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The Association between the Response to Rituximab with Sociodemographic Data and Disease Characteristics Among a Sample of Iraqi Patients with Rheumatoid Arthritis

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Abstract

Background: Rheumatoid arthritis (RA) is a chronic inflammatory autoimmune disease. Rituximab (RTX), a monoclonal antibody with anti-CD20 action, is now used as a treatment. Even with proper RTX use, some patients showed variations in response. ***Objective***: To assess the association of different sociodemographic data and disease characteristics with RTX responsiveness in RA patients. ***Methods***: A cross-sectional study was conducted in the Specialized Center of Rheumatology at Baghdad Teaching Hospital in Baghdad, Iraq. The study included 90 RA patients who received a 1000mg RTX intravenous infusion for at least six months. The collected sociodemographic data included age, gender, smoking status, body mass index (BMI), disease characteristics such as co-morbidities, and the use of previous biological agents. The activity of RA was assessed by the 28-joint Disease Activity Score (DAS28) and Clinical Disease Activity Index (CDAI). ***Results***: Upon measuring the DAS28, the enrolled patients were divided into RTX responders (50 patients) and RTX non-responders (40 patients). Patients with a family history of RA were significantly higher in the RTX responders (21% versus 2% in the non-responders group). The responders had a significantly longer RA duration (p=0.030).The mean of CDAI and DAS28 were significantly higher in patients with no family history of RA than in those with a family history of RA. ***Conclusions***: Disease duration, family history, and the use of previous biological agents could be considered as possible predictors of response to RTX, thereby saving time and treatment costs.

Keywords: DAS28, Rheumatoid arthritis, Rituximab, Responsiveness.

العلاقة بين الاستجابة لريتوكسيماب مع البيانات الاجتماعية الديموغرافية وخصائص المرض لدى عينة من المرضى العراقيين المصابين بالتهاب المفاصل الرثوي

الخلاصة

الخلفية: التهاب المفاصل الرثوي (RA) هو أحد أمراض المناعة الذاتية الالتهابية المزمنة. ريتوكسيماب (RTX)، وهو جسم مضاد وحيد النسيلة مع عمل مضاد ل CD20 يستخدم الآن كعلاج. حتى مع الاستخدام السليم ل RTX، أظهر بعض المرضى اختلافات في الاستجابة. **الهدف**: تقييم ارتباط البيانات الاجتماعية الديموغرافية المختلفة وخصائص المرض باستجابة RTX في مرضى التهاب المفاصل الرثوي. **الطريقة**: أجريت دراسة مقطعية في المركز التخصصي لأمراض الروماتيزم في مستشفى بغداد التعليمي في بغداد، العراق. شملت الدراسة 90 مريضا من التهاب المفاصل الرثوي الذين تلقوا mg RTX1000 عن طريق الحقن في الوريد لمدة ستة أشهر على الأقل. تضمنت البيانات الاجتماعية الديموغرافية التي تم جمعها العمر والجنس وحالة التدخين ومؤشر كتلة الجسم (BMI) وخصائص المرض مثل الأمراض المشتركة واستخدام العوامل البيولوجية السابقة. تم تقييم نشاط المرض من خلال 28 نقطة نشاط المرض (DAS28) ومؤشر نشاط المرض السريري (CDAI). **النتائج**: عند قياس DAS28 ، تم تقسيم المرضى المسجلين إلى مستجيبين ل RTX (50 مريضا) وغير مستجيبين (40 مريضا). كان المرضى الذين لديهم تاريخ عائلي من التهاب المفاصل الروماتويدي أعلى بكثير في المستجيبين (21%) مقابل 2٪ في مجموعة غير المستجيبين. كان لدى المستجيبين مدة RA أطول بكثيروكان متوسط CDAI و DAS28 أعلى بشكل ملحوظ في المرضى الذين ليس لديهم تاريخ عائلي من التهاب المفاصل الرثوي مقارنة بأولئك الذين لديهم تاريخ عائلي من المرض. **الاستنتاجات**: يمكن اعتبار مدة المرض وتاريخ العائلة واستخدام العوامل البيولوجية السابقة بمثابة تنبؤات محتملة للاستجابة ل RTX ، وبالتالي توفير الوقت وتكاليف العلاج.

