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# The EULAR 2014 Report



## The EULAR 2014 Report

Analysis of Key Research  
Presented at the 15th Annual  
European Congress of Rheumatology

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MEDICAL COMMUNICATIONS

## Welcome to the EULAR 2014 Report

The Annual European Congress of Rheumatology, hosted by the European League Against Rheumatism (EULAR), once again showed why it is recognized as the primary platform for European rheumatology education and information exchange in the world. More than 14,000 attendees from 130 countries came to this year's EULAR Congress in Paris to hear the best in rheumatology research and clinical advances. The scientific program contained presentations selected from 4,041 abstracts submitted.

The EULAR 2014 Report brings you highlights of some of the best presentations, focusing on the sort of clinical and therapeutical findings that change the way rheumatologists practice medicine. We hope that you will enjoy these accounts of the latest in rheumatology clinical and translational research.

Many of the research reports that you will find here also include access to video interviews with the presenters.

For details about the EULAR Congress, please visit [www.eular.org](http://www.eular.org).  
Best wishes and see you again next June in Rome for EULAR 2015!



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# Annual European Congress of Rheumatology

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# Proposed PMR Guidelines Aim to Standardize Therapy

BY MICHELE G. SULLIVAN

**N**ew international guidelines for polymyalgia rheumatica will focus on standardizing treatment practice across specialties.

When adopted, the proposed guidelines will succeed those published by the British Society of Rheumatology in 2009, according to Dr. Bhaskar Dasgupta, a primary author of the new guidelines and leader of the study group.

“This is the first transatlantic EULAR-ACR [European League Against Rheumatism–American College of Rheumatology] guideline in rheumatology,” he said at the Congress. “It is very patient centered and was developed with patient input.”

There has been a great need for a document such as this, he said. Primary care physicians are almost always on the front line of diagnosing polymyalgia rheumatica and often the first to treat these patients – with variable success, said Dr. Dasgupta, head of the Southend Hospital rheumatology department, Essex, England.

“This disorder is as common as – or more common than – rheumatoid arthritis, with a very high prevalence and incidence,” he said. “It’s often diagnosed by general practitioners, with patients referred to nonrheumatologists. Yet there is a very wide variation in practice and a lot of uncertainty in the diagnosis. We are concerned that we have handed this over to primary care physicians when it needs so much clinical acumen to tease this out from other conditions.”

The guidelines were developed using GRADE (Grading of Recommendations Assessment, Development and Evaluation) methodology and involved appraisal of 445 relevant publications in polymyalgia rheumatica (PMR), published since 1970. The document was reviewed on several occasions by an international panel that included 51 investigators from the United States and represented countries in Western and



Click [here](#) to view a video interview with Dr. Bhaskar Dasgupta.

Eastern Europe, as well as Australia, New Zealand, Brazil, South America, Japan, and India. All recommendations were adopted unanimously without the need to vote, according to Dr. Dasgupta.

According to the proposed document, most patients are diagnosed and treated in primary care settings, but there are no well-elucidated referral algorithms for referral to specialty care. This can contribute to variability in treatment.

For instance, “a proportion of PMR patients do not adequately respond to glucocorticoid therapy and suffer frequent relapses and dependency on long-term high doses,” according to the guidelines. “Prolonged glucocorticoid therapy is associated with considerable side effects especially when high doses are employed.” Dr. Dasgupta said the proposed guidelines address groups that are at especially high risk for these problems. “While effective, steroids have the potential to cause serious side effects,” he said. “It is important to know how to use them correctly in PMR. The subgroups that are vulnerable to side effects – such as patients with diabetes, hypertension, osteoporosis, and glaucoma, and high

disease activity should be recognized – [as should those of] female sex and those with peripheral arthritis or high inflammatory markers.”

The guidelines are structured as a treatment algorithm, which begins with accurate diagnosis and patient assessment. They recommend that most patients be started on oral prednisone at the equivalent of 12.5-25 mg/day, or if the patient is at high risk of steroid-related side effects, to begin with intramuscular glucocorticoids.

If there is inadequate response, the guidelines recommend an increase in glucocorticoid dose or methotrexate for those at high risk of side effects, relapse, or prolonged therapy.

If there is improvement within 4 weeks, consider a gradual tapering of steroids. If not, a confirmation of the diagnosis is in order, the guidelines note. Patients who respond well to the taper will likely go into remission and may continue the taper. Patients who relapse should have a diagnostic confirmation and/or specialist referral.

“Ultimately, in order to be accepted, the guidelines will require confirma-

*Continued on following page*



# Biosimilars Match Infliximab, Etanercept for RA Treatment

BY MITCHEL L. ZOLER

**T**wo different biosimilar drugs, one a mimic of infliximab, the other modeled on etanercept, closely matched the efficacy and safety of their brand-name counterparts in a pair of separate, randomized, controlled studies.

In one study, treatment with infliximab and a biosimilar agent showed virtually identical efficacy and safety performance at several time points during the first 16 weeks of treatment of 189 patients with rheumatoid arthritis in a head-to-head, randomized comparison done at 23 centers in India.

In the second study, an agent produced to match etanercept showed very similar efficacy and safety to the branded formulation in a total of 233 randomized patients treated for 24 weeks at several centers in Korea.

The study run in India was the “first clinical trial of a biosimilar infliximab to demonstrate and report kinetics of response to treatment at multiple time points prior to the plateau phase,” which starts at about week 16, Dr. Jonathan Kay said at the Congress. It provides “convincing evidence of therapeutic equivalence,” and also serves as a “new paradigm for comparative effectiveness testing of biosimilars,” said Dr. Kay, a professor of medicine at the University of Massachusetts in Worcester.

Dr. Kay and his colleagues randomized 62 patients with active rheu-

matoid arthritis (RA) on stable doses of methotrexate to infliximab and 127 patients to BOW015, the biosimilar under study. They measured the proportion of responders at 2, 6, 14, and 16 weeks, with the study’s primary



DR. JONATHAN KAY



DR. SANG-CHEOL BAE

endpoint the percentage of patients showing an American College of Rheumatology 20 (ACR20) response at 16 weeks. The proportion of responders at each of these four time points was virtually identical, Dr. Kay reported. At 16 weeks, the percent of ACR20 responders was 86% in the infliximab arm and 90% in the biosimilar arm. The percent of ACR50 and ACR70 responders was also virtually the same in both treatment arms at 16 weeks, and the percent of ACR20 responders was virtually identical in the two treatment arms at weeks 2, 6, and 14.

The safety profiles of the two drugs also showed no statistically significant differences for any parameter measured except for the incidence of skin disorders, which occurred in one patient treated with the biosimilar and

four patients treated with infliximab, a statistically significant difference.

At the same session, Dr. Sang-Cheol Bae of the Hanyang University Hospital for Rheumatic Diseases, Seoul, South Korea, presented findings from a randomized, controlled trial that compared the etanercept biosimilar HD203 with etanercept. Dr. Bae and his colleagues randomized 115 patients with active rheumatoid arthritis to HD203 and 118 patients to etanercept, both in combination with methotrexate, with the primary endpoint set as the proportion of patients achieving ACR20 by week 24. No statistically significant differences were seen between the patient groups for this

primary endpoint, and equivalence in efficacy was demonstrated within predefined margins. The percent of ACR20 responders at 24 weeks was 79% in the biosimilar arm and 76% with etanercept.

Secondary analyses showed that the ACR50 responses occurred in 65% of the patients on the biosimilar at 24 weeks and in 53% of patients on etanercept, a statistically significant difference; and after 48 weeks of treatment, the ACR50 rate was 68% in the biosimilar arm and 55% with etanercept, also a statistically significant difference. The two study groups showed no significant difference in the rate of ACR70 responders after 24 or 48 weeks, and also no statistically significant difference in the rate of ACR20 responders after 48 weeks.

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tion of their usefulness in clinical practice. PMR recommendations endorsed by both the ACR and EULAR would have a significant impact on clinical decision making, would reduce practice variation, and would stimulate further research in areas

where there is currently lack of adequate evidence.”

