Safety of biologics approved for the treatment of rheumatoid arthritis and other autoimmune diseases: a disproportionality analysis from the FDA Adverse Event Reporting System (FAERS)

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Abstract

Introduction The molecular and pharmacological complexity of biologics modifying-antirheumatic drugs used for the management of rheumatoid arthritis (RA) favors the occurrence of adverse drug reactions (ADRs), which should be constantly monitored in post-marketing safety studies.

Objective The aim of this study was to identify signals of disproportionate reporting (SDR) of clinical relevance related to the use of biologic drugs approved for RA and other autoimmune diseases.

Methods All suspected ADRs registered in the FDA Adverse Event Reporting System (FAERS) between January 2003 and June 2016 were collected. The reporting odds ratio (ROR) was used as a measure of disproportionality to identify possible SDRs related to biologics. Those involving Important Medical Events (IME) and Designated Medical Events (DME) were prioritized.

Results In total, 2,602 SDRs were prioritized. The most commonly reported were 'Infections and infestations' (32.2%) and 'Neoplasms benign, malignant, and unspecified' (20.4%), and were mainly related to use of infliximab (25.3%, $p < 0.001$, and 28.8%, $p = 0.002$, respectively). Sixty-three signals involving DMEs were identified, most of which were related to rituximab ($n = 27$), and were mainly due to ‘blood disorders’. Amongst the DMEs detected for more than one biologic, 'intestinal perforation' and 'pulmonary fibrosis' were related to most of them.

Conclusions The results of this study highlight possible safety issues associated with biologics, whose relationship should be more thoroughly investigated. Our results contribute to future research on the identification of clinically relevant risks associated with these drugs, and may help contribute to their rational and safe use.

Key Points

This study identified 2,602 Important Medical Events (IME) of clinical relevance related to the use of biologics for RA in the analysis of the database FAERS.

We highlighted a high frequency of signals of disproportionate reporting (SDR) involving adverse events, such as infections and neoplasms, mainly related to the use infliximab.

The results of our study indicated possible safety issues that need to be further investigated for identification of clinically relevant risks amongst these biologic drugs.

1. Introduction

The development of biologic disease-modifying antirheumatic drugs in the last two decades was considered a revolution in the treatment of rheumatologic/autoimmune diseases. These drugs have enabled better control of disease progression in rheumatoid arthritis (RA) [1, 2], ulcerative colitis, Chron's disease [3], psoriasis [4], psoriatic arthritis, and ankylosing spondylitis [5]. However, they are associated with serious, rare, and unpredictable adverse events, such as risk of serious infections [6, 7], what makes it difficult to detect and evaluate their safety only by pre-marketing trials [8].

Therefore, post-marketing data are crucial to elucidate the true safety profile of these therapies in patients [9]. In this context, spontaneous reports of adverse events organized within databases represent a valuable source of information for post-marketing surveillance [10] as they allow early identification of possible safety signals. These signals are defined as suspected adverse drug reactions (ADRs) as the relationship between these reactions and the drugs are still not well established and require further analysis [11, 12]. For the detection of an unknown adverse reaction, the signal of disproportionate reporting (SDR) is firstly observed. Then the accumulation of data strengthens its signal, which is thus validated in order to establish the causality between the ADR and the specific therapy. Having this information makes it possible

to confirm, quantify and explain this interaction. This process can be slow and long, and may last for years.

In order to evaluate SDRs of biologics used in rheumatologic/autoimmune diseases, we carried out a descriptive study of spontaneous reports of adverse events from the Food and Drug Administration (FDA) Adverse Event Reporting System (FAERS) database.

2 Methods

2.1 Data Source

Data were obtained from the FAERS, which records all reports of suspected ADRs occurring in the United States of America, as well as serious ADRs reported by other countries.

The data from these reports are divided in seven groups: patient demographic and administrative information (DEMO); drug/biologic information (DRUG); preferred terms (PTs) of the Medical Dictionary for Regulatory Activities (MedDRA) for the events (REAC); patient outcomes for the event (OUTC); indications of use (diagnosis) for the reported drugs (INDI); therapy start dates and end dates (THER); and report sources for the event (RPSR). The records comply with the International Conference on Harmonization of Technical Requirements for Registration of Pharmaceutical Products for Human Use (ICH) E2B [13] and are available for public access in quarterly archives on the FDA website [14].

2.2 Data preparation

The drugs included in this study were abatacept, adalimumab, anakinra, certolizumab pegol, etanercept, golimumab, infliximab, rituximab and tocilizumab [Electronic Supplementary Material Online Table S1]. Generic and brand names of all the approved biologics for RA, as well as their acronyms, were used in this study. They were identified through searches on specialized websites, regulatory agencies (FDA and European Medicines

Agency - EMA), and clinical guidelines for treatment of RA (last updated in June 2016) [15-22]. These names were used as keywords to identify notifications related to these biologics. All notifications recorded between January/2003 and June/2016 in which specific biologics were considered the primary or secondary suspect (PS or SS, respectively) cause of ADR were collected.

The files from January/2003 to September/2012 were made available by Wong *et al*., who standardized the names of the drugs reported within this period [23]. The files from October/2012 to June/2016 were in turn directly downloaded from the FDA website. Data were managed using Microsoft Access® version 15.0.

Patients' ages were standardized in years. The notifying countries were identified by codes according to International Organization for Standardization (ISO) 3166 [24]. Adverse events and indications of use were classified by preferred terms in the MedDRA® version 19.1 dictionary from the ICH [25]. Outcomes were classified according to seriousness in: death, life-threatening, hospitalization (initial or prolonged), disability, congenital anomaly, requiring intervention to prevent, permanent impairment or damage, or other Important Medical Events (IMEs).

Records without the notification or case number, and without the name of the suspected drug or the adverse reaction, were excluded. Reports that did not include the patient's age, or referred to patients younger than 18 years or older than 74 years, were excluded to minimize bias due to important physiological changes due to age and susceptibility to ADRs [26, 27]. Duplicate reports were deleted prior data analysis [9]. All reports with the same case number and suspect drug were identified and only the most recent version was documented [28]. Cases with the same date of the event, age and gender of the patient, notifying country, drug name, and suspected adverse event, were identified and documented as a single record

[29]. In the final table, only one record was maintained for each drug-adverse reaction combination reported, corresponding to the number of ADRs analyzed.

