

CONCISE REPORT

Rituximab in psoriatic arthritis: an exploratory evaluation

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ABSTRACT

Background/objective Current therapies for psoriatic arthritis (PsA) comprise synthetic drugs and tumour necrosis factor inhibitors. In contrast, other biologicals including rituximab (RTX) are available for treating rheumatoid arthritis (RA). RTX is effective in autoantibody positive RA patients, although some efficacy has been reported in seronegative individuals. RTX has not yet been assessed in PsA. Therefore, an open label study of RTX in PsA was performed.

Patients and methods Nine patients with PsA and 14 with RA received RTX at 1000 mg twice within 14 days and were evaluated over 6 months.

Results A PsA response criteria response was attained in 56% of patients. DAS28 improved from 6.2 to 4.9 (medians) in PsA and 6.4 to 5.2 in RA, and Health Assessment Questionnaire from 1.5 to 1.0 and from 2.1 to 1.4, respectively (all $p \leq 0.05$). Disease Activity index for Psoriatic Arthritis changed from 52.0 to 32.5 ($p < 0.05$); C reactive protein and Psoriasis Area and Severity Index did not change significantly. RTX was tolerated well.

Conclusions In this exploratory open study, RTX exhibited significant efficacy in PsA patients with long-standing disease. Thus, RTX may have efficacy in PsA warranting a randomised controlled clinical trial.

PATIENTS AND METHODS

General considerations

Nine patients received open label RTX at 1000 mg intravenously on days 0 and 14 with appropriate comedication.⁶ Since this study lacked a control arm, we assessed the responses in 14 RA patients recruited at the same period into open label RTX therapy; this allowed comparing potential 'open label' effects in PsA with RA patients in a similar setting.

RA patients were recruited into the 'Rituximab In RA' part of this report at five centres and PsA patients into the 'Rituximab In PsA' (RIPA) part at three centres. Patients received full information, and gave their consent according to the Declaration of Helsinki 1996; the study was approved by the Ethical Committees of the Medical University of Vienna and each site and was registered (www.controlled-trials.com/ISRCTN76859006).

Inclusion criteria

Adult PsA patients fulfilling classification criteria⁷ had a disease duration of ≥ 6 months and active disease despite maximum tolerated methotrexate (MTX) dose (to be stable for ≥ 8 weeks before inclusion). PsA patients had to fulfil at least two of the following additional criteria: ≥ 4 swollen joints on a 66 joint count (JC), ≥ 6 tender joints on a 68 JC (SJC, TJC), elevated erythrocyte sedimentation rate (ESR, ≥ 28 mm/h) or C reactive protein level (CRP, > 1 mg/dl), and be rheumatoid factor negative. Lower SJC was required for PsA versus RA (see below) to allow inclusion of patients with oligoarthritis or isolated distal interphalangeal joint involvement.

Adult RA patients⁸ had disease ≥ 6 months and insufficient response to ≥ 1 TNFi. Active disease was required with ≥ 6 SJC and TJC on a 66/68 JC and one of the following three variables: ESR ≥ 28 mm/h, CRP ≥ 1.5 mg/dl or morning stiffness ≥ 45 min, erosions, anticitrullinated peptide or rheumatoid factor positivity.

In all patients, NSAIDs had to be at a stable dose and glucocorticoids stable at ≤ 10 mg prednisone/day for at least 2 weeks prior to first administration of RTX.

Exclusion criteria

Patients were ineligible if they were pregnant women, nursing or planning a pregnancy within

INTRODUCTION

The current treatment armamentarium for psoriatic arthritis (PsA)¹ comprises various synthetic disease modifying antirheumatic drugs (sDMARDs),² but many patients do not improve sufficiently and require tumour necrosis factor inhibitors (TNFi) which have proven effective in PsA.²⁻³ However, patients not experiencing significant improvement on TNFi are currently without alternative targeted therapies.

