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Evaluation of the effect of rituximab on fatigue in rheumatoid arthritis using the Chalder Fatigue Scale

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Abstract

Objective. Fatigue is a frequent extra-articular manifestation of rheumatoid arthritis (RA), with a reported prevalence ranging from 40% to 90%. It affects physical, emotional, and cognitive aspects of daily life and significantly impairs quality of life. Although biologic therapies may improve fatigue, the specific effect of rituximab on this symptom remains insufficiently documented. This study aimed to evaluate the effect of rituximab on fatigue at baseline (M0), 4 months (M4), and 6 months (M6) using the Chalder Fatigue Scale (CFS).

Methods. This prospective, observational, single-center study included patients fulfilling the 2010 American College of Rheumatology/European Alliance of Associations for Rheumatology classification criteria for RA and treated with rituximab. Rituximab was administered as two intravenous infusions (500 mg or 1000 mg) on day 0 and day 15. Fatigue was assessed at M0, M4, and M6 using the CFS, with a score ≥ 4 indicating clinically significant fatigue. Clinical and biological data were collected at each visit. Statistical analyses were performed using Jamovi version 2.4.14.

Results. Ninety-four patients were included (mean age 57 ± 9 years; 88% female). The median CFS score decreased from 4 [2-6] at M0 to 2 [0-4] at M4 ($p < 0.001$) and remained stable thereafter through M6 ($p = 0.11$ for the M4-M6 comparison). Disease activity improved in parallel, with the Disease Activity Score 28 using C-reactive protein (DAS28-CRP) decreasing from 4.7 ± 1.1 at M0 to 2.9 ± 0.9 at M4 and remaining stable at M6. Functional status assessed by Health Assessment Questionnaire also improved significantly. In multivariable analysis, higher M0 DAS28-CRP was associated with a greater reduction in fatigue.

Conclusions. Rituximab therapy was associated with a significant improvement in fatigue in patients with RA, parallel to reductions in disease activity and functional disability.

Introduction

Fatigue is a frequent and disabling extra-articular manifestation of rheumatoid arthritis (RA), with a reported prevalence ranging from 40 to 90% depending on the population studied, the definitions applied, and the assessment tools used (1-3). It affects the physical, emotional, and cognitive dimensions of daily life and can only be attributed to RA after exclusion of other potential causes (1).

Alongside pain, fatigue represents the most common symptom of the disease, reported by more than 80% of patients and considered severe in approximately half of them (1, 4, 5). Despite optimized treatment with conventional or biologic disease-modifying antirheumatic drugs (DMARDs), fatigue persists in 30% to 40% of cases (2, 4-6).

The mechanisms involved are complex and multidimensional, combining factors related to the disease itself (inflammatory activity, pain, disability, anemia), individual characteristics (age, sex, educational level, anxiety, depression), treatment exposure, and environmental determinants such as stress, social support, and isolation (3, 7-9). Cross-sectional studies have consistently identified disease activity, pain, sleep disturbance, functional impairment, and depression as key factors associated with fatigue (3, 7-9), but longitudinal studies have not clearly established a causal relationship. The large French COME-DRA cohort has highlighted in particular the importance of comorbidities, cognitive and emotional function, and social characteristics in the development of fatigue (10).

By controlling inflammation, biologic therapies can improve several patient-reported outcomes (PROs), and several agents have demonstrated beneficial effects on fatigue (11, 12). Rituximab, a chimeric monoclonal antibody directed against CD20+ B lymphocytes, has shown proven efficacy in reducing RA disease activity and preventing structural damage (13, 14). However, its specific impact on fatigue remains poorly documented, and prospective data using validated fatigue assessment tools are scarce. The objective of the present study was therefore to evaluate the effect of rituximab on fatigue in RA patients using the Chalder Fatigue Scale (CFS), a validated instrument that explores both the physical and mental components of fatigue.

Materials and Methods

Study design

This was a prospective, observational, single-center study conducted over a 12-month period in the Department of Rheumatology.