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INTRODUCTION

Disease-modifying antirheumatic drugs (DMARDs) reduce disease activity and halt the progression of RA [1]. Biologic drugs in rheumatology are recommended to be started as a second-line treatment [2]. Unfortunately, between 20 and 40% of RA patients do not respond to these drugs [3]. The resistance to treatment regimens among patients with rheumatoid arthritis can increase the risk of suboptimal treatment, prolong time spent with painful symptoms, and lead to the progression of joint damage, diminishing patients' current and future quality of life [4]. Rheumatoid arthritis is considered a chronic inflammatory autoimmune disease. It is characterized by joint swelling, tenderness, and the demolition of synovial joints, cartilage, bone, and, less frequently, extra-articular sites [5]. While the frequency of RA is only 0.24% worldwide [6], it was 1% in Iraq until 2019 [7]. Although several genetic and environmental factors implicated in immune responses have been found, the specific etiology of RA is still unknown [8]. The primary goal of RA treatment is to improve patients' quality of life through pain relief, preservation, or functional ability enhancement [9]. To achieve and sustain appropriate control over their disease, many RA patients require a variety of medications [10]. These are formally categorized as conventional synthetic disease-modifying antirheumatic drugs (csDMARDs) and biological DMARDs, including biological original and biosimilar DMARDs; targeted synthetic DMARDs, including the only ones currently approved, are Janus kinase inhibitors [10,11]. Non-steroidal anti-inflammatory drugs (NSAIDs) commonly manage RA symptoms [12]. However, NSAIDs cause side effects, mainly gastrointestinal ulcerations [13]. Short-term glucocorticoids are considered part of the primary treatment approach or as bridging therapy; shifting towards csDMARDs is proposed [14]. However, DMARD medication is suggested to be used as soon as possible after diagnosis [15]. RTX, a chimeric monoclonal antibody, undergoes genetic modification to integrate human constant region sequences with light-chain and heavy-chain variable region sequences from mice [16]. It is directed against the B cell surface's CD20 antigen, thus depleting this type of cell by different mechanisms, including direct signaling, complement-mediated cytotoxicity (CMC), and antibody-dependent cellular cytotoxicity (ADCC). It is now considered a mainstay in the therapy for a broad variety of B-cell malignancies, attacking both healthy and cancerous B cells. It is now used to treat rheumatoid arthritis and other autoimmune diseases [17]. Despite the abundance of research on RTX's effectiveness, there is still uncertainty regarding the precise mode of action, the ideal dosage, and the recognition of RA patients who could benefit from it [18]. This study aimed to assess the relationship between different sociodemographic data, disease characteristics, and the degree of responsiveness to RTX in RA patients.

METHODS

Study design and setting

A cross-sectional study was conducted 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. The current study included a convenient sample of ninety adult patients already diagnosed with RA according to the revised "2010 American College of Rheumatology/European League and Rheumatism classification" criteria [19].

Sample selection

Patients enrolled in this study should receive RTX intravenous infusions of 1000 mg on day 1 and then on day 14 per cycle for at least one cycle of six months duration and willingness to participate in the study. However, we excluded patients taking another biological agent (anti-TNFs), those previously diagnosed with chronic autoimmune diseases or malignancies, and those taking steroids.

Data collection and outcome measurements

The information was gathered using a structured questionnaire that asked about the person's age, gender, and smoking status, as well as their medical history and examination (including family history of RA, history of chronic diseases, and body mass index (BMI)) and the person's disease characteristics (including how long they've had RA, what biologics they've tried in the past, and which ones didn't work). In addition, the data included the values of serum hemoglobin, white blood cell (WBC), aspartate aminotransferase (AST), alanine transaminase (ALT), erythrocyte sedimentation rate (ESR), blood urea, and serum creatinine. DAS28 and CDAI assessed the disease activity. DAS28 records the swollen joint count (SJC) and the tender joint count (TJC) in the proximal interphalangeal joints, metacarpophalangeal joints, knee joints, wrist joints, elbow joints, and shoulder joints, along with the visual analogue scale (VAS) of 100 mm and either C-reactive protein or erythrocyte sedimentation rate [20]. 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 [21]. By combining single measures, the CDAI creates a continuous overall measure of RA activity. It includes the 28 swollen joint counts, the 28 tender joint counts, the patient global assessment using a 10 cm visual analogue scale, and a physician global assessment using a 10 cm VAS. Patients with CDAI >22 were considered to have high disease activity, >10 but ≤22 have moderate disease

activity, >2.8 but ≤10 have low disease activity, and ≤2.8 have remission [22].

