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ORIGINAL ARTICLE

Adverse events involving biological medicines used in the treatment of rheumatoid arthritis reported in the Brazilian reporting system

Eventos adversos relacionados a medicamentos biológicos utilizados no tratamento da artrite reumatoide notificados no Sistema Nacional de Notificação Brasileiro (Vigimed)

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Abstract

Objectives: To describe suspected adverse drug events (ADEs) involving biological disease-modifying anti-rheumatic drugs (bDMARDs) used in the treatment of rheumatoid arthritis (RA) reported in VigiMed, the Brazilian reporting system. **Methods:** Descriptive study of reports carried out in the VigiMed system, between 1st January 2019 and 31st March 2023, involving people aged 19 or over, using bDMARDs. **Results:** 3,037 suspected ADEs involving bDMARDs were reported during the referred period, with the greater part of reports presenting at least one serious reaction/event. The Reporting Odds Ratio (ROR=3.10; 95%IC 2.81-3.42) demonstrated that reports involving at least one serious reaction/event were most frequent for this class than for other products. The majority of suspected ADEs involved female (n=1,979; 65.2%) and adult (n=2,404; 79.2%) patients. The bDMARD most frequently involved in suspected ADEs was infliximab (75.4%), and in only 431 (12.5%) of the reports the identifiability and traceability of the bDMARDs involved in the suspected ADEs were ensured. A total of 9,069 reactions/events involving bDMARDs were reported and a predominance of these were related to general disorders and administration site conditions (15.3%). **Conclusion:** The results of this study highlight possible safety issues involving bDMARDs, that should be considered when decision-making in pharmacotherapy in RA. This is especially relevant since biological medicines have substantial differences in the safety profile as compared with small molecules. Furthermore, by analysing the reports registered in the VigiMed system, it is possible to identify which initiatives should be adopted to educate and engage notifiers to improve the quality of report.

Keywords: arthritis, rheumatoid, biological therapy, drug-related side effects and adverse reactions, adverse drug reaction reporting systems, pharmacovigilance.

Resumo

Objetivos: Descrever as suspeitas de eventos adversos relacionados a medicamentos (EAMs) envolvendo medicamentos modificadores do curso da doença

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biológicos (MMCDbio) utilizados no tratamento da artrite reumatoide (AR) notificados no VigiMed, o sistema de notificação brasileiro. **Métodos:** Estudo descritivo que avaliou as suspeitas de notificações realizadas no sistema VigiMed, entre 1º de janeiro de 2019 e 31 de março de 2023, envolvendo pessoas com 19 anos ou mais, em uso de MMCDbio. **Resultados:** 3.037 suspeitas de EAMs envolvendo MMCDbio foram notificadas durante o período em questão, com a maior parte das notificações apresentando pelo menos uma reação/sintoma grave. A razão de chances de notificação, do inglês Reporting Odds Ratio (ROR=3,10; IC 95% 2,81-3,42) demonstrou que notificações envolvendo pelo menos uma reação/sintoma grave foram mais frequentes para esta classe do que para outros produtos. A maioria dos EAMs suspeitos envolveu pacientes do sexo feminino (n=1.979; 65,2%) e adultos (n=2.404; 79,2%). O MMCDbio mais frequentemente envolvido em EAMs suspeitos foi o infliximabe (75,4%), e em apenas 431 (12,5%) das notificações a identificabilidade e rastreabilidade dos MMCDbio envolvidos nos EAMs suspeitos foram asseguradas. Um total de 9.069 reações/sintomas envolvendo MMCDbio foram relatados, sendo observada uma predominância destes relacionada a distúrbios gerais e quadros clínicos no local de administração (15,3%). **Conclusão:** Os resultados deste estudo destacam possíveis problemas de segurança envolvendo MMCDbio, que devem ser considerados na tomada de decisão em farmacoterapia na AR. Isso é especialmente relevante, pois os medicamentos biológicos têm diferenças substanciais no perfil de segurança em comparação com moléculas pequenas. Além disso, ao analisar as notificações registradas no sistema VigiMed, é possível identificar quais iniciativas devem ser adotadas para educar e engajar os notificadores para melhorar a qualidade da notificação.

