Use of infliximab in juvenile onset rheumatological disease-associated refractory uveitis: efficacy in joint and ocular disease

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There is an identified disparity between the efficacy of tumour necrosis factor (TNF) inhibition in the treatment of uveitis in paediatric onset inflammatory arthritis and that of joint disease.[1–5]

We retrospectively reviewed the case notes of six patients with aggressive, refractory joint and ocular paediatric-onset disease treated with infliximab in a multidisciplinary clinic. Our report uses the Standardised Uveitis Nomenclature (SUN) grading system[6] for uveitis and steroid dose as an outcome measure. All patients received weekly infliximab infusions at 0, 2, 6 and 8 weeks.

Patients were maintained on low dose immunosuppression with methotrexate while receiving treatment. Five of six patients had previously been treated with another anti-TNF agent (three with adalumimab and two with etancercept).

At the time of commencing treatment, patients were aged 8–18 (median 14) years. Six patients were treated with infliximab. Two patients were treated for 6 months, two for 9 months, one for 12 months and 1 for 15 months, with four of six requiring a dose increase to 6 mg/kg to obtain adequate control. Infliximab was stopped at 15 months in one patient owing to a satisfactory response and at 1 year owing to treatment failure.

Drug induced remission on infliximab occurred in three (50%) patients, with improvement of ocular inflammation in two other patients; complete resolution of joint involvement occurred in five of six patients. In this cohort, patients were able to reduce steroid requirement from an average monthly dose of 250 mg in the year before infliximab treatment and 120 mg per month while receiving infliximab. There was a reduction in the daily oral prednisolone dose to 5 mg in three patients as a result of treatment.

Finally, biological therapy was associated with gain in vision in four of six patients, where there was at least a halving of the visual angle in one eye (approximating to a three-line improvement in the Snellen acuity). Use of infliximab also suppressed inflammatory activity to permit intraocular surgery in three patients without the need for high dose steroids.

While receiving infliximab, one child developed new psoriasis, and in others psoriasis failed to improve. Infliximab was well tolerated with no serious adverse event.

Our data confirm, in part, other reports of successful anti-TNF treatment suppressing joint disease more effectively than uveitis[7]; we, in addition, observed that infliximab was well tolerated and successfully suppressed ocular inflammation.[8] Of note, we could not prove that failure of a previous biological agent predicts failure with infliximab.

Outside a clinical trial, the clinical setting can make outcomes difficult to interpret. For example, patient D had worsening joint and ocular inflammation after 1 year of treatment with infliximab. This patient had stopped methotrexate of her own accord for approximately 6 weeks. Whether this is treatment failure of infliximab is arguable, given that there had been good control of disease until methotrexate was stopped.

The use of a threshold steroid dose—for example, 5 mg/day[6]—has limitations in clinical practice for children. A number of patients already had osteoporosis or delayed growth where further oral steroid treatment was relatively contraindicated or weight gain undesirable. We observed a reduction in the average monthly dose of prednisolone, and additional intravenous or oral high dose steroid treatment was not required. This would support a genuine steroid-sparing role of infliximab therapy.

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REFERENCES

1 **Tynjala P**, Lahdenne P, Vahasalo P, Kautiainen H, Honkanen V. Impact of anti-TNF treatment on growth in severe juvenile idiopathic arthritis. *Ann Rheum Dis* 2006;**65**:1044–9.
2 **Richards JC**, Tay-Kearney ML, Murray K, Manners P. Infliximab for juvenile idiopathic arthritis-associated uveitis. *Clin Exp Ophthalmol* 2005;**33**:461–8.
3 **Saurenmann RK**, Levin AV, Rose JB, Parker S, Rabinovitch T, Tyrrell PN, *et al*. Tumour necrosis factor {alpha} inhibitors in the treatment of childhood uveitis. *Rheumatology (Oxford)* 2006;**45**:982–9.
4 **Ravindran T**, Rajaraman, Yukiko K, Li S, Haines K, Chu DS. Retrospective case review of paediatric patients with uveitis treated with infliximab. *Ophthalmology* 2006;**113**:308–14.
5 **Smith JA**, Thompson DJ, Whitcup SM, Suhler E, Clarke G, Smith S, *et al*. A randomized, placebo-controlled, double-masked clinical trial of etanercept for the treatment of uveitis associated with juvenile idiopathic arthritis. *Arthritis Rheum* 2005;**53**:18–23.
6 **Jabs DA**, Gérard HC, Wei Y, Campbell AL, Hudson AP, Akpek EK, *et al*. Standardization of uveitis nomenclature for reporting clinical data. Results of the First International Workshop. *Am J Ophthalmol* 2005;**140**:509–16.
7 **Smith JR**, Levinson RD, Holland GN, Jabs DA, Robinson MR, Whitcup SM, *et al*. Differential efficacy of tumor necrosis factor inhibition in the management of inflammatory eye disease and associated rheumatic disease. *Arthritis Rheum* 2001;**45**:252–7.
8 **Suhler EB**, Smith JR, Wertheim MS, Lauer AK, Kurz DE, Pickard TD, *et al*. A prospective trial of infliximab therapy for refractory uveitis: preliminary safety and efficacy outcomes. *Arch Ophthalmol* 2005;**123**:903–12.

