

Bulletin Board

Scientists demonstrate validity of novel rheumatoid arthritis blood test

A research team from the University of Alabama at Birmingham (AL, USA) has recently published work describing the validation of a new blood test that may be useful in tracking the progression of rheumatoid arthritis (RA) disease activity. The team's work, published in *Arthritis Care and Research*, discusses the validity of the test, which uses 12 RA biomarkers to monitor disease progression.

The test, named Vectra DA (Crescendo Bioscience, CA, USA), is a multibiomarker disease activity (MBDA) test that measures joint inflammation by looking at 12 cytokine markers for RA. The biomarkers included in the test were selected from a panel of 396 potential markers; the team developed an algorithm weighing the significance of the different markers to produce a composite score to be used in the assessment of RA. The score produced by the MBDA test was found to have a strong correlation with Disease Activity Score 28 (DAS28)-CRP score, a commonly used score in the analysis of RA in clinical trials, in both seropositive and seronegative patients. Following the divisions of the data in subgroups based on the variables age, sex, BMI and treatment, the MBDA score was found to be associated with DAS28-CRP in most of the seronegative subgroups and all of the seropositive subgroups. Also, improvements in the DAS28-CRP at 6–12 weeks in response to treatment with anti-TNF or methotrexate were detectable using MBDA.

"The team's work ... discusses the validity of the test, which uses 12 rheumatoid arthritis biomarkers to monitor disease progression."

In their study, the researchers analysed serum samples from 512 patients selected from the InFoRM, BRASS and Leiden Early Arthritis Clinic cohorts.

Commenting on the need for new diagnostic tools for assessing RA, lead author of the study Jeffrey Curtis said, "Previously, the disease activity of RA was assessed through clinical observation by a physician, noting the number of tender and swollen joints and assessing pain and functional abilities ... This blood test measures the underlying amount of RA activity within the joints using sophisticated biochemical means intended to reflect the underlying pathophysiology of the disease. A highly reproducible, easily standardized blood test that measures multiple biologic pathways to augment a physician's and patient's clinical assessment has not been previously available to physicians."

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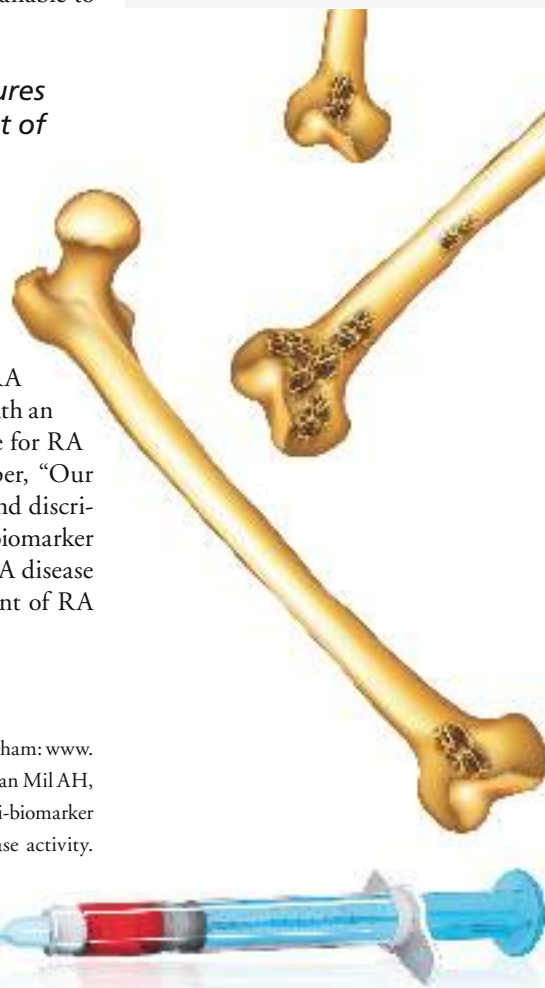
The researchers are optimistic that their MBDA score can act as a complimentary tool for RA practitioners and provide them with an objective and consistent measure for RA disease, concluding in their paper, "Our findings establish the criterion and discriminant validity of a novel multi-biomarker test as an objective measure of RA disease activity to aid in the management of RA patients."

– Written by Sean Fitzpatrick

Sources: University of Alabama at Birmingham: www.uab.edu/news; Curtis JR, van der Helm-van Mil AH, Knevel R *et al.* Validation of a novel multi-biomarker test to assess rheumatoid arthritis disease activity. *Arthritis Care Res.* doi:10.1002/acr.21767 (2012) (Epub ahead of print).

