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Understanding the Experience of Hospital Pharmacists with the Effectiveness, Safety, Adverse Drug Reaction Reporting and Interchangeability of Biopharmaceutical Medicines

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Abstract

The study objectives were to 1) explore the real-world experience of hospital pharmacists with the differences in effectiveness safety, and interchangeability between biosimilar medicines and their reference biological counterparts, 2) reveal pharmacist recommendations to enhance the safety of biopharmaceutical medicines in public hospitals.

The study has a mixed-method design where the core component was qualitative (interviews) and the supplemental component was quantitative (adverse drug reaction, ADR, reports). This qualitative component included semi-structured (mostly face-to-face) interviews involving hospital pharmacists from different hospitals with experience with biological or biosimilar medicines. The interviews were conducted from Nov 2020 through Feb 2021. Thematic analyses were used to analyze qualitative data generated from the interviews.

The study sample included 25 pharmacists from ten governmental hospitals in Baghdad, Iraq. The pharmacists were 21 women and 4 men. Because most pharmacists had a short experience with biosimilar medications, they were unsure about their effectiveness and safety. Most pharmacists preferred reference biological over biosimilar medicines because of their effectiveness. However, they believed that initial prescribing and switching between a reference and counterpart biosimilar rely on their availability. The pharmacists tended to underreport biopharmaceutical ADRs.

The non-sustainable supply of the same biopharmaceutical medicines in public hospitals negatively impacted pharmacist evaluation of the effectiveness and safety of biosimilar medicines. Both pharmacist interviews and the Iraqi Pharmacovigilance Center (IqPhvC) data showed under-reporting of biopharmaceutical ADRs. Medicine procurement in healthcare settings should focus on sustainably securing high-quality biopharmaceuticals rather than looking only at costs to enhance patient clinical outcomes. Providing pharmacist training, electronic reporting, promoting documentation, and following up with patients is pivotal to prevent, monitor and treat their ADRs.

Keywords: Biological medicines, Biosimilar medicines, Biopharmaceutical medicines, Hospital pharmacists, effectiveness, safety, Interchangeability, Perceptions, Qualitative study.

فهم تجارب صيادلة المستشفيات مع فعالية وسلامة والتبليغ عن التفاعلات الدوائية الضارة والتبديل للادوية البايولوجية والبدائل الحيوية

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الخلاصة

استقصاء الخبرة الواقعية لصيادلة المستشفيات حول الاختلافات في الفعالية والسلامة بين الأدوية الحيوية ونظيراتها البيولوجية المرجعية، الكشف عن توصيات الصيدلي لتعزيز سلامة الأدوية الصيدلانية الحيوية في المستشفيات العامة

تضمنت هذه الدراسة المختلطة وبشكل رئيسي جزء نوعي متمثل بالمقابلات والجزء الثاني هو تقارير التفاعلات الجانبية للأدوية البيولوجية المرسلة الى المركز العراقي لليقظة الدوائية. المقابلات كانت في غالبيتها وجهًا لوجه شملت صيادلة من مستشفيات مختلفة ممن لديهم خبرة في الأدوية البيولوجية و / أو الأدوية لحيوية. أجريت المقابلات بين تشرين الثاني ٢٠٢٠ وشباط ٢٠٢١. واستخدمت التحليلات المواضيعية لتحليل البيانات النوعية الناتجة عن المقابلات

تضمنت عينة الدراسة ٢٥ صيدلياً من عشرة مستشفيات حكومية في بغداد، العراق. كان عدد الصيادلة ٢١ امرأة و٤ رجال. وبسبب أن معظم الصيادلة لديهم خبرة قليلة مع الأدوية البايوسملر ، لم يكونوا متأكدين من فعاليتها وسلامتها. يفضل معظم الصيادلة الادوية البيولوجية المرجعية على الادوية الحيوية . ومع ذلك ، الاعتقاد أن الوصف الاول والتبديل بين الادوية البايولوجية ونظائرها الادوية الحيوية يعتمد على مدى توفرها. يميل الصيادلة إلى عدم الإبلاغ عن التفاعلات الدوائية السلبية للادوية الحيوية الصيدلانية

يجب أن يركز شراء الأدوية من قبل وزارة الصحة في أماكن الرعاية الصحية على تأمين الأدوية الحيوية عالية الجودة بطريقة مستدامة بدلاً من النظر فقط إلى التكاليف لتعزيز النتائج السريرية للمريض. يعد تعزيز التوثيق و الإبلاغ الإلكترونية ومتابعة التأثيرات االخاصة بالادوية البايولوجية أمرًا محوريًا لمنع ورصد وعلاج التفاعلات الدوائية الضارة .

الكلمات المفتاحية: الادوية البايولوجية ، الادوية الحيوية ، صيادلة المستشفيات، الفعالية، السلامة ، الاعتقاد.

Introduction

Since the development of recombinant human insulin in 1982, the use of biological medications (also called therapeutic proteins) has continued to overgrow [(1)]. Recombinant DNA (rDNA) molecules are introduced into different living systems to express proteins of therapeutic interest, termed biopharmaceuticals [(2)].

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Biopharmaceutical (reference biological and biosimilar) medicines are revolutionized medicines used to treat many serious diseases across different specialties such as cancer, rheumatoid arthritis, colitis, diabetes mellitus, Crohn's disease, anemia, immunologic diseases, osteoporosis, and other diseases [3].

Originator (also known as reference biological) medicine is a single product of the innovating company (innovator) and approved by regulatory authorities based on a full complement of safety and effectiveness data [4]. After the patent of reference, biological medicines have expired, biosimilars (similar biological medicinal products) can be authorized [3, 4]. A biosimilar is a biologic treatment manufactured by other producers from other cell lines [5]. Biosimilar medicines should be equivalent to an authorized reference product in terms of quality, safety, and effectiveness [3, 6], but they are not identical [7].

