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Cost-effectiveness Analysis of Reference Infliximab (Remicade) Compared to its Biosimilar (Remsima) in Iraqi Patients with Rheumatoid Arthritis (Conference Paper)[#]

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Abstract

The study objective was to conduct a pharmacoeconomic cost-effective analysis between infliximab reference (Remicade) and its biosimilar (Remsima) in patients with rheumatoid arthritis (RA) in two Iraqi hospitals.

This is a retrospective study (natural trial)) that involved a prospective data collection phase as well in which data were collected from patients' medical records and face-to-face interviews from December 2021 to April 2022.

The study included 57 patients who were categorized into two groups according to the type of infliximab they received. 27 patients received reference infliximab (Remicade) and 30 patients received biosimilar infliximab (Remsima). The two groups had comparable demographic and baseline disease parameters, with a mean age of 49.6 years and a BMI of 30.0. The vast majority of participants were women (82.5%) with a low level of formal education (65%). Overall, both infliximab biopharmaceuticals had good effectiveness to reduce RA disease activity (CDAI) and improve patient quality of life. They both had comparable adverse reactions including UTI, fatigue, and headache. There was no significant difference (P-value >0.05) in disease activity between the two groups according to RA clinical disease activity index (CDAI) score across all three-time series: before biological therapy, 14 weeks post-therapy, and 30 weeks post-therapy.

In 2019, Remicade was slightly linked with better quality of life, but costlier ($41,896 per QALY) than Remsima. It was not clear whether the reference biologic (Remicade) or its biosimilar (Remsima) was more cost-effective. In 2021, Remicade was more cost-effective compared to Remsima because Remicade was less expensive and relatively more effective according to its measurement by CDAI and EQ-5D-5L scores. Registering and purchasing both reference infliximab and its biosimilar is a good idea to keep the competition in price and maintain infliximab procurement for Iraqi RA patients.

Keywords: Cost-effectiveness, Rheumatoid arthritis, Infliximab, Biosimilar, Quality of life, Iraq.

دراسة الجدوى الاقتصادية لدواء الانفلكسيماب (Infliximab) المرجعي الرميكيد (Remicade) مقارنةً بالبديل الحيوي الرمسيما (Remsima) في مرضى التهاب المفاصل الرثوي (بحث مؤتمر)[#]

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 # المؤتمر العلمي العاشر لكلية الصيدلة، جامعة بغداد ٢ – ٣ حزيران٢٠٢٢
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الخلاصة

الهدف من هذه الدراسة هو اجراء دراسة الجدوى الاقتصادية بين دواء الانفلكسيماب المرجعي (الريميكيد) وبديله الحيوي (الرمسيما) في مرضى التهاب المفاصل الرثوي في المستشفيات العراقية .

تم اجراء هذا التحليل للاقتصاد الدوائي في مستشفيتين تعليمية حكومية في بغداد العراق التي تحتوي على مراكز لإعطاء دواء الانفلكسيماب المرجعي وبديله الحيوي لمرضى التهاب المفاصل الرثوي. تم جمع البيانات من السجلات الطبية للمريض والمقابلات الشخصية مع المرضى من شهر كانون الاول سنة ٢٠٢١ الى شهر نيسان سنة ٢٠٢٢.

شملت الدراسة ٥٧ مريضا يعانون من التهاب المفاصل الرثوي. تم تصنيف المرضى الى مجموعتين وفقا لنوع الانفلكسيماب الي تلقوه خلال ٣٠ اسبوع .. ٢٧ مريضا تلقى الانفلكسيماب المرجعي(الريميكيد) وتلقى ٣٠ مريض البديل الحيوي (الرمسيما). كان لدى المجموعتين صفات مرضية وديموغرافية واساسية متشابهة، بمتوسط عمر يبلغ ٤٩.٦ عاما ومعدل كتلة جسم يبلغ ٣٠. كانت الغالبية العظمى من المشاركين من النساء (٨٢.٥%) مع مستوى منخفض من التعليم الرسمي (٦٥%). بشكل عام كان كلا من الانفلكسيماب المرجعي وبديله الحيوي فعالية جيدة جدا لتقليل نشاط مرض التهاب المفاصل الرثوي وتحسين نوعية حياة المريض. كان للدوائين اعراض جانبية غير مرغوبة مماثلة بما في ذلك التهاب المسالك البولية والتعب والصداع. لم يكن هناك فرق كبير في نشاط المرض بين المجموعتين وفقا لمؤشر نشاط المرض السريري (CDAI) عند جميع نقاط القياس الثلاثة .. قبل العلاج البايولوجي و ١٤ اسبوعا بعد العلاج و ٣٠ اسبوعا بعد العلاج .في عام ٢٠١٩ كان الريميكيد اكثر فعالية قليلا ويوفر جودة حياة افضل ولكنه اكثر كلفة جدا (٤١،٨٩٦ دولارا لكل QALY) مقارنة بالرمسيما . لذلك لم يكن من الواضح ما اذا كان الدواء البيولوجي المرجعي (الريميكيد) او البديل الحيوي (الرمسيما) اكثر فعالية من حيث التكلفة. في عام ٢٠٢١ كان الريميكيد اكثر فعاليه من حيث التكلفة (افضل جدوى اقتصادية) مقارنة بالرمسيما لان الريميكيد كان اقل تكلفة واكثر بقليل من حيث الفعالية وفقا لنتائج .

