The Whole Experience of Public Hospital Physicians from Several Specialties with Biopharmaceutical Effectiveness, Safety, and Interchangeability: A Qualitative Study

Supplementary 2: Interview themes, subthemes and representative quotes

Table A: The perceptions of physicians from different disciplines about the effectiveness and safety of biopharmaceutical medicines

Theme	Subtheme	Representative quote
The effectiveness of reference biological medications in different field	Reference biological medications are effectiveness for multiple indications	Rheum 5: REMICADE® (infliximab) has good effect in ankylosing spondylitis, systemic lupus erythematosus, dermatomyositis; Etanercept (Enbrel) has a good effect in rheumatoid arthritis, psoriatic arthritis and Humira (Adalimumab) has a good effect in juvenile idiopathic arthritis Oncolo 1- Biological medications are effectiveness such as Trastuzumab (Herceptin) in breast cancer, Bevacizumab (Avastin) in brain tumor, CA colon and ovarian carcinoma, Rituximab (Mabthera) in non-Hodgkin lymphoma, and anti BDL1 (immune check inhibitor) in melanoma Nephro 3 – In case of highly indicated, actually they are effective. For example, Rituximab (Mabthera) is very effective in case of idiopathic membranous nephropathy (MPGN) and antibody mediated transplant rejection and minimal change disease (MCD), and it is first line in membranous glomerulonephritis syndrome
Reference biological medications adverse reactions	Reference biological medications have manageable side effects	Rheum 3 - Adverse effects happen with all biological drugs, but more so with Infliximab (Remicad). For example allergy, hypertension, site of injection reaction, reaction of tuberculosis (in patient has latent tuberculosis) , drug induce lupus . Oncolo 4- For example, Trastuzumab (Herceptin) causes cardiotoxicity, Bevacizumab (Avastin) causes hypertension. Neuro 3- For example, Avonex, Rebif and Betaferon can cause injection site allergy, pancytopenia, and increase liver enzymes.
Prescribed biosimilar medications	Biosimilars are Prescribed in most disciplines according to the availability	Oncolo 1-The first biosimilar was Zarxio (filgrastim) of Sandos company before 3 years, rituximab (Zytux). Nephro 2 - Yes, sure I prescribed human erythropoietin (alfa rh Epo) (Binocrit) Three out of five rheumatologist prescribed Remsima (infliximab)(biosimilar) Derma 2 – Biosimilars are not available in the hospital.

Effectiveness of biosimilar medications compared to their biological counterparts	They have comparable effectiveness Inadequate data about biosimilar effectiveness due to non-sustainability Reference medicines are more effective	Rheum 3: Biosimilars are not inferior to biologicals (comparable efficacy). For example, Ramcema (Infliximab) of al Hikma company and Remsima (infliximab, biological). Oncolo 3- It is impossible to compare between them in terms of effectiveness because we need at least a five-year follow-up, but the biosimilar medications have been available for about one year. Biosimilars need long period of patient follow up. Nephro 3 – If the biosimilar is from a good company, its effectiveness is up to 80 % of the reference. Neuro 1- Biological medications are more effective and have less adverse reactions compared to biosimilar medications.
Adverse reactions of **biosimilar** medications compared to their biological counterparts	Biologicals and biosimilars have comparable adverse reactions Biosimilar may have more adverse reactions than reference medicines	Oncolo 5 – There are comparable side effects of both biological and biosimilar medications. Nephro 2 – They are cost-effective. The new era be biosimilars era globally, but more experience and observation studies are required. Adverse reactions regarding biosimilars are almost the same as biologicals Neuro 1- Biological medications are more effective and have less adverse reactions compared to biosimilar medications. Rheum 1 Hypersensitivity from treatment with biosimilar medications in some patients more than biological medications, so it must be discontinued.
The hospital documentation of reference/biosimilar effectiveness and adverse reactions	It varies according to the hospital Not all hospitals had adequate medical documentation	Neuro 3: Biosimilars are available in Neurology Department at Baghdad Teaching Hospital, Medical City and Hospital for Neurosciences, but are not available in Al Salam Teaching Hospital / Mosul. Nephro 1 - Medical records are available in Nephrology and Renal Transplantation Center, the Medical City, Baghdad Ophtha 2- Yes, there is an electronic medical record. Old tests can be compared with new tests, and Improved visibility and follow-up. Ophtha 4- We have a hospital computer that includes the names of all biological drugs, and after choosing the treatment we choose the number of injections and how many times. Oncolo 2: Documentation is a very poor in all Iraq hospitals.