Although they have been very effective in treating certain medical conditions, many biologics are expensive. In 2019, the global biologics market was approximately $269,152.8 million, with a 12.6% increasing in a compound annual growth rate (CAGR) since 2015 [8]. Biosimilar medications may result in price reductions for reference biological medicines as they open the market to competition [9]. The manufacture of biosimilar agents is complicated by the requirement for their production in biological systems, slight variations that can influence the biosimilar products' structure, activity, and metabolism [11]. Altering the molecule structure of biopharmaceutical medicines can impact their effectiveness and safety by changing biological activity and causing immunogenicity, leading to a loss of effectiveness [12].

The published literature has raised concerns regarding the use of biosimilar medicines [13]. These concerns include a lack of confidence that biosimilar medicines can provide equivalent clinical outcomes for patients [13, 14], their indications are approved based on extrapolation of clinical data for the reference medicine, in addition to perceptions of risk in "switching" of patients already receiving a reference biologic medicine to a biosimilar medicine [13].

Iraq is one of the Middle Eastern countries that has authorized its biosimilar approval guidelines recently (2019) through the Biologics and Biosimilars Registration Committee (BBRC), which mainly relies on the European Medicines Agency (EMA) guidelines [10]. According to biosimilar guidelines, the Iraqi Ministry of Health (MOH) approved 18 biosimilar medicines within a short period [10]. The switching to biosimilar medicines could save the Iraqi health system more than 50 million dollars over several years [10].

Although there is increasing support for biosimilar medicines by the MOH, there is scarce information about whether hospital pharmacists accept these medicines and support movement toward replacing reference medicines with their biosimilar counterparts. Exploring the experience of hospital pharmacists with biopharmaceutical medications can help to evaluate their safety and effectiveness in the Iraqi public healthcare sector and send feedback to health officials to assess their policy regarding these medications.

The study objectives were to 1) explore the real-world experience of hospital pharmacists with the differences in efficacy, safety, and interchangeability between biosimilar medicines and their reference biological counterparts, and 2) reveal pharmacist recommendations to enhance the safety of biopharmaceutical medicines in public hospitals.

Methods

Study design

The study has a mixed-method design where the core component is qualitative (interviews) and the supplemental component is quantitative (IqPhvC ADR reports) [15]. The study had two sources of information: qualitative data from pharmacist interviews and the IqPhvC reports of biopharmaceutical ADRs. The reason for using two methods is "complementarity to seek elaboration, enhancement, illustration, clarification of the results" from the qualitative method with the results from the quantitative method. [15]

Qualitative source

The primary source of information included face-to-face or phone semi-structured interviews involving hospital pharmacists (from different wards) who have experience with biological and/or biosimilar medicines. The interviews were conducted from November 2020 through February 2021. The sample size relied on saturation point, which is an essential role in such studies. In other words, the researcher stopped data collection after reaching a point when new participants were repeating the same previous answers. Researchers usually define data saturation as "the point when no new information or themes are observed in the data."[16] Semi-structured interviews were conducted by an MSc candidate who is a pharmacist with 10 years of hospital experience.

Settings

Pharmacists from ten public hospitals in Baghdad participated in the study. Twenty-one interviews were conducted face-to-face in public hospitals, while four interviews were conducted via phone. Only three of them agreed to audio-record their interviews. Each interview lasted about 30-60 minutes.

Inclusion criteria

Hospital pharmacists have experience with biological and/or biosimilar medications (have dispensed them) in addition to the agreement for participation in the interviews.

Participant recruitment

Two sampling techniques were used to recruit the participating pharmacists: Purposive and snowballing. Initially, a purposive sampling of hospital pharmacists within public hospitals in Baghdad province was used. Purposive sampling was used to select "individuals that are especially knowledgeable about or experienced with a phenomenon of interest "[17, 18]. The contact information of some participants was obtained from the IqPhvC. Additionally, the researchers used snowballing technique which means the researcher asked the participants about other pharmacists interested in participating and meeting the inclusion criteria. The interviews were arranged either in-person or via phone calls and conducted by face-to-face researcher meetings at the hospitals or over the phone. The researcher targeted the pharmacists working in the included 10 hospitals, but not all of them had experience with biopharmaceutical medicines. Additionally, some who met the inclusion criteria denied participation due to their workload during working hours. The interview guide was sent to the participants via WhatsApp before the interview. The interviews continued until we reached saturation in the information.

Verbal consent was obtained from interviewees before the interviews and the comments were de-identified to keep their confidentiality. The audio recording of the interviews was voluntary. The vast majority of the face-to-face interviews have not consented to audio-record the interview. Thus, note-taking and hand-reporting were conducted by the interviewer. The interview was semi-structured with open-ended questions. Each interview was conducted in a quiet place and lasted for about 30-60 minutes. The interviews were conducted in English and Arabic (according to the participants' convenience), and then the interview transcripts were translated to English by two bilingual authors.

Thematic analyses

Thematic analyses were used to analyze qualitative data, which was generated from the interviews. The researchers extracted qualitative data from the participant comments to identify and generate themes. The researchers followed the six phases of thematic analysis described by Braun and Clarke, 2006 which include familiarizing with data (comments), generating initial codes, searching for themes, reviewing themes, defining and naming themes, and producing the report[19].

The research team cross-checked the comments. Inductive analytic methodology (data-driven) was used, and the constructivist paradigm was followed [17]. This means we did not rely on a previous framework to develop the themes, but we constructed the themes from the common trends emerging from the participant comments. The data item was each sentence within the participant comments. Finally, to enhance the credibility and trustworthiness of the findings, peer checking/debriefing was performed two times to validate the qualitative analysis.

Interview guide

The interview guide included four sections: 1) The participant's professional characteristics, 2) their experience with the effectiveness and safety (ADRs) of biopharmaceutical medications, 3) experience with the IqPhvC role and its regulations about reporting ADRs of biopharmaceutical medications, and 4) pharmacist recommendations to enhance medication safety of biopharmaceutical medications in public hospitals. The interview schedule started with introducing the researcher and the research objective. The inclusion question was:" Do you have experience with biological/ biosimilar medications? (if they answered no, the interview was discontinued).