In contrast, patients with rheumatoid arthritis (RA) have a number of biologics available,⁴ including B lymphocyte depleting therapy (rituximab, RTX). While PsA is not accompanied by autoantibodies and seronegative RA responds less to RTX than seropositive, B cells are present in PsA synovial membranes⁵ and may bear antigen presenting cell (APC) capacity; elimination of APC might affect the events operative in PsA. With this background in mind, we explored the potential efficacy of RTX in PsA.

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6 months after the last scheduled treatment, used cyclosporine or tacrolimus or had chronic infections.

Assessments

Variables were assessed at baseline, 2, 6, 12–14 and 22–26 weeks, comprising SJC, TJC; patient pain, patient and evaluator global assessments (PtGA, EGA) using a 10 cm visual analogue scale; Health Assessment Questionnaire (HAQ) for evaluating physical function using validated German or Slovak versions;⁹ and laboratory assessments (ESR, CRP and haemoglobin). JC and EGA were done by an assessor unaware of study details and purpose.

The PsA group underwent additional assessments for spine involvement by Bath Ankylosing Spondylitis Disease Activity Index (BASDAI);¹⁰ enthesitis by Maastricht Ankylosing Spondylitis Enthesis Score;¹¹ and dactylitis by quantitative assessment. PsA patients also underwent assessment of skin involvement using the Psoriasis Area and Severity Index¹² and the Dermatology Life Quality Index.¹²

Composite scores were calculated in all patients: 28 JC disease activity score (DAS28), the simplified and clinical disease activity indices (SDAI, CDAI);¹³ for PsA, also psoriatic arthritis response criteria (PsARC)¹⁴ and Disease Activity index for Psoriatic Arthritis (DAPSA).¹⁵

Endpoints

The primary endpoint in the RIPA part was PsARC improvement by 30% of tender and swollen JC or, if only one fulfilled, then 30% improvement of visual analogue scale PtGA or EGA also.¹⁴ The primary endpoint in the RA group was frequency of low disease activity or remission by CDAI (≤ 10). Secondary endpoints were changes in the following: DAS28, SDAI, CDAI,¹³ DAPSA¹⁵ and HAQ.

Exclusion due to ineffective treatment was left at the discretion of investigator and patient. All PsA patients reached the 24 week timepoint. RTX therapy was not repeated.

Statistical analyses

Descriptive statistics are presented as medians and ranges due to non-normal distribution. Responses to RTX after 6 months were compared with baseline. The primary endpoint was first assessed; subsequently, the other variables were calculated using Kruskal Wallis Test (MedCalc Statistical Software, Mariakerke, Belgium); $p < 0.05$ was considered significant.

RESULTS

Baseline demographics and clinical variables are outlined in table 1. All patients had longstanding, DMARD resistant PsA or RA. Among PsA patients, 5 (55%) had previously received ≥ 2 DMARDs and one also a TNFi (etanercept). All RA patients had active disease despite ≥ 1 TNFi. Ten RA patients (71%) had failed ≥ 2 TNFi.

Analysis of efficacy

The primary endpoint for PsA, $\geq 30\%$ improvement by PsARC, was attained in five of nine PsA patients (56%). All composite disease activity measures improved significantly (table 2); CDAI, SDAI and DAPSA decreased $>40\%$ and HAQ improved $>25\%$. CRP decreased $>25\%$, although missing significance. One patient who previously failed etanercept did not experience notable improvement (DAPSA change from 72.4 to 64.4). Three PsA patients (33%) attained an ACR20 response; none an ACR50 or ACR70 response.