In addition, he said, the role for early methotrexate in treatment of the condition is now emerging and will be included in the guidelines for consideration in special subgroups.

The guidelines must still be ratified by both the ACR and EULAR. Once

that happens, they will be simultaneously published in both associations’ journals – no later than mid-2015, Dr. Dasgupta said.

Dr. Dasgupta disclosed that he has helped design clinical trials for a number of drug companies and has received remuneration for educational symposia from others.

# Systemic Lupus Erythematosus Patients In Remission Safely Stop Immunotherapy

BY MITCHEL L. ZOLER

**W**hen patients with lupus who were in remission on an immunosuppressant drug and a low dosage of prednisone stopped their immunosuppressant, 70% remained flare free 2 years off immunosuppressant treatment, in a review of 99 patients treated at one Canadian center.

Half of the patients were able to remain flare free off immunosuppressant treatment for at least 3 years, and patients who reached 3 years off treatment without flaring tended to remain stable, with a very low flare rate during 2 additional years of follow-up, Dr. Zahi Touma reported at the Congress.

The results “confirm that stopping immunosuppressants is possible in a selected group of lupus patients,” Dr. Touma said in an interview. “Patients in clinical remission for at least 1 year and off corticosteroids or on small doses of 7.5 mg/day or less are appropriate candidates” for attempting to taper down and eventually withdraw immunosuppressant treatment, said Dr. Touma of the division of rheumatology at the University of Toronto.

“There are no guidelines on how or when to taper and stop immunosuppressants in lupus patients. At present, it is all individual physician preference. In the Toronto Lupus Clinic, in patients with clinically inactive lupus, we first aim to stop corticosteroids or reach a dose of no more than 7.5 mg/day before tapering immunosuppressants.

“Both physician and patient should agree on immunosuppressant withdrawal and discuss the possible consequences of this approach. In our study, among the 99 patients studied, 25 flared within 2 years, and 17 patients experienced a flare after year 2.”

When a flare occurs in these patients, they usually restart standard of



Click [here](#) to view a video interview with Dr. Zahi Touma.

MITCHEL L. ZOLER/FRONTLINE MEDICAL NEWS

care treatment, with a cortico-steroid or an immunosuppressant or both. The new study did not follow outcomes in patients who flared and then restarted standard treatment, but Dr. Touma noted that “in our clinical practice, we have witnessed patients who achieved remission after flaring, although this has not been specifically addressed in this study.” He also was not sure how often patients in routine community practice who meet these criteria attempt to taper down and withdraw immunosuppressant treatment because of the lack of evidence supporting this approach.

The results also showed that a more gradual tapering down of the immunosuppressant dosage linked with a more durable remission once patients were completely off the immunosuppressant. “We have shown that the rate of flare after stopping immunosuppressants was lower in the group of patients who tapered gradually versus faster,” Dr. Touma said. “In our center, we aim to taper by 25% from the baseline dose of immunosuppressant in stages, reducing by 25% every 3-6 months so that complete withdrawal is accom-

plished over 1-2 years.”

The review included 1,678 patients with lupus seen at the Toronto Lupus Clinic, of whom 973 ever received immunosuppressant drug treatment, and 99 of whom reached remission while on a prednisone dosage of 7.5 mg/day or less and also had no proteinuria or lupus-related thrombocytopenia or leucopenia.

More than half of those 99 patients had been maintained on azathioprine prior to stopping their immunosuppressant drug, with smaller numbers of patients maintained on either methotrexate or mycophenolate mofetil.

After 2 years, 25 of the 99 patients had flared, which worked out to a 30% flare rate in a Kaplan-Meier analysis. In the same analysis, 46% of patients flared after 3 years off treatment, and 51% by 5 years off treatment. Patients who were serologically active at the time they stopped immunosuppressant therapy were more likely to flare, but Dr. Touma did not suggest using this as a criterion to select patients to withdraw from treatment.

Dr. Touma said that he had no disclosures.

# Physically Demanding Jobs Link to Worse Ankylosing Spondylitis Progression

BY MITCHEL L. ZOLER

**P**atients with ankylosing spondylitis who worked at more physically demanding jobs showed greater radiographic progression than did patients who performed more sedentary jobs in a prospective cohort study with 136 patients.

The findings immediately raised questions about “our commonly given advice to patients with spondylarthritis to strenuously exercise. Should physically demanding labor be discouraged?” Dr. Sofia Ramiro asked at the Congress.

Dr. Ramiro stressed that the find-

Ramiro, a researcher at the Amsterdam Rheumatology Center, University of Amsterdam.

“I’m not saying that we would stop recommending exercise and that patients with AS should stay quiet at home, but perhaps we will advise against certain types of exercise,” Dr. Ramiro said in an interview.

Dr. Ramiro and her associates previously reported this year that disease activity contributed longitudinally to radiographic AS progression during up to 12 years of follow-up (*Ann. Rheum. Dis.* 2014 [doi:10.1136/annrheum-



Physically demanding jobs had significant indirect effects on radiographic progression.

ing needs confirmation from studies in other cohorts of patients with ankylosing spondylitis (AS), but it raises the possibility that certain stresses and loads on the spine, from work or exercise, can worsen disease severity.

“If we can confirm that mechanical stress has an impact on radiographic progression, then I think we would have to analyze further and identify the type of activity having this impact, and then recommend the activity not be done,” said Dr.

dis-2014-205178]). They further evaluated patients in the same cohort, 184 AS patients enrolled in OASIS (the Outcome in AS International Study), for additional factors that might affect radiographic progression either directly or indirectly. In addition to documenting a link between disease activity and radiographic progression, the report earlier this year had identified sex and disease duration as modifiers of the

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## VIEW ON THE NEWS

### Tailor Findings to Patients' Options

**T**he relationships reported in this study between both job type and smoking and more extensive radiographic progression in patients with ankylosing spondylitis are probably true. This is not the first study of patients with ankylosing spondylitis to produce results



that show these relationships, and the job-related effect is consistent with animal models of AS and the impact of chronic mechanical stress on progression.

Pain and other symptoms of AS improve with activity, but the findings by Dr. Ramiro and her colleagues as well as by others suggest that certain types of activity can worsen progression.

How this may apply to managing patients depends on the magnitude of the effect, and what options a patient might have. Many patients do not have a real choice about the work they do.

In addition, we continue to advise patients to do what we consider therapeutic exercises, ideally 20-30 minutes daily. It is possible that therapeutic exercises could counterbalance the bad effects from work-related mechanical stress.

*Dr. Martin Rudwaleit is a professor of rheumatology and nephrology at the Endokrinologikum in Berlin. He said that he has been a consultant to and has received honoraria from nine drug companies. He made these comments in an interview.*



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impact of disease activity. This impact on radiographic progression was greater in men, and early during the course of AS.

The new analysis looked for possible effects from smoking, and for chronic activity patterns using the surrogate marker of job type. The 184 patients in OASIS were sorted by their type of regular work, which identified 65 people with physically demanding (blue collar) jobs and 71 with relatively sedentary (white collar) jobs. The other 48 patients had either missing employment data or jobs with less clear links to activity levels, such as students or homemakers.

The findings showed that neither smoking nor job type appeared to

have a direct influence on radiographic progression, but that smoking and a physically demanding job each had significant indirect effects. A physically demanding job linked with a 1.19-U increase in a measure of radiographic progression (the modified Stoke AS Spine Score, or mSASSS) for every 1-U increase in a measure of disease activity (the AS Disease Activity Score, or ASDAS) during 2 years of follow-up, Dr. Ramiro reported. In contrast, the impact of a sedentary job was a 0.20-U rise in mSASSS for each 1-U rise in ASDAS. Smoking produced a 1.95-U rise in the mSASSS for each 1-U rise in ASDAS, significantly more than the 0.35 rate among nonsmokers.

Personal income, family income, and education each showed no statistically significant link with radio-

graphic progression.

