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Safety Profile of Biological Drugs in Clinical Practice: A Retrospective Pharmacovigilance Study

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Abstract

Biological drugs have an active substance that is made by a living organism or derived from a living organism. They are one of the important therapy options used in a wide range of diseases especially life-threatening diseases. Biological therapy opens new opportunities for treating different diseases for which drug therapy is minimal, but they have considerable differences in the safety consequences in comparison with non-biological drugs. The aim of the current study was to assess the post-marketing safety profile of biological drugs used in Iraqi hospitals by the analysis of the reported adverse drug reactions regarding their severity, seriousness, preventability, expectedness, and outcome. It is a retrospective study of the individual case safety reports from the Iraqi Pharmacovigilance Center/Ministry of Health. There were 446 individual case safety reports in the research, involving 899 adverse drug reactions. Rituximab was found to be the drug with the highest number of adverse drug reactions with 241 adverse drug reactions (26.81% out of total adverse drug reactions). Most of the adverse drug reactions were related to general disorders and administration site conditions (22.25%). Regarding severity of adverse drug reactions, the majority of adverse drug reactions were observed in moderate levels [Level 4 (26%), and Level 3 (18%)]. The severe adverse drug reactions in patients below 18 years age group were significantly higher compared to adults and elderly. Seriousness assessment showed that the majority of adverse drug reactions were serious (52%). Rituximab was the drug for which the highest number of serious adverse drug reactions was reported (41.28% of total serious adverse drug reactions), Most of the adverse drug reactions (66%) were probably preventable. Fatality outcome was reported for 3% of adverse drug reactions while 43% of adverse drug reactions were recovered/resolved.

Keywords: Safety profile, Adverse drug reactions, Iraqi pharmacovigilance center, Biological Drugs.

سلامة الادوية البايولوجية في الممارسة السريرية: دراسة استرجاعية لليقظة الدوائية

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الخلاصة

العقاقير البايولوجية هي الأدوية التي تتكون مادتها الفعالة من كائن حي أو مشتقة من كائن حي وهي واحدة من خيارات العلاج الهامة المستخدمة في مجموعة واسعة من الأمراض وخاصة الأمراض التي تهدد الحياة. يفتح العلاج البايولوجي فرصًا جديدة لعلاج الأمراض المختلفة التي يكون العلاج الدوائي فيها ضئيلًا ، لكن لها اختلافات كبيرة في عواقب السلامة مقارنة بالأدوية غير البايولوجية. الهدف من الدراسة الحالية هو تقييم برنامج الأمان بعد التسويق للأدوية البيولوجية المستخدمة في المستشفيات العراقية من خلال تحليل التفاعلات الدوائية الضارة المبلغ عنها فيما يتعلق بشدتها ، وخطورتها ، وإمكانية الوقاية منها ، والتوقع ، والنتيجة. الدراسة ذات أثر رجعي لتقارير سلامة الحالات الفردية من مركز التيقظ الدوائي العراقي / وزارة الصحة. كان هناك ٤٤٦ تقرير لحالة السلامة الفردية في البحث ، بما في ذلك ٨٩٩ تفاعل دوائي ضار. وجد أن ريتوكسيماب هو الدواء الذي يحتوي على أكبر عدد من التفاعلات الدوائية الضارة مع٢٤١تفاعل دوائي ضار (٢٦,٨١٪ من إجمالي التفاعلات الدوائية الضارة). كانت معظم التفاعلات الدوائية الضارة مرتبطة باضطرابات عامة و اضطراب موضع الحقن (٢٢,٢٥٪). فيما يتعلق بشدة التفاعلات الدوائية الضارة ، لوحظت غالبية التفاعلات الدوائية الضارة في مستويات معتدلة [المستوى ٤ (٢٦٪) ، والمستوى ٣ (١٨٪) كانت التفاعلات الدوائية الضارة الشديدة في المرضى الذين تقل أعمارهم عن ١٨ عامًا أعلى بشكل ملحوظ مقارنة بالبالغين وكبار السن. أظهر تقييم الخطورة أن غالبية التفاعلات الدوائية ا الضارة كانت خطيرة (٥٢٪). كان ريتوكسيماب هو الدواء الذي تم الإبلاغ عن أكبر عدد من التفاعلات الدوائية الضارة الخطيرة (٤١,٢٨٪ من إجمالي التفاعلات الدوائية الضارة الخطيرة) ، وربما كان من الممكن الوقاية من معظم التفاعلات الدوائية الضارة (٦٦٪). تم الإبلاغ عن نتيجة الوفيات لـ ٣٪ من التفاعلات الدوائية الضارة بينما ٤٣٪ من التفاعلات الدوائية الضارة تم معالجتها.

