



The whole experience of public hospital physicians from several specialties with biopharmaceutical effectiveness, safety, adverse drug reactions and interchangeability: A qualitative study

Hiba Leith Fahmi, MS^a, Ali Azeez Al-Jumaili, MPH, PhD^{b,d,e,*}, Manal Mohammed Younus, PhD^c

^a Al-Rusafa Health Directorate, Ministry of Health, Baghdad, Iraq

^b University of Baghdad College of Pharmacy, Baghdad, Iraq

^c Iraqi Pharmacovigilance Center, Ministry of Health, Baghdad, Iraq

^d UC Davis School of Medicine / Public Health Department, CA, USA

^e University of Iowa College of Pharmacy, IA, USA

ARTICLE INFO

Keywords:

Biological medicines
Biosimilar
Physician
Hospital
Effectiveness
Safety
Interchangeability
Qualitative
Iraq
Adverse drug reactions
Biopharmaceuticals
Interview

ABSTRACT

Background: Although there is increasing support for biosimilar medicines by the Iraqi Ministry of Health (MOH), there is scarce information about whether physicians accept these medicines and support movement toward replacing reference medicines with their biosimilar counterparts.

Objectives: The study objectives were to 1) explore in-depth the perceptions of Iraqi physicians working in public hospitals about the difference in effectiveness and safety between biosimilar medicines and their reference biological counterparts, 2) evaluate physicians' barriers to prescribing biosimilar medicines, 3) assess the adherence of physicians to the new pharmacovigilance regulations on reporting biopharmaceutical adverse drug reactions (ADRs) and 4) identify any barriers facing physicians to reporting biopharmaceutical- ADRs.

Methods: This qualitative study included face-to-face and virtual semi-structured interviews involving physicians from different disciplines who had experience with biological or biosimilar medicines. The interviews were conducted between November 6, 2020, and February 7, 2021. Thematic analyses were used to analyze qualitative data generated from the interviews.

Results: The study sample included 36 physicians (6 women and 30 men) from seven different specialties at ten governmental hospitals mainly in Baghdad, and one physician was from Mosul, Iraq. Because most physicians had insufficient experience with biosimilar medications and were not sure about their effectiveness, the majority were hesitant to prescribe them. Most physicians preferred to prescribe reference biological medicines initially. However, the initial prescribing and switching between a reference and counterpart biosimilar relies on its availability. They chose biosimilar medications that have been approved by the U.S. FDA or EMA. Most physicians were unaware about the new pharmacovigilance regulations to report adverse biopharmaceutical reactions. The physicians tended to underreport biopharmaceutical ADRs and believed that inadequate physician-pharmacist collaboration negatively impacts preventing and reporting ADRs.

Conclusions: Medicine procurement in healthcare settings should focus on sustainably securing high-quality biopharmaceuticals rather than looking only at costs to enhance physician experience and patient clinical outcomes. Promoting documentation, monitoring, and physician-pharmacist collaboration is pivotal to prevent, monitor, and treat biopharmaceutical ADRs.

1. Introduction

Biological medicines are fast-growing in numbers and are medicines used to treat complicated diseases across various disciplines, including oncology, rheumatology, endocrinology, nephrology, neurology, gastroenterology, and ophthalmology.¹ Reference biological medicines (originators)

are approved by regulatory authorities (such as the U.S. Food and Drug Administration, FDA) based on a full robust criteria of safety and efficacy data.² After the patents of reference biological medicines have expired, biosimilars (similar biological medicines) can be marketed.^{1,2} A biosimilar is a biologic treatment that is highly similar to an authorized reference product in terms of quality, safety, and efficacy,^{1,3} but biological medicines

* Corresponding author at: The University of Iowa, College of Pharmacy, Iowa, USA.

E-mail addresses: heba.fahmi1206@copharm.uobaghdad.edu.iq (H.L. Fahmi), ali.baraak@copharm.uobaghdad.edu.iq (A.A. Al-Jumaili), manalyounus@gmail.com (M.M. Younus).

are not identical due to their inherent variability.⁴ Interchangeability refers to the possibility of replacing an originator with a biosimilar (or vice versa) or replacing one biosimilar with another.⁵ According to the EMA, switching is defined as the exchanging one medicine to another that is expected to have the same clinical effects with prescriber permission.⁵

The high costs of biological medicines impose a financial burden on healthcare systems. Biosimilar medicines can potentially save millions of dollars and promote patient access to biologics.¹⁰ A report by the European Commission has found that the introduction of biosimilar competition can result in lower market prices.⁶ Such savings, if reinvested appropriately, could be used to increase patient access to expensive biological treatments.^{7,8}

Many countries around the world are currently developing regulatory pathways for biosimilar authorization, mostly based on the World Health Organization (WHO), European Medicines Agency (EMA), or US FDA guidelines.⁹ Iraq is a Middle Eastern country that has authorized its own biosimilar approval guidelines very recently (2019) through the Biologics and Biosimilars Registration Committee (BBRC), which mostly relies on EMA guidelines.¹⁰ There are twenty biological and biosimilar medication approved in Iraq are also approved in the EMA or the US-FDA.¹⁰ However, few additions regarding the box of three and five and the possibility to rely on US FDA guidelines in issues that are not covered by the EMA guidelines. The box in general refers to the maximum number of generic pharmaceutical products that can be approved to a reference one. In Iraqi Ministry of Health (MOH), three or five biosimilars can be approved for a reference biological product. This depends on the molecular weight (lower or higher than 30 kDa) and posttranslational modifications (glycosylation) status. The more complicated molecule with higher molecular weight will be subjected to the box of three.

Using these biosimilar guidelines, the Iraqi MOH approved 18 biosimilar medicines within a period of three years.¹⁰ In Iraq, approval of the first biosimilar products by the Iraqi national regulatory agency based on national biosimilar guidelines resulted in a cost savings of nearly 4.2 million USD for the Iraqi Ministry of Health (MOH).^{10,11} In 2020, approval of several biosimilar medicines by the MOH led to a total cost savings of more than 50 million USD.¹⁰ The first biosimilar to be approved in 2020 by the Iraqi MOH was Rixathon 500 mg.

