Clinical Rheumatology (2019) 38:2399–2402
https://doi.org/10.1007/s10067-019-04578-2

ORIGINAL ARTICLE

Efficacy of rituximab in resistant palindromic rheumatism: first report in literature

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Received: 27 January 2019 / Revised: 15 April 2019 / Accepted: 23 April 2019 / Published online: 10 May 2019

Abstract

Background Rituximab (RTX) provides significant clinical benefits in active rheumatoid arthritis (RA) patients with inadequate response to DMARDs and anti-TNF. There is no data regarding efficacy of RTX in seropositive Palindromic Rheumatism (PR), a forerunner of RA.

Aim To determine the efficacy and safety of RTX treatment in active PR patients exhibiting inadequate response to conventional synthetic DMARDs (csDMARDs).

Methods The retrospective study, over a period of 3 years, included seropositive (RF ± antiCCP) PR patients with inadequate control of PR (> 4 attacks per months) despite combination csDMARDs and were treated with RTX. All the patients were treated with an initial dose of 500 mg RTX and later with a second infusion after 2 weeks' period in those who did not achieve adequate/complete disease control. Patients were continued on csDMARDS and retreated with RTX on relapse of symptoms.

Results Thirty-three seropositive PR patients with a mean age of 48.15 ± 14.2 years, mean disease duration of 68.4 ± 68.2 months, mean follow up period of 24.3 ± 10.8 months, were treated with RTX. 88% patients were on combination DMARDS and 79% patients were females. All patient achieved rapid and complete control of palindromic attacks with RTX. Fifteen patients had a relapse after a mean duration of 10.4 ± 5.5 months and needed repeat RTX infusions following which remission was achieved. None of the patients progressed to RA till the end of the follow-up. No serious adverse effects were recorded.

Conclusion RTX treatment could be effective in achieving disease control in active palindromic rheumatism not responding to csDMARDs.

Key Points

- *PR is thought to be a forerunner of RA and rituximab (RTX) has been found to be effective in RA.*
- *Our study supports the hypothesis that B cells play an important role in the pathophysiology of PR and that the combination (RTX+ conventional drugs) can prevent the disease evolution into RA.*
- *This 3-year retrospective study showed that rituximab was found to be effective in those who responded poorly to conventional drugs and remission was achieved in all patients.*
- *Although it is a rare disease, we see palindromic rheumatism patients in India more often. As the symptoms are very debilitating in these patients, in those patients, not controlled on conventional drugs, rituximab offers newer promise in controlling the attacks and prevents further progression to RA.*

Keywords csDMARDs · Palindromic rheumatism · Rheumatoid arthritis · Rituximab

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Introduction

Palindromic rheumatism (PR) is a clinical entity originally described by Hench and Rosenberg 70 years ago [1]. It is a rare inflammatory arthritis which is characterized by the recurrent short lasting episodes of joint pain and swelling at variable or irregular intervals. Between periods of attacks, patients are usually asymptomatic. Although several attacks may take place over a period of year, there is no permanent articular damage. Prevalence of PR is approximately 1/8 to 1/20 that of RA. About 50%, especially those who are seropositive may progress to rheumatoid arthritis [2]. There are neither treatment guidelines nor approved outcome measures for palindromic rheumatism, probably due to rarity of the disease.

Although there are no controlled studies, conventional synthetic DMARDs (csDMARDS) like hydroxychloroquine, penicillamine, sulphasalazine, and gold have been found to be useful in palindromic rheumatism too [3–5]. csDMARDs like chloroquine are helpful in reducing frequency and duration of attacks and delay its progression to RA [6]. Although most of the cases are mild and responds to csDMARDs, some tend to have severe attacks of migratory arthritis, affecting the quality of life of the patient and can be non-responsive to csDMARDS.

Rituximab, a chimeric monoclonal antibody, targeting the CD20 molecules expressed on the surface of B cells, has been widely studied in the treatment RA patients showing inadequate response to csDMARDs, including one or more anti-tumor-necrosis-factor (TNF) biologics [7, 8]. Several studies have reported very good efficacy of RTX in the management of seropositive RA [7, 9]. Based on the generalization that seropositive PR is a forerunner of RA, we hypothesized that RTX, a very effective agent in the management of seropositive RA would also be effective in the treatment of seropositive PR, which has inadequate response to csDMARDS. Literature-based evidence on the efficacy and safety of RTX in PR is not available. The present study is intended to determine the efficacy and safety of RTX treatment in active PR patients exhibiting inadequate response to conventional drugs.

