimilars were shown to have an increased probability of being reported as suspected drugs in infusion reactions and a decreased probability of being reported as suspected drugs in cases of lack of efficacy or infection. Considering the potential advantages offered by the utilization of biosimilars in clinical practice, we believe that the use of biosimilars, including those of infliximab, should be supported. In order to achieve this aim, increased knowledge on safety and efficacy of biosimilar drugs should be obtained from real world clinical practice.

Electronic supplementary material The online version of this article (https://doi.org/10.1007/s40259-018-0313-2) contains supplementary material, which is available to authorized users.

Extended author information available on the last page of the article

Key Points

Our study demonstrated that the rapid increase in the utilization of infliximab biosimilars across Italy during 2015–2017 has been accompanied by an increase in reporting infliximab biosimilar-induced adverse drug reactions. Overall, 459 individual case safety reports reported infliximab as a suspected drug; of these, 34 cases were categorized as preventable.

Compared to infliximab originator, biosimilars had an increased probability of being reported as suspected in individual case safety reports related to the occurrence of infusion reactions and a decreased probability of being reported as suspected in individual case safety reports reporting infections or lack of efficacy.

1 Introduction

With the gradual expiration of patents of biotech drugs, new copy versions of these medicines have become available for patients—the biosimilars. Such drugs are defined by the European Medicines Agency (EMA) as "a biological medicine highly similar to another biological medicine already approved in the EU" [1]. EMA has led the way in biosimilar regulation through the implementation of a solid framework for their development and approval, and with the comparability exercise, which aims to ensure that the biosimilar and the reference medicine have the same features in terms of quality, efficacy, and safety [2–7].

From 2006 until September 2018, EMA authorized 46 biosimilars [8]. Infliximab was the first biosimilar of a monoclonal antibody (mAb) to be approved. Infliximab is a chimeric mAb, acting as a tumor necrosis factor-α (TNF-α) blocker.

Infliximab was approved by EMA in 1999, under the market name of Remicade®, as an intravenous injection for the treatment of Crohn's disease, ulcerative colitis, rheumatoid arthritis, ankylosing spondylitis, psoriatic arthritis, and plaque psoriasis [9]. Following Remicade® patent expiration, four infliximab biosimilars obtained marketing authorization by EMA: Remsima® and Inflectra®, which were authorized in 2013, became available in Italy for use in clinical practice in 2015; Flixabi®, which was approved in 2016, obtained classification for pricing and reimbursement in Italy in May 2017; Zessly®, approved by EMA in May 2018, is not yet available on the Italian market.

The comparability exercise for Remsima® and Inflectra® consisted of several nonclinical and clinical studies, including a phase 1 study in patients with ankylosing spondylitis [10] and a phase 3 study in patients affected by rheumatoid arthritis [11]. After the approval of Remsima® and Inflectra®, amongst the many post-marketing studies that have evaluated their safety profile, a recent pharmacovigilance study performed by our group confirmed, through the analysis of data reported in individual case safety reports (ICSRs), the comparable safety profile of infliximab originator and its biosimilars in five Italian regions [12].

An important pillar of biosimilars' development is the evaluation of the safety profile. Safety issues mainly include immunogenicity and an increased risk for other adverse effects, such as serious infections [9, 13–18]. Immunogenicity can induce the occurrence of acute infusion reactions, delayed hypersensitivity reactions, and loss of efficacy as a direct consequence of the production of neutralizing and non-neutralizing antidrug antibodies (ADAs) [8, 19–21]. In virtue of the aforementioned safety concerns, specific risk minimization measures have been introduced for infliximab, such as the contraindication for patients with a history of hypersensitivity, tuberculosis or other severe infections, and special warnings and precautions related to the co-administration of infliximab with other biological medicinal products or in patients affected by malignancies or lymphoproliferative disorders. All these elements are reported in infliximab's Summary of Product Characteristics (SPC) [6]. However, to date, it is not known to what extent these measures are followed in routine clinical practice.

In this regard, it should be highlighted that adverse drug reactions (ADRs) that occur in the presence of risk factors are the most preventable type of ADRs and, for them, the World Health Organization claims an improved effort for their identification and minimization. While several studies have been conducted for a panel of medicinal products [22–24], to date, there is no available evidence for infliximab on the magnitude of preventable ADRs identified through spontaneous reporting systems. To fill this gap in knowledge, for this study, we retrieved from the Italian Pharmacovigilance Database all ICSRs that reported infliximab as the suspected drug among those sent through Campania, Lombardy, Sicily, Tuscany, and Veneto spontaneous reporting systems; we searched for preventable and not preventable ADRs; and we compared the probability of reporting infections, infusion reactions, lack of efficacy, and hypersensitivity as ADRs as opposed to other types of ADRs between originator and biosimilars of infliximab.

2 Methods

2.1 Study Design

A safety evaluation study was conducted based on data reported in the Italian Pharmacovigilance Database, and included a case series of preventable/not-preventable ADRs.

2.2 Data Source

For the purpose of this study, we retrieved from the Italian Pharmacovigilance Database all ICSRs that reported infliximab as the suspected drug among those sent through Campania, Lombardy, Sicily, Tuscany, and Veneto spontaneous reporting systems from October 2015 to October 2017. Overall, these regions cover almost 30 million citizens, 49% of the Italian population. In Italy, healthcare professionals and consumers can send ICSRs directly to the local pharmacovigilance manager (local health unit/hospital) or to the marketing authorization holder/national competent authority. Local pharmacovigilance managers perform the data entry into the Italian Pharmacovigilance Database. Marketing authorization holders, furthermore, perform the data entry directly in EudraVigilance. However, through rerouting, ICSRs collected on the Italian national territory are automatically transferred to the Italian Pharmacovigilance Database. Prior to data entry, both local pharmacovigilance managers and marketing authorization holders evaluate the quality and validity of each ICSR, and whenever necessary, they retrieve additional information for the causality assessment.

Data on the utilization of infliximab's products in Campania, Lombardy, Sicily, Tuscany, and Veneto were obtained from IMS Health.

