Safety signals assessed by the pharmacovigilance risk assessment committee: biologics vs conventional medicines

Sinais de Segurança analisados pelo comité de avaliação do risco em farmacovigilância: biológicos vs terapêutica convencional

Margarida Estudante, Teresa Lopes, Dinah Duarte
CBIOS – Universidade Lusófona' Centro de Pesquisa de Ciências e Tecnologias da Saúde, Campo Grande, 376, 1749-024, Lisboa, Portugal
Email: margarida.estudante@ulusofona.pt

Abstract

The Pharmacovigilance Risk Assessment Committee (PRAC) is responsible for medicines safety monitoring in Europe. Biologic drugs (BDs) have more recently been developed and reinforced the treatment of serious and chronic diseases. Because of their specificities, BDs have become a new challenge for pharmacovigilance. This work evaluates safety signals generated by PRAC for BDs vs. conventional therapy (CT) between September 2012 and December 2018 (819 signals). Normalizing the results by the number of molecules (INN) in each drug class we found the proportion of safety signals by therapy type to be 4 for BDs vs. 2.5 for CT. The System Organ Classes (SOCs) affected by safety signals triggered for BDs and CT were compared. The three most relevant System Organ Classes (SOCs) found to be related to CT signals are general disorders and administration site conditions (14%), skin and subcutaneous tissue disorders (7%) and gastrointestinal disorders (6%). Signals related to BDs are mainly associated with blood and lymphatic system disorders (14%), skin and subcutaneous tissue disorders (13%) and nervous system disorders (10%). During the study period safety signals for BDs were proportionally 1.6 higher than safety signals for CT.

Keywords: Conventional therapy; biologics; safety signals; PRAC; pharmacovigilance

Resumo

O Comité de Avaliação do Risco em Farmacovigilância (PRAC) monitoriza a segurança dos medicamentos na Europa. Os medicamentos biológicos (MBs) reforçaram o tratamento de doenças graves e crónicas, mas, devido às suas especificidades, tornaram-se num desafio para a farmacovigilância. Este trabalho avalia os sinais de segurança gerados pelo PRAC para MBs vs. medicamentos tradicionais (MTs) entre setembro de 2012 e dezembro de 2018 (819 sinais). Considerando o número de moléculas (DCI) em cada classe de medicamentos, obteve-se a proporção de sinais de segurança por tipo de terapêutica: 4 para MBs vs. 2,5 para MTs . Foram comparadas as Classes de Sistemas e Órgãos (SOCs) afetadas pelos sinais de segurança gerados por MBs e MTs. As principais SOCs associadas aos sinais dos MTs são perturbações gerais e condições no local de administração (14%), distúrbios da pele e dos tecidos subcutâneos (7%) e doenças gastrointestinais (6%). Para os MBs, os sinais estão principalmente relacionados com doenças do sangue e do sistema linfático (14%), distúrbios da pele e dos tecidos subcutâneos (13%) e do sistema nervoso (10%). Durante o período do estudo, os sinais de segurança para MBs foram proporcionalmente 1,6 mais elevados do que os gerados para os MTs.

Palavras-Chave: Medicamentos tradicionais; biológicos; sinais de segurança; PRAC; farmacovigilância
Introduction

All medicines are likely to cause adverse drug reactions (ADRs). Pharmacovigilance began about 170 years ago, not being recognized as such at that time (1, 2). Safety monitoring for all medicines throughout their lifecycles is now a regulatory requirement in order to protect public health. Pharmacovigilance methodology and regulations constitute a constant challenge as new scientific discoveries evolve (3). Since thalidomide tragedy (4) and the emergence of the first Pharmacovigilance Systems, there has been a constant evolution in the access and data processing of medicines’ safety data (5).

Another important milestone occurred in 2010, with the publication of new European pharmacovigilance legislation aiming to join efforts between all Member States and the Marketing Authorisation Holders (MAHs). This new legislation focuses in the constitution of a Pharmacovigilance Risk Assessment Committee (PRAC) within the European Medicines Agency (EMA). The PRAC was formally established in July 2012 and finalized its constitution in the spring 2013 with the appointment of patient and health-care professional organization representatives as full voting members. The Committee includes independent experts in pharmacoepidemiology, clinical pharmacology, biologics, signal detection, risk communication, and vaccine vigilance (6).

