Rituximab therapy for refractory systemic-onset juvenile idiopathic arthritis

Systemic-onset juvenile idiopathic arthritis (SOJIA), formerly called Still's disease, is a subset of juvenile arthritis that describes patients with fever, rash, arthritis, serositis and visceromegaly. In up to 30% of cases the disease has a chronic course and management requires high doses of glucocorticoids, disease-modifying antirheumatic drugs (DMARD), tumour necrosis factor alpha (TNFα) inhibitors or anakinra.[1–6] However, this therapeutic arsenal is unable to control the disease in all patients.

Recently, rituximab, a chimeric anti-CD20 monoclonal antibody, has been successfully used in two patients with refractory adult-onset Still's disease.[7] As the similarity of clinical and laboratory features present in SOJIA and adult-onset Still's disease implies that these conditions have similar pathogenic mechanisms,[1 2] we tested rituximab in three patients with severe active SOJIA who had an inadequate response or were intolerant to current treatment options. The patients' main characteristics at rituximab treatment initiation and outcome data are summarised in table 1. In all cases the disease persisted into adulthood, and at the time of the study they presented with intermittent fever, rash, persistent destructive polyarthritis and recurrent serositis (one patient). They had all received at least four DMARD (range four to six), intravenous immunoglobulin, one or more TNFα inhibitor and anakinra, none of which proved to be successful.

Rituximab treatment consisted of two endovenous infusions of 1 g per treatment cycle (except in one patient, who received 500 mg in the first cycle as a result of weighing only 40 kg), separated by a 2-week interval (days 1 and 15). In one patient rituximab was administered alone, whereas in the other two cases it was given in combination with methotrexate. All patients received premedication (100 mg methylprednisolone or equivalent) to prevent infusion reactions.

The three patients showed a significant clinical improvement, with remission of the systemic symptoms (fever, rash and serositis). Arthritis improved partly in two cases, with re-treatment being required 6–7 months later; in the other patient, a low degree of activity was achieved and no further treatment was required until 12 months later. Clinical improvement was accompanied by a parallel improvement in biological markers of inflammation, although in none of the cases were the acute phase reactants normalised. The concomitant oral steroid dose could be reduced to more than half of the initial dose.

One of the patients presented with a severe hypersensitivity reaction during the second infusion of the second treatment cycle, but no other adverse effects were observed. None of the

Table 1 Patients' main characteristics at rituximab treatment initiation and outcome data under therapy

	Patient 1	Patient 2	Patient 3
Sex/age (years)	F/29	F/30	F/29
Disease duration (years)	27	18	22
Previous treatments	Anakinra, AZA, CsA, ETA, GS, IG, MTX	Anakinra, CQ, ETA, GS, IFX, LF, MTX	Anakinra, ADM, CsA, DP, GS, IFX, IG, LF, MTX, SSZ
Main symptoms at RTX treatment initiation	Fever, rash, arthritis, pleuritis, pericarditis	Fever, rash, arthritis	Fever, rash, arthritis
ESR (mm/h)/CRP (mg/l)	75/171	104/258	64/128
TJC 28/SJC 28	9/5	25/24	11/6
DAS28	6.31	8.68	6.43
Dose of prednisone (mg/day)	30	10	30
Concomitant treatment associated with RTX	MTX 15 mg/week	MTX 15 mg/week	None
Outcome			
Response at month 6	Remission of systemic symptoms	Remission of systemic symptoms	Remission of systemic symptoms
	ESR 81/CRP 143	ESR 67/CRP 180	ESR 40/CRP 32
	TJC 28 4/SJC 28 1	TJC 28 6/SJC 28 6	TJC 28 1/SJC 28 0
	DAS28 4.62	DAS28 5.70	DAS28 3.28
	Re-treatment: Yes	Re-treatment: Yes	Re-treatment: No
	(severe hypersensitivity reaction during 2nd infusion)		
Response at 1 year	Remission of systemic symptoms	Remission of systemic symptoms	Remission of systemic symptoms
	ESR 53/CRP 94	ESR 65/CRP 141	ESR 44/CRP 47
	TJC 28 5/SJC 28 2	TJC 28 7/SJC 28 5	TJC 28 3/SJC 28 2
	DAS28 5.20	DAS28 5.59	DAS28 4.57
		Re-treatment: Yes	Re-treatment: Yes
Comments	Prednisone daily dosage reduced to 10 mg	Prednisone daily dosage reduced to 5 mg	Prednisone daily dosage reduced to 5 mg