2.3 Data analysis

Data were analyzed considering the main recommendations described in Good Signal Detection Practices [30]. The reports were separated into three groups according to age (18-35, 36-64, and 65-74 years), which were divided further according to the patient's gender (female, male, and uninformed), resulting in nine subgroups [31]. In each subgroup, the reporting odds ratio (ROR) was used as a measure of disproportionality between the notifications for each biologic versus the notifications for all other drugs registered in FAERS.

A two-by-two contingency table was composed for each adverse event comparing: (a) notifications of the biologic drug with the evaluated ADR; (b) notifications of the biologic drug with other ADRs; (c) notifications of other drugs with the evaluated ADR; and (d) notifications of other drugs with other ADRs. A 95% confidence interval (95% CI) was considered. An adverse event was associated with one of the biologics SDR when the lower ROR confidence interval was greater than 1, and the number of notifications for this combination was greater than 2 [32]. These signals are defined as suspected ADRs in which the relationship between these reactions and the drugs are still not well established and require further analysis [11, 12]. Safety-relevant clinical signals were prioritized. IMEs and Designated Medical Events (DMEs) were selected according to the lists developed and updated by the EMA [33, 34]. All statistical analyses were performed using Microsoft Excel®, and a p-value < 0.05 was defined as the threshold for statistical significance.

ADRs were grouped by System Organ Classes (SOC) according to the MedDRA® dictionary. The frequency of signs in the most common SOCs were analyzed through the binomial proportion test, using the software Action® and Microsoft Excel®. The analyses were

conducted considering the drug that presented the highest frequency compared to the other drugs.

3 Results

Within the adopted time range, 8,464,871 spontaneous reports were identified in the FAERS in which the drug was considered as primary or secondary suspect cause of ADR. 1,326,337 (16.1%) reports were excluded in the process of standardization and removal of duplicates. Also excluded were 2,849,75 (33.7%) reports that did not describe the patient's age , 249,992 (3.0%) reports referring to patients aged under 18 years, and 676,839 (8.0%) reports related to patients aged over 74 years.

In total, 3,326,628 reports (17,075,380 ADRs) were included in this study, of which 411,063 (1,339,374 ADRs) referred to biologics approved for the treatment of rheumatoid arthritis and other autoimmune diseases, and 2,915,565 reports (15,736,006 ADRs) notified for other medications. Biologics represented 12.4% of the reports analyzed, involving 10,103 different types of adverse events (amongst the 1,339,374 ADRs).

3.1 General characteristics of spontaneous reports for biologics

Considering the 411,063 spontaneous reports identified for biologics for RA and other autoimmune diseases (Table 1), the mean age of affected patients was 51.1 years (standard deviation, SD=14.2 years), with most patients aged between 36-64 years in 259,215 (63.1%) of the reports . Of the total number of reports, 268,360 (65.3%) were in females.

The consumers were the main contributors in the reporting process, registering 188,963 (46.0%) of the reports, followed by physicians, 141,386 (34.4%) reports. Other health professionals notified 61,601 (15.0%) reports and pharmacists 7,285 (1.8%).

Most reports came from North America, 235,230 (57.2%), with the United States predominating as the most common notifying country, 215,331(52.4%). Europe was responsible for 44,823 (10.9%) of the reports, whilst 22,972 (5.6%) were registered by other continents. More than one quarter, 108,038 (26.3%) reports, did not state the notifying country.

By the analysis of the distribution of spontaneous reports for each biologic, tumor necrosis factor inhibitor (TNFi) drugs were the suspected cause in 380,900 (92.7%) of them. Etanercept was the most frequently mentioned, and was a suspected drug in 172,225 (41.9%) reports, followed by adalimumab 148,586 (36.1%), and infliximab 41,920 (10.2 %). Certolizumab pegol was notified in 11,419 (2.8%) reports and golimumab in 6,750 (1.6%). Amongst the non-TNFi drugs, rituximab was a suspected drug in 19,788 (4.8%), followed by abatacept in 9,200 (2.2%), tocilizumab in 6,719(1.6%) and anakinra in 655 (0.2%) (Table 1). See [Electronic Supplementary Material Online - Table S2] for more details.

Serious outcomes were found in 177,031 (43.1%) of the reports. The most frequent serious outcomes within these cases were IMEs and hospitalization or prolongation (108,982 (26.5%) and 83,093 (20.2%), respectively). Risk to life was notified in 7,428 (1.8%) of the reports, death in 13,192 (3.2%), disability in 4,208 (1.0%), and need for intervention to prevent permanent damage in 1,560 (0.4%). There were 75 reports of congenital anomalies for the biologics analyzed.

Of the reports, 53,027 (30.0%) were related to etanercept, whilst 45,284 (25.6%) were related to adalimumab, 39,832 (22.5%) to infliximab, 7,374 (4.2%) to certolizumab pegol, and 5,193 (2.9%) to golimumab. Amongst the non-TNFi, rituximab was notified in 19,425 (11.0%) of the serious reports, tocilizumab in 6,466 (3.7%), abatacept in 5,016 (2.8%), and anakinra in 547 (0.3%) (Table 1).

Analyzing the number of reports by indication of use for each biologic, RA predominated in the reports by tocilizumab (84.6%), abatacept (68.0%), anakinra (59.4%)

etanercept (54.6%), and golimumab (45.5%). A similar frequency of indication of use was reported for both RA and Crohn's disease for infliximab (25.2% and 29.2%, respectively), and certolizumab pegol (35.8% and 43.9%, respectively). For adalimumab, in 31.8% of the reports the indication of use was RA, in 27.6% it was Crohn's disease, and in 22.9% Psoriatic disease. The indications for rituximab were very different from the other biologics, with 19.0% of reports designing for use in RA and 68.9% for other conditions with low frequency, of which 12.4% were non-Hodgkin's lymphoma and 10.1% chronic lymphocytic leukemia [Electronic Supplementary Material Online – Table S2]. More details about DME associated with Rituximab by calculated ROR are described in Electronic Supplementary Material Online – Table S3.

3.2 Disproportionality analysis for biologics

Of the 10,103 different adverse events reported for the biologics, 3,103 were statistically related to these drugs after calculation of the ROR. Of these, 1,223 were on the IME list, corresponding to 2,602 SDRs considered of clinical relevance.