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Preference in prescribing	Prefer to prescribe reference medicines It depends on the availability	Derma 4- Biological medications are better to be prescribed in government hospital because the effectiveness of brand companies is high while biosimilar medications are better to be prescribed (if available) in the private clinic because they are cheaper for the patient. Nephro 2 -I prefer to prescribe biological medications, but it depends on the availability. If the only available medications are biosimilars, I have to prescribe them.
Biosimilar products role to optimize therapy	Physicians support the use of biosimilar It relies on the manufacturer and international certifications of biosimilars	Oncolo 6- If biosimilar medications are 100% available, we can get long-term experience. Derma 4 - Yes, especially if biosimilars are available in the private sector. Rheum3- Yes, definitely, cost is very important. Nephro 3- Yes, but not all biosimilar products are reliable; It depends on the company.

Table B : Barriers facing physicians to report biopharmaceutical adverse reactions and adherence to the national pharmacovigilance center regulations of ADR reporting

Theme	Subtheme	Representative quote
Inadequate awareness about the IqPhvC regulations about reporting biopharmaceutical adverse reactions	Inadequate collaboration between pharmacovigilance pharmacists and physicians regarding ADR reporting	Oncol 1: I am unaware, the IqPhvC does not have great role in the hospital and it is inactive. Physicians do follow up and everything while the hospital pharmacists don't have any role in anything related to drug -drug interactions, and adverse events. Neuro 2: Actually, there is no good communication between the IqPhvC pharmacists and physicians, lack of the system although it is very important. The IqPhvC pharmacists should inform physicians about the reporting regulations. The Ministry of Health is required within its educational plan to give Pharmacovigilance more attention and reach out the doctors as they are the prescribing agency for treatment. Rheum 3: Yes, I am aware, but not all of physicians are aware about the IqPhvC reporting regulations. Last year's pharmacovigilance unit in the MOH promoted the awareness.
Reported biopharmaceutical adverse reactions to the IqPhvC	No serious biological/ biosimilar adverse reactions	Ophtha 4 - 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. Gastro 3 – We reported ADRs of 2 medications to the pharmacy department in the hospital including Remsima (biosimilar medication)(Infliximab) of AL- HIKMA , Remicade (biological medication) (Infliximab) of Janssen use in treatment of ulcerative colitis and Crohn's disease. Rheum 3 – All biological medications cause adverse events. For example, a case of pancreatitis (reversible) in patient with ankylosing spondylitis lead to attack of abdominal pain and increased lipase. We discontinued the biological drug and when followed up found all things are normal (no reporting)

Barriers to report their adverse reactionsto the IqPhvC	Inadequate physician-pharmacist communications	Rheum 3 – Workload, a large number of patients and inadequate collaboration of pharmacists in reporting of adverse effects of medications (little contact with pharmacists) Neuro 2: The pharmacist-physician communication is very primitive. Gastro 1 – There is no communication between the hospital and the Iraqi Pharmacovigilance Center.
No change in physician reporting behavior after the recent regulations of the IqPhvC about reporting ADRs of biopharmaceutical medications	Most physicians have not changed their reporting behavior because they were unaware about the new reporting regulations	Rheum 2 -No, I am not familiar with recent regulations of the MOH about reporting adverse reactions of biopharmaceutical medications; I have not received them. Oncol 1 -No, few numbers of biosimilar medications are available in Iraq. Any regulations reach to the hospital pharmacy department, the pharmacists should inform all departments about any regulations related biological /biosimilar adverse events.
Physician recommendations to the IqPhvC about reporting biopharmaceutical ADRs	Switching to electronic reporting Reaching out to physicians Collaborate with physicians	Oncol 2- It is better to convert paper reports into electronic reports which is easier and faster Neuro 1 - Organize an inspection tour from time to time for health institutions or they should create a form in which we write any adverse reactions that occur to the patient from treatment and send it to the Iraqi Pharmacovigilance Center. Dermo 5-Train a representative explains the nature of the center work and what is required from us. Neuro 2: The IqPhvC personnel should introduce themselves to physicians and if any complication and adverse reactions occur to patients from medications, should be reported to the IqPhvC and give batch number of medications.

Table C: The recommendations of the participating physicians to health officials and healthcare providers about biopharmaceutical medicines.

Theme	Subtheme	Representative quote
Physician recommendations to the MOH about procuring biopharmaceutical medications	Sustainable providing of same biosimilar medicines to hospitals	Rheum 3 – The MOH needs to provide biosimilar medications to the largest number of patients, especially if the treatment is the same effectiveness, safety, and lower price compared to biological medication. Derma 4 - We want the MOH to provide us with many biosimilar drugs in order to gain experience and notice the adverse effects of the drugs and send reports to the Iraqi Pharmacovigilance Center
	Promote awareness of HCPs about biosimilar.	Rheum 3: More education for physicians, pharmacists and patients about biosimilar medications is needed.
	Not relying on the medicine price as the only determinant to switch between different biopharmaceuticals every year	Rheum 3- Not registering more than 2 biosimilar medications for the same molecule to avoid interchangeability. If we take the price as a main determinant, it is possible in this year we registered biosimilar medications and in the next year, another company may offer biosimilar medications with lower price, so all patients should be converted to cheaper biosimilar medications and this is so far not universally accepted (automatic substitution). Ethically, in all the world, if patients are stable on treatments and have good response, it is not an easy to switch them to another treatment. Nephro 3- I prefer biologicals, but since the country is on the verge of a financial crisis and austerity, we encourage biosimilars. However, the most important thing is for biosimilar medicines should be tested and have approved/ used in the country of the manufacturer.
	Provide the required tests to use these biopharmaceutical medicines	Oncol 6- Meet the needs of the discipline. For example, oncology, in addition to medications, certain tests must be available, and the laboratories must be strengthened in order to be able to use the medications for the best use. For example, the company provides Herceptin must provide the HER test as well

