SPOTLIGHT ON RESEARCH
Juvenile Arthritis
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Unraveling the Mystery of JIA

Scientists are getting closer to determining the causes of juvenile idiopathic arthritis and finding more effective, targeted treatments for the disease. These three researchers tell how they're accomplishing those goals.

BY JO CAVALLO

Juvenile arthritis (JA) is one of the most common diseases found in children, affecting about 300,000 adolescents and children under the age of 16. Commonly referred to as juvenile idiopathic arthritis (JIA), the term actually encompasses several diseases, all of which are different from adult onset rheumatoid arthritis, and all the subtypes may be biologically different as well. The three main subtypes of JIA are oligoarticular (formerly known as pauciarticular), which typically affects four or fewer joints, usually the knees, ankles or elbows. The most common subtype of JIA, oligoarticular is diagnosed in about 50 percent of all children with juvenile arthritis. About 30 percent of children are diagnosed with polyarticular JIA in which five or more smaller joints, such as the hands and feet, are affected, although large joints can be affected as well. Generally, polyarticular JIA is found more often in girls than in boys. The third subtype is systemic onset JIA in which the whole body is affected. The least common form of JIA, systemic juvenile arthritis affects about 20 percent of children with JIA and can cause spikes in fever, rash and inflammation of internal organs such as the heart, liver, spleen and lymph nodes. If inadequately treated, this type of JIA can result in lifelong severe joint problems.

An incurable autoimmune disease, JIA can have a devastating, long-term impact on children, producing severe joint and tissue damage and even prohibit bone development and growth, greatly affecting the quality of life of patients. About half the children afflicted with JIA will outgrow their disease and about half will continue to have arthritis for the rest of their lives.

Since the founding of the Arthritis Foundation 62 years ago, it has funded over $400 million in arthritis research. In 2011, the Arthritis Foundation will fund about $3 million in JIA research, including $750,000 to support the Childhood Arthritis & Rheumatology Alliance (CARRA), a national network of pediatric rheumatologists dedicated to basic, translational and clinical research in JIA.

"Our major thrust in investing in the CARRA network is to enable its success, so that we can, one, improve the approach to the treatment of children with JIA. And, two, have a more effective way of tracking the benefit and any side effects that occur from new drugs to treat JIA," says John Hardin, MD, Vice President for Research for the Arthritis Foundation.

The Arthritis Foundation's investment in JIA research has yielded important breakthroughs in the understanding of the causes of JIA and in the development of more effective treatments for the disease. Over 25 years ago, research supported by the Arthritis Foundation resulted in the discovery of the overexpression of interleukin-1 (IL-1)—a molecule that fights infection but that can cause tissue inflammation when it is over produced—in patients with rheumatoid arthritis. That discovery led to the development of Kineret, a drug that inhibits IL-1 activity and is used to treat JIA.

Other advances include a class of biologic drugs called tumor necrosis factor-alpha blockers, or TNF inhibitors, used in the treatment of JIA, such as Humira (adalimumab) and Enbrel (etanercept).

"Certainly the anti-TNF inhibiting therapies have changed the whole outlook of kids with juvenile arthritis," says Norman T. Ilowite, MD, Chief, Pediatric Rheumatology at the Children's Hospital at Montefiore, Bronx, New York. Dr. Ilowite's current research on the IL-1 inhibitor rilonacept (Arcalyst) in the treatment of systemic JIA is featured on page 3 of this newsletter.

Gaining a better understanding of the causes of JIA and the development of more effective, targeted therapies to stop progression of the disease also the focus of the investigations of Yukiko Kimura, MD, and Terri H. Finkel, MD, PHD, profiled on the following pages.

The Arthritis Foundation's investment in JIA has yielded important breakthroughs in the understanding of the causes of JIA and in the development of effective treatments.

Terri H. Finkel, MD, PHD

Joseph Lee Hollander Professor of Pediatric Rheumatology, University of Pennsylvania School of Medicine and Chief, Division of Rheumatology, The Children's Hospital of Philadelphia

When Terri H. Finkel, MD, PHD, began her residency in pediatric rheumatology, the "tool kit" she had available to treat rheumatic diseases was very blunt, she says. "We had methotrexate and gold injections, but there were no magic bullets in our armamentarium and a lot of our care was palliative [treatment used to relieve symptoms]. Unfortunately, back then, many of the children with juvenile idiopathic arthritis were crippled for life."

Thirty years later, the treatment landscape is much more promising thanks to the development of biologic agents, especially the tumor necrosis factor-alpha blockers, or TNF inhibitors, used in the treatment of JIA, such as Humira (adalimumab) and Enbrel (etanercept). However, even with more effective treatment, many children still suffer some joint deformity from their disease and loss of quality of life that can extend into adulthood, impacting their social life and career.

