

Bulletin Board

Two biologicals prove successful for systemic juvenile idiopathic arthritis in Phase III trials

Clinical trials of two new biologicals, tocilizumab and canakinumab, have shown the drugs could potentially be used in the treatment of systemic juvenile idiopathic arthritis (JIA). The trials, published in the *New England Journal of Medicine*, demonstrated that both drugs improved clinical response and resulted in a reduced need for treatment with glucocorticoids in patients with systemic JIA.

Nocolino Ruperto was the lead investigator on the two randomized trials of canakinumab, and a coauthor on the paper describing the randomized trial of tocilizumab. Dr Ruperto from the Pediatric Rheumatology Department at the Istituto G Gaslini in Genova (Italy) and senior scientist at the Pediatric Rheumatology International Trials Organization said, "Systemic [JIA] is a form of severe arthritis that, until [a] few years ago, was treated mainly with corticosteroids, with the known side effects, especially growth impairment. The availability of both [tocilizumab and canakinumab] will give new possibilities for the treatment of these children," Dr Ruperto said.

The tocilizumab trial involved 112 children aged 2–17 years. The patients were randomly assigned to either tocilizumab or placebo given every 2 weeks for 12 weeks, followed by an open-label extension study. A total of 85% of the tocilizumab group reached the primary end point of adapted JIA ACR 30 response (no fever and a 30% or greater improvement in the ACR core set for JIA, with no more than one variable worsening by more than 30%; $p < 0.001$) compared with 24% of the placebo group.

This improvement was seen to continue and at week 52 an improvement of at least 70% with no fever was seen in 80% of patients receiving tocilizumab. In addition,

48% of patients receiving tocilizumab no longer had any joints with active arthritis and 52% had discontinued the use of glucocorticoids at 52 weeks.

The first of the trials of canakinumab involved 84 patients with active systemic JIA who were randomly assigned to a single subcutaneous dose of the drug or placebo. Of those treated with canakinumab, 84% reached the primary outcome of adapted JIA ACR 30 response compared with only 10% of the placebo group ($p < 0.001$).

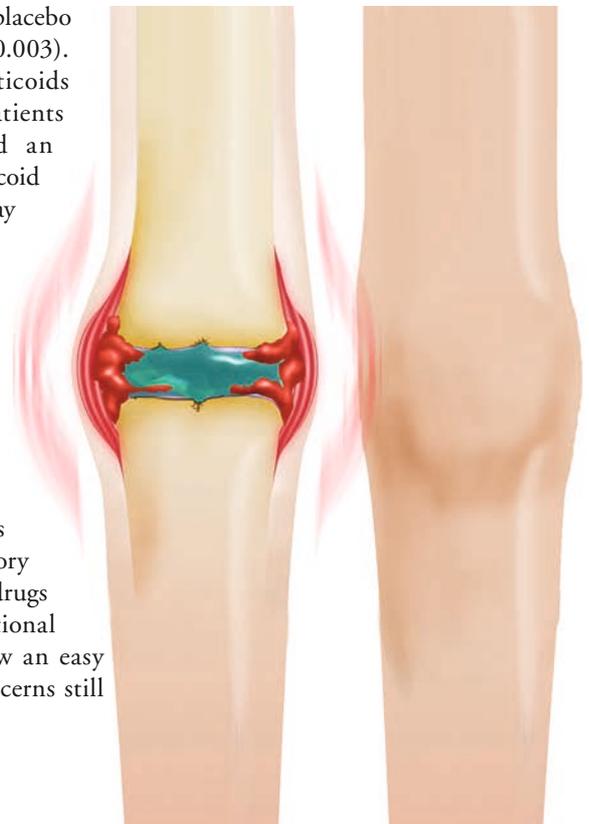
The second trial of canakinumab was a 32-week open-label study, following which responders were tapered off glucocorticoids and randomly assigned to receive continued canakinumab or placebo. Of the 100 patients who underwent randomization, 74% had no JIA flares – the primary outcome – compared with 25% in the placebo group (hazard ratio: 0.36; $p = 0.003$). Discontinuation of glucocorticoids was seen in one-third of patients receiving canakinumab and an average reduction in glucocorticoid dose from 0.34 to 0.05 mg/kg/day was observed.

