The autoimmune disorder juvenile rheumatoid arthritis may be effectively treated with the TNF inhibitor adalimumab

Adalimumab may be effective treatment for juvenile rheumatoid arthritis, report suggests

Results from a new study suggest that adalimumab may be an effective treatment for children suffering from juvenile rheumatoid arthritis. Juvenile rheumatoid arthritis, also known as juvenile idiopathic arthritis, is the most common form of arthritis affecting children. It is an autoimmune disorder characterized by joint swelling, stiffness and occasionally reduced motion. As the tumor necrosis factor has been shown to have a pathogenic function in juvenile rheumatoid arthritis, the researchers assessed the effectiveness and safety of adalimumab, a TNF inhibitor derived from a fully human monoclonal antibody, in children.

The study included 171 patients aged 4–17 years suffering from active juvenile rheumatoid arthritis. All of the patients had been prescribed nonsteroidal anti-inflammatory drugs previously. After stratifying the patients according to methotrexate use, they were given 24 mg of adalimumab (brand name Humira®) per square meter of body surface area subcutaneously every other week for a total of 16 weeks. At this point, patients with an American College of Rheumatology Pediatric 30% (ACR Pedi 30) response were randomized to receive either adalimumab or placebo in a double-blind manner every alternate week for up to 32 weeks. This response measure is an indication of the improvement in symptoms of the patient.

In the group not receiving methotrexate, 74% of the patients were found to have an ACR Pedi 30 response at week 16, whereas in the group who had been treated with methotrexate, 94% had an ACR Pedi 30 response at this time point. The patients who had an ACR Pedi 30 response were the ones who had shown an improvement in the symptoms and were eligible for the next phase of the study. The researchers found that amongst the patients who did not receive methotrexate, 43% of those treated with adalimumab and 71% of those given placebo reported disease flares. The latter was the main outcome measure of the study. In the other group consisting of the methotrexate-treated patients, 37% of those treated with adalimumab experienced disease flares, as did 65% of those given placebo. These results were statistically significant.

After 48 weeks of treatment, the scientists found that the percentages of patients amongst the methotrexate-treated group, who had an improvement in their symptoms (as indicated by the ACR Pedi 30, 50 or 70 responses) were significantly greater for those treated with adalimumab compared with those receiving placebo. The differences between those receiving adalimumab and those receiving placebo in the group of non-methotrexate-treated patients were not statistically significant. The response rates were maintained for 104 weeks of treatment. A total of 14 serious adverse events, out of which half were serious infections, that could be related to adalimumab were reported in the study.

Owing to insufficient sample size and duration, the researchers could not establish the risks for rare adverse events. In addition, they were also unable to identify differences between patients treated with methotrexate and those not receiving it due to insufficient power of the study.

"Adalimumab, alone or in combination with methotrexate, appears to be an efficacious option for the treatment of children with polyarticular juvenile rheumatoid arthritis. Responses were sustained through two years of continued treatment," the authors stated.

Source: Lovell DJ, Ruperto N, Goodman S et al.*; Pediatric Rheumatology Collaborative Study Group; Pediatric Rheumatology International Trials Organisation: Adalimumab with or without methotrexate in juvenile rheumatoid arthritis.* N. Engl. J. Med. *359(8), 810–820 (2008).*

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Neuroblastoma: first example of pediatric cancer oncogene found

Scientists at the Children's Hospital of Philadelphia, USA, have discovered the group of genetic mutations responsible for the development of the inherited aggressive childhood cancer neuroblastoma. The mutations have also been implicated in the high-risk form of sporadic neuroblastoma, the most common type of the disease. Germline mutations in the anaplastic lymphoma kinase (*ALK*) gene were detected in several cases of familial neuroblastoma under investigation at the Children's Hospital, with researchers drawing on data accumulated worldwide. This current study also represents the first account of a childhood cancer caused by oncogenic mutations, and helps to further establish ALK as a crucial neuroblastoma oncogene.

"This discovery enables us to offer the first genetic tests to families affected by the inherited form of this disease," said pediatric oncologist Dr Yael P Mossé, of The Children's Hospital of Philadelphia, PA, USA, the first author of the study. "Furthermore, because there are already drugs in development that target the same gene in adult cancers, we can soon begin testing those drugs in children with neuroblastoma."

