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Mapping the Safety Profile of Biologicals

A Disproportionality Analysis Using the WHO Adverse Drug Reaction Database, VigiBase

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Abstract

Background: Biologicals have specific characteristics, as compared with the small molecule drugs, and carry specific risks. Safety problems, for example infliximab and the risk for tuberculosis, have been identified via spontaneous reports of suspected adverse drug reactions (ADRs). However, in general there is limited data on the nature of spontaneously reported suspected ADRs for biologicals.

Objective: To map the safety profile of biologicals as compared with all other drugs. In addition, mechanistic classes of biologicals will be compared.

Methods: Data was obtained from the ADR database (VigiBase) maintained by the WHO Collaborating Centre for International Drug Monitoring. A disproportionality analysis was performed in which case reports for biologicals and all other drugs (the reference group), reported between January 1995 and December 2008, were selected. Vaccines were not included in the analysis. Suspected ADRs were classified according to Medical Dictionary for Regulatory Activities (MedDRA®) version 12.0 at the System Organ Class (SOC) level. Biologicals were classified into mechanistic classes: antibodies, cytokines, enzymes, growth factors, hormones (reference group), interferons, receptors and others/various. The safety profile of the biologicals versus all other drugs in the database and of the various mechanistic classes of biologicals was compared using the proportional reporting ratio (PRR).

Results: 191 004 case reports containing 546 474 suspected ADRs were reported for 62 different biologicals, and 2 556 209 case reports containing 8 761 522 suspected ADRs were reported for all other drugs (the reference group). It was found that two-thirds of all suspected ADRs reported for biologicals were reported for five active substances: etanercept (20.3%), interferon-β-1a (15.6%), infliximab (11.6%), teriparatide (10.7%) and adalimumab (9.0%).

Comparison of the safety profile of biologicals and the reference group showed that suspected ADRs for biologicals were more frequently reported in the SOCs 'Infections and infestations' (PRR 4.5), 'Surgical and medical procedures' (PRR 2.4) and 'Neoplasms benign, malignant and unspecified' (PRR 2.1), and less frequently reported in the SOCs 'Psychiatric disorders' (PRR 0.4), 'Vascular disorders' (PRR 0.4) and 'Pregnancy, puerperium and perinatal conditions' (PRR 0.4).

Regarding the differences in safety profile between various mechanistic classes of biologicals, compared with hormones (reference group), 'Infections and infestations' were more frequently reported for receptors and antibodies. 'Neoplasms benign, malignant and unspecified' were more frequently reported for antibodies, cytokines, interferons and receptors, and less frequently for enzymes as compared with the reference group.

Conclusions: In VigiBase, five biologicals comprise two-thirds of the suspected ADRs reported for biologicals, which might distort the relation found between a specific biological and a specific adverse event in case of quantitative signal detection. Therefore the choice of reference group to be used in case of quantitative signal detection should be considered very carefully.

This study confirmed that biologicals have a different safety profile compared with all other drugs in the database and, within the group of biologicals, differences exist between mechanistic classes. Infections are, for example, frequently reported for receptors and antibodies, which often have an immune compromising effect. Such predictable safety issues should be specifically studied by preregistration clinical trials and/or targeted pharmacovigilance. In addition, since not all adverse reactions can be predicted or detected during development, spontaneous reporting remains an important tool for the early detection of signals.

Background

Biologicals, also called biopharmaceuticals, are important treatment options for a variety of chronic and sometimes life-threatening diseases.[1] However, compared with the traditional chemically synthesized small molecules, biologicals have specific characteristics that influence their safety profile. For example, biologicals are large, complicated molecules with a very complex production and purification process, a high potential for immunogenicity and limited predictability of preclinical data to clinical outcomes.[1-4] These characteristics may result in more uncertainties about the safety profile of biologicals at the point of approval, which was confirmed by a previous study. In this study it was shown that, at the moment of marketing, safety concerns for biologicals are less frequently classified as 'identified risks' and more frequently as 'missing information' compared with the small molecule drugs.[5]

Because of the limitations of randomized clinical trials, including the often limited sample size and a homogenous population, pharmacovigilance is required to further study the safety of drugs in the postmarketing setting.[6] We demonstrated that approximately one in four of all biologicals approved in the US and/or the EU required a safety-related regulatory action, defined as a

communication to healthcare professionals and/or a 'black-box' warning, after marketing of the drug.[7] This study also demonstrated that the safety concerns requiring a regulatory action were different between biologicals and small molecules. Safety concerns for biologicals often concerned infections, malignancies and reactions related to immunological events,[7] whereas safety concerns for small molecules are known to be often related to the classes 'Cardiac disorders', 'Hepatobiliary disorders', 'Blood and lymphatic system disorders' and 'Nervous system disorders'.[8-10]