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Open-label Phase II trial of ozoralizumab produces promising results

Pharmaceutical company Ablynx (Ghent, Belgium) have recently announced that it has obtained positive results in ongoing Phase II trials of the company's anti-TNF- α nanobody ozoralizumab treating RA patients that are experiencing insufficient response to treatment with methotrexate. The results are from a 48-week open-label extension of the international and Japanese Phase II trials.

In total, 266 patients (85%) from the Phase II trials continued into the open-label portion of the study. Initially, all patients had an 8–12-week washout period, with no study drug; following this, the open-label participants received ozoralizumab 10 mg via subcutaneous injection every 4 weeks of the trial extension in addition to methotrexate. The extension study lasted 48 weeks in total and dose escalation was permitted at the treating physician's discretion up to a maximum of 80 mg every 4 weeks.

Of the 266 patients, 86% completed the study; of these, 56% were receiving 80 mg of ozoralizumab after the 48 weeks, with 29% receiving 30 mg and 15% of participants receiving the initial 10-mg dose.

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Infection was the adverse event experienced by study participants most frequently and of these, three events per 100 patient-years were found to be serious,

comparable to rates found with other TNF- α drugs.

Commenting on the new data, Edwin Moses, Chairman and CEO of Ablynx, said, “We always believed in this program and now the data from this long-term study have even positively surprised us. We now have extensive efficacy data that are potentially as good, if not better, than other commercially available anti-TNF- α products ... and, in terms of immunogenicity, an unexpected and potentially major advantage over Humira[®], the world's biggest selling anti-TNF- α and any of its biosimilar competitors that may be launched in the future. We believe that we now have the components of a much stronger and differentiating licensing package than we had previously.”

– Written by Sean Fitzpatrick

Source: Ablynx press release: www.ablynx.com/en/news-press/press-releases

An epigenetic cause of osteoarthritis has been discovered

A new epigenetic cause of the degenerative joint disease osteoarthritis may have been discovered. Osteoarthritis is caused by the cleavage of type II collagen within the matrix by MMP13. As we have an aging population this disease is becoming more of a social and economic problem. Published recently in the *FASEB* journal a team of investigators led by David A Young (Musculoskeletal Research Group, Newcastle University, Newcastle, UK) used human tissue samples to assess the methylation status of the *MMP13* promoter and explored the epigenetic nature of the disease.

The investigators used cartilage from patients with osteoarthritis and from healthy controls who were at a similar age. They found that at the -104 CpG promoter site of the *MMP13* gene there was more demethylation in osteoarthritis tissue samples than in normal cartilage,

which correlated with an increase in *MMP13* expression. They then also found that treatment with the cellular transcription factor CREB increased the demethylation of the -104 CpG sites, increasing *MMP13* expression and causing cartilage destruction.

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Using chromatin immunoprecipitation they then confirmed that CREB was the regulatory factor that binds to the *MMP13* promoter when -104 CpG is demethylated,

causing MMP13 to increase. These findings provide a novel link between epigenetic status and arthritic disease. It is hoped that this research can be valuable to future therapeutics discovery in this disease. Speaking about the research Young said: “Our work provides a better understanding of the events that cause cartilage damage during osteoarthritis and provides hope that tailored drug development to prevent the progress of disease will improve the quality of life and mobility of many arthritis sufferers.”

– Written by Claire Attwood

Source: Bui C, Barter MJ, Scott JL *et al.* cAMP response element-binding (CREB) recruitment following a specific CpG demethylation leads to the elevated expression of the matrix metalloproteinase 13 in human articular chondrocytes and osteoarthritis. *FASEB J.* 26(7), 3000–3011 (2012).

Call for osteoporosis screening in men

In recently published guidelines The Endocrine Society along with the American College of Preventive Medicine and the National Osteoporosis Foundation recommend that screening for osteoporosis in men aged 70 years and older would be beneficial.

The guidelines published in the June issue of the *Journal of Clinical Endocrinology and Metabolism* were put together by a committee who evaluated systematic evidence reviews. The Grading of Recommendations, Assessment, Development and Evaluation (GRADE) system was used to describe the strength of recommendations and the evidence quality.

In a new set of clinical guidelines, the society recommends dual-energy x-ray absorptiometry imaging for men aged

70 years and older, as well as for those aged 50–69 years who are considered to have certain risk factors including, but not limited to, history of fracture after the age of 50 years, hypogonadism, hyperthyroidism, chronic obstructive pulmonary disease or history of smoking.

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The authors of the paper recommend that scans to check the spine and hip should be carried out every 1–2 years. They suggested that men with or at risk for osteoporosis should get 1000–1200 mg

of calcium each day, either from dietary sources or supplements. Vitamin D supplements were suggested for those with blood 25(OH)d levels under 30 ng/ml. Exercise, smoking cessation and low alcohol intake could also be beneficial.

Although the US Preventive Services Task Force recommends osteoporosis screening for women aged 65 years and older and younger women with risk factors, it has deemed the evidence for screening in men to be insufficient.