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مؤشر نشاط المرض السريري (CDAI) وجودة الحياة (EQ-5D-5L). كان تسجيل وشراء كل من النوعين لدواء الانفلكسيماب له فكرة جيدة للحفاظ على المنافسة في السعر والحفاظ على توفير علاج الانفلكسيماب لمرضى التهاب المفاصل الرثوي

الكلمات المفتاحية: اقتصاديات الدواء, التهاب المفاصل الرثوي ، دواء الانفلكسيماب، البديل الحيوي، جودة الحياة .

Introduction

Rheumatoid arthritis (RA) is a lifelong, systemic autoimmune inflammatory disease that can cause severe joint inflammation and ultimately joint damage [(1)]. Bone and cartilage deterioration and erosions are hallmarks of rheumatoid arthritis (RA), which is characterized by persistent inflammation of cartilaginous diarthrodial joints[(2)]. Pain, stiffness, and inflammation of peripheral joints are the primary symptoms of RA[(3)]. It has a negative impact on patients' quality of life and impairs their ability to carry out daily tasks [(4)]. The global prevalence of RA is 0.46% [(5)]. The prevalence of RA in Iraq was 1% in 1978 and the incidence was 3% in 2011 [(6,7)]. This disease is associated with considerable health and economic costs [(8)]. The objective of treating RA is to diminish impairments in physical function and quality of life by obtaining remission or low disease activity [(9)].

Conventional synthetic disease-modifying antirheumatic drugs (csDMARDs) like methotrexate (MTX) are suggested as first-line therapy for RA [(9)]. The use of biologic DMARDs (bDMARDs), such as a tumor necrosis factor inhibitor (TNFi), is advised by the European League Against Rheumatism (EULAR) for patients who do not respond adequately to conventional DMARDs [(10)].

Infliximab is a monoclonal antibody that inhibits TNF- alpha and is used to treat rheumatoid arthritis and other autoimmune diseases [(11)]. The development of targeted biological therapy for rheumatoid arthritis (RA) is one of the major achievements of contemporary medicine. This is especially true for rheumatoid arthritis (RA), [(12)].

Due to the complexity of biological medicine research and manufacturing processes, the prices of these medicines are quite expensive, and they create a significant strain on healthcare systems. Furthermore, the lack of patient access to biological medicines has been a growing problem in several countries [(13,14)]. Numerous reference biological medicines are reaching patent expiration, prompting the development of so-called 'biosimilar' pharmaceuticals. A biosimilar is described as "a biotherapeutic product that is equivalent in quality, safety, and effectiveness to an existing licensed reference biotherapeutic product" [(15)]. The introduction of biosimilars has resulted in price competition and a significant drop in the net prices of biological therapy [(11,16)]. In various countries, biosimilar infliximab (Remsima) has been approved for use in all indications approved for reference infliximab (Remicade) including rheumatoid arthritis [(17)]. Remicade is manufactured and marketed by Janssen Biotech while Remsima is developed by Celltrion Healthcare and commercialized by Hikma Pharmaceuticals. The common infliximab ADRs include fatigue, rash, back pain, headache, nausea, infections (such as urinary tract infection and respiratory tract infection), infusion-related reaction, and dyspepsia [(23)].

The State Company for Marketing Drugs and Medical Appliance (KIMADIA), formed in 1964, is the organization in charge of procuring and distributing medications, medical appliances, and equipment for public health care settings (public hospitals and primary healthcare settings) throughout Iraq [(18)]. One of the main causes for the recent lack of important medications in Iraq has been insufficient funding granted to KIMADIA [(18)]. In order for biosimilars to be successfully included in treatment regimens in Iraq, healthcare professionals and government decision-makers must possess an extensive understanding of biosimilars [(19)].