Pharmacovigilance comprises a variety of activities, including the collection of spontaneously reported suspected adverse drug reactions (ADRs) reported by both patients and healthcare professionals, and proactive pharmacovigilance activities, including post-authorization safety studies.[11] Spontaneous reporting of suspected ADRs has shown to be an important tool for the detection of new, serious and/or rare potential ADRs,[12] although assessment to establish whether the relationship between a drug and a clinical event is causal is complicated.[13] Causality assessment, however, might be even more complicated for biologicals due to a prolonged effect of the biological resulting in the occurrence of potential ADRs weeks or months after administration of the last dose and since patients treated with biologicals are often treated with multiple other drugs and/or have multiple diseases.[4] Two examples illustrate the impact spontaneous reporting of suspected ADRs can have on clinical decision making. First, an analysis in the US FDA spontaneous reporting system MedWatch suggested an association between the occurrence of tuberculosis with the use of infliximab, which had not been previously seen.[14] Current clinical guidelines now include the recommendation that patients should be tested for latent tuberculosis before treatment with infliximab is initiated and, if latent tuberculosis is shown, this should be eradicated first.[15,16] Second, three confirmed case reports of progressive multifocal leukoencephalopathy with the use of efalizumab, two of which were detected via spontaneous reporting, made the European regulators conclude that the benefits no longer outweigh the risk, which led to withdrawal of the drug from the market.[17] These two examples illustrate the occurrence of a specific ADR with a specific biological. At the moment there is limited data available on the nature of spontaneously reported suspected ADRs for biologicals from a broader perspective and how this relates to the spontaneously reported suspected ADRs for the traditional small molecule drugs. Therefore, the present study aims to further map the safety profile of biologicals, based on spontaneously reported suspected ADRs, as compared with all other drugs and for specific mechanistic subclasses of biologicals. In addition, general characteristics of the spontaneously reported suspected ADRs for biologicals will be collected in terms of (changes in) the number of suspected ADRs reported over time, and the identification of drugs frequently implicated. This study will therefore add to the knowledge on the safety profile of biologicals as compared with the traditional small molecule drugs.

Methods

Setting

The data has been obtained from the WHO Global Individual Case Safety Report (ICSR) database, VigiBase, which is maintained by the Uppsala Monitoring Centre. VigiBase contains summaries of suspected ADR case reports originally submitted by healthcare professionals and patients to national pharmacovigilance centres in 98 countries all over the world. As of May 2010, this database contained over 5 million case reports of suspected ADRs regarding specific, but anonymous, patients. The reports contain details on administrative, patient, ADR and medication data, and additional information. The information in these reports is not homogenous, at least with regard to origin, completeness of documentation or the likelihood that the suspected drug caused the suspected ADR. Suspected ADRs are transferred from the national pharmacovigilance centres to the Uppsala Monitoring Centre and recorded with the lowest level term either in the WHO Adverse Reaction Terminology (WHO-ART) or the Medical Dictionary for Regulatory Activities (MedDRA®), depending on the terminology

used at the national centre. Since there is a bridge between the two terminologies in VigiBase these two methods of coding suspected ADRs are compatible and data can be retrieved using either WHO-ART or MedDRA®.[18] In the present study, ADRs were coded according to MedDRA®.

For this study, all suspected ADRs reported to VigiBase between January 1995 and December 2008 for biologicals approved between January 1995 and December 2008 in the EU and/or US were taken into account. Biologicals were defined according to the European Medicines Agency definition, in which biologicals are defined as products that are produced by or extracted from a biological source.[19] The following biologicals were excluded: vaccines (ATC class J07), allergenic products (allergen patch test and allergenic extracts; ATC classes V01AA and V04CL), biological products for further manufacture, and biological products for transfusion purposes and maintenance of circulating blood volume. All other suspected ADRs reported to VigiBase between January 1995 and December 2008 were used as the reference group (vaccines were also excluded from the reference group).

Design and Definition

A disproportionality analysis was conducted in which all suspected ADRs reported between January 1995 and December 2008 for biologicals and the drugs in the reference group were followed over time. Biologicals were classified according to the mechanistic classes: antibodies (including monoclonal antibodies), cytokines, enzymes, growth factors, hormones, interferons, receptors and others/various.[7]

For both biologicals and the reference group, data was obtained on the number of suspected ADRs in the case reports at the lowest level term, changes in the number of reports over time, mean age and sex distribution of the patients. The safety profile of the biologicals and the reference group was characterized and compared according to the spontaneously reported suspected ADRs. Suspected ADRs were classified according to MedDRA® version 12.0 in the primary System Organ Class (SOC). The safety profile was also characterized and compared for the different mechanistic classes of biologicals. Within this analysis, specific attention was given to the MedDRA® SOCs 'Infections and infestations', 'General disorders and administration site conditions', 'Immune system disorders' and 'Neoplasms benign, malignant and unspecified', since our previous study showed that safety-related regulatory actions for biologicals were specifically triggered for these classes of suspected ADRs.[7] Other MedDRA® SOC classes, which were among the five SOCs in which suspected ADRs were most frequently reported in the present study, were also taken into account.

Since infections, neoplasms and ADRs related to immunological events frequently trigger a safety-related regulatory action,[7] these ADRs were evaluated in more depth. Suspected ADRs reported in the SOC 'Infections and infestations' were further classified into opportunistic infections and other infections. Opportunistic infections were defined as an infection caused by an organism that does not normally cause disease, which occurs in patients with weakened immune systems.[20] Suspected ADRs reported in the SOC 'Neoplasms benign, malignant and unspecified' were further classified as haematological malignancies, solid malignancies and others (mainly including benign neoplasms). Immunological events can range from transient appearance of antibodies without any clinical significance to severe life-threatening conditions. Potential clinical problems include loss of efficacy of the biological due to neutralizing antibodies, hypersensitivity reactions and antibodies that cross-react with an endogenous counterpart.[19,21] However, because of the large variety of suspected ADRs that can be considered immunological events, these events were classified as either *definite* immunological or *possible* immunological. Suspected ADRs that were classified as definite immunological events include, for example, hypersensitivity reactions, antibodies to a specific biological, etc., and suspected ADRs that were classified as possible immunological comprise the less specific terms, e.g. fever and hypotension. Immunological events were classified as definite or possible immunological based on the MedDRA® preferred term level, so ADRs

classified in different SOCs were included in this analysis.

