https://doi.org/10.31351/vol33iss(4SI)pp222-229

Correlation of the Complement Decay Accelerating Factor, Tumour Necrosis Factors-alpha, and Interleukin-1 Beta with the Response to Rituximab in Rheumatoid Arthritis Patients

Haidar Mohammed Hussein*,[1] and Ali Abdulhussein Kasim[1]

[1] Department of Clinical Laboratory Sciences, College of Pharmacy, University of Baghdad, Iraq.

***Corresponding author**

Received 19/4/2024, Accepted 29/7/2024, Published 15/2/2025

Abstract

Rituximab (RTX) is one of the biological medications that has been used in the treatment of autoimmune diseases and cancer. However, a high percentage of patients may experience resistance to RTX therapy. The study aims to investigate the potential association of serum levels of the complement decay accelerating factor (DAF), as well as the pro-inflammatory cytokines, tumour necrosis factor-alpha (TNF-α) and interleukin-1 Beta (IL-1β); with response to RTX treatment in rheumatoid arthritis patients. A cross-sectional study was conducted under specialized physician supervision in the Specialized Center of Rheumatology at Baghdad Teaching Hospital in Baghdad/Iraq. Ninety adult patients who were already diagnosed with rheumatoid arthritis and receiving RTX intravenous infusion, for at least six months, were enrolled in the study. The selected patients were either responders to RTX (45 patients), or non-responders to RTX (45 patients). The response to RTX was assessed according to the 28-joint Disease Activity Score (DAS28). The serum level of the DAF was significantly higher in RTX non-responders in comparison with RTX responders, (P-value <0.001). Similarly, serum levels of TNF- α and IL-1β, were significantly higher in RTX non-responders in comparison with RTX responders, (P-value <0.001; for each). The serum level of the estimated markers showed a high significant correlation with the 6 months change in DAS28 (P-value <0.001; for each). The Cut-off values, sensitivity, and specificity of DAF, TNF-α, and IL-1β in identifying responders to RTX were (≤417.58 µg/L, 97.8%, and 100%), (≤67.69 ng/L, 97.8%, and 100%), and (≤5.38 ng/L, 95.6%, and 95.6%), respectively. In conclusion, serum levels of DAF, TNF-α, and IL-1β have good potential to be used as markers for the assessment of the response to RTX therapy in rheumatoid arthritis patients.

Keywords: DAF, IL-1β, Response, Rheumatoid arthritis, Rituximab, TNF-α.

Introduction

Rheumatoid arthritis is a chronic autoimmune disorder that primarily targets the joints but may also have prominent extra-articular manifestations. It is characterized by persistent inflammation, leading to symptoms such as pain, swelling, stiffness, and joint damage. Over time, the inflammation and joint deterioration can result in disability if left untreated that has a detrimental effect on patients quality of life or work capability.[1-3] Rheumatoid arthritis is the most prevalent inflammatory joint disease globally. In 2020, more than 17 million people were reported to have rheumatoid arthritis worldwide[4].

The etiopathogenesis of rheumatoid arthritis involves the interplay of predisposing genetic factors and environmental triggers that result in a disruption of immune tolerance and lead to synovial inflammation, occurring in a distinctive symmetric pattern[5-9]. The key pro - inflammatory cytokines in the pathogenesis of rheumatoid arthritis, IL-1 and TNF-α act together to promote inflammation and matrix damage of the arthritic joints[10]. The complement system has essential roles in the clearance of circulating immune complexes; clearance of the trapped immune complexes in the articular tissues causes further damage in these tissues[11]. However, persistent unwanted and unregulated activation complement system was reported to be associated with many inflammatory diseases including rheumatoid arthritis.[12] The imbalance in complement regulation can lead to chronic inflammation in the joints in the context of rheumatoid arthritis[13]. Complement regulators are proteins that control the activation and amplification of the complement cascade. [14] The decay-accelerating factor (DAF) is a complement regulatory protein that protects cells from complement-mediated lysis. It is expressed in a subgroup of fibroblast-like synoviocytes found in the synovial lining[15].

The role of DAF in rheumatoid arthritis is rather complex. Expression of DAF has been correlated with development and progression of inflammatory rheumatoid arthritis in murine model[16]; whereas the opposite was reported in the immune-complex mediated rheumatoid arthritis model[15]. In human, DAF has been shown to be overexpressed on fibroblast-like synoviocytes isolated from patients with rheumatoid arthritis[17]. Holers *et al.* has suggested that DAF expression rises with inflammation, tissue damage and complement activation.[18]

Rituximab (RTX) is a chimeric monoclonal antibody that depletes B cells by binding to the CD20 molecule located on their surface. It is indicated for patients with severe active rheumatoid arthritis who failed to response or intolerant to one or more TNF inhibitors. However, RTX is also given as a first-line biological disease-modifying antirheumatic drug (DMARD) to patients with contraindications to TNF inhibitors. RTX is effective, safe, and well tolerated medication[19-21]. Despite effective depletion of circulating B cells in nearly all patients and complete resolution of inflammation in some of them, only half however respond to RTX treatment[22] .