This committee proactively monitors all aspects related to the safety of marked medicines, including signal evaluation and management of post-marketing benefit-risk assessments (7).

The new pharmacovigilance legislation led to the development of a set of guidelines by the EMA on good pharmacovigilance practices (GVPs) (8), and endorsed the creation of an European (EU) database, the EudraVigilance database. EudraVigilance is an EU centralized system for recording and analyzing ADRs occurred with medicines with marketing authorization in Europe, and is a main resource for safety signal detection (5). Evaluation of generated signals requires a scientific based approach in order to prioritize and manage new information. The PRAC is responsible for this task, including updating product information and restrictions for use, among other recommendations (6). Signal detection and evaluation are essential elements of current pharmacovigilance, having been extensively studied during the last few years, throughout different European projects, in order to define good signal detection practices (9-11). EMA’s GVP Module IX-Signal management (12) describes the process of signal detection and validation within the EU.

A safety signal can be originated by several sources, in-
cluding observational and/or experimental studies. An important source of signals in drug safety is the spontaneous reporting system, which relies on the reporting of ADRs by health-care professionals and consumers to National Competent Authorities or pharmaceutical companies (13).

A signal can be related to information about a new and unknown potentially causal association, or a novel aspect of an already known association between events that requires further investigation. Differences in frequency, duration, severity, or outcome of a known association should be analyzed (12). PRAC results regarding signals identified through the regulatory European network have been subject of several publications (14, 9, 15). This study compares the pattern of safety signals generated and published by PRAC for medicines obtained through biological sources (biological medicines or biologics) and conventional medicines over a defined time period (September 2012 to December 2018).

Conventional medicines are understood as the use of drugs containing small molecules with pharmacological activity, obtained by chemical synthesis. Conventional medicines are currently the main therapeutic resource (16). Biological medicines are complex drugs produced by living organisms and have limited utilization experience, having only been launched in the 1980’s (17). Biologics are macromolecules larger in size than synthetic small molecule drugs, require more resources for production, and have a higher cost. The development of biologics led to the treatment improvement of several serious and chronic diseases such as cancer, autoimmune conditions, diabetes, and anemia (18-21).

Knowledge about the safety profile of new drugs is not complete at the time of approval (Marketing Authorization – MA), primarily due to intrinsic limitations of clinical trials, among other reasons. Furthermore, during the pre-approval phase, safety profile assessment is more difficult for biologics than for chemically synthesized molecules because of limited predictability of animal studies and a high immunogenicity potential. Post-marketing safety data is therefore essential to evaluate new potential safety concerns in clinical practice. Moreover, the biologics manufacturing or formulating process may change over time (22).

Based on the different features and marketing experience of biologics in comparison to conventional medicines, we defined the primary objective of this work as a preliminary comparison of the safety signals pattern generated for biological medicines against the safety signals generated for conventional medicines, from available data (September 2012 to December 2018). To this end, we defined as secondary objectives:

- A signal can be related to information about a new and unknown potentially causal association, or a novel aspect of an already known association between events that requires further investigation. Differences in frequency, duration, severity, or outcome of a known association should be analyzed (12). PRAC results regarding signals identified through the regulatory European network have been subject of several publications (14, 9, 15).

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- Based on the different features and marketing experience of biologics in comparison to conventional medicines, we defined the primary objective of this work as a preliminary comparison of the safety signals pattern generated for biological medicines against the safety signals generated for conventional medicines, from available data (September 2012 to December 2018). To this end, we defined as secondary objectives:
- the comparison of the means of signals frequencies in the biologics group and conventional medicines group;
- the comparison of the three most relevant System Organ Classes (SOC) affected by the signal in the two study samples;
- the computation of the relative risk (RR) of biologics vs. conventional medicines by SOC.

Material and Methods

This study is designed as an observational retrospective longitudinal study. Data on the variable under analysis (safety signals generated and published by the PRAC from September 2012 to December 2018) was obtained by consulting the “List of safety signals discussed since September 2012” available at the EMA website (23). The safety signals generated and published by the PRAC were selected as the study variable due to their reliability on bringing new information on medicinal safety, resulting from the analysis of a large European ADR database (Eudravigilance) with validation by an expert committee (PRAC) (14). Other important factors associated with the selection of this variable were its open access and regular update, allowing study continuity (23).