When the investigators analyzed job activity in subgroups divided by sex, they found that the relationship between a more physically demanding job and increased radiographic progression remained statistically significant in men, but the relationship was no longer significant in women.

The researchers could not include leisure activity or sports participation in their analysis as these data were not available. In addition, analysis by leisure activity may pose problems because baseline data on leisure activity may not extrapolate long-term, and patients can also have recall bias when reporting leisure activity, Dr. Ramiro said.

Dr. Ramiro said that she had no disclosures.

## Treat to Target Shows Durable Improvements in Psoriatic Arthritis

BY JENNIE SMITH

**T**hanks to anti-tumor necrosis factor inhibitors and other highly effective biologic therapies, rheumatologists are increasingly embracing treat to target, a strategy in which patients are closely monitored and medications adjusted until a patient has the least disease activity possible.

Ample evidence from randomized, controlled trials has shown treat to target – sometimes referred to as tight control – to result in better outcomes than standard therapy in rheumatoid arthritis patients.

But in psoriatic arthritis (PsA), a more heterogeneous disorder with skin and nail manifestations as well as joint and connective tissue involvement, remission has historically been less well defined. Only in recent years have endpoints been developed and validated for minimal disease activity in PsA, and evidence in support of a treat-to-target approach is now slowly trickling in.

At the Congress, Dr. Arthur Kavanaugh of the University of California, San Diego, presented results from a



**The study provides some evidence that treat to target could well be a valuable goal for PsA, Dr. Arthur Kavanaugh said.**

5-year extension of a randomized, controlled trial of golimumab in patients with PsA that showed better long-term outcomes in those able to achieve minimal disease activity (MDA) through a treat-to-target strategy.

“I think [the study] does provide some evidence suggesting that treat to target could well be a valuable goal for PsA,” Dr. Kavanaugh said. “Right

now, RA has the advantage of more studies showing this.”

The study by Dr. Kavanaugh and his colleagues used data from an open-label extension of a clinical trial in which about 400 patients were randomized to receive golimumab at 50 mg or 100 mg, or placebo; all placebo patients were crossed over to golimumab treatment at 24 weeks and during the long-term, open-label extension of the trial, were followed for as long as 252 weeks. Patients were assessed at 14, 24, and 52 weeks, then yearly until week 252. The investigators used a validated composite endpoint that included measures of skin, joint, and enthesitis involvement.

About half of the patients (44.2% of those randomized to placebo and 51.7% of those randomized to active treatment) achieved persistent MDA over three or more consecutive time points during follow-up, and investigators saw significantly better clinically meaningful Health Assessment Questionnaire improvement and less radiographic progression in patients

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# EULAR Releases Its First-Ever Spondyloarthritis Imaging Guidelines

BY JENNIE SMITH

**R**apid advances in imaging, combined with a new emphasis on early diagnosis and treatment, have led to the need for evidence-based guidelines for imaging in axial and peripheral spondyloarthritis, or SpA.

New EULAR guidelines address which imaging modalities best visualize each pathological element in SpA. The recommendations, 10 in all, put forward certain modalities as optimal in diagnosis; in monitoring and predicting outcomes; and in assessing spinal fractures and osteoporosis, which are commonly seen in SpA.

“This is the first time that we’ve tied together evidence to substantiate how to use imaging if you want to diagnose and monitor axial and peripheral SpA,” said Dr. Lene Terslev and Dr. Peter Mandl, who formulated the recommendations along with other key members of the EULAR task force group on imaging in SpA.

The 21-member EULAR task force, which included rheumatologists and radiologists, based the recommendations on an extensive literature review and expert opinion.

The guidelines, which are the first to deal with the entire SpA group of diseases, are intended to be useful to rheumatologists, radiologists, and general practitioners in daily clinical practice, Dr. Terslev and Dr. Mandl said at the Congress.

Indeed, Dr. Mandl, of the Medical University of Vienna, said that the task force worked “to be as encompassing as possible to try and look at the whole scope of the disease and what it means in clinical practice.” This also meant, he said, taking into consideration the resources available in clinical settings. Cost and availability concerns were among the reasons that the task force opted to preserve x-rays in several diagnostic and monitoring scenarios.



DR. LENE TERSLEV



DR. PETER MANDL

The guidelines emphasize MRI as an alternative to radiography in diagnosing axial SpA. “We’re still considering x-rays as the first imaging method to be used for the detection of sacroiliitis,” Dr. Mandl said. “But in certain cases, such as in young patients or patients in whom symptom duration is very short, MRI is an alternative. It is important to emphasize, however, that if the diagnosis of axial SpA cannot be established based on clinical features and x-ray, and axial SpA is still

suspected, MRI of the SI [sacroiliac] joints is recommended.”

MRI is also recommended for monitoring axial SpA beyond the structural changes that can be picked up on x-ray. “MRI inflammatory activity has been reported to be a predictor of a good clinical response in axial SpA,” added Dr. Mandl. X-rays can also help predict disease progression: “We have very strong evidence for the presence of initial radiographic changes predicting severe outcome,” he said.

In peripheral SpA, the guidelines highlight ultrasound and MRI for supporting the diagnosis by detecting enthesitis and other possible peripheral pathologies, such as tenosynovitis and arthritis. Both imaging modalities may be used for monitoring disease activity, especially arthritis and enthesitis, but no added value was found for the use of ultrasound contrast medium, said Dr. Terslev of Copenhagen University Hospital, Glostrup, Denmark.

The task force generally had more and better evidence for its axial SpA recommendations than for its peripheral SpA recommendations, Dr. Mandl said. X-ray, MRI, ultrasound, and, to a lesser extent, CT are the main modalities featured in the recommendations, as the researchers found only little evidence supporting the role of other modalities in the management of either axial or peripheral SpA.

Dr. Terslev and Dr. Mandl declared that they had no conflicts of interest.

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who had achieved MDA, regardless of treatment allocation.

Patients who achieved MDA after crossing over had improvements that were similar to those who started on golimumab at baseline, suggesting that delayed treatment initiation does not result in a worsening of physical function or radiographic progression.

“When it comes to patients, we cannot always control when we will see them in the course of disease,” Dr. Kavanaugh said. “These data suggest that even though a patient may show up with months of uncontrolled disease, it is still a viable goal to treat them to try to get MDA.”

Dr. Kavanaugh said that further studies in PsA patients were needed to confirm that treat-to-target strategies

resulted in better long-term disease outcomes. “It would be helpful to have data from studies using medications with other mechanisms of action to support treat to target,” he added.

Dr. Kavanaugh disclosed research and grant support from Abbott, Amgen, Janssen, and UCB. His coauthors on the study disclosed financial support from additional manufacturers, and three were employees of Janssen.

# Gut Cell Migration Implicated in Development of Ankylosing Spondylitis

BY KAREN BLUM

**G**ut-derived innate lymphoid cells are widely found in the peripheral blood, synovial fluid, and inflamed bone marrow of ankylosing spondylitis patients and produce cells that are key in the development of the disease, Italian researchers have found.

Dr. Francesco Ciccia, assistant professor of rheumatology at the University of Palermo, Italy, and his colleagues have worked to better characterize the immunologic origin and behavior of innate lymphoid cells (ILCs) in the gut, synovial fluid, and bone marrow of ankylosing spondylitis (AS) patients. At the Congress, Dr. Ciccia and his associates reported that gut-derived interleukin (IL)-23 receptor-expressing ILCs, which are found widespread in AS patients, produce IL-17 and IL-22, cytokines suggested as key players in the pathogenesis of AS.

The work is important because “understanding the complex interactions between bacteria – genotype – innate immunity occurring in the gut of AS patients may clarify many aspects of the pathogenesis of AS and may offer new therapeutic strategies in the treatment



DR. FRANCESCO CICCIA

of AS,” Dr. Ciccia said in an interview.

