Treatment options in refractory rheumatoid arthritis

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Abstract

Objective: to evaluate rituximab efficacy in refractory rheumatoid arthritis treatment. *Method:* patients with active rheumatoid arthritis, who failed to achieve remission during DMARDs and biological (TNF inhibitors) therapies and received rituximab (1g intravenously on days 0 and 14 initially, the same scheme at 6 and 12 month) were assessed at baseline (T_0), after 2 weeks (T_1), 24 weeks (T_2) and 48 weeks (T_3) by: sera parameters (ESR values, CRP level, RF titer, anti-CCP antibody titers), disease activity (DAS 28 score) and ability to perform activities of daily living (HAQ-DI score). *Results:* twelve patients with highly active rheumatoid arthritis (10 females and 2 males, mean age 51.83 ± 13.07 years)were included in the study group. Treatment led to significant decrease in all investigated parameters, with a clinical and functional improvement at week 48. No major side effects were detected. *Conclusions:* decreasing disease activity and improving functional, with no major side effects in 1 year period, rituximab may represents the solution for refractory rheumatoid arthritis cases. Further studies on larger groups are required.

Key words*: rheumatoid arthritis, rituximab, disease activity*

Rezumat

Obiective: evaluarea eficacității rituximabului în cazul pacienților cu poliartrită reumatoidă refractară la tratament. *Metoda.* pacienții cu poliartrită reumatoidă activă, cu un răspuns inadecvat la tratamentul cu agenți DMARD şi biologici (anti-TNF) au fost tratați cu rituximab (1g în perfuzie în zilele 0 şi 14, cu repetarea acestei scheme de tratament în luna a 6-a şi a 12-a); au fost evaluați la începerea studiului (T_0), la 2 săptămâni (T_1), 24 săptămâni (T_2) şi 48 săptămâni (T_3), prin monitorizarea parametrilor inflamatori (VSH, proteina C reactivă), a factorului rheumatoid, anticorpilor antipeptid cyclic citrulinat, a activității

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bolii (scorul DAS28) şi a abilităţii de a performa activităţile vieţii zilnice (scorul HAQ-DI). *Rezultate:* 12 pacienţi cu poliartrită reumatoida activă (10 femei şi 2 bărbaţi, cu o vârstă medie de 51,83±13.07 ani) au fost incluşi în studiu. Tratamentul a determinat o diminuare a tuturor parametrilor investigaţi, cu o îmbunătăţire clinică şi functională semnificativă în săptămâna 48. Nu au fost înregistratate reacţii adverse majore. *Concluzii:* determinând o ameliorare a activităţii bolii şi a statusului funcţional pe o perioadă de 1 an, în absenţa unor reacţii adverse majore, rituximabul reprezintă o soluţie pentru tratamentul cazurilor de poliartrită reumatoidă. Sunt necesare studii pe grupuri mai mari de pacienţi.

***Cuvinte cheie**: poliartrita reumatoida, rituximab, activitatea bolii*

Introduction

Rheumatoid arthritis (RA) is a chronic, systemic, autoimmune disease, characterized by synovial inflammation and progressive destruction of the affected joints, leading to joint deformity, loss of physical function, severe disability and impaired quality of life [1-3]. There have been significant improvements in patients' outcomes since the introduction of conventional DMARDs (disease modifying antirheumatic drugs), such as methotrexate, and of biologic DMARDs with different mechanism of action, such as tumor necrosis factor α (TNF α) inhibitors, interleukin (IL)-1 inhibitors, IL-6 inhibitors, B-cell depleting antibodies, or inhibitors of T-cell co-stimulation [4,5].

Even with these advances in RA treatment, a population with refractory RA exists. Studies have shown that 25-40% of patients have an inadequate or partial response to the TNF-α inhibitors [6-8], and more patients lose efficacy during treatment [9] or experience adverse effects. In these cases a biologic agent with a different mode of action (such as B cell depletion) may be more effective at controlling disease activity than an alternative TNF-α inhibitor [10, 11].

Rituximab has been shown to be effective in suppressing disease activity in both methotrexate-resistant [12], and in anti-TNF-α therapy resistant RA[6]. Rituximab is a monoclonal antibody that selectively depletes CD20+ B-cells, which play an important role in the pathogenesis of RA.

The aim of this study is to evaluate the efficacy of Rituximab in patients with active RA refractory to anti-TNFα therapies.