Ethical approval

We conducted the current study in accordance with the requirements of the Helsinki Declaration. The Ethical Committee of the College of Pharmacy, Mustansiriyah University, approved it (official letter No. 77 dated August 30, 2023). We informed all participants about the purpose and documented their agreements to participate.

Statistical analysis

The categorical variables were displaced as numbers and percentages, and the continuous variables were presented as mean±standard deviation. We used the Chi-Square test and Fisher's exact to test the significance of the difference between groups for the categorical variables, and the independent samples t-test to assess the significance of the difference between groups for the continuous variables. *p*-values less than 0.05 were accepted as significant.

RESULTS

This study included 90 patients who were divided into two groups (the RTX responders group included 50 patients and the RTX non-responders group included 40 patients) according to the DAS28 assessment. The age, gender, and smoking status did not differ significantly between the RTX responders and non-responders groups (*p*-values were 0.090 for age, 0.377 for gender, and 0.626 for smoking) (Table 1).

Table 1: Sociodemographic data according to patient response to Rituximab

Variables		RTX responders (n=50)	RTX non-responders (n=40)	*p*-value
Age (year)		50.38±12.22	54.43±9.54	0.090[a]
Sex	Male	4(8.0)	1(2.5)	0.377[b]
	Female	46(92.0)	39(97.5)	
Smoking status	No	47(94.)	39(97.50)	0.626[b]
	Yes	3(6.0)	1(2.50)	

Values were expressed as frequencies, percentages, and mean±SD. [a]Independent *t*-test; [b]Fisher's exact test.

In comparison to the RTX non-responder group, the RTX responders had a significantly longer RA duration (*p*= 0.030). The proportion of patients with hypertension was significantly higher in the RTX responders group compared to the RTX non-responder group (*p*= 0.003) while the proportion of patients with diabetes mellitus was significantly lower in the RTX responders group compared to the RTX non-responder group (*p*= 0.008). Compared to the RTX non-responders group, the proportion of patients with a family history of RA was significantly higher. The proportions of patients who used Etanercept or Infliximab were significantly lower in the RTX responder group compared to the RTX non-responder group (*p*-values were 0.001 and 0.026, respectively). The number of patients in the RTX responder group who had a primary failure of previous biologics was much lower than in the RTS non-responder group, and the number of patients who had a secondary failure of previous biologics was much higher (Table 2).

Table 2: Medical history and disease conditions according to patient response to Rituximab

Variables		RTX responders (n=50)	RTX non-responders (n=40)	*p*-value
Hypertension	No	32(64.0)	13(32.5)	0.003[b]
	Yes	18(36.0)	27(67.5)	
Diabetes mellitus	No	35(70.)	37(92.5)	0.008[b]
	Yes	15(30.0)	3(7.5)	
Interstitial lung disease	No	44(88.0)	39(97.5)	0.127[c]
	Yes	6(12.0)	1(2.5)	
Miscellaneous	No	38(76.0)	39 (97.5)	0.004[b]
	Yes	12(24.0)	1 (2.5)	
BMI (kg/m^2)		28.4±5.17	30.52±5.4	0.060[a]
Duration of RA (year)		12.6±9.99	8.98±5.18	0.030[a]
Family history for RA	No	29(58.0)	38(96.0)	<0.001
	Yes	21(42.0)	2(4.0)	
Previous biologic	Adalimumab	11(22.0)	14(35.0)	0.173[b]
	Etanercept	25(50.0)	34(85.0)	<0.001[b]
	Infliximab	17(34.0)	23 (57.5)	0.026[b]
Failure of previous biologics	Not received	8(16.0)	2(5.0)	
	Primary	14 (28.0)	28(70.0)	<0.001[b]
	Secondary	28(56.0)	10(25.0)	

Values were expressed as frequencies, percentages, and mean±SD. [a]Independent *t*-test, [b]Chi-square test, [c]Fisher's exact test.

