Anakinra treatment in patients with adult-onset Still's disease is fast, effective, safe and steroid sparing: experience from an uncontrolled trial

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Adult-onset Still's disease (AOSD) is characterised by a group of clinical and laboratory findings indicating systemic inflammation.[1] Recent data support the hypothesis that interleukin 1 is essential in mediating inflammation, particularly in recalcitrant AOSD.[2 3]

From December 2003 we treated 10 patients with AOSD diagnosed according to proposed criteria.[4] Four of these 10 consecutive patients, 4 had refractory AOSD with persistently active disease, despite administration of high-dose steroids. Herein, we report that all four patients rapidly responded to administration of anakinra (100 mg/day) and were promptly weaned from high-dose steroids. Table 1 shows the patients' demographics, clinical and laboratory features and response to anakinra. Furthermore, patient 1 developed a life-threatening macrophage activation syndrome during the course of the disease, whereas patient 3 was refractory to methotrexate and etanercept.

In all four patients systemic symptoms disappeared within a few hours after the first injection of anakinra. Moreover, fever, fatigue, myalgias and arthralgias relapsed in patient 1 within a few days on discontinuation of anakinra and resolved again within hours after anakinra reinstitution. Polyarthritis in patient 3 improved in 24 h after administration of anakinra. Inflammatory markers (white blood cells, platelet count, erthrocyte sedimentation rate, C reactive protein and ferritin levels) reverted to normal within 2–4 weeks; liver enzyme increases normalised within 3 weeks (table 1). Apart from a self-limited injection-site erythema (present in all four patients), we recorded no other adverse events during the follow-up period (5–17 months). Initiation of anakinra treatment was the factor that permitted for fast and uneventful steroid tapering in our patients, and, in particular, patients 1, 2 and 4 totally discontinued steroid intake. In all patients, remission could not be maintained on low steroid doses and, in fact, all four patients had a suboptimal clinical and biochemical response even to high (40–60 mg/day prednisolone) steroid doses. Three of the four patients required readmissions to

Abbreviations: AOSD, Adult-onset Still's disease

Table 1 Patients' demographics, clinical and laboratory characteristics and response to anakinra treatment

Demographics/symptoms/signs/ laboratory findings	Patient 1	Patient 2	Patient 3	Patient 4
Sex	F	M	M	M
Age (years)	36	18	54	17
Fever >39°C	Yes	Yes	Yes	Yes
Arthritis/arthralgias	Arthralgias	Arthralgias	Symmetric polyarthritis	Arthralgias
Sore throat	Yes	Yes	No	Yes
Rash	Maculopapular	No	No	No
Lymphadenopathy/splenomegaly/ hepatomegaly	Lymphadenopathy/hepatomegaly	Lymphadenopathy	Lymphadenopathy	Splenomegaly
Serositis	Pleural effusion	Polyserositis	Pleural effusion	No
Serum ferritin (ng/ml)	>5000	Not applicable	3743	2456
Neutrophils/mm^3 (%)	13200 (87)	35 000 (83)	17890 (87.5)	31200 (93)
ESR (mm/h)	77	85	81	115
CRP (mg/dl) (normal <0.8)	9.8	22	22	29
Abnormal liver function tests	AST: 226 U/l ALT: 365 U/l	AST: 113 U/l ALT: 350 U/l	AST: 82 U/l ALT: 87 U/l	AST: 68 U/l ALT: 118 U/l γ-GT:71
Diagnostic examination for infections, malignancy and other rheumatic diseases*	Negative	Negative	Negative	Negative
Resolution of symptoms on initiation of anakinra	Within a few hours	Within a few hours	Within a few hours	Within a few hours
Response of serum markers of inflammation on initiation of anakinra	Within 3 weeks	Within 4 weeks	Within 3 weeks	Within 2 weeks