Due to the rising usage of infliximab and its biosimilar in Iraq as a routine treatment for moderate-to-severe rheumatoid arthritis, their cost-effectiveness must be evaluated. Such a pharmacoeconomics study can provide more information and feedback to the Ministry of Health (MOH) officials to assist them to approve and procure biopharmaceutical medicines in a way that saves money and enhances the patient clinical outcome. This is the first Pharmacoeconomics study in Iraq measuring the cost-effectiveness of reference biological medicine (infliximab) compared to its biosimilar. The study objective was to conduct a Pharmacoeconomics study (cost-effective analysis) between reference infliximab reference (Remicade) and its biosimilar (Remsima) in patients with rheumatoid arthritis in Iraqi hospitals.

Patients and Method

Study design

This is a retrospective multicenter study (natural trial) that involved a prospective data collection phase as well. The study was conducted at two large teaching governmental hospitals in Baghdad, Iraq (Baghdad Teaching Hospital and Al-Yarmouk Teaching Hospital), which normally provide infliximab to RA Iraqi patients. Data were collected from patients' medical records and face-to-face interviews with the patients from December 2021 to April 2022.

Patients and settings

This study recruited a convenient sample of 57 adult outpatients who were diagnosed according to the Iraqi medical practice which usually follows the American College of

Rheumatology/European League Against Rheumatism (ACR/EULAR) 2010 criteria [20]. Those RA patients who received their infliximab doses at Baghdad Teaching Hospital or Al-Yarmouk Teaching Hospital: 30 patients received Remsima and 27 patients received Remicade. Thus, the inclusion criteria were RA patients who received infliximab for at least 14 weeks and had a medical record with infliximab follow-up data. The exclusion criteria were: 1) patients with other autoimmune diseases; 2) cognitive impairment that prevents them from understanding or completing the questionnaires and data collections forms; 3) missing data from their medical records regarding disease activity scores from previous visits, and 4) patients who developed immunogenicity to infliximab and switched to another medication.

The infliximab intravenous dose for the treatment of moderate to severe RA was 3-5 mg/kg and given as an induction regimen at 0, 2, and 6 weeks, followed by a maintenance regimen of 3-5 mg/kg every 8 weeks. According to the data that is currently available, the clinical response is often attained within three months after therapy initiation [21,22]. The dose and type of infliximab given to the patients were determined by rheumatologists. Each rheumatologist is responsible for a small number of patients.

Data collection

Data were collected from medical files using a previously prepared data collection form. Additionally, demographic and clinical data were also collected directly from the patient. *At the time of approaching the patient, the interview, demographic information (age, gender, weight, height, disease duration, smoking, type of occupation, and prior biological medicines used for RA) was collected.*

The frequency of drug adverse reactions (ADRs) was evaluated by asking the patients to report any ADRs that they suffered after adding infliximab to the treatment regimen.

Before each dose, the attending physician assessed the infliximab efficacy using the rheumatoid arthritis clinical disease activity index (CDAI) and noted it in the patient's medical records. The CDAI score ranged from 0 to 76. The CDAI was calculated using the following formula: CDAI = TJC + SJC + PDGA + EDGA. The TJC is the tender joint count of 28 joints (0-28). The SJC is the swollen joint count of 28 joints (0-28) The PDGA is the patient disease global assessment of disease activity on a visual analog scale (VAS)(0–10). The EDGA is the evaluator/physician disease global assessment of disease activity on a visual analog scale (0–10) (23). Remission per CDAI is defined as a score < 2.8; low disease activity is when the CDAI score equals 2.8–10; moderate disease activity is with a score of 10–22; high disease activity is when the score > 22 (24). To measure the clinical response in term of CDAI score (CDAI improvement), the following formula was used (CDAI improvement = $CDAI_{week\ 0} - CDAI_{week\ x}$).