Materials and methods

Patients with active RA despite conventional and biologic DMARDs therapies were recruited. The inclusion criteria were: (1) > 18 years of age; (2) 1987 American College of Rheumatology (ACR) criteria for the diagnosis of RA [13]; (3) active disease as defined by a 28 joint disease activity score (DAS28) >5.1, despite therapies with conventional and biologic DMARDs for at least 3 months; (4) stable doses of conventional DMARDs for at least 8 weeks prior to screening.

Patients received Rituximab (1000 mg by intravenous infusion on days 0 and days 14 initially, repeating the same scheme at 6 and 12 months) plus methotrexate (20 mg/week) plus leflunomide (20 mg/day).

Clinical assessments (DAS28 score, Health Assessment Questionnaire Disability Index – HAQ-DI) and laboratory assessments (erythrocyte sedimentation rate – ESR, C-reactive protein – CRP, rheumatoid factor titer – RF, anti citrullinated cyclic peptide antibodies titer – anti-CCP) were performed

at baseline (T_0), 2 weeks (T_1), 24 weeks (T_2) and 48 weeks (T_3). The primary outcome was the evolution of RA activity as measured by changes from baseline in the DAS28 score. Secondary outcomes were changes from baseline of ESR, CRP, RF and anti-CCP titer, and HAQ-DI.

Results

12 patients (10 women, 2 men; 51.83 ± 13.07 years) with RA met the study inclusion criteria. The demographic and baseline characteristics are presented in Table I. All patients failed to achieve remission during conventional DMARDs (methotrexate 20mg/week plus leflunomide 20mg/day, for 6 months) and biological DMARDs (infliximab, n=5; etanercept, n=2; adalimumab, n=5) therapies. Patients had highly active disease at baseline, as defined by the DAS28 score of 6.33±1.06, and by elevated ESR (63.58±34.43 mm/h) and CRP (53.14±25.76 mg/L) levels. The mean baseline HAQ-DI was high, with a value of 2.38±0.4 (0=performing activity of daily living without difficulty, 3=unable to perform without assistance).

Table I. Patients demographic and baseline characteristics

Characteristic	Values
Age (mean±SD, years)	51.83±13.07
Sex	
Female (number (%) of patients)	10 (83.33)
Male (number (%) of patients)	2 (16.67)
RF positive (number (%) of patients)	12 (100)
RF titer (mean±SD, UI/ml)	408.4±348.93
Anti-CCP antibodies titer (mean±SD, UI/ml)	244,18±140.54
Erythrocyte sedimentation rate (mean±SD, mm/h)	63.58±34.43
C-reactive protein (mean±SD, mg/l)	53.14±25.76
DAS 28 score (mean±SD)	6.33±1.06
HAQ-DI score (mean±SD)	2,38±0,4
Previous treatments	
Conventional DMARDs	
Methotrexate plus leflunomide (number of patients)	12
Biologic DMARDs	
Infliximab (number of patients)	5
Adalimumab (number of patients)	5
Etanercept (number of patients)	2

At week 48, a reduction of all investigated parameters could be seen in all 12 patients treated with rituximab plus conventional DMARDs (methotrexate plus leflunomide), as it can be seen in Table II.

Table II. Evolution over time of investigated parameters

Parameter	T_0	T_1	T_2	T_3	p
DAS28	6.33±1.06	5.17±1.12	1.6±0.86	1.12±0.72	<0.001
ESR (mm/h)	63.58±34.43	40.88±29.75	33±16.79	20.42±18.41	<0.01
CRP (mg/l)	53.14±25.76	44.52±32.11	21.96±10.70	10.7±6.48	<0.01
RF (i.e./ml)	408.4±348.93	356.87±16.95	254.98±125.64	199.23±65.78	< 0.05
Anti-CCP (i.e./ml)	244.18±340.54	200.35±127.63	182.87±88.99	152.37±231.87	<0.05
HAQ-DI	2.38±0.4	1.92± 0.7	1.33±0.6	1.11±0.8	<0.05

The mean DAS28 score revealed a statistically significant decrease from 6.33±1.06 at baseline to 1.12±0.72 at week 48 ($p<0.001$) (Figure 1).

The inflammatory parameters decreased during the 48 week follow up (Figure 2), but their mean values haven't reached the normal levels. The differences of RF and anti-CCP levels (Figure 3) were also statistically significant ($p<0.01$).