The production of biosimilar medicines is more complicated task compared to produce generic (chemically synthesized) medicines because they are made by living organism.¹² Thus, biological variability is a real problem and may impact their structure, pharmacokinetics and pharmacodynamics.¹³ The heterogeneous nature, high molecular weight, batch-to-batch variability and complexity of many biological substances means there may be some differences between same biopharmaceutical medicines.¹² Minor changes in the production process or sites of biopharmaceutical medicines may alter the molecule structure (such as post-translational glycosylation, oxidation and deamidation), which can impact their efficacy and safety through changing biological activity and causing immunogenicity.¹⁴

According to a review of the European Medicines Agency (EMA) regulations to monitor biopharmaceuticals (reference biological and biosimilar medicines), these medicines require additional post-marketing monitoring for efficacy and safety since they may cause immunogenicity. Thus, the EMA requires a statement (this medicinal product is subject to additional monitoring) on the packaging with an inverse black triangle sign (▼) to warn healthcare providers (HCPs) and patients to report ADRs or efficacy concerns.^{15,16}

In the Iraqi MOH, the National Board of Drug Selection is the agency responsible for approval of any new medications and requires certain documentation from marketing authorization holders that demonstrates the efficacy and safety of the medicines in addition to its cost-effectiveness compared to the previously approved alternatives.¹⁷ The State Company for Procurement of Medicines and Medical Appliances (KIMADIA) in the MOH is responsible for procuring of biopharmaceutical medicines for the public healthcare settings through tendering procedures.¹⁷ The medicines are provided for free at public healthcare

settings.¹⁷ KIMADIA usually has one-year contract with marketing authorizing holder (MAH) according to their annual budget.¹⁸ This annual procurement may lead to non-sustainable supply of some essential medicines. In 2019, KIMADIA was able to secure 60% of the medications in the Essential Medicine List.¹⁷

It is worth to be mentioned that obtaining biopharmaceutical medicines from public sector is totally subsidized by government and patients receive them either for free or for heavily subsidized fees (few US dollars). In contrast, in the private sector, medicines are not subsidized and patients should pay their full cost out of pocket (hundreds of USD) to purchase them from community pharmacies (Al-Jumaili et al., 2021).

The Iraqi Pharmacovigilance Center (IqPhvC) is part of the Pharmacy Department, Directorate of Technical Affairs at Iraqi MOH. The IqPhvC is responsible for post-marketing surveillance for all medicines in both public and private sectors.¹⁷ The recent (in July 2019) IqPhvC regulations recommend that physicians follow-up with the safety of pharmaceutical medicines and report the ADRs of biopharmaceutical medicines using batch numbers and, trade and company names rather than using their scientific names only.

Although there is increasing support for biosimilar medicines by the Iraqi MOH, there is scarce information about whether physicians accept these medicines and support movement toward replacing reference medicines with their biosimilar counterparts. This is the first in-depth study to investigate the facilitators and barriers to biosimilar prescribing among Iraqi physicians.

The study objectives were to 1) explore in-depth the perceptions of physicians working in public hospitals about the differences in efficacy and safety between biosimilars and their reference biological counterparts, 2) evaluate the barriers facing physicians to prescribing biosimilar medicines, 3) assess the adherence of physicians to the new pharmacovigilance regulations on and 4) identify in-depth any barriers facing physicians to reporting biopharmaceutical-related adverse drug reactions (ADRs).

2. Methods

2.1. Study design

This qualitative study included individual interviews involving physicians from different specialties who had experience with biological or biosimilar medicines. However, the sample size was determined by the data saturation point, which plays an essential role in such studies. In other words, the stopped data collection after reaching a saturation point when no new data was being collected (i.e. new participants were repeating the same previous answers). Semi-structured interviews were conducted by a trained pharmacist, MSc student researcher (a pharmacist with 10 years of hospital experience).

2.2. Settings

Almost all interviews ($N = 29$) were conducted face-to-face in public hospitals except for seven interviews that were virtual (using Zoom). Main hospitals in Baghdad with biopharmaceutical medicines (different specialized hospitals: oncology, nephrology, gastroenterology, ophthalmology, rheumatology, general hospitals with multi-specialties) were the study target settings. Each interview lasted 30–60 min.

2.3. Inclusion criteria

The study included physicians who were working in public hospitals, dealing with biopharmaceuticals (reference or biosimilar medicines), having one of the following specialties (oncology, rheumatology, gastroenterology, dermatology, ophthalmology, nephrology or neurology) and agreed to participate.

2.4. Participant recruitment

A purposive convenience sampling of physicians working in public hospitals in Baghdad Province was conducted between November 6, 2020 and February 7, 2021. Purposive sampling is used to select “individuals that are especially knowledgeable about or experienced with a phenomenon of interest”.^{19,20} The contact information of some participants was obtained from the Iraqi Pharmacovigilance Center (IqPhvC), and the researchers also used a snowballing technique. Snowballing means we asked the participants about physicians who may be interested in participating in the study and meeting the inclusion criteria. Thus, the study used two methods of sampling: Purposive and snowballing. The interviews were arranged either in-person or via phone calls and conducted by one researcher in face-to-face meetings at the hospitals or virtually over Zoom. Some participants requested to receive the interview guide before the interview to be familiar with the interview questions and save time during the interview. The interviews continued until we reached the data saturation point.

The audio-recording was optional since it might discourage proposed interviewees from participating. Indeed, some physicians did not agree to audio-record the interview. To overcome this limitation, the hand-written answers were sent to those who declined the recording for member checking (participant validation). The interviews were semi-structured with open-ended questions. Verbal consent was obtained from interviewees before the interview, and their information was kept confidential. Each interview was conducted inside the hospitals and lasted for 30–60 min. Most interviews were conducted in both English and Arabic (mixed language according to the participant English skills) and then the Arabic sentences (transcripts) were translated to English by two bilingual authors.

2.5. Interview guide

The study was conducted to assess the experience of physicians with biopharmaceutical medications in terms of safety and efficacy and to explore the impact of the IqPhvC regulations on adverse reactions reporting by brand and not scientific name.

The interview guide included four sections (see full interview guide in the supplementary). Part 1: The participant characteristic included gender, profession, degree, professional title, specialty, years of experience and Workplace. Part 2 included the experience and perceptions about the effectiveness and ADRs of the reference biological and biosimilar medicines. Part 3 covered the barriers facing physicians to report biopharmaceutical adverse reactions and adherence to the IqPhvC regulations ADR reporting. Part 4 included physician recommendations to health officials and healthcare providers (HCPs) to enhance medication safety of biopharmaceutical medications.

The interview started with introducing the researcher and the research objective. Participant names were not reported. Participants were asked an inclusion question: “Have you had experience with biopharmaceutical (reference or biosimilar) medications?” The researcher excluded physicians who were not prescribing/ dealing with any biopharmaceutical (neither reference nor biosimilar) medicines.