Number of signals published by PRAC for biologics compared to conventional medicines

In order to assess differences in the means of signals published by the PRAC for biological medicines compared to conventional medicines, we used the Mann-Whitney nonparametric test for two independent samples with a confidence level of 95%. The similarity of the distributions of the two samples was confirmed by the Levene test. Statistical treatment was performed using IBM SPSS 2019 software.
Comparison of SOC associated with signals published by PRAC for biologics and conventional medicines

In order to evaluate potential differences in the distribution of signals generated by System and Organ Classes (SOCs) affected by the signal, we calculated the Relative Risk (RR) by SOC for biologicals in relation to conventional medicines (RR = relative frequency of biological medicines signal by SOC / relative frequency of conventional medicines signal by SOC) (24, 25). The relative frequency of the signal per SOC for each drug class is given by the total signals in a given SOC in the drug class / total signals in the drug class.

If RR is greater than 1, the relative risk of generating a signal in that SOC category is higher for the biological medicines than for the conventional medicines.

Results

Number of signals published by PRAC for biologics compared to conventional medicines

A total of 819 signals were generated by the PRAC from September 2012 to December 2018. Of these, 175 (21.37%) originated from biological medicines and 644 (78.63%) from conventional medicines. The number of molecules analyzed by the PRAC during the study period was different for each class of drugs: 42 molecules for biologics vs. 255 molecules for conventional medicines. The number of molecules analyzed by the PRAC during the study period was different for each class of drugs: 42 molecules for biologics vs. 255 molecules for conventional medicines. The frequency mean of signals published in the biological medicines sample was 4.17 compared to a mean of 2.52 for conventional medicines, with statistical significant difference (p <0.05). Regarding the frequency of published signals per year of study, no statistically significant differences were observed between the two samples (p> 0.05) (Table 1).
The results of our study show that the three most relevant System Organ Classes (SOCs) found to be related to traditional medicines signals were general disorders and administration site conditions (14.29%), skin and subcutaneous tissue disorders (7.45%) and gastrointestinal disorders (6.21%). Regarding to biological medicines, signals were mainly related to blood and lymphatic system disorders (13.71%), skin and subcutaneous tissue disorders (13.14%) and nervous system disorders (10.29%) SOCs (Table 2). Results related to the computed RR are presented in Table 2 and discussed with more detail in the next section.

| Year/ Ano | Biologics / Biológicos (n=42) | Conventional / Convencional (n=255) |
|-----------|-------------------------------|-------------------------------------|
| September until December 2012/ setembro até dezembro de 2012 | 8 (5%) | 38 (6%) |
| 2013 | 26 (15%) | 97 (15%) |
| 2014 | 18 (10%) | 99 (15%) |
| 2015 | 39 (22%) | 102 (16%) |
| 2016 | 28 (16%) | 103 (16%) |
| 2017 | 16 (9%) | 100 (16%) |
| January until June 2018/ janeiro a junho de 2018 | 40 (16%) | 105 (16%) |
| Total/ Total | 175 (100%) | 644 (100%) |
| Mean / Média | 4.17* (4.17=175/42) | 2.52 (2.52=644/255) |

**Comparison of SOCs associated with signals published by PRAC for biologics and conventional medicines**

De acordo com os resultados do estudo, as principais SOCs relacionadas com os sinais dos medicamentos tradicionais são perturbações gerais e condições no local de administração (14,29%; inclui interações medicamento-sas, entre outras), distúrbios da pele e dos tecidos subcutâneos (7,45%) e doenças gastrointestinais (6,21%). No que diz respeito aos medicamentos biológicos, os sinais estão principalmente relacionados com SOC relacionadas com doenças do sangue e do sistema linfático (13,71%), distúrbios da pele e dos tecidos subcutâneos (13,14%) e do sistema nervoso (10,29%) (Tabela 2). Foi ainda avaliado o Risco Relativo (RR) por SOC dos sinais pelo pelo PRAC para medicamentos biológicos em comparação com os convencionais, cujos resultados se encontram na Tabela 2 e serão discutidos na próxima seção.
### Table 2 / Tabela 2

Relative Risk (RR) by System Organ Class Classification (SOC) of signals raised by PRAC for biological medicines in comparison to conventional medicines. **not applicable / Risco Relativo (RR) por Classificação Sistema Órgão Classe (SOC) de sinais gerados pelo PRAC para medicamentos biológicos em comparação com convencionais. **não aplicável.