Neuroblastoma is the most common solid tumor of early childhood, accounting for approximately 8% of all childhood cancers, but is, however, responsible for 15% of all cancer deaths in children owing to the aggressive nature of the disease.

The current study performed a genome-wide scan of DNA samples from 20 families with familial neuroblastoma, with the initial identification of a significant predisposition locus at chromosome bands 2p23–24. Further investigation of that region on chromosome 2 revealed three separate germline missense aberrations in the tyrosine kinase domain of the *ALK* gene common to eight of the families under observation.

Next, the researchers focused on whether *ALK* mutations could be somatically acquired in the more common occurrence of noninherited neuroblastoma. Tumor samples from 194 high-risk cases of the sporadic form of the disease were analyzed, and *ALK* mutations were found in over 12% of cases.

These discoveries thus offer amenable therapeutic drug targets for the inhibition of tumors, and several pharmaceutical companies are currently developing *ALK* inhibitors, with one already undergoing early-phase adult clinical trials.

Source: Mossé YP, Laudenslager M, Longo L et al.*: Identification of* ALK *as a major familial neuroblastoma predisposition gene.* Nature *doi:10.1038/nature07261 (Epub ahead of print) (2008).*

About the Bulletin Board

The Bulletin Board highlights some of the most important events and research in medicine.

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New research suggests that use of antipsychotic drugs is associated with a higher risk of stroke

A recent study from the London School of Hygiene and Tropical Medicine, UK, has investigated the association between the use of typical and atypical antipsychotic drugs and the incidence of stroke in patients with and without dementia. Published in the *British Medical Journal*, the results suggest that all antipsychotics are associated with an increased risk of stroke, and that the risk may be higher in patients receiving atypical antipsychotics compared with those receiving typical antipsychotics. In addition, people with dementia appear to be at a higher risk of an associated stroke compared with those without dementia.

Participants included in the study were identified with the use of UK-based electronic primary care records of more than 6 million patients from over 400 general practice clinics. A total of 6790 patients (905 of whom had received an atypical antipsychotic) with a recorded incident stroke and at least one prescription for any antipsychotic drug before the end of 2002 were included in the analysis. At the time of first drug exposure, the median patient age was 80 years and 64% were women.

The results demonstrated that use of any antipsychotic drug was associated with a rate ratio for stroke of 1.73. In addition, the rate ratio for stroke among patients taking typical antipsychotics was 1.69 compared with 2.32 among patients taking atypical antipsychotics. In patients receiving any antipsychotic drug, the rate ratios were 3.50 for those with dementia compared with 1.41 for those without dementia

"This implies that the use of antipsychotics might be acceptable in elderly patients without dementia, although as with all treatment choices, a wider consideration of all potential risks and benefits would need to be taken into account," comment the researchers.

Source: Douglas IJ, Smeeth L: Exposure to antipsychotics and risk of stroke: self controlled case series study. Br. Med. J. *(2008) (Epub ahead of print).*

Approved antihistamine may be used to treat Alzheimer's disease

Dimebon, a drug once approved as an antihistamine in Russia, has now been shown to improve cognitive decline in patients with Alzheimer's disease. Lead author of the study, Dr Rachelle Doody, professor of neurology at the Baylor College of Medicine in Houston, TX, USA, is encouraged by the results.

The study, which was conducted at 11 sites in Russia, enrolled 183 patients with mild-to-moderate Alzheimer's disease. Patients were randomized to receive either oral dimebon, 20 mg twice-daily or placebo. The effects of dimebon were analyzed over a 12-month period, where patient progress was assessed on five different outcomes: thinking and memory ability, overall function, psychiatric and behavioral symptoms, and ability to perform daily activities. During this time, the researchers observed a continued improvement in patients. "What we saw in the clinical trial is that people on the medication continued to improve over time. Those on placebo continued to decline", said Doody. "Usually at this point in a drug's development, we are happy to see improvement in one of the outcome measures, we saw improvement in all five."

The data suggests that dimebon is safe, well-tolerated and has caused significant improvements in the clinical course of patients suffering from mild-to-moderate Alzheimer's disease. Currently, the safety, tolerability and efficacy of dimebon is being evaluated in an ongoing Phase III study in several international locations, including the USA.

