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Effectiveness and safety of the use of rituximab in patients with active rheumatoid arthritis – 5 years' personal observations

Skuteczność i bezpieczeństwo stosowania rytuksymabu u pacjentów z aktywnym reumatoidalnym zapaleniem stawów – 5-letnie obserwacje własne

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Key words: rheumatoid arthritis, rituximab, biological therapy.

Słowa kluczowe: reumatoidalne zapalenie stawów, rytuksymab, leczenie biologiczne.

Summary

The aim of this study was to assess the effectiveness and safety of rituximab (RTX) treatment in patients with severe, active rheumatoid arthritis (RA) in the years 2007–2012.

Material and methods: The study was conducted on 38 adult patients with active RA (DAS28 > 3.2) who were enrolled in the RTX treatment program as a second or third line drug. The primary or secondary ineffectiveness of anti-TNF therapy was observed in those patients. The group consisted of 31 women (81.6%) and 7 men (18.4%). The average age was 54.6 ±11.25 years, and the average duration of RA was 16.3 ±7.9 years. The RTX effectiveness was assessed during 36 months using EULAR criteria.

Results: At the 6th, 12th, 24th, 30th and 36th month of observation a good response to RTX treatment was demonstrated by 18.4%, 30.0%, 21.7%, 64.3% and 88.9% of patients, respectively. At the same time a moderate response was found in 73.7%, 53.3%, 60.9%, 14.3% and 0.0% and no response in 7.9%, 16.7%, 17.4%, 21.4% and 11.1% of patients, respectively. There were 2 non-responders (5.3%) to the initial treatment with RTX. We observed secondary ineffectiveness of RTX therapy in 10 patients (26.3%).

During the course of RTX treatment the number of patients receiving oral corticosteroids was reduced from 34 (89.5%) to 16 (42.1%) ($p < 0.001$). In the remaining patients the mean dose of corticosteroids was lowered by 23.8%. The following adverse effects during RTX infusion were recorded in 3 (7.9%) patients: Quincke's edema, hypotonia and itching of the skin. Infections were observed in 5 (13.1%) of the treated patients.

Conclusions: RTX treatment is a safe and effective form of therapy in patients with active, long-term RA previously treated with various DMARDs.

Streszczenie

Celem pracy była ocena skuteczności i bezpieczeństwa leczenia rytuksymabem (RTX) stosowanym w latach 2007–2012 zgodnie z wytycznymi programu terapeutycznego u chorych z ciężką, aktywną postacią reumatoidalnego zapalenia stawów (RZS).

Materiał i metody: Rytuksymab stosowano jako leczenie drugo- lub trzecioliniowe u 38 dorosłych chorych z aktywnym RZS (DAS28 > 3,2), u których wystąpiła pierwotna lub wtórna nieskuteczność leczenia inhibitorami czynnika martwicy nowotworu (*tumor necrosis factor* – TNF). W grupie badanej było 31 kobiet (81,6%) i 7 mężczyzn (18,4%). Średni wiek chorych wynosił 54,6 ±11,2 roku, a średni czas trwania RZS wynosił 16,3 ±7,9 roku. Skuteczność leczenia oceniano przez 36 miesięcy, posługując się kryteriami EULAR (*The European League Against Rheumatism*).

Wyniki: W 6., 12., 24., 30. i 36. miesiącu obserwacji dobrą odpowiedź na leczenie RTX stwierdzono u odpowiednio 18,4%, 30%, 21,7%, 64,3% i 88,9% chorych. Umiarkowaną odpowiedź uzyskano u 73,7%, 53,3%, 60,9%, 14,3% i 0% chorych odpowiednio w 6., 12., 24., 30. i 36. miesiącu obserwacji. Brak odpowiedzi na leczenie odnotowano u 7,9% chorych w 6. miesiącu obserwacji, u 16,7% chorych w 12. miesiącu, 17,4% w 24. miesiącu, 21,4% w 30. miesiącu i u 11,1% w 36. miesiącu obserwacji. Brak pierwotnej odpowiedzi na leczenie RTX stwierdzono u 2 chorych (5,3%), natomiast utratę odpowiedzi na leczenie u 10 chorych (26,3%).

