Association between Interleukin-6 Levels, Rituximab Response, and Disease Activity in Patients with Rheumatoid Arthritis

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Abstract:

Background: Interleukin-6 (IL-6) significantly affects rheumatoid arthritis (RA) and its associated conditions, playing a crucial role in acute inflammation by promoting the synthesis of most acute-phase proteins.

Aim: The present study aimed to assess the potential association between Rituximab (RTX) response and IL-6 level in RA patients

Patients and method: The current study was conducted in Baghdad-Iraq during the period from January to March 2023. The study included a convenient sample of ninety adult patients who were already diagnosed with RA and received intravenous infusions of RTX for at least six months. Clinical Disease Activity Index (CDAI) was adopted to evaluate RA activity.

Results: The proportion of patients with high disease activity according to CDAI was significantly higher in the RTX non-responders group compared to the RTX responders' group. The IL-6 level was significantly higher in the RTX non-responders' group than in the RTX responders' group (P-value<0.001). The IL-6 level was significantly higher in patients with high disease activity than other patients.

Conclusion: In RA patients who treated with RTX, IL-6 levels are correlated with increased clinical disease activity and may be used as a proxy for RTX responsiveness in RA patients.

Keywords: Interleukin-6, rheumatoid arthritis, Rituximab, response

العلاقة بين مستوى مصل إنترلوكين-ستة واستجابة دواء الريتوكسيماب ونشاط المرض بين المرضى العراقيين المصابين بالتهاب المفاصل الرثوي

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الخلاصة

الخلفية: يؤثر إنترلوكين-6 بشكل كبير على التهاب المفاصل الروماتويدي والحالات المرتبطة به، ويلعب دورًا حاسمًا في الالتهاب الحاد من خلال تعزيز تخليق معظم بروتينات المرحلة الحادة.

الهدف: تهدف الدراسة الحالية إلى تقييم العلاقة بين مستوى الانترلوكين-6 واستجابة للريتوكسيماب لدى المرضى الذين يعانون من التهاب المفاصل الروماتويدي .

المرضى والطريقة: أجريت الدراسة الحالية في بغداد-العراق خلال الفترة من كانون الثاني إلى اذار 2023. وتضمنت الدراسة عينة مناسبة من تسعين مريضًا بالغًا تم تشخيص إصابتهم بالتهاب المفاصل الروماتويدي وتلقوا علاج الريتوكسيماب لمدة ستة أشهر على الأقل. تم تقييم نشاط المرض من خلال مؤشر نشاط المرض السريري.

النتائج: كانت نسبة المرضى الذين يعانون من نشاط مرضي مرتفع وفقًا لمؤشر نشاط المرض السريري أعلى وبدلالة احصائية في مجموعة غير المستجيبين للريتوكسيماب مقارنة بمجموعة المستجيبين للريتوكسيماب. كان مستوى الانترلوكين-6 أعلى وبدلالة احصائية في مجموعة غير المستجيبين للريتوكسيماب منه في مجموعة المستجيبين للريتوكسيماب (قيمةالاحتمالية=0.001). كان مستوى الانترلوكين-6 أعلى وبدلالة احصائية في المرضى الذين يعانون من نشاط مرضي مرتفع مقارنة بالمرضى الآخرين.

الاستنتاج: يرتبط مستوى الانترلوكين-6 بتحسن نشاط المرض السريري لدى المرضى المستجيبين للريتوكسيماب ويمكن استخدامه كعلامة لاستجابة للريتوكسيماب بين المرضى الذين يعانون من التهاب المفاصل الروماتويدي.
في المرضى الذين يستجيبون للريتوكسيماب ، ترتبط مستويات الانترلوكين-6 بزيادة نشاط المرض السريري ويمكن استخدامها لاستجابة مرضى التهاب المفاصل الروماتويدي للريتوكسيماب.

الكلمات المفتاحية: إنترلوكين-6، التهاب المفاصل الروماتويدي، ريتوكسيماب، الاستجابة

Introduction

RA is defined as one of the autoimmune diseases, it is marked by persistent inflammation of the joint leading to bone damage and significant disability [(1)]. While the frequency of RA is only 0.24% worldwide[(2)], in Iraq, it was 1% [(3)]. Although several genetic and environmental factors implicated in immune responses have been found, the specific etiology of RA is still unknown[(4)]. Pro-inflammatory and anti-inflammatory cytokines are the two primary categories of cytokines[(5, 6)]. Since IL-6 induces acute-phase proteins, it is believed to have some anti-inflammatory properties[(7)]. IL-6 is a crucial cytokine that modulates the immune response and controls various pathological and physiological processes[(8, 9)]. It significantly affects RA and its associated complications[(10)]. The major goals of RA treatment are to increase patients' quality of life through pain relief, preservation or enhancement of functional ability, and prevention of impairment[(11)]. To achieve and sustain appropriate control over their disease, many RA patients require a variety of medications[(12)].Rituximab (RTX) has demonstrated efficacy in alleviating disease manifestations and limiting damage in patients with RA[(13)]. It targets the CD20 antigen that is located on the surfaces of cancerous and normal B cells[(14)].

The present study aimed to assess the potential association between RTX response and IL-6 level in RA patients.