Palavras-chave: artrite reumatoide, terapia biológica, efeitos colaterais e reações adversas relacionadas a medicamentos, sistemas de notificação de reações adversas a medicamentos, farmacovigilância.

Introduction

Rheumatoid arthritis (RA) is a chronic disease that affects approximately 17.6 million people worldwide (1). It is defined by chronic autoimmune inflammatory reactions that mainly involve the joints, principally of the hands, wrists, and knees. In addition, patients with RA may present changes in multiple organs, including the heart, kidney, lungs, eyes, skin, nervous and digestive systems (2, 3).

People living with RA usually present a progressive worsening of joint structure and chronic pain, causing functional limitation, loss of work capacity, overall reduction in quality of life and life expectancy. Furthermore, RA involves high individual, medical, and societal costs (1, 4, 5).

However, it is important to highlight that the management of RA has improved considerably over the years, and the introduction of new medicines is particularly important in this context (1, 2, 5). In addition to conventional synthetic disease-modifying anti-rheumatic drugs (csDMARDs), biological DMARDs (bDMARD) and targeted synthetic DMARDs (tsDMARDs) have been introduced into the management of RA (2, 5).

Among those medicines, bDMARD have added an important improvement in RA management. This class of medicines ends up being used as the disease progresses naturally, since they promote better control in more advanced stages of the disease and have an overall adequate safety profile when compared to other options (5). Despite this, the expanding use of bDMARD in the real world encompasses more advanced age groups and with different polymorbidity profiles (6). This scenario requires investigations that provide better knowledge about the occurrence of adverse drug events (ADE) involving bDMARD.

Additionally, biological medicines are more complex than small molecules. Therefore, they are more susceptible to structural variability due to their production methods, and they have potential to induce an immune response. In this sense, the continuous assessment of the safety profile of bDMARD through pharmacovigilance studies is essential, with nationwide reporting systems being important sources for this type of surveillance (6, 7).

However, to the authors' knowledge, there are no studies that evaluate reports of suspected ADE involving biologicals used in RA reported in the Brazilian reporting system. It is important to highlight that only studies were found that evaluated suspected ADE involving biologicals registered in the Food and Drug Administration Adverse Event Reporting System (FAERS) (8) or, even, studies that examined individual institutional data addressing ADE involving biologics, such as the study that evaluated the immediate complications of anti-TNF drugs at the "Center for Dispensation of High Cost Medications" of Hospital das Clínicas of the Medical School of Universidade de São Paulo (HC-FMUSP) (9). Thus,

we aim to describe suspected ADE involving bDMARD used in the treatment of RA reported in the Brazilian reporting system.

Methods

This is a descriptive study regarding suspected ADE involving biological medicines used in the treatment of RA reported to the Brazilian ADE reporting system. As this study only used collective data obtained from the blind and public database of the Brazilian regulatory agency (from portuguese, *Agência Nacional de Vigilância Sanitária*, (Anvisa)), approval from a research ethics committee was not necessary.

The Anvisa adopted VigiMed as the Brazilian ADE reporting system from 10th December 2018. In September 2023, all data available on the Brazilian Federal Government's open data portal regarding the VigiMed system for the period from January 1st 2019 to March 31st 2023 were collected by exporting available data into a Microsoft Excel® software spreadsheet. Data from the first month of system implementation were excluded, considering the adaptation of the notifiers and possible system instabilities.

The information contained in the reports is made available in Anvisa's public domain, in the "open pharmacovigilance data" area, as Microsoft Excel® spreadsheets. This data refers to suspected adverse events, that is, information about reports without causality assessment (10, 11).

In this study, all suspected ADE referring to biological medicines used in the treatment of RA, involving adult individuals (19 years or older) were analysed. Biological medicines used to treat RA were defined according to the medicines listed as biological in the Brazilian guideline on the management of RA (4), as well as in other guidelines on RA management included in the systematic review (2). Therefore, only reports which involved the following biological medicines were selected: adalimumab, certolizumab, etanercept, golimumab, infliximab, abatacept, rituximab, tocilizumab, sarilumab, sirukumab, clazakizumab, and anakinra.