Inclusion criteria

Eligible participants were adults aged ≥ 18 years who fulfilled the 2010 American College of Rheumatology/European Alliance of Associations for Rheumatology classification criteria for RA and were receiving rituximab either as first-time treatment or as retreatment.

Rituximab administration

Rituximab was administered according to standard practice as two intravenous infusions of either 500 mg or 1000 mg, given on day 0 (J0) and day 15 (J15).

Data collection

For each patient, demographic, clinical, and therapeutic variables were recorded at baseline, including age, sex, disease duration, presence of extra-articular manifestations, results of rheumatoid factor and anti-CCP antibody tests, comorbidities, previous use of conventional DMARDs or tumor necrosis factor (TNF) antagonists, as well as the medications and corticosteroids prescribed at rituximab initiation. Follow-up data were prospectively collected at baseline (M0) and during follow-up visits at 4 months (M4) and 6 months (M6). At each time point, fatigue was assessed using the CFS. Disease activity was simultaneously evaluated through clinical

and laboratory parameters, including the Disease Activity Score 28 using C-reactive protein (DAS28-CRP), CRP and erythrocyte sedimentation rate.

Chalder Fatigue Scale

Fatigue was assessed using the CFS, a validated self-administered questionnaire developed to evaluate both physical and mental components of fatigue (15, 16). The validated Arabic version of the CFS was used (16). The final version consists of 11 items assessing symptoms such as tiredness, sleepiness, lack of energy, muscle weakness, and difficulties in concentration or memory. Each item is rated on a 4-point Likert scale (“less than usual,” “no more than usual,” “more than usual,” and “much more than usual”), with scores ranging from 0 to 3. The total score ranges from 0 to 33, higher scores indicating more severe fatigue. A bimodal scoring system (0-0-1-1) can alternatively be applied, giving a total score from 0 to 11. Using this method, a score ≥ 4 indicates clinically significant fatigue (15). The CFS shows excellent internal consistency, with Cronbach’s α values between 0.88 and 0.90, confirming its reliability (15).

Objectives

The primary objective of this study was to evaluate the effect of rituximab on fatigue in patients with RA, by assessing changes in fatigue scores at three time points: M0, M4, and M6, using the CFS. The secondary objective was to determine the factors that may influence the response to rituximab in terms of fatigue improvement at M6.

Statistical analyses

Statistical analyses were performed using Jamovi version 2.4.14. Quantitative variables were expressed as mean $\pm$ standard deviation or median (interquartile range) depending on distribution. Comparisons across time points were performed using univariate analyses with paired *t*-tests or Wilcoxon signed-rank tests as appropriate. Factors associated with significant fatigue improvement were further explored using multivariable linear regression analysis. Given the repeated-measures structure of the data and the presence of missing values at M6, a linear mixed-effects model with a random intercept per patient was additionally used to estimate changes in fatigue (CFS) over time, using all available data without excluding patients with incomplete follow-up. Effect estimates (mean differences) with 95% confidence intervals (CI) and effect sizes (Cohen’s *d*) were calculated for all paired comparisons to quantify the magnitude and precision of change over time, independently of statistical significance. Effect sizes were interpreted according to conventional thresholds (small: $d \approx 0.2$; moderate: $d \approx 0.5$; large: $d \geq 0.8$) (17). A *p*-value < 0.05 was considered statistically significant.

Results

A total of 94 patients with RA were included in the analysis. The mean age of the study population was 57 ± 9 years, and there was a female predominance with women representing 88% of the cohort. The median duration of disease evolution was 16 years (9-24 years), reflecting a population with long-standing RA. Almost all patients (95%) were seropositive for rheumatoid factor and/or anti-citrullinated peptide antibodies, while a small subset (2.1%) met the criteria for difficult-to-treat RA, which is consistent with the low rate of prior biologic exposure in this cohort. At M0, the majority of patients (91.5%) were receiving rituximab as first-line biologic therapy, reflecting the local practice of using rituximab as a first-line biologic agent, notably in the context of tuberculosis endemicity, whereas the remainder were treated as part of a retreatment cycle. The baseline demographic and clinical characteristics of the patients are summarized in Table 1.