Disproportionality analysis was performed on subgroups of age and sex amongst the 2,602 SDRs. 1,139 (43.8%) were detected in more than one subgroup analyzed, and 1,463 (56.2%) were detected in only one of these subgroups. The majority of the SDRs related to only one of the subgroups were for female and male patients aged 18-35 years, comprising 496 (33.9%) and 38pml1 (26.0%), respectively. The subgroup aged 65-74 years were responsible for 239 (16.3%) and 172 (11,8%) of the SDRs for women and men, respectively. The analysis of subgroups of patients aged 18-35 also contributed to identify 107 (7.3%) SDRs among women and 61 (4.2%) among men. In the subgroups for which the sex was not informed, it was possible to detect 5 SDRs for patients aged 36-64 years and 2 SDRs for patients aged 18-35 years. Infliximab and rituximab were the most frequent drugs, related to 646 (24.8%) and

529 (20.3%) of the detected SDRs, respectively. Amongst the other TNFi, 421 (16.2%) signals were detected for adalimumab, 329 (12.6%) for etanercept, 172 (6.6%) for certolizumab pegol, and 119 (4.6%) for golimumab. Amongst the other non-TNFi, 199 (7.6%) SDRs referred to tocilizumab, 136 (5.2%) to abatacept, and 51 (2.0%) to anakinra.

Figure 1 presents a comparison of the total number of reports and reports involving serious ADR notified (Table 1), in addition to the number of SDRs for biological TNFi and non-TNFi (Table 2). More than 75% of the reports were related to etanercept and adalimumab, although these two drugs were associated with a lower proportion of serious reports when compared with other biologics. Infliximab and rituximab showed a higher proportion of serious reports, and comprised together for almost half of the safety problems detected (24.8% and 20.3%, respectively). For the other biologics, a greater proportion of serious events were also observed; however, the low relative frequency of events compared to the total ADRs hampered a deeper comparative analysis amongst these other drugs.

When grouped by SOC (Table 2**)**, most of the SDRs belonged to the SOCs 'infections and infestations' (32.2%) and ´malignant and unspecified benign neoplasms' (20.4%). 'Gastrointestinal disorders' and 'surgical and medical procedures' accounted for 8.2%, nervous system disorders for 4.5%, respiratory, thoracic and mediastinal disorders for 3.2%, and musculoskeletal and connective tissue disorders for 3.2%, whilst the other SOCs had a frequency less than 3% in the total SDRs detected.

Statistically significant differences between infliximab and other biologics were observed for the SOCs 'infections and infestations' and 'neoplasms benign, malignant, and unspecified'. These SOCs were more frequent within the signals for infliximab in comparison to other biologics (25.3%; $p < 0.001$ and 28.8%; $p = 0.002$, respectively). An association between infliximab and progressive multifocal leukoencephalopathy (PML) was also detected in male patients aged 65-74 years (data not shown).

In the SOC 'blood and lymphatic system disorders', rituximab stood out in comparison to the other drugs. It was described in 29 out of the 51 detected signals ($p < 0.001$), despite the low overall frequency of this SOC (2.0%).

Thirty-five DMEs were reported, of which 13 were associated with TNFi (Table 3) and 32 with non- TNFi (Table 4), which represents 63 detected SDRs (for complete table with ROR values by subgroups see Electronic Supplementary Material Online – Tables S4 and S5). Rituximab was associated with 27 signals. Fifteen out of the 20 DMEs associated with only one biologic referred to rituximab; 10 of which belonged to the SOC 'blood and lymphatic system disorders'. Acute pancreatitis and drug-induced liver injury were only associated with tocilizumab, whilst autoimmune hepatitis and angioedema were associated with infliximab, and hepatic necrosis with anakinra. Amongst the 14 DMEs described for more than one drug, most were associated with intestinal perforation (infliximab, adalimumab, certolizumab pegol, golimumab, rituximab, abatacept, and tocilizumab) and pulmonary fibrosis (infliximab, etanercept, adalimumab, certolizumab pegol, rituximab, abatacept, and tocilizumab). Overall, the frequency of DMEs related to these biologic drugs was low, being that the association between rituximab and progressive multifocal leukoencephalopathy was the most reported, representing 10.7% of the total reports obtained on the FAERS.

4 Discussion

Our study has provided an overview of the possible safety concerns associated with biologics approved for the treatment of RA. Our findings are based on the reporting of ADRs of major clinical relevance.

The main divergence between our results and previous studies was the low frequency of SOCs related to 'general disorders and administration site conditions', probably due to the prioritization of the detection of serious adverse events. Several studies have highlighted this

SOC as an important group of ADRs associated with the use of biologics, mainly due to the high occurrence of administration site reactions [9, 28, 35, 36]. However, these ADRs usually do not result in serious outcomes or treatment discontinuation [29]. Moreover, in most studies, the detection of SDRs was performed by classifying suspected ADRs by their SOC term, which is a broader concept of adverse reaction, and covers both serious and non-serious ADRs. On the other hand, in our study, we detected signals using the PT, a more specific concept used to define an ADR [37]. Hence, we were able to provide a better evidence regarding prioritization for adverse events management to guide clinicians, regulators, and industry to focus on the most relevant signals.

Our focus on the occurrence of serious events may also explain why infliximab and rituximab were associated with higher frequencies of safety problems, despite the similar commercialization times between these and other drugs, especially etanercept. Although etanercept had the highest percentage of ADRs reported, which may be due to increased use of this drug in recent years, this medication presented low proportion of serious events and SDRs, which may indicate a lower occurrence of serious events associated with its use. Registry studies have also shown a lower rate of discontinuation due to adverse events for etanercept in comparison to infliximab and adalimumab [38].

Our study also highlighted a large frequency of infections and neoplasms. Other studies have also reported these ADRs as major safety concerns associated with the use of biologic drugs [9, 28, 35, 36, 39-41]; however, there is still no consensus on the actual risk and the role of individual differences regarding these drugs, which suggests that these safety issues are still not well established and require further investigation [8, 42].

Despite belonging to the same class of drugs, TNFi agents present some particularities in their composition and mechanisms of action. Adalimumab, golimumab and infliximab are monoclonal anti-TNF antibodies (the first two are totally humanized and the last one is human–

murine), whilst etanercept consists in a soluble TNF receptor protein with an Fc fragment, and certolizumab pegol is a Fab' fragment of TNF alpha, with no Fc fraction. These characteristics provide to TNFi agents different specificity, affinity and avidity for TNF-alpha, which may explain the reason for the occurrence of some specific adverse events. For instance, studies have shown that infliximab promotes granulomatous infections more often when compared to other TNFi [43-45]. In our study, the statistically significant association between infliximab use and infections and neoplasms may reflect an increased risk of specific adverse events for this drug. Nevertheless, it is still not established whether these differences are related to the drug's mechanism of action (monoclonal antibody versus receptor) or to the pharmacokinetics (intravenous versus subcutaneous use) [8, 46]. Regarding neoplasms, some studies have identified a higher frequency of TNFi-related skin cancer [47], and also found a greater risk associated with infliximab compared to etanercept [48]. However, it is difficult to determine causality of neoplasms as they can occur naturally in the population and are usually developed after the exposure but without clear temporal relationship between the development of the neoplasm and the use of the drugs. Moreover, in these cases, the study of spontaneous notifications is not considered the most appropriate design, which better suits for the detection of ADRs of short latency [49]. Further research detailing the nature of the signals detected for infections and neoplasms is needed in order to better clarify the relationship between them and the use of biologics.