الكلمات المفتاحية : سلامة الادوية ، التفاعلات الدوائية الضارة ، مركز اليقظة الدوائية العراقي ، الأدوية البايولوجية.

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Introduction

Pharmacovigilance is defined by the World Health Organization (WHO) as "the science and activities related to the detection, assessment, understanding, and prevention of adverse effects and other drug related safety problems".

Pharmacovigilance is aimed to avoid the adverse reactions of drugs that may occur in humans during the life cycle of these drugs. Furthermore, pharmacovigilance includes identifying prescription errors, a lack of effectiveness data, off-label use, acute and chronic toxicity, drug-related mortality evaluation, drug abuse and misuse, and adverse drug interactions with chemicals and other medications [(1)]. A pharmacovigilance research may be clinical, epidemiological, experimental (such as detecting an adverse effect in animals and establishing the mechanism required for human protection), or diagnostic (based on imputable methods). As a result, pharmacovigilance is a tool for specifically describing and optimizing a drug's benefit/risk ratio throughout its life cycle [(2)]. The International Conference of Harmonization (ICH) guidelines for Good Clinical Practice (GCP) had defined Adverse Drug Reactions as "any response to any medicinal product which was noxious and unintended and occurs at doses normally used in humans for prophylaxis, diagnosis or therapy of disease or the modification of physiological function which includes the terms out of marketing authorization such as off-label uses, overdose, misuse, abuse, and medication errors" [(3)].

Biological drugs are an effective treatment choice for a variety of diseases, especially those that are life-threatening. Biological medicinal products have an active ingredient that was produced or derived from a biological source. These include medicinal substances derived from living-cells or organisms. "Biologics include a wide variety of molecules, e.g., hormones, growth factors, interleukins, monoclonal antibodies, which differ in size and structural complexity (e.g., their molecular mass ranges from 5 kDa for insulin to more than 150 kDa for monoclonal antibodies)" [(4)].

In most countries, the production and use of biological drugs is booming, as these drugs provide new therapeutic options for diseases for which drug therapy is restricted. They are a clinical innovation, but they also reflect an unknown environment with negative side effects and events that endanger patient safety [(5)]. Adverse events associated with these agents are typically attributable to an increase in documented pharmacologic activities, such as the risk of infections and malignancies, or to immunologic and infusion reactions, such as the production of anti-drug antibodies as a result of the protein nature of these agents [(6)]. Many biologics, such as monoclonal antibodies, have a longer half-life and duration of action than small molecules. They are usually injectable medications that can cause mild cutaneous or hypersensitivity reactions. Since biologics may trigger immune reactions including mild hypersensitivity, infusion reactions, and cross-reactions with endogenous molecules, immunogenicity is a major safety concern. This may result in a loss of efficacy or deficiency syndromes (e.g., thrombocytopenia as a result of neutralizing antibodies blocking endogenous thrombopoietin after treatment with recombinant thrombopoietin or neutralizing antibodies with human growth hormone) [(7)].

Biological drugs can cause certain immune responses by producing "anti-drug" antibodies. Specific adverse effects are related to several biological drugs due to their mechanism of action. This motivated the researchers to further evaluate the benefit/risk ratio of these drugs [(8)]. Biological drugs have specific characteristics that include a complicated manufacturing procedure, restricted evaluation of the preclinical to clinical data, and increased possibility of immunogenicity. For biological drugs, as well as for all drugs, pharmacovigilance is necessary to discover, detect, and characterize the adverse drug effects in the post-marketing safety profile due to the inherent limitations of clinical trials [(9)].