Dr Ruperto said "The studies confirmed preliminary findings about the potential effectiveness of these new drugs. Currently, tocilizumab is already approved for use in children by both the US FDA and the [EMA], while canakinumab is still under evaluation by regulatory authorities. It is likely that both drugs will be widely used if the national reimbursement rules will allow an easy prescription of the drugs. Concerns still remain about costs."

– Written by Sarah Jones

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Sources: De Benedetti F, Brunner HI, Ruperto N *et al.* Randomized trial of tocilizumab in systemic juvenile idiopathic arthritis. *N. Engl. J. Med.* 367, 2385–2395 (2012); Ruperto N, Brunner HI, Quartier

P *et al.* Two randomized trials of canakinumab in systemic juvenile idiopathic arthritis. *N. Engl. J. Med.* 367, 2396–2406 (2012); Sandborg C, Mellins ED. A new era in the treatment of systemic juvenile

idiopathic arthritis. *N. Engl. J. Med.* 367, 2439–2440 (2012); Medscape medical news—systemic JIA: 2 biologicals succeed in Phase III trials: www.medscape.com/viewarticle/776492

Arthritis research breakthrough made

A better understanding of a common form of arthritis may now be possible thanks to a breakthrough made by researchers at Western University (Ontario, Canada).

Diffuse idiopathic skeletal hyperostosis (DISH) affects between 6 and 12% of North Americans, usually those over 50 years, and is the second most common form of arthritis after osteoarthritis, according to the Arthritis Society. DISH, which is characterized by the formation of excessive mineral deposits along the sides of the vertebrae in the neck and back, is classified as a form of degenerative arthritis. Spine pain and stiffness are common symptoms with difficulty swallowing and damage to spinal nerves seen in advanced cases. There are no specific treatments for DISH and the cause is, as yet, unknown.

Research published online in the *Journal of Bone and Mineral Research* from Western University's Bone and Joint Initiative (Ontario, Canada), with collaborator Doo-Sup Choi at the Mayo

Clinic in Rochester (MN, USA) describes the discovery of the first ever mouse model of the disease.

“...adenosine may be involved in causing the abnormal mineralization seen in diffuse idiopathic skeletal hyperostosis.”

Corresponding author Cheryle Séguin from the Skeletal Biology Laboratories and the Department of Physiology and Pharmacology at Western's Schulich School of Medicine & Dentistry said, “This model will allow us for the first time to uncover the mechanisms underlying DISH and related disorders. Knowledge of these mechanisms will ultimately allow us to test novel pharmacological treatments to reverse or slow the development of DISH in humans.”

It was observed by graduate student Derek Bone, under the supervision of pharmacologist James Hammond, that genetically modified mice that lacked a specific membrane protein that transports adenosine developed abnormal calcification (mineralization) of spinal structures.

An interdisciplinary team characterized changes in the backbone of these mice. The observed spinal mineralization was found to resemble DISH in humans. These findings suggest that adenosine may be involved in causing the abnormal mineralization seen in DISH.

– Written by Sarah Jones

Source: Western University researchers make breakthrough in arthritis research: www.eurekalert.org/pub_releases/2012-12/uowo-wur120312.php

New study of the genetics of gout sheds light on the ‘disease of kings’

Scientists have provided an insight into why some people are more susceptible to gout than others. The main cause of the disease is increased levels of uric acid in the blood and a new study has identified 18 genetic variations involved in this process. The main symptoms of the disease, once called the ‘disease of kings’, are caused by high levels of uric acid, which leads to the formation of small crystals in joints and tissues, resulting in pain and swelling.

Gout, which affects up to 2% of the world's population, is the most common form of inflammatory arthritis. There is a potential to improve treatment and prevention of the disease if we can come to understand how these common genetic

variants increase levels of uric acid in the blood. Research in this area could also lead to the development of urate-lowering drugs.

According to the international team of researchers who carried out the study, including scientists from the University of Edinburgh (Edinburgh, UK) and Queen Mary, University of London (London, UK), levels of gout are increasing in the developed world. An aging population and increasing levels of obesity are probably partly to blame for this.

At least one in 70 adults in the UK are affected by gout, with approximately 900,000 people suffering an attack of the disease in their lifetime.