Ethical consideration

Verbal consent was obtained from the participant before launching the interviews. The participation was voluntary and the interview recording was optional. The interviewees were anonymous (without names) to keep participants confidentiality. No incentive was offered to the participants. The study received ethical approval from both the Central Scientific Committee at the University of Baghdad College of Pharmacy and the Ethical Committee at the MOH before starting data collection.

Quantitative source

The IqPhvC shared with the researchers the reports of ADRs received from 2014 through April 2021. These reports were mainly submitted from healthcare providers (HCPs) at public hospitals across the country to the IqPhvC, Ministry of Health (MOH). The ADR data from the IqPhvC reports were used as a source of comparison between the reported biopharmaceutical-ADRs and the pharmacists' perceptions about ADRs and the reporting process.

Results

The qualitative (interviews') findings

The study interviewed 25 pharmacists from 10 governmental hospitals in Baghdad. The participating pharmacists included 21 women and four men**.** Table 1 shows the demographic and professional characteristics of the participating pharmacists.

Table 1. Demographics characteristic of pharmacists.

Code	Gender	Degree	Professional title	Years of Experience	Workplace
Ph1	female	BS Pharm	Chief Pharmacist, Outpatient pharmacy	19 years	1. AL-Kadhemia Teaching Hospital
Ph2	female	BS Pharm	Practicing pharmacist/ Internal Pharmacy	5 years	2. Al-Amal Oncology Hospital
Ph 3	female	BS Pharm	Trainee pharmacist	1.5 year	3. Yarmouk Teaching Hospital
Ph 4	female	BS Pharm	Practicing pharmacist	5 years	Al-Amal Oncology Hospital
Ph 5	female	BS Pharm	Resident pharmacist	3 years	Al-Amal Oncology Hospital
Ph 6	female	Master clinical pharmacology	Specialist clinical pharmacist, Pharmacovigilance	10 years	Yarmouk Teaching Hospital
Ph 7	female	BS Pharm	trainee pharmacist	1.5 years	Yarmouk Teaching Hospital
Ph 8	female	BS Pharm	Practicing pharmacist	5 years	4. Kidney Diseases and Transplant Center/ Medical City
Ph 9	female	BS Pharm	Trainee pharmacist	1.5 years	5. Gastroenterology and Hepatology Hospital /Medicine City- Baghdad
Ph 10	male	Master Clinical Pharmacy	Specialist clinical pharmacist	5 years	Gastroenterology and Hepatology Hospital /Medicine City- Baghdad
Ph 11	female	BS Pharm	Practicing pharmacist, pharmacovigilance|,outpatient pharmacy	4 years	6. Oncology Teaching Hospital/ Medical City
Ph 12	female	BS Pharm	Practicing pharmacist, Internal Pharmacy	6 years	Kidney Diseases and Transplant Center/ Medical City
Ph 13	male	BS Pharm	Practicing clinical pharmacist/pharmacovigilance	6 years	7. Al-Kindi Teaching Hospital
Ph 14	female	BS Pharm	Trainee pharmacist	2 years	Kidney Diseases and Transplant Center/ Medical City
Ph 15	female	MSc in Pharmaceutical Chemistry	Specialist pharmacist	8 years	Yarmouk Teaching Hospital
Ph 16	female	BS Pharm	Practicing pharmacist	6 years	Kidney Diseases and Transplant Center/ Medical City
Ph 17	female	BS Pharm	Chief Pharmacist	16 years	Oncology Teaching Hospital/ Medical City
Ph 18	female	PhD. Clinical pharmacy	Specialist pharmacist	12 years	Oncology Teaching Hospital/ Medical City
Ph 19	female	Master in Clinical Pharmacy	Specialist clinical pharmacist	9 years	Yarmouk Teaching Hospital
Ph 20	female	BS Pharm	Trainee pharmacist	1 year	Kidney Diseases and Transplant Center/ Medical City
Ph 21	female	BS Pharm	Practicing pharmacist, Pharmacovigilance	14 years	8. Dr. Saad Al Watri Hospital for Neurosciences
Ph 22	female	BS Pharm	Practicing clinical pharmacist	10 years	9. Ibn Al Haytham Hospital for Ophthalmology
Ph 23	female	BS Pharm	Practicing pharmacist pharmacovigilance,	9 years	Ibn Al Haytham Hospital for Ophthalmology
Ph 24	male	BS Pharm	Clinical pharmacist	8 years	Baghdad Teaching Hospital
Ph 25	female	BS Pharm	Chief pharmacist, practicing clinical pharmacist	7 years	10. Baghdad Teaching Hospital

BS Pharm=Bachelor of pharmacy. Practicing pharmacist=done with rotation, training (at least has 3 years of experience). Trainee pharmacist=within the first 3 years of employment.

The effectiveness of reference biological medications

There was a general agreement among the participating pharmacists that reference biological medications are effective and give good results according to their indications. Most participating pharmacists had adequate experience with reference biological medications. They treat many diseases, including different types of cancers, inflammatory bowel diseases, autoimmune diseases, retinal diseases, and renal diseases.

"Biological medicines are very effective in decreasing disease symptoms and making patients more committed to treatment because they receive treatment in hospital before they return home" (Ph. 9).

“They are effective drugs and used in many diseases like multiple sclerosis (MS), GUT disease, Rheumatology arthritis (RA). Most patients have a good response to biological treatment” (Ph-24).

The adverse reactions of reference biological medications

Most of the participating pharmacists confirmed that reference medications have manageable adverse effects such as allergic reactions and rash at the injection site. The pharmacists believed that no serious adverse effects had been reported with biological medicines used in various disciplines when used with caution, proper indications and patients are follow-ups by physicians and pharmacists.