Dr. Finkel's earlier work in the study of the signaling pathways of T-cells and how T-cells help B cells kill viruses and keep the immune system in balance, led her to investigate the malfunctions of the immune system in JIA and the possible genetics involved in those immunologic malfunctions. Five years ago, with a grant from the Arthritis Foundation, Dr. Finkel started a patient database at The Children's Hospital of Philadelphia called CHOP 100 to track the possible genetic and other factors involved in children who achieved remission with the goal to then try to replicate those factors so that eventually 100 percent of JIA patients could achieve remission.

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"At the time, the literature said that only about one-third of children with JIA were achieving remission and we had the impression that we were doing much better than that, but we didn't have the data to prove it," says Dr. Finkel. The remission criteria built into the database include no joints with active arthritis; no fever, rash or other generalized symptoms of JIA; no uveitis eye inflammation; a normal inflammation sedimentation rate or C-reactive protein level; and no disease activity according to the physician's assessment of the child.

With additional funding from the Arthritis Foundation, Dr. Finkel and her colleagues were able to identify an area on chromosome 9 that houses two genes, TRAF1 and C5, which may be the "master switch" that regulates development of autoimmune diseases like JIA. However, juvenile arthritis is such a complex disease, says Dr. Finkel, the cause is probably a combination of genetics and environmental triggers. "There are probably many different things in the environment that can have different effects on the various genes," she says.

In Dr. Finkel's current research she's using a new approach called genome-wide association to more accurately identify the risk factors for JIA. "Genome-wide association takes the guessing game out of our hands and looks everywhere in the genome to show how patients with JIA are different from healthy kids," says Dr. Finkel. Her research has already led to the identification of the first chemokine receptor pathway that's linked to juvenile arthritis. The next step is to confirm that this genetic variant is present more often in children with JIA than in those without the disease, whether the gene is malfunctioning and if it is causing production of more tumor necrosis factor cytokines. The answers could lead to more targeted therapy for JIA.

"It happens that there are already drugs on the market that are targeting the protein that is made by this gene and we're starting to look at those drugs. Our immediate goal is to determine how the gene works in the development of JIA. Then when we know that, we can ask if these drugs can change that process," says Dr. Finkel.

Norman T. Ilowite, MD

Chief, Pediatric Rheumatology,
The Children's Hospital at Montefiore;
Professor of Pediatrics,
Albert Einstein College of Medicine, Bronx, New York;
Chair, Childhood Arthritis & Rheumatology Research Alliance

Thirty years ago, when Norman T. Ilowite, MD, was a resident in pediatrics at Children's National Medical Center in Washington, D.C., pediatric rheumatology was just being recognized as a subspecialty of internal medicine in the treatment of childhood rheumatologic disorders. After taking care of a young boy with systemic juvenile idiopathic arthritis (JIA), then called systemic juvenile rheumatoid arthritis, Dr. Ilowite decided to devote his medical career to the care of adolescents and children with JIA.

"I found the boy to be a wonderful child and I found the disease to be very interesting and there wasn't much known about JIA at the time," says Dr. Ilowite. "I was lucky enough to be in a residency program that had just hired a pediatric rheumatologist to direct a Division of Pediatric Rheumatology and I learned that there was a possibility of specializing in pediatric rheumatology. Until then I hadn't heard of it as a subspecialty."

Since then, Dr. Ilowite has seen progress made in the area of genetic factors that may play a role in the development of JIA, including the HLA genes. "The genes that seem to have the most effect in increasing risk for JIA are the molecules encoded by the HLA genes that regulate the immune response," says Dr. Ilowite. "We all have unique genotypes for these genes and they're all considered normal, but there are certain HLA genes that place you at risk for one disease or another and there have been some that have been identified that increase certain forms of JIA." Once the exact genes involved in JIA onset are identified and the role of those genes in the pathogenesis of the disease can be studied, says Dr. Ilowite, the knowledge will be directly translated into targeted therapy.

Currently, Dr. Ilowite is the principal investigator of RAPPORT, a uniquely designed phase II/III multi-center randomized placebo study of rilonacept (Arcalyst) in the treatment of systemic JIA. In the study, one group is given rilonacept injections and one group is given a placebo at study entry but is then put on active treatment at week four. "Instead of putting patients on a placebo for long periods of time and see who does better, this trial design enables all participants to receive the active drug eventually and it's the time to response that we're using as a readout for efficacy," says Dr. Ilowite.

