Letters to the Editor

Efficacy of rituximab in patients with rheumatoid arthritis refractory or with contra-indication to anti-tumor necrosis factor-alpha drugs in daily practice: an open label observational study

Sirs,

Rheumatoid arthritis (RA) is a chronic disease that leads to inflammation and joint damage. Despite the efficacy of disease-modifying antirheumatic drugs (DMARDs) such as methotrexate and biologic DMARDs agents, 30% of patients have no response or unsustained response (1). While the exact pathogenesis of RA has not been fully established, evidence suggest the importance of B lymphocytes in RA (2). Therefore, randomised controlled trials indicated that selective depletion of B cells led to sustained clinical improvements for patients with active RA despite methotrexate (3, 4) or anti-tumor necrosis factor (TNF)-alpha agents (5). Our aim was to determine, in routine care, the safety and efficacy of rituximab treatment in patients who had experienced an inadequate response to treatment with anti-TNF-alpha agents or had a contra-indication to these drugs and to compare the effects in these 2 groups.

Twenty-one patients with active, seropositive RA (American College of Rheumatology (ACR) revised criteria) (6) were included but the complete follow-up was available for 18 patients (3 had moved up). The mean age was 55 ± 11 years and mean disease duration 12 ± 7 years. Nine patients had a contra-indication to anti-TNF drugs (past of recurrent infections (n = 4), tuberculosis under anti TNF drugs (n = 1), personal of familial past of multiple sclerosis (n = 2), cardiac heart failure (n = 1), vasculitis under etanercept (n = 1)) and 9 had an inadequate response to anti-TNF (7 with failure of the 3 available anti-TNF drugs). Concomitant therapy consisted in methotrexate (12.5-20 mg/w). The patients had highly active disease as shown by the baseline values in Table I. Rituximab was administered as a 1000-mg intravenous infusion on days 1 and 15 with corticosteroids to attenuate possible infusion related symptoms: methylprednisolone 100 mg was associated at days 1 and 15 followed by an oral dose of prednisone (3). The study was performed in accordance with recommendations of the Helsinki Declaration; all the investigations were those routinely required for the evaluation of the patients. The primary end point was the proportion of patients with EULAR response at week 24 (7).

At week 24, 13 (72%) patients were responders; DAS score and CRP changes are provided in Table I. The clinical improvements were in line with those observed in the three randomised controlled trials currently available: 83 to 85% (4) and 67-73% (3) for patients refractory to methotrexate and 65% for patients refractory to anti-TNF. Although there was a trend toward a better response in the group of patients with contra-indication to anti-TNF drugs (3/9 good response *vs* 0/9), this did not reach significance (Table I). The further selection of patients the more prone to receive rituximab will have to be determined by further investigations with larger sample size.

Among the unanswered questions about rituximab, the requirement for subsequent infusions is emerging. In our study, among the 13 responders, another infusion was performed at week 24 in 7/13 patients and was delayed by the clinician because of sustained effectiveness in 6/13 patients. The follow-up is ongoing but this suggests that some patients may have sustained improvement without the need of re-infusion which is clinically and economically interesting but further data are required to investigate which patients may have this benefit.

One infusion-related reaction occurred in the group of patients with failure of anti TNF drugs and one pulmonary infection occurred in the group of patients with contra-indication to anti-TNF drugs without other side-effects confirming the good tolerance observed in randomised trials (3-5) or open labelled studies (8, 9). Thus, in this study of daily practice, a single course of two infusions of rituximab, in combination with continued methotrexate, provided significant improvement in disease activity at week 24.

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References

1. CRISCIONE LG, ST CLAIR EW: Tumor necrosis factor-alpha antagonists for the treatment of rheumatic diseases. *Curr Opin Rheumatol* 2002; 14: 204-11.
2. DORNER T, BURMESTER GR: The role of B cells in rheumatoid arthritis: mechanisms and therapeutic targets. *Curr Opin Rheumatol* 2003; 15: 246-52.
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: Results of a phase IIB randomized, double-blind, placebo-controlled, dose-ranging trial. *Arthritis Rheum* 2006; 54: 1390-400.
4. EDWARDS JC, SZCZEPANSKI L, SZECHINSKI *et al.*: Efficacy of B-cell-targeted therapy with rituximab in patients with rheumatoid arthritis. *N Engl J Med* 2004; 350: 2572-81.
5. COHEN SB, EMERY P, GREENWALD MW *et al.*: Rituximab for rheumatoid arthritis refractory to anti-tumor necrosis factor therapy: Results of a multicenter, randomized, double-blind, placebo-controlled, phase III trial evaluating primary efficacy and safety at twenty-four weeks. *Arthritis Rheum* 2006; 54: 2793-806
6. ARNETT FC, EDWORTHY SM, BLOCH DA *et al.*: The American Rheumatism Association 1987 revised criteria for the classification of rheumatoid arthritis. *Arthritis Rheum* 1988; 31: 315-24.
7. FRANSEN J, VAN RIEL PL:The Disease Activity Score and the EULAR response criteria. *Clin Exp Rheumatol* 2005; 23: S93-9.
8. HIGASHIDA J, WUN T, SCHMIDT S *et al.*: Safety and efficacy of rituximab in patients with rheumatoid arthritis refractory to disease modifying antirheumatic drugs and anti-tumor necrosis factor-alpha treatment. *J Rheumatol* 2005; 32: 2109-15.
9. BRULHART L, CIUREA A, FINCKH A *et al.*: Efficacy of B-cell Depletion in Rheumatoid Arthritis Patients Refractory to Anti-Tumour Necrosis factor (TNF)-α Agents An open label observational study. *Ann Rheum Dis* 2006 Mar 15; [Epub ahead of print].

Table 1. Characteristics of patients at week 0 and 24 regarding DAS 28, EULAR response and CRP values.

Median [range] value; *p< 0.05	DAS28 week 0	DAS28 week 24	CRP(mg/L) week 0	CRP(mg/L) week 24	EULAR response	EULAR good response
All patients (n = 18)	5.75 (4.2-8.6)	4.2 (1.8-10.6)*	26 (6-292)	10 (1-99)*	13/18	3/18
Refractory to anti-TNF; (n = 9)	6.5 (5.2-8.6)*	4.8 (3.4-6.5)*	30 (6-292)*	14 (1-99)*	5/9	0/9
Contra-indication to anti-TNF; (n = 9)	4.9 (4.2-6.7)*	3.5 (1.8-10.6)*	24 (8-67)*	10 (2-82)*	8/9	3/9