The researchers took ileal gut biopsies from 20 HLA-B27-positive AS patients with active axial disease and 15 healthy subjects. The AS patients had a mean Bath Ankylosing Spondylitis Disease Activity Index score of 6.7. They paired samples of peripheral blood and synovial fluid from knee joints of 10 of the AS patients and 10 osteoarthritis patients. They also studied five bone marrow biopsies each from patients with inflamed sacroiliac joints and from patients with suspected monoclonal gammopathy. Additional experiments measured the ILCs’ ability to produce IL-17 and IL-22; studied the presence of a4b7 integrin,

which promotes homing of T cells to intestinal sites, and its counter-receptor MADCAM-1 in ileal and bone marrow samples; looked at the expression of IL-7 and IL-15, which are involved in ILC differentiation, and of IL-17, IL-22, and IL-23p19; analyzed protein expression of IL-17, IL-22, IL-23p19, IL-7, and IL-15; and assessed the tissue distribution of lymphoid tissue inducer (LTi) cells.

The scientists found that type III ILCs expressing IL-23 receptor “were significantly expanded in the gut, synovial

fluid, and bone marrow of AS patients, compared with controls and produced high levels of IL-17 and IL-22.”

Type III ILCs isolated from AS patients’ peripheral blood, synovial fluid, and bone marrow “displayed a significant overexpression of a4b7.” In addition, increased co-expression of MADCAM-1 was seen in both bone marrow and ileal samples, “suggesting the presence of an active recirculation of a4b7-bearing cells between the gut and the inflamed bone marrow of AS patients,” Dr. Ciccia said. Strong expression of both IL-17 and IL-22 also was seen in the bone marrow of AS patients, and IL-7 was significantly increased in the AS patients’ guts, compared with those of controls, especially near Paneth cells lining the small intestine and surrounded by clusters of LTi cells that were demonstrated to be precursors of type III ILC gut cells.

“The increased expression of IL-7 in the AS gut and the presence of clusters of LTi cells close to Paneth cells suggest an important role of innate intestinal immunity in the differentiation of type III ILCs,” Dr. Ciccia said. “The increased intestinal and bone marrow expression of MADCAM-1 occurring in AS also suggests the presence of an active homing axis between the gut and the inflamed sacroiliac joints.”

Dr. Ciccia and his colleagues did not have any relevant disclosures.

## Gut Inflammation Linked to Worsening Spondyloarthritis

BY MITCHEL L. ZOLER

**S**pondyloarthritis patients with microscopic gut inflammation had to start anti-tumor necrosis factor treatment sooner in the course of their disease than patients without gut inflammation in a prospective, observa-

tional study of 63 Belgian patients with the axial form of spondyloarthritis, the peripheral form, or both.

The finding “is in line with the hypothesis that in SpA [spondyloarthritis] gut inflammation may drive disease,” Dr. Heleen Cypers said at the Congress.

SpA patients with microscopic gut inflammation initiated anti-tumor necrosis factor (TNF) therapy roughly twice as quickly as those without gut inflammation at each time period examined – at 6, 12, and 18 months after their initial diagnosis. After 18 months, 56%

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of patients with inflammation were on treatment with an anti-TNF agent, compared with almost 29% of the followed patients without microscopic gut inflammation, said Dr. Cypers, a rheumatologist at Ghent University in Belgium.

The link between microscopic gut inflammation and a faster need to start on biologic treatment occurred at nearly identical rates in the subset of 11 patients with acute gut inflammation and the subset of 21 patients with chronic inflammation.

Previous research by Dr. Cypers' group had shown that chronic inflammation in the gut was associated with more extensive bone marrow edema of the sacroiliac joints, a higher risk of progression to ankylosing spondylitis, and a higher risk of developing Crohn's disease. But no information existed on the impact of gut inflammation on therapeutic decision making in SpA.

The current study followed the

Ghent Inflammatory Arthritis and Spondylitis Cohort (GIANT) of 63 newly diagnosed patients who underwent an ileocolonoscopy at baseline. Patients were not taking anti-TNF agents and were followed for 18 months. Anti-TNF treatment decisions were made by a rheumatologist who was unaware of the patient's gut history.

SpA patients who had microscopic gut inflammation at baseline were more likely to start anti-TNF treatment sooner than were patients without gut inflammation. During follow-up, just under a third of patients (9 of 31) with normal

gut histology started anti-TNFs, compared with over half (18 of 32) of the patients with gut inflammation at baseline.

In most cases, anti-TNF drugs were started because first-line therapy had failed. Dr. Cypers's analysis also showed that initiation of an anti-TNF drug during follow-up was significantly linked with a higher level of C-reactive

protein at baseline. The findings support the hypothesis that bowel inflammation in SpA induces a more chronic, persevering disease, according to Dr. Cypers.

"The findings identify gut inflammation as a marker of a poor prognosis and have relevance for therapeutic decision making in daily clinical practice. It is conceivable that assessment of gut inflammation will be included in future models for risk stratification of SpA," she said in an interview.

The underlying mechanisms explaining the link are still under investigation, but several studies have suggested that inflammation in the gut may be a triggering factor for SpA development. Interactions in the intestinal immune system also may play an important role, she said.

Future research by the group will focus on ruling out the interdependency of all of these factors, predicting response to biologic therapy based on gut histology, and determining whether therapies aimed at treating microscopic gut inflammation can affect the evolution of the disease.

Dr. Cypers said that she and her associates had no disclosures.



DR. HELEEN CYPERS

## Higher Risk of Death Seen With Oral Steroids in RA Interstitial Lung Disease

BY JENNIE SMITH

**T**he use of prednisone for 3 or more months at a time was associated with a significantly elevated risk of death in patients with rheumatoid arthritis and interstitial lung disease in a retrospective cohort study.

Interstitial lung disease is present in about 5% of patients with rheumatoid arthritis. For years, oral steroids were commonly used in patients with the disease, but today's rheumatologists "no longer view oral steroids as optimal treatment in RA-ILD [rheumatoid arthritis-associated interstitial lung disease], and our data now confirm that," said Dr. Clive Kelly of Queen

Elizabeth Hospital in Gateshead, England, senior investigator of the study. He added that clinicians should avoid long-term treatment with steroids in this patient group whenever possible.

Dr. Kelly led the British Rheumatoid Interstitial Lung (BRILL) Network's cohort study of 260 patients with RA-ILD diagnosed over a 25-year period. The BRILL study compared patients with RA-ILD and an equal number of RA controls without lung involvement who were matched for age, sex, and time of diagnosis.

At the Congress, Dr. Kelly reported that steroid-treated RA-ILD patients, who represented nearly 60% of the cohort, had an elevated relative risk of all-cause death, compared with those

who had never been treated with steroids (RR, 1.65; 95% confidence interval, 1.2-2.3;  $P = .002$ ). Although the relative risk of respiratory death was significantly increased for RA-ILD patients, regardless of treatment, when compared with RA patients without ILD, the risk was higher in those who had been on steroids (RR, 2.75; 95% CI, 1.6-4.7;  $P = .0002$ ) than in those who had not received steroids (RR, 2.06; 95% CI, 1.1-3.8;  $P = .02$ ), the investigators found.

The comparison also revealed other important findings related to RA-ILD. Patients with RA-ILD had significantly higher mortality than did those with RA alone. Over the course of the 25-

*Continued on following page*



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year study period, however, mortality progressively improved among the RA-ILD patients, with median age at death rising from 63 to 76 years. This steady improvement, Dr. Kelly said, is partly the result of better and earlier diagnosis of lung involvement.

Also likely affecting the improved mortality seen over the cohort's study period is a change in therapeutic approach. While RA-ILD patients diagnosed in the first half of the study period were likely to have been treated with only prednisone and azathioprine, in the latter half they were more likely to have received cyclophosphamide and methylprednisolone or mycophenolate. Over the last 12 years, more were treated with biologics, and in the final 6 years of the cohort, patients requiring biologics

tended to be treated with rituximab, a B-cell inhibitor, rather than anti-tumor necrosis factor (anti-TNF) agents, the BRILL investigators found.

Mortality was lower among RA-ILD patients treated with mycophenolate than in those treated with other immunosuppressive agents. Among biologic agents used in the cohort, rituximab treatment was associated with improved mortality, but anti-TNF inhibitors were seen to be associated with elevated risk of death.