The study aims to investigate the serum levels of the complement regulator DAF; as well as of the pro-inflammatory cytokines, TNF-α and IL-1β, to assess their potential association with response to RTX therapy in rheumatoid arthritis patients.

Patients and Methods

A cross-sectional study was conducted at the Specialized Center of Rheumatology at Baghdad Teaching Hospital in Baghdad/Iraq during the period from January to November 2023. Ninety adult patients who are already diagnosed with rheumatoid arthritis according to the revised 2010 American College of Rheumatology (ACR)/European League and Rheumatism (EULAR) classification criteria, selected under a consultant rheumatologist supervision, were enrolled in the study[23].

The enrolled patients were those who were on RTX for at least 6 months as a monotherapy; administered as two 1000 mg intravenous infusions, given 2 weeks apart, this cycle is repeated every 24 weeks. Patients receiving other DMARDs steroids or biological agents, and patients with chronic autoimmune diseases or malignancy were excluded.

The selected patients were either responders to RTX (45 patients), or non-responders to RTX (45 patients). The response to RTX was assessed according to the 28-joint Disease Activity Score (DAS28). According to DAS28, the tender joint count (TJC) and swollen joint count (SJC) in 28 joints, including the shoulder, elbow, wrist, knee, metacarpophalangeal and proximal interphalangeal joints are recorded in addition to the measure of the visual analogue scale (VAS) of 100 mm, and erythrocyte sedimentation rate or C-reactive protein. The final value of DAS is calculated according to the following formula[24]:

$$\mathbf{DAS28\ (CRP)} = \mathbf{0.56} \times \sqrt{(\mathbf{TJC28})} + \mathbf{0.28} \times \sqrt{\mathbf{SJC28}} + \mathbf{0.01} \times \mathbf{GH} + \mathbf{0.36} \times \mathbf{ln}(\mathbf{CRP} + \mathbf{1}) + \mathbf{0.96}.$$

$$\boldsymbol{DAS28\ (ESR)} = \mathbf{0,56} * \sqrt{(\boldsymbol{TJC28})} + \mathbf{0,28} \times \sqrt{(\boldsymbol{SJC28})} + \mathbf{0,014} \times \boldsymbol{GH} + \mathbf{0,70} \times \boldsymbol{ln}(\boldsymbol{ESR}),$$

A reduction of DAS28 by at least 0.6 and to a value less than 5.1 from the baseline score after 6 months of RTX therapy was considered indicative of clinical response. Patients who did not show such a reduction in DAS28 were considered non-responders[25]. Sociodemographic data were collected from the patients by direct interview; clinical data were obtained from patient medical records.

Serum levels of DAF, TNF-α, and IL-1β were measured by sandwich-type enzyme-linked immunosorbent assay (ELISA) using the corresponding human ELISA kits purchased from (Nanjing Pars Biochem CO. Ltd; China) according to the manufacturer's instructions. The measurements were performed using HumaReader HS microplate reader (Human Diagnostics, Wiesbaden; Germany)

Data analysis was conducted using the Statistical Package for the Social Science (SPSS) version 25 for Windows. The categorical data was presented as frequencies and percentages; the continuous data was presented as mean ±standard deviation (SD). The normality of data distribution was assessed by Shapiro-Wilk test; the data were normally distributed and parametric tests were used for analysis. The independent t-test was performed to compare the means of continuous variables between the two groups of the study; while Fisher's exact test was performed to compare the categorical variables. Pearson's correlation was performed to study the correlation between variables. P-values less than 0.05 were accepted as significant.

Results and Discussion

The mean age of responders was 48.58±12.6 years, which was significantly lower than the mean age of non-responders (54.22±9.53 years); (P-value = 0.019). Most patients were female, only 5 (11.1%) were male in responders and only 1 (2.2%) was non-responder male; the sex of patients was not significantly different between the two study groups; (P-value = 0.203). Patients in the two study groups were significantly different with regard to family history, of first-degree relatives, to rheumatoid arthritis, (P-value <0.001); (95.6%) of

the RTX non-responders had a positive family history of rheumatoid arthritis. The body mass index (BMI) of RTX non-responders was significantly higher (30.49±5.17 kg/m^2) in comparison to that of the responders (28.09±5.54 kg/m^2), (P-value= 0.037). Erythrocytes sedimentation rate (ESR) and rheumatoid factor (RF) were significantly higher in the RTX non-responders, (P-value= 0.008 and <0.001; respectively). There was no significant difference among patients in the two study groups with regard to smoking status, serum levels of the hepatic enzymes, alanine transaminase (ALT) and aspartate transaminase (AST), and duration of rheumatoid arthritis; (P-value >0.05 for each). The serum levels of ALT and AST of patients in the two study groups were within the reference range.

