

Anakinra Offers Neonatal-Onset Disease Benefits

BY DIANA MAHONEY
New England Bureau

Daily injections of the interleukin-1 β antagonist anakinra significantly improved the peripheral and central nervous system manifestations of neonatal-onset multisystem inflammatory disease in patients with and without the genetic mutation that is associated with the rare systemic disease, a study found.

Neonatal-onset multisystem inflammatory disease (NOMID) often develops in patients who have mutations in the cold-induced autoinflammatory syndrome 1 (CIAS1) gene that is associated with regulating inflammation.

Previous studies have linked interleukin-1 β pathways to NOMID, and isolated case reports have suggested that by inhibiting interleukin-1 β , anakinra (Kineret) may be effective in the treatment of rash and the constitutional symptoms of disease.

To assess anakinra efficacy on these manifestations, as well as those that affect the central nervous system, Dr. Raphaela Goldbach-Mansky of the National Institute of Arthritis and Musculoskeletal and Skin Diseases in Bethesda, Md., and colleagues enrolled 18 patients with active disease, including 12 with identifiable CIAS1 mutations, into an open-label investigation (N. Engl. J. Med. 2006;355:581-92).

All of the patients were between the ages of 4 and 32 years old (mean age 11 years) and presented with at least two of the following clinical manifestations of NOMID: urticarial rash, central nervous system involvement, or epiphyseal or patellar overgrowth on radiography. Additionally, all of the patients had undergone previous treatment with nonsteroidal anti-inflammatory drugs, disease-modifying antirheumatic drugs, and/or corticosteroids.

Each patient received daily subcutaneous anakinra injections of 1-2 mg/kg of body weight and underwent efficacy assessments at 1, 3, and 6 months.

The primary end points of the study were changes in symptom scores for fever, rash, headache, joint pain, and vomiting as measured in a daily diary, changes in acute-phase reactants, including serum amyloid A, C-reactive protein, and erythrocyte sedimentation rate from baseline to 3 months and from 3 months until a flare. Secondary end points were childhood health assessment questionnaire scores, audiography and vision assessments, MRI of the brain, and lumbar puncture results.

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The initial study design included an inpatient withdrawal phase at 3 months for patients who responded to anakinra treatment in order to induce a clinical flare, followed by a reintroduction of therapy and continuation in an ongoing extension period. The withdrawal phase was discontinued after the first 11 patients because of the severity of the flares, which included pericarditis in 1 patient, corneal infiltrates in 3 patients, and uveitis in 2 patients, according to the authors.

In all of the patients, anakinra treatment produced an immediate clinical response, including disappearance of rash and conjunctivitis within 3 days, significantly decreased diary scores at 3 months, and significant decreases in C-reactive protein, serum amyloid A, and erythrocyte sedimentation rates. Of the 11 patients who underwent an inpatient withdrawal period for up to 7 days, 10 experienced a flare that met prespecified criteria at a median of 5 days. All of the patients responded to resumed anakinra therapy promptly, and the improvements were sustained at the 6-month follow-up.

Additional findings included improved

hearing in six patients and stable hearing in patients relative to baseline, stable vision in all patients, and significant improvements on the pain, parent, and physician global assessment, and Childhood Health Assessment Questionnaire scores.

With respect to central nervous system manifestations, median daily headache scores decreased significantly in all patients, with complete resolution of headaches in eight patients at 3 months. Intracranial pressures, protein levels, and white cell counts decreased significantly in the 12 patients for whom cerebrospinal fluid was evaluated. Additionally, MRI showed significant improvement from baseline in cochlear and leptomeningeal lesions, the authors wrote.

Overall, anakinra was well tolerated in the patients. Eight experienced a localized, erythematous, sometimes painful injection-site skin reaction that disappeared by 6 weeks, 15 had upper respiratory events during treatment, 3 had urinary tract infections, and 1 was hospitalized for dehydration from nonbacterial diarrhea. No patients withdrew from the study because of adverse events, according to the authors.

Dr. Goldbach-Mansky reported no conflicts of interest with respect to this study. Some coinvestigators reported having received consulting fees, lecture fees, and/or research support from Amgen (maker of anakinra), Genentech, and Abbott. ■

SLE Drugs Found to Trigger Osteonecrosis

BY MARY ELLEN SCHNEIDER
New York Bureau

The use of cytotoxic drugs and glucocorticoids are both risk factors for the occurrence of symptomatic osteonecrosis in patients with systemic lupus erythematosus, Dr. Graciela S. Alarcón of the University of Alabama, Birmingham, and her colleagues reported.