W czasie leczenia RTX liczba chorych przyjmujących glikokortykosteroidy zmniejszyła się z 34 (89,5%) do 16 (42,1%) chorych ($p < 0,001$). Leczenie RTX pozwoliło na obniżenie średniej dobowej dawki steroidów o 23,8%. Działania niepożądane (obrzęk Quinckego, hipotonia i świąd skóry) podczas infuzji RTX wystąpiły u 3 chorych (7,9%). Istotne powikłania infekcyjne w czasie terapii RTX obserwowano u 5 chorych (13,1%).

Wnioski: Rytuksymab jest bezpieczną i skuteczną formą terapii u chorych na aktywną postać wieloletniego RZS leczonego poprzednio wieloma lekami modyfikującymi przebieg choroby.

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Introduction

Rheumatoid arthritis (RA) is a chronic, progressive, autoimmune inflammatory disease that leads to joint destruction and disability and, in addition, reduces patients' lifespan. Tremendous progress has been made in recent years in the treatment of RA; one unquestionable breakthrough has been the introduction of biological agents with their various mechanisms of action, such as anti-cytokine agents, including tumor necrosis factor (TNF) inhibitors (infliximab, etanercept, adalimumab, golimumab), the interleukin-6 receptor inhibitor (tocilizumab), the interleukin-1 receptor inhibitor (anakinra), T-lymphocyte co-stimulator modulators (abatacept), as well as agents that act on B cells (rituximab). Modern therapy, based on neutralization of proinflammatory cytokines, such as TNF, is effective in many patients [1]. However, some patients fail to respond to anti-cytokine agents (primary failure) or else develop loss of initial response to treatment after periods of varying duration (secondary failure). In such cases, in accordance with the guidelines of therapeutic programs involving biological agents in force in Poland, the next therapy of choice is an agent that acts on B cells – rituximab (RTX).

Rituximab (Mabthera) is a chimeric murine/human monoclonal antibody with the ability to selectively bind to the membrane-spanning CD20 antigen, located on pre-B lymphocytes and mature B-lymphocytes. Its administration leads to the elimination of (CD20+) B-lymphocytes by means of, among others, complement-dependent cytotoxicity, antibody-dependent cellular cytotoxicity, and also through the induction of programmed cell death. Randomized, multicentre clinical studies have demonstrated the high effectiveness of RTX in combination with MTX in the treatment of active forms of RA, including patients who did not have satisfactory improvement with classic disease-modifying anti-rheumatic drugs (DMARDs) and/or one or more TNF-α inhibitors [2, 3]. In addition, it has been noted that RTX significantly slows progression of radiological changes compared with MTX [4].

Rituximab was registered for use in the European Union in September 2006, for the treatment of adult patients with severe, active RA and unsatisfactory response or intolerance to other DMARDs, including at least one TNF inhibitor. In December 2007, RTX was granted funding in Poland in the form of a drug program. According to the RTX therapeutic program, RTX may be administered in combination with MTX as second- or third-line therapy in adult patients with severe, active RA with an unsatisfactory response or intolerance to other DMARDs, including one or more TNF inhibitors.

A single course of treatment consists of 2 intravenous infusions containing a dose of 1000 mg/infusion given 14 days apart, and a subsequent course of treatment may be administered after an interval of at least 180 days. Premedication with a small dose of glucocorticosteroids (GCS) given intravenously, an antihistamine drug and paracetamol is recommended in order to reduce the risk of allergic reactions precipitated by RTX.

The aim of the study was to evaluate the course of RTX treatment in patients with severe, active RA from 2007 to 2012, administered in accordance with therapeutic program guidelines, with regard to the effectiveness of the therapy and the frequency and types of adverse effects.