2.6. Ethical consideration

Verbal consent was obtained from the participants before launching the interviews. Participation was voluntary. The interview recording was voluntary. No incentive was offered to the participants. The interviewees were anonymous (without names) to keep participants' confidentiality. The names of work settings were de-identified. The study received approval from both the Central Scientific Committee at the University of Baghdad College of Pharmacy (No. 353) and the Ethical Committee at the Ministry of Health before starting data collection.

2.7. Thematic analyses

Thematic analyses were used to analyze qualitative data which was generated from the interviews. During the thematic analysis of the data, two authors (AA and HF) identified and generated themes from the participant comments. We followed the six phases of thematic analysis described by Braun and Clarke, which include familiarizing with data (comments), generating initial codes, searching for themes, reviewing themes, defining and naming themes and producing the report.²¹ The completed sentences (preferably with examples) were chosen as quotations.

The transcription was cross-checked by the research team. An inductive analytic methodology (data-driven) was used, and a constructivist paradigm was followed.¹⁹ This means we did not rely on an existing framework to come up with the themes but constructed the themes from common trends emerging from the participant comments. Finally, peer checking/ debriefing was performed twice to validate the findings (i.e., third author checked the findings).

3. Results

3.1. Demographics

The study sample included 36 physicians from ten governmental hospitals in Baghdad and Mosul. The median experience years of the participating physicians were 14. The participating physicians included 6 women and 30 men: 6 oncologists, 5 rheumatologists, 5 dermatologists, 5 nephrologists, 5 internal medicine specialists and 5 ophthalmologists. The years of experience ranged from 5 to 30. All physicians were from public teaching hospitals where the medications are provided for free or highly subsidized.¹⁷ Table 1 shows the demographic and professional characteristics of participating physicians.

The physicians have used reference biological medications in all seven specialties (oncology, rheumatology, dermatology, nephrology, neurology, gastroenterology and hepatology, ophthalmology). Biopharmaceutical medications that were approved by the Iraqi National Board of Drug Selection are listed in Table 2. Biosimilar medications were not used in dermatology or ophthalmology because they were not available in the hospitals (Table 2). The main themes and subthemes, along with representative interviewee quotes, are included in three tables (Table 3,4,5).

3.2. The perceptions of physicians about the effectiveness and safety of biopharmaceutical medicines

3.2.1. Reference biological medications can be well effective

There was a general agreement among the participating physicians ($N = 30$, 89%) that reference biological medications are effective and give the expected results when used as recommended (Table 3).

“Reference biological medications are effective such as Trastuzumab (Herceptin) for breast cancer, Bevacizumab (Avastin) for brain, colon and ovarian cancers, Rituximab (Mabthera) for non-Hodgkin lymphoma, anti BDL1 (immune check inhibitor) for melanoma” (Oncol 1).

3.2.2. Reference biological medications have manageable adverse reactions in general

Most of the participating physicians ($N = 29$, 81%) confirmed that reference biological medications have manageable adverse reactions (Table 3).

“Biological medications such as Humira® (Adalimumab) and Enbrel® (etanercept) have manageable adverse reactions include increased liver enzymes, chest infection, cause Tuberculosis (TB) if the patient has latent TB, allergic reaction, effect on complete blood count. These can be tolerable compared to conventional medicines which have more adverse reactions” (Rheum 5).

Table 1
The characteristics of the participating (interviewee) physicians.

Code	Gender	Specialty	Years of Experience as physician	Years of Experience in specialty	Workplace
Oncol 1	Male	Oncology	15		General Teaching Hospital
Oncol 2	Male	Oncology	10		Oncology National Hospital
Oncol 3	Male	Oncology	24	5	General Teaching Hospital
Oncol 4	Male	Radiation oncology	10		Oncology National Hospital
Oncol 5	Male	- F.I.C.M.S. medical oncology	13		Oncology National Hospital
Oncol 6	Male	Clinical oncologist	26		General Teaching Hospital
Rheum 1	Male	Rheumatology and medical rehabilitation	5		General Teaching Hospital
Rheum 2	Male	Rheumatology	10		General Teaching Hospital
Rheum 3	Male	Rheumatology	20	20	General Teaching Hospital
Rheum 4	Male	Rheumatology	17	6	General Teaching Hospital
Rheum 5	Female	Rheumatology	9	6	General Teaching Hospital
Derma 1	Male	Dermatology	26		General Teaching Hospital
Derma 2	Male	Dermatology	12	6	General Teaching Hospital
Derma 3	Female	Dermatology	11	5	Public Teaching hospital - Dermatology and Venereology Center
Derma 4	Male	Dermatology	22	19	General Teaching Hospital
Derma 5	Male	Dermatology	20	9 (post board)	Public Teaching hospital - Dermatology and Venereology Center
Neuro 1	Male	Neurology	11	1	Public Hospital for Neurosciences
Neuro 2	Male	Neurology	20	15	Public Hospital for Neurosciences
Neuro 3	Male	Neurology	12	4	General Teaching Hospital / Mosul
Neuro 4	Male	Neurology	19	11	General Teaching Hospital
Neuro 5	Male	Neurology	14		General Teaching Hospital
Nephro 1	Male	Nephrology	12		Nephrology and Renal Transplantation Center/ Public Teaching hospital
Nephro 2	Male	Nephrology	38	28	Nephrology and Renal Transplantation Center/ Public Teaching hospital
Nephro 3	Male	Nephrology and internal medicine	20	10	Nephrology and Renal Transplantation Center/ Public Teaching hospital
Nephro 4	Female	Nephrology	15	1	Nephrology and Renal Transplantation Center/ Public Teaching hospital
Nephro 5	Female	Nephrology	11	7	Nephrology and Renal Transplantation Center/ Public Teaching hospital
Gastro 1	Male	Gastroenterology and Hepatology.	15	5	Gastroenterology and Hepatology Hospital / Public Teaching hospital
Gastro 2	Male	Gastroenterology and Hepatology.	9	6	General Teaching Hospital
Gastro 3	Female	Gastroenterology and Hepatology	20	5	Gastroenterology and Hepatology Hospital / Public Teaching hospital
Gastro 4	Male	Gastroenterology and Hepatology	14	2	Gastroenterology and Hepatology Hospital / Public Teaching hospital
Gastro 5	Male	Internal medicine	12	3	Public Teaching Hospital
Ophtha 1	Female	Ophthalmology	13	3	Public Teaching Eye Hospital
Ophtha 2	Male	Ophthalmology	30	20	Public Teaching Eye Hospital
Ophtha3	Male	Ophthalmology	13	4	Public Teaching Eye Hospital
Ophtha 4	Male	Ophthalmology	21	12	Public Teaching Eye Hospital
Ophtha 5	Male	Ophthalmology			Public Teaching Eye Hospital

3.2.3. The perceptions of physicians toward the effectiveness of biosimilar medications compared to their reference (originator) counterparts

The physician's perceptions regarding to the effectiveness of biosimilar medicines widely varied. Neurologists ($N = 4$, 11%) believed that reference medicines are more effective, while all ophthalmologists and dermatologists ($N = 10$, 28%) had no experience with biosimilar medicines. Other specialists ($N = 10$, 28%) (rheumatologists, nephrologists, gastroenterologists) reported that the effectiveness of biosimilar and reference medicines is comparable. The oncologists were divided between believing incomparable effectiveness, the superiority of originators, and not enough experience with biosimilar medicines to decide.