“No adverse events associated with biological medications; they are generally safe” (Ph 7). “[They have] well-tolerated adverse events” (Ph 18).

“MabThera (retuximab) can cause allergic reactions in the administration site”(Ph 14). "Mabthera (rituximab) can cause an allergic reaction, and Gilenya (fingolimod) can cause severe hypotension"(Ph 24).

Dispensed biosimilar medications

Fifteen out of 25 of the participating pharmacists dispensed biosimilar medications like Remsima (infliximab), Bevacizumab (Suivant), Aryotrust (Trastuzumab), Retacrit (epoetin alfa - epbx). According to the availability, not all hospitals had biosimilar medications. The pharmacists preferred biosimilar medications licensed by the U.S. Food and Drug Administration (FDA) or European Medical Agency (EMA). It is worth mentioning; the majority mentioned that biosimilar medicines were available for a short period in their hospitals.

“ Yes, I have approximately 3 months experience with Remsima (infliximab)” (Ph 3). “ Yes, [I have experience with] Eprex (human erythropoietin), and Retacrit (epoetin alfa - epbx)” (Ph 16).

“Yes [I have experience with] Aryotrust (trastuzumab), and Stivant (bevacizumab)”(Ph 17).

“The biosimilar medicine (bevacizumab) was available for two weeks only in the hospital, and not all doctors agreed to dispense it because it was bevacizumab (Stivant) for Iranian company (CinnaGen) and did not have FDA/EMA approval” (Ph 4).

Effectiveness of biosimilar medications compared to biological medications

The pharmacists' perceptions regarding the effectiveness of biosimilar medicines widely varied. The majority (10) of the pharmacists believed that reference biological medicines are more effective than biosimilar medicines. At the same time, the rest either had not enough experience with biosimilars (10) or believed they are comparable (3). Only two pharmacists believed that biosimilar medications were more effective.

“Biological medications are more effective than biosimilar medications” (Ph 2, Ph 4, Ph 5, Ph 10, Ph 12, Ph 14, and Ph 24).

“There is no comparison because the effectiveness of biosimilar drugs is much lower than biological drugs; According to the lectures held in the hospital, after the fifth dose of the biosimilar treatment for patients, a telescope was made for them, and no evidence for mucosal healing” (Ph 9).

Adverse reactions of biosimilar medications compared to their biological counterparts

The pharmacists' perceptions regarding the ADRs of biosimilar medicines widely varied. The majority of the pharmacists have not had adequate experience with biosimilar medications due to their short availability. A pharmacist who had 12 years of experience and practice in Oncology Teaching Hospital, expressed:

“The biosimilar was available for the insufficient period, and all patients took only one dose, and some of them did not take any dose, so I cannot compare" (Ph. 18).

Some pharmacists believed that biosimilar medicines either have the same or more adverse reactions compared to the originators.

“Both have same side effects” (Ph-12).

“Biosimilars have more adverse events” (Ph-11)

Documentation inpatient medical records varied among hospitals.

The availability of adequate data about the biopharmaceutical medicines inpatient medical records has varied among hospitals. Six departments at different hospitals had adequate documentation about the effectiveness and ADRs of biopharmaceutical medicines. Only one hospital (for ophthalmology) had electronic health records. In contrast, there was no adequate documentation in the other five departments/hospitals.

"The patient medical records in the hospitals cannot give enough information to measure the effectiveness and safety of biological or biosimilar medicines"(Ph 26). "There is inadequate documentation about the biopharmaceutical medicines which is insufficient to measure the effectiveness and adverse reactions of these medicines. There are a small number of biopharmaceutical doses given for a short period and not enough to be used for evaluation" (Ph 18).

Interchangeability between biological and biosimilar medications relies on availability.

The pharmacists either disagreed with interchangeability between reference biological and biosimilar medications or agreed, depending on the availability. The common theme was the switching by the prescriber can be recommended in case of unavailability, which frequently happens in public hospitals. Thus, the switching (by a physician) was not optional in most cases.

A pharmacist 5 years of experience and practicing in Al-Amal National Hospital for Oncology, disagreed with the interchangeability when the biosimilar medicines do not have U.S. FDA approval.

"I disagree if the biosimilar medications do not have FDA approval such as Bevacizumab (Suivant) of Cinnagen Company (Iran), but I agree if the biosimilar medications have FDA approval and the same effectiveness of biological medications"(Ph. 4)

"I agree according to the medicine availability because patients suffer from severe anemia (hemoglobin level reaches 3 g / l), so I prefer giving patients the available treatment rather than keeping them untreated" (Ph 8).

"No, because the safety and the efficacy of the products cannot be tracked if the patient switches many times between biological and biosimilar products" (Ph 25).

The future role of biosimilar products to optimize therapy

Most pharmacists supported the use of biosimilar medicines and their potentially positive role in their field future, particularly those having international certifications. Eleven pharmacists said "yes" and six said "maybe" for the future role of biosimilar medicines.

"The use of biosimilar medications depends on their manufacturer" (Ph 18).

"If a biosimilar medication works well and with a good price, it can invade the field and if it is less effective, it cannot" (Ph 12).

"It depends on the prescriber's experience with the biosimilar" (Ph 26).

Under-reporting of biopharmaceutical adverse reactions to the IqPhvC

According to the interviews, only four out of 25 pharmacists reported ADRs of biopharmaceutical medicines. Most of the interviewees believed there are no serious ADRs associated with biopharmaceutical medicines. In general, there was underreporting of biopharmaceutical ADRs to the IqPhvC, which mainly relies on healthcare provider (HCP) reporting.

" No, I have not reported adverse effects because they are reversible and do not occur with all patients, and there is a pharmacist responsible for drug monitoring, and these are his duties" (Ph 25).

"No, I did not write any report on the adverse events of biological or biosimilar medications because there is a pharmacist in charge for these tasks" (P 17).

Most pharmacists relied on a medication safety pharmacist who is responsible for reporting any ADRs to the IqPhvC.