The baseline DAS28 (the reported score before 6 months) was significantly higher in the RTX responders (5.71±0.80), in comparison with that of the non-responders (5.26±0.99); (P-value 0.02). After 6 months of RTX therapy, DAS28 was significantly lower in the RTX responders (4.12±1.6) in comparison with the non-responders (5.62±0.8); (P-value <0.001). Finally, the RTX responders had a significant reduction in DAS28 after 6 months of RTX therapy compared to the non-responders (P-value<0.001) (Table1).

Table 1. Sociodemographic and clinical characteristics of patients according to RTX response

Variables		RTX responders (45)	RTX non-responders (45)	P-value
Age (year)		48.58±12.6	54.22±9.53	**0.019***
Sex	Male	5 (11.1)	1(2.2)	0.203
	Female	40 (88.9)	44(97.8)	
Family history of rheumatoid arthritis	No	18(40)	2(4.4)	**<0.001***
	Yes	27(60)	43(95.6)	
BMI (kg/m^2)		28.09±5.54	30.49±5.17	**0.037***
Smoking status	No	43(95.6)	43(95.6)	1.0
	Yes	2(4.4)	2(4.4)	
ESR (mm/hour)		37.56±29.65	53.29±34.29	**0.008***
RF (ng/L)		36.12±17.74	118.28±32.48	**<0.001***
ALT (IU/L)		22.94±12.14	18.31±8.77	0.073
AST (IU/L)		20.76±7.39	20.66±8.44	0.775
Duration of disease (year)		11.86±9.43	9.09±5.18	0.318
Baseline DAS28		5.71±0.80	5.26±0.99	**0.020***
Current DAS28		4.12±1.6	5.62±0.8	**<0.001***
Change in DAS28		1.6±0.9	-0.36±0.7	**<0.001***

Where BMI: body mass index; ESR: erythrocytes sedimentation rate; RF: rheumatoid factor; ALT: alanine transaminase; AST: aspartate transaminase; DAS28: 28-joint disease activity score; RTX: rituximab. Continuous data are presented as mean ± SD; categorical data are presented as frequency (%).* refers to a statistically significant difference with a P-value <0.05.

The response rate of women to rheumatoid arthritis therapies was reported to be lower than that of men[26, 27]. Nevertheless, the effect of sex on the response to RTX therapy exhibits inconsistent findings. A lower response rate in females than in males has been reported by the British Society for Rheumatology Biologics Register[28]. In contrast, the French Autoimmunity and Rituximab registry showed that, after 12 months of RTX therapy, remission rates were higher in women who did not receive prior anti-TNF medications proposing that sex might not be the determinant of response to RTX therapy, but being naïve to anti-TNF medications[29]. In an observational study, Mielnik *et al.* showed that there was no significant association between the therapeutic efficacy of RTX therapy in Norwegian rheumatoid arthritis patients and age; however, there was a slight tendency towards a reduced response to RTX in patients aged over 65 years in the later period of the observation[30]. The findings of the present study regarding age and sex in relation to response of RTX therapy were also in partial agreement with that of a retrospective study conducted in Spain, which reported no significant difference in sex and age in active rheumatoid arthritis patients between RTX-responders and RTX non-responders; some of the patients in this study were on other rheumatoid arthritis therapies, and some were receiving RTX as first-line biological therapy [31]. Obesity interferes with B cell development and leads to a dysregulated immune response[32]. Both dysregulated cytokine secretion and hindered B cell development in obesity may contribute to the reduced effectiveness of RTX therapy. Ottaviani *et al.* have reported a negative association between

BMI and reduction in tender and swollen joint count during RTX treatment in rheumatoid arthritis patients; with a lack of association with other response parameters including the change in DAS28[33], which disagrees with the findings of the present study in this regard. The disparity in findings regarding age, gender and BMI of the present study from the aforementioned studies may be attributed, at least in part, to the fact that these studies were large retrospective cohort studies that enrolled patients over a long time interval, thus the treatment plans during the time of observation were subjected to modifications, compared to the present study.

The serum level of the DAF was significantly higher in the RTX non-responder patients (766.44±231.59 µg/L) in comparison with the responder patients (245.2±87.63 µg/L); (P-value <0.001). Similarly, the serum levels of the proinflammatory cytokines were significantly higher in the RTX non-responders in comparison with responders; (P-value <0.001 for each). Serum levels of TNF-α were (145.52±36.03 ng/L) in the non-responders, and (40.8±18.62 ng/L) in the responders; while, serum levels of IL-1β were (8.73±2.32 ng/L) in the non-responders, and (3.58±1.6 ng/L) in the responders; as shown in Table 2.