For each VigiMed report, there may be more than one related reaction/event. Also, a medicine may be associated with the occurrence of more than one reaction/event. Therefore, it is necessary to adopt three units of analysis: 1) suspected ADE reports; 2) reaction/event; and 3) medicines.

The suspected ADE reports (N = 3,037) involving bDMARD used to treat RA identified during the study period were described according to the following characteristics: type of report: spontaneous report, study report, or others; total number of reports; number of reports involving at least one serious reaction/event and number of reports containing only non-serious reactions/events; number of reports involving bDMARD that resulted in death or were life-threatening; and, type of report entry: health service, patient/health professional, or pharmaceutical company.

The reports were also described according to the following characteristics of the patients involved: sex: female, male, or uninformed; age group: adults (19 to 64 years old), older adults (≥ 65 years old), uninformed; and pregnancy or lactation: yes or no.

Data referring to reactions/events were described using descriptive statistics as follows: type of reactions/events according to the System Organ Class (SOC) level of the Medical Dictionary for Regulatory Activities (MedDRA) classification system; and, the reactions/events included in the five most frequent SOC levels were also described at the Preferred Term (PT) level, which is a more specific level of the MedDRA classification system. All PTs that had a frequency equal to or greater than 50 were described.

The medicines involved in the reactions/events were described according to the following characteristics: most frequent medicines; commercial medicine name and/or specific manufacturer (present *vs* absent); batch (present *vs* absent); and, frequency of concomitant availability of data regarding to the batch number and the commercial name of biological medicines and/or the specific manufacturer.

For data analysis, Stata® software was utilized. For all variables, descriptive analysis was used, with absolute and relative frequency measures.

In addition, a graphic description of the number of reports was developed.

Additionally, a disproportionality analysis was carried out comparing reports containing at least one serious reaction/event involving bDMARD *vs* other products. For this, the Reporting Odds Ratio (ROR) measure was adopted with its respective 95% confidence interval (95%IC) (12).

Results

A total of 161,685 suspected ADE reports was identified in the VigiMed system during the period evaluated. Among these, 3,037 (1.9%) reports involved bDMARD used to treat RA, and adults. All the characteristics of reports of suspected ADE involving bDMARD are listed in **Table 1**.

TABLE 1 - CHARACTERISTICS OF REPORTS OF SUSPECTED ADVERSE DRUG EVENTS INVOLVING BDMARD (N=3,037). BRAZIL, JANUARY 2019 TO MARCH 2023.

Report characteristics, n(%)	**N=3037**
Type of report	
Spontaneous	2,848 (93.8)
Study reports	74 (2.4)
Others	115 (3.8)
Type of report entry	
Pharmaceutical company	2,117 (69.7)
Health service	683 (22.5)
Patient/health professional	237 (7.8)
Sex of the patient involved	
Female	1,979 (65.2)
Male	1,045 (34.4)
Uninformed	13 (0.4)
Age group of the patient involved	
Adults	2,404 (79.2)
Older adults	633 (20.8)
Non-pregnant patient	3,036 (99.7)
Non-lactating patient	3,037 (100.0)

bDMARD, disease-modifying anti-rheumatic drugs.

The total number of reports, the number of reports containing at least one serious reaction/event and the number of reports containing only non-serious reactions/events over the months within the analysed period are shown in **Figure 1**. Among the reports involving bDMARD, 207 (6.8%) reports resulted in death or were life-threatening. According to the disproportionality analysis, reports involving at least one serious reaction/event were more frequent among bDMARD (83.0% of reports) than among non-bDMARD products (61.0% of reports), generating a ROR=3.10 (95%CI = 2.81 - 3.42).