2.3 Case-by-Case Assessment

As part of their routine pharmacovigilance activities, Campania, Lombardy, Sicily, Tuscany, and Veneto Pharmacovigilance Regional Centers perform the causality assessment for all drug–event couples reported through their spontaneous reporting systems using the Naranjo algorithm [25]. For this study, furthermore, a trained multiregional team composed of pharmacists and clinical pharmacologists experienced in pharmacovigilance assessed the preventability of ADRs using the P-method. The P-method [26] involves the use of a validated algorithm, which aims to assess the preventability of ADRs reported in ICSRs among those sent through spontaneous reporting systems. In our study, the preventability assessment was performed in two steps and exclusively for those ICSRs with a causality assessment that resulted as at least "possible" according to the Naranjo scale. In particular, the first step was the determination of the potential mechanism for ADRs. The second step was the evaluation of the critical criteria or risk factors for the development of an ADR, or rather, answering a questionnaire composed of 20 questions for which assessors could answer positively, negatively or state that the question was "not applicable" or "unknown" for the case. If at least one positive answer was given, the case was classified as preventable (i.e., more than one critical criterion was detectable). If no positive answers were given, the case was classified as not preventable. Cases with insufficient information to assess critical criteria were classified as not assessable. Full agreement among clinical pharmacologists and pharmacists involved in the preventability assessment was reached for all preventable cases.

2.4 Statistical Analyses

We plotted the number of ICSRs involving infliximab, the number of infliximab vials distributed, and the relative reporting rate stratified by semester. According to our study aims, we presented a case series of all preventable cases involving infliximab as the suspected drug. Being aware of the limits of disproportionality methods for comparative drug safety analyses [27], we used the reporting odds ratio (ROR) to compare the probability of reporting infections, infusion reactions, lack of efficacy, and hypersensitivity as ADRs as opposed to other types of ADRs between infliximab originator and biosimilars. A multivariable logistic regression model was used to adjust RORs by age, gender, comorbidities, indication of use, region, and number of concomitant drugs/medications as shown by Rothman and colleagues [28]. In particular, the ROR was adjusted for the aforementioned covariates because previous studies have proved that confounding may potentially be reduced [29–31]. For descriptive purposes, clinical and demographic characteristics of cases, type of reporter, and the seriousness and outcome of ADRs stratified by originator/biosimilar were reported.

3 Results

From October 2015 to October 2017, 459 ICSRs reported infliximab as the suspected drug among those sent through Campania, Lombardy, Sicily, Tuscany, and Veneto regions' spontaneous reporting systems. In the same period, 81,906 vials of infliximab were distributed, resulting in a reporting rate of six ICSRs/1000 vials. In January 2017, for the first time, biosimilar vials reached over 50% of overall vials distributed in the aforementioned Italian regions, with an increasing trend over the years (Fig. 1). Immediately after the marketing authorization of infliximab biosimilars, an increase in the reporting rate of ICSRs for those drugs was observed (Fig. 2). For both originator and biosimilars, demographic and clinical characteristics are provided in Table 1. In total, 222 ICSRs reported Remicade® as suspected and 237 ICSRs reported biosimilars (Remsima® and Inflectra®). Patients who experienced an ADR to infliximab (both originator and biosimilars) had a mean age of 48.0 ± 15.5 years, and 54.5% of them were female. Therapeutic indications reported in ICSRs for Remicade®, Remsima® and Inflectra®

were those authorized (rheumatoid arthritis 34%; Crohn's disease 24.6%; ulcerative colitis 18.3%; spondylitis 16.3%; psoriasis 6.8%) (Table 1). The highest number of ICSRs sent to the Italian Pharmacovigilance Database were from Lombardy (38.1%) and Sicily (29.4%), followed by Tuscany (14.4%), Veneto (12.2%) and Campania (5.9%). More than 60% of patients who experienced an ADR with infliximab were concomitantly receiving at least one further medication, and more than 80% of those patients had at least one comorbidity, mainly cardiac disorders, dyslipidemia, and acute/chronic infections (Table 1).

3.1 Preventable Cases

In total, 34 cases out of 459 (7.41%) were considered as preventable (see the electronic supplementary material, Supplementary Table 1). The reporting rate of preventable cases was four cases/10,000 vials distributed, and the underlying mechanism of ADRs was, for the majority of cases, susceptibility related (14/34; 41.2%) (Fig. 3). Thirty-eight critical criteria related to healthcare professionals' practices were detected. The most detected critical criteria were "documented hypersensitivity to administered drug or drug class" (12/38; 31.6%), "inappropriate prescription for patient's underlying medical condition" (11/38; 28.9%) and "incorrect dose" (7/38; 18.4%).

3.2 Disproportionate Reporting of Infections, Infusion Reactions, Lack of Efficacy, and Hypersensitivity Between Biosimilars and Originator of Infliximab

In unadjusted analyses, biosimilars had an increased probability of being reported as suspected in ICSRs reporting hypersensitivity and infusion reactions as opposed to other types of ADRs when compared to Remicade®. Analogously, biosimilars have, in unadjusted analyses, a reduced probability of being reported as suspected in ICSRs reporting lack of efficacy or infection (Fig. 4). In adjusted analyses, aforementioned associations were found for infections (ROR 0.33; 95% confidence interval [CI] 0.12–0.89; p value = 0.029), lack of efficacy (ROR 0.35; 95% CI 0.20–0.61; p value < 0.001) and infusion reactions (ROR 4.09; 95% CI 1.26–13.32; p value = 0.019).

4 Discussion

This is the first study assessing the utilization pattern and the safety profile of infliximab products (through a spontaneous reporting system) as well as the magnitude of preventability of ADRs induced by these products. Our study shows that from October 2015 to October 2017, infliximab biosimilars' utilization gradually increased in Italy, with an increase in the reporting rate of ICSRs for biosimilars. Overall, 459 ICSRs reported infliximab as a suspected drug. All ICSRs reported as suspected a defined medical product, originator or biosimilar; in our study, no ICSRs reported as suspected infliximab without the identification of the brand name. This is in line with the current European regulation on post-marketing biological medicines' traceability that is aimed at the identification and distinction between biological medicines by the trade name and batch number in order to identify any safety signals associated with each biological product [32]. As expected, the number of ICSRs related to infliximab biosimilars "physiologically" increased immediately after the marketing availability of those medicine in Italy, which can be partly interpreted as a result of the increasing number of patients being exposed to biosimilars. Meanwhile, a direct correlation between the increased attention that all biosimilars, including those of infliximab, have received from clinicians and patients and the increased reporting of ADRs induced by infliximab biosimilars cannot be excluded. In support of this could be the fact that, after reaching a peak, the reporting rate for infliximab biosimilars reduced substantially despite the distributed vials of infliximab increasing over time.