All patients experienced a clinically improvement in function, defined as a significant decrease in the HAQ-DI (Figure 4). Changes in the mean HAQ-DI scores between baseline and week 48 exceeded 0.22 points, considered to be the minimum clinically important difference (MCID) [14].

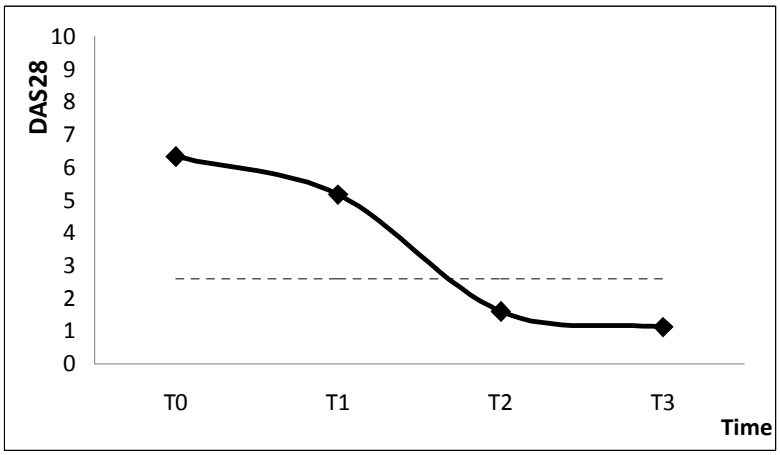

Figure 1. Changes from baseline of DAS28 score. The longitudinal improvement in RA disease activity (DAS28) over the average time on treatment is represented. Remission line – DAS28 < 2.6.

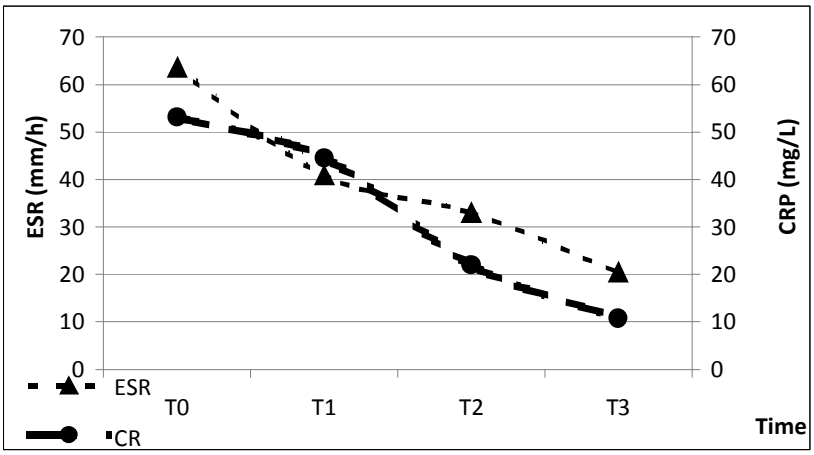

Figure 2. Changes from baseline of inflammatory parameters**.** The longitudinal improvement of inflammatory parameters (ESR, CRP) over time on treatment is represented

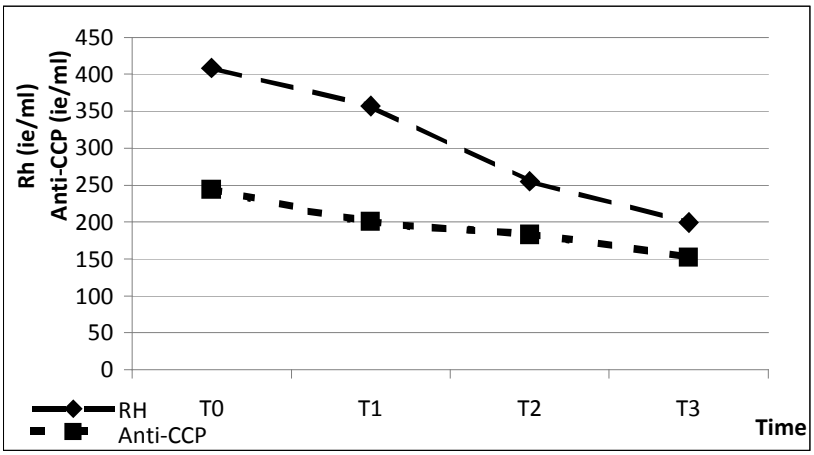

Figure 3. Changes from baseline of RH and anti-CCP. The longitudinal improvement of rheumatoid factor and anti-citrullinated cyclic peptide antibodies over time on treatment is represented