Data Analysis

Descriptive statistics were used to summarize the general characteristics of the case reports for biologicals and the reference group. The line that best-fitted the cumulative number of case reports over time was calculated using the square of the correlation coefficient.

The safety profile of the biologicals and the reference group (all other drugs) was compared by calculation of the proportional reporting ratio (PRR) and their corresponding 95% CI. The PRR is calculated in a similar way to a relative risk in a cohort study, whereby the proportion of a specific ADR or group of ADRs of interest is calculated for biologicals and divided by the proportion of these ADR(s) for all other drugs in the database (reference group) [figure 1].[22,23] In the calculation of the PRR, each suspected ADR classified at the lowest level term was classified at the SOC level and included in the analysis. Three sensitivity analyses were planned to analyze the effect of specific characteristics on the estimated PRRs. First, an analysis was done after exclusion of the five biologicals most frequently implicated. Second, an analysis was done after exclusion of the reports from the US since most reports were retrieved from the US (84.3% of the reports for biologicals and 62.8% of the reports in the reference group were from the US). Third, an analysis was done in which reports from countries that only report ADRs involving small molecules were excluded from the reference group. The third analysis showed that only 0.7% of the suspected ADRs reported for the reference group were reported by countries that had not reported for biologicals. This is, therefore, expected to have a very limited effect on the results found, and the sensitivity analysis without these reports was not done. PRRs were also calculated to compare the different mechanistic classes. Within this analysis the mechanistic class hormones was used as the reference. All statistical analyses were done using SPSS 16.0 statistical software (SPSS Inc., Chicago, IL, USA). All analyses were unadjusted since this study was descriptive and not aetiological in nature.

Results

General Characteristics of Case Reports

Between January 1995 and December 2008, 191 004 case reports containing 546 474 suspected ADRs were reported for 62 different active biological substances. A total of 2 556 209 case reports containing 8 761 522 suspected ADRs were reported for all other drugs (reference group). From this data it can be estimated that 7.0% of the case reports reported to VigiBase concerned biologicals. The mean age for patients treated with a biological was 35.9 years, whereas the mean age for patients treated with a drug from the reference group was 50.7 years. For patients treated with biologicals, 27.8% were male and 68.5% were female compared with 37.5% males and 55.9% females for the reference group. Information on sex was missing in 3.7% of the reports for biologicals and 6.6% of the reports for the reference group. A case report for a biological contained, on average, 2.86 suspected ADRs, and a case report for a drug included in the reference group (mostly

	Suspected ADR of interest	All other suspected ADRs	Total
Biologicals	a	b	a + b
All other drugs (reference group)	c	d	c + d
Total	a + c	b + d	a + b + c + d

Fig. 1. A two-by-two table for a drug-suspected adverse drug reaction (ADR) combination in spontaneously reported data. Proportional reporting ratio = [a/(a + b)]/[c/(c + d)].

