Iraqi Journal of Biotechnology, 2025, Vol. 24, No. 2, 165-175

The Relationship Between the Biosimilar (Ixifi®) Trough Level, and the Biomarkers Rheumatoid Factor, and Anti-Cyclic Citrullinated Peptide Antibody Levels in a Selected Sample of Iraqi Rheumatoid Arthritis Patients

[1]Reem G. Hussein , [2]Mohammed Q. Yahya Malallah A. Al-Atrakji

[1,2] Department of Pharmacology, College of Medicine, University of Baghdad, Baghdad, Iraq.

Received: June 6, 2024 / Accepted: July 4, 2024 / Published: July 5, 2025

Abstract: Rheumatoid arthritis is an inflammatory autoimmune disorder that affects large and small joints. Ixifi, a biosimilar medication, is produced from infliximab, a protein that targets Tumor Necrosis Factor-α exclusively. The study determines the effect of Ixifi trough level on disease activity, rheumatoid factor, and anti-cyclic citrullinated peptide antibody. A cross-sectional observational study, which included forty-two patients, who had a diagnosis of Rheumatoid arthritis. Three months after initiation of the Ixifi therapy, Ixifi level, CDAI, Anti-CCP, and RF biomarkers were determined. The Ixifi trough level was (5.45 ± 0.28µg/ml) in remission and (3.57 ± 0.14 µg/ml), (2.2 ± 0.17 µg/ml), and (0.66 ± 0.14µg/ml) in the mild, moderate, and severe groups, respectively. The Rheumatoid Factor serum level for the remission was (24.94 ± 0.92 IU/ml), mild was (35 ± 1.93 IU/ml), moderate and severe groups were (60.55 ±1.89 IU/ml) and (70 ±3.18 IU/ml), respectively. Anti-Cyclic Citrullinated Peptide, the serum level for the remission was (22.25 ±1.35 IU/ml), for the mild was (31±1.62 IU/ml), and for the moderate and severe groups was (57.18±2.54 IU/ml, and 67 ±2.3 IU/ml) respectively. The decrease in the Ixifi levels leads to an increase in disease severity and inflammation, whereas high concentrations of Ixifi decrease the disease activity, Rheumatoid Factor, and Anti-Cyclic Citrullinated Peptide Antibody Serum.

Keywords: Anti-Cyclic Citrullinated Peptide, Rheumatoid factor, Rheumatoid Arthritis, Ixifi.

Corresponding author: (Email: Reem.Ghanem1106b@comed.uobaghdad.edu.iq).

Introduction

Rheumatoid arthritis (RA) is a progressive autoimmune inflammatory disease that mostly affects the smaller joints of the body and also has a secondary effect on the bigger joints of the body (1,2). Rheumatoid arthritis is characterized by chronic pain, stiffness, tenderness, increased warmth, and inflammation in the joints (3).

Rheumatoid arthritis has the potential to limit movement and impede the ability to carry out everyday chores. (4,5). The prevalence rate of RA is as high as 1%(6). The prevalence of RA in Iraq is reported to be 1% (7-9). The exact cause of RA is still unknown, although it is believed to be the consequence of a complicated interaction of genetic, environmental, and hormonal factors (10-12). Over the years, several treatment methods have been used to improve the health of patients, reduce the number of negative occurrences, and evaluate the safety and efficacy of new active substances (13,14). The therapy

for RA may be divided into two major categories: Conventional synthetic disease-modifying anti-rheumatic drugs (csDMARDs) and Biological DMARDs, which encompass both the biological originator and biosimilar DMARDs. Janus kinase inhibitors are the sole officially authorized targeted synthetic DMARDs (disease-modifying anti-rheumatic medicines) (15). On the contrary, there are some drugs used with therapy at the start, during disease flare-ups, or when a change needs to be made between conventional synthetic disease-modifying anti-rheumatic medicines (csDMARDs), such as steroid and nonsteroidal anti-inflammatory drugs (16, 17). Biological anti-tumor necrosis factor medications are extremely effective therapies for Rheumatoid Arthritis (18). Ixifi is a monoclonal chimeric antibody, designed to bind to the tumor necrosis factor. For all eligible applications of the reference medication Remicade® (infliximab), Ixifi is utilized in the treatment of numerous autoimmune disorders; it has obtained authorization as a biosimilar drug (19).

Patients and Methods

Study design.

