Highlights of the Latest Pediatric Rheumatology Research

Written by Muriel Cunningham

Rolando Cimaz, MD, University of Florence, Florence, Italy, reviewed a number of publications from the past 12 months that he considers the most important in the field of pediatric rheumatology.

Advances in technology have led to the discovery of genetic mutations that are responsible for certain rare phenotypes. A recently published case study describes a 9-month-old infant of Tunisian consanguineous parents with recurrent fevers with pericarditis, joint pain, abdominal pain, liver and spleen enlargement, and diarrhea [Melki I et al. *Pediatrics* 2013]. The presence of hyperpigmented, hypertichotic cutaneous patches, Rosai-Dorfman histiocytosis, and sensorineural hearing loss led the investigators to suspect a genetic mutation, and a homozygous mutation in exon 6 of the *SLC29A3* gene was found. The infant failed to thrive and did not respond to any treatments (colchicine, anakinra, canakinumab, adalimumab). In another published case study, an infant of Tunisian consanguinous parents presenting with generalized pustular psoriasis did not respond to high-potency topical glucocorticoids (GC) and retinoic acid [Rossi-Semerano L et al. *Pediatrics* 2013]. Genetic analysis revealed a homozygous missense mutation in the interleukin (IL)-36 receptor antagonist gene, *IL36RN*, and the patient responded to treatment with the IL-1 inhibitor anakinra.

Two publications established a link between adenosine deaminase 2 (ADA2) deficiency and vascular disease. The first report found a link between recessive mutations in the ADA2-encoding gene *CECR1* and polyarteritis nodosa vasulopathy (PNV) [Navon Elkan P et al. *N Engl J Med* 2014]. A pedigree of 6 families with multiple cases of systemic and cutaneous PNV indicated autosomal recessive inheritance with childhood disease onset and highly variable phenotypes. The second publication described 3 unrelated children with recurrent fever, early-onset (<5 years of age) and recurrent strokes, livedoid rash, mild immunodeficiency, hepatosplenomegaly, and systemic vasculopathy [Zhou Q. et al. *N Engl J Med* 2014]. They had recessively inherited *CECR1* mutations and almost no active ADA2 concentrations in plasma compared with controls.

A randomized, multicenter, open-label clinical trial was conducted to determine the effects of attenuated measles-mumps-rubella (MMR) vaccine booster on juvenile idiopathic arthritis (JIA) disease activity [Heijstek MW et al. *JAMA* 2013]. In total, 137 patients aged 4 to 9 years with JIA were enrolled, and treatment with biologics was discontinued at 5 times their half-lives prior to vaccination. The investigators found that JIA activity was not worsened in 63 children receiving MMR boosters (Juvenile Arthritis Disease Activity Score 27 [JADAS-27], 2.8; 95% CI, 2.1 to 3.5] compared with 69 control patients who did not receive boosters (JADAS-27, 2.4; 95% CI, 1.7 to 3.1). On the basis of these data, physicians can reassure parents that vaccinations can be given to their children, that they are immunogenic, and that they will not flare disease, stated Prof. Cimaz. Key findings from other studies in JIA are presented in Table 1.

Kawasaki disease (KD) is routinely treated with intravenous immunoglobulins (IVIG). Current guidelines recommend waiting ≥6 months after IVIG treatment to administer the MMR vaccine. A retrospective study was conducted to determine the effect of IVIG infusions on the first dose of MMR vaccine in patients with KD [Tacke CE et al. *J Allergy Clin Immunol* 2013]. One hundred fifty-five patients were separated into 3 groups: those who were vaccinated before IVIG, those who were vaccinated after IVIG, and those who did not receive IVIG because of a delay in diagnosis. Patients vaccinated before IVIG and healthy controls had comparable immunoglobulin G concentrations and seroprotection (p>0.10 for all) to measles, mumps, and rubella. Patients vaccinated after IVIG had lower responses at 9 months. The authors therefore recommended delaying MMR vaccination until ≥9 months after IVIG treatment for KD.