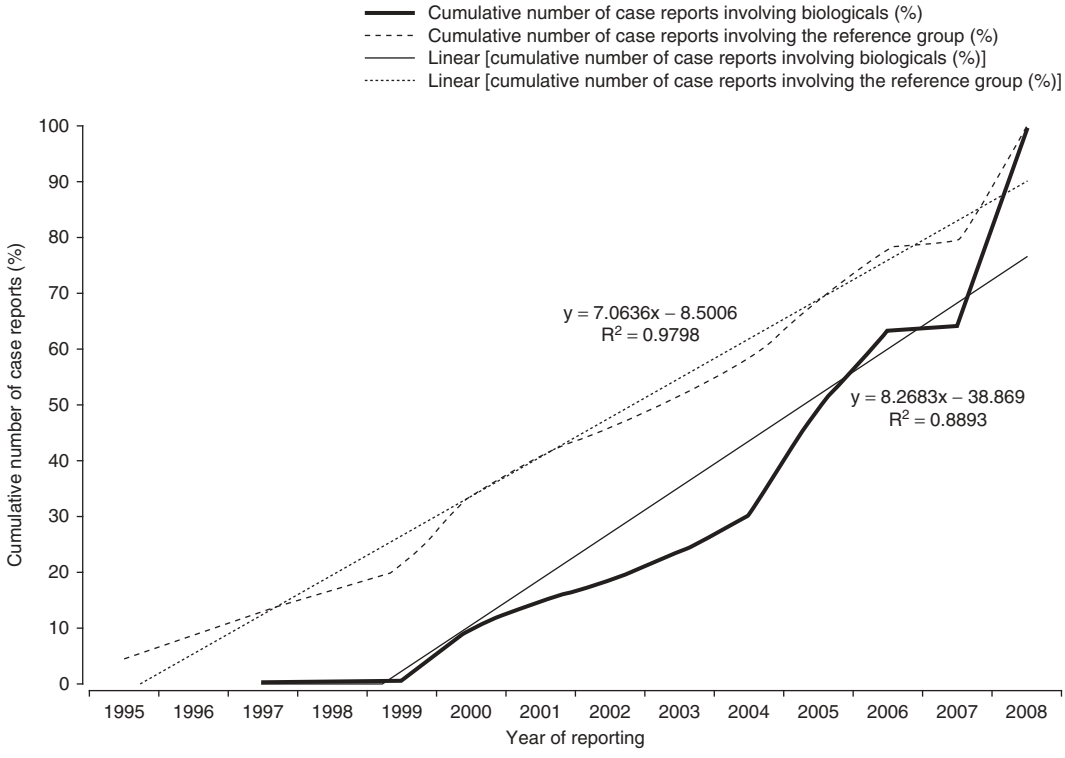

Fig. 2. Cumulative number (%) of case reports reported for biologicals and the reference group. $\mathbf{R^2}$ = square of the correlation coefficient.

including small molecule drugs) contained, on average, 3.43 suspected ADRs. Figure 2 shows the cumulative number of case reports reported for the biologicals and the reference group available in VigiBase. The line of best fit for both groups seems to approach linear, which suggests that there was a constant number of case reports reported to VigiBase over the years. For the biologicals it was found that approximately two-thirds of all suspected ADRs were reported for five active substances: etanercept (20.3%), interferon-β-1a (15.6%), infliximab (11.6%), teriparatide (10.7%) and adalimumab (9.0%).

Nature of Suspected Adverse Drug Reactions for Biologicals versus the Reference Group

A comparison of the nature of the suspected ADRs reported for biologicals and the reference group showed clear differences between the suspected ADRs reported (figure 3). Suspected ADRs for biologicals were more frequently reported in the SOCs 'Infections and infestations' (PRR 4.5), 'Surgical and medical procedures' (PRR 2.4), 'Neoplasms benign, malignant and unspecified' (PRR 2.1), 'General disorders and administration site conditions' (PRR 2.1) and 'Respiratory, thoracic and mediastinal disorders' (PRR 1.9) than for the reference group. Suspected ADRs in the SOCs 'Psychiatric disorders' (PRR 0.4), 'Vascular disorders' (PRR 0.4), 'Pregnancy, puerperium and perinatal conditions' (PRR 0.4), 'Reproductive system and breast disorders' (PRR 0.5) and 'Social circumstances' (PRR 0.6) were more frequently reported for the reference group than for biologicals. The analysis was also conducted without the five biologicals most frequently implicated to evaluate their effect on the calculated PRRs (figure 4). Without these five biologicals, 57 282 case reports remained, including 178 595 suspected

ADRs, and it was found that the SOCs 'Neoplasms benign, malignant and unspecified' and 'General disorders and administration site conditions' were no longer among the five SOCs in which suspected ADRs for biologicals were most frequently reported. These were replaced by 'Investigations' (PRR 1.7) and 'Eye disorders' (PRR 1.6). Certain SOCs were more frequently reported for biologicals with the five biologicals included and less frequently without, and *vice versa*. This includes the SOCs 'Musculoskeletal and connective tissue disorders' (PRR from 1.8 with the five biologicals most frequently implicated included to 0.9 without these five biologicals), 'Blood and lymphatic system disorders' (PRR from 0.7 to 1.4) and 'Metabolism and nutrition disorders' (PRR from 0.7 to 1.4).

The analysis without the reports from the US did not have a major impact on the results. Only for the SOC 'Injury, poisoning, and procedural complications' the PRR changed from 1.0 (US reports included) to 0.5 (US reports excluded), and for the SOC 'Neoplasms benign, malignant and unspecified' the PRR changed from 2.1 with US reports to 8.7 without US reports.

Safety Profile of Biologicals Further Elucidated and Mechanistic Classes Compared

The safety profile of the biologicals was studied in more detail by stratification by mechanistic classes, with specific interest for the SOCs mentioned previously. However, because of the small percentage (0.9% of the total number) of suspected ADRs reported in the SOC 'Immune system disorders', this SOC was not studied in more detail.

'Infections and infestations' involved 8.7% of the total number of suspected ADRs reported for biologicals. Stratification by mechanistic class showed that more than 10% of the suspected ADRs reported for antibodies and receptors involved