The study confirmed previous findings that glucocorticoid use in systemic lupus erythematosus (SLE) patients is associated with osteonecrosis. "Our data suggest that exposure to high doses of glucocorticoids and probably the duration of use are the most important factors underlying this known association," the researchers reported (Ann. Rheum. Dis. 2006;65:785-90).

However, the researchers noted in the study that they could not draw any definitive conclusions about the glucocorticoid association related to the route of administration, the mean dose, the cumulative dose, or the highest dose used.

The findings highlight the fact that glucocorticoids and cytotoxic drugs should be used only when "strictly indicated," the researchers wrote.

The findings are based on a nested matched case-control design drawing on patients from a large, multiethnic, longitudinal lupus cohort—the LUMINA (Lupus in Minority Populations: Nature vs. Nurture) trial. The trial was made up of 571 SLE patients at the time the case-control study was conducted. The LUMINA study included participants from three ethnic groups—Hispanics from Texas and Puerto Rico, African Americans, and whites.

Within the LUMINA cohort, the researchers identified 33 cases of symptomatic osteonecrosis. One case was excluded because the diagnosis of osteonecrosis was made before the SLE diagnosis. Using the LUMINA database, researchers attempted

to match two controls for each osteonecrosis case included in the study. Controls were matched by age, sex, ethnicity, disease duration, and study location. In five cases, only one control subject could be matched.

Researchers analyzed 91 patients (32 cases and 59 controls). Most patients (57%) were African American, 22% were Hispanics from Texas, 2% were Hispanics from Puerto Rico, and 19% were white. The mean total disease duration of patients included in the study was about 46 months.

Patients were evaluated at baseline and received follow-up care every 6 months for the first year and annually thereafter.

The results of multivariate analyses show that both cytotoxic drug use and glucocorticoid use were associated with symptomatic osteonecrosis, but the average daily dose of glucocorticoids had only "borderline significance," according to the researchers. The odds ratio for the use of cytotoxic drugs was 3.89 when analyzed by the average daily dose of glucocorticoids and 3.04 when evaluated looking at the highest dose of glucocorticoids. The odds ratio was 1.03 for glucocorticoid use in the average dose model, as well as in the highest dose model.

There was also a "significant" negative association between osteonecrosis and serum triglycerides. In the model of average daily dose of glucocorticoids, the odds ratio was 0.99 and was statistically significant. Serum triglycerides also had an odds ratio of 0.99 in the highest dose of glucocorticoids but the significance was "borderline," the researchers wrote.

Despite the findings related to serum triglycerides, the researchers concluded that they could not identify any protective factors for symptomatic osteonecrosis. The study also failed to show a link between other suspected risk factors for osteonecrosis, such as Raynaud's phenomenon, arthritis, and antiphospholipid antibodies. ■

Connective Tissue Disease May Induce Skin Eruption

MANCHESTER, ENGLAND — Reactive perforating collagenosis has been reported in a patient with severe connective tissue disease for the first time, adding to the list of underlying disorders associated with this skin eruption.

A 17-year-old female was referred with a 9-month history of a rash on the arms, shoulders, and legs. It had appeared post partum, coinciding with the onset of painful symptoms of Raynaud's phenomenon, fatigue, anger, and pauciarticular arthritis, Dr. Anne-Marie Tobin said at the annual meeting of the British Association of Dermatologists.

The patient also had recently had a tonsillectomy for recurrent sore throat and was being tested for microcytic anemia.

The rash consisted of keratotic papules and plaques, typical of a perforating dermatosis.

An initial skin biopsy suggested a reactive folliculitis, but a repeat biopsy revealed acanthosis and an underlying perivascular infiltrate said Dr. Tobin of the department of dermatology, Waterford (Ireland) Regional Hospital. It also showed collagen entrapment in the epidermis and elimination through an epidermal depres-

sion, confirming the diagnosis of perforating collagenosis.

Because the rash worsened and the lesions became tender and unsightly, a course of 18 sessions of bath photochemotherapy (PUVA) was undertaken, she said. The cumulative dose was 20 J/cm², and the results were excellent. Her connective tissue disease remains intractable, however. Trials of corticosteroids, mycophenolate mofetil, azathioprine, and colchicine have all been unsuccessful.

She required admission to the hospital on three occasions for infusions of iloprost to alleviate digital ischemia, but the endothelin receptor antagonist bosentan is now being used and appears to have stabilized her Raynaud's symptoms.

Recently, she was admitted because of myalgias, fatigue, elevated serum creatinine kinase, and raised serum aldolase. "The rash has also recurred, and we are awaiting resolution of the myositis to recommence bath PUVA," Dr. Tobin said.

Other treatments that have been used successfully in reactive perforating collagenosis include UVB, allopurinol, doxycycline, and rifampin.

—Nancy Walsh