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Interleukin-1–Receptor Antagonist in the Muckle–Wells Syndrome

TO THE EDITOR: Studies of hereditary inflammatory disorders have identified novel genes and pathways that may be involved in inflammation and apoptosis generally. Mutations in one such gene, variously named *NALP3*, *CIAS1*, and *PYPAF1*, were recently identified as the cause of the Muckle–Wells syndrome and the familial cold autoinflammatory syndrome[1] and have lately also been associated with neonatal-onset multisystem inflammatory disease.[2] Interleukin-1 is a key proinflammatory cytokine that contributes to increased synthesis of serum amyloid A protein by hepatocytes during the acute-phase response. The availability of a recombinant interleukin-1–receptor antagonist for clinical use enabled us to undertake a trial of this agent in two patients with the Muckle–Wells syndrome and the nephrotic syndrome due to AA amyloidosis whose inflammatory disease and abundant production of serum amyloid A protein had not been suppressed despite the administration of many drugs.

The patients were a man from northern India (Patient 1) and a British–Spanish man (Patient 2) who were both heterozygous for the *NALP3*/*CIAS1*/*PYPAF1* variant R262W (also noted as R260W), as previously reported.[3] Clinical features included daily fevers, rashes, conjunctival inflammation, arthralgic limb pain, and an intense but variable acute-phase serum amyloid A protein response. AA amyloidosis is usually progressive and life-threatening, but if inflammation remits and the production of serum amyloid A protein decreases to trace levels, the amyloid deposits often gradually regress, and the nephrotic syndrome may resolve.[4] Treatment with colchicine, low-dose corticosteroids, chlorambucil, antihistamines, dapsone, azathioprine, mycophenolate mofetil, and infliximab had been unsuccessful, as determined by clinical measures and monthly estimates of the plasma concentration of serum amyloid A protein. High-dose corticosteroids and, in one patient, thalidomide had been partially effective.

Both patients consented to undergo a therapeutic trial of the recombinant human interleukin-1–receptor antagonist anakinra (Kineret, Amgen) given by subcutaneous injection at a dose of 100 mg daily, which is the schedule recommended for rheumatoid arthritis. Their inflammatory symptoms ceased within hours of the first injection, and both patients' plasma concentrations of serum amyloid A

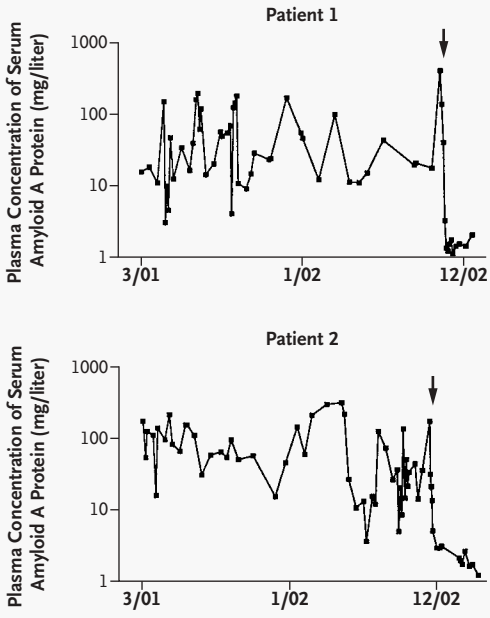

Figure 1. Serial Measurements of Plasma Concentrations of Serum Amyloid A Protein in Two Patients with the Muckle–Wells Syndrome.

The arrows indicate when treatment with the recombinant human interleukin-1–receptor antagonist began. The median plasma concentration of serum amyloid A protein in Patient 1 between May 1998 and October 2002 was 22 mg per liter (interquartile range, 12 to 56), and the median concentration in Patient 2 between August 1998 and November 2002 was 48 mg per liter (interquartile range, 14 to 82).

protein decreased to normal base-line values within three days and remained below 2 mg per liter (normal range, <10 mg per liter) on frequent testing for two months (Fig. 1). This response has now been sustained for six months in both patients, and the amyloid-related proteinuria has diminished substantially, with protein excretion decreasing from 11.2 g to 4.9 g per day in one patient and from 10.2 g to 2.3 g per day in the other. Glomerular filtration has remained normal in both cases.

Recombinant human interleukin-1–receptor antagonist is modestly effective in rheumatoid arthritis,[5] whereas its remarkable effect in the Muckle–Wells syndrome supports in vitro findings[2] that point to the fundamental role of interleukin-1 in the pathogenesis of this disorder. The pathways and interactions of proteins in the *NALP/CIAS/PYPAF* superfamily are complex, but clinical studies with highly specific biologic drugs may contribute to their elucidation. The efficacy of interleukin-1–receptor antagonist in the Muckle–Wells syndrome strongly supports studies of this agent for the treatment of neonatal-onset multisystem inflammatory disease and the familial cold autoinflammatory syndrome.

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