The most prevalent suspected adverse drug reactions (ADRs) for biologics, according to a Vigibase study, were "infections and infestations," "surgical and medical procedures," and "neoplasms benign, malignant, and unspecified." [(10)]. In the Italian Spontaneous Reporting System, administration-site conditions, infections, and neoplasms were more likely to be diagnosed with biologics than with non-biologics[8]. Because of the inclusion criteria and limited sample size in pre-marketing clinical trials, rare and unexpected adverse effects are difficult to identify. Furthermore, biological drugs may be associated with adverse effects (AEs) that are unrelated to their mechanism of action, such as the production of anti-drug antibodies [(11)].

Minor variability (microheterogeneity) is possible but must be kept within acceptable limits to ensure positive benefit-risk profiles in biologics generated with recombinant DNA technology. Even within or between batches of the same biologic, microheterogeneity can be observed, particularly when the manufacturing process is modified, as it may be during the drug's commercial lifespan. "Natural variability is intrinsic to all biologics, and strict controls are often in place during processing to ensure that it does not impact the way the drug functions or its protection" according to the European Medicines Agency (EMA)[(4)]. The aim of the current study was to determine the safety profile of biological drugs used in Iraqi public hospitals by evaluating the ADRs that occur with these drugs (regarding their severity, seriousness,

preventability, expectedness, and outcome) using the Iraqi Pharmacovigilance Center (IPVC) database.

Materials and Methods

Individual case safety reports (ICSRs) submitted to the Iraqi Pharmacovigilance Center / Ministry of Health are the subject of this review, which is a retrospective analysis (Sent from 2009 to the end of 2020). Before beginning the report, the Iraqi Ministry of Health/Department of Research and Development and the College of Pharmacy/University of Baghdad's scientific committees gave their approval. The data source is Vigiflow – Iraq. Vigiflow is a database that belongs to Uppsala Monitoring Center (UMC) that is a WHO collaborating center for ADRs from many national centers around the world [(12)].

The inclusion criteria were to choose all the ICSRs for biological drugs available in the Vigiflow – Iraq database. Exclusion criteria were duplicated reports and non-relevant reports (medication error, and not mentioning the ADRs). The ICSRs included in the study were analyzed for demographic distribution, ADRs Classification, severity, expectedness, preventability, seriousness, and outcomes. Age distribution was: neonate (4 weeks), child (1-12 years), adolescent (13-18 years), adult (over 18 years), and elderly (over 65 years) [(13)].

The ADRs were listed using the System Organ Classification (SOC), which categorizes adverse reactions according to the affected system-organ [(14)]. The severity was assessed using the modified Hartwig and Seigel severity scale (Table 1) [(15)]. It classified ADRs into seven severity categories. Levels 1 and 2 are considered mild, Levels 3 and 4 are considered moderate, and Levels 5, 6, and 7 are considered severe[(16)]. The SmPC for medicinal drugs, which is a primary reference guide that advises healthcare professionals on how to use the medicinal product safely and effectively, is used to assess the expectedness of ADRs [(17)]. As a result, ADRs were categorized as "expected" if they were mentioned in the SmPC and "unexpected" if they were not [(18)].

The Schumock and Thornton criteria (Table 2) were used to determine whether ADRs could be prevented. This criterion has three parts in its updated form: preventable, probably preventable, and non-preventable. Section A comprises five questions while section B has four questions. All the answers are categorized as "Yes" or "No". ADRs were "definitely preventable" if the answer was "yes" to one or more questions in section A. If answers were all negative, then we proceeded to section B. ADRs were "probably preventable" if the answer was "yes" to one or more questions in section B. If answers were all negative, then we proceeded to section C. In Section C the ADRs were non-preventable [(19)].