The role of physicians to enhance the medication safety of biopharmaceutical medications	Regular monitoring with lab tests Educate patients about dealing with adverse effects	Rheum 5 – Physicians should monitor patients with lab tests regularly such as monthly for first three months (complete blood count, liver function test, renal function test, general urine examination) then every three months (complete blood count, liver function test, renal function test , chest x-ray , tuberculosis skin test ,interferon gamma release assay). Oncol 6- Patients and their family should be educated about adverse reactions of drugs and how to deal with them Gastro 5 - Biosimilar/biological medications should be given under supervision of the doctors and we should report any potential side effect that may occur to the patient to prevent recurrence in the future. Additionally, we should be notified about side effects and we should prepare emergency medications for these side effects.
Physician recommendations to the hospital pharmacists to enhance the safety of biopharmaceutical medications	Enhance medication safety through educating patients about prescribed medicines	Ophtha 2- Pharmacists should follow up with patients, store the drugs in a correct manner and direct patients to use the treatment within the specified period.

	Follow-up with patients Enhance collaboration with physicians about prescribed medications and reporting of ADRs	Oncol 1- Pharmacists should follow -up with drug effects and patients and ask the patients who return to the pharmacy after 3 weeks of treatment about the adverse effects if they occurred or not. Rheum 3- Pharmacists should have a greater role. A monthly visit of pharmacists to biological drug dispensing centers, meeting with physicians and reminding them of reporting cases. Pharmacists can train and educate physicians with awareness webinars on how to report ADRs. Neuro 2- Pharmacists should have good connections with physicians. Discussing and talking about every prescribed medication between physician and pharmacist is very important. Oncol 6 - Develop a team of pharmacists to conduct their own/national clinical studies.

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Supplementary 3: Interview guide

Inclusion question: Have you had experience with reference biological and/or biosimilar medications? (If no, discontinue the interview)

Part 1: The participant characteristic: Gender, profession, degree, professional title, specialty, years of experience, and workplace.

Part 2: Experience and perceptions about reference biological and biosimilar medicines

1. Have you prescribed (physician)/dispensed (pharmacist) reference biological medications before (please give examples)?

2. What is your perception of the effectiveness of reference biological medications in your field?

3. What is your perception about reference biological medications adverse reactions (with examples)?

4. Have you prescribed/dispensed biosimilar medications? (if yes, please give examples)

5. What is your perception about the effectiveness of biosimilar medications compared to their reference biological counterparts?

6. What is your perception about biosimilar adverse reactions compared to their reference biological counterparts?

7. Do you have in the hospital patient medical records with adequate information that can be used to measure the effectiveness and adverse events of biopharmaceutical mediations?

8. What do you prefer prescribing first: reference biological or biosimilar medications? And why? (for physicians)

9. Do you agree with switching (interchangeability) between reference biological and biosimilar medications for the same patient? and why?

10- Do you think biosimilar products will eventually play a greater role in the optimal therapy in your field?

In other words? do you think biosimilars may have a substantial impact on the range of treatment options in your field?

11. Could you tell us about your experience with biopharmaceutical mediations in terms of effectiveness and their adverse reactions?

Part 3: Experience with the role of the IqPhvC in biopharmaceutical medicines' safety

12. Are you aware of the IqPhvC regulations about reporting biopharmaceutical ADRs?

13. Have you reported biopharmaceutical adverse reactions to the IqPhvC?

If yes, more details (name of biosimilar/reference/indication (disease) /company name/ date/ how many times).

14. Do you experience any barriers to report their adverse reactions to the IqPhvC?

15. Have you changed your reporting behavior after the recent regulations of the MOH about reporting ADRs of biopharmaceutical medications? If no, why?

16. Do you have any recommendations to the IqPhvC about reporting biopharmaceutical ADRs?

17. Do you have any recommendations to the MOH about procuring (buying) biopharmaceutical medications? given that biosimilar medications are usually less expensive compared to their originator (reference) counterparts.

Part 4-Last part: General recommendation to enhance medication safety of biopharmaceutical medications

18. How can physicians enhance the medication safety of biopharmaceutical medications?

19. How can hospital pharmacists enhance the medication safety of biopharmaceutical medications?

Finally, any additional comments about biopharmaceutical medications in terms of effectiveness, safety, availability, reporting their ADRs, and the MOH regulations?

Thank you for your participation