"There is a pharmacist dedicated to making reports on the adverse events of medications linked to the Iraqi Pharmacovigilance Center" (Ph 18).

"Yes, I reported ADRs of biologics medications like Rituximab (Mabthera) related to Roche Company" (Ph 8).

Pharmacist unawareness of the Iraqi Pharmacovigilance Center (IqPhvC) regulations about reporting biopharmaceutical ADRs

Most pharmacists were unaware of the IqPhvC regulations. Indeed, only 7 out of 25 pharmacists were aware of IqPhvC regulations. Hence, most pharmacists (20) have not changed their ADR reporting behavior after the 2019 IqPhvC reporting regulations. Therefore, some pharmacists who were aware of the IqPhvC regulations have not changed their reporting behavior.

" I am unaware of the IqPhvC recent regulation about reporting ADRs of biological and biosimilar medications" (Ph 1).

"I am not aware of the recent regulations of the MOH about reporting ADRs of biological medications, but I do not send any report before referring it to our division official who determines the report 's format according to the letter received from the IqPhvC"(Ph 9).

It seems that the current regulations of the IqPhvC did not reach most of the participating pharmacists. The participants believed that the IqPhvC does not have an influential role in most Iraqi hospitals related to reporting the adverse reactions of biopharmaceutical medicines since most HCPs were not aware of its reporting regulations.

Barriers to reporting biopharmaceutical adverse reactions to the IqPhvC

The majority (19) believed no barriers are preventing ADR reporting.

"No, there are no barriers, but no adverse events to report" (Ph 19).

However, some pharmacists listed a few barriers to report biopharmaceutical ADRs such as inadequate time and high workload. The main barriers were the over workload and lack of time. Ph 16, who had 6 years of experience practicing in kidney diseases and Transplant Center, Medical City, revealed:

"Yes, there is no enough time for preparing all reports of adverse drug events" (Ph 16) "Yes [there are barriers], the website is down for now" (Ph 10).

The pharmacist recommendations to the IqPhvC about reporting biopharmaceutical ADEs

The pharmacists had some recommendations for the IqPhvC, such as following up with hospitals, providing education to pharmacists, and adopting electronic means for ADR reporting.

"The IqPhvC should follow up with the centers to ensure the pharmacists understanding about their recommendations for biological / biosimilar medicines in order to report properly any ADR" (Ph 25).

"Conducting courses for pharmacists about biological and biosimilar medications in order to monitor their effectiveness and side effects" (Ph 6).

"Providing means of communication via any quick electronic means in order to send reporting ADRs from health institutions to the IqPhvC and to receive instructions or notifications from the IqPhvC to health institutions" (Ph 15).

Most of the participating pharmacists were unaware of the IqPhvC functions and regulations due to a lack of contact between health institutions and the center. Consequently, they under-report biopharmaceutical ADRs.

The pharmacist recommendations to the MOH about procuring biopharmaceutical medications

Most pharmacists recommended that the MOH should provide reference biological medicines to public hospitals in a sustainable manner to avoid treatment interruption. Additionally, the MOH should consult the prescriber (physician) before replacing references with biosimilar medicines. This is because procuring biosimilar medicines to replace reference biological medicines is not always acceptable by physicians from an effectiveness and safety point of view.

"Providing an adequate and large quantity of expensive biological medicines for patients because most patients cannot buy medicines to avoid interruption of treatment for the patient such as Avastin (bevacizumab)" (Ph 7).

"I prefer the MOH to buy biological medications, especially the Simulect (basiliximab) that belong to Novartis company because it has very good and effective results." (Ph 8).

Buying biological medications in large quantities in order to cover the largest possible number of patients. For example, Avastin is used for metastatic cancer, and MabThera is used for lymphoma" (Ph 15).

"The MOH should take the prescribers' opinion before buying the biosimilar in order not to switch from the biological to the biosimilar suddenly for all patients" (Ph 25)

Because the pharmacists had little experience with biosimilar medications, most participating pharmacists were afraid of a biosimilar. However, most pharmacists agreed to use biosimilar medications if the FDA or EMA has approved them or are from reputable international companies.

The pharmacist recommendations for physicians to enhance the medication safety of biopharmaceutical medications

The participating pharmacists recommended that physicians following up with patients taking biopharmaceutical medicines to monitor ADRs. Monitoring can be done by ordering lab data before and after prescribing biopharmaceutical medicines. Follow-up, the ADRs of biopharmaceutical medications, is critical to enhancing patient safety. Some pharmacists recommended that physicians should educate patients about the common ADRs. e

"Physicians should follow-up with a patient after each [biopharmaceutical] dose, and it is preferable to have a physician present during treatment, especially the first dose"(Ph 9).

"Physicians should order liver function test (LFT), kidney function test (KFT), complete blood culture (CBC), X-ray before prescribing biopharmaceutical medications" (Ph 9).

"Physicians should inform patients about the common ADRs since they will be in touch with patients in the first and follow-up visits" (Ph 21).

The participant recommendations for hospital pharmacists to enhance the medication safety of biopharmaceutical medications

The participating pharmacists had different recommendations for hospital pharmacists to enhance medication safety. They recommended promoting pharmacists' knowledge about biopharmaceutical ADRs, following up on the ADRs in patients taking biopharmaceutical medicines, and educate patients about their ADRs.

"The pharmacists should have all information about the safety of medications and reporting any side effects" (Ph 5).

"Organizing a follow-up form for patients who take biological or biosimilar medications after taking each dose to follow up on the adverse events of treatment, if any, as well as the effectiveness of the treatment for comparison and transferring information to physicians"(Ph 9).

"Follow up and educate patients about the effect and adverse effects" (Ph 2).