Material and methods

A total of 40 patients were enrolled to receive treatment with RTX in the Chair and Department of Rheumatology and Connective Tissue Diseases in Lublin (*Katedra i Klinika Reumatologii i Układowych Chorób Tkanki Łącznej w Lublinie*) in the years 2007–2012. An analysis of the effectiveness and safety of treatment with RTX was ultimately conducted on 38 patients, because 2 patients decided to discontinue treatment. The analyzed group of patients consisted of 31 females and 7 males (amounting to 81.6% and 18.4%, respectively). Patients had a mean age of 54.6 ±11.2 years and the mean duration of RA was 16.3 ±7.9 years. The detailed demographic and clinical characteristics of the patients are presented in Table I.

Based on the EULAR criteria, at the time of RTX treatment initiation, 31 patients (81.6%) in the study group had high RA disease activity (DAS28 > 5.1) and 7 patients (18.4%) had moderate disease activity (3.2 > DAS28 ≤ 5.1) (DAS – Disease Activity Score). The mean DAS28 score at the time of RTX treatment initiation was 5.9 ±1.0. All patients received MTX: 22 (57.9%) orally, at a mean dose of 21.1 mg/week ±4.9 mg (dose range: 10–25 mg) and 16 (42.1%) subcutaneously, at a mean dose of 20.1 mg/week ±3.7 mg (dose range: 15–25 mg). At the time of RTX treatment initiation, 34 patients (89.5%) were receiving GCS orally, at a mean daily dose of 8.0 mg converted to prednisone equivalents. All patients had been previously treated with various DMARDs in monotherapy (Table II). Twenty-one evaluated patients (55.3%) had received combination therapy in a variety of combinations (Table III).

All the patients had undergone prior treatment with anti-TNF agents, of which 26 had received infliximab, 21 were given etanercept, and 5 had been treated with adalimumab. Prior to the initiation of treatment with RTX, 26 patients (68.4%) had been treated with one biological drug, 11 patients (29%) had received two, and one patient (2.6%) had received three biological drugs. Biological treatments administered prior to RTX therapy are presented in Table IV.

Rheumatoid arthritis activity was assessed based on the Disease Activity Score (DAS28) [5]. Clinical response to treatment with RTX was assessed using the EULAR crite-

Table I. Demographic and clinical characteristics of patients with rheumatoid arthritis (RA) treated with rituximab (RTX)

Number of patients	38
Age (years ± SD)	54.6 ±11.2
Sex (F/M) (%)	31/7 (81.6/18.4)
Duration of RA (years ± SD)	16.3 ±7.9
Seropositive RA (n/%)	31/81.6
Seronegative RA (n/%)	7/18.4
Anti-CCP antibodies present (n/%)	29/76.3
ANA present prior to treatment (n/%)	15/39.5
ANA – seroconversion during treatment (n/%)	2/5.3
dsDNA positive (n/%)	3/7.9
QuantiFERON positive	
- prior to treatment	4/10.5
- seroconversion during treatment	1/2.6
HBsAg positive (n/%)	0/0
anti-HCV positive (n/%)	0/0
anti-HIV positive (n/%)	0/0

Table III. Disease-modifying anti-rheumatic drugs administered in combination therapy prior to treatment with RTX

Drug	Number of patients	Proportion of patients (%)
LEF + CQ + MTX	2	5.3
CSA + MTX	6	15.8
LEF + MTX	5	13.1
SS + MTX	4	10.5
CQ + MTX	4	10.5

CQ – chloroquine, CSA – cyclosporine, LEF – leflunomide, MTX – methotrexate, SS – sulfasalazine

Table II. Disease-modifying anti-rheumatic drugs administered as monotherapy prior to treatment with RTX