Cross-sectional observational research was conducted at the Specialised Centre of Rheumatology/ Baghdad Teaching Hospital in Baghdad, Iraq from Jan.2023 to Jan.2024. A professional physician directed the study.

Sample selection

The current study included a sample of forty-two adult patients diagnosed with RA following the criteria provided by the "European League and Rheumatism Classification" and the "Revised 2010 American College of Rheumatology". The sample has been chosen conveniently (20).

Inclusion criteria: Patients who confirmed diagnosis of rheumatoid arthritis and received Ixifi treatment for more than 3 months. Additionally, individuals must agree to participate in the required evaluations before being included in the research.

Exclusion criteria: Patients with impaired renal function, those who received alternative biological therapies, pregnant women, individuals with other autoimmune conditions, and patients with infection were ineligible to participate in the study.

Data collection

Demographic data

A properly designed questionnaire was used to gather demographic information (such as age, gender, and smoking status), physical examination findings, family history of RA, and body mass index (BMI). In addition, the data also included further investigations such as CDAI, Anti-CCP, and, RF, as well as Ixifi serum levels.

Clinical disease activity

The Clinical Disease Activity Index (CDAI) was utilized to evaluate the disease's activity. 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). Remission per CDAI is defined as a score < 2.8; low or mild disease activity is when the CDAI score equals 2.8–10; moderate disease activity is with a score of 10–22; high or severe disease activity is when the score> 22 (21).

IXIFI® serum trough level

The serum level of IXIFI® is measured using solid phase enzyme-linked immunosorbent assay (ELISA) by measuring the concentration in the serum samples using the ELISA Kit (MATRIKS BIOTEK, Turkey).

Test Procedure

The assay begins with the preparation of the well plate. 100 µL of Assay Buffer was pipetted into each well. Then, 100 µL of each standard, low-level control, high-level control, and diluted sample was added to the corresponding wells. The plate was covered with adhesive foil and incubated for 30 minutes at room temperature.

During the incubation, the antibodies in the Assay Buffer bind to the target molecule in the samples. The conjugate then binds to the antibodies, forming a complex. The color of the complex changes from blue to yellow when it is exposed to the substrate.

After the incubation, the adhesive foil was removed, and the incubation solution was discarded. The plate was washed three times with 300 µL of Wash Buffer each time. The excess solution was removed by tapping the inverted plate on a paper towel. This step removes any unbound antibodies or conjugate.

Next, 100 µL of Conjugate is added to each well. The plate was covered with adhesive foil and incubated for 30 minutes at room temperature. During this incubation, the conjugate binds to any remaining target molecules in the samples.

After the incubation, the adhesive foil was removed, and the incubation solution was discarded. The plate was washed three times with 300 µL of Wash Buffer each time. The excess solution was removed by tapping the inverted plate on a paper towel. This step removes any unbound conjugate.

Finally, 100 µL of Substrate was added to each well. The plate was incubated for 10 minutes without adhesive foil at room temperature in the dark. The substrate reaction was stopped by adding 100 µL of Stop Solution to each well.

The plate is briefly mixed and the color changes from blue to yellow. The optical density was measured with a photometer at OD 450nm with reference wavelength 650 nm (450/650 nm) within 30 minutes after pipetting the Stop Solution.

The intensity of the yellow color was proportional to the concentration of the target molecule in the sample. The optical density was used to determine the concentration of the target molecule in the sample.

The assay takes a total of 70 minutes to complete.

Rheumatoid factor (RF)

The serum concentration of RF was measured based on sandwich enzyme-linked immune-sorbent assay technology enzyme-linked immunosorbent assay (ELISA) by measuring the concentration in the serum samples using ELISA Kit (Fine test ® - China).

Test procedure

The standards are prepared in a range of concentrations that cover the detection range of the assay.

The diluting samples and reagents were mixed completely.

First, set standard, pilot samples, and control (blank) wells on the pre-coated plate respectively, and then, recorded their positions.

Second, Standards and samples loading: Aliquot 100ul of zero tube, 1st

tube, 2nd tube, 3rd tube, 4th tube into each standard well. Also, add 100ul sample dilution buffer into the control (blank) well. Then, 100ul pilot samples were added into each sample well. Seal the plate and static incubate for 90 minutes at 37°C then mix gently and without touching the sidewall and foam the sample.