About 95% of RA-ILD patients are anticyclic citrullinated peptide (anti-CCP) antibody positive, compared with 55%-60% of the RA population as a whole, Dr. Kelly said, "so there's a strong statistical association of seropositivity, and in those who are seropositive, rituximab works well."

The finding that rituximab was associated with improved survival in the

cohort not only has implications for RA-ILD, he said, but also, potentially, for people with idiopathic pulmonary fibrosis (IPF) who are anti-CCP antibody positive. "What [rheumatologists] have, and chest physicians traditionally don't, is access to rituximab and mycophenolate. But these might be worth trying in IPF as well," he said.

Dr. Kelly noted that prospective trials in RA-ILD are beginning to enroll patients with progressive disease to compare azathioprine and mycophenolate, allowing for the use of oral steroids, as well as patients with active RA and ILD to compare anti-TNF inhibitors against rituximab, also allowing oral steroids.

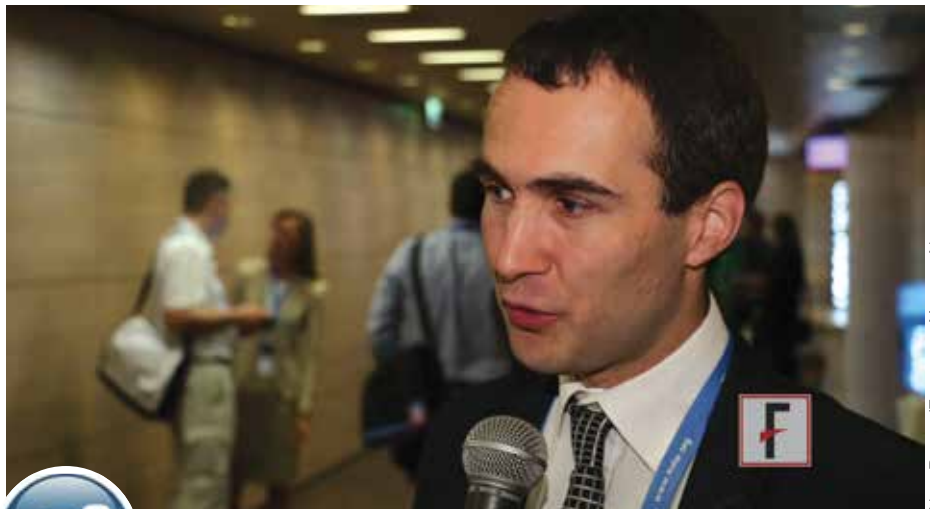
Dr. Kelly reported that he had no conflicts of interest related to his findings and that none of his fellow BRILL investigators had conflicts.

## Gene Profiling Could Signal Start of Personalized Medicine in RA

BY JEFF EVANS

**A** set of genetic polymorphisms is beginning to allow researchers to predict which patients with rheumatoid arthritis will have a severe disease course, as well as determine their response to treatment and risk of death.

Changes in amino acids at positions 71 and 74 of the HLA-DRB1 gene, which are a part of the "shared epitope" that is already known to increase genetic susceptibility for rheumatoid arthritis, as well as a new polymorphism at position 11 of the HLA-DRB1 gene that is outside the shared epitope, are key to this effort. These polymorphisms predicted the radiologic outcome of rheumatoid arthritis patients, response to anti-tumor necrosis factor therapy, and mortality in an analysis of blood samples from three independent multicenter, prospective cohort studies. The three polymorphisms defined 16 haplotypes whose effects on RA susceptibility



Click [here](#) to view a video interview with Dr. Sebastien Viatte.

range from protective to increasing risk and were perfectly correlated with the observed levels of disease susceptibility.

Further studies will be necessary to validate the associations observed with the sets of polymorphisms, said Dr. Sebastien Viatte, first author of the study and a research fellow at the

Centre for Musculoskeletal Research at the University of Manchester in England. Nonetheless, the results are an important step in showing that "genetics can be used to predict disease outcomes and is ... likely to enter the clinic within 5-10 years," he said at the Congress.

# Balance the Risks, Benefits of Systemic Steroids in Rheumatoid Arthritis

BY SHARON WORCESTER

**S**ystemic glucocorticoids have disease-modifying effects and are frequently prescribed for patients with rheumatoid arthritis, but balancing the risks and benefits can be a challenge.

At the Congress, Prof. Johannes W.J. Bijlsma shared recent recommendations from the EULAR Task Force on Glucocorticoid Therapy regarding clinical trials and daily practice.

Registry data from Sweden and Germany suggest that about half of all RA patients use glucocorticoids, and another recent study shows that long-term use of low dosages of glucocorticoids increased 34% between 1990 and 2010, according to Prof. Bijlsma of University Medical Center Utrecht, the Netherlands.

With increasing exposure comes increased risk, however.

Recently reported findings from the RABBIT (RA observation of biologic therapy) study show that the adjusted hazard ratios for death among patients who used glucocorticoids for 12 months increased with the dose. The hazard ratios were 1.05 among those using 1-5 mg/day, 1.46 among those using more than 5-10 mg/day, 2.0 for more than 10-15 mg/day, and 3.59 for more than 15 mg/day (Ann. Rheum. Dis. 2013 Nov. 29 [doi:10.1136/annrheumdis2013-204021]).

To assist clinicians with balancing the risks and benefits, the task force has previously developed evidence-based recommendations on the management of systemic glucocorticoid therapy in rheumatic diseases (Ann. Rheum. Dis. 2007;66:1560-7). The more recent guidelines from the task force are evidence-based and

consensus-based recommendations on the management of medium- to high-dose glucocorticoid therapy in rheumatic diseases (Ann. Rheum. Dis. 2013;72:1905-13).

“These new recommendations are based on the most recent literature, and – in contrast to the first recommendations – also cover the use of higher dosages of glucocorticoids to make them more broadly applicable. The recommendations now cover education and prevention, dosing and risk/benefit ratio, and monitoring,” he said.



PROF. JOHANNES W.J. BIJLSMA

With respect to education and prevention, the task force advises:

► Explaining to patients, family members, and/or caretakers the goals of medium-/high-dose glucocorticoid treatment

and the potential risks associated with such therapy.

► Discussing measures to mitigate such risks, including diet, regular exercise, and awareness of delayed wound healing.

► Providing appropriate preventive/therapeutic interventions to patients with – or at risk of – glucocorticoid-induced osteoporosis.

► Providing appropriate, practical advice to patients and their treatment teams regarding the management of glucocorticoid-induced hypothalamic-pituitary-adrenal axis suppression.

► Providing an accessible resource to promote best practice in the use of medium-/high-dose glucocorticoids to general practitioners.

Recommendations regarding dosing and risk/benefit analysis include:

► Considering comorbidities – such as diabetes, cardiovascular disease, chronic infections, severe immunosuppression, and osteoporosis that may predispose to adverse events prior to starting glucocorticoids

– and maintaining especially tight control in those with such comorbidities.

► Selecting the appropriate starting dose as the expected minimum required to achieve a therapeutic response.

► Constantly reviewing and titrating the dose against therapeutic response and development of adverse effects.

► Considering glucocorticoid sparing therapy in those with anticipated long-term medium-/high-dose therapy.

As for monitoring, the task force recommends that all patients be monitored regularly for frequent, clinically significant adverse effects.

“Based on their individual risk factors, patients should be monitored for diabetes, hypertension, lipids, weight gain, edema, osteoporosis, hidden infections, osteonecrosis, myopathy,

**‘Based on their individual risk factors, patients should be monitored for diabetes, hypertension, lipids, weight gain, edema, osteoporosis, hidden infections, osteonecrosis, myopathy, eye problems, skin problems, and neuropsychological adverse events.’**

eye problems, skin problems, and neuropsychological adverse effects,” according to Prof. Bijlsma.

He noted that many of the adverse effects can be avoided or dealt with when glucocorticoids are used prudently.