Table 2. Serum levels of DAF, TNF-α, and IL-1β according to RTX response

Variable	RTX responders (45)	RTX non-responders (45)	P-value
DAF (µg/L)	245.2±87.63	766.44±231.59	**<0.001***
TNF-α (ng/L)	40.8±18.62	145.52±36.03	**<0.001***
IL-1β (ng/L))	3.58±1.6	8.73±2.32	**<0.001***

Where RTX: rituximab; DAF: complement decay accelerating factor; TNF-α: tumour necrosis factor-alpha; IL-1β: interleukin 1- beta.Data are presented as mean ± SD.* refers to a statistically significant difference with a P-value <0.05.

The results of the present study regarding the complement regulatory protein DAF, are consistant with the findings of Viecceli *et al.* proposed that basal expression of complement regulatory proteins is a predictor of clinical response to RTX therapy in rheumatoid arthritis patients[34]. The DAF is one of the complement regulatory proteins; it is a glycoprotein anchored on most cell types. A soluble form of DAF is also present in most body fluids. Both the membrane-bound and the soluble forms have a key role in protecting the host cell from complement-mediated lysis by accelerating the decay of C3 and C5 convertases, which are essential in the amplification of the classical and alternative complement cascade[35]. Administration of RTX to rheumatoid arthritis patients causes fast and nearly total depletion of CD20-positive B cells in the bloodstream, yet only partial depletion in synovial tissue[36, 37]. The resistance of B cells to RTX action in synovial tissue may be attributed to the expression of protective factors including the complement regulators [38]. It has been suggested that DAF expression levels on B cells may influence the response to RTX therapy. Higher DAF expression has been associated with resistance to RTX, while lower DAF expression has been linked to improved treatment outcomes[39]. The major source of DAF in peripheral circulation is that released from neutrophils, monocytes, lymphocytes, and platelets[40]. Makidono *et al.*reported that inflammatory cytokines increase the serum level and surface expression of DAF on peripheral leukocytes in ulcerative colitis patients, and serum DAF level decreases following medical therapy [41]. In addition, the results of the present study regarding the proinflammatory cytokines, TNFα and IL-1β, were in concordance with the results of Tchetina *et al*. who reported that the gene expression of TNFα and IL-1β was negatively associated with the response to RTX[42]. TNF-α and IL-1β play a pivotal role in the pathophysiology of RA and exerts a diverse array of effects[10]; thus failure to response to RTX is highly expected to be associated with elevated serum levels of those proinflammatory cytokines.The correlation study of serum levels of the complement regulator, DAF, with the demographic biochemical and clinical variables revealed that serum levels of DAF have a significant positive correlation with RF and the current DAS28; while they have a significant negative correlation with the change in DAS28 after RTX therapy. On the other hand, the correlation study of the serum levels of the proinflammatory cytokines with the demographic biochemical and clinical variables revealed that serum levels of both TNF-α and IL-1β have a significant positive correlation with RF and the current DAS28; while they have a significant negative correlation with the baseline DAS28, and the change in DAS28 after 6 months of RTX therapy. While there were significant positive correlations between the serum levels of DAF with that of TNF-α and of IL-1β; as shown in Table 3.

Table 3. Correlation of the serum levels of the DAF, TNF-α, and IL-1β with the demographic biochemical and clinical variables

Variable	DAF		TNF-α		IL-1β	
	r	P-value	r	P-value	r	P-value
Age	0.202	0.056	0.206	0.052	0.131	0.219
BMI	0.183	0.084	0.179	0.091	0.204	0.054
Duration of disease	-0.207	0.050	-0.189	0.074	-0.192	0.070
RF	0.850	**<0.001***	-0.115	0.297	-0.146	0.184
ALT	-0.192	0.079	0.041	0.708	-0.038	0.732
AST	-0.020	0.853	0.890	**<0.001***	0.920	**<0.001***
Baseline DAS28	-0.146	0.169	-0.263	**0.012***	-0.254	**0.016***
Current DAS28	0.534	**<0.001***	0.501	**<0.001***	0.472	**<0.001***
Change in DAS28	-0.616	**<0.001***	-0.670	**<0.001***	-0.637	**<0.001***
DAF	-	-	0.924	**<0.001***	0.795	**<0.001***

Where DAF: complement decay accelerating factor; TNF-α: tumour necrosis factor-alpha; IL-1β: interleukin 1-beta; BMI: body mass index; RF: rheumatoid factor; ALT: alanine transaminase; AST: aspartate transaminase; DAS28: 28-joint disease activity score; r: Pearson's correlation coefficient. * refers to a statistically significant difference with a P-value <0.05.