Table 1 Baseline demographic and disease characteristics*

Characteristic	PsA (N=9)	RA (N=14)
Male/female	4/5	3/11
Age, years (mean $\pm$ SD)	50 $\pm$ 11	50.6 $\pm$ 9.6
Duration of arthritis, years (mean $\pm$ SD)	9 $\pm$ 7	9.6 $\pm$ 6
Duration of psoriasis, years (mean $\pm$ SD)	12 $\pm$ 7	NA
MTX dose (mg/week; mean $\pm$ SD)	11.0 $\pm$ 7.0	15.6 $\pm$ 5.3
Steroid dose (mg prednisolone; mean $\pm$ SD)	4.1 $\pm$ 3.5	6.3 $\pm$ 3.7
Previous DMARDs (median, range)	2 (1–3)	4.5 (1–8)
Swollen 28 JC (mean $\pm$ SD)	7.3 $\pm$ 2.7	11.2 $\pm$ 5.4
Tender 28 JC (mean $\pm$ SD)	12.8 $\pm$ 4.1	15.9 $\pm$ 7
BASDAI (mean $\pm$ SD, n=5)	6.3 $\pm$ 2.2	NA
Dactylitis (n; %)	4 (44%)	NA
Enthesitis (n; %)	8 (89%)	NA

*Other baseline characteristics are shown in table 2.

BASDAI, Bath Ankylosing Spondylitis Disease Activity Index; DMARD, disease modifying antirheumatic drug; JC, joint count; NA, not applicable; PsA, psoriatic arthritis; RA, rheumatoid arthritis.

Dactylitis, present in four patients (44%), did not improve. However, enthesitis score changed dramatically from a median of 4 (range 0–7) to 2 (0–3; $p=0.016$). Psoriasis Area and Severity Index did not improve (baseline: 13.3 (0.6–31.3); month 6: 12.0 (0.6–31.2)). Among the five patients with axial involvement, BASDAI was 6.3 $\pm$ 2.2 at baseline and 5.9 $\pm$ 3.0 at 6 months ($p=0.57$).

The primary endpoint for the RA cohort, proportion of CDAI low disease activity (≤ 10), was achieved by two patients (14%). By the new CDAI response criteria,¹⁶ four patients (29%) achieved CDAI50 (minor response) and two patients CDAI70 (moderate response). In line with the relationship of CDAI and ACR response¹⁶ four patients (29%) reached ACR20, 3 (21%) ACR50 and none ACR70 response. Some details are shown in table 2. Overall, changes in the PsA cohort were similar to RA; CRP decreased almost significantly in RA (table 2).

Safety

Among PsA patients, no serious adverse event was observed; one patient experienced cellulitis, another candida skin infection, but none required intravenous therapy. One RA patient had pneumonia classified as a serious adverse event.

Table 2 Composite measures of disease activity, Health Assessment Questionnaire (HAQ) and C reactive protein (CRP) at baseline and month 6 in PsA and rheumatoid arthritis patients treated with rituximab

	PsA baseline		RA baseline	
	month 6	p $\leq$ Value	month 6	p $\leq$ Value
DAS28	6.2 (5.8–6.6) 4.9 (4.4–5.4)	0.01	6.4 (5.8–7) 5.2 (4.3–6.1)	0.008
CDAI	34.1 (27.5–38.2) 18.2 (16.3–23.8)	0.007	42.2 (28.4–47.1) 26 (19.1–40.7)	0.01
SDAI	44.2 (30.6–52.2) 26.1 (20.4–41.8)	0.02	37.5 (29.5–41.2) 21.9 (16.6–30.1)	0.05
DAPSA	52 (37.7–62) 30.7 (21.4–54.2)	0.05		NA
HAQ	1.5 (1.1–1.7) 1.1 (0.6–1.6)	0.03	2.1 (1.3–2.3) 1.4 (1.1–2)	0.04
CRP	3.0 (1.4–3.8) 2.2 (0.4–4.2)	0.8	5.2 (1.2–5.7) 1 (0.5–2)	0.06

CDAI, Clinical Disease Activity Index; DAPSA, Disease Activity index for Psoriatic Arthritis; DAS28, 28 joint count Disease Activity Score; NA, not applicable; PsA, psoriatic arthritis; SDAI, Simplified Disease Activity Index.

p Values denote the significance of the difference between the 6 month and baseline values.

DISCUSSION

The data obtained in this open label study suggest that RTX may be weakly effective in PsA: 56% of patients attained the primary endpoint (PsARC 30% response). Overall improvements in composite activity measures and HAQ amounted to 30%–40%, similar to those seen in refractory RA patients treated at about the same time in an open label fashion.