"As we continue research, we hope to replicate these results," Doody said. "My belief is that this drug will turn out to be useful for Alzheimer's disease, regardless of the stage of the disease."

Source: Doody RS, Gavrilova SI, Sano M et al.*: Effect of dimebon on cognition, activities of daily living, behaviour, and global function in patients with mild-to-moderate Alzheimer's disease: a randomised, double-blind, placebo-controlled study.* Lancet *372(9634), 207–215 (2008).*

The careHPV test shows promise as a primary screening method for cervical cancer prevention in low-resource regions

A new rapid screening test for the human papillomavirus (HPV), created for use in developing countries, has been tested recently on a group of local women in the Shanxi province in eastern China and has been shown to be 90% accurate in detecting precancerous cervical disease.

The test in question is called the careHPV, and was designed by Attila Lorincz, a Professor of Molecular Epidemiology at Barts and The London School of Medicine and Dentistry, UK. It can be used to carry out screening in rural areas by personnel with minimal training. The test is able to detect 14 high-risk types of carcinogenic HPV and it can be performed in approximately 2.5 h.

Countries in the developed world have the necessary infrastructure to provide cytologic screening, which has led to a 50–80% decrease in mortality. However, to date it has been difficult to use cytologic screening in low-resource settings; there have been problems with taking smears and analyzing them correctly.

Research into the development of a rapid, simple and cheap HPV DNA screening test that could be used in rural and low-resource regions was carried out in collaboration with the Program for Appropriate Technologies in Health (PATH, Seattle WA, USA) and funded by the Bill and Melinda Gates Foundation.

> *"The new test needs to be studied in many countries to confirm its suitability for cervical cancer screening on the global stage."*

The test is modified from the Hybrid Capture test, the gold-standard routine HPV DNA test, which was created by Lorincz for use in developed countries. It is a signal amplification assay that can be performed in a small bench-top work space. There is no requirement for mains electricity or running water. The short assay time of approximately 2.5 h allows testing and clinical follow-up on the same day.

Using the prototype careHPV test, a total of 2388 women between the ages of 30 and 54 years, from the Shanxi province in China, were screened. The sensitivity of the test to detect precancerous cells was found to be 90%. "The clinical performance of my new HPV test in China appears promising – it is based on decades of research and I hope it will be employed widely to save the lives of millions of women. The new test needs to be studied in many countries to confirm its suitability for cervical cancer screening on the global stage," commented Lorincz.

Source: Qiao YL, Sellors JW, Eder PS et al.*: A new HPV-DNA test for cervical-cancer screening in developing regions: a cross-sectional study of clinical accuracy in rural China.* Lancet Oncol. *(2008) (Epub ahead of print).*