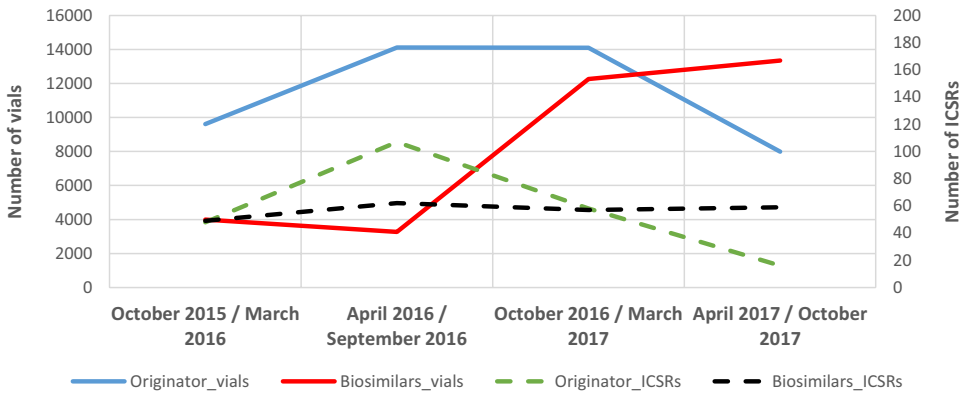

Fig. 1 Trends of individual case safety reports (ICSRs) sent through the regional spontaneous reporting system and the number of vials of infliximab originator and biosimilars distributed in Campania, Lombardy, Sicily, Tuscany, and Veneto regions from October 2015 to October 2017

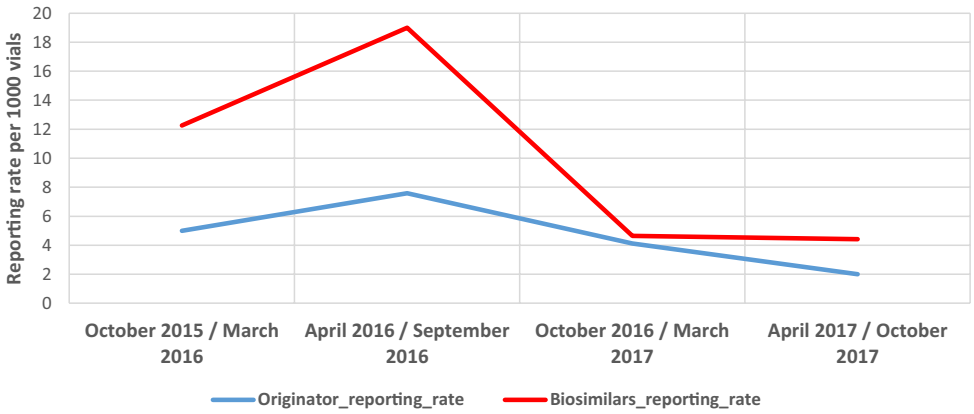

Fig. 2 Infliximab originator and biosimilar reporting rates of individual case safety reports sent through Campania, Lombardy, Sicily, Tuscany, and Veneto regions' spontaneous reporting systems from October 2015 to October 2017

In our study, the mean age of patients who experienced an ADR was 48.0 ± 15.5 years; this is in line with what is reported in the literature regarding the mean age of onset of the diseases for which infliximab is indicated [33, 34]. ADRs occurred slightly more frequently in female patients compared to male ones. This is not surprising considering that a higher prevalence of use of infliximab could be found in the female population, due to a higher prevalence of diseases for which this drug is indicated, including Crohn's disease [35] and rheumatoid arthritis [36]. Moreover, female patients have a greater risk of developing an ADR compared with male ones, mainly for gender-related differences related to pharmacokinetic, immunological and hormonal factors [14, 37, 38]. According to our results, arthritis, Crohn's disease and ulcerative colitis were more commonly reported as therapeutic indications in ICSRs; this could be explained by the different prevalence of those diseases. As a matter of fact, the prevalence of all immune-mediated inflammatory diseases in Western countries ranges from 5 to 7%, with a higher prevalence for rheumatoid arthritis and inflammatory bowel diseases, followed by ankylosing spondylitis and psoriasis [39, 40]. We also found that 45% of patients who experienced ADRs induced by infliximab originator received the drug for the treatment of rheumatoid arthritis, while more than 50% of patients who experienced ADRs induced by infliximab biosimilars received the drug for the treatment of inflammatory bowel diseases (Crohn's disease and ulcerative colitis). In our opinion, these differences could be a direct consequence of the higher acceptance of biosimilars by rheumatologists compared to gastroenterologists, who seem to be more reluctant to accept biosimilars [41]. On the other hand, the regional differences that we have found among Italian regions could be directly related to a different use of biosimilars in clinical practice, mainly due to decrees that have regulated biosimilars' prescription as well as ADR reporting. This heterogeneity in biosimilars' utilization, which could be linked to different reporting features, was previously found in another study performed in a real-life setting [42].

In our study, the majority of patients had one or more comorbidities and were concomitantly receiving further medications. This is not surprising considering that comorbidities, including infective, cardiovascular, renal, and cancer diseases, are commonly present in patients diagnosed with immune-mediated inflammatory diseases and hugely contribute to the burden of disease and impairment of quality of life [43, 44]. Moreover, it should be noted that immune-mediated diseases usually require combination therapy [45, 46].

Our results also show that 7.41% of all cases were considered as preventable. With regard to preventable ADRs due to a documented hypersensitivity, according to literature data, infliximab therapy is associated with a well-known risk of hypersensitivity reactions, the exact etiology and pathogenesis of which is still unclear. Considering that such ADRs could be potentially serious, several preventive measures have been proposed, such as instructions for infusion rates and preventive medications [47, 48]. Moreover, according to information reported in the infliximab's SPCs [49] as well as in the literature [50], a history of hypersensitivity to infliximab represents a contraindication, and routine retreatment in patients who have already experienced serious infusion reactions to infliximab should not be recommended. Among our cases, the second main cause of preventability was an inappropriate prescription according to patient's characteristics, mainly related to the occurrence of infections or cancer in patients with a prior history of those conditions. It is widely recognized that, by inhibiting the activity of the immune system, infliximab may predispose patients to an increased risk of developing malignancies and infections [51–54]. This risk is statistically associated with chronic hepatitis B or C, a history of cancer and a history of infectious events [55–57]. Similarly, immunosuppression therapy is not recommended for at least 5 years after a diagnosis of cancer [58–60]. An important finding of our study is that few preventable cases were related to incorrect dose administration. According to what is reported in Section 4.2 of the SPCs [6, 49], the clinical response with infliximab is usually achieved with a dose