There are also a number of ancillary studies attached to RAPPORT, including one looking at gene expression scores to predict response to rilonacept and measure disease activity. Another study is investigating whether monocyte phenotypes are the cause or effect of the overexpression of interleukin-1. "We're also banking patient tissue at Cincinnati Children's Hospital Medical Center for future studies that we haven't conceived yet," says Dr. Ilowite.

As Chair of the Childhood Arthritis & Rheumatology Research Alliance (CARRA), Dr. Ilowite is also spearheading CARRA-Rx, an endeavor to develop consensus-driven best treatments for four childhood arthritis disorders: systemic JIA, juvenile dermatomyositis, localized scleroderma and childhood lupus nephritis. "We're coming up with treatment plans that are consensus based and not evidence based to narrow the variation in treatment among the pediatric rheumatologists in North America, therefore, enabling observational studies with great power to detect differences and comparative effectiveness among our patients," says Dr. Ilowite.

Although currently there are no treatments that cure JIA, Dr. Ilowite is optimistic that one will be found eventually. In the meantime, new therapies are being studied that promise to be more effective in halting disease progression. "Most of the current novel work is being done with small molecules that are taken orally and target specific signaling pathways within cells. Also, there are a number of biologics given by injection or infusion in various stages of development that are being tested in children," says Dr. Ilowite.

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Yukiko Kimura, MD

Chief, Pediatric Rheumatology, the Joseph M. Sanzari Children's Hospital, Hackensack University Medical Center in New Jersey; Chair, JIA Research Committee of the Childhood Arthritis & Rheumatology Alliance

Yukiko Kimura, MD, was inspired to become a pediatric rheumatologist after witnessing the pain and disability of young patients with juvenile arthritis when she was a pediatric resident over 20 years ago. She was also intrigued by the concept of autoimmunity and by a set of diseases that most physicians found mysterious and for which there was little effective treatment. The progress she's seen over the last two decades, she says, has been revolutionary.

"When I first started practicing medicine, we didn't have any of the biologic agents we have today and we weren't using methotrexate very effectively and the children with JIA often had poorly controlled disease," says Dr. Kimura. "The most dramatic change between then and now has been what we don't see anymore. Back then it was not uncommon to see kids in wheelchairs. Now, thankfully, that's rare and most of the time you can't even tell that these children have arthritis."

Still, says Dr. Kimura, JIA can cause great physical disability and destroyed joints if children are not treated properly. In addition, there are still many unknowns about the safety of new treatments for juvenile idiopathic arthritis (JIA) and the long-term outcomes of patients. Funding from the Arthritis Foundation for the Childhood Arthritis & Rheumatology Alliance (CARRA) is helping provide answers to those questions.

"CARRA is developing a large-scale registry of children and adolescents with rheumatic diseases that will give us basic, but essential, information about these diseases, such as the number of children with a given diagnosis, ages of the patients when they were diagnosed, complications of the diseases and the medications used to treat them," says Dr. Kimura. The children enrolled in the CARRA registry will be followed into adulthood to better understand their long-term outcomes.

"The FDA recently reported a possible increased risk of some forms of cancer in JIA patients taking anti-TNF medications [but we haven't established a cause and effect] because we don't know what the underlying chances are of any child with JIA developing cancer regardless of the medications they are exposed to. It is possible that having arthritis itself, like rheumatoid arthritis in adults, increases cancer risk in JIA patients," says Dr. Kimura.

So far CARRA has enrolled more than 4,000 patients in 60 registry sites around the country. "The goal is to enroll as many patients as possible into the CARRA registry in order to gather important epidemiologic information about these diseases. Only then will we be able to answer some of these critical questions," says Dr. Kimura.

Another problem that researchers are trying to solve is how to tell which patients are cured of their arthritis once disease progression is halted. "We don't know yet how to predict which patients are truly cured and can safely stop their medications and which patients are likely to relapse and so shouldn't stop their medications," says Dr. Kimura. "There is an ongoing study in a number of sites in which blood samples are being collected prior to stopping the patients' medications. Through this research, we hope to find that answer."

While curing JIA for every patient isn't on the near horizon, says Dr. Kimura, it's an area of intense research. "If we can identify what actually causes JIA, then a cure will not be far behind. We have made huge advances in JIA treatment and greatly improved the quality of life for many children with JIA but right now the medications we have don't cure the disease. They are able to stop the inflammatory process very effectively, which is so incredibly important, but for now that often means that the patient has to stay on the medication in order for the disease to be in remission. Our ultimate goal is to find a cure: a way to make the disease stay in remission without having to take anything."

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