The seriousness was determined using guidelines established by the national pharmacovigilance center or regional centers located in health directorates in Iraq. These criteria are available in the ICSR, which is a paper reporting format for all ADRs encountered in Iraqi hospitals. If the included seriousness in the ICSR was correct, the seriousness was selected; otherwise, the seriousness was evaluated by the researcher (Figure 1) [(20)]. According to the WHO, the outcome of each ICSR was registered and classified into one of the following categories: (1) recovered / resolved, (2) recovering /resolving, (3) not recovered/not resolved / ongoing, (4) recovered / recovered with sequelae, (5) fatal, and (6) unknown in the case of missing details [(12)].

Table 1. The modified Hartwig and Seigel severity scale [(15)].

Level of severity	The criteria
Level 1	An ADR occurred but required no change in treatment with the suspected drug
Level 2	The ADR required that treatment with the suspected drug be held, discontinued, or otherwise changed. No antidote or other treatment requirement was required. No increase in LOS.
Level 3	The ADR required that treatment with the suspected drug be held, discontinued, or otherwise changed. AND/ OR an Antidote or other treatment was required. No increase in LOS
Level 4	Any Level 3 ADR which increases length of stay by at least 1 day. OR The ADR was the reason for the admission.
Level 5	Any Level 4 ADR which requires intensive medical care.
Level 6	The adverse reaction caused permanent harm to the patient.
Level 7	The adverse reaction either directly or indirectly led to the death of the patient.

ADR: adverse drug reaction**; LOS**: length of stay

Table 2. Schumock and Thornton preventability assessment criteria [19].

	Question	Yes	No
Section A: Definitely Preventable ADR			
1	Was there a history of allergy or previous reaction to the drug?		
2	Was the drug involved inappropriate for patient's Clinical Condition?		
3	Was the dose, route, or frequency of administration inappropriate for the patient's age, weight or disease state?		
4	Was a toxic serum concentration or a laboratory monitoring test documented?		
5	Was there a known treatment for ADR?		
Section B: Probably Preventable ADR			
6	Was there any required therapeutic drug monitoring, or other laboratory tests not performed?		
7	Was a drug interaction involved in the ADR?		
8	Was poor compliance involved in the ADR?		
9	Were preventative measures not prescribed or administered to the patient?		
Section C: Non-Preventable ADR			
10	If all the above criteria not fulfilled		

ADR: adverse drug reaction

Do you consider the reaction to be serious? Yes ☐ No ☐	
If yes, please tick (✓) to indicate why the reaction is considered to be serious:	
☐ The patient died due to the reaction	☐ Involved or prolonged inpatient hospitalization
☐ Life threatening	☐ Involved persistent or significant disability or incapacity
☐ Congenital anomaly	☐ medically significant, please give details:
Treatment given: No ☐	☐ Yes (please specify):----------

Figure 1. Seriousness assessment in the Individual Case Safety Report [20].

Statistical analysis

The extracted data from the ICSR reports was arranged in Excel spreadsheets, then the parameters' criteria were applied, and the findings were displayed in bar charts, before being statistically analyzed with the "Statistical Package for the Social Sciences (SPSS) program" version 26. Descriptive statistics were used to quantify the frequency and the percentage of each ADR reported and the Chi-square test "to demonstrate the significance of the relations between gender and age group with the severity, seriousness and outcome of the ADRs. The P-value for the data sets were calculated and the value of less than 0.05 was considered a statistically significant relation.

Results

During the study period, a total of 899 ADRs (from 446 ICSR reports) were reported corresponding to 15 biological drugs. The ICSRs analysis showed that reports for the female gender were more than the reports for the male gender (60.09% females' reports versus 31.61% males' reports, and 8.30% of the reports had no information for the gender). Regarding age group, the ICSRs were assessed to the following categories: Adult 291(65.25%), Unknown 110 (24.66%), Elderly 28 (6.28%), Child 9 (2.02 %), Adolescent 7 (1.57 %) and Neonate 1(0.22%), respectively. Pharmacists were responsible for the majority of the reports, with 215 (48.21% of total reports) (Table 3).

Regarding the frequencies of ADRs and ICSRs for each of the 15 biological drugs, the highest number ADRs was for Rituximab with 241 ADRs (26.81%) while the highest number of ICSRs was for Interferon beta-1a with 112 reports (25.11%) (Table 4).