Another important finding in our results was the association between the use of rituximab and the occurrence of blood disorders. An assessment of the long-term safety of rituximab in patients with RA has not revealed important serious events [50], but in another study that examined the use of rituximab in various pathologies, especially in anti-neoplastic therapeutic regimes, researchers have highlighted the occurrence of serious ADRs, including blood disorders. [51]. Our results may be due to the variability in indications of use of this drug

in comparison to other biologics. In almost 20% of the ADRs, rituximab was indicated for the treatment of blood neoplasia, implying that there was a higher frequency of individuals with different pathophysiological conditions compared to the usual population that uses the other types of biologics. Pathophysiological differences are considered to be one of the determining factors in the variability of susceptibility to ADRs [52]. A higher frequency of patients with poor prognostic factors, advanced stage of disease, and greater immune system weakness may also have influenced these results, considering that rituximab is generally recommended for RA for patients who have failed to respond to previous TNFi [23, 54].

The association between PML and rituximab may be due to the greater immunological weaknesses of these patients. A review of the literature has shown that immunocompromised patients are more susceptible to PML, and that in cases where this event was observed with the use of rituximab, patients were on immunosuppressive medication [53]. The association between this event and use of infliximab was highlighted as an important safety concern, especially in autoimmune diseases. Although the number of reports associated with infliximab was low, careful and intensive monitoring of PML cases associated with biologics is needed [8, 42].

Several SDRs were identified in only one subgroup of patients, what suggests that the use of disproportionality analyses by subgroups can help to identify groups with greater susceptibility to specific adverse events in addition to increasing the sensitivity for the detection of SDRs compared with crude or stratified analyses [31].

The results of our study provide insight into potential safety issues that need to be evaluated by further analytical studies, so as to provide an accurate risk assessment of the occurrence of ADRs [54, 55]. We were able to identify a few priorities in order to guide clinicians' investigations.

Amongst the drugs, infliximab stood out, as it was most frequently related to the SOCs ‘infections and infestations’ and ‘malignant and unspecified benign neoplasms’. A literature review of randomized controlled trials, meta-analyses, national registry articles, and case reports have shown a small, yet significantly increased risk of serious infection in RA patients treated with infliximab, etanercept, and adalimumab [56]. Moreover, a few published studies have suggested an increased risk of malignancy in RA patients receiving TNFi. However, the published literature points out that this result is still inconclusive, and more studies are needed to elucidate the association between these therapies and cancer risk [57-59].

Rituximab stood out within the SOC ‘blood and lymphatic system disorders’. These adverse events were reported in a clinical review on the use of rituximab, showing that almost 50% of patients with non-Hodgkin lymphoma in use of this biologic presented grade 3 and 4 cytopenias [51]. Nevertheless, events related to blood and lymphatic system disorders should be further investigated in RA patients on treatment with rituximab [60].

Regarding separate events, attention should be drawn to infliximab, which was related to autoimmune hepatitis and angioedema in the present study. The published literature encompasses case reports of autoimmune hepatitis triggered by TNFi therapies [61, 62], as well as angioedema related to the use of infliximab [63].

Moreover, several biologics were found to be associated with intestinal perforation and pulmonary fibrosis in the present study, which also have been demonstrated in the available literature. Tocilizumab, for instance, was related to the occurrence of acute pancreatitis in a study addressing a case report and reviewing the data from the FDA Adverse Event Reporting System [64]. This drug was also related to increased risk of lower intestinal perforation when compared to other biologics [65].

Other adverse events, such as pulmonary toxicity, have also been associated to the use of biologics, notably TNFi, in clinical studies [66]. Lastly, special focus should be given to the

event progressive multifocal leukoencephalopathy, which was the most reported DME associated with rituximab in the present study. The events cited above should be prioritized in future investigations.

Although ROR has a good correlation with Relative Risk, it cannot be interpreted as such. It is important to identify the drug-reaction pairs with significant ROR, and not the value of it as the value is related to the disproportionality between the notifications and not with the risk of causing the reaction. The ROR should be interpreted with caution; it can be important in the prioritization of signs that should deserve more attention in pharmacovigilance, but it cannot be used for guide clinical decisions [55].

The use of an international open-source database such as FAERS, which provides a large volume of data, allows higher powered statistical analyses and a better ability to detect relevant clinical associations between drugs and events [37, 67]. In this context, the participation of consumers and health professionals in the process of reporting ADRs is essential in order to minimize bias and enable early detection of major adverse events. We observed that most of the ADRs related to biologics were reported by consumers. Studies have reinforced the importance of this reporting category in pharmacovigilance, with no evidence of poor quality and no increase in the reporting of irrelevant events [68, 69]. On the other hand, we observed a low frequency of ADRs reported by pharmacists; professionals could lead to a substantial improvement in the spontaneous reporting system [70]. A recent analysis showed that the low participation of these professionals may be related to the limited access that they have to the systems of health care, as well as critical gaps that still exist in the knowledge of ADR communication; this reinforces the need for continuous development programs in this area [71]. It may be also due to the fact that most biologics are prescribed and monitored in hospital settings, without the presence of the pharmacist.

Our study has several limitations. Possible biases, such as underreporting, the Weber effect, and the effect of notoriety, can overestimate the number of SDRs or delay the detection of important ADRs [72, 73]. Underreporting and the Weber effect may have had little influence on our results. The variation in underreporting rates is considered small, mainly between drugs of the same class or with similar indications [74], and the use of disproportionality methods diminishes this bias as it is likely to also occur for the other drugs used as a group comparator [68]. The Weber effect is more relevant in the first two years of commercialization [75], and all the biologics analyzed in this research have been approved for more than five years, and are no longer considered new drugs. In addition, a study suggests that the pattern described by Weber has not been observed in most of the modern adverse event reporting into FAERS [76]. Another limitation of the present study was the lack of case-causality assessment derived from clinical evaluation of spontaneous reports when performing signal detection. Additionally, reporting biases may have occurred in this study as a result of lawyer advertisements in US media on adverse events which may increase reporting, and this may have occurred in other countries.