“Both Remsima® (infliximab, biosimilar medicine) and Remicade® (reference medicine) approximately have the same effectiveness in treating patients with Crohn's disease or ulcerative colitis” (Gastro 4).

On the other hand, Oncol 6 stated: “I have no personal experience with biosimilar medications, and I do believe the biosimilar medications is a good way for money-saving”.

Oncol 3 commented “It is impossible to compare between them in terms of effectiveness because we need at least a five-year period of follow-up, but the biosimilar medications have been available for about one year”.

3.2.4. The noticeable adverse reactions of biosimilar medications compared to their reference counterparts

The physicians had different experiences with biosimilar medications. The majority reported comparable adverse drug reactions (ADRs) of

originators and their biosimilar counterparts. For example, physicians from four disciplines (Oncology, Rheumatology, Nephrology, Gastroenterology, and Hepatology) believed that biological and biosimilar medicines have comparable ADRs.

Neuro 1 stated: “Biological medications are more effective and have less adverse reactions compared to biosimilar medications”. Oncol 6 stated: “If the biosimilar medications are always available in sufficient quantities (100% of time) and large number of patients take them for a long period (approximately 10 years), we can have a perception about their effectiveness and the adverse events. However, we had reference for 80% of the time and biosimilar for 20% of the time, and in this case, we cannot have perception about biosimilar in terms of effectiveness and adverse events.” Another neurologist revealed: “most of the time, the patient is switched from reference to biosimilar drugs or vice versa according to the availability. Therefore, it is difficult to compare between reference and biosimilar medicines in terms of adverse reactions”.

3.2.5. Medical record documentation varied according to the hospital or discipline

The availability of adequate data about biopharmaceutical medicines in patient medical records varied among hospitals. Ten departments at different hospitals had adequate documentation about the effectiveness and ADRs of reference and biosimilar medicines. In contrast, there was no adequate documentation in the other six departments/hospitals. For example, adequate medical records are not available in the oncology departments at two public hospitals.

“Medical recording is available in one Teaching Hospital, but it is not specified whether the drug prescribed is reference or biosimilar. For example, Bevacizumab has not mentioned whether it is Avastin (reference) or Stivant (biosimilar)” (Oncol 1).

3.2.6. Physicians preferred to prescribe reference biological medicine initially

Most physicians ($N = 25,70\%$) from different specialties (Rheumatology, Dermatology, Nephrology, Oncology, and Ophthalmology) preferred prescribing reference medications initially because all participating physicians have more experience with reference medicines.

“I prefer to prescribe reference biological rather than biosimilar but if I have no other choice, I would prescribe biosimilar because it is better than nothing” (Neuro 2).

“Reference biological medications are effectiveness such Trastuzumab (Herceptin) for breast cancer, Bevacizumab (Avastin) for cancers of brain, colon and ovaries, and Rituximab (Mabthera) for non-Hodgkin lymphoma” (Oncolo 1).

3.2.7. Prescribing preference also depends on biopharmaceutical availability and settings

The prescribing also depends on the availability of these biological medicines in hospitals. If reference medicine is not available in public hospitals, physicians may prefer to prescribe biosimilar alternatives since patients would buy them out of pocket from the private sector, given that biosimilar medicines are cost-effective.

“If both are available, I prefer to prescribe reference medications because the data of reference medications are mature to me (real-world data). However, if only one (biopharmaceutical) is available, I have no choice and I will prescribe according to the availability” (Oncol 6).

3.2.8. Interchangeability between originator and biosimilar medications for the same patient

The perceptions of physicians toward the interchangeability ranged between the possibility and hesitancy. The common theme was the switching can be recommended in case of unavailability, which occasionally happens in public hospitals. Thus, the switching was not optional in 42% ($N = 15$) of the cases.

“It depends on the availability of medications, I do not agree to switch between reference and biosimilar if both are available, but I would agree if only one is provided. It is better than leaving patients without treatment. Sometimes when medicine is out of the hospital stock, patients are forced to buy medications out of pocket given that reference biological medicines are expensive” (Nephro 5).

The reason for the hesitancy among physicians about the switching between a biosimilar and reference medications was due to not all physicians from different specialties have experience with biosimilar medications. Additionally, some physicians were not satisfied with the effectiveness of biosimilar medicines compared to their reference counterparts. The reasons of nonsatisfaction can attribute to the physicians' clinical experiences of some biosimilar medicines from neighboring countries or related to a distrust in the amount of evidence underlying the marketing approval of biosimilars particularly toward those without the U.S. FDA/EMA certifications. For example, Oncolo 6 mentioned: “I don't believe in switching and interchangeability due to the effectiveness issue.”

Furthermore, some physicians (4, 11%) considered the name of the company producing the biosimilar medications before prescribing them to their patients since they prefer European and American companies.

3.2.9. The future role of biosimilar medicines relying on the manufacturer and international certifications

Some physicians ($N = 11, 31\%$) supported the use of biosimilar medicines by relying on the manufacturer and international certifications. Additionally, they advocated the potentially positive role of biosimilar medications in their field future. However, some clinicians believed that the effectiveness of biosimilar medicines and consequently their trust in them varies according to the manufacturer.

“Yes, but not all biosimilar medicines are reliable. It depends on the company” (Nephro 3). “Yes, some biosimilar drugs have been prescribed that have approval from the FDA or EMA such as Zarxim (filgrastim) or that were produced by companies that have their name and reputation in global markets” (Oncol 2).