Third, wash twice and Remove the cover, then absorb the liquid in the plate or tap the plate on a clean absorbent paper two or three times. Add 350ul wash buffer into each well without immersion. Discard the liquid in the well and tap on the absorbent paper again. This step was repeated twice.

After that add Biotin-labeled Antibody 100ul biotin-labeled antibody working solution into each well. Seal the plate and static incubate for 60 minutes at 37°C. Wash three times Remove the cover, then absorb the liquid in the plate or tap the plate on a clean absorbent paper two or three times. Add 350ul wash buffer into each well and immerse for 1min. Discard the liquid in the well and tap on the absorbent paper again. Repeat the washing step three times. HRP-Streptavidin Conjugate (SABC): Add 100ul SABC working solution into each well. Seal the plate and static incubate for 30 minutes at 37°C. (Put the whole bottle of TMB into the 37°C incubator to equilibrate for 30 minutes.)

Wash five times to remove the cover, and then wash the plate with wash buffer five times.

Add 90ul TMB Substrate into each well, seal the plate and static incubate at 37°C in the dark for 10-20 minutes. Run the microplate reader and preheat for 15 minutes.

Then keep the liquid in the well after staining. Add 50ul stop solution into each well. The color will turn yellow immediately. The order for adding the stop solution and TMB substrate solution was the same. Read the O.D. absorbance at 450nm in a microplate reader immediately.

Anti-Cyclic Citrullinated Peptide Antibody

The serum concentration of Anti-Cyclic Citrullinated Peptide Antibody (Anti-CCP) was measured based on sandwich enzyme-linked immune-sorbent assay technology enzyme-linked immunosorbent assay (ELISA) by measuring the concentration in the serum samples using ELISA Kit (Fine test ® - China)

Test procedure:

As in the previous procedure.

Statistical analysis:

The study's data was entered by GraphPad Prism version 8 (RRID: SCR_002798). we considered the P-value of ≤ 0.05 as statistically significant. The characteristic data was presented as frequencies and percentages; the continuous data was displayed as mean ± standard error of the mean (SEM). The investigation comprised doing correlation analysis to investigate the relationships between the data, followed by performing linear regression.

Results and Discussion

The research study included forty-two participants who had been confirmed to have rheumatoid arthritis (RA) and were undergoing treatment with Ixifi. Table (1) provides a clear overview of the patient's features and characteristics of the disease.

The study's participants were classified into four groups according to their disease activity: remission, mild disease, moderate disease, and severe disease activity.

Table (1): Patient and disease characteristics.

Variable N=42	Results	
Age(years)	Mean±SD	52±18
BMI(k2/m2)	Mean ± SD	27± 3.2
Duration of diseases	Mean ± SD	13± 5
Gender No. (%)	Male	7(17%)
	Female	35(83%)
Smoker status No.(%)	Yes	11(36%)
	No	31(64%)
Marital status No.(%)	Single	6(15%)
	Married	36(85%)
Family history(%)	Yes	23(55%)
	No	19(45%)
Extra-articular manifestation(%)	Yes	13(30%)
	No	29(70%)

***Data expressed as No.: number, %: percentage, Mean±stander deviation.**

The results revealed that among the 42 patients, 16 were in remission, representing 38.09%. the patients with modest disease activity were 8 individuals, representing 19% of the total. According to the categorization of moderate illness, there were a total of 11 individuals, representing 26.19% of the whole population. After analyzing the patients with severe disease activity, it was found that 7 people (16.6%) had as seen in Figure (1).

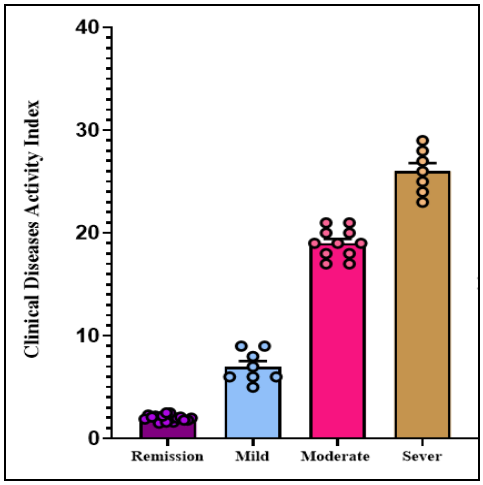

Figure (1): Distribution of patients based on clinical disease activity index.