Drug	Number of patients	Proportion of patients (%)
methotrexate	38	100
sulfasalazine	25	65.8
chloroquine	15	39.5
leflunomide	18	47.4
cyclosporine A	11	28.9
gold salts	8	21.1
azathioprine	2	5.3

CQ – chloroquine, CSA – cyclosporine, LEF – leflunomide, MTX – methotrexate, SS – sulfasalazine

Table IV. Biological therapies administered prior to RTX therapy

Drug of patients	Number of patients (%)	Proportion
1 drug	**26**	**68.4**
infliximab	17	44.7
etanercept	7	18.4
adalimumab	2	5.3
2 drugs	**11**	**29.0**
infliximab, etanercept	9	23.7
etanercept, adalimumab	2	5.3
3 drugs		
infliximab, tocilizumab, adalimumab	**1**	**2.6**

CQ – chloroquine, CSA – cyclosporine, LEF – leflunomide, MTX – methotrexate, SS – sulfasalazine

ria, based on baseline calculation and subsequent changes in DAS28 scores [6]. The effectiveness of the treatment was evaluated over a period of 36 months (at 6, 12, 24, 30, and 36 months).

Statistical analysis

Mean values and standard deviations were calculated. Statistical comparisons were performed using Student's *t*-test and the χ^2 test and the level of statistical significance was set at $p < 0.05$.

Results

Among the 38 patients treated with RTX, 12 (31.6%) received a single course of treatment, i.e. two intravenous infusions containing 1000 mg of RTX given 14 days apart; 6 patients (15.8%) received two courses of treatment;

9 patients (23.7%) received three courses; 6 patients (15.8%) were given four courses, and 5 patients (13.1%) were treated with five courses of RTX. The mean interval between the first two courses of RTX therapy was 9.1 months (range: 6–19 months). The mean interval over all courses of RTX therapy was 9.7 months (range: 6–19 months).

At 6 months, 18.4% of patients had a good response to treatment with RTX and 73.7% had a moderate response, whereas 7.9% of patients had not achieved response to treatment. At 12 months, 30% of patients had achieved a good response and 53.3% had achieved a moderate response while 16.7% of patients had failed to respond. An assessment of the effectiveness of treatment with RTX conducted at 24 months revealed that 21.7% of patients had achieved a good response, 60.9% had a moderate response, and 17.4% of patients had shown no improvement. At 30 months, 64.3% of patients had achieved a good response, 14.3% had achieved a moderate response, and 21.4% of evaluated patients had failed to respond to treatment. At 36 months, 88.9% of patients were found to have achieved a good response to treatment with RTX; there were no patients with moderate improvement whereas 11.1% of patients had failed to respond to treatment (Table V).

Among the group of 38 patients started on RTX therapy, 9 have to date achieved 36 months of follow-up. Primary response failure to treatment with RTX was observed in 2 patients (5.3%), whereas loss of initial response to treatment was seen in 10 patients (26.3%). Adverse effects, observed during RTX infusions, occurred in 3 patients (7.9%). One patient developed angioedema during the first infusion of the fourth course of therapy, which led to discontinuation of treatment. One patient experienced hypotonia during the course of the first RTX infusion and another patient developed pruritus. Rituximab therapy was continued in both cases, because the adverse reactions subsided following reduction of the RTX infusion rate and medication with intravenous GCS and an antihistamine agent. During the course of RTX therapy, significant complications, in the form of infections, were observed in 5 patients (13.1%); 3 patients had recurring urinary tract infections, one patient developed purulent bursitis of the elbow joint, and one had appendicitis. Recurring urinary tract infections that required the use of antibiotics and surgical intervention, in the case of appendicitis, were the cause of temporary discontinuation of treatment with RTX in 2 patients, and in 2 other patients they led to a lengthening of the interval between successive courses of therapy.