Doses of 7.5 or 10 mg/day appear to be best for disease-modifying effects in RA, and duration of therapy should be at least 6 months.

However, optimal choices regarding glucocorticoid use and monitoring for adverse events are patient specific, he said.

Prof. Bijlsma reported having no disclosures.

# RA Patients' Response to Anti-TNFs Might Be Measured in miRNAs

BY MARY JO M. DALES

**M**easures of changes in micro-RNAs during the induction phase of anti-TNF-alpha therapy can be as objective as clinical and inflammatory parameters for monitoring therapeutic response in patients with rheumatoid arthritis, according to Dr. Chary López-Pedraera.

After anti-TNF-alpha treatment, significant changes occur in the serum levels of a number of micro-RNAs (miRNAs) that are associated with autoimmunity, inflammation, cardiovascular disease, and lymphocyte B and T activation, Dr. López-Pedraera, of Reina Sofia Hospital, IMIBIC (Instituto Maimónides de Investigación Biomédica de Córdoba, Spain), reported at the Congress.

Deregulated miRNAs are closely correlated with a positive response to treatment, underlying their potential as biomarkers and novel targets for treatment in patients with RA, she said in an interview.

In a study conducted by Dr. López-Pedraera and her colleagues, responders to anti-TNF-alpha therapy had a stronger increase than did nonresponders in miR-16, miR-23a, miR-125b, miR-126a, miR-146a, and miR-223a.

It is too soon, however, to speculate on the utility of miRNAs for predicting response to therapy, Dr. López-Pedraera said. "Because of the clinical heterogeneity of patients, our data must be confirmed in larger studies. In addition, specific studies on the mechanisms underlying the altered expression of those miRNAs after anti-TNF-alpha treatment, as well as identification of the mechanisms and cellular sources of those extracellular miRNAs, are still required to determine the utility of miRNAs for predicting response to therapy."

For the study, the researchers enrolled 95 RA patients; 54 were treated with infliximab, 25 with etanercept, and 15 with adalimumab. At baseline and after 6 months of therapy, serum samples were analyzed for miRNA in 10 patients, complementary DNA was transcribed and pooled, and treatment response was assessed. With each pool of samples, human serum and plasma miRNA polymerase chain reaction arrays for 84 different miRNAs were performed. Subsequently, a set of selected miRNAs were analyzed

in a validation cohort consisting of miRNA from the sera of all patients in the study. Additionally, inflammatory parameters were examined and correlated, as were clinical and serological variables.

At 6 months of treatment, 86% of patients had responded to the induction therapy and 18% had achieved clinical remission. Irrespective of the agent used, clinically important improvements were noted in all disease parameters examined, including the 28-joint Disease Activity Score

(DAS28), Simple Disease Activity Index, Health Assessment Questionnaire, Visual Analog Scale, erythrocyte sedimentation rate, and C-reactive protein. Similarly, rheumatoid factor and interleukin-6 and -17 levels were reduced.

Of the 10 miRNAs selected for validation, 6 (miR-16, miR-23a, miR-125b, miR-126a, miR-146a, and miR-223a) were significantly up-regulated by treatment.

Dr. López-Pedraera and her colleagues declared having no financial conflicts of interest.



DR. CHARY LÓPEZ-PEDRERA

# JAK3 Inhibitor Decernotinib Boosts Response to Methotrexate in RA

BY MARY JO M. DALES

**D**ecernotinib, a novel selective Janus kinase 3 inhibitor also called VX-509, improved symptoms of rheumatoid arthritis in comparison with placebo when administered in combination with stable background methotrexate therapy in a 24-week study.

The results were noted in a double-blind trial designed to examine

the efficacy and safety of four dosing regimens of decernotinib and placebo in 358 patients who had active RA and were taking stable background methotrexate therapy. Patients were evenly randomized to one of five groups – decernotinib at either 100 mg four times per day, 150 mg four times per day, 200 mg four times per day, or 100 mg twice per day or to placebo.

While the active groups were signif-

icantly better than the placebo group, none of the differences between the active therapy dosing groups were statistically significant. In the placebo and methotrexate group, for example, about 3% of patients achieved an ACR70 and in the active treatment groups 15%-25% of patients achieved an ACR70. In the decernotinib dosing groups, patients reached ACR20 responses in 61%-63%,

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compared with 17% for placebo, and ACR50 responses in 38%-47%, compared with 7% for placebo, Dr. Ronald F. van Vollenhoven, professor and chief of the Unit for Clinical Therapy Research, Inflammatory Diseases (ClinTRID) at the Karolinska Institute, Stockholm, reported at the Congress.

Compared with placebo, decernotinib was associated with small increases in adverse event rates, and serious adverse events occurred in similar proportions of patients receiving decernotinib (7.3%) and placebo (5.6%). However, serious infections

were more common in the active treatment groups (3.5% vs. 1.4%). "We have not yet analyzed for predictors of infections, although I rather suspect these will be similar to the predictors in the general RA population, such as higher age, comorbidities, and concomitant use of corticosteroids," Dr. van Vollenhoven said in an interview.

He noted that the study's sponsor, Vertex, intends to partner on a global basis on the further

development of decernotinib.

Dr. van Vollenhoven disclosed that he receives grants and research support from numerous pharmaceutical companies and is a consultant for Vertex Pharmaceuticals, the maker of decernotinib. His colleague in the study, Dr. Mark C. Genovese, also received research support and is a consultant for Vertex Pharmaceuticals. Their other study colleagues are Vertex employees.



DR. RONALD F. VAN VOLLENHOVEN

## Obesity May Drive Symptom Severity in Rheumatoid Arthritis

BY MARY JO M. DALES

The higher disease activity scores seen in obese patients with rheumatoid arthritis may be driven by the proinflammatory state that is associated with obesity, Dr. Christopher Sparks reported in a press conference at the Congress.

Although obese RA patients tend to have less radiographic joint damage than do normal-weight RA patients, they have comparable DAS (Disease Activity Score) 28. With the clinical focus on treat to target, an approach guided by DAS scores, obese RA patients may be getting more aggressive treatment. The finding may explain why obese patients with RA have better outcomes than normal-weight and thin RA patients, said Dr. Sparks, a clinical research fellow at the University of Liverpool, England.

Dr. Sparks and his colleagues used an international RA database to examine two patient subgroups: those diagnosed with RA in the previous year and those with long-standing RA. The 3,534 patients were stratified by their body mass index into five groups: underweight (less than 18.5 kg/m<sup>2</sup>), normal weight (18.5-24.9 kg/m<sup>2</sup>), overweight (25-29.9

kg/m<sup>2</sup>), obese (30-34.9 kg/m<sup>2</sup>), and obese II (35 kg/m<sup>2</sup> or more). In the 1,981 patients with longstanding disease, median disease duration was about 7 years; the other 1,553

count; and visual analog scale disease activity.

After adjusting for RA risk factors, obesity (BMI of 28 kg/m<sup>2</sup> or greater) was significantly associated with



Click [here](#) to view a video of Dr. Christian Beyer (left) interviewing Dr. Christopher Sparks.

patients had disease duration of 1 year or less.

About 73% of each cohort was female, and the distribution of BMI measures was similar for the two cohorts.

The groups were compared by BMI and RA disease measures that included DAS28, erythrocyte sedimentation rate, tender joint count; swollen joint

a DAS28 exceeding 5.1, an elevated erythrocyte sedimentation rate, high tender joint count, and high visual analog scale score. For instance, compared with normal weight and overweight patients, underweight and both groups of obese patients were 1.5-2.2 times as likely to have a DAS28 exceeding 5.1, Dr. Sparks reported.

He had no financial disclosures.

# International RA Risk Tool for CV Disease Comes Closer to Reality

BY NICOLA GARRETT

**A**n international collaboration of experts has developed a cardiovascular risk calculator specifically for rheumatoid arthritis patients that has the potential to become part of routine rheumatology clinical practice in many parts of the world.