According to ADRs classification based on the SOC system. It was found that most of the ADRs were related to general disorders and administration site conditions with 200 ADRs (22.25%), followed by skin and subcutaneous tissue disorders with 126 ADRs (14.02%), respiratory, thoracic and mediastinal disorders with 114 (12.68%), and gastrointestinal disorders with 98 ADRs (10.90%) as shown in (Table 5).

Table 3. Age group, gender, and reporter qualification distribution of ICSRs.

Gender	**Number of ICSRs (%)**
Female	268 (60.09 %)
Male	141(31.61%)
N/A	37 (8.3%)
Age group	**Number of ICSRs (%)**
Adult	291(65.25%)
Unknown	110 (24.66%
Elderly	28 (6.28%)
Child	9 (2.02 %)
Adolescent	7 (1.57 %)
Neonate	1(0.22%)
Reporter Qualification	**Number of ICSRs (%)**
Pharmacist	215 (48.21%)
Consumer or other Non-Health Professional	104 (23.32%)
Physician	68 (15.25%)
Other Health Professional	59 (13.23%)

N/A : Not Available , ICSR: Individual Case Safety Report

Table 4. ICSRs and ADRs for each of the biological drugs.

Drug Name	**ADRs No. & (%)**	**ICSRs No. & (%)**
Rituximab	241 (26.81%)	91 (20.4%)
Interferon beta-1a	200 (22.25%)	112 (25.11%)
Infliximab	113 (12.57%)	70 (15.7%)
Trastuzumab	101 (11.23%)	51 (11.43%)
Etanercept	70 (7.79%)	47 (10.54%)
Filgrastim	45 (5.01%)	25 (5.61%)
Bevacizumab	35 (3.89%)	14 (3.14%)
Bortezomib	29 (3.23%)	12 (2.69%)
Epoetin alfa	22 (2.45%)	12 (2.69%)
Interferon alfa 2b	20 (2.22%)	1 (0.22%)
Interferon beta1b	9 (1%)	5 (1.12%)
Natalizumab	6 (0.67%)	2 (0.45%)
Adalimumab	5 (0.56%)	2 (0.45%)
Peginterferon alfa 2a	2 (0.22%)	1 (0.22%)
Aflibercept	1 (0.11%)	1 (0.22%)
Total	**899 (100%)**	**446 (100%)**

Table 5. ADRs classification based on the SOC system.

ADRs in System Organ Classification	**Number & (%) of ADR**
General disorders and administration site conditions	200 (22.25%)
Skin and subcutaneous tissue disorders	126 (14.02%)
Respiratory, thoracic and mediastinal disorders	114 (12.68%)
Gastrointestinal disorders	98 (10.90%)
Nervous system disorders	86 (9.57%)
Musculoskeletal and connective tissue disorders	48 (5.34%)
Immune system disorders	38 (4.23%)
Investigations (e.g., Ejection fraction decreased)	30 (3.34%)
Infections and infestations	25 (2.78%)
Cardiac disorders	23(2.55%)
Eye disorders	20 (2.22 %)
Surgical and medical procedures	17 (1.89%)
Injury, poisoning and procedural complications	15 (1.67%)
Psychiatric disorders	13 (1.45%)
Renal and urinary disorders	12 (1.33%)
Neoplasms benign, malignant and unspecified (including cysts and polyps)	9 (1.00%)
Blood and lymphatic system disorders	8 (0.88 %)
Metabolism and nutrition disorders	8 (0.89%)
Hepatobiliary disorders	3 (0.33%)
Product issues (Suspected counterfeit product)	2 (0.22%)
Social circumstances	2 (0.22%)
Ear and labyrinth disorders	1(0.11%)
Reproductive system and breast disorders	1 (0.11%)
Congenital , familial and genetic disorders	0 (0%)
Endocrine disorders	0 (0%)
Pregnancy, puerperium and perinatal conditions	0 (0%)

Regarding severity of ADRs, the majority of ADRs were observed in Level 4 (26%), followed by Level 3 (18%) and Level 2 (13%) . With respect to expectedness of the ADRs, the expected ADRs represented 68% while the unexpected ADRs counted for 32% of the total ADRs. Concerning preventability assessment of ADRs, more than half (66%) of the ADRs were probably preventable, 4% were preventable, and 30% were non-preventable. Seriousness assessment showed that serious ADRs account for the majority of the ADRs with 52% of the ADRs, while non-serious ADRs were 46% for

the encountered drugs. Only 2% of the ADRs were missing some data to assess their seriousness and are presented in the N/A (Not Available) category. Outcome analysis of the ADRs showed that in 44% of the cases the outcome was unknown, and most of the ADRs were in the recovered category with 43% as illustrated in (Table 6).