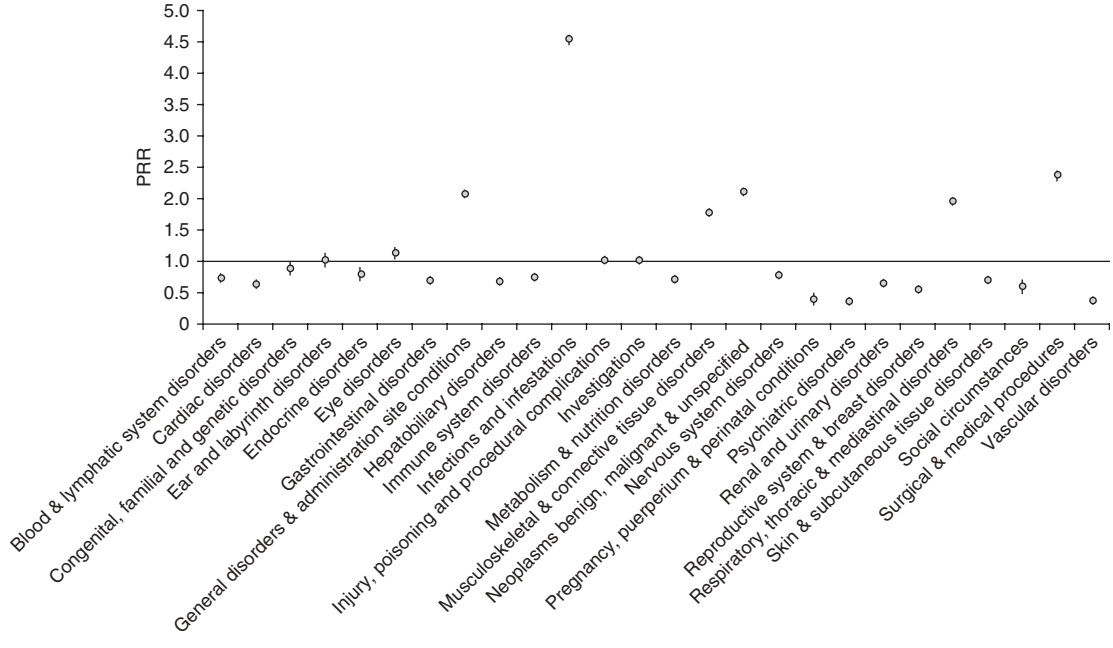

Fig. 3. Comparison of suspected adverse drug reactions reported for biologicals and the reference group at the System Organ Class level according to the Medical Dictionary for Regulatory Activities (MedDRA®) version 12.0 (proportional reporting ratios [PRRs]). Vertical bars on the point estimates represent 95% CIs. PRR >1: more frequently reported for biologicals; PRR <1: more frequently reported for the reference group.

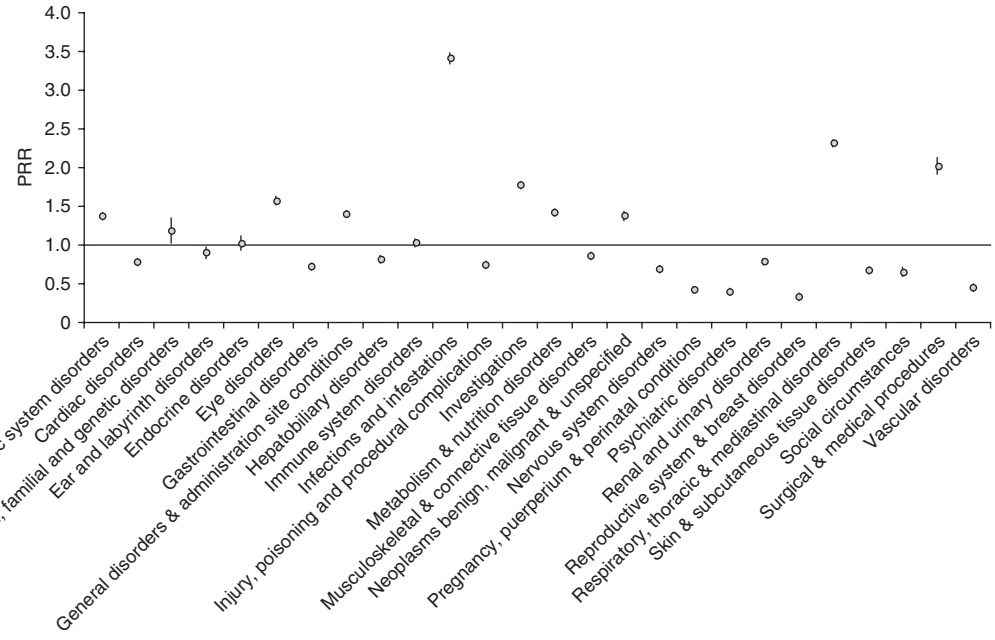

Fig. 4. Comparison of suspected adverse drug reactions reported for biologicals, without the five biologicals most frequently implicated, and the reference group at the System Organ Class level according to the Medical Dictionary for Regulatory Activities (MedDRA®) version 12.0 (proportional reporting ratios [PRRs]). Vertical bars on the point estimates represent 95% CIs. PRR >1: more frequently reported for biologicals; PRR <1: more frequently reported for the reference group.

the SOC 'Infections and infestations' whereas these were less frequently reported for enzymes (4.7%) and hormones (3.1%) [table I]. Compared with the mechanistic class hormones it was shown that 'Infections and infestations' were more frequently reported for all other mechanistic classes (table II). Further classification of suspected ADRs reported in this SOC into opportunistic and other infections showed that for all biologicals, about 16.9% of the reported infections could be classified as opportunistic infections. Opportunistic infections were mainly reported for antibodies (22.7%) and cytokines (23.3%).