Table 1 Demographic and clinical characteristics of individual case safety reports having infliximab (originator and biosimilars) as suspected drug sent through Campania, Lombardy, Sicily, Tuscany, and Veneto Regions' spontaneous reporting systems from October 2015 to October 2017

Variable	Level	Biosimilars ($n=237$)	Originator ($n=222$)	Total ($n=459$)
Age	Mean (SD), years	48.5 (15.4)	47.4 (15.6)	48.0 (15.5)
	Missing	16	3	19
Gender	Female	126 (53.2)	124 (55.9)	250 (54.5)
	Male	111 (46.8)	98 (44.1)	209 (45.5)
Indication for use	Crohn's disease	70 (29.5)	43 (19.4)	113 (24.6)
	Rheumatoid arthritis	56 (23.6)	100 (45.0)	156 (34.0)
	Ulcerative colitis	57 (24.1)	27 (12.2)	84 (18.3)
	Psoriasis	23 (9.7)	8 (3.6)	31 (6.8)
	Spondylitis	31 (13.1)	44 (19.8)	75 (16.3)
Region	Lombardy	56 (23.6)	119 (53.6)	175 (38.1)
	Campania	4 (1.7)	23 (10.4)	27 (5.9)
	Sicily	81 (34.2)	54 (24.3)	135 (29.4)
	Tuscany	50 (21.1)	16 (7.2)	66 (14.4)
	Veneto	46 (19.4)	10 (4.5)	56 (12.2)
Number of reported concomitant drugs	1	136 (57.4)	145 (65.3)	281 (61.2)
	2	35 (14.8)	23 (10.4)	58 (12.6)
	3	25 (10.5)	19 (8.6)	44 (9.6)
	4	11 (4.6)	7 (3.2)	18 (3.9)
	5	12 (5.1)	3 (1.4)	15 (3.3)
	6	6 (2.5)	4 (1.8)	10 (2.2)
	7	3 (1.3)	10 (4.5)	13 (2.8)
	8	2 (0.8)	3 (1.4)	5 (1.1)
	9	2 (0.8)	5 (2.3)	7 (1.5)
	≥ 10	5 (2.1)	3 (1.4)	8 (1.7)
Number of reported comorbidities	0	198 (83.5)	180 (81.1)	378 (82.4)
	1	19 (8.0)	19 (8.6)	38 (8.3)
	2	9 (3.8)	10 (4.5)	19 (4.1)
	3	7 (3.0)	5 (2.3)	12 (2.6)
	4	0 (0.0)	1 (0.5)	1 (0.2)
	5	4 (1.7)	7 (3.2)	11 (2.4)
Cardiac disorders	Yes	12 (5.1)	18 (8.1)	30 (6.5)
Respiratory disorders	Yes	2 (0.8)	4 (1.8)	6 (1.3)
Dyslipidemia	Yes	2 (0.8)	14 (6.3)	16 (3.5)
Diabetes mellitus	Yes	1 (0.4)	1 (0.5)	2 (0.4)
Thyroid disorders	Yes	4 (1.7)	0 (0.0)	4 (0.9)
Acute/chronic infections	Yes	5 (2.1)	5 (2.3)	10 (2.2)
Psychiatric disorders	Yes	6 (2.5)	1 (0.5)	7 (1.5)
Neurological disorders	Yes	1 (0.4)	3 (1.4)	4 (0.9)
Electrolyte disorders	Yes	3 (1.3)	7 (3.2)	10 (2.2)
Bone disorders	Yes	3 (1.3)	5 (2.3)	8 (1.7)
Hematological disorders	Yes	2 (0.8)	6 (2.7)	8 (1.7)

SD standard deviation

that ranges from 3 to 7.5 mg/kg, depending on the therapeutic indication. In our preventable cases, we have noticed that these recommended dosages were not respected. However, since the literature on this is still limited, we cannot exclude that the choice to treat the patient with a dose outside the recommended range was driven by an appropriate clinical evaluation performed by the clinician.

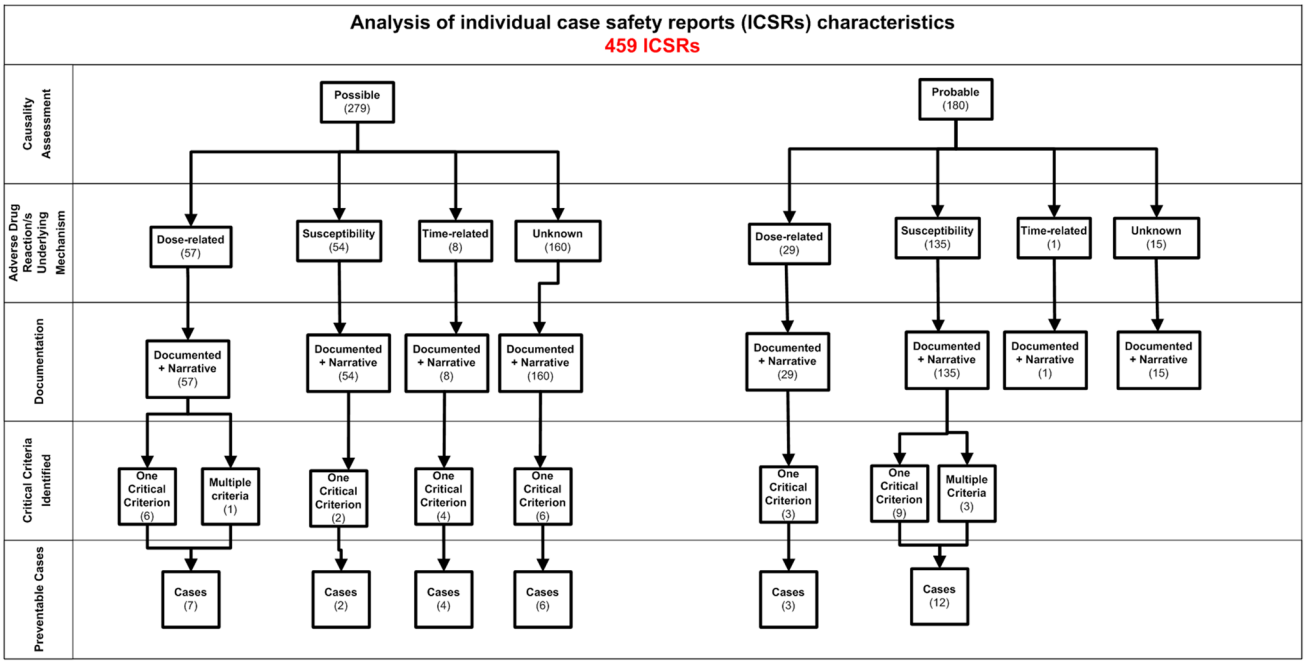

Fig. 3 Flowchart of preventability assessment procedures performed for individual case safety reports (ICSRs) reporting infliximab as the suspected drug