| System Organ Class Classification (SOC) / Classificação Sistema Órgão Classe (SOC) | Biologics / Biológico Total% | Conventional / Convencional Total % | RR Biologics vs Conventional / RR Biológico vs Convencional |
|---|---|---|---|
| Blood and lymphatic system disorders / Doenças do sangue e do sistema linfático | 24 (13.71) | 26 (4.04) | 3.4 |
| Cardiac disorders / Cardiopatias | 5 (2.86) | 36 (5.59) | 0.51 |
| Congenital, familial and genetic disorders / Afeções congênitas, familiares e genéticas | 0 (0.00) | 9 (1.40) | 0 |
| Ear and labyrinth disorders / Afeções do ouvido e do labirinto | 3 (1.71) | 2 (0.31) | 5.52 |
| Endocrine disorders / Doenças endócrinas | 3 (1.71) | 17 (2.64) | 0.65 |
| Eye disorders / Afeções oculares | 4 (2.29) | 24 (3.73) | 0.61 |
| Gastrointestinal disorders / Doenças gastrointestinais | 8 (4.57) | 40 (6.21) | 0.74 |
| General disorders and administration site conditions / Perturbações gerais e alterações no local de administração | 7 (4.00) | 92 (14.29) | 0.28 |
| Hepatobiliary disorders / Afeções hepáticas e hepatobiliares | 1 (0.57) | 14 (2.17) | 0.26 |
| Immune system disorders / Doenças do sistema imunitário | 10 (5.71) | 16 (2.48) | 2.3 |
| Injuries and infestations / Infecções e infestações | 14 (8.00) | 15 (2.33) | 3.43 |
| Injury, poisoning and procedural complications / Complicações de intervenções relacionadas com lesões e intoxicações | 1 (0.57) | 24 (3.73) | 0.15 |
| Investigatory exams / Exames complementares de diagnóstico | 2 (1.14) | 22 (3.42) | 0.33 |
| Metabolism and nutrition disorders / Doenças do metabolismo e da nutrição | 4 (2.29) | 32 (4.97) | 0.46 |
| Musculoskeletal and connective tissue disorders / Doenças musculo-esqueléticas e dos tecidos conjuntivos | 4 (2.29) | 28 (4.35) | 0.53 |
| Neoplasms benign, malignant and unspecified (incl. cysts and polyps) / Neoplasias benignas malignas e não especificadas (incl. quistos e polipos) | 9 (5.14) | 23 (3.57) | 1.44 |
| Nervous system disorders / Doenças do sistema nervoso | 18 (10.29) | 34 (5.28) | 1.95 |
| Pregnancy, puerperium, and perinatal conditions / Situações na gravidez, no puerpério e perinatais | 1 (0.57) | 21 (3.26) | 0.18 |
| Product problems / Problemas de produtos | 3 (1.71) | 2 (0.31) | 5.52 |
| Psychiatric disorders / Perturbações do foro psiquiátrico | 0 (0.00) | 23 (3.57) | 0 |
| Renal and urinary disorders / Doenças renais e urinárias | 8 (4.57) | 22 (3.42) | 1.34 |
| Reproductive system and breast disorders / Doenças dos órgãos genitais e da mama | 0 (0.00) | 9 (1.40) | 0 |
| Respiratory, thoracic and mediastinal disorders / Doenças respiratórias, torácicas e do mediastino | 7 (4.00) | 35 (5.43) | 0.74 |
| Skin and subcutaneous tissues disorders / Afeções dos tecidos cutâneos e subcutâneos | 23 (13.14) | 48 (7.45) | 1.76 |
| Social circumstances / Circunstâncias sociais | 0 (0.00) | 0 (0.00) | ** |
| Surgical and medical procedures / Procedimentos cirúrgicos e médicos | 0 (0.00) | 1 (0.16) | 0 |
| Vascular disorders / Vasculopatias | 16 (9.14) | 29 (4.50) | 2.03 |
| **Total** | **175 (100%)** | **644 (100%)** | **** |
Discussion

Number of signals published by PRAC for biologics compared to conventional medicines

Biologics were only introduced in the market in the 1980’s, and therefore it was foreseen that fewer biological medicines were present in our search, a fact that was supported by the difference found in study sample sizes (Table 1). Our results demonstrate that, during the period observed by the study, the occurrence of new safety signals for biological medicines was significantly higher than the occurrence of new safety signals for conventional medicines. The frequency mean of safety signals is 4.17 for biologics compared to 2.52 for conventional medicines (p<0.05) (Table 1). These results suggest that awareness and knowledge about the safety profiles of biologics are on an ascending trend, compared to conventional medicines. As more recently available medicines, with different specificities and lower marketing experience, biologics are prone to the identification of new safety signals as marketing experience increases.