Quantitative Findings

The Biopharmaceutical-ADRs Reported to the IqPhvC

From 2014 through April 2021, the IqPhvC received 282 reports of ADRs about 11 biopharmaceutical medicines; 43% of them were serious (Figure 1A). The most common ADRs were related to five biopharmaceutical medicines: Infliximab (65, 23.0%), rituximab (59, 20.9%), interferon (56, 19.9%), etanercept (48, 17.0 %) and trastuzumab (34, 12.1%) (Table 2). The ADRs afflicted more females (62%) compared to males (38%). The reports of the biopharmaceutical ADRs have not specified whether the causative drugs were reference or biosimilar medicines. Patients were aged 18-44 years and 45 – 64 years had the highest ADR experience rates, 53.2% and 30.2%, respectively (Table 3).

The ADRs led to different levels of consequences: Medically important conditions (34.8%), prolonged hospitalization (29.5%), life-threatening conditions (22.0%), disabling (7.6%), and death (6.1%)(Figure 1B). Pharmacists (41.7%) and physicians (26.5%) were the most common reporters of biopharmaceutical-ADRs to the IqPhvC (Figure 1C). The most common reported ADRs: General and administration site disorders (20.4%), CNS disorders (11.2%), skin disorders (11.0%), respiratory disorders (10.5%), and gastrointestinal disorders (6.5%)(Table 4). The last three years had the highest number of ADR reports: 2018 (64), 2019 (114), and 2020 (61) (Figure 1D).

Table 2. The number of ADRs reported to the IqPhvC regarding each biopharmaceutical medicine

	Biopharmaceutical	**N**	**%**
1	Infliximab	65	23.0
2	Rituximab	59	20.9
3	Interferon	56	19.9
4	Etanercept	48	17.0
5	Trastuzumab	34	12.1
6	Epoetin alfa	8	2.8
7	Adalimumab	7	2.5
8	Pertuzumab	2	0.7
9	Bevacizumab	1	0.4
10	Binocrit	1	0.4
11	Erythropoietin	1	0.4
	Total	282	23.0

Table 3. The patient and the reported biopharmaceutical-ADR characteristics

Character	**Subcategories**	**N**	**%**
Gender	Male	98	38.0
	Female	160	62.0
Age categories	0-27 days	1	0.4
	2-11 years	4	1.7
	12-17 years	7	3.0
	18-44 years	125	53.2
	45 – 64 years	71	30.2
	65 – 74 years	22	9.4
	≥ 75 years	5	2.1

Table 4. The reported adverse drug reactions to the IqPhvC for each biopharmaceutical medicine from 2014 through April 2021

	Adalimumab	Bevacizumab	Binocrit	Erythropoietin	Etanercept	Epoetin alfa	Infliximab	Interferon	Pertuzumab	Rituximab	Trastuzumab	Total
General and administration site condition	4		1		12	3	11	36		20	5	92
CNS disorders							19	19		9	5	52
Skin disorders		1			10	1	4	4	1	19	8	48
Respiratory disorders					5	1	4	4	1	19	14	48
Gastrointestinal disorders			1		1	1	9	9	1	8	4	34
Immune system disorders	2				2	1	10			9	1	25
Infections					10	2	4	4		2		22
Musculoskeletal disorders					2		6	8		3	3	22
Investigations	1				6	1	2	2		1	7	20
Injury and procedural disorder					5		3	1		9	1	19

Continued table 4.

	Adalimumab	Bevacizumab	Binocrit	Erythropoietin	Etanercept	Epoetin alfa	Infliximab	Interferon	Pertuzumab	Rituximab	Trastuzumab	Total
Cardiac disorders					1	1	1	2		4	9	18
Psychiatric disorders					1		7	7				15
Vascular disorders				1		1	1			6		9
Renal disorders			1		4	2	1	1				9
Eye disorders					3		1	3			1	8
Hepatobiliary disorders					2		1	1				4
Reproductive system		1					1	1				3
Blood and lymphatic disorders						1	1			1		3
Surgical	1											1

Note: One ADR report may include more than ADRs for the same patient due to biopharmaceutical medicine