Variable	Comparison	Estimation	95% CI low	95% CI high	Type	Estimation [95%CI]
Infection	Biosimilars vs Originator	0.54	0.37	0.80	Unadjusted	0.54 [0.37, 0.8]
Infusion reactions	Biosimilars vs Originator	1.78	1.38	2.30	Unadjusted	1.78 [1.38, 2.3]
Lack of efficacy	Biosimilars vs Originator	0.48	0.37	0.61	Unadjusted	0.48 [0.37, 0.61]
Hypersensitivity	Biosimilars vs Originator	1.95	1.67	2.27	Unadjusted	1.95 [1.67, 2.27]
Infection	Biosimilars vs Originator	0.33	0.12	0.89	Adjusted	0.33 [0.12, 0.89]
Infusion reactions	Biosimilars vs Originator	4.09	1.26	13.32	Adjusted	4.09 [1.26, 13.32]
Lack of efficacy	Biosimilars vs Originator	0.35	0.20	0.61	Adjusted	0.35 [0.20, 0.61]
Hypersensitivity	Biosimilars vs Originator	1.60	0.96	2.68	Adjusted	1.60 [0.96, 2.68]

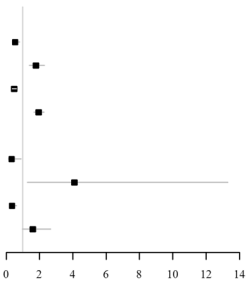

Fig. 4 Disproportionate reporting of infections, infusion reactions, lack of efficacy, and hypersensitivity between biosimilars and originator infliximab. *CI* confidence interval

Finally, we observed for infliximab originator and biosimilars a different probability of being reported as suspected in ICSRs reporting infusion reactions, infections and lack of efficacy. During the last months, several post-marketing studies evaluating the safety profile of infliximab products were published in scientific literature. Most of these studies have evaluated the effects of the switch from infliximab originator to its biosimilars, revealing no safety or efficacy concerns [61–63]. Those studies that have compared the safety profile of originator and biosimilars have showed a similar rate of ADRs [64, 65], but to our knowledge, no study has yet compared the rate of occurrence of infections, loss of efficacy or infusion reactions. However, available studies suggest that infliximab biosimilars, along with Remicade®, can be associated with the occurrence of such ADRs [66–68]. Furthermore, considering that among Italian regions, as dictated by the aforementioned decrees, the use of biosimilars is strongly recommended, especially in naïve patients, it is conceivable that the increased risk of infusion reactions in biosimilar users could be a direct consequence of the first administration of the drug. However, considering the differences in the decrees adopted by each of the Italian regions involved in this pharmacovigilance study, we cannot exclude their key role in the increase in the number of ICSRs related to infliximab biosimilars as well as in the reporting of specific ADRs versus others.

This study has a number of limitations and strengths. First of all, it is based on the spontaneous reporting system, and it is well known that it is affected by constraints that include underreporting, lack of clinical data, and improper causality

attribution [69, 70]. Considering these intrinsic limitations, we cannot rule out the presence of other information not listed in ICSRs which might have influenced the proper evaluation of each report (i.e., the lack of the date of infliximab's administration, the dose, concomitant clinical conditions or medications). Despite these limitations, we present a comprehensive evaluation of safety data related to infliximab products in five Italian regions that account for almost 50% of the entire Italian population. Therefore, the safety data that we have collected for this study represent a cross-section of patients treated with infliximab in a real-life setting who experienced ADRs to these medical products. Furthermore, despite its intrinsic limitations, the spontaneous reporting system still represents a valuable and inexpensive tool, able to detect rare and serious ADRs not identified during premarketing clinical trials. In this regard, further pharmacovigilance global data, such as those derived from the drug safety data repository Vigibase, could represent a valuable source of information able to confirm and improve our findings. Moreover, considering the historic moment in which we are living regarding issues relating to the utilization of biosimilars, we are able to share with the healthcare community reassuring data on the safety profile of these medicines. Nowadays, indeed, it is recognized worldwide that real world studies, performed during the post-marketing phase [71], represent one of the best sources of information regarding improving knowledge in the field of medicine safety profiles.

5 Conclusion

Our study showed that, along with a rapid increase in the utilization of infliximab biosimilars in five Italian regions, there was also an increase in the ADR reporting rate, mainly as a result of the increasing number of patients being exposed to these medicines. Moreover, our results showed that 7.41% of ICSRs reported ADRs that were preventable. For these cases, the detected critical criteria were mainly related to "documented hypersensitivity to administered drug or drug class," "inappropriate prescription for patient's underlying medical condition" and "incorrect dose." According to our results, no new safety issues have emerged for infliximab originator or its biosimilars.

Considering the potential advantages offered by the increase in biosimilar utilization in clinical practice, both for patients and healthcare systems, we believe that the use of biosimilars, including those of infliximab, should be undoubtedly supported in clinical practice. In order to achieve this aim and to counteract any doubts that persist among clinicians who prescribe biosimilars, a better knowledge on the safety and efficacy of biosimilar drugs should be obtained from the promotion of real world studies and the analysis of real world data, which represent an innovative tool to implement knowledge on health services, generate new evidence, and respond to unsolved clinical questions. In this context, the conduct of prospective studies will help to fill this gap in knowledge and to better translate into clinical practice valuable data on the safety profile of infliximab products, also aiming to reduce the burden of medical errors leading to preventable ADRs.