Recent drug approvals

Trade name	Generic name	Indication	Region	Manufacturer	Date approved
Oncology					
Aloxi®	Palonosetron hydrochloride	Chemotherapy-induced nausea and vomiting	USA	Helsinn Healthcare	August 2008
Sancuso®	Granisetron	Prevention of nausea and vomiting in patients receiving moderately and/or highly emetogenic chemotherapy regimens of up to 5 consecutive days duration.	USA	Strakan International, Ltd.	September 2008
Velcade®	Bortezomib	Previously untreated multiple myeloma	EU	Janssen-Cilag/Ortho Biotech	September 2008
Ontak®	Denileukin diftitox	Cutaneous T-cell lymphoma	USA	Eisai Corporation	October 2008
Ceplene®	Histamine dihydrochloride	Adults with acute myeloid leukemia	EU	EpiCept Corp	October 2008
Neurology					
Cymbalta®	Duloxetine	Generalized anxiety disorder	EU	Eli Lilly (USA) and Boehringer Ingelheim (Germany)	August 2008
Xenazine®	Tetrabenazine	Huntington's chorea	USA	Prestwick Pharmaceuticals, Inc.	August 2008
KEPPRA XR™	Levetiracetam	Partial onset seizures in patients 16 years of age and older with epilepsy	USA	UCB INC	September 2008
Vimpat®	Lacosamide	Partial-onset seizures with or without secondary generalization in patients with epilepsy aged 16 years and older	EU	UCB	September 2008
Vimpat®	Lacosamide	Add-on therapy for the treatment of partial-onset seizures in people with epilepsy who are 17 years and older	USA	UCB	October 2008
Seroquel XR®	Quetiapine fumarate	Treatment of both depressive and manic episodes associated with bipolar disorder	USA	AstraZeneca	October 2008
Cardiology					
Tracleer®	Bosentan	Mildly symptomatic pulmonary arterial hypertension	EU	Actelion Ltd	August 2008
Cleviprex™	Clevidipine Butyrate	Mild-to-moderate hypertension	USA	The Medicines Company	August 2008
Hematology					
Nplate™	Romiplostim	Treatment of thrombocytopenia in patients with chronic immune (idiopathic) thrombocytopenic purpura	USA	Amgen Inc	August 2008
Kogenate®	Antihemophilic factor (recombinant)	Routine prophylaxis in children with hemophilia A	FDA	Bayer HealthCare	October 2008
Xarelto®	Rivaroxaban	Prevention of venous blood clots in adults undergoing elective hip or knee-replacement surgery.	EU	Bayer	October 2008
Infectious disease					
Cefepime in plastic container	Cefepime hydrochloride	Pneumonia; empiric therapy for febrile neutropenic patients; uncomplicated and complicated urinary tract infections; uncomplicated skin and skin structure infections; and complicated intra-abdominal infections	USA	Baxter Healthcare Corporation	August 2008

Recent drug approvals

Trade name	Generic name	Indication	Region	Manufacturer	Date approved
Intelence™	Etravirine	HIV-1	EU	Tibotec Pharmaceuticals, Ltd; Janssen-Cilag International NV	September 2008
Prezista®	Darunavir	Expanded indication for once-daily dosing as part of HIV combination therapy in treatment-naïve adults	USA	Tibotec Pharmaceuticals	October 2008
Endocrinology & metabolism					
Novolog® mix 50/50	Insulin aspart protamine recombinant; insulin aspart recombinant	Control of hyperglycemia in patients with diabetes mellitus	USA	Novo Nordisk Inc.	August 2008
Apidra®	Insulin glulisine injection	Improve glycemic control in children (4 years and older) with diabetes mellitus	USA	Sanofi-aventis	October 2008
Diagnostics					
Adreview™	Iobenguane I 123	Detection of primary or metastatic pheochromocytoma or neuroblastoma as an adjunct to other diagnostic tests	USA	GE Healthcare	September 2008
AK-FLUOR® 10%	Fluorescein sodium	Diagnostic fluorescein angiography or angioscopy of the retina and iris vasculature	USA	Akorn Inc.	August 2008
AK-FLUOR® 25%	Fluorescein sodium	Diagnostic fluorescein angiography or angioscopy of the retina and iris vasculature	USA	Akorn Inc.	August 2008
Urology					
Rapaflo™	Silodosin	Treatment of enlarged prostate	USA	Watson Pharmaceuticals	October 2008
Other					
Cinryze™	C1 Inhibitor (human)	Adolescent and adult patients with hereditary angioedema	FDA	Lev Pharmaceuticals, Inc.	October 2008
	Pirfenidone	Idiopathic pulmonary fibrosis	Japan	InterMune, Inc	October 2008
Vaprisol® premixed in 5% dextrose	Conivaptan hydrochloride injection	Euvolemic and hypervolemic hyponatremia in hospitalized patients	USA	Astellas Pharma US, Inc	October 2008
Alli®	Orlistat 60 mg	Obesity	EU	GlaxoSmithKline	October 2008
Akten™ gel 3.5%	Lidocaine hydrochloride ophthalmic gel	Ocular surface anesthesia during ophthalmologic procedures	USA	Akorn Inc.	October 2008
Astepro® nasal spray	Azelastine hydrochloride	Relief of symptoms of seasonal allergic rhinitis in patients 12 years of age and older	USA	MedPointe Pharmaceuticals	October 2008
LoSeasonique®	Levonorgestrel/ethinyl estradiol tablets 0.10/0.02 mg and ethinyl estradiol tablets 0.01 mg	Oral contraceptive for the prevention of pregnancy	USA	Barr Pharmaceuticals, Inc.	October 2008