The ATACC-RA (A TransAtlantic Cardiovascular Risk Calculator for Rheumatoid Arthritis) consortium will be constructed from data collected at 13 rheumatology centers in 10 countries, Elke Arts said at the Congress.

The current version, which is still undergoing validation, contains data from eight rheumatology centers in seven countries (Greece, the Netherlands, Norway, South Africa, Sweden, the United Kingdom, and the United States), said Ms. Arts, a rheumatology researcher at Radboud University Medical Centre in Nijmegen, the Netherlands.

So far, ATACC-RA contains pooled data from 3,176 RA patients without cardiovascular disease. Individual data were collected on CV risk factors and outcomes and then combined with RA-specific information, such as disease duration, seropositivity, rheumatoid factor and/or anti-citrullinated protein antibodies, 28-joint Disease Activity Score (DAS28), and acute phase reactants.

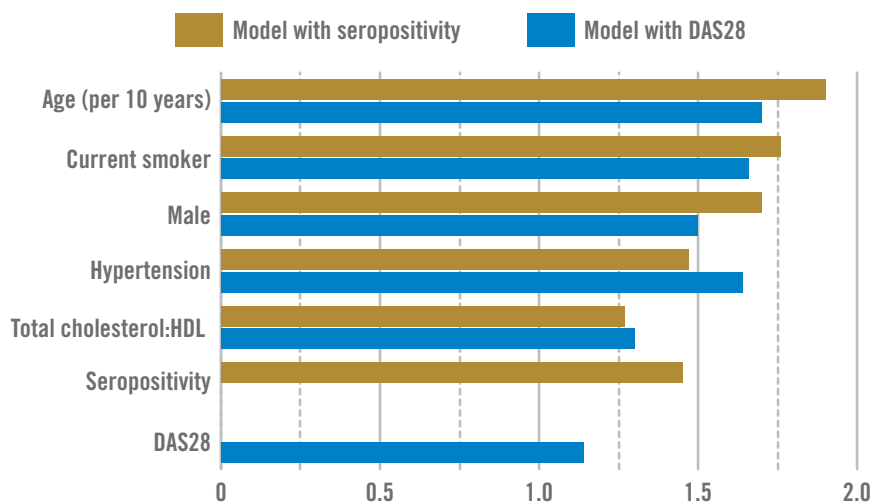
During an average of almost 8 years of follow-up comprising 24,733 patient-years, 314 patients developed cardiovascular disease (CVD).

Two possible models came out of multivariable risk score modeling for predicting the RA-specific 10-year risk of CVD. Each incorporated the traditional risk factors of age, sex, current smoking, presence of hypertension, and ratio of total cholesterol to HDL cholesterol, but also either seropositivity or DAS28. The

consortium specifically chose to assess potential risk factors that would be easily available to the health professional regardless of the setting (for example, primary, secondary, and tertiary care, and even private

dating it in completely independent cohorts. The continued growth of the consortium will help make this a reality within the next couple of years. The end result may be a risk calculator that can be adapted to ac-

## Hazard ratios for ATACC-RA risk models



**Note:** Based on data from 3,176 rheumatoid arthritis patients without cardiovascular disease.

**Source:** Ms. Arts

practice).

The models that included seropositivity or DAS28 both demonstrated good discrimination and calibration, when compared with the Framingham or SCORE (Systematic Coronary Risk Evaluation) algorithms. The models also showed good concordance with each other (see chart).

“By pooling data from many centers, it appears possible to develop an RA-specific CVD risk algorithm which is more accurate at predicting CVD in people with RA than the currently available risk algorithms, which have been developed for the general population,” members of the consortium wrote in response to e-mailed questions.

The consortium is now working to validate the ATACC-RA calculator, with the ultimate aim of vali-

count for the underlying risk of each patient population.

Once the algorithm is validated, the consortium hopes it will become part of routine rheumatology clinical practice, much the same as the Framingham or SCORE algorithms are used currently in the general population, but more specifically applied to patients with RA.

“The models proved to be quite robust,” Ms. Arts said. “If this holds true through the additional analysis and external validation, we may have one that will be applicable to a wide variety of patients all over the world.”

Once fully validated, the investigators plan to produce the tool in a user-friendly application for computers or even smartphones.

The investigators had no conflicts of interest to declare.

# Stem-Cell Transplants Growing Routine For Severe Systemic Sclerosis

BY MITCHEL L. ZOLER

**A**utologous stem-cell transplantation has emerged as an effective and feasible treatment for selected patients with severe systemic sclerosis who inadequately respond to conventional treatments, said two U.S. experts.

In addition, convincing evidence documenting the overall beneficial effect of autologous stem-cell transplantation will soon appear in a published report from the Autologous Stem Cell Transplantation International Scleroderma (ASTIS) trial, Dr. Dinesh Khanna said in a talk at the Congress.

The ASTIS results show that among 79 scleroderma patients randomized to treatment with autologous stem-cell transplant, 8 (10%) died from treatment-related causes, compared with none in the control arm of patients who received conventional treatment with

**'Before and after treatment, patients look completely different. Some patients you can't tell that they had scleroderma. ... There is high mortality early, but if you select patients correctly the benefits will outweigh the risks.'**

cyclophosphamide. But during follow-up, a total of 16 of the 79 (20%) stem-cell transplant patients died, compared with 24 of the 77 (31%) control patients, results that showed an overall mortality benefit from stem-cell transplantation.

The transplanted patients also showed "large improvements" in their skin score and "substantial improvements" in their forced vital capacity and in their activity as measured by the Health Assessment Questionnaire Disability Index (HAQ-DI), noted Dr. Khanna, direc-



DR. DINESH KHANNA



DR. DANIEL FURST

tor of the scleroderma program at the University of Michigan in Ann Arbor.

"Before and after treatment, patients look completely different. Some patients [treated with stem-cell transplants] you can't tell that they had scleroderma. But you need to select the right patients," he cautioned. "There is high mortality early, but if you select patients correctly the benefits will outweigh the risks. This is what we now offer to patients" who don't respond to conventional treatments and are suitable for transplantation, Dr. Khanna said.

Researchers had previously reported these ASTIS results during the EULAR 2012 meeting.

Stem-cell treatment is appropriate for "the 10%-15% of patients with scleroderma who are the worst," commented Dr. Daniel Furst, a professor of rheumatology at the

University of California, Los Angeles. "The next step is to move this treatment from the worst patients to those who are less severe. In some centers in Europe, stem-cell transplantation is becoming widely used, even for patients with only skin symptoms," Dr. Furst said in an interview.

A major attraction of stem-cell transplantation is that over time it produces regression of fibrosis and collagen deposits and healing of prior organ damage. But the treatment also carries the risk of causing substantial immunosuppression while the immune system repopulates, leaving patients vulnerable to infections and other complications.

The upcoming publication of the ASTIS findings should further cement the role of stem-cell transplantation in scleroderma management, but "I'm more of a skeptic. I would like to see it reproduced" in a second trial, Dr. Furst said. Specifically, he means the North American-based Scleroderma: Cyclophosphamide or Transplantation (SCOT) trial now in progress. A positive result in SCOT is still needed to convince many insurers to cover the cost of stem-cell transplantation, Dr. Furst said. For example, when enrolling patients into SCOT, insurers were willing to reimburse the treatment of about a quarter of the patients who otherwise qualified for enrollment, he said.

Dr. Khanna has received research grants from 14 different drug companies. Dr. Furst has been a consultant to or speaker for 11 different drug companies, and has received research grants from 10 different companies.



# FVC Inadequate When Assessing Scleroderma Interstitial Lung Disease

BY MITCHEL L. ZOLER

**T**he traditional way to assess the status of interstitial lung disease in patients with systemic sclerosis, forced vital capacity, may not be the best way, based on a new analysis of 83 patients enrolled in a scleroderma treatment trial.