The genetic data of more than 140,000 people from more than 70 individual studies from Europe, the USA, Japan and Australia were analyzed by researchers, and this represents the largest study worldwide on this area. The work is published in *Nature Genetics*.

Dr Veronique Vitart, from the Medical Research Council Human Genetics Unit at the University of Edinburgh, and one of the lead authors of the study said: “Abnormal levels of uric acid have been associated with various common diseases and conditions, but causal relationships are not always clear. Gaining insight into the genetic components of uric acid levels offers a very useful tool to tackle these

issues and to further our understanding of these conditions.”

Professor Mark Caulfield, from the William Harvey Research Institute at Queen Mary, and a lead author said: “Existing therapies to avoid attacks of gout sometimes cause side effects.

Our findings identify new potential mechanisms for gout and offer opportunities for new therapies that may improve prevention of this debilitating condition in the future.”

– Written by Sarah Jones

Sources: Köttgen A, Albrecht E, Teumer A *et al.* Genome-wide association analyses identify 18 new loci associated with serum urate concentrations. *Nat. Genet.* doi:10.1038/ng.2500 (2012) (Epub ahead of print); ScienceDaily®. Gout Study Offers Genetic Insight Into ‘Disease of Kings’: www.sciencedaily.com/releases/2012/12/121223152730.htm

Rituximab could combat noncriteria manifestations of antiphospholipid syndrome

New research suggests that clinical problems that are unresponsive to anticoagulation therapy could be relieved by rituximab in antiphospholipid antibody-positive patients.

Antiphospholipid syndrome (APS), which can be associated with systemic lupus erythematosus, is a life-threatening condition that can cause venous thrombosis, arterial thrombosis and fetal loss. APS is quite common in antiphospholipid antibody (aPL)-positive individuals, as they have an increased production of proteins responsible for the formation of clots. Other symptoms of APS, including cognitive dysfunction, skin ulcers and kidney disease, are classified as noncriteria manifestations of APS.

Previous research had shown that aPLs are secreted by B cells, and that APS could be prevented from developing if B cells were eliminated. Rituximab, which has already been approved for the treatment of leukemia and rheumatoid arthritis, is able to destroy B cells. “The idea is if you kill the inflammatory B cells, they cannot secrete antiphospholipid antibodies that cause problems,” explained author of the study Doruk Erkan, a rheumatologist at the Hospital for Special Surgery (NY, USA). Case reports have also supported the theory that APS may respond to rituximab.

Researchers at the Hospital for Special Surgery carried out a Phase II pilot trial in 19 aPL-positive patients with noncriteria manifestations of APS. Investigators measured aPL profiles and clinical outcomes monthly up to 6 months after treatment with rituximab. Improved outcomes were noted in several patients at completion of the study. Four out of five patients with cognitive dysfunction had at least partial response, similarly, three out of five patients with skin ulcers had complete responses and one patient has a partial response. However, none of the patients with cardiac valve disease demonstrated a response.

“Researchers are hopeful that rituximab will be a viable option to treat some, if not all, noncriteria antiphospholipid syndrome manifestations.”

Interestingly, the aPL antibody profiles of the patients did not change during the study. The reason for this may be due to the fact that B cells are active in many

intricate ways in the immune system, including helping other inflammatory cells. Therefore, the B cells may be acting through other channels to dampen down the effect of aPLs.

Researchers are hopeful that rituximab will be a viable option to treat some, if not all, noncriteria APS manifestations. Their next step will be to predict the response and identify which patients will respond to rituximab.

– Written by Sophie Breeze

Sources: Erkan D, Vega J, Ramon G, Kozora E, Lockshin MD. A pilot open label Phase II trial of rituximab for non-criteria manifestations of antiphospholipid syndrome. *Arthritis Rheum.* doi:10.1002/art.37759 (2012) (Epub ahead of print); Erkan D, Vega J, Ramon G, Kozora E, Lockshin MD. A pilot open label Phase II trial of rituximab for non-criteria manifestations of antiphospholipid syndrome. *Arthritis Rheum.* doi:10.1002/art.37759 (2012) (Epub ahead of print); Hospital for Special Surgery press release: www.hss.edu/newsroom_rituximab-shows-promise-antiphospholipid-antibodies.asp

About the Bulletin Board

The Bulletin Board highlights some of the most important events and research in the field of rheumatology. If you have newsworthy information, please contact:

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