Anakinra's Benefit in NOMID Bears New Insights

Cochlear abnormality improvements indicate they are inflammatory rather than structural in origin.

BY BRUCE JANCIN
Denver Bureau

VIENNA — The interleukin-1 receptor antagonist anakinra (Kineret) proved "dramatically effective" in treating both the clinical and laboratory manifestations of neonatal-onset multisystem inflammatory disease in a controlled trial, Scott Canna reported at the annual European congress of rheumatology.

Particularly exciting was the observed improvement in both the CNS and cochlear abnormalities that typify neonatal-onset multisystem inflammatory disease (NOMID), indicating that these lesions are inflammatory rather than structural in origin.

The study also serves as a striking example of the efficacy of targeted therapy in a cytokine-mediated disease.

MR. CANNA

"This finding raises hope that the hearing loss and possibly even the cognitive impairment could be halted or even prevented with early anakinra, although, of course, long-term treatment will be needed to prove these hypotheses," noted Mr. Canna, who reported the results on behalf of the principal investigator of the study, Raphaela Goldbach-Mansky, M.D., a clinical investigator at the National Institute of Arthritis and Musculoskeletal and Skin Diseases, Bethesda, Md.

NOMID, also known as chronic infantile neurologic cutaneous and articular syndrome, or CINCA, is a severe genetic disease characterized by chronic aseptic meningitis, mental retardation, sensorineural hearing loss, uveitis, severe headaches due to increased intracranial pressure, and fevers.

Pathognomonic for NOMID is a disabling arthropathy that most often affects the knees. It is due to epiphyseal bony overgrowth that can lead to contractures and inability to walk.

Affected individuals are born with a persistent urticarial rash or develop it soon after birth. The rash is characterized by dermal infiltration of polymorphonuclear cells, histiocytes, and rare eosino-phils.

Although NOMID is rare, the NIAMS trial takes on considerable clinical import because it identifies anakinra, a drug approved for the treatment of rheumatoid arthritis, as the first highly effective and well-tolerated treatment for the diverse organ manifestations of this debilitating pediatric disease. The study also serves more broadly as a striking example of the efficacy of targeted therapy in a cytokine-mediated disease, Mr. Canna said at the congress, sponsored by the European League Against Rheumatism.

In 2001 Dr. Goldbach-Mansky and her coinvestigators at NIAMS identified the genetic defect involved in roughly 60% of NOMID cases. It involves mutations in the *CIAS-1* gene, which codes for cryopyrin. It's believed the protein cryopyrin activates the IL-1 converting enzyme caspase-1, which upregulates the inflammatory cytokines IL-1 and IL-1 β and encourages apoptosis. The result is a chronic autoimmune inflammatory state. The NIAMS team reasoned that blocking IL-1 might be beneficial.

Mr. Canna, a medical student who worked on the trial, shared the results on 18 NOMID patients aged 4-18 years who were started on 1 mg/kg per day of anakinra by daily subcutaneous injection, increasing to 2 mg/kg per day as needed.

Therapeutic response was extremely rapid. Indeed, the lifelong rash disappeared within 3 days in all patients. Daily disease diary scores dropped from a baseline of 3.35 to 0.55 at 3 months. Mean intracranial pressure dropped from 294 to 201 mm H_2O. CSF protein levels and WBC count decreased significantly as well.

Mean systemic corticosteroid dose fell from 0.85 to 0.44 mg/kg per day. High-resolution MRI showed improvement in the inner ear and leptomeningeal lesions. Joint pain decreased. Vision and hearing problems stabilized.

COURTESY DR. RAPHAELA GOLDBACH-MANSKY

An x-ray shows the bony changes typically associated with NOMID.

The study plan called for halting anakinra after 3 months to determine whether relapse would occur. But after the first 11 patients to stop treatment flared dramatically in a mean of just over 4 days, the drug withdrawal phase was halted for ethical reasons.

Acute phase reactant levels dropped dramatically and stayed low through the first 6 months, except during the anakinra withdrawal episode.