Patients and methods

The retrospective study was conducted at CARE, Cochin, India. Palindromic rheumatism was diagnosed based on the criteria proposed by Hannonen P et al. [10]. The data of the patients who had a diagnosis of PR who were treated with RTX from 2014 to 2017 were obtained from EMR. Seropositive (ACPA± RF positivity) PR patients with active disease, despite 3 months of combination conventional synthetic DMARDS (csDMARDs) or maximum tolerable dose of csDMARDs were treated with RTX. RF was determined using nephlometry (cut of value 30, Kit from AGAPE) and ACPA by ELISA (cut off value 5). Active disease was defined as > 4 attacks per month requiring intake of NSAIDS.

All the patients were started with 500 mg dose of RTX after baseline work-up (viral serology screen, percentage of peripheral B cells, routine complete blood counts). Peripheral B cell depletion was assessed by flow cytometry at 2 weeks. Pre- and post drug infusion blood samples were obtained in EDTA vacutainer (BD Biosciences, USA) and tested on 3-laser FACS Aria II (BD Biosciences, San Jose, CA) using DiVa 6.1.1 software. Instrument calibration was performed and tested weekly. Fifty microliters of fresh blood samples were incubated with CD19 APC monoclonal antibody (BD Biosciences, USA) for 15 min at room temperature in the dark. Erythrocytes were lysed by incubating with 2 ml of 1:10 diluted BD FACS lysing solution for 15 min. After incubation, cells were pelleted by centrifugation (1500 rpm for 5 min at room temperature); the supernatant was aspirated and the cells were washed once with PBS. After the final wash, the cells were re-suspended. If the B cells were not depleted at 2 weeks or patients did not achieve complete control of disease activity in 4 weeks, another 500-mg infusion of RTX was administered. The background csDMARDS were continued, and repeat dose of RTX was given to patients if they develop clinical relapses, as evidenced by recurrence of palindromic attacks. As there were no outcome measures, we used absence of attacks for more than 1 month as control of disease activity and occurrence of more than two attacks per month as relapse. The study was performed in accordance with the Declaration of Helsinki and received approval from the institutional ethics committee. Informed consent was not relevant as it was a retrospective study.

Statistical analysis

Data with normal distribution were represented as mean ± SD, those without normal distribution as median (range), and categorical data as counts. Delta analysis was performed for comparison of pre- and post-data. The analysis' results were quantified as improved, stable-remained, unchanged, or worsened. The obtained counts data were documented. Delta analysis was performed for data with repeated measures. The results were quantified as increase, decrease, or same. All the statistical analyses were performed using Medcalc software version 14.8.1.

Result

Thirty-three seropositive patients with PR who were treated with rituximab (RTX) over a period of 3 years were included in the study. Their mean age was 48.15 ± 14.2 years and majority were females. The descriptive details of clinical and demographical variables of the subjects are provided in Table 1.

Table 1 Descriptive data of clinical and demographic variables of subjects with PR

Variables	Value ($n = 33$)
Age (years)	48.2 ± 14.2#
Gender	
Female	26 (78.8%)*
Male	7 (21.2%)*
Duration of symptoms (months)	68.4 ± 68.2#
Duration of csDMARDs prior to Rituximab (months)	22.3 ± 13.8#
RF positive	25 (75.7%)*
Anti-CCP positive	25 (75.7%)*
ESR (prior to 1st infusion)	42.5 ± 28.6#
ESR (post 1st infusion)	25.7 ± 18.2#
CD19 (prior to 1st infusion)	10.7 ± 3.7#
CD19 (post 1st infusion)	0.1 ± 0.6#
Total no. of infusions	No of patients*
One	18 (54.6%)
Two	6 (18.2%)
Three	7 (21.2%)
Four	2 (6.1%)
Frequency of DMARDs used	No of patients*
Methotrexate	25 (69.7%)
Hydroxychloroquine	30 (90.9%)
Sulphasalazine	18 (54.5%)
Leflunomide	5 (15.2%)
Low-dose corticosteroids	15 (45.4%)

1 DMARD - 4 (12%); 2 DMARD - 15 (45.5%); 3 DMARD - 12 (36.4%); 4 DMARD - 2 (6%)

mean ± SD, *n (%)

At the time of inclusion in the study, they had mean disease duration of 68.4 ± 68.2 months. They were followed for a mean (SD) duration of 24.3 ± 10.8 months. Majority of them were on combination csDMARDs (88%) (Table 1). Most of them were on HCQs. Only 3 patients on combination DMARDS were off HCQ either due to intolerance or adverse effects due to HCQ . Some of the patients were only on single csDMARDs with low-dose corticosteroids as they developed intolerance or adverse effects to other csDMARDS when added. Mean duration of csDMARDs prior to rituximab infusion was 22.3 ± 13.8 months.