ADM, adalimumab; AZA, azathioprine; CQ, chloroquine; CRP, C-reactive protein; CsA, ciclosporin A; DAS28, disease activity score in 28 joints; DP, D-penicillamine; ESR, erythrocyte sedimentation rate; ETA, etanercept; GS, gold salts; IG, intravenous polyvalent immunoglobulin; IFX, infliximab; LF, leflunomide; MTX, methotrexate; RTX, rituximab; SJC, swollen joint count; SSZ, sulfasalazine; TJC, tender joint count.

patients suffered severe bacterial or opportunistic infections; serum immunoglobulin levels remained within the normal limits during treatment in all cases.

Our preliminary results suggest that rituximab seems to be a useful therapeutic alternative in patients with active SOJIA in whom previous treatments (including TNFα antagonists and anakinra) have failed. Our experience is that rituximab produces a substantial clinical improvement (remission of the systemic symptoms and moderate European League Against Rheumatism response of the arthritis), although the disease does not enter into remission. Of interest, our experience with rituximab is similar to the French experience with IL-1 receptor antagonist treatment in SOJIA/adult-onset Still's disease.[6] In that study, the benefits with anti-IL-1 therapy seem to be fair in the systemic manifestations but reduced in the articular complaints.

Further studies are needed to determine the place of specific B-cell depletion in the treatment of refractory SOJIA.

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REFERENCES

1. **Adams A,** Lehman TJ. Update on the pathogenesis and treatment of systemic onset juvenile rheumatoid arthritis. *Curr Opin Rheumatol* 2005;**17**:612–16.
2. **Ramanan AV,** Grom AA. Does systemic-onset juvenile idiopathic arthritis belong under juvenile idiopathic arthritis?. *Rheumatology* 2005;**44**:1350–3.
3. **Ohlsson V,** Baildam E, Foster H, Jandial S, Pain C, Strike H, *et al*. Anakinra treatment for systemic onset juvenile idiopathic arthritis (SOJIA). *Rheumatology* 2008;**47**:555–6.
4. **Eberhard BA,** Ilowite NT. Response of systemic onset juvenile rheumatoid arthritis to etanercept: is the glass half full or hald empty?. *J Rheumatol* 2005;**32**:763–5.
5. **Billiau AD,** Cornillie F, Wouters C. Infliximab for systemic onset juvenile idiopathic arthritis: experience in 3 children. *J Rheumatol* 2002;**29**:1111–14.
6. **Lequerré T,** Quartier P, Rosellini D, Alaoui F, De Bandt M, Mejjad O, *et al*. Interleukin-1 receptor antagonist (anakinra) treatment in patients with systemic-onset juvenile idiopathic arthritis or adult onset Still disease: preliminary experience in France. *Ann Rheum Dis* 2008;**67**:302–8.
7. **Ahmadi-Simab K,** Lamprecht P, Jankowiak C, Gross WL. Successful treatment of refractory adult onset Still's disease with rituximab. *Ann Rheum Dis* 2006;**65**:1117–18.

Corrections

The cover caption for the supplement published in December 2008 (volume 67, suppl iii) was inadvertently missed from the contents page. It should have read "Part of 'Augustine Roulin with her infant' by Vincent van Gogh (1889). Mrs Roulin suffered from psoriatic arthropathy. Metropolitan Museum of Art, New York, USA."

The authors JWJ Bijlsma and PMJ Welsing of the editorial "The art of medicine in treating osteoarthritis: I will please" (*Ann Rheum Dis* 2008;**67**:1653–5) regret that a reference to an important work by Dr Franklin G Miller (Department of Bioethics, National Institute of Health) and co-workers was not included on p1654, first paragraph, right column. This part explains findings reported in reference 12 and also text extracted from the following reference: Miller FG, Kaptchuk TJ. The power of context: reconceptualizing the placebo effect. *J R Soc Med* 2008;**101**:222–5. This reference should have been included together with reference 12.

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