Rituximab in patients with rheumatoid arthritis and vasculitis-associated cutaneous ulcers

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Received on March 9, 2010; accepted in revised form on March 16, 2010.

Clin Exp Rheumatol 2010; 28 (Suppl. 57): S81-S83.

Key words: Rituximab, vasculitis, cutaneous ulcer, rheumatoid arthritis

Conflict of interest: Dr Pfreundschuh has received honoraria and research support, and is a member of the Advisory Board of Roche; the other co-authors have declared no competing interests.

ABSTRACT

Objective. *To test the efficacy of treatment with rituximab in refractory rheumatoid vasculitis in patients with rheumatoid arthritis (RA).*

Methods. *Retrospective study of four female patients with histologically proven RA associated vasculitic cutaneous ulcers. All patients developed the lesions on long term treatment with methotrexate or leflunomide, and three of them with tumour necrosis factor alpha (TNF) blockers. All patients were refractory to prednisolone in the dosage between 0.5 and 1 mg/kg body weight for at least 4 weeks prior to rituximab. Rituximab were administered in two intravenous applications in the interval of 14 days accompanied by continued treatment with methotrexate or leflunomide and prednisolone.*

Results. *Three out of four patients achieved a rapid clinical remission of the lesions within 4 to 6 weeks after rituximab therapy continuing at least for four months with a successful corticoid reduction till prednisolone 10 mg a day. One patient showed no remission of the skin lesions accompanied by increasing levels for ESR and CRP.*

Conclusions. *Rituximab treatment seems to be very effective in several cases of vasculitis-associated cutaneous ulcers in RA patients. However, the effectiveness of rituximab in cases with this indication remains to be shown in larger number of patients.*

Introduction

Rheumatoid vasculitis (RV) is an extraarticular manifestation of rheumatoid arthritis (RA) with less than 10% of RA patients affected (incidence $1/10^5$) (1). It is typically involving small vessels of fingers and toes and rarely the aortic trunc and coronary arteries. Typically RV manifests late after several years of disease course of rheumatoid factors (RF) and anti-CCP highly-positive RA (2, 3). About 75% of display circulating anti-endothelial antibodies (4). Immunopathologically immune complexes cause vascular damage by endothelial damage and result in increased complement turnover. Standard of therapy is like in primary systemic vasculitides Cyclophosphamide and steroids for remission-induction followed by methotrexate or azathioprine maintenance therapy (5). Refractory cases may be treated by the biologicals employed for refractory RA (tumour necrosis factor alpha (TNF) blockers, abatacept, rituximab). To our knowledge, up to now no controlled clinical trial is available.

Rituximab, a chimeric monoclonal antibody that binds to CD20 expressed on the surface of B cells, leads to a B cell depletion by complement mediated activities and through antibody dependent cellular cytotoxicity. Besides its established use in refractory RA, controlled clinical trials with rituximab in patients with refractory ANCA associated vasculitides demonstrate its therapeutic effectivity (6), even with non-inferiority to cyclophosphamide (7). In order to look for a potential synergistic effect of rituximab against articular and vasulitic RA manifestation we employed rituximab in refractory RV patients. Here we report our experience of four RV patients subsequently treated with rituximab according to a standardised protocol.

Material and methods

All patients were treated in the University Saarland Medical School, Homburg/Saar, Germany. They fullfilled the diagnosis for RA according to the ACR criteria from 1987. All patients did not suffer from high arthritis activity, the DAS28 (activity score) in all patients was lower than 4.0 (moderate arthritis activity). Vasculitis-associated cutaneous ulcers were diagnosed by cutaneous biopsy-specimens and histologically confirmed as immune complex vasculitis. The diagnostic procedure was completed with ultrasound of abdominal

Table I. Characteristics of four female RA patients with skin vasculitis treated with rituximab.

	Patient N1	Patient N2	Patient N3	Patient N4
Age (years)	64	70	71	48
Gender	female	female	female	female
RA disease duration (years)	12	22	36	17
RF, A-CCP ±	RF+, A-CCP-	RF+, A-CCP+	RF+, A-CCP-	RF+, A-CCP+
Vasculitis lesions localised	Lower leg, 3 lesions	Dorsal part of the finger ray, 4 lesions	Dorsal part of the toes, 3 lesions	Back of the hands, 6 lesions
Treatment	Rituximab 1000mg, twice within 2 weeks, Prednisolon 70mg/day, Methotrexate 20mg/week s.c.	Rituximab 1000mg, twice within 2 weeks, Prednisolon 70mg/day, Methotrexate 20mg/week s.c.	Rituximab 1000mg, twice within 2 weeks, Prednisolon 70mg/day, Leflunomide 20mg/day.	Rituximab 1000mg, twice within 2 weeks, Prednisolon 30mg/day, Leflunomide 20mg/day.
Previous therapy	Remicade+methotrexate	methotrexate	remicade	Adalimumab+leflunomide
Clinical remission ±	– (progression)	+	+	+
Time (weeks) to clinical remission	–	3	4	6
ESR prior/after treatment	30/46	30/30	46/42	16/11
CRP prior/after treatment	9/226	100/10	19/15	21/4
C3-/C4 complement prior/after reatment	Normal/normal	Decreased/normal	Normal/normal	Normal/normal
Treatment complication	–	–	–	–