The goal of this classification was to compare the concentration of Ixifi in different groups, analyze the statistical findings, test its effectiveness in disease activity groups, and evaluate the treatment rest. According to this study, Ixifi was able to establish remission in 38% of the participants in the sample. This proportion aligns with the findings of the study conducted by Koh *et al*. (22) and the one by Al-Salama (23).

In the beginning, the data expressed as mean ± standard error of the mean (SEM) for the trough level of Ixifi in remission is found to be 5.45 ± 0.28 µg/ml. In the mild, moderate, and severe groups, the trough levels of Ixifi are as follows: 3.57±0.14µg/mL,

2.2±0.17µg/mL, and 0.66 ± 0.14 µg/ml. When the group of patients who were in remission was compared to the groups of patients who had mild, moderate, and severe illness, it was discovered that all the statistical data were significant between the three groups. These findings highly had P values of 0.0001, 0.0001, and 0.0001, respectively, which were all significant. The findings of this study suggest that there exists a noteworthy difference between the group experiencing remission and the other groups experiencing illness ($P < 0.01$). When compared to the groups with moderate and severe disease activity, the group with mild disease had P values of 0.0051 and 0.0001, respectively ($P < 0.01$), indicating highly significant differences between the three groups included.

The comparison between the moderate and severe groups showed a highly significant difference with a P value of 0.0071 ($P < 0.01$), as shown in (Figure 2, Table 2).

Table (2): Ixifi trough level (TL) (µg/ml) according to disease activity (Remission, Mild, Moderate Sever disease status).

Colum 1	Colum 2	Colum 1 Mean + - SEM	Colum 2 Mean + - SEM	P Value
Remission (n=16)	Mild (n=8)	5.45± 0.28	3.575 ±0.14	0.0001**
Remission (n=16)	Moderate (n=11)	5.45± 0.28	2.2 ± 0.17	0.0001**
Remission (n=16)	Sever (n=7)	5.45 ± 0.28	0.66 ± 0.14	0.0001**
Mild (n=8)	Moderate (n=11)	3.575± 0.14	2.2 ± 0.17	0.005**
Mild (n=8)	Sever (n=7)	3.575± 0.14	0.66 ± 0.14	0.0001**
Moderate (n=11)	Sever (n=)	2.2± 0.17	0.66 ± 0.14	0.007**

***One-way ANOVA followed by Tukey's multiple comparisons post hoc test. Data expressed as mean ± SEM (Standard Error of Mean). *=P<0.01; highly significant results.**

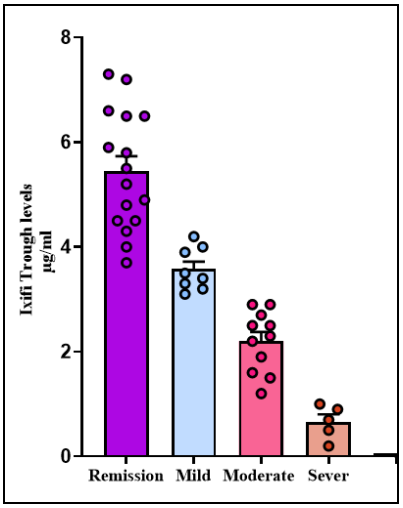

Figure (2): Serum trough level (TL) of Ixifi in RA patients, based on CDAI.

This research aims to increase knowledge regarding the relationship between Ixifi TL and disease severity categories in RA patients. The evaluation of Ixifi TL demonstrated distinct patterns across different disease groups, offering valuable insights into the possibility of its use in predicting disease progression, as well as in evaluating the efficacy of treatments. The fluctuations observed in the trough levels Ixifi among patients diagnosed with RA, who have varying degrees of disease severity, offer significant insights into the cause of the condition and the efficacy of therapeutic interventions. Following previous research, for example, those of Sakane *et al.,* (24) and Valido *et al*. (25), the findings of which indicate that higher Ixifi concentrations are associated with better clinical outcomes.

The significant variations in TL among remission and different disease severity groups show the potential of these values to serve as indicators of disease activity. The distinctions observed among the mild and moderate disease groups, as well as the moderate and severe illness groups, demonstrate the alterations in the Ixifi response that transpire in tandem with the progression of disease severity, as mentioned in the research by Kamil *et al*. (26).