Before RTX infusion, patients had 5.27 ± 1.99 palindromic attacks per month. The RTX infusion achieved disease remission in all patients. Fifteen patients had relapse after a mean duration of 10.4 ± 5.5 months. Remaining 18 patients remained in remission for a mean period of 19.3 ± 7.5 months. The second infusion of RTX was given for 15 patients who relapsed. Of these, six patients achieved remission for a mean period of 8.67 ± 3.8 months, and nine patients relapsed after a mean duration of 12.6 ± 7.8 months. A third infusion was given to these nine patients, out of which seven patients achieved mean remission for 15.4 ± 5.9 months and two patients relapsed after a mean duration of 9.5 ± 0.5 months. They received the fourth infusion, and both patients achieved a mean remission for 11.5 months until the end of the study. None of the patients reported serious adverse effects, and the erythrocyte sedimentation rate (ESR) and CD 19 levels were noted to decrease with the treatment (Table 1, Fig. 1).

Discussion

PR has been generally considered as a benign disease as it does not cause erosions or deformity, and it responds very well to csDMARDs. But in a few patients, PR may not respond to combination DMARDs leading to poor quality of life which is compounded by sudden unpredictable onset of attacks. There is paucity of data regarding use of biologicals in these patients who have inadequate response to csDMARDs. The present study is the first of its kind to have studied the efficacy and safety of RTX for the treatment of these patients. The retrospective study, involving 33 patients, has shown that all the patients achieved

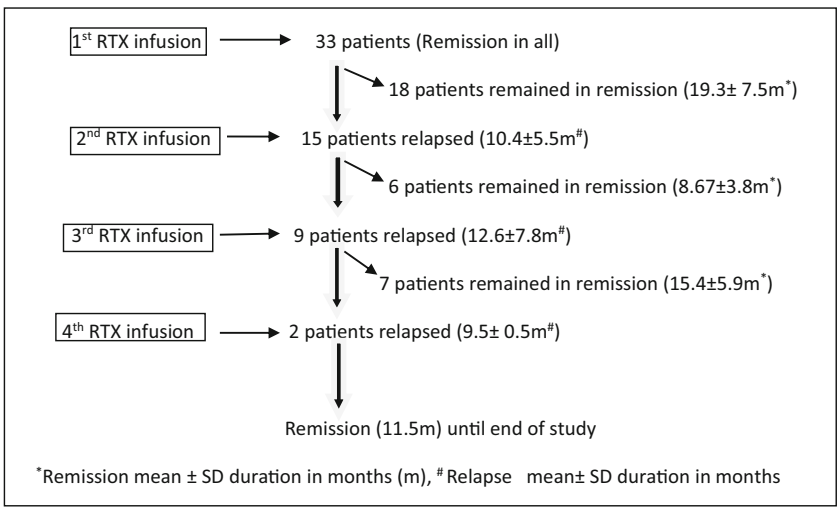

Fig. 1 Flowchart depicting PR patients' remission and relapse after each RTX infusion

complete control of disease in 4-week time. Although this rapid effect may be attributed to the effect of iv steroids administered at the time of RTX infusion, to prevent infusion reactions, persistence of disease control for months cannot be attributed to steroids and is due to the effect of RTX infusion. Additionally, it has been noted that 500 mg RTX is effective in most of the patients. Although 2 g is the recommended dose in RA, now, there is data proving that 1 g dose is non inferior to 2 g [11]. In rheumatoid arthritis, higher doses of rituximab will be required as there will be established TLO (tertiary lymphoid organ) in the synovium of the joints. To eliminate the B cells from the TLO, higher doses of rituximab are required. However, in palindromic rheumatism, as joint involvement is migratory, we presumed that there will be lesser TLO in these patients and hence even lower doses will be effective in these patients.