Evolution of fatigue

At study entry (M0), the burden of fatigue was considerable. The CFS median score was 4 (2.0-6.0), consistent with a high prevalence of clinically significant fatigue. After 4 months of treatment

with rituximab (M4), a marked improvement was observed, with the median CFS score decreasing to 2 (0.0-4.0). This improvement was maintained at M6, while the median score remained at 2 (0.0-4.0) (Figure 1). At M6, fatigue data were available for 82 patients. A total of 12 patients (12.8%) had missing fatigue data at M6 and were therefore excluded from the month-6 analysis. The analysis at M6 was performed on complete cases only. The 12 patients with missing data at M6 were lost to follow-up, primarily due to missed appointments, unavailability by phone, or travel-related constraints. No patient was known to have discontinued treatment due to a documented adverse event. Detailed reasons for loss to follow-up were not systematically documented for each patient, which represents a limitation of the study. The comparison between M0 and M4 was based on 94 patients, while the comparison between M0 and M6 was based on 82 patients, as detailed in Table 2. The mean change in CFS between M0 and M4 was -1.33 points (95% CI -1.67 to -0.99; $p<0.001$; Cohen's $d=0.81$), and -1.46 points between M0 and M6 (95% CI -1.84 to -1.08; $p<0.001$; $d=0.85$), both corresponding to large effect sizes. No further significant change was observed between M4 and M6 (mean difference -0.16; 95% CI -0.36 to 0.04; $p=0.11$), indicating that the improvement in fatigue occurred predominantly by M4 and was subsequently maintained rather than continuing to decrease. The linear mixed-effects model confirmed a significant reduction in CFS scores at M4 (estimate = -1.33; 95% CI -1.63 to -1.03; $p<0.001$) and at M6 (estimate = -1.50; 95% CI -1.81 to -1.18; $p<0.001$) compared with baseline, consistent with the results of the paired comparisons. These findings indicate that fatigue scores decreased rapidly within the first 4 months following rituximab treatment, and this improvement was maintained through month 6.

Changes in disease activity and function

Improvement in fatigue was accompanied by significant reductions in disease activity and functional impairment. The DAS28-CRP decreased from a mean of 4.7 ± 1.1 at M0, indicating high disease activity, to 2.9 ± 0.9 at M4. This level was maintained at 2.9 ± 1.1 at M6 ($p<0.001$ for both time points compared with M0), reflecting a transition to remission (DAS28-CRP <2.6) in 40.2% of patients at M4 and 48.8% at M6, and to low disease activity (DAS28-CRP 2.6-3.2) in an additional 26.8% at M4 and 12.2% at M6. This reduction in disease activity corresponded to a mean change of -1.78 points (95% CI -2.02 to -1.55; $p<0.001$; Cohen's $d=1.57$) at M4 and -1.75 points (95% CI -2.02 to -1.47; $p<0.001$; $d=1.38$) at M6, both reflecting large treatment effects. Similarly, the Health Assessment Questionnaire (HAQ) score, which measures functional disability, improved from a median of 1.0 (0.8-1.5) at M0 to 0.8 (0.4-1.0) at M4 and further to 0.6 (0.3-1.0) at M6 ($p<0.001$), as shown in Table 2. The corresponding mean change in HAQ was -0.38 (95% CI -0.45 to -0.32; $p<0.001$; $d=1.17$) at M4 and -0.40 (95% CI -0.49 to -0.30; $p<0.001$; $d=0.91$) at M6, also reflecting large treatment effects. These parallel improvements highlight the positive impact of rituximab not only on joint inflammation but also on PROs such as physical function and fatigue.