3.3. Barriers facing physicians to report biopharmaceutical adverse reactions and adherence to the national pharmacovigilance center regulations of ADR reporting

3.3.1. Under-reporting of biopharmaceutical adverse reactions to the national pharmacovigilance center

In general, there was underreporting of biopharmaceutical ADRs to the IqPhvC which mainly relies on HCPs to report ADRs. Additionally, most interviewees (30, 78%) believed there are no serious ADRs associated with biopharmaceutical medicines (Table 3).

“No direct report has been sent to the IqPhvC, but note is submitted to the hospital administration only if any adverse reactions appear” (Oncol 2). “Once in the last year, there was an adverse effect of Avastin for a patient with Proliferative Diabetic Retinopathy which I reported to the Technical Department of the hospital” (Ophtha 4).

3.3.2. Barriers to reporting their adverse drug reactions (ADRs) to the IqPhvC

The physicians experienced several barriers to report biopharmaceutical ADRs. The main reported barriers were inadequate physician-pharmacist communications, the over workload and lack of time due to a small physician-to-patients' ratio in public hospitals. They revealed inadequate cooperation of pharmacists in following up ADRs and reminding physicians of the necessity to submit the reports of ADRs to the IqPhvC (Table 4).

“Workload, large number of patients and inadequate collaboration of pharmacists in reporting of adverse effects of medications” (Rheum 3).

“The pharmacist-physician communication is very primitive” (Neuro 2).

3.3.3. Inadequate awareness of the pharmacovigilance center regulations about reporting biopharmaceutical adverse reactions

Most physicians ($N = 25, 70\%$) were unaware of the IqPhvC regulations (July 2019) about biopharmaceutical ADR reporting. Thus, most of them ($N = 28, 78\%$) have not changed their ADR reporting behavior because they were unaware about the recent pharmacovigilance reporting regulations (Table 3). The regulations emphasized to report the biopharmaceutical company to differentiate between the reference and biosimilar medicines ADRs. Indeed, only 10 out of 36 physicians from various specialties were aware about IqPhvC regulations. The participants believed that the IqPhvC does not effectively role in most Iraqi hospitals related to reporting ADRs of biopharmaceutical medicines since most physicians were not aware of its reporting regulations (Table 3).

“No, I am not familiar with recent regulations of the Ministry of Health about reporting adverse reactions of biopharmaceutical medications; I have not received them” (Rheum 2).

3.3.4. Physician recommendations to the IqPhvC about reporting biopharmaceutical ADRs

The main three themes of the physician recommendations to the IqPhvC included promote HCP awareness (reaching out to physicians), collaborate with physicians and switch to electronic reporting. Many physicians were unaware of the IqPhvC, and its function due to inadequate communication between health institutions and the center (Table 5).

“The method of communication must be easier between the hospital and the Iraqi Pharmacovigilance Center” (Gastro 1). “It is better to convert the paper report into an electronic report which is easier and faster” (Oncol 2).

3.4. The physician recommendations to health officials and healthcare providers about biopharmaceutical medications

3.4.1. Physician recommendations to health officials about sustainable procuring of the same biopharmaceutical medicines

Physician recommendations to the MOH included sustainable providing of same biosimilar medicines to hospitals, not relying on the medicine price as the only determinant to switch between different biopharmaceutical tenders every year, promote awareness of HCPs about biosimilar medicines, and provide the required tests to use these biopharmaceutical medicines. For example, human epidermal growth factor receptor 2 (HER2) test is needed before prescribing breast cancer biological therapy.

“Continuous availability of same medications is necessary to avoid interchangeability between reference and biosimilar medications and continue to give patients the same prescribed treatment whether it is a reference or biosimilar medication” (Rheum 1).

3.4.2. Physician role in enhancing the medication safety of biopharmaceutical medications

The main themes of the participant recommendations to enhance physicians' role in medications safety included monitoring patient lab tests and educating patients about dealing with adverse effects of biopharmaceutical medications (Table 5).

“Patients and their families should be educated about adverse reactions of drugs and how to deal with them. For example, Herceptin® (trastuzumab) is a very effective and safe drug used for the treatment of adjunctive and metastatic breast cancer. Cardiotoxicity is an expected adverse event with trastuzumab (Herceptin). After 3–4 cycles of treatment, the patient needs to do echocardiography (Echo). If the ejection fraction is 50 or less, the drug should be discontinued and needs to consult a cardiologist, and most likely the patient should take Beta Blocker medication; after three weeks, if the patient settles down and the ejection fraction increases over 50%, we can give the patient a reload of Herceptin” (Oncol 6).

3.4.3. Physician recommendations to hospital pharmacists to enhance the safety of biopharmaceutical medications

The main three themes of physician recommendations to hospital pharmacists to enhance medication safety included 1) communicating with physicians, 2) educating patients about prescribed medicines and 3) following up/reporting ADRs (Table 5).

“Pharmacists should follow -up with drug effects and patients by asking the patients who return to the pharmacy after 3 weeks of treatment about the adverse effects if they occurred or not” (Oncol 1).

“I hope that pharmacists will take lectures to learn what are biological medicines, what are their indications, what are their side effects, and how physicians can benefit from this. For example, they can advise

physicians on switching and inform physicians when any side effect of treatment occurs and report ADRs to the Iraqi Pharmacovigilance Center” (Gastro 5).

“Pharmacists should report any side effects that appear with biopharmaceutical medicines and inform doctors in order to avoid them for other patients” (Rheum 5).

4. Discussion

4.1. Demographics

One of the strengths of this study was covering almost all specialties using biopharmaceutical medicines, and most participants were high-rank specialists in their field with extensive experience. The study targeted physicians who had knowledge/experience with biopharmaceutical medicines and the findings may not represent all physician perspectives.

4.2. Reference biological medications are well effective with manageable adverse reactions

They confirmed that originators are effective with manageable adverse reactions. A review of studies conducted in several Asian countries found biological medicines are effective. However, most Asian patients cannot afford their high costs due to the countries' economic problems.²² Iraq may have similar experience to the Asian countries since the Iraqi MOH was not able to provide all essential medicines in sustainable way although the MOH secured reference biological medicines for certain time. For example, according to the Iraq country profile 2020, KIMADIA was able to secure only 60% of the essential medicines in 2019¹⁷ Thus, the MOH started to approve biosimilar alternatives to replace reference biological medicines to save money since it has limited budget.