The relation between the severity of the reported ADRs to the gender of the patients were tested. It was found that there is a significant relation between the severity level of the ADRs and the gender of the patients as shown in (Table 7). The mild ADRs were significantly higher in male patients, while moderate ADRs were significantly higher in females. There is no significant difference in severe ADRs between male and female. The relation between the severity of the ADRs and the age of the patients were also tested. The severe ADRs in patients below-18 age group was significantly higher and the mild ADRs was significantly lower compared to adults and elderly (Table 8).

Rituximab was the drug for which the highest number of serious ADRs was reported with 194 serious ADR (41.28% of total serious ADRs), followed by trastuzumab with 76 serious ADR (16.17% of total serious ADRs) and infliximab with 59 serious ADR (12.55% of total serious ADRs) as shown in (Table 9).

Table 6. Severity levels, expectedness, preventability and outcome of ADRs reported for biological drugs.

Severity assessment	**Number of ADRs (%)**
Level 1	80 (9%)
Level 2	117 (13%)
Level 3	164 (18%)
Level 4	236 (26%)
Level 5	11 (1%)
Level 6	10 (1%)
Level 7	37(4%)
Under assessment	244 (27%)
Expectedness	**Number of ADRs (%)**
Expected	610 (68 %)
Unexpected	289 (32 %)
Preventability	**Number of ADRs (%)**
Probably Preventable	593 (66%)
Non-Preventable	296 (30%)
Preventable	37 (4%)
Outcomes	**Number of ADRs (%)**
Unknown	397(44%)
Recovered	383(43%)
Recovering	45(5%)
Not Recovered / Ongoing	39(4%)
Fatal	29(3%)
Recovered with Sequelae	6(1%)

Table 7. Severity levels distribution among gender.

Severity / Gender		**Male**	**Female**	**P-Value**
Mild	Count & % within gender	93 (41.52%)	92 (24%)	**0.00000621***
Moderate	Count & % within gender	106 (47.32%)	263 (68.67%)	**0.0000002***
Severe	Count & % within gender	25 (11.16%)	28 (7.31%)	0.10492778

*Significant (P-value <0.05) according to Chi square test.

Table 8. Severity levels distribution among age groups.

Severity / Age group		**Below 18**	**Adult**	**Elderly**	**P-Value**
Mild	**Count & % within Age group**	**7 (12.5%)**	**160 (33.4%)**	**22 (33.33%)**	**0.006***
Moderate	**Count & % within Age group**	**36 (64.285%)**	**284 (59.29%)**	**40 (60.6%)**	**0.765**
Severe	**Count & % within Age group**	**13 (23.214%)**	**35 (7.3%)**	**4 (6.06%)**	**0.0002***

*Significant (P-value <0.05) according to Chi square test.

Table 9. Seriousness of the ADRs.