The EQ-5D-5L was utilized to assess the patient's quality of life (QoL) after receiving approval from the European EuroQol Group's foundation. A validated Arabic version of the EQ-5D-5L was used to conduct in-person interviews with RA patients and assess their QoL at two points. The first point is before starting infliximab treatment which is measured retrospectively (recall QoL) and the second point is at present (visit) time. The EQ-5D-5L is a QoL tool that has been implemented across a variety of illness areas. It consists of the five dimensions: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. Each dimension has five possible responses (no problems, mild problems, moderate problems, severe problems, and extreme problems). Answers are displayed as a single-digit number between 1 and 5 for each dimension, indicating the chosen severity level [25]. By using the EQ-5D-5L Index Value set for the general population of Zimbabwe, we were able to convert the health status reported in the EQ-5D-5L questionnaire into a utility value [26]. The researchers hypothesized that among the nine nations for which a value index is available, Zimbabwe's living conditions are more comparable to those of Iraq. The utility is a single numerical value, often between 0 and 1. that reflects the individual's health-related QoL at a given moment [27]. The utility value is used to calculate Quality-adjusted life years (QALY) which is used as an outcome measure in our cost-effectiveness analysis. QALY was calculated using the following formula ($QALY = (Utility_{before\ treatment} - Utility_{after\ treatment}) *$ duration of time spent in health state).

The costs of the reference infliximab (Remicade) and its biosimilar (Remsima) for the years (2019 & 2021) were obtained from the KIMADIA website [28]. After data collection, the direct cost of infliximab was determined. The cost-effectiveness analysis was conducted from a payer (Iraqi Ministry of Health) perspective.

The incremental cost-effectiveness ratio (ICER) was calculated by dividing the difference in total costs (incremental cost) of two medications by the difference in the chosen measure of health outcome (incremental effect) between the two medications using this equation

$$\boldsymbol{ICER} = (\boldsymbol{Cost\ Remicade - Cost\ Remsima}) / (\boldsymbol{Outcome\ Remicade - Outcome\ Remsima})$$ [29].

The ICER result is the 'extra cost per extra unit of health effect'. In this study, the ICER was calculated by two health outcomes. The first one is CDAI improvement after 14 weeks of therapy initiation, and the second one is quality-adjusted life years (QALY).

The ethical approval of the study proposal was obtained from the University of Baghdad College of Pharmacy and the two participating hospitals. Also, verbal approval was obtained from the patients before the face-to-face interview.

Statistical analysis

Descriptive statistics (means, standard deviation, frequencies, and percentages) were conducted for all study items. Data were analyzed using Statistical Package for the Social Sciences (SPSS) software version 25. Since most variables were not normally distributed, we used non-parametric tests to measure the difference between the two groups and when multiple measures of each group. The Mann-Whitney Test was used to measure the differences in CDAI, utility, and QoL measures between the two infliximab groups. Pearson Chi-square was used to measure the association between the infliximab adverse reactions and the type of infliximab used. Friedman's Test and Pairwise Comparisons were used to measure the difference across the three measures of CDAI (baseline, 14 weeks, and 30 weeks post-treatment) within each group. The Wilcoxon Signed Ranks Test was used to measure the difference in the utility, and QoL domains pre- and post-treatment within each group. A P-value of less than 0.05 was considered statistically significant.

Results

The study sample was 57 patients with rheumatoid arthritis (RA). The patients were categorized by the rheumatologists into two groups according to the type of infliximab they received for more than 14 weeks: 27 patients received reference infliximab (Remicade) and 30 patients received biosimilar infliximab (Remsima). The two groups had comparable demographic and baseline disease parameters, with a mean age of 49.6 years and a BMI of 30.0. The vast majority of participants were women (82.5%) with a low level of formal education (65%) (Table 1).

Table 1. The characteristics of the participating rheumatoid arthritis patients

Parameter	**All (n=57) Mean (Std. dev)**	**Remicade (n=27) Mean (Std. dev)**	**Remsima (n=30) Mean (Std. dev)**
Age (Years)	49.58 (10.25)	49.59 (11.29)	49.57 (9.42)
Weight (Kg)	79.14 (16.93)	81.63 (16.05)	76.90 (17.65)
Height (cm)	162.12 (8.78)	163.63 (6.93)	160.77 (10.10)
BMI *	29.99 (5.47)	30.38 (5.05)	29.65 (5.88)
Total Dose (mg)	308.70 (78.56)	296.30 (80.77)	320.00 (76.11)
Dose (mg/Kg)	3.99 (0.99)	3.71 (1.07)	4.24 (0.84)
	N (%)	**N (%)**	**N (%)**
GENDER			
• Male	10.0 (17.50)	6.0 (22.20)	4.0 (13.30)
• Female	47.0 (82.50)	21.0 (77.80)	26.0 (86.70)
Smokers	6.0 (10.55)	1.0 (3.70)	5.0 (16.70)
Occupation			
• Sedentary	51.0 (89.50)	24.0 (88.90)	27.0 (90.00)
• physical	6.0 (10.50)	3.0 (11.10)	3.0 (10.00)
Education level			
• Illiterate or Primary	37.0 (64.90)	15.0 (55.60)	22.0 (73.30)
• Secondary	13.0 (22.80)	7.0 (25.90)	6.0 (20.00)
• Graduated	7.0 (12.30)	5.0 (18.50)	2.0 (6.70)

