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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Accepted 18 February 2007

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Cryopyrin-associated autoinflammatory syndrome: a new mutation

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Ann Rheum Dis 2007;**66**:843–844. doi: 10.1136/ard.2006.064899

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.

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

Table 1 Dose dependent response to Anakinra

Age (years)	Anakinra (mg/kg/day)	WBC ($10^3/\mu\text{l}$)	Platelets ($10^3/\mu\text{l}$)	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.

parental genetic testing identified an identical nucleotide mis-sense substitution in the mother, but not in the father.

Improved clinical symptoms after inhibition of interleukin 1 (IL 1) activity by anakinra was reported in all of the cryopyrin-associated autoinflammatory syndromes, although treatment failure has also been reported.¹⁻⁴ Therapy with IL 1 antagonism was begun in our patient at 9 years and a clinical response was reported within days. On taking Anakinra (~0.90 mg/kg/day) his energy level improved, his rash appeared less frequently and his arthritis and conjunctivitis were resolved. His erythrocyte sedimentation rate, white cell count and platelet count all improved (table 1). The patient's family temporarily reduced the dose of anakinra to 0.30 mg/kg/day, and he again experienced clinical and laboratory evidence of disease flare, indicating a dose-dependent response (table 1).

In all, 60 different dominantly inherited missense mutations within exon three of CIAS1 have been associated with the three heterogeneous cryopyrin-associated autoinflammatory syndromes.⁵⁻⁶ Previous patients described with characteristics of both familial cold-induced autoinflammatory syndrome and Muckle-Wells syndrome have had other unique cryopyrin mutations that were distinct from the new mutation described here.¹⁻⁷ It is interesting to note that two other mutations that would cause different amino acid substitutions at this site (Thr436Ile; Thr436Asn) were reported in patients with chronic infantile neurological cutaneous articular syndrome.⁸ These findings would suggest that specific amino acid substitutions at this site are solely responsible for the clinical phenotype. However, phenotypic heterogeneity, including incomplete penetrance among family members, has been described among individuals carrying identical mutations.⁷⁻⁹⁻¹⁰ Thus there is probably an effect of additional modifier genes or environmental factors in the phenotypic expression of the cryopyrin-associated autoinflammatory syndromes.⁸

ACKNOWLEDGEMENTS

Helpful input and comments from Dr John Carey are appreciated.

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Accepted 18 February 2007

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DNA microarray analysis of labial salivary glands of patients with Sjögren's syndrome

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Ann Rheum Dis 2007;**66**:844-845. doi: 10.1136/ard.2006.063370

Sjögren's syndrome (SS) is a chronic autoimmune disease characterised by dry eyes, dry mouth and focal lymphocytic infiltration in lacrimal and salivary glands. The infiltrating lymphocytes are mainly CD4 α/β T cells,¹ especially T helper 1 (Th1) type T cells, because they produce both interferon (IFN) γ and interleukin 2.²⁻³ To understand the pathogenesis of SS, several molecules in labial salivary glands (LSGs) have been screened by microarray analysis in human SS. Hjelmervik *et al*⁴ and Gottenberg *et al*⁵ reported that the upregulated genes in SS salivary glands were IFN-inducible genes, such as IFN-stimulated transcription factor 3, IFN-regulatory factor 1 and B cell-activation factor of the TNF family. However, there is little or no information on the essential genes involved in the generation of sialoadenitis in

patients with SS. We screened abnormally expressed genes in LSGs of patients with SS using cDNA microarray technology to elucidate the SS susceptibility genes.

The cDNA array was performed using total RNA from LSGs of three patients with primary SS and from three healthy subjects (control) with a DNA chip including 775 genes (JGS, Tokyo, Japan). The DNA chip contained immunoglobulins, human leucocyte antigens (HLAs), complements, T cell receptors (TCRs), IFN-inducible proteins, cytokines, transcriptional factors and other autoimmune disease-related genes. Abnormally

Abbreviations: HLA, human leucocyte antigen; SS, Sjögren's syndrome; IFN, interferon; LSG, labial salivary gland; Th1, T helper cell; TCR, T cell receptor