Comparison of SOCs associated with signals published by PRAC for biologics and conventional medicines

The results of our study show that the three most relevant System Organ Classes (SOC) found to be related to traditional medicines signals are general disorders and administration site conditions (14.29%), skin and subcutaneous tissue disorders (7.45%) and gastrointestinal disorders (6.21%). General disorders and administration site conditions SOC includes generic signals such as drug-drug interactions, withdrawn and rebound, pain and discomfort, body temperature changes, among others. These conditions are familiar as adverse reactions of conventional medicines.

Regarding to biological medicines signals were mainly related to blood and lymphatic system disorders (13.71%), skin and subcutaneous tissue disorders (13.14%) and nervous system disorders (10.29%) SOC (Table 2).

The described safety profile for biologics includes ADRs that are usually linked to their pharmacologic actions and immunologic reactions, such as immunogenicity and administration-site reactions (26). This can result in a loss of efficiency or deficiency syndromes (for example, thrombocytopenia) (27, 28).

The relative risk (RR) for SOC of signals collected by PRAC was also evaluated for biological medicines in comparison with the conventional medicines (Table 2). If RR is greater than 1, the relative risk of generating a signal in the category of SOC was higher for

Discussão

Número de sinais publicados pelo PRAC para medicamentos biológicos comparativamente aos medicamentos convencionais

Os medicamentos biológicos foram introduzidos no mercado apenas na década de 1980 sendo expectável que menos medicamentos biológicos tenham sido encontrados nesta avaliação, em comparação com os medicamentos convencionais, facto que pode suportar a diferença na dimensão das amostras encontrada no período observado pelo estudo (Tabela 1). Foi encontrado um valor médio para a frequência de sinais publicados na amostra de medicamentos biológicos (4,17) estatisticamente superior ao valor médio da amostra para medicamentos convencionais (2,52) (p<0,05). Sendo medicamentos mais recentes, com diferentes especificidades e uma menor experiência de comercialização, os medicamentos biológicos revelam suscetibilidade à identificação de novos sinais de segurança à medida que a experiência de utilização aumenta.

Comparação das SOC associadas aos sinais publicados pelo PRAC para medicamentos biológicos e medicamentos convencionais

De acordo com os resultados do estudo, as principais SOC relacionados com os sinais dos medicamentos convencionais são perturbações gerais e condições no local de administração, distúrbios da pele e dos tecidos subcutâneos e doenças gastrointestinais. A SOC perturbações gerais e condições no local de administração inclui sinais genéricos, tais como interações fármaco-fármaco, falta de adesão à terapêutica, síndrome de abstinência, dor e desconforto, alterações de temperatura corporal, entre outros. Estas condições são familiares como RAMs dos medicamentos tradicionais.

No que diz respeito aos medicamentos biológicos, os sinais estão principalmente relacionados com doenças do sangue e do sistema linfático, distúrbios da pele e dos tecidos subcutâneos e do sistema nervoso. As RAMs associadas aos medicamentos biológicos estão ligadas às suas ações farmacológicas e reações imunológicas, tais como reações de imunogenicidade e reações no local de administração (26). Isto pode resultar numa perda de eficácia ou de síndromes de deficiência (por exemplo, trombocitopenia) (27, 28).