The influence of the effect of notoriety should be considered in our results. This effect occurs mainly from safety alert publications in relation to a suspected ADR associated with a specific drug. The alert can induce greater notification of this ADR, overestimating the disproportionality (the ROR value). This effect can also create a ripple effect, which is an increase in the notification of the same ADR for all other drugs within the same pharmacological class as the suspected drug [77]. The various safety issues that have not yet been well established in relation to biologics contribute to the ongoing publication of security alerts in relation to these drugs, and may have overestimated the detected signals.

5 Conclusion

In this study we have highlighted potential safety problems associated to the use of biologics , particularly rituximab and infliximab, like the association between rituximab and blood disorders and PML, besides the association between infliximab and infections and neoplasms and PML., These findings should be validated to guide clinicians, regulators and industry to focus on the most relevant signals also in addition to the information already included in the summary of product characteristics.

Our results may directly contribute to future research, identifying clinically relevant risks and guiding the rational and safe use of these drugs. The benefit/risk ratio of biologics appears to remain favorable, considering the high effectiveness and the low frequency of fatal outcomes and/or DMEs associated with the use of these drugs. Further detailed analysis of the data is still needed to better characterize the nature of the identified signals, and to investigate other associations.

Compliance with ethical standards

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Conflict of interest Ariane G. S. Araujo, Helena H. L. Borba, Fernanda S. Tonin, Luana Lenzi, Rafael Venson, Roberto Pontarolo, and Astrid Wiens have no conflicts of interest directly relevant to the content of this article.

Ethical approval Ethical approval was not required for this study.

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Fig. 1 *Relative frequencies of total reports, serious reports, and signals of disproportionate reporting (SDR) related with each biologic.*

Table 1. General characteristics of spontaneous reports for biologics approved for the treatment of rheumatoid arthritis **and other autoimmune diseases in the FAERS**

Characteristics of reports (N = 411,063)	
Patients' age (years), mean (SD)	51.1 (14.2)
Frequency of reports by gender (Female %)	268,360 (65.3)
Reporter (%)	
Consumers	188,963 (46.0)
Physicians	141,386 (34.4)
Other professionals	61,601 (15.0)
Pharmacists	7,285 (1.8)
Not informed	11,828 (2.9)
Reporting origin (%)	
North America	235,230 (57.2)
US	215,331 (52.4)
Europe	44,823 (10.9)
Other continents	22,972 (5.6)
Missing data	108,038 (26.3)
Report to each biologics (%)*	
TNFi	380,900 (92.7)
Infliximab	41,920 (10.2)
Etanercept	172,225 (41.9)
Adalimumab	148,586 (36.1)
Certolizumab pegol	11,419 (2.8)
Golimumab	6,750 (1.6)
non-TNFi	36,362 (8.8)
Rituximab	19,788 (4.8)
Anakinra	655 (0.2)
Abatacept	9,200 (2.2)
Tocilizumab	6,719 (1.6)
Serious reports (%)*	177,031(43.1)
IMEs	108,982 (26.5)
Hospitalization or prolongation	83,093 (20.2)
Death	13,192 (3.2)
Risk to life	7,428 (1.8)
Disability	4,208 (1.0)
Need for intervention to prevent permanent damage	1,560 (0.4)
Congenital anomalies	75 (0.02)
Serious reports to each biologics(%)*	
TNFi	150,710 (85.1)
Infliximab	39,832 (22.5)
Etanercept	53,027 (30.0)
Adalimumab	45,284 (25.6)
Certolizumab pegol	7,374 (4.2)
Golimumab	5,193 (2.9)
non-TNFi	31,435 (17.8)
Rituximab	19,425 (11.0)
Anakinra	547 (0.3)
Abatacept	5,016 (2.8)
Tocilizumab	6,466 (3.7)

Indication of the use of biologics (%)*	
Rheumatoid arthritis	173,201 (42.1)
Psoriatic disease	85,331 (20.8)
Crohn's disease	58,082 (14.1)
Ankylosing spondylitis	20,332 (4.9)
Colitis ulcerative	13,579 (3.3)
Other indication**	23,841 (5.8)
Unknown indication	39,167 (9.5)

TNFi = tumor necrosis factor inhibitors, IMEs = important medical events, FAERS: Adverse Event Reporting System,

*= a report may contain more than one suspected drug, serious outcome and/or indication of the use,

**= individual frequency less than 1%

Table 2 Distribution of signals of disproportionate reporting (SDR) classified according to the SOC level for the total and stratified by biologic drug (%)

System Organ Class	All biologics N = 2.602	Infliximab N = 646	Etanercept N = 329	Adalimumab N = 421	Certolizumab pegol N = 172	Golimumab N = 119	Rituximab N = 529	Anakinra N = 51	Abatacept N = 136	Tocilizumab N = 199
Infections and infestations	32.2	25.3	12.4	16.2	7.5	6.4	17.9	1.8	5.4	7.0
Neoplasms benign. malignant and unspecified	20.4	28.8	16.5	14.1	5.5	4.1	20.7	1.3	3.8	5.3
Gastrointestinal disorders	8.2	25.8	3.8	25.4	11.7	3.8	14.1	0.5	3.3	11.7
Surgical and medical procedures	8.0	28.2	27.8	20.1	6.2	4.3	4.8	1.0	5.3	2.4
Nervous system disorders	4.5	20.3	6.8	15.3	4.2	4.2	32.2	2.5	7.6	6.8
Respiratory. thoracic and mediastinal disorders	3.2	22.6	3.6	2.4	7.1	2.4	34.5	4.8	8.3	14.3
Musculoskeletal and connective tissue disorders	3.2	18.3	20.7	17.1	7.3	7.3	9.8	1.2	7.3	11.0
Injury. poisoning and procedural complications	2.8	19.4	12.5	34.7	5.6	1.4	12.5	0.0	6.9	6.9
Eye disorders	2.1	27.3	14.5	16.4	3.6	3.6	18.2	0.0	5.5	10.9
Blood and lymphatic system disorders	2.0	11.8	5.9	5.9	2.0	2.0	56.9	5.9	0.0	9.8
Cardiac disorders	1.9	22.0	0.0	2.0	8.0	2.0	30.0	8.0	18.0	10.0
Immune system disorders	1.8	22.9	10.4	6.3	4.2	0.0	41.7	2.1	4.2	8.3
Hepatobiliary disorders	1.8	19.1	0.0	12.8	2.1	4.3	36.2	6.4	2.1	17.0
Renal and urinary disorders	1.6	21.4	9.5	11.9	4.8	7.1	33.3	2.4	2.4	7.1
Vascular disorders	1.5	15.8	2.6	15.8	2.6	2.6	28.9	5.3	7.9	18.4
Skin and subcutaneous tissue disorders	1.4	29.7	10.8	13.5	10.8	2.7	16.2	2.7	2.7	10.8
Other*	3.3	2.6	2.7	4.0	2.3	0.8	4.3	5.9	4.4	3.0

a: Percentages were calculated based on the total of SDRs with important medical events (N) associated with each biologic drug.
*: Individual frequency of SDRs less than 1%
SOC = System Organ Class