'Neoplasms benign, malignant and unspecified' involved 2.3% of the total number of suspected ADRs reported for biologicals. Of the suspected ADRs reported for antibodies, 3.1% involved this class whereas neoplasms were less frequently reported for enzymes, growth factors and hormones (table I). This is also reflected in the calculated PRRs where a significantly higher PRR was calculated for antibodies, cytokines, interferons and receptors, and a significantly lower PRR for enzymes as compared with the reference group (hormones) [table II]. Subclassification of the suspected ADRs reported in this class showed that about 20% of the reported neoplasms for all biologicals involved haematological malignancies, 70% involved solid malignant tumours and about 10% were classified as other neoplasms. Differences between mechanistic classes were observed in the haematological malignancies and other neoplasms. Haematological malignancies were mainly reported for antibodies and cytokines, whereas for growth factors, two of five of the neoplasms reported involved mostly benign tumours.

'General disorders and administration site conditions' involved 20.8% of the suspected ADRs reported for all biologicals, whereas 29.1% of the suspected ADRs reported for receptors involved this SOC (table I).

Classification of the reported immunological events in definite immunological events and possible immunological events showed that 17.0% of

Table I. Distribution of reported suspected adverse drug reactions (ADRs) classified at the System Organ Class level for the total cohort of biologicals and stratified by mechanistic classes (%)[a]

System Organ Class[b]	All biologicals	Antibodies	Cytokines	Enzymes	Growth factors	Hormones	Interferons	Receptors
Infections and infestations	8.7	10.9	7.9	4.7	8.4	3.1	6.7	12.4
Neoplasms benign, malignant and unspecified	2.3	3.1	2.4	0.4	0.5	1.1	2.7	2.1
General disorders and administration site conditions	20.8	17.6	24.4	16.1	27.8	21.2	17.5	29.1
Nervous system disorders	9.5	7.3	5.9	11.5	7.4	10.1	15.4	7.1
Investigations	7.4	7.4	7.7	13.2	1.9	10.9	6.9	4.0
Gastrointestinal disorders	7.2	8.2	6.2	7.2	6.2	7.3	6.3	6.3
Other	44.1	45.5	45.5	46.9	47.8	46.3	44.5	39.0

a Percentages are calculated based on the total number of suspected ADRs reported for biologicals and the individual mechanistic classes.

b Suspected ADRs classified according to the Medical Dictionary for Regulatory Activities (MedDRA®) version 12.0.

the suspected immunological ADRs could be classified as definite immunological and 83.0% as possible immunological.

Discussion

This study of the spontaneously reported suspected ADRs for biologicals in the WHO Global ICSR database, VigiBase, showed that approximately 7.0% of all case reports reported to VigiBase in the period from January 1995 to December 2008 concerned biologicals (vaccines were excluded from the analysis). Patients treated with biologicals for whom a suspected ADR was reported were, in general, younger than patients treated with the drugs in the reference group. This might have influenced the nature of the reported events for instance because older patients are more likely to develop various diseases related to their age. On the other hand, biologicals are often used to treat severe and/or life-threatening diseases,[1] which might have shifted the reporting of suspected ADRs to more serious events influencing the nature of the reported suspected ADRs.

In the present study, approximately two-thirds of all suspected ADRs were reported for five biologicals: etanercept, interferon-β-1a, infliximab, teriparatide and adalimumab. Etanercept, infliximab and adalimumab were in the top ten biotech drugs with the highest revenues in 2008 and 2007,[24] and etanercept and infliximab were both in the top ten biotech drugs with the highest US sales in 2005 and 2006.[25] Although sales and revenues can only be considered to give an indication

Table II. Safety profile of mechanistic classes compared [proportional reporting ratio (95% CI)][a]

Mechanistic class	Infections and infestations	Neoplasms benign, malignant and unspecified	General disorders and administration site conditions	Nervous system disorders	Investigations	Gastrointestinal disorders	Others
Hormones (reference)	1 (1.0, 1.0)	1 (1.0, 1.0)	1 (1.0, 1.0)	1 (1.0, 1.0)	1 (1.0, 1.0)	1 (1.0, 1.0)	1 (1.0, 1.0)
Antibodies	3.8 (3.7, 3.9)	2.8 (2.6, 3.0)	0.8 (0.8, 0.8)	0.7 (0.7, 0.7)	0.7 (0.6, 0.7)	1.1 (1.1, 1.2)	1.0 (1.0, 1.0)
Cytokines	2.6 (2.4, 3.0)	2.2 (1.8, 2.6)	1.2 (1.1, 1.3)	0.6 (0.5, 0.6)	0.7 (0.6, 0.8)	0.8 (0.7, 0.9)	1.0 (1.0, 1.1)
Enzymes	1.5 (1.4, 1.7)	0.3 (0.3, 0.5)	0.7 (0.7, 0.7)	1.2 (1.1, 1.2)	1.2 (1.2, 1.3)	1.0 (0.9, 1.1)	1.0 (1.0, 1.1)
Growth factors	2.8 (2.2, 3.5)	0.4 (0.2, 1.1)	1.4 (1.2, 1.6)	0.7 (0.6, 0.9)	0.2 (0.1, 0.3)	0.8 (0.7, 1.1)	1.1 (0.9, 1.2)
Interferons	2.2 (2.1, 2.3)	2.4 (2.3, 2.6)	0.8 (0.8, 0.8)	1.6 (1.6, 1.7)	0.6 (0.6, 0.6)	0.8 (0.8, 0.9)	0.9 (0.9, 0.9)
Receptors	4.4 (4.2, 4.6)	1.9 (1.7, 2.0)	1.5 (1.5, 1.6)	0.7 (0.7, 0.7)	0.3 (0.3, 0.4)	0.9 (0.8, 0.9)	0.7 (0.7, 0.7)

a Suspected adverse drug reactions classified according to the Medical Dictionary for Regulatory Activities (MedDRA®) version 12.0.