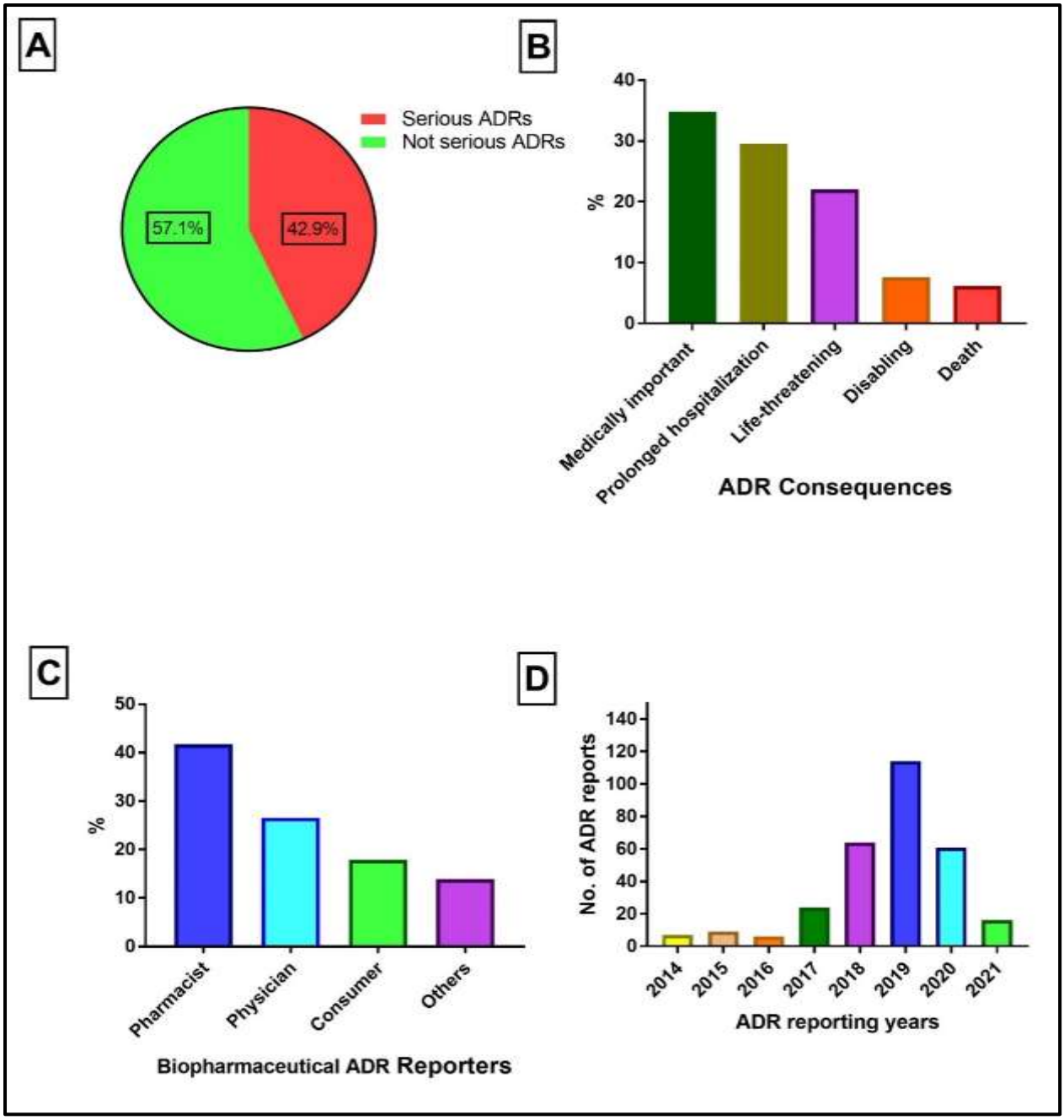

Figure 1. The descriptions of the reported biopharmaceutical ADRs to the IqPhvC

A. The seriousness of the reported biopharmaceutical-ADRs
B. The percentages of ADR consequences
C. The percentages of biopharmaceutical ADR reporters
D. The number of reported ADRs to the IqPhvC across several years

Discussion

Using two sources of information in this study helped integrate the interviews' findings, and the ADR reports from the IqPhvC. The study compared the reported ADRs to the IqPhvC and the pharmacist perceptions about the biopharmaceutical ADRs and reasons for the under-reporting process. The study findings can also help assess the effectiveness of the Iraqi Pharmacovigilance Center (IqPhvC) regulations regarding biopharmaceutical medications. Since the reporting of ADRs is voluntary and mainly relies on healthcare providers (HCPs), both pharmacist interviews and the IqPhvC data showed under-reporting over the last several years.

Most participants in the interviews were female pharmacists because they represent most pharmacy college students and, consequently, most pharmacists in public hospitals [22].

Effectiveness of reference biological medications

Most participating pharmacists had adequate experience with reference biological medications since they were available for several years. The pharmacists believed that their effectiveness depends on the use within the approved indications and have manageable ADRs if patients take precautions. Similarly, a study in the U.S. found that biological medications are helpful in the management of a variety of illnesses. However, their costs, which are typically higher than small-molecule drugs, strain the healthcare system. [23].

Adverse reactions of the reference biological medications

The participants indicated that reference biological medicines have manageable ADRs. However, the IqPhvC reports showed some serious and fatal biopharmaceutical-ADRs. On the other hand, a study in Columbia found comparable biological ADR reports to the IqPhvC with respiratory system disorder (16.8%), skin disorder (15.6%), body -general disorder (10.3%), and gastrointestinal disorder (7%)[24]. A Brazilian study found that more than 43.0% of patients with rheumatoid arthritis and psoriatic arthritis taking biological medicines had one or more adverse effects, with an average of 1.6 events per patient. Additionally, 25% of them had one or more serious ADRs, with the majority requiring hospitalization [25]. Thus, pharmacists should follow up reports about ADRs of biological medications.

Effectiveness of biosimilar medications compared to biological medications.

Most pharmacists needed to have more experience with biosimilar medicines by making them permanently available in hospitals. Similarly, a study conducted in Poland found that 87% of hospital pharmacists believed that the essential benefit of biosimilars is that they are less expensive compared to reference medicines. However, 88% of them were concerned about biosimilar medicines in terms of immunogenicity and pharmacokinetics. [26]. Similarly, the U.S. health leaders and stakeholder representatives believed that the lack of long-term data on biosimilar medicines could deter their use despite the potential benefits of cost-saving [23]**.**

Adverse reactions of biosimilar medications compared to their biological counterparts

Most participants had inadequate experience with biosimilar medicines due to short-term of use. In contrast, a Polish study found that 65.6% of hospital pharmacists were very familiar with biosimilars, whereas 32.8% were somewhat familiar with these medications [26]. Again, the MOH should provide biopharmaceutical medicines in sustainable supply to avoid treatment interruptions and help HCPs assess their effectiveness and safety.

The hospital patient medical records

In general, there was inadequate documentation in public hospitals, which is probably because most hospitals do not have trained physician assistants to help in medical data entry and a high workload on physicians. In other words, medical records need skilled data entry personnel who are not available in almost all Iraqi hospitals. Additionally, most Iraqi public healthcare settings do not implement electronic health records[20]. In the United States, several existing systems allow for post-marketing pharmacovigilance surveillance of biopharmaceutical medicines, including voluntary ADR reporting, the FDA's Sentinel system, and the Academy of Managed Care Pharmacy's (AMCP) eDossier system. The Sentinel system is a national electronic system for monitoring the safety of FDA-regulated medical products, including biopharmaceutical medicines. The AMCP's eDossier system is a web-based tool that provides qualified health care decision-makers the opportunity to quickly review, evaluate, and compare products to make an evidence-based evaluation [23]. In Iraq, post-marketing pharmacovigilance surveillance relies on voluntary reporting from HCPs and patients [27]. Since the documentation is critical to follow up with the safety and effectiveness of the medications, our hospitals or health officials should work to have adequate documentation about biopharmaceutical medications.