Drug Name	Yes No. & (%)	No No. & (%)	N/A No. & (%)
Rituximab	194 (41.28%)	39 (9.42%)	8 (53.33%)
Trastuzumab	76 (16.17%)	22 (5.31%)	3 (20.00%)
Infliximab	59 (12.55%)	54 (13.04%)	0 (0.00%)
Etanercept	38 (8.09%)	32 (7.73%)	0 (0.00%)
Bortezomib	22 (4.68%)	5 (1.21%)	2 (13.33%)
Bevacizumab	19 (4.04%)	16 (3.86%)	0 (0.00%)
Filgrastim	19 (4.04%)	26 (6.28%)	0 (0.00%)
Interferon beta-1a	14 (2.98%)	185 (44.69%)	1 (6.67%)
Epoetin alfa	13 (2.77%)	9 (2.17%)	0 (0.00%)
Interferon alfa 2b	6 (1.28%)	14 (3.38%)	0 (0.00%)
Natalizumab	4 (0.85%)	1 (0.24%)	1 (6.67%)
Interferon beta1b	3 (0.64%)	6 (1.45%)	0 (0.00%)
Peginterferon alfa 2a	2 (0.43%)	0 (0.00%)	0 (0.00%)
Adalimumab	1 (0.21%)	4 (0.97%)	0 (0.00%)
Aflibercept	0 (0.00%)	1 (0.24%)	0 (0.00%)
Total	**470 (52.28 % of total ADRs)**	**414 (46.05% of total ADRs)**	**15 (1.67% of total ADRs))**

N/A : Not Available

Discussion

Awareness about clinical information of side effects secondary to biologic agents will improve the use of biologic agents and improve outcomes of patients. Biological drugs require special pharmacovigilance considerations, and more regular monitoring to ensure their efficacy and safety [(21)]. Biological drugs are more commonly associated with adverse events than synthetic drugs (approximately 20% of existing drugs are biological drugs), some of which are serious and even lethal [(22, 23)]. According to the findings of this research, ADRs associated with biological drugs were more prevalent among female patients. A similar trend in results was recorded in previous studies such as a study conducted in Spain and found that 82.9% of ADRs were reported in females [(24)]. Another research in the United States discovered that females recorded 75.5 % of ADRs [(25)], and in Italy, studies found that 54.3% [(26)] and 71.3% [(8)] of ADRs were associated with females. Females are at an elevated risk for a variety of causes, including gender-related variations in pharmacokinetics, immunological, and hormonal factors, as well as differences in drug usage by females versus males [(27)].

Analyzing the ADRs of biological drugs with the consideration of patients' age showed that the main age group in the reported ADRs was in adults followed by the elderly. This may be due that the use of biologics in the pediatric population is still limited because of unknown long-term safety profile and absence of large-scale studies [(28)]. The results also revealed that the reporters of the ADRs were primarily pharmacists which specifies that the pharmacovigilance responsibility in the healthcare facilities is more carried by pharmacists. Among the biological drugs related to the ADRs encountered in the present study, rituximab had 241 ADRs (26.81% of total ADRs) which probably because rituximab is one of the important drugs that is used in combination with chemotherapy and it is more effective as a first- or second-line therapy than chemotherapy alone in providing tumor remission and patient survival in the treatment of non-Hodgkin's lymphoma (NHL), Chronic Lymphocytic Leukemia (CLL). Also, it is frequently used for treating resistant and special cases of moderately to severely active rheumatoid arthritis (RA) which is prevalent in about 1% of the Iraqi population [(29)].

It is worth mentioning that the most reported ADRs in the present study were related to general disorders and administration site conditions, followed by skin and subcutaneous tissue disorders, respiratory, thoracic, and mediastinal disorders, and gastrointestinal disorders. While most ADRs recorded in other different studies were related to infections [(25, 26, 30, 31)], general disorders and administration site conditions[(32-34)], and the skin or

subcutaneous tissues[8, 32-35]. Injection site reactions (ISRs) are a local phenomenon defined as a constellation of symptoms, including swelling, erythema, pruritus, and pain around the site of injection. ISRs are major complications of all FDA-approved injectable biological agents, both in adults and children, with studies showing an incidence rate of 0.5-40% [36]. Inappropriate injection techniques, injection close to blood vessels, the chemical and physical properties of the injected drug and a reaction to the vehicle component are probable causes for the irritative reactions [37] which represent general disorders and administration site conditions.