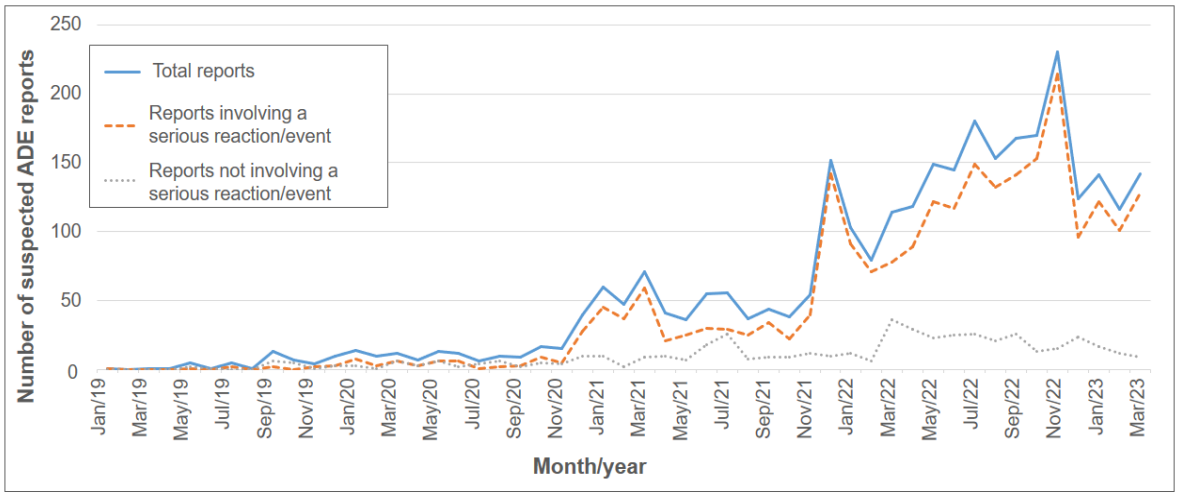

FIGURE 1 - Frequency of suspected ADE reports involving bDMARD in VigiMed by month and year. Brazil, 2019 to 2023. ADE**,** adverse drug event, bDMARD, disease-modifying anti-rheumatic drugs.

A total of 9,069 reactions/events involving bDMARD were reported, highlighting that a report may be associated with several different reactions/events. Regarding the classification of reactions/events according to the SOC, there was many those related to "general disorders and administration site conditions" and "gastrointestinal disorders" (**Table 2**). For the five most frequent SOC levels, reactions/events classified at the PT level were described (**Table 3**).

TABLE 2 - FREQUENCY OF REACTIONS/EVENTS INVOLVING BDMARD REPORTED TO VIGIMED ACCORDING TO THE SOC LEVEL OF THE MEDDRA CLASSIFICATION SYSTEM. BRAZIL, 2019 TO 2023.

SOC, n(%)	n=9,069
General disorders and administration site conditions	1,385 (15.3)
Gastrointestinal disorders	1,273 (14.0)
Injury, poisoning and procedural complications	1,195 (13.2)
Musculoskeletal and connective tissue disorders	763 (8.4)
Skin and subcutaneous tissue disorders	687 (7.6)
Respiratory, thoracic and mediastinal disorders	561 (6.2)
Nervous system disorders	538 (5.9)
Infections and infestations	526 (5.8)
Vascular disorders	392 (4.3)
Investigations	279 (3.1)
Surgical and medical procedures	188 (2.1)
Immune system disorders	186 (2.1)

TABLE 2 - FREQUENCY OF REACTIONS/EVENTS INVOLVING BDMARD REPORTED TO VIGIMED ACCORDING TO THE SOC LEVEL OF THE MEDDRA CLASSIFICATION SYSTEM. BRAZIL, 2019 TO 2023. (CONT.).

SOC, n(%)	n=9,069
Cardiac disorders	165 (1.8)
Eye disorders	152 (1.7)
Psychiatric disorders	145 (1.6)
Uninformed	111 (1.2)
Neoplasms benign, malignant and unspecified	104 (1.1)
Blood and lymphatic system disorders	92 (1.0)
Metabolism and nutrition disorders	81 (0.9)
Hepatobiliary disorders	61 (0.7)
Renal and urinary disorders	60 (0.7)
Reproductive system and breast disorders	34 (0.4)
Product issues	32 (0.4)
Ear and labyrinth disorders	31 (0.3)
Social circumstances	20 (0.2)
Endocrine disorders	3 (0.0)
Pregnancy, puerperium and perinatal conditions	3 (0.0)
Congenital, familial and genetic disorders	2 (0.0)

bDMARD, disease-modifying anti-rheumatic drugs; MedDRA, Medical Dictionary for Regulatory Activities; SOC, System Organ Class.