*BMI = Body mass index

The adverse drug reactions with the highest prevalence were fatigue (26.3%), nausea (22.80%), headache (17.50%), and urinary tract infection (UTI) (29.90%) **(**Table 2). The Remsima-containing treatment regimen was associated with a significantly higher incidence of nausea (76.9%) compared to the Remicade-containing treatment regimen group (23.2%). On the other hand, there was no significant association (P-value > 0.05) between the type of infliximab-containing regimen (reference vs biosimilar) regarding the incidence of other main three adverse reactions (headache, fatigue, and UTI) (Table 2).

Table 2. The adverse reactions of infliximab-containing treatment regimen in the participating RA patients.

Adverse reaction	**All (N=57) (%)**		**Remicade (n=27) (%)**		**Remsima (n=30) (%)**		**P-value**
Nausea	13.0	(22.80)	3.0	(11.10)	10.0	(33.30)	.046*
Headache	10.0	(17.50)	3.0	(11.10)	7.0	(23.30)	.304
Fatigue							.241
• Mild	11.0	(19.30)	4.0	(14.80)	7.0	(23.30)	
• Moderate-Severe	4.0	(7.00)	1.0	(3.70)	3.0	(10.00)	
Urinary tract infection							.576
• Mild	3.0	(5.30)	1.0	(3.70)	2.0	(6.70)	
• Moderate-Severe	14.0	(24.60)	6.0	(22.20)	8.0	(26.70)	
Allergic Reaction	8.0	(14.00)	4.0	(14.80)	4.0	(13.30)	NA
Rash	3.0	(5.30)	1.0	(3.70)	2.0	(6.70)	NA
Dyspepsia	3.0	(5.30)	1.0	(3.70)	2.0	(6.70)	NA
Respiratory tract infection	2.0	(3.50)	0.0	(0.00)	2.0	(6.70)	NA

*Significant (P-value <0.05) according to Pearson Chi-Square. NA=not applicable due to the small sample.

The majority of patients (71.9%) were new to biological disease-modifying antirheumatic drugs (DMARDs), with comparable percentages between the Remicade (74.1%) and Remsima (70.0%) groups. Other rheumatoid arthritis drugs were also used as concurrent treatments, such as methotrexate and non-steroidal anti-inflammatory drugs (NSAIDs). More than half of the RA patients were taking methotrexate concomitantly with infliximab (59.30% of the Remicade group and 63.30% of the Remsima group**)** (Table 3).

Table 3. The medication history of the participating RA patients

Other RA medicines	All, N=57 (%)		Remicade, n=27 (%)		Remsima, n=30 (%)	
Methotrexate use	35.0	(61.40)	16.0	(59.30)	19.0	(63.30)
NSAID* drug use	27.0	(47.40)	11.0	(40.70)	16.0	(53.30)
Corticosteroids drug use	22.0	(38.60)	9.0	(33.30)	13.0	(43.30)
Infliximab treatment duration						
• Patients reached 14 weeks	57.0	(100.00)	27.0	(100.00)	30.0	(100.00)
• Patients reached 30 weeks	41.0	(71.90)	24.0	(88.89)	17.0	(56.67)
Previous biological therapy						
• No Previous biological therapy	41.0	(71.90)	20.0	(74.10)	21.0	(70.00)
• Etanercept	16.0	(28.10)	7.0	(25.90)	9.0	(30.00)
• Adalimumab	4.0	(7.00)	3.0	(11.10)	1.0	(3.30)
• Rituximab	2.0	(3.50)	2.0	(7.40)	0.0	(0.00)
Other medications						
• Leflunomide	5.0	(8.80)	2.0	(7.40)	3.0	(10.00)
• Pregabalin	2.0	(3.50)	2.0	(7.40)	0.0	(0.00)
• SSZ*	2.0	(3.50)	0.0	(0.00)	2.0	(3.50)
• HCQ*	8.0	(14.00)	4.0	(14.81)	4.0	(13.33)

*NSAIDs=non-steroidal anti-inflammatory drugs. SSZ =sulfasalazine. HCQ =Hydroxychloroquine.