Two patients were diagnosed with neoplastic disease during treatment with RTX, which resulted in discontinuation of therapy. One female patient was diagnosed with breast cancer two months after the third course of treatment with RTX (26 months after initiation of therapy). The patient underwent a mastectomy in February 2012 and is currently undergoing chemotherapy. Twelve months after the initiation of RTX therapy, one female patient was diagnosed with planoepithelial spinocellular cancer of the skin (she had received 1 course of treatment). Thirty-one months after initiating treatment with RTX (after the fourth course of therapy), one patient underwent fine needle biopsy and the biopsy report raised the suspicion of a benign growth of the right parotid gland – Warthin's tumor (adenolymphoma). The patient is currently awaiting surgical excision of the parotid gland.

One patient became pregnant twice during the course of treatment with RTX, despite having signed written consent to use an effective method of contraception. The first pregnancy was determined approximately 24 months after the third course of RTX and the second approximately one

40Table V. Assessment of the effectiveness of treatment with RTX according to EULAR criteria

Response	At 6 months	At 12 months	At 24 months	At 30 months	At 36 months
Good (ΔDAS28 > 1.2 and DAS28 ≤ 3.2)	18.4% 7/38	30% 9/30	21.7% 5/23	64.3% 9/14	88.9% 8/9
Moderate (0.6 < ΔDAS28 ≤ 1.2 and 3.2 < DAS28 ≤ 5.1 or ΔDAS28 > 1.2 and DAS28 > 5.1)	73.7% 28/38	53.3% 16/30	60.9% 14/23	14.3% 2/14	0% 0/9
Absent (ΔDAS28 ≤ 0.6 or ΔDAS28 < 1.2 and DAS28 > 5.1)	7.9% 3/38	16.7% 5/30	17.4% 4/23	21.4% 3/14	11.1% 1/9

month after the fourth course of treatment. The course of both pregnancies was unremarkable and the patient delivered two healthy babies at term.

At the time RTX treatment was initiated, 34 patients (89.5%) were receiving GCS orally whereas, after treatment with RTX, the number of patients taking GCS had decreased to 16 (42.1%); this result had high statistical significance with $p < 0.001$. At the time of RTX therapy initiation, the mean daily dose of GCS, converted to prednisone equivalents, was 8.0 mg while treatment with RTX enabled a 23.8% reduction to 6.1 mg, converted to prednisone equivalents (no statistical significance).

Discussion

Treatment of RA is not always effective, despite using several classic DMARDs as well as biological agents, including TNF inhibitors. Clinical studies conducted to date have shown that following treatment with various TNF inhibitors (infliximab, etanercept, adalimumab) 25–40% of patients were unable to achieve an improvement of at least 20% according to American College of Rheumatology (ACR) criteria [7–9]. In the absence of an initial favorable response to TNF inhibitors or exacerbation of RA in a patient who initially achieved a good response to treatment with TNF inhibitors, the next medication of choice is RTX.

Initial open-label pilot trials have demonstrated the high clinical efficacy and good tolerance of RTX by patients with active RA [10, 11], as have multicenter randomized, double-blinded clinical trials [2–4]. An assessment of the effectiveness of multiple courses of RTX was only possible after several years of administration of the drug. May 2012 saw the publication of a report presenting data from the REFLEX multicenter study, assessing the results of 5 years of follow-up of patients treated with multiple courses of RTX [12]. The study demonstrated that multiple, repeated RTX infusions can maintain or enhance the effectiveness of treatment for RA, evaluated based on ACR and EULAR criteria. The results obtained by the authors of this paper are consistent with other reports and confirm the initial effectiveness and sustained clinical improvement over subsequent years of treatment with RTX. The results also point to an increase in the proportion of subjects who experience an improved response to treatment with extended administration of RTX. Furthermore, multiple courses of RTX made it possible to reduce the dose of GCS or discontinue concomitant GCS entirely. The analysis of adverse effects is similar to reports by other authors [12] and points to the relative safety of multiple courses of RTX.