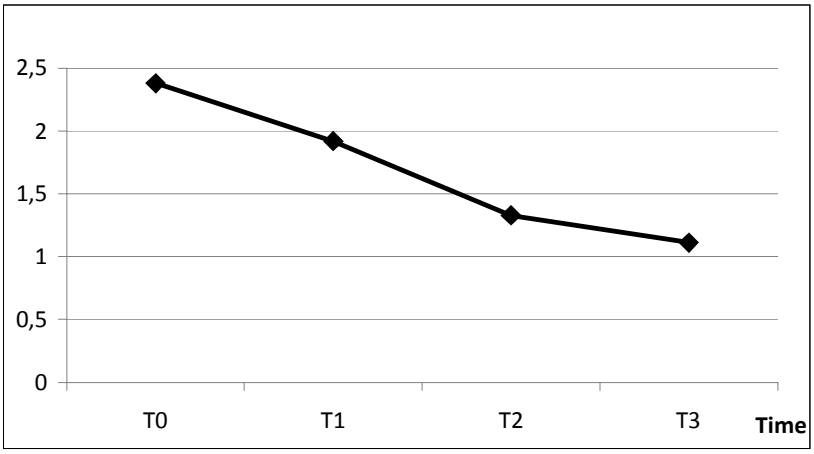

Figure 4. Changes from baseline of HAQ-DI score**.** The longitudinal improvement of ability to perform activity of daily living (HAQ-DI) over time on treatment is represented. (0 = performing activity of daily living without difficulty, 3 = unable to perform without assistance).

Discussion

In this 48-week study, we evaluated the efficacy of rituximab in patients with severe, highly active RA, who experienced an inadequate response to conventional plus biologic DMARDs therapies (TNF-α inhibitors). At 48 weeks, patients receiving rituximab (three courses of two 1000mg infusions) in combination with conventional DMARDs (methotrexate plus leflunomide) demonstrated statistically significant improvement in primary and secondary outcomes. Improvement of all investigated The final assessment (at 24 weeks) revealed significant clinical and functional improvement [6, 15-18].

One study evaluated the efficacy of one single course of rituximab alone or in combination with conventional DMARD and demonstrated that a substantial proportion of RA patients with inadequately response to multiple DMARDs experienced clinical and physical improvement for up to 2 years following a single course of rituximab with continuing methotrexate [19].

In the present study, after the initial course of rituximab, patients received a fixed re-treatment at 24 and 48 weeks. After the second course, the T_2 evaluation indicated a significant decrease of all investigated parameters, with an improvement of clinical and functional status. At T_2 evaluation, mean value of DAS28 showed remission (DAS28<2.6), and the mean change from baseline of the HAQ-DI exceeded the MCID. Disease activity (DAS28, inflammatory parameters), ability to perform the activity of daily living, RF and anti-CCP titers have shown a significant improvement at T_3 evaluation, compared to baseline.

The safety and efficacy of rituximab retreatment were evaluated by Keystone et al.[20] and by Popa et al.[21] These studies suggest that repeated courses of rituximab produce consistent and parameters was seen already at T_1, and the rates increased over the 48-week study period. No major adverse events were detected.

There are studies which demonstrated the efficacy, safety and prevention of structural joint damage of rituximab in refractory RA [6,15-18]. In these studies, patients with refractory RA received a single course of two 1000 mg infusions of rituximab, on days 1 and 15 and continued to take stable dosages of methotrexate.

sustained efficacy relative to the original baseline, with no new adverse events in patients with previously inadequate response to TNF inhibitors[20].

Teng et al., in his study, demonstrated that there are no major differences between fixed and on-demand retreatment with rituximab over 1-year follow-up period [22].

Conclusions

Our results demonstrate that a single course of two 100 mg infusion of rituximab in day 0 and 14, followed by a fixed retreatment (at 6 and 12 months), in association with conventional DMARDs (methotrexate plus leflunomide), determine significant clinical and functional improvement in patients with highly active rheumatoid arthritis with an inadequate response to other biologic DMARDs (TNF inhibitors).

Rituximab was safe, with no reports of major adverse effects. On-going studies will continue to further evaluate the efficacy and safety of repeated courses of rituximab in RA patients with previously inadequate response to anti-TNFα therapies.

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