Rheumatoid factor is a diagnostic biomarker that is specific to inflammation and has the potential to be utilized for predicting disease activity and evaluating treatment efficacy. The following are the Rheumatoid factor values of RA patients who were treated with Ixifi as shown in Figure 3, the RF value was as follows: (24.94±0.92 IU/ml) for the remission group, (35±1.93 IU/ml) for the mild disease group, (60.55±1.89 IU/ml) for the moderate disease group, and (70±3.18 IU/ml) for the severe disease group.

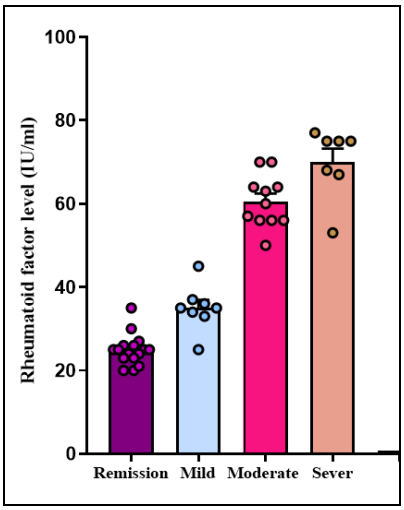

Figure (3): Serum Rheumatoid factor level in RA patients treated with IXIFI®.

This study examined the capacity of the Rheumatoid factor, to estimate disease activity and treatment outcomes in individuals diagnosed with RA. The mean of the Rheumatoid factor measurements showed a significant difference across the disease activity categories, as seen in Figure (3). These differences suggest that RF can assess the severity of the illness. This result is in agreement with the findings of the research done by

Greenblatt *et al*. (27) the study conducted by van der Linden *et al*. (28) as well as the study authorized by Atiqi *et al*. (29)

Anti-CCP is a biomarker for diagnosis specific to inflammation that has the potential to be applied for predicting disease activity and evaluating treatment efficacy. As shown in Figure 4, the Anti-CCP values for RA patients treated with Ixifi were as follows: (22.25±1.35 IU/ml) for the group in remission, (31±1.62 IU/ml) for the group with mild disease, (57.18±2.54 IU/ml) for the group with moderate disease, and (67±2.3 IU/ml) for the group with severe disease.

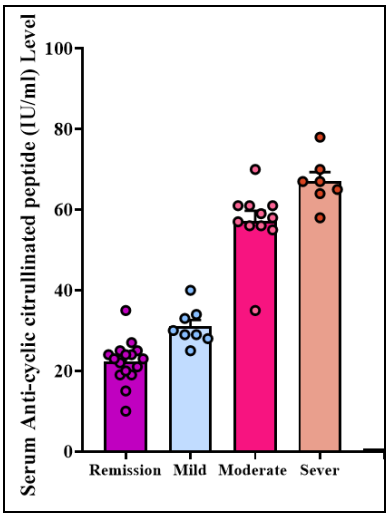

Figure (4): Serum Anti-cyclic citrullinated peptide level in RA patients treated with IXIFI®.

According to the result of this study, there is a relationship between anti-CCP levels and the severity of the diseases, as the Anti-CCP can also determine the outcomes of the therapy, as can be seen in Figure (4). The mean of the Anti-CCP level is evaluated in several different disease activity groups, and the results demonstrate a significant variance between them. The evidence presented here substantiates the substantial role that Anti-CCP plays in determining the severity of RA. This conclusion is corroborated by the studies conducted by Ahmad *et al*. (30) and agrees with the study done by Al-Derzi *et al*. (31).

On the other hand, this study aims to assess the correlation between Ixifi trough levels and RF, and Anti-CCP can be utilized to determine the effect that Ixifi level has on RF and Anti-CCP, as shown in Table (3).

According to the available data, a significant inverse relationship exists between the Ixifi level and both the RF and Anti-CCP. As shown in Figure 5 and Table 3, this would indicate that the concentrations of the biomarkers continue to decline while the Ixifi trough level continues to rise.

Table (3): Correlation of Remicade trough levels with ESR and CRP.