Conclusions

1. Multiple courses of RTX are an effective method of treating patients with severe, active forms of RA.
2. Over a short, 6-month period following initiation of RTX, observations revealed that over 92% of patients with active RA achieved a good or moderate response according to EULAR criteria (including 18.4% with a good response).
3. Observations conducted over a longer period of time, beginning at 30 months, involving patients who were permitted to continue RTX therapy in accordance with the regulations of the therapeutic program, revealed an evident increase in the number of patients who achieved a good response to RTX, amounting to 64.3% at 30 months and 88.9% at 36 months.
4. Two patients (5.3%) had a primary response failure to treatment and 10 patients (26.3%) experienced loss of response to treatment.
5. The safety of multiple courses of RTX is similar to the safety of other biological agents.

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References

1. Filipowicz-Sosnowska A. Skuteczność i bezpieczeństwo inhibitorów TNF – wyniki długotrwałych badań obserwacyjnych. Reumatologia 2007; 45: 32-39.
2. Edwards JC, Szczepanski L, Szechinski J, et al. Efficacy of B-cell-targeted therapy with rituksimab in patients with rheumatoid arthritis. N Engl J Med 2004; 350: 2572-2581.
3. Emery P, Fleischmann R, Filipowicz-Sosnowska A, et al. The efficacy and safety of rituximab in patients with active rheumatoid arthritis despite methotrexate treatment. Arthritis Rheum 2006; 54: 1390-1400.
4. Cohen SB, Keystone E, Genovese MC, et al. Continued inhibition of structural damage over 2 years in patients with rheumatoid arthritis treated with rituximab in combination with methotrexate. Ann Rheum Dis 2010; 69: 1158-1161.
5. Prevoo ML, van't Hof MA, Kuper HH, et al. Modified disease activity scores that include twenty-eight-joint counts. Development and validation in a prospective longitudinal study of patients with rheumatoid arthritis. Arthritis Rheum 1995; 38: 44-48.
6. van Gestel AM, Prevoo ML, van't Hof MA, et al. Development and validation of the European League Against Rheumatism response criteria for rheumatoid arthritis. Comparison with the preliminary American College of Rheumatology and the World Health Organization/International League Against Rheumatism Criteria. Arthritis Rheum 1996; 39: 34-40.
7. Lipsky PE, van der Heijde DM, St Clair EW, et al. Infliximab and methotrexate in the treatment of rheumatoid arthritis. Anti-Tumor Necrosis Factor Trial in Rheumatoid Arthritis with Concomitant Therapy Study Group. N Engl J Med 2000; 343: 1594-1602.
8. Weinblatt ME, Kremer JM, Bankhurst AD, et al. A trial of etanercept, a recombinant tumor necrosis factor receptor:Fc fusion protein, in patients with rheumatoid arthritis receiving methotrexate. N Engl J Med 1999; 340: 253-259.

9. Weinblatt ME, Keystone EC, Furst DE, et al. Adalimumab, a fully human anti-tumor necrosis factor alpha monoclonal antibody, for the treatment of rheumatoid arthritis in patients taking concomitant methotrexate: the ARMADA trial. Arthritis Rheum 2003; 48: 35-45.
10. Edwards JC, Cambridge G. Sustained improvement in rheumatoid arthritis following a protocol designed to deplete B lymphocytes. Rheumatology (Oxford) 2001; 40: 205-211.
11. Kramm H, Hansen KE, Gowing E, Bridges A. Successful therapy of rheumatoid arthritis with rituximab: renewed interest in the role of B cells in the pathogenesis of rheumatoid arthritis. J Clin Rheumatol 2004; 10: 28-32.
12. Keystone EC, Cohen SB, Emery P, et al. Multiple Courses of Rituximab Produce Sustained. Clinical and Radiographic Efficacy and Safety in Patients with Rheumatoid Arthritis and an Inadequate Response to 1 or More Tumor Necrosis Factor Inhibitors: 5-Year Data from the REFLEX Study. J Rheumatol 2012; 39: 2238-2246.