of the actual number of users, it is interesting to note that other biologicals that have been in the top ten selling biotech drugs for the last 4 years, e.g. bevacizumab, rituximab (which was approved in the same year as interferon-β-1a) and pegfilgrastim (which was approved in the same year as adalimumab) are not among the five most reported biologicals.[24,25] Teriparatide, on the contrary, was approved in the US and EU around the same time as adalimumab and is not included in the top ten selling biologicals but is included in the top five products for which most suspected ADRs were reported to VigiBase. Within this context one should take into consideration the benefit-risk balance of the drug and the number of patients exposed and should not only rely on the number of suspected ADRs reported. In general, more serious ADRs are accepted for drugs used to treat serious and/or life-threatening conditions than for drugs used to treat less serious conditions.

In our study, the nature of the suspected ADRs reported for biologicals differed from that of the reference group. For biologicals, suspected ADRs related to 'infections', 'surgical and medical procedures', 'neoplasms', 'general disorders and administration site conditions', and 'respiratory, thoracic and mediastinal disorders' were more frequently reported than for the reference group. It is known from previous studies that infections in connection with the use of biologicals with an immunosuppressive action are important complications to be identified and communicated to healthcare professionals in the postmarketing setting.[7,26,27] Biologicals are mostly administered by the parenteral route of administration, which makes these drugs more likely to cause infusion-like reactions and difficulties with their administration. Suspected ADRs related to infusion-like reactions are mostly classified in the SOC 'General disorders and administration site conditions'. The more frequent reporting of suspected ADRs in the SOC 'Respiratory, thoracic and mediastinal disorders' might be due to non-specific symptoms resulting from an immunological process, such as dyspnoea, asthma and shortness of breath. For the reference group, suspected ADRs related to 'Psychiatric disorders', 'Vascular disorders', 'Pregnancy, puerperium and perinatal conditions', 'Reproductive system and breast disorders', and 'Social circumstances' were more frequently reported. The low PRR calculated for the SOC 'Psychiatric disorders' could be explained by the reduced likelihood of biologicals to cross the blood-brain barrier due to their high molecular weight[28] limiting their effects on the CNS. Two of five of the SOCs in which suspected ADRs were more frequently reported for the reference group concerned suspected ADRs related to pregnancy and the reproductive system, which shows that ADRs related to pregnancy and the reproductive system are more frequently reported for the reference group. This might possibly be due to the reluctance of healthcare professionals to administer biologicals to pregnant women because of these agents being a relatively new class of drugs limiting their exposure and/or suspected ADRs related to pregnancy being more frequently reported for the reference group. A previous study, in which mostly small molecules were included, found that black-box warnings concerning risk in pregnancy were issued for 11% of the total number of black-box warnings issued. Risk in pregnancy was the fourth most frequent drug-related safety problem that triggered a black-box warning.[8] It was found that suspected ADRs for biologicals were more frequently reported in the SOC 'Surgical and medical procedures' and suspected ADRs for the reference group were more frequently reported in the SOC 'Social circumstances'. In this context it is important to note that the total number of suspected ADRs reported in these SOCs was less than 1.2% of the total number of ADRs reported, and it can be debated if events classified in these SOCs should be considered suspected ADRs. However, since the ADRs classified in these SOCs were considered to be related to the use of a specific biological or drug by the reporter it was decided to include the suspected ADRs reported in these SOCs in the study.

The SOCs in which suspected ADRs are most frequently reported for biologicals might include some important potential safety signals, which need to be studied in more depth during future studies. The example of tuberculosis with the use of infliximab[14] has already been discussed but it seems likely that there might be other specific

safety signals for a biological or a group of biologicals within the SOC 'Infections and infestations'. The PRR of the SOC 'Neoplasms benign, malignant and unspecified' changed from 2.1 to 1.3 after the five biologicals most frequently implicated were not included in the dataset. This suggests that neoplasms are relatively frequently reported for (some of) these five active substances, which need to be elucidated further. A recent report referred to 121 case reports in VigiBase of leukaemia during the use of the tumour necrosis factor-α antagonists adalimumab, etanercept and infliximab,[29] which are all among the five biologicals most frequently implicated.

Our previous study showed that safety-related regulatory actions for biologicals were most frequently issued in the SOCs 'General disorders and administration site conditions', 'Infections and infestations', 'Immune system disorders' and 'Neoplasms benign, malignant and unspecified'.[7] The present study showed that suspected ADRs were most frequently reported in the SOC 'General disorders and administration site conditions' (20.8% of the total number of suspected ADRs reported for biologicals) [table I] and also that suspected ADRs in the SOC 'Infections and infestations' (8.7% of the total number of suspected ADRs reported for biologicals) were frequently reported. 'Neoplasms benign, malignant and unspecified' frequently triggered a safety-related regulatory action, but this SOC was only reported in 2.3% of the suspected ADRs reported for biologicals. However, a safety-related regulatory action is issued after a balanced assessment by the regulatory authorities and the need to inform healthcare professionals.[7] Because of their seriousness, safety issues related to neoplasms frequently trigger a safety-related regulatory action. In the current study, only 0.9% of the suspected ADRs were reported in the SOC 'Immune system disorders'. This might be explained by the reporting of less specific suspected ADRs, which are related to immunological events that are classified in different SOCs.