The physicians revealed that no serious adverse reactions had been reported with the reference biological medicines when they are used with caution for proper indications and patients are monitored by physicians and pharmacists. Similarly, a study conducted in the Middle East found the major complications of all self-injectable biological agents are injection site reactions (ISRs), including swelling, erythema, pruritus, and pain around the site of injection.²³ It was found that the incidence rates in both adults and infants ranging from 0.5 to 40%. Enhancing injection procedures, patient counseling, and training can help to minimize the local reactions to injectable biological medicines.²³ It is better to have adequate documentation in Iraqi healthcare settings to enhance the safety of biological medications.

4.3. Effectiveness and adverse reactions of biosimilar medications compared to their reference counterparts

Since the MOH approved some biosimilar medicines that did not have the EMA or FDA certifications before 2020, some physicians were against prescribing such biosimilars. A recent Iraqi survey found that physicians have concerned about biosimilar immunogenicity (78%), quality (93.2%), safety profile (95.1%), and efficacy profile (95.7%)²⁴

Some physicians recommended long-term follow-up between reference and such biosimilar counterparts to measure any difference between them in terms of efficacy and safety. Thus, both biosimilar and reference medicines should be available in public hospitals all the time to provide enough period for the follow-up. compared to our interview findings which targeted only physicians who had experience with biopharmaceuticals.

4.4. Medical record documentation about biopharmaceuticals was inadequate

The reasons behind not availability of adequate documentation probably are high workload on physicians, and not all hospitals have trained

staff to help in medical data entry. Furthermore, electronic medical records are not available in almost all Iraqi hospitals, which mainly rely on paper medical records. Periodic safety update reports were used to evaluate existing post-approval safety monitoring for three biosimilar medicines (Epoetin alfa, Somatropin, and Filgrastim), which reflected approximately 350 million patient days of care.²⁶ Since the documentation is very important to follow up with the safety and effectiveness of biopharmaceuticals, our hospitals or health officials should pay more attention to have adequate documentation about these medications in a patient health record.

4.5. Prescribing and interchangeability preferences depend on biopharmaceutical availability and specialties

Most physicians preferred to prescribe reference biological medicines initially when they are available in the hospital. However, the physicians may have no choice other than switching to the available biopharmaceutical to avoid leaving patients without treatment. Likewise, a recent study found that Iraqi physicians prefer the brand over generic medicines because they believe that brand medicines are more effective and safer compared to their generic counterparts.²⁷ A recent Iraqi survey found 52.8% of physicians do not prescribe biosimilar medications in their daily practice because they are not available in their public hospital pharmacies.²⁴ On the other hand, another Iraqi survey found that 40.2% of the pharmacists agreed with the automatic replacing of reference biologic medicines with its biosimilar counterparts.²⁸ Non-sustainable supply of biopharmaceutical medicines is probably due to the short-term (1 year) procuring contract between KIMADIA, the MOH and pharmaceutical companies (MAHs) to supply medicines for public healthcare settings.

Since most Iraqi physicians did not have long experience with biosimilar medications, they prefer biosimilar medications that have been approved by the U.S. FDA and EMA. In other countries, the availability of reference biopharmaceutical medicines is more sustainable. Countries are willing to include biosimilar medicines for reimbursement, but for commercial reasons they are not always marketed.²⁹ The main reason that the reference medicines are not always available in Iraqi public hospitals can be due to the limited budget in addition to procurement by the State Company for Marketing Drugs and Medical Appliances (KIMADIA) is conducted annually and preferred offers with the lowest price.³⁰ The National Board of Drug Selection (NBDS), has the authority to approve new medications, requests cost-effectiveness analysis about biological medicines from Data analysis Unit before approving new medications into the Essential Medicine List to select the most cost-effective ones.¹⁷ Switching between comparable forms of the same active substance has been licensed under European Union (EU) law to the member states.⁵

Similar to the initial prescribing, the switching between a reference and counterpart biosimilar relies on the availability. A recent systematic review included a total of 178 studies about the outcomes of switching between reference biological and biosimilar medicines. In this review, most randomized controlled trials and real-world evidence indicated that switching from a reference to a biosimilar is not associated with any major efficacy, safety, or immunogenicity problems [29]. However, placebo effects may cause discontinuation of biosimilar medicines after switching from reference medicines [30].

4.6. The future role of biosimilar products to optimize therapy

Physicians believed that their prescribing behavior can be impacted by the economic situation of the country, given that reference medications are costlier than their biosimilar counterparts. The increasing use of biosimilar medicines in the neighboring and European countries encourages Iraqi physicians to prescribe them if they are available in public hospitals. Similarly, a previous study found physicians with adequate knowledge of biosimilar (s) can help patients in transitioning to biosimilar medicines for immune-mediated inflammatory diseases.³¹ The partnership between biosimilar developers and health officials would help to ensure patients have sustainable access to cost-effective treatments.³¹

4.7. Under-reporting and barriers facing physicians to report biopharmaceutical ADRs to the national pharmacovigilance center

In general, the physicians tended to underreport biopharmaceutical ADRs. The physicians believed that inadequate physician-pharmacist collaboration negatively impacts the preventing and reporting ADRs. A study of European system over five-year found that detecting ADRs to the level of the manufacturer is helpful to identify potential safety signals for biopharmaceutical medicines.³² On the other hand, a previous study found that many Latin American countries are also lagging behind Europe and the United States in terms of developing regulatory guidance and efficient pharmacovigilance programs for biosimilars.³³ According to an Iraqi survey to hospital HCPs, three factors significantly influence physician-pharmacist collaborative care including role specification, relationship initiation and trustworthiness.³⁴

4.8. Physician recommendations to the IqPhvC about reporting biopharmaceutical ADRs

Most of the physicians were unaware of the new IqPhvC regulations about the reporting of ADRs of biopharmaceutical medicines using their trade names. The IqPhvC is responsible for post-marketing surveillance for all medicines in both public and private sectors.¹⁷ For instance, a recent Iraqi study found that the IqPhvC also receives reports from the private sector about substandard and falsified medications and ADRs.³⁵ The EMA also requires the marketing authorization holder to submit and maintain a pharmacovigilance plan as part of a risk management plan (RMP) in accordance with European regulations.³⁶

To overcome the barrier of reporting, an electronic application can be implemented to send the ADR reports quickly and easily. Likewise, a previous study recommended adopting the guidelines that allow HCPs to accurately record the safety and performance of a biosimilar as experienced by patients in real-world situations. This can have a significant positive effect on the reporting of biosimilar ADRs to the national pharmacovigilance center.¹⁵

4.9. Physician recommendations to the MOH about procuring reference or biosimilar medications

Because some physicians had inadequate experience with biosimilar medications, the majority were hesitant to prescribe them. Therefore, most physicians agreed to prescribe biosimilar medications only if they have been approved by the U.S. FDA or EMA or they are manufactured by large international companies having good reputation. A recent Iraqi study also refers to the preference of the Ministry of Health to biosimilar medicines who have FDA or EMA certificates.¹⁰ Most Iraqi hospitals have been suffering from the interruption in the availability of treatment, whether reference or biosimilar medications or both, which affects the patient's health condition. Iraqi MOH should procure biosimilar medicines with the EMA/FDA certifications(s) to replace reference medicines which help to save money and secure quantity for larger number of patients. Educational campaign should target physicians to enhance their awareness of biosimilar medicines and increase their acceptance. The procurement of medicines should be sustainable to enhance the clinical outcome of patients. The MOH should seek physician recommendations in addition to conducting the cost-effectiveness analysis of any new biopharmaceutical medicines (see Table 4).