with the disease activity markers is anticipated on the base of their role in the pathophysiology of rheumatoid arthritis. Several *in vitro* studies suggest a potential link between DAF and TNFα as well as IL-1β in the context of different conditions; and that the proinflammatory cytokines lead to shedding of DAF from cell membrane surfaces[43-45]. Nevertheless, the exact nature of this correlation remains to be fully elucidated in rheumatoid arthritis. The receiver operating characteristic (ROC) curve was used to assess the potentials of serum levels of the studied complement regulator and the proinflammatory cytokines in determining non-response to RTX therapy in rheumatoid arthritis patients. Serum levels of DAF, TNF-α, and IL-1β showed very good potential in differentiating responders and non-responders; Table 4 illustrates the cut-off value, the sensitivity and specificity of those biomarkers in this regard. The positive correlation of serum DAF, TNF-α, and IL-1β levels To the best of our knowledge, no previous study has assessed the use of serum levels of DAF, TNF-α, and IL-1β as indicators of response to RTX therapy in rheumatoid arthritis patients; thus we could not compare the findings of the present study in this regards with others.

Table 4. ROC curve analysis of serum levels of DAF, TNF-α, and IL-1β in identifying response to RTX therapy

Variables	AUC	Cut-off value	Sensitivity	Specificity	P-value
DAF (µg/L)	0.990	≤417.58	97.8	100	**<0.0001***
TNF-α (ng/L)	0.988	≤67.69	97.8	100	**<0.0001***
IL-1β (ng/L)	0.970	≤5.38	95.6	95.6	**<0.0001***

Where AUC: area under the curve; DAF: complement decay accelerating factor; TNF-α: tumour necrosis factor-alpha; IL-1β: interleukin 1- beta. * refers to a statistically significant difference with a P-value <0.05.

Conclusion

The serum levels of DAF, TNF-α, and IL-1β are higher in RTX non-responder rheumatoid arthritis patients, and they have good potential to be used in the assessment of the response to RTX therapy among patients with rheumatoid arthritis.

Conflicts of Interest

There is no conflict of interest.

Funding

No sources of financing.

Ethics Statements

This study was performed according to the Helsinki Declaration and approved by the Ethical Committee of the College of Pharmacy, University of Baghdad. All participants were informed about the purpose, and the expected benefits of the study before the agreements of participation were documented.

Author Contribution

The authors confirm their contribution to the paper as follows: study conception and design: Haidar Mohammed Hussein, Ali Abdulhussain Kasim; data collection: Haidar Mohammed Hussein ; analysis and interpretation of results: Ali Abdulhussain Kasim; draft manuscript preparation: Haidar Mohammed Hussein. All authors reviewed the results and approved the final version of the manuscript.