Compliance with Ethical Standards

Conflict of interest Scavone C., Sessa M., Clementi E., Corrao G., Leone R., Mugelli A., Rossi F., Spina E. and Capuano A. declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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References

1. European Medicine Agency. Biosimilar medicines [Internet]. EMA Website. http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/general/general_content_001832.jsp Accessed 19 July 2018.
2. Quianzon CC, Cheikh I. History of insulin. J Community Hosp Intern Med Perspect. 2012. https://doi.org/10.3402/jchimp.v2i2.18701.
3. European Medicine Agency. Human Medicines European Public Assessment Report (EPAR): Retacrit [Internet]. EMA Website. http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Assessment_Report_-_Variation/human/000872/WC500116652.pdf Accessed 14 May 2018.
4. Tsuruta LR, Lopes dos Santos M, Moro AM. Biosimilars advancements: moving on to the future. Biotechnol Prog United States. 2015;31:1139–49.
5. Pavlovic M, Girardin E, Kapetanovic L, Ho K, Trouvin J-H. Similar biological medicinal products containing recombinant human growth hormone: European regulation. Horm Res Switzerland. 2008;69:14–21.
6. European Medicine Agency. Remsima®—CHMP Assessment Report [Internet]. EMA Website. http://www.ema.europa.eu/docs/en GB/document library/EPAR - Public assessment report/human/002576/WC500151486.pdf Accessed 19 July 2018.
7. Morrow T, Felcone LH. Defining the difference: what makes biologics unique. Biotechnol Healthc United States. 2004;1:24–9.
8. Scavone C, Sportiello L, Berrino L, Rossi F, Capuano A. Biosimilars in the European Union from comparability exercise to real world experience: what we achieved and what we still need to achieve. Pharmacol Res. 2017;119:265–71.
9. Scavone C, Rafaniello C, Berrino L, Rossi F, Capuano A. Strengths, weaknesses and future challenges of biosimilars'

development. An opinion on how to improve the knowledge and use of biosimilars in clinical practice. Pharmacol Res Netherlands. 2017;126:138–42.
10. Park W, Hrycaj P, Jeka S, Kovalenko V, Lysenko G, Miranda P, Mikazane H, Gutierrez-Ureña S, Lim M, Lee YA, Lee SJ, Kim H, Yoo DH, Braun J. A randomised, double-blind, multicentre, parallel-group, prospective study comparing the pharmacokinetics, safety, and efficacy of CT-P13 and innovator infliximab in patients with ankylosing spondylitis: the PLANETAS study. Ann Rheum Dis. 2013;72:1605–12.
11. Yoo DH, Hrycaj P, Miranda P, Ramiterre E, Piotrowski M, Shevchuk S, Kovalenko V, Prodanovic N, Abello-Banfi M, Gutierrez-Ureña S, Morales-Olazabal L, Tee M, Jimenez R, Zamani O, Lee SJ, Kim H, Park W, Müller-Ladner U. A randomised, double-blind, parallel-group study to demonstrate equivalence in efficacy and safety of CT-P13 compared with innovator infliximab when coadministered with methotrexate in patients with active rheumatoid arthritis: the PLANETRA study. Ann Rheum Dis. 2013;72:1613–20.
12. Clementi E, Corrao G, Leone R, Mugelli A, Rossi F, Spina E. Report di un'analisi descrittiva del profilo prescrittivo e di tollerabilità in 5 Regioni italiane. Biosimilars. Periodico di aggiornamento e informazione sull'uso del farmaco biosimilare nella pratica clinica. Edizioni Internazionali srl Divisione Edimes Edizioni Medico Scientifiche—Pavia. 2018.
13. Zabana Y, Domènech E, Mañosa M, Garcia-Planella E, Bernal I, Cabré E, Gassull MA. Infliximab safety profile and long-term applicability in inflammatory bowel disease: 9-year experience in clinical practice. Aliment Pharmacol Ther. 2010;31:553–60.
14. Scavone C, Sportiello L, Sullo MG, Ferrajolo C, Ruggiero R, Sessa M, Berrino PM, di Mauro G, Berrino L, Rossi F, Rafaniello C, Capuano A, BIO-Cam Group. Safety profile of anticancer and immune-modulating biotech drugs used in a real world setting in Campania Region (Italy): BIO-Cam Observational Study. Front Pharmacol. 2017;8:607.
15. Porter ML, Lockwood SJ, Kimball AB. Update on biologic safety for patients with psoriasis during pregnancy. Int J Women's Dermatol. 2017;3:21–5.
16. Mikuls TR. Co-morbidity in rheumatoid arthritis. Best Pract Res Clin Rheumatol. 2003;17:729–52.
17. Furst DE. The risk of infections with biologic therapies for rheumatoid arthritis. Semin Arthritis Rheum United States. 2010;39:327–46.
18. Bonovas S, Fiorino G, Allocca M, Lytras T, Nikolopoulos GK, Peyrin-Biroulet L, Danese S. Biologic therapies and risk of infection and malignancy in patients with inflammatory bowel disease: a systematic review and network meta-analysis. Clin Gastroenterol Hepatol. 2016;14(1385–1397):e10.
