Canakinumab Excels For CAPS Treatment

BY SHARON WORCESTER

FROM THE ANNUAL MEETING OF THE AMERICAN COLLEGE OF RHEUMATOLOGY

ATLANTA – Canakinumab was safe, well tolerated, and highly effective in the long-term treatment of cryopyrin-associated periodic syndromes in pediatric patients in an open-label phase III extension study.

Treatment of cryopyrin-associated periodic syndromes (CAPS) in 47 patients, aged 3-17 years, was associated with a rapid and sustained clinical and biochemical remission across varying disease severity phenotypes.

Five patients had familial cold autoinflammatory syndrome (FCAS), 23 had Muckle-Wells syndrome (MWS), and 18 had chronic infantile neurologic, cutaneous, and articular syndrome/neonatal-onset multisystem inflammatory disease (CINCA/NOMID). One child was found to not have a CAPS disease phenotype, said Dr. Jasmin B. Kuemmerle-Deschner.

Of the 47 patients, 38 had not previously been treated with the human interleukin-1 beta monoclonal antibody, and 9 were "rolled over" from earlier phase II or III studies. Of the 38 canakinumab-naive patients, 68% achieved a complete response based on physician global assessment of disease activity and skin assessment, plus normalization of C-reactive protein (CRP) and lowering of serum amyloid A (SAA) to less than 10 mg/L for both measures. More than 80% of the canakinumab-naive patients were relapse-free after a median of 290 days of exposure to treatment, and normal CRP and SAA levels were also maintained throughout the study period in the rollover patients, said Dr. Kuemmerle-Deschner, a pediatric rheumatologist at Universitaetsklinikum Tuebingen (Germany).

The response in the treatment-naive patients was rapid, with CRP and SAA falling within 7 days from 14.8 to 2.5 mg/L, and from 40.6 to 7.4 mg/L, respectively. In addition, 8 of the 11 patients who had an incomplete response within 7 days developed a complete response by 14 days, and the remaining patients had a partial response, she said.

All patients were treated with 150 mg (or 2 mg/kg for those weighing 40 kg or less) of subcutaneous canakinumab once every 8 weeks. In cases of incomplete response, more frequent dosing or an additional dose of 300 mg (or 4 mg/kg for patients weighing 40 kg or less) was allowed. Doses were adjusted in 17 patients, she said. ■

VITALS

Major Finding: Of 38 canakinumab-naive patients, 68% achieved a complete response based on physician global assessment of disease activity and skin assessment, and normalization of C-reactive protein and serum amyloid A. More than 80% of the canakinumab-naive patients were relapse-free after a median of 290 days of exposure to treatment, and normal levels were also maintained throughout the study period in the rollover patients.

Data Source: From an open-label, single treatment arm, phase III extension study of canakinumab for CAPS.

Disclosures: Dr. Kuemmerle-Deschner disclosed that she has received research grants and consulting fees from Novartis Pharmaceuticals, the maker of canakinumab (Ilaris).

Methotrexate Averts Flares In Juvenile Scleroderma

BY SHARON WORCESTER

FROM THE ANNUAL MEETING OF THE AMERICAN COLLEGE OF RHEUMATOLOGY

ATLANTA – Methotrexate was an effective, well-tolerated treatment for juvenile localized scleroderma in a randomized, double-blind, placebo-controlled trial of 70 patients with active disease.

At the end of the 12-month study, 31 of 46 patients randomized to receive methotrexate had responded to treatment and were flare-free, compared with 7 of 24 patients given placebo, Dr. Francesco Zulian reported.

Participants were aged 6-17 years, and had active localized scleroderma of linear, generalized, or deep subtypes with onset before age 16.

Methotrexate patients received an oral dose of 15 mg/m^2 (maximum, 20 mg) weekly for 12 months or until flare of disease. The placebo group received a placebo administered in the same fashion for 12 months or to flare. Both groups received prednisone at a dose of 1 mg/kg per day, with a maximum dose of 50 mg, for 3 months. They were then tapered to 0 over 1 month. During the initial 3 months of the study, treatment response was comparable for the two groups. Differences in response rates began to emerge after that point, said Dr. Zulian of the University of Padua (Italy).

Mean skin score fell from 1.0 at baseline to 0.79 in the methotrexate group, but did not fall in the placebo group.