Determinants of fatigue improvement

To identify factors influencing the change in fatigue, a multivariable linear regression analysis was performed adjusting for age, sex, comorbidities, fibromyalgia, and anemia. Among the variables tested, only the M0 DAS28-CRP score remained independently associated with the magnitude of fatigue improvement at M6. Specifically, a higher baseline disease activity was associated with a greater decrease in the CFS score ($\beta=-0.51$; 95% CI -0.94 to -0.07; $p=0.02$) (the results of the multivariable regression analysis are presented in Table 3). This cross-sectional association should be interpreted with caution and does not establish a causal relationship between baseline disease activity and the extent of fatigue improvement. To further explore this association, an exploratory sensitivity analysis was conducted, additionally including the change in DAS28-CRP (M6-M0) and, separately, baseline HAQ, in the multivariable model. In this analysis, the change in DAS28-CRP was associated with the change in CFS score ($\beta=0.53$; 95% CI 0.13 to 0.93; $p=0.010$, $n=76$), while the baseline DAS28-CRP association was attenuated, likely reflecting the mathematical relationship

between baseline DAS28-CRP and its subsequent change. Baseline HAQ was not independently associated with fatigue improvement ($p=0.34$).

Discussion

In the present study, fatigue scores, as assessed by the CFS, decreased significantly following rituximab treatment, with this improvement observed as early as M4 and maintained through M6. This improvement was accompanied by a concomitant reduction in inflammatory activity (DAS28-CRP) and an improvement in functional disability (HAQ).

These findings are consistent with previously published data regarding the effect of rituximab on PROs, including fatigue, pain, and physical quality of life (17, 18). The work by Keystone *et al.* demonstrated, in a cohort of 520 patients with active RA refractory to anti-TNF agents, a significant improvement in the FACIT-Fatigue score and in the SF-36 vitality component after 24 weeks of rituximab therapy, in parallel with the reduction in DAS28 (18). Similarly, Harrold *et al.* reported, in a real-world observational cohort, that approximately 49% of patients experienced a clinically meaningful improvement in fatigue at 12 months, correlated with decreases in both pain and inflammatory activity (19).

Our findings also align with those of Gossec *et al.*, who conducted a multicenter observational study including 175 patients with RA receiving rituximab. That study reported a mean reduction of 3.1 points in the FACIT-Fatigue score at 6 months ($p<0.01$), along with significant improvements in pain and physical-function scores (20). The authors suggested that the beneficial effect of rituximab on fatigue extends beyond inflammatory control and may involve central mechanisms of fatigue perception.

In a similar vein, Rigby *et al.* published a large randomized controlled trial involving more than 700 patients with active RA, comparing rituximab + MTX vs. placebo + MTX. After 24 weeks, a mean reduction of 6.8 points in FACIT-Fatigue was observed in the rituximab group compared with 2.1 points in the placebo group ($p<0.001$) (21). Notably, fatigue improvement was also seen in some patients who did not experience a major decrease in DAS28, suggesting the existence of additional mechanisms independent of joint inflammation control.

In a recent study by Goñi *et al.*, conducted in 54 RA patients, the CFS was used to define fatigue responders using a threshold of $\Delta\text{CFS}\geq 2$ points, considered clinically meaningful (22). After 6 months of follow-up, 22 patients (40.7 %) met this threshold, and the authors demonstrated that brain imaging markers [structural magnetic resonance imaging (sMRI) and diffusion tensor imaging (DTI)] predicted fatigue improvement more accurately than conventional clinical variables, with an sMRI model accuracy of 67.9 %. These results confirm that the CFS captures changes extending beyond peripheral inflammatory processes.