In contrast to RA, PsA is not characterised by the presence of autoantibodies, a potential reason not to use B cell depleting therapy; however, the exact mechanism of action of RTX in RA is not fully understood and may involve depletion of APC.⁶ Antigen presentation is presumably pivotal in PsA.¹⁷ Moreover, B cell aggregates were observed in PsA synovial membranes,⁵ further supporting the rationale for B cell depleting therapy.

Currently, no biologics other than TNFi are approved for PsA. While only a third of the PsA patients attained an American College of Rheumatology (ACR20) response, it was in the same order as in the RA cohort assessed in parallel. Moreover, the PsARC 30% response of 56% by far exceeds the placebo ACR20 response rate seen in an abatacept trial of PsA¹⁸ and is similar to the response observed with abatacept. Further, DAPSA improved by >40% and also CRP decreased by >25%, a finding usually not made upon placebo treatment.

A recent abstract on RTX treatment of PsA is in line with our finding of a weak therapeutic effect;¹⁹ moreover, RTX has shown some efficacy in patients with ankylosing spondylitis (AS), a related disease,²⁰ further expanding our notion on the efficacy of this principle.

The major limitation of our study is its open nature which precludes firm conclusions. However, it was meant to raise the hypothesis that RTX may be an effective and safe approach for PsA; the data presented allow generating this hypothesis. Open label studies were frequently performed to inform on the potential efficacy of an agent. Indeed, tocilizumab was studied in a case series of patients with AS and shown to be ineffective,^{21 22} and infliximab was evaluated in an open label fashion in AS, a study that provided the initial insights on efficacy of TNF blockers,²³ subsequently confirmed in randomised controlled trials. Also, in light of reports on the development of psoriasis in patients treated with RTX,²⁴ it was important evaluating RTX safety regarding the skin; there were no such safety signals in our small study. Of note, reports on the improvement of psoriasis upon B cell depletion²⁵ expand our findings. Another limitation is the use of the PsARC, a dichotomous measure with high placebo response;¹⁴ however, other secondary endpoints unrelated to joint involvement (enthesitis, dactylitis, skin or axial involvement) were assessed. Finally, the RA patients had more refractory disease than PsA patients and all RA patients had been treated with ≥1 TNFi; however, in the present study we assessed the RA patients primarily for judging the extent of an open label (placebo) response.

While in our study the BASDAI did not change significantly, Song *et al*²⁰ reported significant BASDAI improvement; however, they focused on AS patients, whereas here only five patients had secondary axial involvement. Further, as we included mostly TNFi-naïve PsA patients in our study, we do not know if TNFi refractory patients show similar responsiveness; however, according to the mentioned abstract, TNFi experienced patients had no response to RTX,¹⁹ and the single PsA patient studied here who had failed a TNFi also failed responding to RTX.

In conclusion, the data provided allow raising the hypothesis that B cell depletion may be an effective therapeutic approach for PsA. Given that TNFi are currently the only biologic agents

approved for treating PsA, the results of our trial and their support from another brief report¹⁹ warrant a double blind placebo controlled clinical trial.

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Contributors EJB, TS and JSS were involved in data analyses. MS was involved in patient assessment. JR, HR, BL, KPM and WBG recruited patients. EJB, TS and JSS wrote the first draft of the manuscript. All authors provided input into the manuscript and approved it prior to submission.

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Competing interests EJB, MS and HR: no conflict. TS received honoraria from Abbott. JR received honoraria from Abbott, MSD and Roche. BL and WG received honoraria from Abbott, BMS, MSD, Pfizer, Roche and UCB. KPM received honoraria from Abbott, MSD and Pfizer. JSS received grant support and/or honoraria from Abbott, Amgen, BMS, Janssen, MSD, Roche, Pfizer and UCB.

Patient consent Obtained.

Ethics approval Approval provided by the Ethics Committee of the Medical University of Vienna and at each site.

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