TABLE 3 - FREQUENCY OF REACTIONS/EVENTS INVOLVING BDMARD REPORTED TO VIGIMED ACCORDING TO THE PT LEVEL FOR MOST FREQUENT SOC OF THE MEDDRA CLASSIFICATION SYSTEM. BRAZIL, 2019 TO 2023.

SOC	**PT, n (%)**	**n=9,069**
GI	Crohn's disease	498 (5.5)
IPPC	Use not described in the medication leaflet (off label)	447 (4.9)
GD	Ineffective medicine	365 (4.0)
SSC	Itching	254 (2.8)
IPPC	Infusion-related reaction	130 (1.4)
MCT	Rheumatoid arthritis	127 (1.4)
IPPC	Problem related to omission of product dose	125 (1.4)
GD	Pain	123 (1.4)
GI	Ulcerative colitis	120 (1.3)
MCT	Ankylosing spondylitis	111 (1.2)
SSC	Erythema	95 (1.0)
GI	Nausea	92 (1.0)
IPPC	Product usage problem	91 (1.0)

TABLE 3 - FREQUENCY OF REACTIONS/EVENTS INVOLVING BDMARD REPORTED TO VIGIMED ACCORDING TO THE PT LEVEL FOR MOST FREQUENT SOC OF THE MEDDRA CLASSIFICATION SYSTEM. BRAZIL, 2019 TO 2023. (CONT.).

SOC	PT, n (%)	n=9,069
GD	Malaise	90 (1.0)
MCT	Arthralgia	85 (0.9)
GI	Abdominal pain	81 (0.9)
GD	Death	75 (0.8)
MCT	Psoriatic arthropathy	73 (0.8)
IPPC	Inadequate dosage of product administration	68 (0.7)
GI	Diarrhea	59 (0.7)
GD	Decreased/incomplete therapeutic product effect	54 (0.6)
SSC	Rash	54 (0.6)
GD	Chest pain/Chest discomfort	52 (0.6)
MCT	Pain in extremity	52 (0.6)
GI	Vomiting	51 (0.6)
Others	Others	5,697 (62.8)

bDMARD, disease-modifying anti-rheumatic drugs; GD**:** General disorders and administration site conditions; GI: Gastrointestinal disorders; IPPC: Injury, poisoning and procedural complications; MCT: Musculoskeletal and connective tissue disorders; MedDRA, Medical Dictionary for Regulatory Activities; SOC, System Organ Class; PT, Preferred term; SSC: Skin and subcutaneous tissue disorders. Note: 25 PTs were listed, those with a frequency equal to or greater than 50.

A total of 3,456 citations of bDMARD were reportedly involved in ADE, highlighting that one report may be associated with one or more medicines. The most frequent bDMARD involved in the ADE reports was infliximab, followed by rituximab. The proportion of bDMARD involved in suspected ADE reports is represented in **Table 4**. It is important to point out that sarilumab, sirukumab, clazakizumab, and anakinra are not registered in the Brazilian regulatory agency, and no reports involving these medicines were registered in VigiMed.

TABLE 4 - FREQUENCY OF BDMARD INVOLVED IN SUSPECTED ADE REPORTED TO VIGIMED. BRAZIL, 2019 TO 2023.

bDMARD, n(%)	N= 3,456
Infliximab	2,604 (75.4)
Rituximab	562 (16.2)
Adalimumab	108 (3.1)
Tocilizumab	78 (2.3)
Etanercept	41 (1.2)
Abatacept	38 (1.1)
Golimumab	20 (0.6)
Certolizumab	5 (0,1)

ADE, adverse drug events; bDMARD, disease-modifying anti-rheumatic drugs.

Regarding the presence of information that would allow the identifiability and traceability of biological medicine involved in suspected ADE, it was observed that in 805 (23.3%) of the reports, data about the commercial name and/or the manufacturer´s name was described. In addition, for 653 (18.9%) of the reports the batch number was informed. Both sets of data were available for only 431 (12.5%) of the reports.