There was no significant difference (P-value > .05) in disease activity between the two groups according to RA clinical disease activity index (CDAI) score across all three-time series: before biological therapy , 14 weeks post-therapy, and 30 weeks post-therapy. The differences between the two groups in terms of the improvements in CDAI score were not statistically significant (P-value >0.05) after 14 weeks of infliximab therapy initiation.

There were no significant differences (P-value > 0.05) in the quality-of-life dimensions and utility of patients between the treatment groups before starting infliximab therapy (Table 4). But after at least 14 weeks of infliximab therapy, the two groups had significant differences according to two QoL measures (pain and anxiety/depression), utility, and duration of disease. In other words, the utility in the Remicade group was significantly (P-value <0.05) higher than that of the Remsima group after treatment (Table 4). Additionally, the two negative dimensions of EQ-5D-5L QoL (pain/discomfort and anxiety/depression) were significantly (P-value <0.05) lower in the Remicade group than that in the Remsima group (Table 4)

Table 4. The difference in the quality-of-life dimensions and utility measures between the groups before treatment and at least 14 weeks after treatment.

			Before treatment		After ≥14 weeks of treatment.	
QoL/utility measures	**Infliximab type**	**N**	**Mean Rank**	**P-value**	**Mean Rank**	**P-value.**
Mobility limitation	Remicade	27	29.22	.916	27.22	.425
	Remsima	30	28.80		30.60	
Self-Care limitation	Remicade	27	25.15	.073	25.76	.128
	Remsima	30	32.47		31.92	
Usual Activities limitation	Remicade	27	27.07	.358	25.63	.134
	Remsima	30	30.73		32.03	
Pain/ Discomfort	Remicade	27	29.07	.970	23.33	.011*
	Remsima	30	28.93		34.10	
Anxiety/ Depression	Remicade	27	27.74	.564	23.70	.017*
	Remsima	30	30.13		33.77	
Utility	Remicade	27	30.96	.369	34.02	.030*
	Remsima	30	27.23		24.48	

*Significant (P-value <0.05) according to Mann-Whitney Test.

After 14 weeks and 30 weeks of receiving Remsima or Remicade therapy, the CDAI scores have significantly improved (P-value <0.05) compared to the baseline (before treatment). However, the CDAI score did not improve significantly (P-value >0.05) between 14 weeks and 30 weeks post-Remsima or Remicade therapy (Table 5A&B) (Table 6 A&B)).

Table 5-A. The difference in CDAI scores across three measures before (baseline) and after Remsima treatment (14 weeks and 30 weeks post-therapy).

Remsima -Null Hypothesis	Test	P-value
The distributions of CDAI 0 time, CDAI 14 weeks and CDAI 30 weeks are the same.	Related-Samples Friedman's Two-Way Analysis of Variance by Ranks	.001*

*Significant (P-value <0.05) according to Friedman's Test

Table 5-B. Pairwise comparisons

Sample 1-Sample 2	Test Statistic	Std. Error	Std. Test Statistic	P-value	Adj. P-value
CDAI 30 weeks - CDAI 14 weeks	.056	.33	.16	.868	1.000
CDAI 30 weeks - CDAI 0 time	1.11	.33	3.33	.001	.003**
CDAI 14 weeks - CDAI 0 time	1.05	.33	3.16	.002	.005**

** Significant (P-value <0.05) according to Pairwise Comparisons test.

Table 6-A. The difference in CDAI scores across three measures before (baseline) and after Remicade treatment (14 weeks and 30 weeks post-therapy).

Remicade-Null Hypothesis	Test	P-value
The distributions of CDAI 0 time, CDAI 14 weeks and CDAI 30 weeks are the same.	Related-Samples Friedman's Two-Way Analysis of Variance by Ranks	.000*

*Significant (P-value <0.05) according to Friedman's Test

Table 6-B. Pairwise comparisons

Sample 1-Sample 2	Test Statistic	Std. Error	Std. Test Statistic	P-value	Adj. P-value
CDAI 30 weeks - CDAI 14 weeks	.10	.28	.36	.718	1.000
CDAI 30 weeks - CDAI 0 time	1.14	.28	3.96	.000	.000*
CDAI 14 weeks - CDAI 0 time	1.04	.28	3.60	.000	.001*

*Significant (P-value <0.05) according to Pairwise Comparisons

The RA patients had a high level of limitations (4.27 to 4.4 out of 5) in their physical activities (mobility, self-care, usual activities) in addition to a high level of pain/discomfort and anxiety/depression (3.9 and 4.53 out of 5) before Remsima therapy (Table 7). Before Remicade therapy, the RA patients had a high level of limitations (3.85 to 4.37 out of 5) in their physical activities (mobility, self-care, usual activities), in addition to a high level of pain/discomfort and anxiety/depression (3.78 and 4.56 out of 5) (Table 7). These QoL dimensions, utility, and VAS scores have been significantly improved (P-value <0.05) after at least 14 weeks of receiving Remsima and Remicade (Tables 7).