Remicade TL	Slop	R square	P value
RF	-8.591	0.7802	0.0001**
Anti-CCP	-8.697	0.7936	0.0001**

***Correlation test followed by Linear Regression test. RA patients treated with Ixifi, RF: Rheumatoid Factor, Anti-CCP Anti-cyclic citrullinated peptide, *=p <0.01; highly significant differences.**

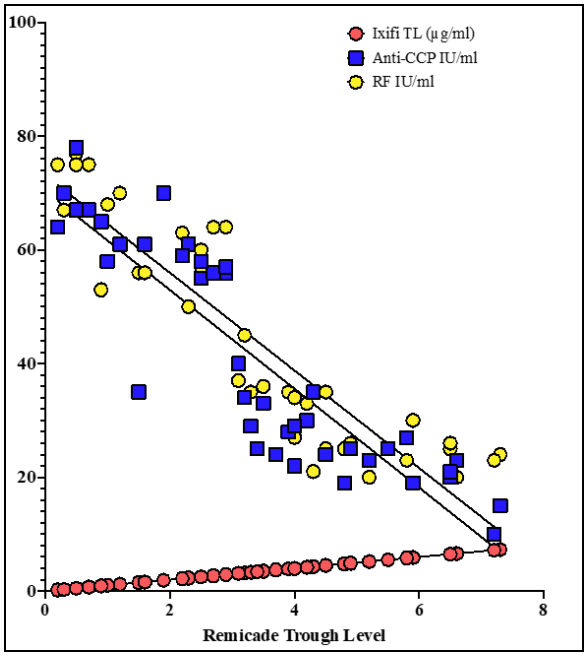

Figure (5): A correlation of Ixifi trough level with RF, and Anti-CCP.

This study assessed the correlations between the Ixifi levels and important biomarkers, which are RF and anti-CCP. The result of the correlation shows a negative regression slope and also shows substantial R-squared values indicating a strong and significant inverse relationship between Ixifi TL and the levels of the crucial biomarkers. The findings provide significant insight into the impact of Ixifi therapy on the alterations in biomarkers associated with disease activity and inflammation. Monitoring the therapeutic levels of Ixifi can control the level of these biomarkers, which may be used to predict and assess the responses to treatment in persons with rheumatoid arthritis. The findings of this inquiry align with the outcomes of the prior investigations (32-34).

Conclusion

There is a clear relationship between higher levels of Ixifi and a reduction in the severity of diseases, as well as a drop in RF and Anti-CCP. These results suggest that the progression of disease severity and inflammation in individuals with rheumatoid arthritis may be caused by a reduction in Ixifi levels.

Acknowledgment

Special thanks to the Center of Rheumatology/ Baghdad Teaching Hospital in Baghdad, Iraq, and the professional physician Dr. Ali Hussein Hafidh for his help in facilitating the collection of data and also the workers in the Center of Rheumatology for their help in this study.

References

1. Mohammed, A. M.; Zayni, S. M.; AL-Anee, M. M.; Corial, F. I. and Al-Rubaee, A. (2023). Diagnostic and predictive values of IL-6 in a group of Iraqi patients with rheumatoid arthritis. Journal of the Faculty of Medicine Baghdad, 65(2), 116-121.
2. Aldouri, L. Y.; Nader, M. I. and Alosami, M. H. (2023). Evaluating TLR4 Gene Expression to Monitor Disease Progression in Iraqi Patients with Rheumatoid Arthritis. Al-Rafidain Journal of Medical Sciences (ISSN 2789-3219), 5(1S), S136-141.
3. Oglah, A. A.; Mohammed, K. I. A. and Alosami, M. H. (2022). A comparative study of serum amyloid A2 with anti-cyclic citrullinated peptide antibody in the prognosis of a group of rheumatoid arthritis