Discussion

The present study characterized reports of suspected ADE involving bDMARD used in the treatment of RA reported in the Brazilian reporting system. It was found that the proportion of reports involving bDMARD in Brazil was considerably lower than that observed in the study by Araujo et al. (12.4%) (8). This finding signals the need to encourage the practice of notifications involving these medicines, and to carry out of pharmacovigilance studies. This type of study is especially relevant to complement the safety data of biological medicines obtained in pre-marketing studies, since their safety profile is not fully delineated at the time of their approval. This is due to the inherent limitations of randomized clinical trials and the different profile of biological medicines in relation to small molecules (6, 13, 14).

From this perspective, pharmacovigilance activities should be encouraged to identify potential ADE involving bDMARD and, based on this, develop strategies to prevent and minimize harm involving these medicines (6, 13, 14). Spontaneous reports, the most frequent type of reports in this study, constitute a low-cost pharmacovigilance method that is important for the early detection of safety signals (6, 8, 13-16). However, for this to happen, it is important to stimulate spontaneous reports among all medicine system stakeholders, so that underreporting does not underestimate the frequency and impact of ADE involving bDMARD (8, 16, 17).

An increasing trend of reports involving bDMARD was observed in this study; another study that evaluated suspected ADE involving biological medicines reported in a Slovakian database also observed an increasing trend in the number of reports between 2001 and 2017 (15). In addition, it is important to highlight that the reports involving at least one serious reaction/event were the most frequent. This finding was also observed in other studies (8, 15), including a study that described ADE reports involving bDMARD in the FAERS (8).

These findings indicate that despite an increase in reports involving bDMARD being observed, there is still possible underreporting of reactions/events considered non-serious; this may be partly because some notifiers make the decision to report only serious reactions/events (17), or even because Brazilian legislation only considers it obligatory to send reports involving serious reactions/events by pharmaceutical companies (18). Consequently, it becomes pertinent to make notifiers aware of the relevance to notify non-serious ADE to better map the safety profile of bDMARD, which will contribute to decision-making in pharmacotherapy.

A higher frequency of reports involving at least one serious reaction/event among bDMARD was observed when compared with other products. Due to the fact that the Brazilian Rheumatoid Arthritis Guideline (4) recommends that patients using bDMARD or their legal guardian be informed about the benefits, potential risks and adverse effects related to the use of these medications, including the mandatory completion of the clarification and responsibility form containing this information, it is believed that patients and/or their legal guardian are more aware of the occurrence of possible ADE and communicate them to the healthcare team, which contributes to the incidence of reports involving bDMARD.

Araujo et al. identified that 5% of the reports involving bDMARD registered between 2003 and 2016 in FAERS resulted in death or were life threatening, in line with the findings of the present study (8). These results highlight the need for an active approach by notifiers in relation to the pharmacovigilance of biological products, in order to quickly unveil the severe ADE profile, and thus implement security barriers.

Regarding the type of report entry, it was ob-

served that that about 70% of the reports were registered by pharmaceutical companies. This high proportion can be justified by the launch of Resolution nº 406/2020 (18), a Brazilian legislation which made it mandatory for pharmaceutical companies to report all serious ADE. This national context signals the need to engage other stakeholders in the pharmacovigilance activities of biological products, such as health services, health professionals, and citizens, since underreporting is still a challenge (17).

The predominance of female patients involved in suspected ADE was observed, as in other studies (8, 19-21). Furthermore, it was found that about 20% of people involved in suspected ADE were 65 years of age or older. These results are consistent with the epidemiology of RA, considering that women are two to three times more likely to experience RA and the diagnosis of this disease is more common with increasing age (1). There were almost no reports involving pregnant and lactating women; this was already expected, considering that the use of bDMARD is contraindicated in this portion of the population (4).

In the present study, as well as other studies that evaluated biological medicines (13, 16, 22), the most frequent types of reactions/events were "general disorders" and "administration site conditions". "Gastrointestinal disorders" were the second most frequent type of SOC identified, as well as in the study by Araujo et al. (8). The high frequency of "administration site conditions" may be due to the difficulties inherent in the administration of bDMARD, since these medicines are administered parenterally, which makes them more likely to cause infusion-related reactions (13).