Results from the stratification of biologicals according to their mechanistic class suggest that pharmacovigilance could be targeted towards specific potential safety concerns for these subclasses, and these potential safety concerns should be specifically studied in the preregistration clinical trials, although the limitations of clinical trials should always be taken into account.[6] 'Infections and infestations' are, for example, frequently reported for antibodies and receptors. These findings might imply that infections should specifically be addressed in the pharmacovigilance plan of a new biological with an immunosuppressive mode of action, which often include biologicals classified in the mechanistic classes of antibodies and receptors. Due to the characteristic of biologicals that safety problems can often be related to an exaggerated pharmacology,[4] mode-of-action-driven safety assessment is important for biologicals and can lead to the prediction of potential safety problems. Many antibodies have, for example, an immunosuppressive effect, giving rise to infections.[30-32] A classification system for biologicals according to their pharmacology was recently proposed;[33] however, a more indepth classification of biologicals according to their specific pharmacology, e.g. depletion of B and/or T cells, seems to be relevant. This is important for the safety assessment of new biologicals to be approved in a specific class, but before this can be established, knowledge on how certain ADRs are related to the immunology of the human body should be obtained.

To our knowledge, this is the first study in which general characteristics of spontaneously reported suspected ADRs of biologicals are described in a broader perspective without the primary objective of finding potential safety signals for a specific active substance. This study, therefore, adds important information to the knowledge on the safety profile of biologicals. However, several potential limitations with this study need to be addressed. First, data was obtained from a spontaneous reporting system without additional causality assessment or qualitative verifications by the authors. Second, underreporting of suspected ADRs is a well recognized problem and is estimated to be in excess of 90%.[12] In addition, potential difficulties in the causality assessment of spontaneous reports of biologicals are expected. Biologicals are often indicated to treat severe and/or life-threatening diseases, patients

treated with biologicals are often (pre)treated with multiple other drugs and/or suffering multiple other diseases,[1] and a relationship between intake of the drug and occurrence of the suspected ADR is often difficult to assess. Treatment with rituximab, for example, results in a depletion of B cells and it is known that it takes about 9–12 months before there is complete B-cell repletion.[34] Suspected ADRs occurring, for example, 6 months after treatment with rituximab is stopped might still be related to the previous treatment with the biological. In addition, at least 1.7% of the case reports in VigiBase were estimated to be duplicate reports,[35] which is especially a problem during signal detection. Since our study is descriptive in nature we feel that duplicate reports will not have a major impact on our results. Third, we found that about two-thirds of all suspected ADRs were reported for only five biologicals. This limits the generalizability of the results since these five biologicals have a large impact on the overall safety findings of the biologicals and it was shown that some results were altered after these five drugs were removed from the analysis. This should be taken into consideration during future analysis in VigiBase since these five drugs might distort the relation studied. This will mainly be a problem in case of quantitative signal detection and not necessarily in the event of the traditional case-by-case approach. Fourth, confounding by indication might have influenced the result. Biologicals are often indicated to treat serious and/or life-threatening diseases[1] and these patients might be more susceptible for the occurrence of suspected ADRs that are disease related. In addition, the nature of the suspected ADRs might also be influenced by the indication for which the drug was used, as shown by the high number of cases of multiple sclerosis (MS), which were mostly reported for interferon-β-1a. The cases of MS reported are likely to be due to disease progression or ineffectiveness of the administered drug instead of a suspected ADR. In addition, biologicals used to treat rheumatoid arthritis are, for example, related to the occurrence of infections. However, these patients already have an increased risk for infections.[16] This underlines the need to carefully think of a representative reference group during safety studies based on patient, disease and drug characteristics.

In this study, suspected ADRs were classified according to MedDRA® terminology. Recently, a novel classification of suspected ADRs for biologicals based on mechanistic considerations was proposed. Although the author states that the classification needs to be evaluated in daily clinical care of patients,[21] this approach might improve signal detection and the ability to predict potential suspected ADRs for biologicals.

Conclusions

This study showed that in countries around the world the number of spontaneously reported suspected ADRs is increasing over time for all drugs, including biologicals, underlining the importance of these data sources for signal detection and hypothesis generation. However, during signal detection with biologicals in the WHO ADR database, VigiBase, one should be aware that five biologicals comprise two-thirds of the reported suspected ADRs, which might distort the relation found between a specific biological and a specific suspected ADR in the case of quantitative signal detection. Therefore, it is necessary to carefully consider the reference group to be used. In addition, causality assessment is expected to be complicated for biologicals.

Our study showed that the safety profile of biologicals and small molecules differed based on spontaneously reported suspected ADRs and that case reports of suspected ADRs to biologicals or classes of biologicals often refer to only a few SOCs, for instance infections with the use of immune suppressants (e.g. antibodies and receptors). This knowledge can be used in targeted preregistration clinical trials and in proactive pharmacovigilance activities to study particular safety issues and safeguard public health earlier and more effectively. In addition, since not all adverse reactions can be predicted or detected during development, spontaneous reporting remains an important tool for the early detection of signals of unexpected adverse reactions, interactions or other problems related to the use of biologicals.

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