Interchangeability between biological and biosimilar medications for the same patient

In Iraqi hospitals, the interchangeability between biological and biosimilar medications is recommended when biological medicines are not available in hospitals to avoid leaving patients without treatment. According to a European article, if interchangeability between reference biological and biosimilar medicines having the same active ingredient is done according to the EU legislation, the switching does not expect to trigger immunogenicity [28].

The future role of biosimilar products to optimize therapy

The majority expected that biosimilar medicines will enhance treatment options by introducing these affordable cutting-edge medicines Likewise, a study in the U.S. concluded biosimilars have great opportunities in the future, but they need a long time to ensure their wide availability in the market. They firmly believe that understanding the concept of biosimilars is crucial for oncologists[29]. The number of biosimilar drugs is expected to increase in the coming years due to the economic situation and the patent expiration for several biological drugs.

Under-reporting of biopharmaceutical ADRs among the hospital pharmacists

Adverse drug reaction (ADR) reporting is essential to enhance medication safety and helps identify rare ADRs [5]. The IqPhvC is responsible for post-marketing surveillance for all medicines in both public and private sectors, which relies mainly on HCP reporting [30, 31]. In 2019, public secondary and tertiary healthcare facilities served 62,958,897 outpatient visits [20, 21]. However, the reported pharmaceutical-ADRs over seven years were 282 cases only; pharmacists submitted 126 reports (18 reports per year) across 15 provinces. The IqPhvC received the highest number of biopharmaceutical-ADR reports in 2019, probably because the IqPhvC sent an official letter to all public healthcare settings emphasizing the reporting of ADRs and requiring the name of the biopharmaceutical company. Therefore, yearly routine reminders from the IqPhvC can encourage healthcare facilities to submit their ADR reports.

Similarly, there was a noticeable under-reporting of biopharmaceutical ADRs among the participating pharmacists. The participating pharmacists claimed there were no serious ADRs to report. In fact, the IqPhvC reports showed 133 serious biopharmaceutical-ADRs over the last seven years. Most pharmacists had the misconception that they do not have to report non-serious ADRs. Some pharmacists indicated they do not have to report ADRs because a safety pharmacist (focal point) connects with the IqPhvC. Although there is such a safety pharmacist in each hospital, all other pharmacists should notify him/her about any ADR incidents in their wards [30]. Therefore, both interviews and the IqPhvC data showed the under-reporting of biopharmaceutical ADRs.

According to a systematic review of 37 studies from 12 western countries, the median under-reporting rate was 94% (interquartile range 82–98%) [12]. Factors contributing to underreporting among HCPs include inadequate awareness, negative attitudes, lack of time and motivation, uncertainty about the real cause of ADRs, and difficulty accessing the reporting form [12, 13]. To increase the safety of biopharmaceutical medicines, ADRs should be reported. To facilitate reporting of biopharmaceutical ADRs to the IqPhvC, training courses for pharmacists and electronic reporting systems are needed. Furthermore, the pharmacovigilance center in every hospital should take a more significant role in following up the circulation of any regulations about reporting ADRs to all departments.

The Pharmacist recommendations to the MOH about procuring biopharmaceutical medications

Most of the 10 public hospitals in Baghdad suffered from interruptions in the availability of treatment, whether biological or biosimilar medications or both for periods, which negatively impacts patient clinical outcomes. Additionally, the procuring of medicines should rely on medical costs and physician experience-based recommendations.

The pharmacist recommendations for physicians to enhance biopharmaceutical safety

Despite the effectiveness of biological drugs in treating many diseases, they have ADRs, similar to other medications. Severe ADRs may become dangerous if the patient is not monitored and treated. Surprisingly, several pharmacists indicated that patient ADR monitoring and follow-up are the responsibility of physicians. That means they did not admit these are sharing responsibilities between pharmacists and physicians.

The participant recommendations for hospital pharmacists to enhance the biopharmaceutical safety

One of the crucial roles of the clinical pharmacist is to monitor ADRs of treatment and notify the physicians if any ADRs occur. Hospital pharmacists should also review prescribed medicines to identify any potential drug-drug interactions [32]. Furthermore, any ADRs of the biosimilar or biological medications need to be reported to protect the patient's life and avoid these symptoms from occurring with other patients.

The study had some limitations. The quantitative component covered two parts which were the biopharmaceutical safety and reported ADRs. The qualitative phase was limited mainly to one province (Baghdad), which has the largest hospitals in the country regarding biopharmaceutical medicines availability. Additionally, most pharmacists declined audio-recording of the interview.

Conclusions

Most of the 10 public hospitals in Baghdad have been experiencing non-sustainable supplies of biosimilar medicines. Inadequate recording of the biopharmaceutical effectiveness and safety information in the patient medical record was common. Most participating pharmacists had adequate experience with the reference biological medications and believed they are effective with manageable ADRs. In contrast, most pharmacists had a short experience with biosimilar medications and were unsure about their effectiveness and safety. Most pharmacists preferred reference biological over biosimilar medicines because of their effectiveness. However, they believed that initial prescribing and switching between a reference and counterpart biosimilar relies on their availability in public hospitals. They preferred biosimilars with the FDA or EMA approval over other biosimilar medicines. Both pharmacist interviews and the IqPhvC data showed under-reporting of biopharmaceutical ADRs.

An electronic application can be implemented to send the ADR reports quickly and easily.

Additionally, the IqPhvC should send regular notifications to encourage healthcare facilities to report their ADR incidents. Medicine procurement in healthcare settings should focus on securing biopharmaceuticals having the FDA or EMA approval in sustainable supply rather than looking only at costs to avoid treatment interruptions and enhance patient clinical outcomes. Providing pharmacist training, electronic reporting, promoting documentation, and following up on biopharmaceutical effects are pivotal to prevent, monitor, and treat biopharmaceutical ADRs.

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