References

1. O'Neil LJ, Alpízar-Rodríguez D, Deane KD. Rheumatoid Arthritis: The Continuum of Disease and Strategies for Prediction, Early Intervention, and Prevention. J Rheumatol. 2024;51(4):337-349.
2. Faiq MK, Kadhim DJ, Gorial FI. The belief about medicines among a sample of Iraqi patients with rheumatoid arthritis. Iraqi J Pharm Sci. 2019;28(2):134-41.
3. Gorial FI, Naema SJ, Ali HO, Hussain SA. The influence of rheumatoid arthritis on work productivity among a sample of Iraqi patients. Al-Rafidain Journal of Medical Sciences. 2021;1:110–117.
4. Black RJ, Cross M, Haile LM, Culbreth GT, Steinmetz JD, Hagins H, *et al*. Global, regional, and national burden of rheumatoid arthritis, 1990–2020, and projections to 2050: a systematic analysis of the Global Burden of Disease Study 2021. The Lancet Rheumatology. 2023;5(10):e594-e610.
5. Ding Q, Hu W, Wang R, Yang Q, Zhu M, Li M, *et al*. Signaling pathways in rheumatoid arthritis: implications for targeted therapy. Signal Transduction and Targeted Therapy. 2023;8(1):68.
6. Mohammed SI, Zalzala MH, Gorial FI. The effect of TNF-alpha gene polymorphisms at -376 G/A, -806 C/T, and -1031 T/C on the likelihood of becoming a non-responder to etanercept in a sample of Iraqi rheumatoid arthritis patients. Iraqi J Pharm Sci. 2022;31(2):113-28.
7. Mutlak QM, Kasim AA, Aljanabi AS. Impact of TYMS gene polymorphism on the outcome of methotrexate treatment in a sample of Iraqi rheumatoid arthritis patients - identification of novel single nucleotide polymorphism: Cross-sectional study. Medicine (Baltimore). 2024;103(23):e38448.
8. Mutlak QM, Kasim AA. Association of the rs1801133 and rs1801131 polymorphisms in the MTHFR gene and the adverse drug reaction of methotrexate treatment in a sample of Iraqi rheumatoid arthritis patients. Pharmacia. 2024;71: 1-8.
9. Naji ZMA, Mohammed SM, Muhammad MF. Uric acid as a natural scavenger of peroxynitrite in a sample of Iraqi patients with rheumatoid arthritis. Iraqi J Pharm Sci. 2012;21(2):51-5.
10. Alunno A, Carubbi F, Giacomelli R, Gerli R. Cytokines in the pathogenesis of rheumatoid arthritis: new players and therapeutic targets. BMC rheumatology. 2017;1(1):1-13.
11. Holers VM, Banda NK. Complement in the initiation and evolution of rheumatoid arthritis. Frontiers in immunology. 2018;9:1057.
12. Kemper C, Ferreira VP, Paz JT, Holers VM, Lionakis MS, Alexander JJ. Complement: The Road Less Traveled. J Immunol. 2023;210(2):119-125.
13. Das N, Anand D, Biswas B, Kumari D, Gandhi M. The membrane complement regulatory protein CD59 and its association with rheumatoid arthritis and systemic lupus erythematosus. Current Medicine Research and Practice. 2019;9(5):182-8.
14. De Boer EC, Van Mourik AG, Jongerius I. Therapeutic lessons to be learned from the role of complement regulators as double-edged sword in health and disease. Frontiers in Immunology. 2020;11:578069.
15. Karpus ON, Kiener HP, Niederreiter B, Yilmaz-Elis AS, van der Kaa J, Ramaglia V, Arens R, Smolen JS, Botto M, Tak PP, *et al.* CD55 deposited on synovial collagen fibers protects from immune complex-mediated arthritis. Arthritis Res Ther 2015;17:6.
16. Tarkowski A, Trollmo C, Seifert PS, Hansson GK. Expression of decay-accelerating factor on synovial lining cells in inflammatory and degenerative arthritides. Rheumatol Int 1992;12:201–205.
17. Karpus ON, Heutinck KM, Wijnker PJ, Tak PP, Hamann J. Triggering of the dsRNA sensors TLR3, MDA5, and RIG-I induces CD55 expression in synovial fibroblasts. PLoS One 2012;7:e35606.
18. Holers VM, Frank RM, Zuscik M, Keeter C, Scheinman RI, Striebich C, Simberg D, Clay MR, Moreland LW, Banda NK. Decay-Accelerating Factor Differentially Associates With Complement-Mediated Damage in Synovium After Meniscus Tear as Compared to Anterior Cruciate Ligament Injury. Immune Netw. 2024;24(2):e17.
19. Garcia-Montoya L, Villota-Eraso C, Yusof MYM, Vital EM, Emery P. Lessons for rituximab therapy in patients with rheumatoid arthritis. The Lancet Rheumatology. 2020;2(8):e497-e509.
20. Hassan EF, Kadhim DJ, Younus MM. Safety profile of biological drugs in clinical practice: A retrospective pharmacovigilance study. Iraqi J Pharm Sci. 2022;31(1):32-42.
21. Gorial FI, Salman S, Abdulazeez ST. Efficacy, safety and predictors of response to rituximab in treatment of Iraqi patients with active rheumatoid arthritis. Al- Anbar Medical Journal. 2019;15(1):16-21.
22. Edwards JC, Szczepanski L, Szechinski J, Filipowicz-Sosnowska A, Emery P, Close DR, Stevens RM, Shaw T. Efficacy of B-cell-targeted therapy with rituximab in patients with rheumatoid arthritis. N Engl J Med. 2004;350(25):2572-81.