BioDrugs

Electronic Supplementary Material Resource Online 1

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Safety of biologic drugs: Disproportionality analysis from the FDA Adverse Event Reporting System (FAERS)

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Table S1 Keywords used for identified suspect ADRs reported for bDMARDs* in the FAERS

DRUG		**BRAND NAME**	**CODES**
Anti-TNF bDMARDs	Infliximab	Remicade, Inflectra, Remsima, Avakine, Flammegis, Revellex	-
	Etanercept	Enbrel, Enbrol, Etanar, Yisaipu	TNFR Fc
	Adalimumab	Humira, Trudexa	D2E7
	Certolizumab pegol	Cimzia, Cimizia	CDP 870
	Golimumab	Simponi	
Non anti-TNF bDMARDs	Rituximab	Rituxan, Mabthera, Ikgdar, Reditux, Ristova	IDEC-C2B8, BI 695500, PF-05280586, IDEC-102, RTXM83 anti-CD20, GP2013
	Anakinra	Kineret, Antril	rIL-1ra, rIL1RN
	Abatacept	Orencia, Ohrencia, Orenica	BMS 188667, LEA 29Y
	Tocilizumab	Actemra, RoActemra, Aktempa, Actembra, Acterma, Atlizumab	-

ADR adverse drug reaction, *bDMARDs* biological disease-modifying antirheumatic drugs, *FAERS* FDA Adverse Event Reporting System; * bDMARDs approved in the treatment of rheumatoid arthritis until june 2016.

BioDrugs

Electronic Supplementary Material Online Resource 2

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Table S1 Distribution of ADRs reported for bDMARDs in FAERs

	Total bDMARDs 1,339,374 (%)	Anti-TNF bDMARDs					Non anti-TNF bDMARDs			
		Infliximab 133,443 (10.0)	Etanercept 543,916 (40.6)	Adalimumab 476,913 (35.6)	Certolizumab pegol 33,689 (2.5)	Golimumab 18,207 (1.4)	Rituximab 76,645 (5.7)	Anakinra 2,582 (0.2)	Abatacept 23,640 (1.8)	Tocilizumab 30,339 (2.3)
Age categories (years)										
18-35	221,237 (16.5)	33,327 (25.0)	60,578 (11.1)	104,405 (21.9)	8,588 (25.5)	2,581 (14.2)	6,861 (9.0)	495 (19.2)	1,405 (5.9)	2,997 (9.9)
36-64	854,083 (63.8)	76,879 (57.6)	377,541 (69.4)	292,332 (61.3)	19,858 (58.9)	10,910 (59.9)	42,882 (55.9)	1,507 (58.4)	14,872 (62.9)	17,302 (57.0)
65-74	264,054 (17.7)	23,237 17.4)	105,797 (19.5)	80,176 (16.8)	5,243 (15.6)	4,716 (25.9)	26,902 (35.1)	580 (22.5)	7,363 (31.1)	10,040 (33.1)
Sex										
Females	912,522 (68.1)	80,751 (60.5)	395,510 (72.7)	315,190 (66.1)	24,222 (71.9)	12,471 (68.5)	41,092 (53.6)	1,674 (64.8)	19,083 (80.7)	22,529 (74.3)
Males	418,477 (31.2)	51,523 (38.6)	145,953 (26.8)	158,803 (33.3)	9,236 (27.4)	5,599 (30.8)	34,289 (44.7)	892 (34.5)	4,438 (18.8)	7,744 (25.5)
Missing value	8,375 (0.6)	1,169 (0.9)	2,453 (0.5)	2,920 (0.6)	231 (0.7)	137 (0.8)	1,264 (1.6)	16 (0.6)	119 (0.5)	66 (0.2)
Serious ADRs	704,372 (52.6)	127,900 (95.8)	215,358 (39.6)	199,951 (41.9)	23,826 (70.7)	14,058 (77.2)	75,584 (98.6)	2,368 (91.7)	15,623 (66.1)	29,704 (97.9)
IMEs	472,848 (35.3)	80,341 (60.2)	166,696 (30.6)	127,394 (26.7)	13,935 (41.4)	9,291 (51.0)	41,037 (53.5)	768 (29.7)	11,619 (49.1)	21,767 (71.7)
Hospitalization	366,424 (27.4)	60,240 (45.1)	93,172 (17.1)	125,974 (26.4)	13,367 (39.7)	6,080 (33.4)	43,564 (56.8)	1,828 (70.8)	7,216 (30.5)	14,983 (49.4)
Intervention	6,544 (0.5)	2,526 (1.9)	698 (0.1)	2,301 (0.5)	13 (0.0)	13 (0.1)	854 (1.1)	82 (3.2)	37 (0.2)	20 (0.1)
Disability/ incapacity	21,844 (1.6)	3,952 (3.0)	4,456 (0.1)	7,455 (1.6)	797 (2.4)	349 (1.9)	2,799 (3.7)	127 (4.9)	532 (2.3)	1,377 (4.5)
Life-threatening	33,192 (2.5)	8,339 (6.2)	4,718 (0.8)	7,732 (1.6)	880 (2.6)	480 (2.6)	7,374 (9.6)	421 (16.3)	849 (3.6)	2,399 (7.9)
death	54,324 (4.1)	10,280 (7.7)	8,992 (0.9)	13,573 (2.8)	1,350 (4.0)	516 (2.8)	15,139 (19.8)	444 (17.2)	1,569 (6.6)	2,461 (8.1)
congenital anomalies	392 (0.0)	62 (0.0)	100 (0.0)	174 (0.0)	16 (0.0)	0 (0.0)	27 (0.0)	0 (0.0)	0 (0.0)	13 (0.0)
indication for use										
Rheumatoid arthritis	587,004 (43,8)	33,278 (24.9)	316,828 (58.2)	153,269 (32.1)	12,289 (36.5)	8,256 (45.3)	19,396 (25.3)	1,451 (56.2)	16,583 (70.1)	25,654 (84.6)
Crohn's disease	191,266 (14.3)	37,769 (28.3)	76 (0.0)	137,738 (28.9)	15,352 (45.5)	292 (1.6)	0 (0.0)	0 (0.0)	39 (0.2)	0 (0.0)
Psoriatic disease	260,440 (19.4)	9,773 (7.3)	144,365 (26.5)	102,988 (21.6)	949 (2.8)	1,988 (10.9)	35 (0.0)	39 (1.5)	247 (1.0)	56 (0.2)
Ankylosing spondylitis	68,367 (5.1)	6,806 (5.1)	34,931 (6.4)	24,098 (5.1)	572 (1.7)	1,866 (10.2)	31 (0.0)	4 (0.2)	40 (0.2)	19 (0.1)
Colitis ulcerative	40,846 (3.0)	11,253 (8.4)	30 (0.0)	28,005 (5.9)	318 (0.9)	1,186 (6.5)	1 (0.0)	0 (0.0)	53 (0.9)	0 (0.0)
other indication*	83,532 (6.2)	8,666 (6.5)	10,393 (1.9)	11,821 (2.5)	661 (2.0)	749 (4.1)	47,273 (61.7)	821 (31.8)	697 (2.9)	2,451 (8.1)
unknown indication	110,861 (8.3)	26,899 (20.2)	37,798 (6.9)	19,610 (4.1)	3,936 (11.7)	3,888 (21.4)	10,206 (13.3)	352 (13.6)	5,995 (25.4)	2,177 (7.2)