patients in Iraq. Journal of the Faculty of Medicine Baghdad, 64(3), 153-158.
4. Bilal, M.; Qindeel, M.; Nunes, L. V.; Duarte, M. T. S.; Ferreira, L. F. R.; Soriano, R. N., *et al*. (2020). Marine-derived biologically active compounds for the potential treatment of rheumatoid arthritis. Marine Drugs, 19(1), 10.
5. Hameed, M. R.; Khaleel, F. M. and Gorial, F. I. (2024). Galectin-3, Matrix Metalloproteinase-3 and TLR-2 Receptor as Novel Biomarkers in the Diagnosis of Rheumatoid Arthritis. Al-Rafidain Journal of Medical Sciences (ISSN 2789-3219), 7(1), 98-108.
6. Al-Rawi, Z. S.; Alazzawi, A. J.; Alajili, F. M. and Alwakil, R. (1978). Rheumatoid arthritis in population samples in Iraq. Annals of the rheumatic diseases, 37(1), 73-75.
7. Mikhael, E. M.; Mohammed, S. I. and Abdulameer, K. A. (2024). Knowledge, Attitudes, and Perceptions about COVID-19 and its Vaccine among Patients with Rheumatoid Arthritis: A Qualitative Study. Al-Rafidain Journal of Medical Sciences (ISSN 2789-3219), 6(1), 14-19.
8. Ali, D. A. A. K.; Mohammed, M. M. and Jassim, N. A. L. (2024). Nephroblastoma-overexpressed protein as a prognostic marker for high disease activity in Iraqi patients with rheumatoid arthritis. Al-Rafidain Journal of Medical Sciences (ISSN 2789-3219), 6(2), 182-188.
9. Fadhil, H. R.; Al-Jumaili, A. A. and Al-Ani, N. A. (2022). Cost-effectiveness analysis of reference infliximab (Remicade) compared to its biosimilar (Remsima) in Iraqi patients with rheumatoid arthritis (conference paper). Iraqi Journal of Pharmaceutical Sciences, 31(Suppl.), 100-110.
10. Khalil, A. M. and Mohammed, S. S. (2022). Duplex ultrasound surveillance for asymptomatic deep venous thrombosis after total knee joint replacement. Journal of the Faculty of Medicine Baghdad, 64(1), 15-21.
11. Hashim, H. H. and Abed, R. M. (2023). Assessment of some Interleukins in Sample of Iraqi Patients with Ankylosing Spondylitis. Iraqi journal of biotechnology, 22(1): 110-115.
12. Al-Saffar, E. A. and Al-Saadi, B. Q. (2022). Study the association of IRAK1 gene polymorphism and some immunological markers with the risk of rheumatoid arthritis incidence in sample of Iraqi patients. Iraqi journal of biotechnology, 21(2): 46-60.
13. Omar, D. M.; Raheem, A. Q. and Hassan, T. Y. (2021). Risk Factors of Knee Osteoarthritis in Patients attending Rheumatology Clinic in Mosul. Journal of the Faculty of Medicine Baghdad, 63(4), 152-157.
14. Taha, M.A. and Hussain, D.A. (2022). Role investigation of interleukin-IL-17 rs763780 T/C gene polymorphism with Iraqi rheumatoid arthritis patients. Iraqi journal of biotechnology, 21(2), 103-114.
15. Altaha, L. H. (2021). Missed symptoms of Behcet's disease. J Fac Med Baghdad, 63(1). 13-17.
16. Mohammed, A. M.; Zayni, S. M.; AL-Anee, M. M.; Corial, F. I. and Al-Rubaee, A. (2023). Diagnostic and predictive values of IL-6 in a group of Iraqi patients with rheumatoid arthritis. Journal of the Faculty of Medicine Baghdad, 65(2), 116-121.
17. Al-Qiam, Z. H.; Al-Saadi, A. H. and Al, A. A. A. K. M. (2019). Association between Ankylosing Spondylitis and the miR-146a Polymorphisms a Samples of Iraqi Patients. Iraqi journal of biotechnology, 18(2): 242-251.
18. Kharlamova, N.; Hermanrud, C.; Dunn, N.; Ryner, M.; Hambardzumyan, K.; Vivar Pomiano, N., *et al.* Fogdell-Hahn, A. (2020). Drug tolerant anti-drug antibody assay for infliximab treatment in clinical practice identifies positive cases earlier. Frontiers in immunology, 11, 1365.
19. Al-Karkhi, M. A.; Al-Ani, M. M. and Jassim, N. A. (2015). Development of Anti-bodies against Infliximab in Iraqi Patients with Rheumatoid Arthritis. Journal of the Faculty of Medicine Baghdad, 57(3), 241-243.
20. Rider, L. G.; Aggarwal, R.; Pistorio, A.; Bayat, N.; Erman, B.; Feldman, B. M., *et al.* Ruperto, N. (2017). 2016 American College of Rheumatology (ACR)-European League Against Rheumatism (EULAR) Criteria for Minimal, Moderate and Major Clinical Response for Juvenile Dermatomyositis: An International Myositis Assessment and Clinical Studies Group/ Paediatric Rheumatology International Trials Organisation Collaborative Initiative. Arthritis and rheumatology (Hoboken, NJ), 69(5), 782–791.