23. Rider LG, Aggarwal R, Pistorio A, Bayat N, Erman B, Feldman BM, *et al*. 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. Annals of the rheumatic diseases. 2017;76(5):782.
24. Shrader J, Popovich J, Gracey G, Danoff J. Navicular Drop Measurement in People With Rheumatoid Arthritis: Interrater and Intrarater Reliability. Physical therapy. 2005;85:656-64.
25. Vander Cruyssen B, Van Looy S, Wyns B, Westhovens R, Durez P, Van den Bosch F, *et al*. DAS28 best reflects the physician's clinical judgment of response to infliximab therapy in rheumatoid arthritis patients: validation of the DAS28 score in patients under infliximab treatment. Arthritis research & therapy. 2005;7:1-9.
26. Jayakumar K, Norton S, Dixey J, James D, Gough A, Williams P, *et al*. Sustained clinical remission in rheumatoid arthritis: prevalence and prognostic factors in an inception cohort of patients treated with conventional DMARDS. Rheumatology (Oxford, England). 2012;51(1):169-75.
27. Jawaheer D, Olsen J, Hetland ML. Sex differences in response to anti-tumor necrosis factor therapy in early and established rheumatoid arthritis -- results from the DANBIO registry. The Journal of rheumatology. 2012;39(1):46-53.
28. Soliman MM, Hyrich KL, Lunt M, Watson KD, Symmons DP, Ashcroft DM. Effectiveness of rituximab in patients with rheumatoid arthritis: observational study from the British Society for Rheumatology Biologics Register. The Journal of rheumatology. 2012;39(2):240-6.
29. Couderc M, Gottenberg JE, Mariette X, Pereira B, Bardin T, Cantagrel A, Combe B, Dougados M, Flipo RM, Le Loët X, Shaeverbeke T, Ravaud P, Soubrier M; Club Rhumatismes et Inflammations. Influence of gender on response to rituximab in patients with rheumatoid arthritis: results from the Autoimmunity and Rituximab registry. Rheumatology (Oxford). 2014;53(10):1788-93.
30. Mielnik P, Sexton J, Lie E, Bakland G, Loli LP, Kristianslund EK, *et al*. Does Older Age have an Impact on Rituximab Efficacy and Safety? Results from the NOR-DMARD Register. Drugs & aging. 2020;37(8):617-26.
31. Narvaez J, Díaz-Torné C, Ruiz JM, Hernandez MV, Torrente-Segarra V, Ros S, *et al*. Predictors of response to rituximab in patients with active rheumatoid arthritis and inadequate response to anti-TNF agents or traditional DMARDs. Clinical and experimental rheumatology. 2011;29(6):991-7.
32. Crouch M, Guesdon W, Shaikh S. Obesity suppresses B cell development and impairs antibody production upon antigen challenge. The FASEB Journal. 2017;31(S1):964.7.
33. Ottaviani S, Gardette A, Roy C, Tubach F, Gill G, Palazzo E, Meyer O, Dieudé P. Body Mass Index and response to rituximab in rheumatoid arthritis. Joint Bone Spine. 2015;82(6):432-6.
34. Viecceli D, Garcia MP, Schneider L, Alegretti AP, Silva CK, Ribeiro AL, *et al*. Correlation between cellular expression of complement regulatory proteins with depletion and repopulation of B-lymphocytes in peripheral blood of patients with rheumatoid arthritis treated with rituximab. Revista brasileira de reumatologia. 2017;57(5):385-91.
35. Christy JM, Toomey CB, Cauvi DM, Pollard KM. Chapter 25 - Decay-Accelerating Factor. In: Barnum S, Schein T, editors. The Complement FactsBook (Second Edition): Academic Press; 2018. p. 261-70.
36. Thurlings RM, Vos K, Wijbrandts CA, Zwinderman AH, Gerlag DM, Tak PP. Synovial tissue response to rituximab: mechanism of action and identification of biomarkers of response. Annals of the rheumatic diseases. 2008;67(7):917-25.
37. Kavanaugh A, Rosengren S, Lee SJ, Hammaker D, Firestein GS, Kalunian K, *et al*. Assessment of rituximab's immunomodulatory synovial effects (ARISE trial). 1: clinical and synovial biomarker results. Annals of the rheumatic diseases. 2008;67(3):402-8.
38. Ramwadhdoebe TH, van Baarsen LGM, Boumans MJH, Bruijnen STG, Safy M, Berger FH, *et al*. Effect of rituximab treatment on T and B cell subsets in lymph node biopsies of patients with rheumatoid arthritis. Rheumatology (Oxford, England). 2019;58(6):1075-85.
39. Macor P, Tripodo C, Zorzet S, Piovan E, Bossi F, Marzari R, *et al*. In vivo targeting of human neutralizing antibodies against CD55 and CD59 to lymphoma cells increases the antitumor activity of rituximab. Cancer research. 2007;67(21):10556-63.
40. Nicholson-Weller A, March JP, Rosen CE, Spicer DB, Austen KF. Surface membrane expression by human blood leukocytes and platelets of decay-accelerating factor, a regulatory protein of the complement system. Blood. 1985;65(5):1237-44.
41. Makidono C, Mizuno M, Nasu J, Hiraoka S, Okada H, Yamamoto K, *et al*. Increased serum concentrations and surface expression on peripheral white blood cells of decay-accelerating factor (CD55) in patients with