In this study, one unique finding that is not deeply explored elsewhere was the frequency of reactions/events according to the PT level of the MedDRA classification. Interestingly, the most frequently reported PTs were specifically autoimmune diseases for which bDMARD are widely used, such as inflammatory bowel disease, ulcerative colitis, Crohn's disease, RA and ankylosing spondylitis. These unexpected effects involving anti-tumour necrosis factor agents (TNF-) represent paradoxical reactions that may occur during treatment, and affect several organs including the skin, liver, lungs, kidneys, nervous system, vascular system, and bowels (23, 24). Thus, the development of new cases of these autoimmune diseases could be attributed to biological agents indicated to treat them, or even that these agents could exacerbate these diseases (24). In this sense, the presence of PT "ineffective medicine" and "pain" is plausible considering that the biological medicine will be considered ineffective in the process of exacerbating the disease, which is manifested mainly through pain in RA (13).

The bDMARD most frequently involved in reports of suspected ADE in the present study were infliximab, rituximab, and adalimumab. These medicines, together with etanercept, were the most cited in reports of ADE involving bDMARD registered in FAERS (8, 25) and VigiBase (13). Three out of four reports evaluated in the present study involved infliximab. To corroborate with the relevance of this result, a Brazilian multicentre study found that the occurrence of adverse effects was the main cause of suspension of infliximab use among patients evaluated with RA (26). In contrast, a national cohort identified that the frequency of infliximab dispensing in Brazil is relatively similar to other bDMARD used in the treatment of RA (27). In view of these findings, future studies that evaluate the causality of ADE related to infliximab may contribute to generating information regarding the safety profile of this medicine.

In addition, unlike other studies (15, 16, 28, 29), almost all reports evaluated in the present study did not present information that allowed the identification and traceability of each biological product involved in the suspected ADE (batch number and manufacture´s information). This result is particularly worrying in the context of pharmacovigilance of biological products, since these medicines are subject to frequent changes in the manufacturing process after their approval in the market (14-16, 28, 29). Therefore, if an adverse event occurs, the presence of this kind of information is crucial to detect and evaluate

emerging issues of product-specific safety and immunogenicity (12, 14, 28). In view of these findings, although the Brazilian regulatory agency makes manuals and various materials available for the qualification and guidance to notifiers, educational actions involving this topic are still needed.

The results of this study must be interpreted in the context of some limitations. First, the analyses carried out were restricted to the possibilities offered by VigiMed system. Second, causal inferences between bDMARD and ADE cannot be drawn from the data, as the role of other medicines used concomitantly with the suspected medicine cannot be completely ruled out.

As strengths, it is worth mentioning that the study evaluated pharmacovigilance data from the VigiMed system, which is an adapted version of VigiFlow, which is the system used by the Uppsala Monitoring Centre (UMC) and offered by the World Health Organization. The data recorded in VigiMed, together with several countries' data, compose the global database called VigiBase, allowing the monitoring of medicines worldwide. In addition, considering that VigiMed was recently implemented in Brazil, carrying out studies that profile the reports registered in this system contributes to the detection of crucial points that require adjustments to the reporting system and the qualification of reports.

The results of this study highlight possible safety issues involving bDMARD that should be considered when pharmacotherapy decisions in RA take place. This becomes even more relevant since biological medicines have substantial differences in the safety profile when compared to medicines with small molecules.

The data from the Brazilian reporting system represents a valuable resource to unravel the role of ADE in public health. Therefore, it is essential to develop initiatives that stimulate ADE reports among all medicine system stakeholders and that promote the necessity of more appropriate and complete reports, especially with regard to filling in information that allow the identification and traceability of biological medicines.

Notes

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Conflicts of interest disclosure

The authors declare no competing interests relevant to the content of this study.

Authors' contributions

All the authors declare to have made substantial contributions to the conception, or design, or acquisition, or analysis, or interpretation of data; and drafting the work or revising it critically for important intellectual content; and to approve the version to be published.

Availability of data and responsibility for the results

All the authors declare to have had full access to the available data and they assume full responsibility for the integrity of these results.

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