4.10. Physician role in enhancing the medication safety of biopharmaceutical medications

Adverse reactions may become dangerous if patients are not followed up and treated quickly. Thus, physicians should be aware of all side effects to treat them appropriately. Similarly, a systematic review of 20 studies found physicians' knowledge of biosimilars ranged from 49 to 76%. Physicians' views on biosimilars varied as well: 54 to 94% were confident in

prescribing them, while 65 to 67% were unsure. Biosimilars were only prescribed to biologic-naïve patients because physicians seemed to prefer biological drugs over biosimilars. When compared to biological drugs, they saw the main advantages of biosimilars as cost savings and a lower price, though their main concerns were safety, efficacy, and immunogenicity.³⁷

4.11. Physician recommendations to hospital pharmacists to enhance the safety of biopharmaceutical medications

Unfortunately, many physicians were dissatisfied with current pharmacist role in following up/ educating patients and reporting ADRs. The physicians disclosed that pharmacists do not exercise their role in terms of educating patients about the treatment and possible side effects. Additionally, the physicians believed that current pharmacists' attempts are ineffective in monitoring the ADRs of biopharmaceutical medicines and alerting the physicians about any ADRs or potential drug interactions. The physicians also emphasized that pharmacists should remind physicians to send reports of serious side effects to the IqPhvC. The physicians also indicated that pharmacists need to report any serious and repeated adverse reactions with any treatment to enhance patient safety and avoid such events from occurring with other patients. In contrast, according to our recent study findings, Iraqi hospital pharmacists considered the following-up with patient safety and reporting pharmaceutical-ADRs as physician responsibilities.³⁸ On the other hand, a study in Ireland found a difference among the HCP groups in the mean knowledge scores related to ADR reporting and the pharmacovigilance of reference biologicals. It found hospital pharmacists had more ADR monitoring expertise and awareness than other practicing HCPs. Most HCPs who use biological medicines in their practice document them by brand name. HCPs think that batch number recording is useful, but it is more complicated than brand name recording.¹⁵ An Iraqi study found inadequate physician-pharmacist agreement about prescribed medications in public hospitals.³⁹

The study was limited mainly to one province (Baghdad), which the largest one in the country in terms of biopharmaceutical availability. As a qualitative study, the findings may not be generalizable to all 18 Iraqi provinces. Additionally, some physicians declined audio-recording of the interview since they are not familiar with research requiring recording. Declining audio-recording may cause missing detailed information mentioned by the physicians during the interview. Furthermore, half of the participating physicians did not conduct member checking since they had no time.

5. Conclusions

Most physicians preferred to prescribe reference biological medicines initially when they are available in the hospital. Some physicians were not satisfied with the effectiveness of some biosimilar medicines compared to their reference counterparts. However, the initial prescribing and switching between a reference and counterpart biosimilar mainly relies on bioavailability. Most physicians agreed to prescribe biosimilar medications only if they have been approved by the U.S FDA/ EMA or they are manufactured by large international companies having good reputations. Most physicians were unaware about the new pharmacovigilance regulations to report adverse biopharmaceutical reactions. The physicians tended to underreport biopharmaceutical ADRs and believed that inadequate physician-pharmacist communications negatively impact the preventing and reporting ADRs. An electronic application can be implemented to send the ADR reports quickly and easily. Promoting documentation, monitoring, and physician-pharmacist collaboration can enhance the experience of physicians with the safety and effectiveness of biopharmaceutical medicines. The MOH can provide more sustainable biopharmaceutical medicines through relying on procurement of biosimilar medicines having U.S FDA/ EMA certification(s). Finally, physicians need additional training due to their lack of knowledge on biosimilar effectiveness and their hesitancy to prescribe more affordable counterparts.

Author contributions

Hiba Leith Fahmi participated in data collection, analyzing the qualitative data, and writing the first manuscript draft.

Ali Azeez Al-Jumaili did the designing, execution of the study, analyzing data, writing and reviewing the manuscript.

Manal Mohammed Younus participated in the study, designing and reviewing the manuscript in addition to recruiting interviewees.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgments

The authors would like to thank all physicians who agreed to participate in this study and shared their experiences. We are also grateful to the Iraqi Pharmacovigilance Center to provide the updated list of approved biopharmaceutical medicines by the Iraqi Ministry of Health.

Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.rcsop.2022.100162>.