Table 7. The measures of utility and QoL dimensions of the RA patients before and after Remsima or Remicade use.

QoL dimensions	Remsima			Remicade		
	N	Mean	Std. Deviation	N	Mean	Std. Deviation
Mobility limitation before treatment	30	4.27	.90	27	4.37	.62
Self-Care limitation before treatment	30	4.37	.89	27	3.85	1.23
Usual Activities limitation before treatment	30	4.40	.89	27	4.26	.81
Pain/Discomfort before treatment	30	4.53	.62	27	4.56	.57
Anxiety/Depression before treatment	30	3.90	1.39	27	3.78	1.28
Utility before treatment	30	.140	.226	27	.189	.19
Mobility limitation after treatment	30	2.70	1.055	27	2.41	1.24
Self-Care limitation after treatment	30	2.37	1.47	27	1.74	1.05
Usual Activities limitation after treatment	30	2.93	1.33	27	2.41	1.21
Pain/Discomfort after treatment	30	3.03	.85	27	2.37	1.21
Anxiety/Depression after treatment	30	2.83	1.28	27	2.04	1.25
Utility after treatment	30	.576	.216	27	.683	.181

According to the listed prices in 2019, Remicade yielded slightly higher QALYs and slightly higher disease activity (CDAI) improvement, but with a higher cost. The incremental cost-effectiveness ratio (ICER) for Remicade was $41,896 to gain one QALY per patient and $405 to reduce one CDAI for one patient (per 14 weeks).

After reducing the cost of Remicade in 2021, Remicade was dominant/more cost-effective compared to Remsima because it yielded slightly higher QALYs and slightly higher (CDAI) improvement with lower cost (Table 10) (Table 11).

Table 10. Cost and benefit of Infliximab.

Cost and benefit of Infliximab			
Cost/Outcome	**Remicade**	**Remsima**	**Difference between Remicade and Remsima**
Cost in 2019 in USD ($) • **One Vial cost (direct cost)** • **Total cost per patient per first 14 weeks** • **Total cost per patient per 1 year**	 $ 405 $ 3,645 $ 10,935	 $ 315 $ 2,835 $ 8,505	 $ 90 $ 810 $ 2,430
Cost in 2021 in USD ($) • **One Vial cost (direct cost)** • **Total cost per patient per first 14 weeks** • **Total cost per patient per 1 year**	 $ 148 $ 1,332 $ 3,996	 $ 200 $ 1,800 $ 5,400	 $ -52 $ -468 $ -1404
Mean CDAI improvement in the first 14 weeks	11.1	9.1	2
Mean QALY gained in 1 year (Utility improvement)	0.494	0.436	0.058
No. of visits in: • **first 14 weeks** • **1 year**	 3 9	 3 9	

Table 11. The incremental cost-effectiveness ratio (ICER) of Remicade to Remsima.

Incremental cost-effectiveness ratio		
	Cost per one CDAI unit in 14 weeks	**Cost per one QALY**
ICER $_{2019}$	$ 405	$ 41,896

Discussion

The majority of participants were illiterate women with an overweight BMI. The RA incidence is higher in women than in men due to sex hormones' role in which estrogens can boost specific immune responses [30]. A higher BMI was connected with a higher incidence of rheumatoid arthritis [31].

In this study, the most common adverse drug reactions (ADRs) of the infliximab-containing regimen were urinary tract infection (UTI), fatigue, nausea, and headache. The incidence of ADRs was comparable in both groups except for nausea, which occurred significantly higher in the Remsima group. UTI was the most common ADR (29.9%) in the participating patients. An American study concluded that infliximab and its biosimilar have a similar safety profile [32]. Infliximab seems to have the highest proportion of adverse drug reactions (23%) reported to the Iraqi pharmacovigilance center (IqPhvC) compared to other biological therapy. [33].