Peer-Reviewed Highlights From the

European League Against Rheumatism 2014 Annual Scientific Meeting

June 11-14, 2014
Paris, France

Table 1. Summary of Notable Juvenile Idiopathic Arthritis Publications

Journal Article Title	Citation	Key Message
Anti-Tumor Necrosis Factor-α Targets Protein Kinase B/c-Akt-Induced Resistance of Effect or Cells to Suppression in Juvenile Idiopathic Arthritis	Wehrens EJ et al. *Arthritis Rheum* 2013	Data suggest a novel etanercept mechanism of action, restoring Teff cell responsiveness to suppression through inhibition of their protein kinase B/c-Akt activation status.
Brief Report: Etanercept Inhibits the Tumor Necrosis Factor α-Driven Shift of Th17 Lymphocytes Toward a Nonclassic Th1 Phenotype in Juvenile Idiopathic Arthritis	Maggi L et al. *Arthritis Rheumatol* 2014	TNFα-induced transition of CD161+ Th17 lymphocytes to the Th17/Th1 and the Th1 phenotype was inhibited by etanercept.
RNA Recognition by Human TLR8 Can Lead to Autoimmune Inflammation	Guiducci C et al. *J Exp Med* 2013	Transgenic mice expressing human TLR8 had increased susceptibility to arthritis. TLR8 is overexpressed in humans with systemic arthritis and correlates with interleukin-1β production and disease activity. Treatment with anakinra normalized TLR8 mRNA in patients with SOJIA.
Effectiveness of First-Line Treatment With Recombinant Interleukin-1 Receptor Antagonist in Steroid-Naive Patients With New-Onset Systemic Juvenile Idiopathic Arthritis: Results of a Prospective Cohort Study	Vastert SJ et al. *Arthritis Rheumatol* 2014	Treatment with anakinra early in the disease course led to high response rates and high rates of sustained remission in patients with SOJIA.

JIA=juvenile idiopathic arthritis; mRNA=messenger ribonucleic acid; RNA=ribonucleic acid; SOJIA=systemic-onset juvenile arthritis; TNF=tumor necrosis factor.

Findings from a Phase 3, randomized, double-blind, placebo-controlled trial of the addition of infliximab to standard therapy for KD were recently reported [Tremoulet AH et al. *Lancet* 2014]. The study enrolled 196 patients but did not meet its primary endpoint of treatment resistance (11.2% for infliximab and 11.3% for placebo; p=0.81). In addition, there are preclinical data indicating that interleukin-1 is crucial for the induction of coronary artery inflammation in KD [Lee Y et al. *Circulation* 2012]. A study of anakinra in children with KD is planned, and Prof. Cimaz hopes results with be available next year.

Five years of follow-up data have been published regarding the treatment of childhood-onset systemic lupus erythematosus (SLE) with rituximab (RTX) and cyclophosphamide (CP) [Lehman TJ et al. *Pediatr Rheumatol Online J* 2014]. Twelve patients were treated with RTX (750 mg/m^2 up to 1 g) or CP (750 mg/m^2). The initial administrations were given 2 weeks apart, followed by 1 administration 6 months later and another 18 months later. This therapy led to rapid reduction of the GC dose without disease flare, thus preventing or resolving GC-associated adverse effects. The authors concluded that this regimen led to sustained relief over 5 years while minimizing the need for GCs. In another study, protein kinase C delta (PKCδ) deficiency was reported as a new form of monogenic SLE [Belot A et al. *Arthritis Rheum* 2014]. This B-cell apoptotic defect results in SLE-related autoimmunity. In humans, PKCδ plays a major role in inducing B-cell tolerance and the removal of self-reactive transitional B cells.

In closing, Prof. Cimaz summarized what he considers to be the single most important publication in pediatric rheumatology from the past year. Rice and colleagues reported that neuroimmunologic features associated with an enhanced interferon state are caused by heterozygous mutations in the cytosolic double-stranded receptor gene *IFIH1* (also known as *MDA5*) [Rice GI et al. *Nat Genet* 2014]. Such mutations result in a gain of function such that the mutant IFIH1 protein binds ribonucleic acid more effectively than wild-type does, leading to increased interferon signaling. Prof. Cimaz stated that these mutations provide new insights into the function of the gene, which will assist with designing treatments.