19. Mellstedt H. Clinical considerations for biosimilar antibodies. EJC Suppl. 2013;11:1–11.
20. van Schouwenburg PA, Rispens T, Wolbink GJ. Immunogenicity of anti-TNF biologic therapies for rheumatoid arthritis. Nat Rev Rheumatol. 2013;9:164–72.
21. Mok CC, Tsai WC, Chen DY, Wei JCC. Immunogenicity of anti-TNF biologic agents in the treatment of rheumatoid arthritis. Expert Opin Biol Ther. 2016;16:201–11.
22. Sessa M, Rossi C, Rafaniello C, Mascolo A, Cimmaruta D, Scavone C, Fiorentino S, Grassi E, Reginelli A, Rotondo A, Sportiello L. Campania preventability assessment committee: a focus on the preventability of the contrast media adverse drug reactions. Expert Opin Drug Saf. 2016;15:51–9.
23. Sessa M, Rafaniello C, Sportiello L, Mascolo A, Scavone C, Maccariello A, Iannaccone T, Fabrazzo M, Berrino L, Rossi F, Capuano A. Campania Region (Italy) spontaneous reporting system and preventability assessment through a case-by-case approach: a pilot study on psychotropic drugs. Expert Opin Drug Saf. 2016;15:9–15.
24. Sessa M, Sportiello L, Mascolo A, Scavone C, Gallipoli S, di Mauro G, Cimmaruta D, Rafaniello C, Capuano A. Campania Preventability Assessment Committee (Italy): a focus on the preventability of non-steroidal anti-inflammatory drugs' adverse drug reactions. Front Pharmacol. 2017;8:305.
25. Naranjo CA, Busto U, Sellers EM, Sandor P, Ruiz I, Roberts EA, Janecek E, Domecq C, Greenblatt DJ. A method for estimating the probability of adverse drug reactions. Clin Pharmacol Ther. 1981;30:239–45.
26. Benkirane R, Soulaymani-Bencheikh R, Khattabi A, Benabdallah G, Alj L, Sefiani H, Hedna K, Ouammi L, Olsson S, Pal SN. Assessment of a new instrument for detecting preventable adverse drug reactions. Drug Saf. 2015;38:383–93.
27. Michel C, Scosyrev E, Petrin M, Schmouder R. Can disproportionality analysis of post-marketing case reports be used for comparison of drug safety profiles? Clin Drug Investig. 2017;37:415–22.
28. Rothman KJ, Lanes S, Sacks ST. The reporting odds ratio and its advantages over the proportional reporting ratio. Pharmacoepidemiol Drug Saf. 2004;13:519–23.
29. Harpaz R, DuMouchel W, LePendu P, Bauer-Mehren A, Ryan P, Shah NH. Performance of pharmacovigilance signal-detection algorithms for the FDA adverse event reporting system. Clin Pharmacol Ther. 2013;93:539–46.
30. Wisniewski AFZ, Bate A, Bousquet C, Brueckner A, Candore G, Juhlin K, et al. Good signal detection practices: evidence from IMI PROTECT. Drug Saf. 2016;39:469–90.
31. European Medicine Agency. Biosimilars in the EU information guide for healthcare professionals. http://www.ema.europa.eu/docs/en_GB/document_library/Leaflet/2017/05/WC500226648.pdf Accessed 4 Sept 2018.
32. Candore G, Juhlin K, Manlik K, Thakrar B, Quarcoo N, Seabroke S, et al. Comparison of statistical signal detection methods within and across spontaneous reporting databases. Drug Saf. 2015;38:577–87.
33. Gabriel SE, Crowson CS, O'Fallon WM. The epidemiology of rheumatoid arthritis in Rochester, Minnesota, 1955–1985. Arthritis Rheum. 1999;42:415–20.
34. Del Val JH. Old-age inflammatory bowel disease onset: a different problem? World J Gastroenterol WJG. 2011;17:2734–9.
35. Ramadas AV, Gunesh S, Thomas GA, Williams GT, Hawthorne AB. Natural history of Crohn's disease in a population-based cohort from Cardiff (1986–2003): a study of changes in medical treatment and surgical resection rates. Gut. 2010;59:1200–6.
36. Lesuis N, Befrits R, Nyberg F, van Vollenhoven RF. Gender and the treatment of immune-mediated chronic inflammatory diseases: rheumatoid arthritis, inflammatory bowel disease and psoriasis: an observational study. BMC Med. 2012;10:82.
37. Sportiello L, Rafaniello C, Sullo MG, Nica M, Scavone C, Bernardi FF, Colombo DM, Rossi F. No substantial gender differences in suspected adverse reactions to ACE inhibitors and ARBs: results from spontaneous reporting system in Campania Region. Expert Opin Drug Saf. 2016;15:101–7.
38. Rafaniello C, Ferrajolo C, Sullo MG, Sessa M, Sportiello L, Balzano A, Manguso F, Aiezza ML, Rossi F, Scarpignato C, Capuano A. Risk of gastrointestinal complications associated to NSAIDs, low-dose aspirin and their combinations: results of a pharmacovigilance reporting system. Pharmacol Res. 2016;104:108–14.
39. El-Gabalawy H, Guenther LC, Bernstein CN. Epidemiology of immune-mediated inflammatory diseases: incidence, prevalence, natural history, and comorbidities. J Rheumatol Suppl. 2010;85:2–10.
40. Sullivan E, Piercy J, Waller J, Black CM, Kachroo S. Assessing gastroenterologist and patient acceptance of biosimilars in