Regarding anti-TNF agents, the literature consistently shows substantial improvements in fatigue, even when the CFS was not the assessment tool used. In the large BSRBR-RA cohort ($n=6835$) of patients initiating anti-TNF therapy, Druce *et al.* reported that among patients with severe baseline fatigue (SF-36 vitality ≤ 12.5), 70 % achieved a clinically meaningful improvement at 6 months and 66% transitioned from the “severe” to the “non-severe” category (1). Among “improvers,” the mean increase in vitality was approximately +33 points, about three times the minimal clinically important difference. These data highlight the responsiveness of fatigue scores under biologic therapy and support the use of multidimensional tools such as the CFS to monitor the “fatigue” component alongside disease-activity indices.

Altogether, these observations converge toward the notion that fatigue, while partly related to disease activity, also reflects central, psychological, and neuromuscular components. The beneficial effect of rituximab on fatigue may therefore result not only from its anti-inflammatory action but also from the indirect modulation of neuro-immunological pathways involved in fatigue perception, including cytokines such as interleukin-6 and TNF- α , as well as hypothalamo-limbic circuits. Taken together, our data align with these pivotal studies and strengthen the hypothesis that B-cell depletion with rituximab may alleviate fatigue through mechanisms partly independent of

inflammatory control, highlighting the importance of considering fatigue itself as a therapeutic target in RA.

Strengths and limitations

This study has several strengths. It is among the few investigations that specifically evaluated the effect of rituximab on fatigue in patients with RA, using a validated instrument—the *CFS*—which allows for the assessment of both the physical and mental dimensions of fatigue. To our knowledge, this is among the first studies to specifically apply the *CFS* to evaluate the longitudinal course of fatigue following rituximab treatment in patients with RA, representing an original contribution to the literature on PROs in this setting. The *CFS* was selected for its ability to capture both physical and mental components of fatigue through its two subscales, offering a more comprehensive and clinically interpretable assessment of fatigue in RA than unidimensional tools such as visual analog scales. The prospective collection of data at three evaluation points (M0, M4, and M6) made it possible to capture the dynamic evolution of fatigue over time. Moreover, the parallel integration of disease activity (DAS28-CRP) and functional disability (HAQ) scores strengthens the robustness of the analysis and the consistency of the observed results.

However, several limitations should be acknowledged. The sample size was relatively small, which may limit statistical power and the generalizability of the findings. The absence of a control or comparator group (such as anti-TNF or other biologic agents) precludes confirming the specificity of the observed effect. The follow-up period, limited to 6 months, does not allow for the assessment of the long-term persistence of fatigue improvement or its potential fluctuations over subsequent treatment cycles. Concomitant therapies (corticosteroids and conventional synthetic DMARDs) were recorded at baseline; changes in these treatments during follow-up were not systematically documented, which represents a limitation, as such changes could have contributed to the observed improvement in fatigue independently of rituximab.

Conclusions

Our study suggests a significant improvement in fatigue among patients with RA treated with rituximab, as assessed by the *CFS* at M6. This reduction in fatigue occurred in parallel with a marked decrease in inflammatory disease activity, reflected by the decline in DAS28-CRP scores, and with a notable improvement in functional disability as measured by the HAQ. The concurrent improvement across these patient-reported and clinical outcomes suggests that fatigue, joint inflammation, and functional disability all decreased following rituximab treatment, and these improvements were maintained through month 6. These findings reinforce the importance of targeting both objective markers of disease activity and subjective symptoms such as fatigue when evaluating the overall effectiveness of biologic therapy in RA.

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Table 1. Baseline demographic and clinical characteristics.

Characteristics	n=94
Age ¹	57.2±9.4
Female sex ³	83 (88)
Disease duration ²	16 [9-24]
Erosive RA ³	69 (81)
Seropositive RA ³	90 (95)
Corticosteroid therapy ³	71 (75)
Comorbidities	
Hypertension ³	29 (30.9)
Diabetes ³	23 (24.5)
Heart disease ³	2 (2.1)
Fibromyalgia ³	25 (26.6)
Anemia ³	24 (25.5)
Depression ³	4 (4.3)
Rituximab initiation ³	86 (91.5)
D2T ³	2 (2.1)
ESR ²	34 [22–55]
CRP ²	15 [7–28]
DAS28-ESR ¹	5.23±1.16
DAS28-CRP ¹	4.72±1.09

RA, rheumatoid arthritis; D2T, difficult-to-treat; CRP, C-reactive protein; DAS28-ESR, Disease Activity Score 28 using erythrocyte sedimentation rate; DAS28-CRP, Disease Activity Score 28 using CRP. ¹Mean±SD, ²Median (quartiles), ³n(%).