Foi ainda avaliado o Risco Relativo (RR) por SOC dos sinais levantados pelo PRAC para fármacos biológicos em comparação com os tradicionais (Tabela 2). Se RR for superior a 1, o risco relativo da geração de um sinal na categoria dessa SOC é superior para o bioló-
the biological compared to traditional medicines. In our analysis the SOCs with RR>1 were: disorders of the blood and lymphatic system, disorders of the immune system, infections and infestations, neoplasms (malignant, benign and unspecified), disorders of the nervous system, product problems, kidney and urinary diseases, disorders of the skin and the subcutaneous tissue, and vascular disorders. Skin and the subcutaneous tissue SOC is among the three more relevant SOC for both samples, however RR is higher for biologics. These results are in agreement with the specificities already mentioned for biological products, taking into account that they are primarily immunogenic proteins, administered intravenously and that the structural variations between batches, or a biosimilar and its reference biological, can lead to significant changes in the profile of efficacy and safety (18). Ear and labyrinth disorders appear with RR>1 due to a sign of deafness that has not been confirmed. The ADRs may be specific for the type of biological medicine, taking into account its mechanism of action: monoclonal antibodies, fusion proteins, enzymes and coagulation factors (mainly associated with skin reactions), cytokines (hematological disorders), and hormones (disturbance of the metabolism and nutrition) (29). Post-marketing studies confirm that the biological medicinal products, due to their effects on specific targets, have different trends in the safety profile in comparison with the conventional medicines (26).

Conclusion

The present study demonstrates that in the period observed by the study the number of signals published by PRAC for biological medicines is higher compared to the signals published for conventional medicines, which can result from an ascending trend on biologic safety profile awareness and knowledge, as they are more recently developed and complex molecules than conventional medicines. The relative risk (RR) for biological medicines is higher than for conventional medicines for signals related to the following System Organ Classes (SOC): disorders of the blood and lymphatic system, disorders of the immune system, infections and infestations, neoplasms (malignant, benign, and unspecified), disorders of the nervous system, problems with the product, kidney and urinary diseases, disorders of the skin and the subcutaneous tissue, and vascular disorders.

gico relativamente aos medicamentos convencionais. Na nossa análise as SOC com RR>1 foram: distúrbios do sistema sanguíneo e linfático, distúrbios do sistema imunológico, infecções e infestações, neoplasias malignas e não especificadas, distúrbios do sistema nervoso, problemas do produto, doenças renais e urinárias, distúrbios da pele e tecido subcutâneo e distúrbios vasculares. Observamos que a SOC distúrbios da pele e dos tecidos subcutâneos se encontra entre as três mais relevantes na análise de segurança para ambos os tipos de medicamentos mas o RR é superior para os medicamentos biológicos.

Estes resultados estão de acordo com o acima mencionado para os medicamentos biológicos, tendo em conta que são principalmente proteínas imunogênicas, administradas por via intravenosa e que as variações estruturais entre lotes, ou um biosimilar e o seu biológico de referência, podem conduzir a alterações significativas no perfil de eficácia e segurança (18). Afeções do ouvido e do labirinto aparecem com RR>1 devido a um sinal de surdez que não foi confirmado. As RAMs podem ser específicas por tipo de biológico, tendo em conta o seu mecanismo de ação: anticorpos monoclonais, proteínas de fusão, enzimas e fatores de coagulação (associa- dos principalmente com reações cutâneas), citocinas (distúrbios hematológicos) e hormonas (perturbações do metabolismo e da nutrição) (29). Os estudos pós-comercialização confirmam que os medicamentos biológicos, devido aos seus efeitos em alvos específicos, possuem diferentes tendências no perfil de segurança em comparação com os medicamentos convencionais (26).

Conclusão

Com base neste estudo podemos concluir que no período observado o número de sinais publicados pelo PRAC para medicamentos biológicos foi superior comparativamente aos sinais publicados para medicamentos tradicionais. Sendo moléculas mais complexas e mais recentes, o resultado encontrado sugere que o conhecimento e consciencialização sobre o perfil de segurança para os medicamentos biológicos se encontra em fase de crescimento. Na nossa análise as SOC com RR>1 para os medicamentos biológicos comparativamente aos convencionais foram: distúrbios do sistema sanguíneo e linfático, distúrbios do sistema imunológico, infecções e infestações, neoplasias benignas malignas e não especificadas, distúrbios do sistema nervoso, problemas do produto, doenças renais e urinárias, distúrbios da pele e tecido subcutâneo e distúrbios vasculares.
These preliminary results will be further explored, namely by mechanism of action or pharmacotherapeutic class, as ADRs may be specific by type of biological medicine.

One of the limitations of this study is that signals generated from EudraVigilance cannot be isolated by country, but comparative analyses with published data from other entities, such as the World Health Organization (WHO), Food and Drug Administration (FDA) and the Australian Therapeutic Goods Administration (TGA) are planned for the near future.

Conflict of Interests

The authors declare that they have no competing interests.

Conflict de Interesses

Os autores declaram que não têm interesses concorrentes.
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