active ulcerative colitis. The Journal of laboratory and clinical medicine. 2004;143(3):152-8.
42. Tchetina EV, Pivanova AN, Markova GA, Lukina GV, Aleksandrova EN, Aleksankin AP, Makarov SA, Kuzin AN. Rituximab Downregulates Gene Expression Associated with Cell Proliferation, Survival, and Proteolysis in the Peripheral Blood from Rheumatoid Arthritis Patients: A Link between High Baseline Autophagy-Related ULK1 Expression and Improved Pain Control. Arthritis. 2016;2016:4963950.
43. Nasu J, Mizuno M, Uesu T, Takeuchi K, Inaba T, Ohya S, Kawada M, Shimo K, Okada H, Fujita T, Tsuji T. Cytokine-stimulated release of decay-accelerating factor (DAF;CD55) from HT-29 human intestinal epithelial cells. Clin Exp Immunol. 1998;113(3):379-85.
44. Cocuzzi ET, Bardenstein DS, Stavitsky A, Sundarraj N, Medof ME. Upregulation of DAF (CD55) on orbital fibroblasts by cytokines. Differential effects of TNF-beta and TNF-alpha. Curr Eye Res. 2001;23(2):86-92.
45. Spiller OB, Criado-García O, Rodríguez De Córdoba S, Morgan BP. Cytokine-mediated up-regulation of CD55 and CD59 protects human hepatoma cells from complement attack. Clin Exp Immunol. 2000;121(2):234-41.

الارتباط بين عامل تسريع الانحلال للنظام المتمم، عامل نخر الورم ألفا، والإنترلوكين -١ بيتا مع الاستجابة للريتوكسيماب في مرضى التهاب المفاصل الرثوي

حيدر محمد حسين[١] و علي عبد الحسين قاسم[١]

[١] فرع العلوم المختبرية السريرية ، كلية الصيدلة، جامعة بغداد، بغداد، العراق.

الخلاصة

ريتوكسيماب هو أحد الأدوية البيولوجية التي تم استخدامها في علاج أمراض المناعة الذاتية والسرطان. ومع ذلك، قد يواجه نسبة عالية من المرضى مقاومة للعلاج .تهدف هذه الدراسة الى تقييم الارتباط المحتمل لمستويات المصل لعامل تسريع الانحلال للنظام المتمم، بالإضافة إلى السيتوكينات المحرضة على الالتهابات (عامل نخر الورم ألفا والإنترليوكين -١ بيتا) مع الاستجابة لعلاج ريتوكسيماب لدى مرضى التهاب المفاصل الرثوي. أجريت هذه الدراسة المقطعية تحت إشراف طبيب اختصاص في المركز التخصصي لأمراض المفاصل في مستشفى بغداد التعليمي في بغداد / العراق. تم اختيار ٩٠ مريضًا بالغًا مصابا بالتهاب المفاصل الرثوي ويتلقون حقن ريتوكسيماب لمدة ستة أشهر مستمرة على الأقل للمشاركة في الدراسة. كان المرضى المختارون إما مستجيبين للريتوكسيماب (٤٥ مريضًا)، أو غير مستجيبين للريتوكسيماب (٤٥ مريضًا). تم تقييم الاستجابة للريتوكسيماب وفقًا لمؤشر درجة نشاط المرض في ٢٨ مفصلًا. كان مستوى عامل تسريع الانحلال للنظام المتمم في المصل أعلى وبدلالة احصائية لدى غير المستجيبين للريتوكسيماب مقارنة بالمستجيبين للريتوكسيماب (قيمة الاحتمالية=٠,٠٠١), وبشكل مشابه كانت مستويات عامل نخر الورم ألفا والإنترليوكين -١ بيتا في المصل أعلى وبدلالة احصائية لدى غير المستجيبين للريتوكسيماب مقارنة بالمستجيبين للريتوكسيماب (قيمة الاحتمالية=٠,٠٠١ لكل منهما) .أظهر مستوى هذه العوامل في المصل ارتباطا ذو دلالة إحصائية عالية مع التغيرالحاصل لمؤشر درجة نشاط المرض في ٢٨ مفصلًا خلال ٦ أشهر (قيمة الاحتمالية=٠,٠٠١ لكل منهم) .كانت القيم الحدية ومقاييس الحساسية والنوعية لعامل تسريع الانحلال للنظام المتمم وعامل نخر الورم ألفا والإنترلوكين -١ بيتا في تحديد الاستجابة للريتوكسيماب (٤١٧,٥٨ ميكروغرام / لتر، ٩٧,٨٪، و١٠٠٪) و (٦٧,٦٩ نانوغرام / لتر، ٩٧,٨ %، و١٠٠٪) و(٥,٣٨ نانوغرام/لتر، ٩٥,٦٪، و٩٥,٦٪)، على التوالي. وكاستنتاج فمن الممكن استخدام مستويات المصل لعامل تسريع الانحلال للنظام المتمم و عامل نخر الورم ألفا والإنترلوكين -١ بيتا كعلامات لتقييم الاستجابة لعلاج الريتوكسيماب في مرضى التهاب المفاصل الرثوي.

الكلمات المفتاحية: عامل تسريع الانحلال للنظام المتمم, الإنترلوكين -١ بيتا ، الاستجابة، ريتوكسيماب،التهاب المفاصل الرثوي، عامل نخر الورم ألفا