ADRs adverse drug reaction, *DMARDs* biological disease-modifying antirheumatic drugs, *FAERS* FDA Adverse Event Reporting System, *anti-TNF* anti-tumor necrosis factor alpha, *: Individual frequency of safety signals less than 1%

BioDrugs

Electronic Supplementary Material Online Resource 3

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Safety of biologic drugs: Disproportionality analysis from the FDA Adverse Event Reporting System (FAERS)

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conclusion

Designed Medical Event (DME)	**Rituximab ROR (95%CI)***
Anaphylactic reaction	1.97 (1.06-3.66)[a]; 1.94 (1.41-2.68)[d]; 1.99 (1.39-2.85)[e]; 2.02 (1.29-3.19)[h]
Anaphylactoid reaction	3.07 (1.53-6.17)[d]
Neutropenic infection	16.70 (9.04-30.87)[e]; 6.61 (2.08-21.00)[g]; 3.99 (1.26-12.61)[h]
Neutropenic sepsis	6.55 (2.09-20.50)[b]; 2.17 (1.20-3.93)[d]; 2.22 (1.26-3.92)[e]; 6.88 (4.71-10.05)[g]; 4.36 (2.94-6.44)[h]
Progressive multifocal leukoencephalopathy	9.89 (4.40-22.25)[a]; 14.45 (7.91-26.39)[b]; 22.91 (19.28-27.21)[d]; 21.02 (17.36-25.45)[e]; 57.51 (46.72-70.80)[g]; 33.49 (27.03-41.50)[h]
Renal failure	3.37 (2.25-5.04)[a]; 1.48 (1.16-1.88)[d]
Pulmonary fibrosis	3.86 (2.53-5.88)[d]; 3.97 (2.63-6.00)[e]; 4.11 (2.76-6.12)[g]; 2.64 (1.80-3.86)[h]

ROR reporting odds ratio, *DME* designed medical event**, *bDMARDs*** biological disease-modifying antirheumatic drugs, *values statistically significant ROR for bDMARDs in each subgroup, *CI* confidence interval

Subgroups: a = female (18-35 years); b= male (18-35 years); c = uninformed sex (18-35 years); d = female (36-64 years); e = male (36-64 years); f = sex not informed (36-64 years); g = female (65-74 years); h = male (65-74 years); i = uninformed sex (65-74 years); CI: confidence interval

Table S1 Designated medical events associated wich Rituximab by calculate ROR continue

Designed Medical Event (DME)	**Rituximab ROR (95%CI)***
Agranulocytosis	7.57 (4.68-12.24)[a]; 6.17 (3.39-11.20)[b]; 5.29 (4.01-6.98)[d]; 5.67 (4.56-7.06)[e]; 5.57 (1.75-17.75)[f]; 4.22 (2.88-6.19)[g]; 2.32 (1.53-3.51)[h]
Aplasia pure red cell	2.73 (1.02-7.31)[d]; 2.68 (1.39-5.17)[e]
Aplastic anaemia	3.97 (2.05-7.69)[e]
Autoimmune haemolytic anaemia	7.85 (4.42-13.94)[d]; 14.22 (9.63-21.01)[e]; 8.15 (4.17-15.94)[g]; 10.35 (6.63-16.17)[h]
Bone marrow failure	7.29 (4.34-12.17)[b]; 4.91 (3.79-6.35)[d]; 5.76 (4.75-7.00)[e]; 4.02 (2.91-5.55)[g]; 2.67 (1.92-3.69)[h]
Febrile neutropenia	10.48 (7.94-13.82)[a]; 5.84 (3.93-8.68)[b]; 16.74 (6.48-43.24)[c]; 5.48 (4.73-6.34)[d]; 9.49 (8.55-10.53)[e]; 4.70 (2.56-8.62)[f]; 7.21 (6.21-8.36)[g]; 5.75 (5.05-6.55)[h]; 2.66 (1.35-5.24)[i]
Granulocytopenia	2.29 (1.32-3.95)[e]
Haemolysis	2.63 (1.55-4.46)[e]; 6.72 (3.93-11.48)[g]
Haemolytic anaemia	2.47 (1.53-3.99)[e]; 2.50 (1.34-4.67)[g]; 2.57 (1.48-4.45)[h]
Immune thrombocytopenic purpura	9.33 (4.41-19.75)[a]; 2.81 (1.46-5.42)[d]; 4.60 (2.88-7.33)[e]; 5.14 (2.74-9.65)[g]; 2.58 (1.28-5.21)[h]
Pancytopenia	3.79 (2.31-6.20)[a]; 4.10 (2.42-6.95)[b]; 3.93 (3.24-4.77)[d]; 3.83 (3.26-4.50)[e]; 4.19 (2.06-8.51)[f]; 2.70 (2.14-3.42)[g]; 2.75 (2.24-3.37)[h]
Thrombotic thrombocytopenic purpura	7.13 (2.65-19.17)[a]; 2.81 (1.33-5.91)[d]
Deafness	2.31 (1.39-3.84)[d]
Sudden hearing loss	5.98 (2.22-16.11)[d]
Blindness	1.95 (1.28-2.96)[e]
Intestinal perforation	2.02 (1.01-4.06)[d]; 3.24 (1.83-5.73)[g]
Neutropenic colitis	4.02 (1.29-12;56)[d]; 8.03 (3.77-17.08)[e]; 11.02 (4.44-27.32)[g]; 5.34 (1.68-16.98)[h]
Acute hepatic failure	4.71 (3.28-6.77)[e]
Hepatic failure	2.58 (2.03-3.27)[e]; 2.08 (1.34-3.24)[g]; 1.93 (1.35-2.75)[h]
Hepatitis fulminant	6.44 (4.17-9.94)[e]; 7.89 (3.69-16.86)[g]; 3.62 (1.93-6.79)[h]