RF: rheumatoid factor; A-CCP: anti-cyclic-citrullinated peptide antibodies

part, chest x-ray, investigation of the urine excluding nephritic sediments in order to screen for or exclude systemic vasculitis' manifestations. Patient characteristics including the disease duration, previous therapy, and laboratory test results are outlined in Table I. All patients were female and developed the cutaneous ulcers 8 to 16 weeks prior to the treatment with rituximab being refractory to prednisolone in the dosage of 0.5 to 1 mg/kg body weight for 4 to 6 weeks. Patient N1 showed 3 ulcers of 5 to 8 cm in diameter, Patients N2 – N4 of 0.5 to 1 cm. The TNF blocker medication were stopped in the concerned patients at least 4 weeks prior to rituximab treatment. All patients were treated with rituximab according to standard RA protocol with two infusions of 1000 mg in the interval of two weeks. The concomitant medication consists in methotrexate or leflunomide and in addition prednisolone (Table I). The observation time after rituximab administration was four months.

Results

Three out of four patients achieved a complete remission within 3 to 6 weeks defined by healing of the cutaneous ulcers. The prednisolone dosage was reduced within 4 weeks to 10 mg daily. Patient N1 however remained refractory requiring 70 mg prednisolone daily during the rituximab/methotrexate treatment combination. The consecutively initiated re-treatment with remicade led to mild improvement but no healing of the lesions. Increasing or decreasing levels for ESR and CRP were in line with the clinical outcome of the lesions. The time to remission, the results for ESR, CRP, and complement factors C3 and C4, respectively prior and after the treatment are presented in Table I. No recurrence occurred in the three successfully treated patients within four months.

Discussion

We documented a rapid treatment success for vasculitis-associated cutaneous ulcers with rituximab in three of four female RA patients. Of note, clinical response to rituximab therapy corresponded well to a decrease of ESR and CRP values but not to serum levels of complement factor C3 and C4. One patient showing larger cutaneuos lesion compared to the remaining patients did not achieve a remission with rituximab during the observation time of 4 months, furthermore, the ESR and CRP values increased considerably. Thus, efficacy of rituximab in RV might be independent from the activity of immune complexes. With respect to the limited number of patients in the here presented study we have to confine that conclusions require more cases of RV treated with rituximab.

Rituximab is a well established therapy for RA refractory to disease-modifying anti-rheumatic drugs (DMARDS) and tumour necrosis factor alpha (TNF) blockers (8, 9). Furthermore, autoimmune complications during the course of RA disease benefited more from rituximab compared with TNF-blockers (10). There are two further case reports with patients that achieved complete remission within 6 to 12 months on rituximab (11, 12).

The efficacy of the B-cell-depletion therapy is supposed to be based not solely on autoantibody formation by CD20+ autoreactive B lymphocytes but also by there multiple immunomodulatry roles in the context of ectopic lymphoid structures that are present in RA synovialitis as well as in systemic vasculitides (13). However, the full

pharmacological mechanisms have not been identified. The immunoregulatory properties of B cells besides antibody formation may explain the documented efficacy of rituximab in seronegative RA as well as in other autoimmune diseases that are not linked to autoantibodies. These findings provide an explanation for the clinical benefit of the here presented RV patients independent from immuncomplex activity (unchangened complement unter rituximab therapy).

As previously published, cutaneous vasculitis could rarely also be induced by TNF-blocker therapy (infliximab, etanercept) preferentially early at the start of the treatment (14, 15). For the here presented RV patients it is unlikely that the remission of RV was an effect of the discontinuation of anti TNF therapy because two of the successfully treated patients were on long-term therapy with the TNF-blocker for more than one year. In addition, the discontinuation of TNF blocker therapy alone showed no effect to the vasculitic ulcers.

In conclusion, rituximab treatment is effective in several cases of rheumatoid vasculitis cutaneous ulcers in RA patients. However, the administration of rituximab in lager numbers of cases with this indication will be required to confirm our observations.

Acknowledgements

We would like to thank the staff and patients of the University of Saarland Medical School, Homburg/Saar, Germany.

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