References

- Declerck P, Danesi R, Petersel D, Jacobs I. The language of biosimilars: clarification, definitions, and regulatory aspects. *Drugs* 2017;77(6):671–677.
- Biosimilar and Interchangeable Products. *US Food and Drug Administration* 2017. Accessed April 24, 2021.
- Giuliani R, Taberner J, Cardoso F, McGregor KH, Vyas M, de Vries EGE. Knowledge and use of biosimilars in oncology: a survey by the European Society for Medical Oncology. *ESMO open* 2019;4(2), e000460.
- Karateev D, Belokoneva N. Evaluation of physicians' knowledge and attitudes toward biosimilars in Russia and issues associated with their prescribing. *Biomolecules* 2019;9(2).
- EMA. Biosimilars in the EU Information Guide for Healthcare Professionals. Commission E, ed.: https://www.ema.europa.eu/en/documents/leaflet/biosimilars-eu-information-guide-healthcare-professionals_en.pdf European Medicines Agency. 2019.
- The Impact of Biosimilar Competition in Europe. IQVIA Inc. 2020
- Haustein R. Saving money in the European healthcare systems with biosimilars. *Gener Biosimilars Initiat J* 2012;1.
- Gulácsi L, Brodsky V, Baji P, et al. Biosimilars for the management of rheumatoid arthritis: economic considerations. *Expert Rev Clin Immunol* 2015;11(suppl 1):S43–S52.
- Mysler E, Pineda C, Horiuchi T, et al. Clinical and regulatory perspectives on biosimilar therapies and intended copies of biologics in rheumatology. *Rheumatol Int* 2016;36(5): 613–625.
- Al-Kinani KK, Ibrahim MJ, Al-Zubaidi RF, et al. Iraqi regulatory authority current system and experience with biosimilars. *Regul Toxicol Pharmacol* 2020;117, 104768.
- Prices for Awarding: Drug Awarding Table. *The State Company for Marketing Drugs and Medical Appliances*. 2019. Accessed April 25, 2021.
- de Mora F. Biosimilar: what it is not. *Br J Clin Pharmacol* 2015;80(5):949–956.
- Scheinberg MA, Kay J. The advent of biosimilar therapies in rheumatology—"O brave new world". *Nat Rev Rheumatol* 2012;8(7):430–436.
- Dörner T, Strand V, Castañeda-Hernández G, et al. The role of biosimilars in the treatment of rheumatic diseases. *Ann Rheum Dis* 2013;72(3):322–328.
- O'Callaghan J, Griffin BT, Morris JM, Bermingham M. Knowledge of adverse drug reaction reporting and the pharmacovigilance of biological medicines: a survey of healthcare professionals in Ireland. *BioDrugs Clin Immunotherap Biopharm Gene Therapy* 2018;32(3):267–280.
- Guideline on good pharmacovigilance practices (GVP). *European Medicines Agency*. 2013. Accessed 29 April 2021.
- Ali Azeez Al-Jumaili MMY, Kannan Yasmine JA, Nooruldeen Zinah E, Al-Nuseirat Adi. Pharmaceutical regulations in Iraq: from medicine approval to post-marketing. *East Mediterr Health J* 2021;27. <https://doi.org/10.26719/emhj.21.025>.
- The State Company For Marketing Drugs and Medical Appliances. *Iraqi Ministry of Health*. 2020.
- Clark JWCavLP. *Designing and Conducting Mixed Methods Research*. 2nd Edition ed. USA: SAGE. 2011.
- Palinkas LA, Horwitz SM, Green CA, Wisdom JP, Duan N, Hoagwood K. Purposeful sampling for qualitative data collection and analysis in mixed method implementation

- research. *Adm Policy Ment Health* 2013;42(5):533–544. <https://doi.org/10.1007/s10488-013-0528-y>.
21. Braun V, Clarke V. Using thematic analysis in psychology. *Qual Res Psychol* 2006;3(2):77–101.
 22. Tsai WC. Update on biosimilars in Asia. *Curr Rheumatol Rep* 2017;19(8):47.
 23. Thomaidou E, Ramot Y. Injection site reactions with the use of biological agents. *Dermatol Ther* 2019;32(2), e12817.
 24. As Mohammed, Kadhim DJ. *Iraqi Physicians' Knowledge and Attitudes Toward Biosimilars Baghdad, Iraq: Clinical Pharmacy Department*. University of Baghdad College of Pharmacy. 2020.
 25. Sagi S, Cohen HP, Woollett GR. Pharmacovigilance of biologics in a multisource environment. *J Manag Care Spec Pharm* 2017;23(12):1249–1254.
 26. Layla Abdullah Mahdi DJK, Al-Jumaili Ali Azeez. Knowledge, perception and attitude regarding generic medicines among Iraqi physicians. *Innov Pharm* 2020;11(1):10.
 27. Mohammed AJ, Kadhim DJ. Knowledge and perception of Iraqi pharmacists toward biosimilar medicines. *Iraqi J Pharm Sci* 2021;30(1):226–232.
 28. Moorkens E, Vulto AG, Huys I, et al. Policies for biosimilar uptake in Europe: an overview. *PLoS One* 2017;12(12), e0190147.
 29. Al-Jumaili AA. Iraq Pharmaceutical Country Profile 2020. In: Health Mo, ed. <https://moh.gov.iq/upload/upfile/ar/1375.pdf> 2020.
 30. Kim H, Alten R, Avedano L, et al. The future of biosimilars: maximizing benefits across immune-mediated inflammatory diseases. *Drugs* 2020;80(2):99–113.
 31. Vermeer NS, Giezen TJ, Zastavnik S, Wolff-Holz E, Hidalgo-Simon A. Identifiability of biologicals in adverse drug reaction reports received from European clinical practice. *Clin Pharmacol Ther* 2019;105(4):962–969.
 32. Castañeda-Hernández G, Sandoval H, Coindreau J, Rodriguez-Davison LF, Pineda C. Barriers toward effective pharmacovigilance systems of biosimilars in rheumatology: A Latin American survey. *Pharmacoepidemiol Drug Saf* 2019;28(8):1035–1044.
 33. Al-Jumaili AA, Al-Rekabi MD, Doucette W, Hussein AH, Abbas HK, Hussein FH. Factors influencing the degree of physician-pharmacist collaboration within Iraqi public healthcare settings. *Int J Pharm Pract* 2017;25(6):411–417.
 34. Ali Azeez Al-Jumaili MMY, Saleh Mena Ziad. The epidemic of substandard and falsified medications in a developing country: evaluating the effectiveness of national pharmacovigilance alerts to community pharmacies. *Pharmac Med* 2021. <https://doi.org/10.1007/s40290-021-00386-9>.
 35. Calvo B, Martinez-Gorostiaga J, Echevarria E. The surge in biosimilars: considerations for effective pharmacovigilance and EU regulation. *Therap Adv Drug Safety* 2018;9(10):601–608.
 36. Sarnola K, Merikoski M, Jyrkkä J, Hämeen-Anttila K. Physicians' perceptions of the uptake of biosimilars: a systematic review. *BMJ Open* 2020;10(5):e034183. <https://doi.org/10.1136/bmjopen-2019-034183>.
 37. Fahmi HL, Al-Jumaili AA. Understanding the experience of hospital pharmacists with the effectiveness, safety, adverse drug reaction reporting and interchangeability of biopharmaceutical medicines. *Iraqi J Pharm Sci* 2022;31(1). <https://doi.org/10.31351/vol31iss1pp72-86>.
 38. Al-Jumaili AA, Jabri AMH, Al-Rekabi MD, Abbood SK, Hussein AH. Physician acceptance of pharmacist recommendations about medication prescribing errors in Iraqi hospitals. *INNOVATIONS in pharmacy* 2016;7(3):1–9.