Successful treatment of adult-onset Still's disease refractory to TNF and IL-1 blockade by IL-6 receptor blockade

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Adult-onset Still's disease (AOSD) is a systemic inflammatory disorder of unknown aetiology.[1] Based on the substantial acute phase responses observed in AOSD, we hypothesised that blockade of the interleukin 6R (IL-6R), neutralising the induction of the acute phase response by IL-6, could be a useful treatment in multidrug-resistant AOSD. We here report on three patients with AOSD who were refractory to standard treatment and cytokine blockade with anakinra and tumour necrosis factor (TNF) blockers and were subjected to treatment with tocilizumab. The characteristics of these three patients are summarised in table 1.

PATIENT 1

A 19-year-old woman was first diagnosed with AOSD in July 2006. Prednisone therapy was started, but multiple relapses occurred during the following 2 years requiring initiation of methotrexate/anakinra combination therapy. Flares only slightly decreased thereafter and acute phase reactants remained high. Methotrexate was continued while anakinra was switched to adalimumab with no improvement. Tocilizumab was then started at a dose of 8 mg/kg body weight every 4 weeks. All symptoms rapidly disappeared and acute phase reactants normalised. After six infusions, tocilizumab was stopped and methotrexate (15 mg/week) and prednisolone (5 mg/day) were continued with ongoing remission (no symptoms, normal acute phase reactants).

PATIENT 2

A 73-year-old man with a suspected diagnosis of psoriatic arthritis had been treated with methotrexate, etanercept and adalimumab without any response. At presentation he had high remittent fever for several weeks, leucocytosis and massively elevated acute phase reactants despite regular use of glucocorticoids. Anakinra was started but without success. Only glucocorticoids at a dose of >20 mg/day were able to suppress the fever, while acute phase reactants remained high. Tocilizumab (8 mg/kg every 4 weeks) was initiated; 4 days after the first infusion the fever had ceased and C reactive protein level and leucocyte counts normalised. Tocilizumab has been continued for 8 months and the patient is still in complete remission.

PATIENT 3

A 19-year-old woman with fever, myalgia, acute phase reactants and a history of rash was diagnosed with AOSD in 2006. Glucocorticoid treatment was started and induced remission over 2 years. In February 2008 she experienced a relapse and glucocorticoid therapy was restarted with no effect on signs and symptoms. In October 2008 anakinra was added with no improvement in symptoms and no decrease in acute phase

Table 1 Characteristics of patients

	Patient 1	Patient 2	Patient 3
Sex	Female	Male	Female
Age (years)	29	73	19
Systemic symptoms	Yes	Yes	Yes
Disease duration (years)	1	3	3
Yamaguchi criteria[10]			
Major criteria	Remittent fever >39°C	Remittent fever >39°C	Remittent fever >39°C
	Salmon coloured rash	–	Salmon coloured rash
	Arthritis	–	Arthritis
	Leucocytosis	Leucocytosis	Leucocytosis
	–	Elevated liver enzymes	–
Minor criteria	RF and ANA negative	RF and ANA negative	RF and ANA negative
		Hepatomegaly	Splenomegaly
			Lymphadenopathy
Laboratory results	CRP 136.1 mg/l	CRP 211.2 mg/l	CRP 136.1 mg/l
	Ferritin 2396 ng/ml	Ferritin 1643 ng/ml	Ferritin 77 ng/ml
	ESR 80 mm/h	ESR 90 mm/h	ESR 36 mm/h
	IL-18 142.0 pg/ml	IL-18 1731.2 pg/ml	IL-18 600.5 pg/ml
Radiographic bone erosions	None	None	None
Previous treatment: type, dosage (duration in months)	Prednisolone 5–60 mg/day (36)	Prednisolone 5–20 mg/day (72)	Prednisolone 5–30 mg/day (6)
	Methotrexate 20 mg/week (15)	Methotrexate 15 mg/week (72)	Methotrexate 15 mg/week (12)
	Anakinra 100 mg/day (6)	Adalimumab 40 mg/2 weeks (25)	Anakinra 100 mg/day (6)
	Adalimumab 40 mg/2 weeks (3)	Etanercept 50 mg/week (25)	
		Rituximab 2000 mg and (52)	
		Anakinra 100 mg/day (1)	
Time (days) to remission of fever (<38.0°C)	1	2	1
Time (days) to remission of arthritis (no swollen/tender joints)	2	5	4
Time (days) to normalisation of CRP (<5 mg/l)	3	7	3

ANA, antinuclear antibody; CRP, C reactive protein; ESR, erythrocyte sedimentation rate; IL, interleukin; RF, rheumatoid factor.

reactants. In February 2009 tocilizumab was started and she responded promptly with normalisation of C reactive protein and cessation of symptoms. After 6 months, tocilizumab therapy was stopped. Three months later fever recurred and acute phase reactants increased. Tocilizumab was restarted, resulting in clinical remission which has continued for 3 months to date.

DISCUSSION

In summary, complete remission was achieved in all three patients with multidrug-resistant AOSD after initiation of tocilizumab. Because of high levels of proinflammatory cytokines in AOSD, specific cytokine blockade has been used in patients who are refractory to standard treatment. IL-6, a cytokine induced by TNFα and IL-1 and thus downstream of the inflammatory cascade, may represent a suitable target for the treatment of AOSD. Serum levels of IL-6 are raised in AOSD and correlate with disease activity.[2–5] So far, three case reports on the use of tocilizumab in AOSD have been published.[6–8] In addition, data from Yokota and colleagues suggest that tocilizumab can induce remission in systemic juvenile idiopathic arthritis and may even be discontinued without relapse.[9] In this case series we show that blockade of IL-6R rapidly achieves complete remission in patients with AOSD who are unresponsive to IL-1 and TNF blockade. This suggests a potential therapeutic role for tocilizumab in AOSD.

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