Patients and methods

This study was done under the supervision of a specialized physician at the Specialized Center of Rheumatology/ Baghdad Teaching Hospital in Baghdad-Iraq during the period from January/2023 to january /2024. It was a cross-sectional study with a convenient sample of ninety adult patients who were already diagnosed with RA and taking RTX for at least one cycle of 6 months duration with high disease activity.Exclusion criteria included taking another biological agent or steroid, chronic autoimmune diseases, or malignancy.

The disease activity was assessed by Disease activity score in 28 joints (DAS28) and Clinical disease activity index CDAI. According to DAS28, the swollen joint count (SJC) and the tender joint count (TJC) in the proximal interphalangeal joints, metacarpophalangeal jpints, knee joints, wrist joints, elbow joints, and shoulder joints are recorded in addition to the measure of the visual analogue scale (VAS) of 100 mm and either C-reactive protein or erythrocyte sedimentation rate.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-respondersin addition,The disease activity was assessed by the CDAI According to which, RA activity is classified as high (>22), moderate (>10 but ≤22), low (>2.8 but ≤10), and remission (≤2.80). [15] .Interleukin 6 (IL-6) serum level were measured by taking 2 ml of venous blood sample and after obtaining the serum, its level was measures by suitable Enzyme-linked immunosorbent assay (ELISA) kit in a specialized private laboratory [16]

The categorial data was presented as frequency and percent, the continuous data was displayed as mean ±standard deviation (SD), paired sample T-test,Fisher's Exact test,Independent sample T-test and Kruscal Wallis test. P-values < 0.05 were accepted as significant.

The Ethics Committee of the College of Pharmacy at Al-Mustansiriyah University provided its agreement for this study (Official letter No. 77 dated 30/8/2023).

Results

In the present study, 90 patients were included: 50 in the RTX responders' group and 40 in the RTX non-responders' group. Although the CDAI was significantly decreased in both groups after the intervention compared to the baseline, this decrease was higher in the RTX responders' group compared to the RTX non-responders' group as shown in table 1.

Table 1: Clinical assessment of rheumatoid arthritis patients using CDAI

CDAI	Before intervention	After intervention	Difference %	P-value
RTX responders	23.8± 4.6	13.6± 7.1	-42.9	<0.001
RTX non-responders	21.6± 6.2	24.8± 6.0	14.9	<0.001

Paired samples T-test

The RTX non-responders group showed a significantly higher proportion of patients with high disease activity according to CDAI compared to the RTX responders' group as shown in table 2.

Table 2: Disease activity according to RTX-response

Disease activity according to CDAI	RTX responders (50)	RTX non-responders (40)	P-value
Remission	2 (4)	0 (0)	<0.001
Low	18 (36)	0 (0)	
Moderate	23 (46)	17 (42.5)	
High	7 (14)	23 (57.5)	

Fisher's Exact Test

Compared to the RTX responders' group, the IL-6 level was significantly higher in the non-responder's group (P-value<0.001) as shown in table 3.

Table 3: Distribution of IL-6 levels according to response

Variables	RTX responders (50)	RTX non-responders (40)	P-value
IL-6 (ng/L)	18.37±55.5	55.48±12	<0.001

Independent samples T-test

The IL-6 levels showed significant differences among patients with different disease activity levels. It was significantly higher in patients who had high disease activity than other patients, in addition, it was significantly higher in patients who had moderate disease activity than those with low disease activity and patients in remission and significantly higher in patients who had low disease activity than those in remission (P-value<0.001) as shown in table 4.

Table 4: Association between IL-6 and disease activity

IL-6 (ng/L)	CDAI				P-value
	Remission	Low	Moderate	High	
	14.54±0.04	15.52±3.27	35.21±23.3	47.37±14.1	<0.001

Kruskal-Wallis Test

Discussion

The first finding was that the IL-6 level was affected by RTX response. In agreement, Das et al. concluded that in RTX non-responders, serum IL-6 was elevated at baseline and was considerably greater than in responders (P-value=0.035). RTX responders experienced a substantial decrease in serum IL-6 (P-value=0.005), but non-responders did not (P-value=0.237)[16]. In comparison, the same results were obtained in another study that was done by Juliánet al and concluded that the IL-6 level significantly decreased after RTX treatment in patients with RA[17]. By attaching itself to the CD20 surface antigen, RTX binds to B-lymphocytes, causing antibody-dependent cellular cytotoxicity and phagocytosis, cell lysis, and apoptosis, which all contribute to the depletion of B cells.

Inflammatory cytokines including IL-6 are widely produced by B-cells[18].

Another finding in the current study was that the IL-6 level was affected by disease activity. In the same line, Eman et al. concluded that Treatment with RTX led to

notable reduction in RA activity and serum level of IL-6[19]. In another study that was conducted by Cristina et al., IL-6 was linked with acute phase reactants and disease activity[20]. Rajaei et al concluded that the serum IL-6 level can be used as a determinant in assessing the severity of RA disease because of its association with activity and severity of the disease[21]. Another study by Camilla et al. reported that elevated levels of IL-6 correlate with elevated CDAI scores and concluded that modifications in IL-6 levels may have an impact on prognosis and disease follow-up[22].

Conclusion: In RA patients who treated with RTX, IL-6 levels are correlated with increased clinical disease activity and may be used as a proxy for RTX responsiveness in RA patients.

Limitations of the study: It is a must to clarify one of the most faced study limitations which is the difficulty to enroll patients who are having an intravenous line to receive their dose of medication, Thus, additional studies with potentially larger sample sizes are required in the future

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