In this study, seropositive (ACPA± RF positivity) PR patients with active disease, despite 3 months of combination, csDMARDs or maximum tolerable dose of csDMARDs were treated with RTX. Active disease was defined as > 4 attacks per month (taken arbitrarily as no literature defines active disease) requiring intake of NSAIDS. As there were no approved outcome measures, we used absence of attacks for more than 1 month as control of disease activity and occurrence of more than two attacks per month as relapse.

The present study suggests the use of RTX for the prevention of PR evolution into RA, as none of the patients developed RA during follow-up. The follow-up conducted by Youssef et al. for 3.6 years, in PR patients, showed development of RA in 23% patients [12]. The paucity of evidence-based therapy in PR due to lack of agreed treatment guidelines and controlled trials has been stressed by other authors too [13]. One of the major reasons for the very limited number of trials on PR is challenges related to the large number of patient recruitment, as the condition is rare. Moreover, recruiting homogenous patient population is highly difficult, as there is no consensus on the proposed disease classification criteria. For treatment studies with very limited sample size, the interpretation of result is challenging due to the variable clinical course of the disease, more over there are no standardized outcome measures.

In conclusion, the present study, first time in literature, demonstrated efficacy of RTX in controlling PR in seropositive patients. As none of the patients progressed to RA, the present study suggests the use of RTX for the prevention of PR evolution into RA.

Conclusion

The present study suggests the use of RTX with csDMARDs in active PR patients who failed to respond to csDMARDs. Additionally, the study supports the hypothesis that B cells play an important role in the pathophysiology of PR. The study also suggets that the combination (RTX + csDMARDs) prevents PR evolution into RA, as none of the cases developed RA during follow-up.

Compliance with ethical standards

Disclosures None.

References

1. Wajed MA, Brown DL, Currey HL (1977) Palindromic rheumatism. Clinical and serum complement study. Ann Rheum Dis 36(1): 56–61
2. Guerne PA, Weisman MH (1992) Palindromic rheumatism: part of or apart from the spectrum of rheumatoid arthritis. Am J Med 93(4): 451–460
3. Hannonen P, Mottonen T, Oka M (1987) Palindromic rheumatism. A clinical survey of sixty patients. Scand J Rheumatol 16:413e20
4. Golding DN (1988) Sulphasalazine for palindromic rheumatism. Br J Rheumatol 27:79
5. Youssef W, Yan A, Russell AS (1991) Palindromic rheumatism: a response to chloroquine. J Rheumatol 18:35e7
6. Gonzalez-Lopez L, Gamez-Nava JI, Jhangri G et al (2000) Decreased progression to rheumatoid arthritis or other connective tissue diseases in patients with palindromic rheumatism treated with antimalarials. J Rheumatol 27:41e6
7. Wendler J, Burmester GR, Sörensen H, Krause A, Richter C, Tony HP, Rubbert-Roth A, Bartz-Bazzanella P, Wassenberg S, Haug-Rost I, Dörner T (2014) Rituximab in patients with rheumatoid arthritis in routine practice (GERINIS): six-year results from a prospective, multicentre, non-interventional study in 2,484 patients. Arthritis Res Ther 16(2):R80
8. Mok CC (2014) Rituximab for the treatment of rheumatoid arthritis: an update. Drug Des Dev Ther 8:87
9. Edwards JC, Szczepański L, Szechiński J, Filipowicz-Sosnowska A, Emery P, Close DR, Stevens RM, Shaw T (2004) Efficacy of B-cell–targeted therapy with rituximab in patients with rheumatoid arthritis. N Engl J Med 350(25):2572–2581
10. Hannonen P, Müttönen T, Oka M (1987) Palindromic rheumatism: a clinical survey of sixty patients. Scand J Rheumatol 16(6):413–420
11. Tak PP, Rigby W, Rubbert-Roth A, Peterfy C, van Vollenhoven RF, Stohl W, Healy E, Hessey E, Reynard M, Shaw T (2011) Sustained inhibition of progressive joint damage with rituximab plus methotrexate in early active rheumatoid arthritis: 2-year results from the randomised controlled trial IMAGE. Ann Rheum Dis 1: annrheumdis–annrheu2010
12. Youssef WA, Yan AL, Russell AS (1991) Palindromic rheumatism: a response to chloroquine. J Rheumatol 18(1):35–37
13. Mankia K, Emery P (2017) What can palindromic rheumatism tell us? Best Pract Res Clin Rheumatol 31(1):90–98