Nearly all participants (50 out of 57) used concurrent medications with Infliximab therapy, including conventional synthetic disease-modifying antirheumatic drugs (CsDMARDs) such as Methotrexate (MTX), Leflunomide, Hydroxychloroquine (HCQ), and Sulfasalazine (SSZ). Josef S Smolen et al., (2020) mentioned that biological disease-modifying antirheumatic drugs (bDMARD) should be combined with CsDMARD for RA patients to increase their efficacy [10]. According to registry data, about 30% of patients receiving biological therapy do not receive a concomitant DMARD [34]. In our study, the majority of RA patients used MTX as a concurrent medication with infliximab therapy. MTX remains the pivotal drug in the RA therapeutics regimen [10]. Additionally, NSAIDs were used occasionally as analgesic and anti-inflammatory for a short period for pain management. The majority of the participating patients were naïve to biological therapy before receiving infliximab, but some of them had received one or two different biological therapy before switching to infliximab. This may be due to a lack of response or availability issues. A previous study mentioned that if one biologic DMARD has failed, adding another biologic DMARD to the treatment regimen should be considered [10].

After 14 weeks of therapy, the disease activity (as measured by the CDAI score) decreased significantly from baseline and remained relatively constant thereafter in both groups. Although there was a higher CDAI score improvement in the Remicade group compared to the Remsima group, this improvement was not statistically significant. This result was comparable with the findings of earlier Swedish and multinational studies [35,36].

The EQ-5D-5L Questionnaire was used to evaluate QoL (utility) in order to compare the two groups and conduct a cost-effectiveness analysis. Because of its uniformity, patient acceptance, and well-established utility, the EQ-5D-5L was selected as the utility outcome [35,36].

All the participating RA patients (in both groups) had a very low QoL before starting Infliximab treatment. It is well known that RA has a significant influence on QoL and functional performance, with QoL being significantly worse compared to the general population [37]. The use of biological infliximab for 14 weeks resulted in a significant improvement in the QoL of patients with RA. Then QoL remained relatively stable for both groups thereafter. A previous study found an enhancement in QoL after receiving infliximab [35]. Remicade was related to a somewhat greater increase in QoL than Remsima, although the difference between the two groups was not statistically significant.

We considered the direct infliximab costs in both 2019 and 2021 since the only cost available at the beginning of the study was 2019 then at the end of the study, the costs changed in 2021. According to the 2019 price list obtained from the KIMADIA website, the total cost of Infliximab per patient for 14 weeks (3 doses) was $ 3,645 for Remicade and $ 2,835 for Remsima. And the one-year total cost (9 doses) was ($ 10,935) for Remicade and ($ 8,505) for Remsima. The Remicade yielded the ICER of $ 405 per one unit reduction of CDAI in 14 weeks and $ 41,896 per QALY. In 2019, Remicade had a higher cost and slightly higher improvement in CDAI and QoL compared to Remsima. In other words, Remicade was more effective but more expensive. Because the Iraqi Ministry of Health (MOH) did not have a specific willingness to pay per QALY, we could not decide which one was more cost-effective. However, if we can assume that willingness to pay is three times the gross domestic product (GDP) per person, Iraqi MOH's willingness to pay can be about $15,000 per QALY (38). In this scenario, Remicade was not cost-effective in 2019 compared to Remsima.

In 2021, there was a reduction in the costs of both Remicade and Remsima according to the price list obtained from the KIMADIA website. The total cost of Infliximab per patient for 14 weeks (3 doses) was $ 1,332 for Remicade and $ 1,800 for Remsima. The one-year total cost (9 doses) was ($ 3,996) for Remicade and ($ 5400) for Remsima. In 2021, the Remicade was dominant (more cost-effective) because it had a lower price and slightly higher improvement in CDAI and QALYs.

The study had some limitations. The study covered two centers in one province (Baghdad) and recruited a relatively small sample size with a follow-up period of 30 weeks.

Conclusion

In 2019, Remicade was slightly more effective and provide a better QoL, but was costlier ($41,896 per QALY) compared to Remsima. Because the Iraqi MOH did not have a specific willingness to pay per QALY, it was not clear whether the reference biologic (Remicade) or its biosimilar (Remsima) was more cost-effective in patients with RA. However, if we can assume that willingness to pay is three times the GDP per person, Iraqi MOH's willingness to pay can be about $15,000 per QALY. In this scenario, Remicade was not cost-effective in 2019 compared to Remsima. In 2021, Remicade was more cost-effective compared to Remsima because Remicade was less expensive and relatively more effective according to CDAI and EQ-5D-5L scores. Overall, both infliximab biopharmaceuticals had good effectiveness in reducing RA disease activity (CDAI) and improving patient QoL. They both had comparable adverse reactions, including UTI, fatigue, and headache. Registering and purchasing both reference infliximab and its biosimilar was a good idea to keep the competition in price and maintain infliximab procurement for RA patients.

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