DR. ZULIAN

Patients' lesions were evaluated using a computerized scoring system, and changes were quantified using a skin score rate. Active lesions were monitored by clinical exam and serial thermography. Mean skin score rates fell significantly from 1.0 at baseline to 0.79 in the patients on methotrexate, but did not decrease in the placebo patients. The mean target lesion temperature on thermography decreased by 44% in the methotrexate group and by 12% in the placebo group, a significant difference, he said.

Adverse events occurred in 26 of 46 patients on methotrexate, and in 11 of 24 on placebo. In the methotrexate group, adverse events included alopecia, nausea, headache, fatigue, hepatotoxicity, weight gain, and striae rubra. The only adverse events in the placebo group were weight gain and striae rubra.

Interestingly, weight gain of more than 5% of body weight occurred in 11% of the methotrexate patients and 42% of the placebo patients, Dr. Zulian said, noting that this may suggest there is a "biological or pathophysiological link" between prednisone and methotrexate that tempers this steroid-related side effect.

None of the side effects was severe enough to stop treatment, but both groups had a high drop-out rate due to relapse or lack of response: 31 of 46 patients on methotrexate, and 7 of 24 in the placebo group, completed the study. ■

VITALS

Major Finding: At the end of the 12-month study, 17 of 24 patients randomized to receive placebo and prednisone experienced a relapse, compared with 15 of 46 patients randomized to methotrexate and prednisone.

Data Source: A randomized, double-blind, placebo-controlled trial of 70 children with juvenile localized scleroderma.

Disclosures: Dr. Zulian said he had no relevant financial disclosures.

Revised Criteria May Increase Accuracy of Marfan Diagnosis

BY DIANA MAHONEY

FROM THE JOURNAL OF MEDICAL GENETICS

Aortic root aneurysm and ectopia lentis are the cardinal clinical features of Marfan syndrome, and the presence of both of them is sufficient for the "unequivocal diagnosis" of the genetic connective-tissue disorder, according to recently revised diagnostic criteria.

The new criteria update the 1996 Ghent nosology, which comprise a stringent set of major and minor manifestations in multiple organ systems. Although the earlier nosology has proven to be a useful diagnostic guide, "some of the diagnostic criteria have not been sufficiently validated, are not applicable in children, or necessitate expensive and specialized investigations," lead author Dr. Bart L. Loeys of Ghent University Hospital, Belgium, and colleagues wrote. The revised Ghent nosology addresses these shortcomings, they stated (J. Med. Genet. 2010 47:476-85).

The revised criteria were developed by an international panel of experts based on a critical review of clinical characteristics in large, published patient cohorts. They include five major changes to the earlier guidelines:

► More weight is given to aortic root aneurysm/dissection and ectopia lentis. "In the absence of findings that are not expected in [Marfan syndrome], the combination of ectopia lentis and aortic root enlargement/dissection should be sufficient to make the diagnosis," the authors wrote, noting that all other cardiovascular and ocular manifestations of the condition, as well as findings in the skeleton, dura, skin, and lungs, "contribute to a systemic score that guides diagnosis when aortic disease is present but ectopia lentis is not."

► Molecular genetic testing of the fibrillin-1 (FBN1) gene, which is mutated in Marfan syndrome, and other relevant genes has a more prominent role. Although the updated nosology does not require FBN1 testing, it "allows its appropriate use when available," they wrote.

► Some of the less specific manifestations identified in the previous criteria, such as joint hypermobility, highly arched palate, recurrent or incisional herniae, and dural ectasia have been removed or had their influence minimized.

► Additional diagnostic considerations and testing are required for individuals who satisfy the criteria for Marfan syndrome, but also show unexpected findings suggestive of conditions with overlapping symptoms, such as Sphrintzen-Goldberg syndrome, Loeys-Dietz syndrome, and the vascular form of Ehlers-Danlos syndrome. "It is essential to consider discriminating features because each of these conditions has a unique risk profile and management protocol," the authors wrote.

► Context-specific recommendations for patient counseling and follow-up are outlined for "sporadic" patients (those with no family history), index patients (those with a definitive family history), and patients younger than 20 years old.

A Web-based diagnostic tool for applying the new criteria is available at www.marfan.org.

The authors reported having no conflicts of interest with respect to this project. Funding for the development of revised nosology for Marfan syndrome was provided by the National Marfan Foundation, March of Dimes, Merck & Co., and Solvay Pharmaceuticals. ■