Table S2 Designated medical events associated wich other non anti-TNF bDMARDs by calculate ROR

Designed Medical Event (DME)	**Anakinra ROR (95%CI)***	**Abatacept ROR (95%CI)***	**Tocilizumab ROR (95%CI)***
Haemolysis	-	-	19.77 (6.31-61.93)[b]
Sudden hearing loss	-	-	9.65 (3.05-30.54)[g]
Intestinal perforation	-	3.38 (1.60-7.10)[d]	5.15 (2.84-9.33)[d]; 4.12 (1.71-9.94)[e]; 6.66 (3.92-11.32)[g]
Pancreatitis	9.19 (2.95-28.63)[g]	-	-
Pancreatitis acute	-	-	8.03 (2.99-21.52)[b]
Acute hepatic failure	35.10 (11.15-110.52)[b]	-	-
Drug-induced liver injury	-	-	2.07 (1.03-4.14)[d]
Hepatic necrosis	26.40 (8.45-82.50)[a]	-	-
Anaphylactic reaction	-	3.72 (1.54-8.95)[a]; 1.85 (1.18-2.90)[d]; 2.72 (1.26-2.32)[e]; 2.04 (1.02-4.10)[g]	5.05 (1.62-15.74)[b]; 2.69 (1.07-2.69)[d]; 3.16 (1.79-5.57)[e]
Anaphylactic shock	6.02 (1.94-18.70)[d]	-	-
Renal failure	5.46 (3.08-9.67)[e]	-	-
Pulmonary fibrosis	-	7.05 (3.16-15.73)[e]; 5.29 (3.12-8.98)[g]; 3.37 (1.26-9.00)[h]	2.71 (1.02-7.24)[e]; 3.41(1.93-6.04)[g]; 3.30 (1.48-7.36)[h]

ROR reporting odds ratio, *DME* designed medical event**, *b**DMARDs* biological disease-modifying antirheumatic drugs, *values statistically significant ROR for bDMARDs in each subgroup, *CI* confidence interval

Subgroups: a = female (18-35 years); b= male (18-35 years); c = uninformed sex (18-35 years); d = female (36-64 years); e = male (36-64 years); f = sex not informed (36-64 years); g = female (65-74 years); h = male (65-74 years); i = uninformed sex (65-74 years); CI: confidence interval

Table S3 Designated medical events associated wich anti-TNF bDMARDs by calculate of ROR

Evento Médico Designado (DME)	Infliximab	Etanercept	Adalimumab	Certolizumab pegol	Golimumab
Aplastic anaemia	-	-	-	5.69 (1.81-17.83)[a]	-
Deafness	-	1.73 (1.02-2.94)[h]	-	-	-
Sudden hearing loss	5.10 (1.59-16.32)[a]	-	2.22 (1.24-3.98)[d]	-	-
Intestinal perforation	6.62 (4.04-10.84)[a]; 6.50 (3.95-10.69)[b]; 4.04 (2.82-5.77)[d]; 3.55 (2.42-5.20)[e]; 2.85 (1.53-5.32)[h]	-	7.25 (5.36-9.81)[a]; 7.16 (5.14-9.98)[b]; 1.55 (1.17-2.06)[d]; 1.71 (1.26-2.32)[e]	8.91 (4.20-18.90)[a]; 7.40 (2.75-19.93)[b]; 6.73 (3.49-12.98)[e]	3.24 (1.21-8.66)[d]
Pancreatitis	1.78 (1.30-2.45)[a]; 2.11 (1.40-3.19)[g]	-	-	2.16 (1.27-3.65)[a]; 4.06 (1.82-9.07)[h]	-
Autoimmune hepatitis	3.58 (2.06—6.23)[a]; 6.66 (3.22-13.76)[b]; 3.18 (2.17-4.65)[d]; 3.00 (1.60-5.62)[e]	-	-	-	-
Anaphylactic reaction	2.66 (2.05-3.45)[a]; 2.70 (1.89-3.84)[b]; 2.00 (1.60-2.51)[d]	-	-	-	-
Anaphylactic shock	2.10 (1.39-3.17)[a]; 2.03 (1.54-2.67)[d]; 1.50 (1.03-2.20)[e]	-	-	-	-
Anaphylactoid reaction	2.54 (1.26-5.14)[a]; 3.92 (1.83-8.38)[b]; 3.94 (2.52-6.14)[d]	-	-	-	-
Neutropenic sepsis	-	-	-	-	7.71 (2.88-20.63)[h]
Progressive multifocal leukoencephalopathy	4.73 (2.67-8.39)[h]	-	-	-	-
Pulmonary fibrosis	2.76 (1.93-3.93)[c]; 2.14 (1.38-3.33)[e]; 12.41 (3.78-40.70)[f]; 3.74 (2.52-5.57)[g]; 2.60 (1.61-4.20)[h]	1.28 (1.03-1.59)[d]; 1.76 (1.35-2.30)[e]; 2.09 (1.65-2.65)[g]; 1.73 (1.23-2.43)[h]	1.63 (1.20-2.22)[g]; 2.02 (1.45-2.81)[h]	3.68 (1.65-8.21)[e]; 3.48 (1.56-7.77)[g]; 8.72 (4.67-16.28)[h]	-
Angioedema	1.52 (1.05-2.22)[a]; 1.52 (1.16-1.98)[d]; 1.61 (1.17-2.21)[e]	-	-	-	-

ROR reporting odds ratio, *DME* designed medical event**, *b**DMARDs*** biological disease-modifying antirheumatic drugs, *values statistically significant ROR for bDMARDs in each subgroup, *CI* confidence interval

Subgroups: a = female (18-35 years); b= male (18-35 years); c = uninformed sex (18-35 years); d = female (36-64 years); e = male (36-64 years); f = sex not informed (36-64 years); g = female (65-74 years); h = male (65-74 years); i = uninformed sex (65-74 years); CI: confidence interval