Regarding the severity of ADRs reported in the current study, the majority of the ADRs were classified as moderate. Level 4 severity accounts for 26% of ADRs and Level 3 in 18% of the ADRs (Table 4). This type of severity necessitates a change in the drug therapy, specific treatment, or an increase in hospitalization by at least 1 day [38]. Due to intervention, the majority of ADRs were of moderate severity (Physicians were controlled the ADRs by discontinuing the offending medication. In other cases, clinical treatments were implemented using antihistamines, corticosteroids, and antidotes to relieve symptoms). The relation between the severity of the reported ADRs in this study to the gender of the patients was assessed too, and it was found that there is a significant relationship between the severity level of the ADRs and the gender of the patients (Table 5). The risk for developing moderate ADRs was more significant in females than in males (moderate ADRs in females correspond to 68.67% of total ADRs, while in males it was 47.32%). A pharmacological explanation for this may be due to lower body size, weight in females, in addition to change in absorption, protein binding, and the volume of distribution, clearance, and metabolism of drugs as well as gender-specific hormones[39]. Regarding relation between the severity of ADRs and age of the patients, the severe ADRs in patients below-18 years ago were significantly higher and the mild ADRs were significantly lower compared to adults and elderly. Adverse drug reactions in children can have a relatively more severe effect when compared to adults. Thus, the ADRs can lead to significant morbidity among children[40].

Most of the ADRs were probably preventable (66%) due to lacking data that makes it hard to assume whether it was preventable or non-preventable. The findings were like those of another study that looked at the preventability of ADRs in four South African hospitals[41], and with a meta-analysis study which also found that approximately half of the adverse drug reactions are preventable[42]. Just a small percentage of ADRs can be avoided, according to some studies [43,44].

The high proportion of expected ADRs (610 ADR that counts for 68 % of total ADRs) found in the present study is an anticipated finding since most biologicals' adverse reactions were labeled and identified in the drug description. As a result, the ADRs identified in this study were not mentioned in a significant number of SmPCs for suspected drugs. Furthermore, the ADRs mentioned in the SmPCs are not always identified using MedDRA's exact PT terminology [38]. Because of this, determining the expectedness of ADRs reported in pharmacovigilance databases is difficult.

The outcome for biologicals' ADRs was mostly recovered/resolved with 43% of ADRs. The data of ADRs outcome were missed in 44% of ICSRs (Table 4). The ADRs caused by biological drugs are mainly treatable. Premedication with corticosteroids, antihistamines, analgesics, and/or slower infusion rates are usually used to treat these forms of reactions [45]. Regarding ADRs seriousness (i.e., fatal, leading to hospitalization, life-threatening), it was found that 52.28% of total ADRs were serious and 46% were nonserious (Table 9). This result may be due to the fact that most biological drugs are used to treat extreme and/or life-threatening diseases, causing the reporting of reported ADRs to switch to more serious adverse events. Rituximab yielded the highest percentage of serious ADRs (41.28% of total serious ADRs). Rituximab is a monoclonal antibody to the B-cell marker CD20 that is commonly used (as a single agent and in combination therapy) to treat B-cell lymphoma, lymphoproliferative disorders, and inflammatory conditions that are resistant to standard care, such as rheumatoid arthritis and certain vasculitis. However, a growing number of severe adverse effects are being linked to the use of rituximab, with many patients requiring admission to an intensive care unit [46].

CD20-expressing B-cell precursors and mature B cells are rapidly depleted by this drug, and their numbers remain low for 6 to 9 months. Many studies have tried to assess immune-mediated consequences in those treated with rituximab because of its peripheral B-cell–depleting effects [47].

Finally, there are certain drawbacks to the current research that must be accepted. The involvement of confusing causes, such as underlying medical conditions and concomitant medications. Aside from the fact that a significant percentage of studies omit critical facts. All of this makes it difficult to determine whether a medication induced a particular ADR in several cases, necessitating the development of educational programs to improve the reporting system.

Conclusions

The highest number of ADRs was reported for Rituximab. Most of the reported ADRs were of moderate severity, expected, serious, probably preventable and with unknown outcomes. The missing information (especially those related to the outcomes) in the ICSRs reports had a clear negative impact on the assessment of the reports which

necessitates the development of educational programs to get a better reporting system. It is important to empower physicians and entire health teams to improve the reporting of adverse reactions and thus optimize and strengthen pharmacovigilance programs. This type of study can support decision makers in aspects that benefit patient safety and interaction with health systems.

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