21. Singh, H.; Kumar, H.; Handa, R.; Talapatra, P.; Ray, S. and Gupta, V. (2011). Use of clinical disease activity index score for assessment of disease activity in rheumatoid arthritis patients: an Indian experience. Arthritis, 2011(1), 146398.
22. Koh, J. H.; Lee, Y.; Kim, H. A.; Kim, J. and Shin, K. (2022). Comparison of remission criteria in patients with rheumatoid arthritis treated with biologic or targeted synthetic disease-modifying anti-rheumatic drugs: results from a nationwide registry. Therapeutic Advances in Musculoskeletal Disease, 14, 1759720X221096363.
23. Al-Salama, Z. T. (2018). PF-06438179/GP1111: an infliximab biosimilar. BioDrugs, 32(6), 639-642.
24. Sakane, H.; Okamura, K.; Inoue, M.; Inoue, H.; Yonemoto, Y.; Mitomi, H.*; et al.* Chikuda, H. (2022). Anti-drug antibodies and rheumatoid factor level in patients with rheumatoid arthritis using the infliximab biosimilar CT-P13. BMC rheumatology, 6(1), 74.
25. Valido, A.; Silva-Dinis, J.; Saavedra, M. J.; Iria, I.; Gonçalves, J.; Lopes, J. P., *et al*. (2019). Efficacy, immunogenicity and cost analysis of a systematic switch from originator infliximab to biosimilar CT-P13 of all patients with inflammatory arthritis from a single center. Acta Reumatologica Portuguesa, 44(4): 303-311.
26. Kamil, M. M.; Jabarah, M. A. H. and Jasim, N. A. (2022). Immunogenicity of the biosimilar CT-P13 infliximab or the original infliximab in Iraqi patients with Ankylosing spondylitis does not correlate with their demographic characteristics. Journal of the Faculty of Medicine Baghdad, 64(4), 261-267.
27. Greenblatt, H. K.; Kim, H. A.; Bettner, L. F. and Deane, K. D. (2020). Preclinical rheumatoid arthritis and rheumatoid arthritis prevention. Current opinion in rheumatology, 32(3), 289-296.
28. van der Linden, M.; Kumari, S.; Montizaan, D.; van Dalen, S.; Kip, A.; Foster, M., *et al.* Chirivi, R. G. (2023, December). Anti-citrullinated histone monoclonal antibody CIT-013, a dual action therapeutic for neutrophil extracellular trap-associated autoimmune diseases. In MAbs, 15(1): 2281763.
29. Atiqi, S.; Hooijberg, F.; Loeff, F. C.; Rispens, T. and Wolbink, G. J. (2020). Immunogenicity of TNF- inhibitors. Frontiers in immunology, 11, 312.
30. Ahmad, A.; Khan, A.; Khan, A. R.; Ahmed, H.; Alajam, R. A.; Alshehri, M. M., *et al.* Esht, V. (2023). Utility of opportunistic infections, joints' involvement and accuracy of various screening tests to diagnose rheumatoid arthritis patients. Medicina, 59(2), 367.
31. Al-Derzi, A. R. (2017). The Contribution of Serum Anti–cyclic Citrullinated Peptide Antibody and Matrix Metalloproteinase-3 in Predicting the Activity of Rheumatoid Arthritis Disease. Journal of the Faculty of Medicine Baghdad, 59(2), 138-144.
32. Kim, H. H.; Kim, J.; Park, S. H.; Kim, S. K.; Kim, O. D. and Choe, J. Y. (2010). Correlation of anti-cyclic citrullinated antibody with hand joint erosion score in rheumatoid arthritis patients. The Korean Journal of Internal Medicine, 25(2), 201.
33. Gr, P.; Dihingia, P.; Jha, A. K.; Gadgade, A. and Agarwal, D. (2022). Rheumatoid arthritis co-relation with anti-CCP antibodies with special reference to its prevalence in asymptomatic first-degree relatives. Mediterranean Journal of Rheumatology, 33(1), 42-47.
34. Al-Rubaye, M. R.; Abdul-Qader, S. N. and Abdul–majeed, N. G. (2012). The Role of Anti-Cathapsin G among Patients with Rheumatiod Arthritis. Journal of the Faculty of Medicine Baghdad, 54(1), 68-72.