– Written by Laura McGuinness

Source: Watts NB, Adler RA, Bilezikian JP *et al.* Osteoporosis in men: an endocrine society clinical practice guideline. *J. Clin. Endocrinol. Metab.* 97(6), 1802–1822 (2012).

Some inflammatory rheumatic disease treatments could increase the patient’s risk of shingles, study suggests

Anti-TNF medications used to treat inflammatory rheumatic disease could be linked with a 75% greater risk of developing herpes zoster, also known as shingles. Both herpes zoster and rheumatic conditions are more common in the elderly population, so geriatricians should be aware of the supposed link.

A study recently presented at the 2012 Annual European Congress of Rheumatology compared patients taking anti-TNF medications for inflammatory rheumatic disease to those with traditional disease modifying anti-rheumatic drugs.

“Anti-TNFs, such as infliximab, adalimumab and etanercept, have become the treatment of choice for patients with inflammatory rheumatic diseases who are uncontrolled on traditional disease-modifying antirheumatic drugs, but it is known that a side effect of these drugs is an increased risk of bacterial infections,” explained the lead author of the story, Helene Che, from Lapeyronie Hospital (France). “This

systematic review and meta-analysis demonstrates that careful monitoring of patients treated with anti-TNFs is required for early signs and symptoms of herpes zoster and raises the issue as to when vaccination against the virus should occur.”

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The meta-analysis included a total follow-up of 124,966 patient-years across five registries. The study authors conducted a literature search in Medline, Embase, the Cochrane library and abstracts from the ACR and European League Against Rheumatism congresses from 2006 to 2010, specifically selecting studies that reported

the respective incidences of herpes infection in anti-TNF and conventional disease modifying anti-rheumatic drug-treated patients. Any incidences of severe herpetic infections, such as multidermatomal lesions, requiring hospitalization or intravenous treatment, were not included in the study.

Herpes zoster, also known as shingles, is a painful, blistering skin rash caused by the varicella-zoster virus. Symptoms include, amongst others, one-sided pain, tingling or burning followed by a rash of small blisters. Shingles is usually treated with antiviral medications to reduce pain and complications, and corticosteroids to reduce swelling.

– Written by Laura McGuinness

Sources: EULAR 2012: www.eular.org/index.cfm?framePage=/congress_home.cfm; Anti-TNFs For Inflammatory Rheumatic Diseases Can Increase The risk of shingles by up to 75 percent: www.medicalnewstoday.com/releases/246330.php

Baricitinib effective in Phase IIb study in treatment of rheumatoid arthritis

Late breaking results presented at the European League Against Rheumatism's Annual European Congress of Rheumatology have demonstrated a positive benefit for Lilly's investigational oral JAK inhibitor baricitinib in the treatment of RA. The Phase IIb trial was a randomized double-blind, placebo-controlled, dose-ranging study that enrolled 301 patients with active RA, receiving stable doses of methotrexate. Patients were randomized to receive 1, 2, 4 or 8 mg of baricitinib, or placebo for a 12-week period. The trial's primary end point was achieved, with a statistically significant difference in American College of Rheumatology 20 (ACR20) response being found; 76% of patients who were randomized to receive 4 or 8 mg of baricitinib had ACR20 response at 3 months, with only 41% of patients that received

placebo experiencing ACR20 response ($p < 0.001$).

Discussing the need for new RA treatments, Edward Keystone (University of Toronto, Canada) and lead author of the study, said, "The JAK1/JAK2 signaling pathway has been shown to be important in the pathobiology of RA and no other JAK1/JAK2 inhibitor treatments have yet been approved for the treatment of RA ... There is still a large proportion of patients who have inadequate responses to currently approved treatments for RA and baricitinib could represent a new, viable treatment option for this group of patients. The results of this study would suggest that the compound appears worthy of future Phase III investigation."

Statistically significant differences were found in study end points as early as 2 weeks into the trial, and were maintained to the 12-week time point.

Adverse events were mild across all of the study groups; the most common side effect experienced was infections, experienced in 12% of the placebo group and in 14% of the 4- and 8-mg treatment groups.

The baricitinib Phase IIb trial has multiple stages and, following on from the positive results of the study, patients are continuing to participate in the open-label long-term extension of the trial.

– Written by Sean Fitzpatrick

Sources: Lilly news: <http://newsroom.lilly.com>; EULAR abstract LB0005: 12-Week results of a Phase IIb dose-ranging study of LY3009104 (INCB028050), an oral JAK1/JAK2 inhibitor, in combination with traditional DMARDs in patients with rheumatoid arthritis. Presented at: *Annual Congress of the European League Against Rheumatism*. Berlin, Germany, 6–9 June 2012.

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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