Table 2. Evolution of Chalder Fatigue Scale, Disease Activity Score 28 using C-reactive protein, and Health Assessment Questionnaire scores at baseline, 4 months, and 6 months.

Variables	M0 (n=94)	M4 (n=94)	M6 (n=82)	p-value
CFS	4 [2-6]	2 [0-4]	2 [0-4]	M0 vs. M4: p<0.0001 M0 vs. M6: p<0.0001
DAS28-CRP	4.7±1.1	2.9±0.9	2.9±1.1	M0 vs. M4: p <0.0001 M0 vs. M6: p <0.0001
HAQ	1 [0.8-1.5]	0.8 [0.4-1]	0.6 [0.3-1]	M0 vs. M4: p <0.0001 M0 vs. M6: p <0.0001

M0, baseline; M4, 4 months; M6, 6 months; CFS, Chalder Fatigue Scale; DAS28-CRP, Disease Activity Score 28 using C-reactive protein; HAQ: Health Assessment Questionnaire

Table 3. Factors predicting changes in Chalder Fatigue Scale score at 6 months.

Variables	Change in Chalder Fatigue Scale score (M6-M0)		
	β	95% CI	p
Age	0.005	[-0.04, 0.05]	0.84
sex	-0.26	[-1.7, 1.2]	0.71
Hypertension	-0.80	[-1.86, 0.25]	0.13
Diabetes	1.01	[-0.08, 2.11]	0.07
Heart disease	2.47	[-0.87, 5.8]	0.14
Fibromyalgia	-0.42	[-1.5, 0.64]	0.42
Anemia	-1.01	[-2.11, 0.08]	0.06
DAS28-CRP	-0.51	[-0.94, -0.07]	0.02

M6, 6 months; M0, baseline; CI, confidence interval; DAS28-CRP, Disease Activity Score 28 using C-reactive protein. Multivariable linear regression analysis adjusted for age, sex, comorbidities, fibromyalgia, and anemia.

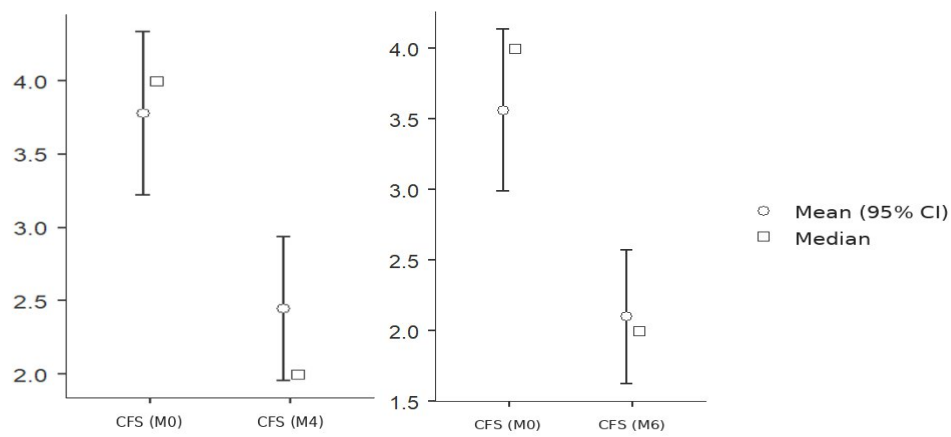


Figure 1. Evolution of the Chalder Fatigue Scale score at baseline, 4 months, and 6 months.