The mean of DAS28 and the proportion of patients with high disease activity according to CDAI were significantly lower in the RTX responders group compared to the RTX non-responders group (*P*= 0.001) (Table 3).

Table 3: Distribution of disease activity according to patient reponse to Rituximab

Indicators		RTX responders (n=50)	RTX non-responders (n=40)	*p*-value
DAS28		4.39±1.13	5.53±0.68	<0.001[a]
Disease activity according to CDAI	Remission	2(4.0)	0(0.0)	<0.001[b]
	Low	18(36.0)	0(0.0)	
	Moderate	23(46.0)	17(42.5)	
	High	7(14.0)	23(57.5)	

Values were expressed as frequencies, percentages, and mean±SD. [a] Independent *t*-test, [b] Fisher's exact test.

The RTX response was associated with a significant decrease in the WBC count and AST (*p*-values were <0.001 and 0.003, respectively) (Table 4). Furthermore, there were no significant associations between age, sex, BMI, and smoking status with the means of CDAI and DAS28 (Table 5). Hypertensive patients had a significantly higher mean of DAS28 than those without hypertension (*p*= 0.005). Compared to patients without interstitial lung disease, patients with interstitial lung disease had a significantly lower mean CDAI (*p*= 0.022). In patients without a family history of RA, the mean CDAI and DAS28 were significantly greater than

in patients with a family history of RA (p= 0.001) (Table 6).

Table 4: Association between response to Rituximab and the level of biomarkers

Variables	RTX responders (n=50)	RTX non-responders (n=40)	*p*-value
Haemoglobin (g/dL)	1.35±11.16	0.65±4.3	0.411[a]
WBC count (cell/µL)	7.76±28.1	25.43±32.19	<0.001[a]
ESR (mm/hour)	6.65±37.99	3.78±35.32	0.200[a]
ALT (IU/L)	48.46±100.58	4.77±9.87	0.414[a]
AST (IU/L)	8.19±1.3	1.29±33.6	0.003[a]
Blood urea (mg/dL)	17.36±54.2	23.15±45.9	0.228[a]
S. creatinine (mg/dL)	1.35±11.16	-0.65±4.3	0.604[a]

Values were expressed as mean±SD. [a] Independent *t*-test.

Table 5: Association between sociodemographic data and disease activity

Variables		CDAI	*p*	DAS28	*p*-value
Age (year)	≤50	17.89±9.58	0.532[a]	4.7±1.21	0.153[a]
	>50	19.06±7.98		5.04±1.02	
Sex	Male	14.2±4.97	0.248[a]	4.3±0.79	0.220[a]
	Female	18.82±8.78		4.93±1.12	
Smoking status	No	18.57±8.49	0.988[a]	4.89±1.04	0.792[a]
	Yes	18.5±13.53		5.04±2.38	

Values were expressed as mean±SD. [a] Independent samples *t*-test.

Table 6: Association between history of chronic diseases and RA disease activity of the patients

Variables		CDAI	*p*	DAS28	*p*-value
Hypertension	No	16.8±8.98	0.052[a]	4.57±1.25	0.005[a]
	Yes	20.33±8.04		5.22±0.84	
Diabetes mellitus	No	18.72±8.86	0.735[a]	4.82±1.16	0.181[a]
	Yes	17.94±8.03		5.21±0.84	
Interstitial lung disease	No	19.17±8.14	0.022[a*]	4.95±1	0.084[a]
	Yes	11.43±11.93		4.2±2	
Miscellaneous	No	18.92±8.9	0.346[a]	4.91±1.16	0.755[a]
	Yes	16.46±7.01		4.81±0.76	
Family history for RA	No	20.96±8.56	<0.001[a*]	5.16±1.07	<0.001[a]
	Yes	11.61±3.95		4.13±0.84	
BMI (kg/m^2)	<30	18.34±8.69	0.751[a]	4.82±1.15	0.405[a]
	≥30	18.94±8.73		5.02±1.05	

Values were expressed as mean±SD. [a] Independent *t*-test.

There were significant positive correlations between the DAS28 and CDAI (p= 0.001) (Table 7).