Table 1 Clinical features after treatment with infliximab

	Eye	Diagnosis	Clinical features of systemic disease	Initial visual acuity (VA)	Inflammatory activity before starting treatment with infliximab (using SUN citeria[9]) AC (grade cells)	Vitreous haze (BIO)	CMO Y/N	Number of active joints (n)	Activity 3 months from start of infliximab	Activity at 6 months	Activity at 9 months*/ 12 months†	Dose of infliximab and additional events	Final VA
A	RE	Psoriatic JIA	Polyarthritis,	0.8	+1	0	Y		Improved activity and CMO	Inactive	Inactive†	3 mg/kg	0.2
		HLA B27+	Psoriasis						0 joints	Improved CMO	No CMO†	1×ST	–0.2
	LE	ANA−	Nail dystrophy Osteoporosis Delayed growth	–0.1	No inflammatory activity			12		1 joint	0 joints†		
B	RE	Psoriatic JIA	Polyarthritis Psoriasis	–0.2	No inflammatory activity				Improved activity	Worse activity	NA	6 mg/kg 1×ST	0
		HLA B27+	Growth failure					3	0 joints	0 joints		1x intravit	
	LE	ANA−	Nail dystrophy, uveitis	2.3	+1	+3	N					LVit'y	2.3
C	RE	Systemic JIA	Polyarthritis	0.2	+2	0	N		Unchanged	Improved activity	Worse†	6 mg/kg	0.2
	LE	ANA−		0.6	+2	0	N	2	activity 0 joints	0 joints	4 joints†		0.2
D	RE	Sarcoidosis	Sarcoid polyarthritis, renal, skin, growth failure	0.2	+1	0	N		Unchanged activity	Improved activity	Improved activity*	6 mg/kg R Vit'y	0.3
	LE			0.6	+1	0	N	2	0 joints	1 joint	0 joints*	R intravit	0.2
E	RE	Psoriatic JIA	Previous posterior fossa	0.2	+2	0	N		Improved activity	Inactive eyes	Inactive eyes*	3 mg/kg	0.2
	LE	ANA−	medulloblastoma	1.0	+1	0	N	1	0 joints	0 joints	0 joints*	L cataract extraction	0.1
F	RE	Multisystem granulomatous disease ANA+	Polyarthritis, epitheloid granulomas of skin, small intestine involvement	0.1	+1	0	N		Inactive.	Inactive		3 mg/kg	0.1
	LE	ACE+		0.1	+2	0	N	2	1 joint	0 joints	NA		0.1

AC, anterior chamber; ANA, antinuclear antibodies; Anterior chamber cells (from SUN workshop[10]: Grade cells in field 0<1, 0.5+ =1–5, 1+ =6–15, 2+ =16–25, 3+ =26–50, 4+ =50; BIO, bioscore; CMO, cystoid macular oedema; HLA, human leucocyte antigen; Intravit, intravitreal steroid; JIA, juvenile idiopathic arthritis; LE, left eye; NA, patient did not receive treatment to this time period; RE right eye; ST subtenons steroid; unchanged, active, inactive and improved are clinical assessments of uveitis activity taken from the SUN workshop[10]; VA, visual acuity; Vit'y, vitrectomy.
*Patient treated for 9 months.
†Patient treated for 12 months.
‡Pre-existing visual loss not related to uveitis.