Genetic Variants Confer Susceptibility to JIA

BY MICHELE G. SULLIVAN

FROM THE ANNALS OF RHEUMATIC DISEASES

Two genetic polymorphisms now appear to be associated with juvenile idiopathic arthritis as well as type 1 diabetes or celiac disease.

The finding lends credence to a growing idea that genetic variability in common loci can predispose a child to different autoimmune disorders, wrote Dr. Anne Hinks of the University of Manchester, U.K.

"The approach of targeting variants associated with other autoimmune diseases is already yielding insights into the genetic complexity underlying susceptibility to this serious childhood disease," Dr. Hinks and her coauthors wrote (Ann. Rheum. Dis. 2010;69:2169-72).

The researchers compared DNA from 1,054 patients with JIA with that of 3,129 healthy controls, focusing on 13 single nucleotide polymorphisms (SNPs) that had already had confirmed associations with type 1 diabetes or celiac disease. One SNP on the preferred translocation partner in lipoma (LPP) gene (rs1464510) was significantly associated with JIA. Another SNP located in the ataxin 2 (ATXN2) gene was marginally associated with JIA, but the association was not significant.

The SNP lying in the LPP domain is particularly interesting, the authors noted, because that gene has a confirmed association with celiac disease. LPP is integral in cell migration and adhesion and is a substrate of tyrosine phosphatase. It also has been linked to Ras signaling, a process important in cell growth, differentiation, and survival.

A third SNP (rs17810546) located in the interleukin 12A gene (IL12A) was significantly associated with enthesitis-related arthritis. The IL12A gene has already been associated with celiac disease. The association with arthritis was a strong one, Dr. Hinks and her colleagues noted, but there were no other associations with any other JIA subtype. The IL12A gene exerts a number of important influences, including encoding a cytokine necessary for the differentiation of T cells and T-cell–independent induction of interferon gamma.

Although this gene has not been associated with ankylosing spondylitis, patients with enthesitis-related arthritis are prone to joint destruction in the spine and sacroiliac joints. ■

VITALS

Major Finding: Two genetic variants with known associations to type 1 diabetes or celiac disease also predispose to juvenile idiopathic arthritis.

Data Source: DNA from 1,054 patients with juvenile idiopathic arthritis was compared with that of 3,129 healthy controls. Thirteen single nucleotide polymorphisms (SNPs) that already had confirmed associations with type 1 diabetes or celiac disease were investigated.

Disclosures: The study was sponsored by Arthritis Research U.K. and supported by the NIHR Manchester Biomedical Research Council. Genotype data used was funded by grants from the Medical Research Council and the Wellcome Trust. The authors said they had no relevant financial disclosures.

Canakinumab Effect in CAPS Confirmed

BY BRUCE JANCIN

FROM THE ANNUAL CONGRESS OF THE EUROPEAN ACADEMY OF DERMATOLOGY AND VENEREOLOGY

GOTHENBURG, SWEDEN – Interleukin-1 blockade with canakinumab provided rapid and sustained clinical remission in the great majority of treated children and adults with cryopyrin-associated periodic syndrome who participated in a large 2-year study.

Most participants experienced significant improvement within a day or two after their first injection and were complete clinical responders with normalized inflammatory markers by day 8. said Dr. Kieron S. Leslie.

In all, 90% of patients remained in remission continuously for the full 2 years on subcutaneous canakinumab (Ilaris) injected once every 8 weeks, added Dr. Leslie, a dermatologist at the University of California, San Francisco.

The new study confirms canakinumab's safety and efficacy over a far longer treatment period. It also provides important new prescribing information: namely, that children with cryopyrin-associated periodic syndrome (CAPS) – as well as adults with the most severe form of the syndrome, known as neonatal-onset multisystem inflammatory disease (NOMID) – often require an upward dosing adjustment to obtain complete response.

CAPS is the latest term for a three-part autoinflammatory disease spectrum caused by mutations in the NLRP3 gene. At the mildest end is familial cold autoinflammatory syndrome (FCAS), an autosomal dominant condition marked by arthralgia, cold-induced rash, and conjunctivitis. In the middle is Muckle-Wells syndrome, also autosomal dominant, and characterized by sensorineural deafness and, in one-quarter of cases, by amyloid A amyloidosis. At the most severe end of the CAPS spectrum is NOMID, which includes the other disease manifestations plus a destructive arthritis and progressive meningitis resulting in visual impairment, deafness, and intellectual impairment.