Table 7: Correlation between CDAI and DAS-28

Variables	CDAI		DAS28	
	r	*p*-value	*r*	*p*-value
CDAI	-	-	0.807	<0.001
DAS28	0.807	<0.001	-	-

r: Pearson correlation coefficient.

DISCUSSION

In this study, more disease activity reduction was obtained if another member of the family had RA; this was in contrast to the age, sex, BMI, and smoking state. These results were in agreement with the results of Narvaez *et al*. (2011), who reported no statistically significant association between RTX response and age and gender [23]. In addition, these results agreed with the Karataş *et al*. study (2023), which reported that obesity did not affect the RTX response [24]. In another study that was done by Moetaza *et al*. (2012), RTX response and smoking were not significantly associated [25]. Nevertheless, this is contradictory to the results of Abdul *et al.* (2012), who reported that smoking independently affected responses to RTX [26]. This finding might be explained by the fact that patients who had a family history of RA had more information about the disease, its treatment and the importance of treatment adherence. In this study, RTX responders had a longer disease duration than RTX non-responders. In contrast, Couderc *et al.* (2013) demonstrated that the duration of the disease was not associated with the RTX response [27], which came in line with the results of the Iraqi study done by Sarha *et al*. (2019) [28]. This discrepancy might be related to other factors that could impact the RTX response. According to the results, diabetes mellitus (but not hypertension) was highly proportional to the RTX response. In contrast, a study by Leslie *et al.* (2017) revealed that the history of hypertension or diabetes mellitus was not significantly associated with the RTX response [29]. In the current study, in contrast to other investigations, AST and WBC counts were significantly affected by the RTX response. In another study, Mohammed *et al*. revealed that the liver may be affected by the treatment of RA [30]. Diabetes mellitus and RA may increase each other's pro-inflammatory pathways, creating a pathogenic vicious circle characterized by inflammation and glucose derangement. The effects of lowering inflammation, primarily through interleukin-1 suppression, may be postulated in individuals with RA and concurrent diabetes mellitus [31]. Accordingly, RTX could have achieved less disease activity among RA patients with diabetes mellitus. The previous use of etanercept or infliximab was associated with a decreased RTX response. Also, RA patients whose first biologics didn't work were more likely to have a poor response to RTX, while RA patients whose second biologic didn't work had a good response. In other studies, there was no significant association between the RTX response and previous use of biological treatment [25,28,32]. This might be related to the extent to which different inflammatory mediators and cells involved in RA pathogenesis, like TNF and B cells, affect the severity of the disease, thus having an impact on the RTX response. Additionally, the disease activity was higher in individuals with a family history of RA, those with interstitial lung disease, and those without hypertension, compared to those with other sociodemographic characteristics, medical history, and disease features. The same results were reported by Peter *et al.* (2021), in which patients with previous cardiovascular disease and RA are more likely to have poor long-term health consequences [33]. In agreement, Ana *et al.* (2020). found no association between smoking status and disease activity [34]. In partial agreement, Takanori *et al.* (2022). found that increased activity of RA was

related to hypertension, diabetes mellitus, respiratory disease, age of the patient, disease durations, and male sex [35]. Thomas et al. (2016), in contrast, concluded that a history of RA did not affect the clinical presentation of RA [36]. As far as we know, no previous study in Iraq addressed the impact of those factors on the responsiveness to RTX treatment in RA patients. The current study revealed a significant correlation between DAS28 and CDAI. Slama et al. (2015) conducted another study in Morocco and found a direct and excellent correlation between DAS-28 and CDAI, as well as between SDAI and DAS-28 [37]. The association between inflammatory markers and clinical features of RA, which RTX responses may affect, could explain this.

Study limitations

It is imperative to address one of the most prevalent study limitations, which is the challenge of enrolling patients who use an intravenous line to receive their medication. Consequently, it is necessary to conduct further study with potentially larger sample sizes in the future.

Conclusion

The disease activity of RA and response to RTX in Iraqi patients may be relatively associated with age, habits, family and medical history. This may pave the way for more studies to develop individualized therapy for RA patients with high disease activity.

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Conflict of interests

No conflict of interests was declared by the authors.

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Data sharing statement

Supplementary data can be shared with the corresponding author upon reasonable request.

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