ALT, alanine aminotransferase; AST, aspartate aminotransferase; CRP, C reactive protein; ESR, erythrocyte sedimentation rate; γ-GT, γ-glutamyltransferase.
*Including: *x* rays, CT scans, PPD tests, microbial cultures (blood, urine, cerebrospinal and pleural fluid), serum cancer markers, tests for anti-nuclear antibodies, extractable nuclear antigens, NA, anti-DNA, anti-neutrophil cytoplasmic antibodies, rheumatoid factor, viral serology (HIV, hepatitis A virus, hepatitis B virus, hepatitis C virus, cytomegalovirus, Epstein–Barr virus, herpes simplex virus), specific antibodies (for toxoplasma, leptospira, leishmania, rickettsias and borrelias), antistreptolysin titre, Widal and Wright tests. For patient 1 thick blood smear examination for plasmodia and liver, skin, muscle and bone marrow biopsies were also performed.

hospital to control relapses with intravenous pulsed methylprednisolone. Sustained high daily prednisolone doses led to the development of Cushing's syndrome in patients 1, 2 and 3, a side effect that promptly subsided after the fast steroid tapering, achieved after the introduction of anakinra.

Despite the lack of randomised controlled trials, the impressive efficacy, the steroid-sparing effect and the good tolerance of anakinra in cases of refractory AOSD, combined with the limited efficacy and/or intolerance of anti-tumour necrosis factor-α regimens,[5] suggest that interleukin 1R antagonism may represent a preferred treatment for patients with refractory AOSD. The steroid-sparing effect of anakinra in our patients represents a notable advantage of this treatment. We report, for the first time, such a striking steroid-sparing effect of anakinra treatment in patients with AOSD. Our study, although limited to four patients, adds to the similarly limited existing published literature.[3 6 7] Despite rarity of AOSD, we suggest that larger clinical trials are important to evaluate the role of anakinra in the treatment of this disease.

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Cryopyrin-associated autoinflammatory syndrome: a new mutation

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Patients with mutations in the gene for cold-induced autoinflammatory syndrome (CIAS1; cryopyrin) have a wide range of disease phenotypes including the familial cold autoinflammatory syndrome, Muckle–Wells syndrome and chronic infantile neurologic cutaneous articular syndrome. We recently identified a new mutation in CIAS1 in a 10-year-old boy who had lifelong inflammatory episodes characterised by non-pruritic urticaria, fevers and articular symptoms. His mother had similar symptoms but no other family member could be identified with similar clinical features. The boy's urticarial lesions typically occurred with exposure to cold temperatures. Skin biopsy showed mixed perivascular inflammatory cells in the superficial dermis suggestive of an early-phase urticarial response. His spiking fevers to 39°C often responded to non-steroidal anti-inflammatory drugs, yet after the febrile episodes he frequently experienced discomfort in the feet. Through his first decade his arthralgias and urticarial lesions became more persistent, and he developed lower extremity large-joint and small-joint arthritis without radiographic changes, as well as conjunctivitis, mild self-resolving headaches, poor weight gain and distal cyanosis with cold exposure. Audiology testing was within normal limits. He never had neurological symptoms to warrant central nervous system imaging.

Table 1 Dose dependent response to Anakinra

Age (years)	Anakinra (mg/kg/day)	WBC (10^3/μl)	Platelets (10^3/μl)	ESR (mm/h)
1.6	–	14		17
2.9	–	18	585	35
3.4	–	13	521	
4	–	8	464	25
8.5	–	12	462	73
9	–	10	377	48
9.3	0.9	7	363	8
9.8	0.3	7	360	31
10.1	1	8	335	22
10.6	1	7	302	9

ESR, erythrocyte sedimentation rate; WBC white blood cells.

Laboratory evidence of persistent inflammation was present from an early age (table 1).

He did not have proteinuria. Mutational analysis identified a heterozygotic change of A→G in the CIAS gene, which can result in a substitution from threonine to alanine at amino acid position 436 (T436A) in the cryopyrin protein. As expected, confirmatory