For example, C-reactive protein fell from a baseline of 6.79 to 0.89 mg/dL; serum amyloid A protein levels dropped from 265 to 31 mg/dL; and the ESR declined from 59.8 to 17.6 mm/hr, Mr. Canna said.

The clinical and laboratory response was equally good in NOMID patients with or without *CIAS-1* mutations. No serious infections occurred during treatment, nor was there a significant increase in minor infections.

The expectation is that anakinra will be used in NOMID patients as a lifelong steroid-sparing therapy.

The plan now is to expand the study population and, with longer follow-up, learn whether early therapy prevents cognitive impairment.

One audience member rose to say he has anecdotally used anakinra in two NOMID patients who had failed high-dose etanercept (Enbrel) and many other drugs. Both children, he added, showed stunning and "virtually instantaneous" clinical benefits. ■

Childhood Mixed CT Disease Outcomes Vary Widely

BY NANCY WALSH
New York Bureau

VIENNA — The prognosis for children with mixed connective tissue disease is highly variable, with some progressing to scleroderma and others developing systemic lupus erythematosus, but in a significant number of cases, the autoimmune disorder improves over the long term, Thomas J.A. Lehman, M.D., said at the annual European congress of rheumatology.

This condition was first described by G.C. Sharp and colleagues in 1972 as a syndrome that included severe myositis, pulmonary hypertension, Raynaud's phenomenon, and esophageal hypomotility. It was felt to be a variant of lupus because patients were antinuclear antibody positive, but many also had features that were not typical of lupus, such as nailfold capillary abnormalities, Gottron's papules, hypergammaglobulinemia, and synovitis. Renal findings almost never included diffuse proliferative glomerular nephritis, although membranous nephritis sometimes was present.

Subsequently, other groups have attempted to refine Sharp's criteria. But even today, precisely what constitutes mixed connective tissue disease remains controversial—there are no official, definitive criteria—and some textbooks categorize the condition as an undifferentiated connective tissue disease or an overlap syndrome.

"Whatever you choose to call it, this is a relatively distinct group that diverges strongly over time, and we don't yet know how to tell who is going to diverge in which direction," he said at the meeting, which was sponsored by the European League Against Rheumatism.

'In my experience, the most common outcome has been for them to get better.' This good outcome, however, requires close monitoring for potentially serious—or lethal—events.

Most patients are strongly antinuclear antibody positive, ribonucleoprotein antibody positive, and Small antibody negative. C3 and C4 are usually normal, and tests for antidouble-stranded DNA most often are negative. Some 20%-50% of patients also have thrombocytopenia.

Careful monitoring can help determine the direction in which the condition will evolve. Urinalysis, for example, can reveal if a patient has become Smith positive and is developing classic lupus. Signs of progressive respiratory compromise may suggest progression to scleroderma, which tends to have the worst outcomes for the patients.

"But in my experience, the most common outcome has been for them to get better," said Dr. Lehman, chief of the division of pediatric rheumatology at the Hospital for Special Surgery in New York City, who cares for many of these children.

This good outcome, however, requires close monitoring for potentially serious—or lethal—events, such as sudden, overwhelming sepsis, he said.

"These patients are functionally asplenic, so if the child develops a fever and signs of infection are present, start antibiotics and worry about false alarms later," he said.

And cough, shortness of breath, or other respiratory problems can signal pulmonary hypertension, so it's wise to suggest an echocardiogram and high-resolution CT, said Dr. Lehman, who is also professor of clinical pediatrics, Weill Medical College of Cornell University, New York City.

The key is treating the individual's symptoms, and this can include the use of low-dose corticosteroids, hydroxychloroquine, and methotrexate, with calcium channel blockers for Raynaud's phenomenon.

"Monitoring the levels of IgG and hemoglobin, as well as the erythrocyte sedimentation rate, will tell you whether your treatment is adequately controlling the disease process," he said at the meeting, which was sponsored by the European League Against Rheumatism.

"I've never had to use any of the immunosuppressive agents, such as cyclophosphamide or mycophenylate mofetil, at least in the early stages before the disease more fully delineates itself," he said. ■