Canakinumab is a fully human monoclonal antibody directed against IgG1 and interleukin-1 beta. It has a half-life of about 25 days. It was licensed last year in both the United States and Europe for treatment of CAPS. The standard weight-based dosing regimen is subcutaneous injection of 150 mg once every 8 weeks in adults, or 2 mg/kg in patients weighing 40 kg or less.

The 2-year, open-label study involved 166 CAPS patients aged 3 years or older, of whom 109 were canakinumab naive, including 38 children. The other 57 patients were rolled over from earlier studies. In all, 91% of subjects completed the 2-year study.

All 57 patients with prior exposure to canakinumab had a complete response to the biologic in this study, as did 85 of 109 treatment-naive patients.

Of the 85 treatment-naive complete responders, 79 achieved their complete response within 8 days; the rest did so during days 10-21.

All 24 canakinumab-naive patients who didn't attain a complete response nonetheless showed lesser clinical improvement. A complete response required a rating of minimal or no disease on the physician's global assessment of disease activity, plus normalization of both C-reactive protein and serum amyloid A levels, inflammatory markers that were typically elevated to 70-100 mg/L before treatment.

A dose increase was required in 36% of the 47 pediatric patients in the study, compared with 19% of the adults.

Children with Muckle-Wells syndrome or NOMID required a mean 5.5 and 5.8 mg/kg, respectively, of canakinumab per injection, compared with the standard 2.0 mg/kg. Of the 32 participants with NOMID, 47% required a dose increase; adults with NOMID required a mean dose of 229 mg rather than the 150 mg listed in the product labeling, the dermatologist continued.

In all, 92% of patients had no injection site reactions. The injection site reactions in the 8% of affected patients were mild to moderate.

Patients on canakinumab reported an increase in mild upper respiratory tract infections. Severe adverse events (mainly urosepsis, other major infections, or vertigo) occurred in 10%. However, only three patients withdrew from the study because of adverse events over the course of 2 years.

Dr. Leslie was asked how canakinumab compares in terms of efficacy and cost to anakinra (Kineret), an interleukin-1 antagonist that has also shown efficacy in CAPS.

He replied that there are no comparative trials, but anecdotally the results are quite comparable. Both drugs bring almost complete remission.

The difference is that anakinra has a half-life of 6 hours and must be administered daily rather than every 8 weeks. And moderate to severe injection site reactions are a problematic issue with anakinra. ■

VITALS

Major Finding: A total of 90% of patients with cryopyrin-associated periodic syndrome remained in remission continuously for the full 2 years on subcutaneous canakinumab injected once every 8 weeks.

Data Source: A 2-year, open-label study of 166 CAPS patients aged 3 years or older, of whom 109 were canakinumab-naive.

Disclosures: The canakinumab study was sponsored by Novartis, which provided Dr. Leslie with grant support.

Adalimumab Eases Childhood Uveitis Over Long Term

BY SHARON WORCESTER

FROM THE ANNUAL MEETING OF THE AMERICAN COLLEGE OF RHEUMATOLOGY

ATLANTA – Adalimumab was more effective than infliximab for the prevention of recurrence of chronic childhood uveitis in a small open-label prospective study.

Remission was achieved within 10-12 weeks in 31 of the 33 children, including 15 of 16 recruited for the adalimumab group, and 16 of 17 recruited for the infliximab group. All were able to discontinue steroid treatment, and no significant differences were seen between the groups in time to remission or time to steroid discontinuation, Dr. Gabriele Simonini reported at the meeting.

At 40 months' follow-up, 60% of the adalimumab patients who achieved remission remained in remission, compared with only 18.8% of those in the infliximab group, said Dr. Simonini of the University of Florence (Italy).

Among those who relapsed, the median number of relapses was 1 (range, 1-3) in the adalimumab group, and 3 (range, 1-5) in the infliximab group.

The difference was statistically significant, Dr. Simonini said. ■

VITALS

Major Finding: At 40 months' follow-up, 60% of the adalimumab patients who achieved remission remained in remission, compared with only 18.8% of those in the infliximab group.

Data Source: An open-label prospective cohort study.

Disclosures: Dr. Simonini reported no relevant financial disclosures.