ulcerative colitis and Crohn's disease across Germany. PLoS One. 2017;12:e0175826.
41. Ingrasciotta Y, Giorgianni F, Bolcato J, Chinellato A, Pirolo R, Tari DU, Troncone C, Fontana A, Ientile V, Gini R, Santoro D, Santarpia M, Genazzani A, Uomo I, Pastorello M, Addario WS, Scondotto S, Cananzi P, Caputi AP, Trifirò G. How much are biosimilars used in clinical practice? A retrospective Italian population-based study of erythropoiesis-stimulating agents in the years 2009–2013. BioDrugs. 2015;29:275–84.
42. Robinson D Jr, Hackett M, Wong J, Kimball AB, Cohen R, Bala M, IMID Study Group. Co-occurrence and comorbidities in patients with immune-mediated inflammatory disorders: an exploration using US healthcare claims data, 2001–2002. Curr Med Res Opin. 2006;22:989–1000.
43. Cohen R, Robinson D Jr, Paramore C, Fraeman K, Renahan K, Bala M. Autoimmune disease concomitance among inflammatory bowel disease patients in the United States, 2001–2002. Inflamm Bowel Dis. 2008;14:738–43.
44. Pastore S, Gubinelli E, Leoni L, Raskovic D, Korkina L. Biological drugs targeting the immune response in the therapy of psoriasis. Biologics Targets Ther. 2008;2:687–97.
45. Lichtenstein L, Ron Y, Kivity S, et al. Infliximab-related infusion reactions: systematic review. J Crohn's Colitis. 2015;9:806–15.
46. Grainger R, Harrison AA. Infliximab in the treatment of ankylosing spondylitis. Biologics Targets Ther. 2007;1:163–71.
47. Miehsler W, Novacek G, Wenzl H, Vogelsang H, Knoflach P, Kaser A, Dejaco C, Petritsch W, Kapitan M, Maier H, Graninger W, Tilg H, Reinisch W, Austrian Society of Gastroenterology and Hepatology. A decade of infliximab: the Austrian evidence based consensus on the safe use of infliximab in inflammatory bowel disease. J Crohns Colitis. 2010;4:221–56.
48. Summary of product characteristics, Remicade. http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/000240/WC500050888.pdf Accessed 11 June 2018.
49. Cheifetz A, Smedley M, Martin S, Reiter M, Leone G, Mayer L, Plevy S. The incidence and management of infusion reactions to infliximab: a large center experience. Am J Gastroenterol. 2003;98:1315–24.
50. Ellerin T, Rubin RH, Weinblatt ME. Infections and anti-tumor necrosis factor alpha therapy. Arthritis Rheum. 2003;48:3013–22.
51. Chakravarty EF, Michaud K, Wolfe F. Skin cancer, rheumatoid arthritis, and tumor necrosis factor inhibitors. J Rheumatol. 2005;32:2130–5.
52. Bongartz T, Sutton AJ, Sweeting MJ, Buchan I, Matteson EL, Montori V. Anti-TNF antibody therapy in rheumatoid arthritis and the risk of serious infections and malignancies: systematic review and meta-analysis of rare harmful effects in randomized controlled trials. JAMA. 2006;295:2275–85 **(Review. Erratum in: JAMA. 2006;295:2482)**.
53. Kalb RE, Fiorentino DF, Lebwohl MG, Toole J, Poulin Y, Cohen AD, Goyal K, Fakharzadeh S, Calabro S, Chevrier M, Langholff W, You Y, Leonardi CL. Risk of serious infection with biologic and systemic treatment of psoriasis: results from the Psoriasis Longitudinal Assessment and Registry (PSOLAR). JAMA Dermatol. 2015;151:961–9.
54. van Montfort L, Loos CM, Anten M, Jansen RLH. Herpes encephalitis: a mortal complication in a patient treated with immunosuppressive drugs because of immune-related adverse events after ipilimumab treatment. Case Rep Oncol. 2017;10:1112–5.
55. Couderc S, Lapeyre-Mestre M, Bourrel R, Paul C, Montastruc JL, Sommet A. Infectious risk of biological drugs vs. traditional systemic treatments in moderate-to-severe psoriasis: a cohort analysis in the French insurance database. Fundam Clin Pharmacol. 2018;32:436–49.
56. Mantzaris GJ. Previous cancer and/or lymphoma in patients with refractory IBD–con: anti-TNF or conventional immunosuppressive treatment. Dig Dis. 2014;32:122–7.
57. Elandt K, Aletaha D. Treating rheumatic patients with a malignancy. Arthritis Res Ther. 2011;13:223.
58. Bombardier C, Hazlewood GS, Akhavan P, Schieir O, Dooley A, Haraoui B, Khraishi M, Leclercq SA, Légaré J, Mosher DP, Pencharz J, Pope JE, Thomson J, Thorne C, Zummer M, Gardam MA, Askling J, Bykerk V, Canadian Rheumatology Association. Canadian Rheumatology Association recommendations for the pharmacological management of rheumatoid arthritis with traditional and biologic disease-modifying antirheumatic drugs: part II safety. J Rheumatol. 2012;39:1583–1602.
59. Shelton E, Laharie D, Scott FI, Mamtani R, Lewis JD, Colombel JF, Ananthakrishnan AN. Cancer recurrence following immunesuppressive therapies in patients with immune-mediated diseases: a systematic review and meta-analysis. Gastroenterology. 2016;151(97–109):e4.
60. Høivik ML, Buer LCT, Cvancarova M, Warren DJ, Bolstad N, Moum BA, Medhus AW. Switching from originator to biosimilar infliximab—real world data of a prospective 18 months follow-up of a single-centre IBD population. Scand J Gastroenterol. 2018;53:692–9.
61. Ratnakumaran R, To N, Gracie DJ, Selinger CP, O'Connor A, Clark T, Carey N, Leigh K, Bourner L, Ford AC, Hamlin PJ. Efficacy and tolerability of initiating, or switching to, infliximab biosimilar CT-P13 in inflammatory bowel disease (IBD): a large single-centre experience. Scand J Gastroenterol. 2018;53:700–7.
62. Jørgensen KK, Olsen IC, Goll GL, Lorentzen M, Bolstad N, Haavardsholm EA, Lundin KEA, Mørk C, Jahnsen J, Kvien TK, NOR-SWITCH study group. Switching from originator infliximab to biosimilar CT-P13 compared with maintained treatment with originator infliximab (NOR-SWITCH): a 52-week, randomised, double-blind, non-inferiority trial. Lancet. 2017;389:2304–16.
63. Chanchlani N, Mortier K, Williams LJ, Muhammed R, Auth MKH, Cosgrove M, Fagbemi A, Fell J, Chong S, Zamvar V, Hyer W, Bisset WM, Morris MA, Rodrigues A, Mitton SG, Bunn S, Beattie RM, Willmott A, Wilson DC, Russell RK. Use of infliximab biosimilar versus originator in a paediatric United Kingdom inflammatory bowel disease induction cohort. J Pediatr Gastroenterol Nutr. 2018.
64. Kaniewska M, Moniuszko A, Rydzewska G. The efficacy and safety of the biosimilar product (Inflectra(®)) compared to the reference drug (Remicade(®)) in rescue therapy in adult patients with ulcerative colitis. Prz Gastroenterol. 2017;12(3):169–74. https://doi.org/10.5114/pg.2017.70468.
65. Binkhorst L, Sobels A, Stuyt R, Westerman EM, West RL. Short article: Switching to a infliximab biosimilar: short-term results of clinical monitoring in patients with inflammatory bowel disease. Eur J Gastroenterol Hepatol. 2018;30:699–703.
66. Scherlinger M, Germain V, Labadie C, Barnetche T, Truchetet ME, Bannwarth B, Mehsen-Cetre N, Richez C, Schaeverbeke T, FHU ACRONIM. Switching from originator infliximab to biosimilar CT-P13 in real-life: the weight of patient acceptance. Jt Bone Spine. 2017 **(pii: S1297-319X(17)30189-6.1)**.
67. Schmitz EMH, Boekema PJ, Straathof JWA, van Renswouw DC, Brunsveld L, Scharnhorst V, van de Poll MEC, Broeren MAC, Derijks LJJ. Switching from infliximab innovator to biosimilar in patients with inflammatory bowel disease: a 12-month multicentre observational prospective cohort study. Aliment Pharmacol Ther. 2018;47(3):356–63. https://doi.org/10.1111/apt.14453.
68. Ralph Edwards I. Spontaneous reporting—of what? Clinical concerns about drugs. Br J Clin Pharmacol. 1999;48:138–41.
69. Palleria C, Leporini C, Chimirri S, Marrazzo G, Sacchetta S, Bruno L, Lista RM, Staltari O, Scuteri A, Scicchitano F, Russo E, et al. Limitations and obstacles of the spontaneous adverse drugs

reactions reporting: Two "challenging" case reports. J Pharmacol Pharmacother. 2013;4:S66–72.
70. Capuano A, Scavone C, Rafaniello C, Arcieri R, Rossi F, Panei P. Atomoxetine in the treatment of attention deficit hyperactivity disorder and suicidal ideation. Expert Opin Drug Saf. 2014;13(Suppl 1):S69–78.
71. Sportiello L, Rafaniello C, Scavone C, Vitale C, Rossi F, Capuano A. The importance of Pharmacovigilance for the drug safety: Focus on cardiovascular profile of incretin-based therapy. Int J Cardiol. 2016;202:731–5. https://doi.org/10.1016/j.ijcard.2015.10.002.

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