“A structural, physiologic, and patient-oriented composite outcome may be a more comprehensive measure of treatment response” for patients with systemic sclerosis (SSc) and interstitial lung disease, Dr. Elizabeth Volkmann said at the Congress. “The most robust” association seen in her analysis did not include forced vital capacity (FVC) but instead focused on the Transition Dyspnea Index (TDI), the scleroderma-modified Health Assessment Questionnaire Disability Index (HAQ-DI), and quantitative, serial assessment of high-resolution CT (HRCT) images of the patient’s lungs, said Dr. Volkmann, a rheumatologist at the University of California, Los Angeles.

Although her main goal in this analysis was to identify the best assessment of lung disease in SSc patients enrolled in clinical trials, the findings also have implications for managing patients with SSc, also known as scleroderma, in routine practice, Dr. Volkmann said in an interview.

Many physicians “rely solely on FVC for following patients, and I think this may not be the best measure. Now that we have great imaging options we should use them. And the strongest correlates [in the

new analysis] were with the HAQ-DI, a measure of what patients can do, and the TDI, in which patients say how much their disease has progressed. They are both patient oriented and tell you how the patient is doing,” Dr. Volkmann said.

“The three were more robust and comprehensive than FVC,” which can be influenced by many factors and has a variability of 10%. Dr. Volkmann conceded that the quantitative assessment of annual HRCT scans done in the study is not widely available,

but she said that visual assessment of HRCT scans highly correlates with quantitative assessment and hence likely makes a reasonable substitute.

A senior collaborator on the study, Dr. Daniel Furst, said that in his opinion it was premature to completely abandon FVC for assessing SSc patients, but it was clearly useful to add the two patient-oriented questionnaires and HRCT imaging.

“We haven’t discarded FVC, but we’ve added the other things,” he said in an interview. “Five years ago we only did FVC, 3 years ago we added the scleroderma HAQ-DI” and now he and his associates also use annual HRCT imaging as well as the TDI. The two questionnaires are administered every 3-6 months, said Dr. Furst, professor of rheumatology at the University of California, Los Angeles.

“Using all four of these tools is not being widely done” right now in U.S. rheumatology practice. “I really think it’s a step forward.” However, Dr. Furst also cautioned that for

adoption into routine practice he would like to see evidence documenting that this approach has a positive impact on patient outcomes.

Dr. Volkmann’s analysis involved the 158 U.S. patients enrolled in the first Scleroderma Lung Study, run in 2000-2004 at 13 U.S. centers to compare treatment with oral cyclophosphamide against placebo in patients with active SSc and interstitial lung disease (N. Engl. J. Med. 2006;354:2655-66). Of the 158 patients enrolled, 125 had an HRCT scan at baseline, and among those, 83 also had a HRCT scan after 12 months. These 83 patients formed the basis for Dr. Volkmann’s analysis, including 41 patients randomized to cyclophosphamide treatment and 42 randomized to placebo.

Multivariate analysis identified the HAQ-DI, TDI, FVC, and a quan-

**‘I think [FVC] may not be the best measure. Now that we have great imaging options we should use them. And the strongest correlates ... were with the HAQ-DI, a measure of what patients can do, and the TDI, in which patients say how much their disease has progressed.’**

titative lung fibrosis score derived from analysis of the serial HRCT images as collectively predicting best the outcomes of these patients. A second model that eliminated FVC was “slightly stronger,” and both of these combined assessments were each “more robust than FVC alone,” Dr. Volkmann said.

Dr. Volkmann said that she had no disclosures. Dr. Furst said that he had no relevant disclosures.



DR. ELIZABETH VOLKMANN

# Monitor Patients With Sjögren's Syndrome Closely for Increased MI Risk

BY JEFF EVANS

**P**atients with Sjögren's syndrome appear to have a higher risk of myocardial infarction, but not stroke or transient ischemic attack, than does the general population, based on an analysis of administrative health data from British Columbia.

"Our findings support monitoring for coronary artery disease in addition to management and modification of cardiovascular disease risk factors to reduce the risk of MI in Sjögren's syndrome patients," Dr. Marko Yurkovich said at the Congress.

An increased risk of MI and cerebrovascular accident (CVA) is already well known in more common rheumatic diseases such as rheumatoid arthritis and systemic lupus erythematosus, but the risk for either MI or CVA at the general population level in patients with Sjögren's syndrome remains unknown, said Dr. Yurkovich, an internal medicine resident at the University of British Columbia, Vancouver.

The investigators used administrative health data from all people in British Columbia who had an outpatient visit or hospitalization during 1990-2010 to locate those who were older than 18 years and met the study's criteria for a diagnosis of Sjögren's syndrome. The criteria were two or more ICD-9-CM codes for the disease 2 or more months apart but within a 2-year period that were made by nonrheumatologists or one or more ICD-9-CM codes for the disease that were made by a rheumatologist or during a hospitalization.

The study excluded patients who had diagnoses of other inflammatory arthritides after the Sjögren's diagnosis or cases in which an initial diagnosis of Sjögren's by a nonrheumatologist was not confirmed by a rheumatologist at a later visit. MI and CVA diagnoses were defined from ICD-9-CM codes from hospital or death certificates.

"This diagnostic algorithm has been

validated in a Canadian context and shown to have quite a high specificity and sensitivity, both over 95%," Dr. Yurkovich said.

In 1,176 patients with Sjögren's syndrome, the investigators identified 28 MIs for an incidence rate of 7.7 per 1,000 person-years, compared with 138 MIs in 11,879 control individuals from the general population matched for birth year, sex, and calendar year of exposure. Patients with Sjögren's had a significantly elevated risk for MI, compared with controls, with an incidence rate ratio of 2.19 (95% confidence interval, 1.40-3.31) and a multivariate relative risk of 2.36 (95% CI, 1.48-3.78), based on incidence rates of 7.7 per 1,000 person-years in patients with Sjögren's and 3.4 per 1,000 person-years in controls. The relative risk for MI did not differ when the results were stratified by sex.

However, risk of incident CVA was

**'We found that the risk of MI was even further elevated within 1 year following initial diagnosis,' with an incidence rate ratio of 3.6 before 1 year of follow-up, which decreased to 1.7 during 1-5 years of follow-up and 1.9 after 5 years.**

not significantly higher among patients with Sjögren's than in the controls, based on an incidence rate of 5.1 per 1,000 person-years among patients and 3.4 per 1,000 person-years in controls that yielded an incidence rate ratio of 1.49 and multivariable relative risk of 1.64.

The multivariable analysis controlled for angina, chronic obstructive pulmonary disease, obesity, Charlson

Comorbidity Index, the number of hospitalizations in the year before the index date, and number of medications, including oral glucocorticoids, cardiovascular drugs, antidiabetic medication, hormone replacement therapy, contraceptives, fibrates, statins, NSAIDs, and COX-2 inhibitors.

"We found that the risk of MI was even further elevated within 1 year following initial diagnosis," with an incidence rate ratio of 3.6 before 1 year of follow-up, which decreased to 1.7 during 1-5 years of follow-up and

1.9 and after 5 years, Dr. Yurkovich said. He suggested that the increased risk of MI in the first year might occur because the acute inflammatory state in Sjögren's is highest at the time of diagnosis or because the most susceptible patients had an MI early on and were no longer included in subsequent analyses.

The results remained statistically significant for MI and not for CVA after the investigators performed sensitivity analyses for unmeasured confounding variables using hypothetical low and high prevalences of 10% and 20% and low and high strengths of association in terms of odds ratios (1.3 and 3.0).

Dr. Yurkovich said that the cohort used glucocorticoids at a significantly higher rate than did the control group (20% vs. 4%), perhaps because they were put on them initially around the time of diagnosis, but nevertheless, the medication was one of the variables they adjusted for in the multivariable analysis. He noted that the investigators did not have antiphospholipid antibody data but they hope to obtain those and other autoantibody profiles for subsequent analyses.

Dr. Yurkovich said that he had no disclosures.



DR. MARKO YURKOVICH

# 24-Hour ECG Findings Can Predict Death in Systemic Sclerosis

BY JENNIE SMITH

**H**olter electrocardiogram monitoring in patients with systemic sclerosis who have signs or symptoms of cardiac involvement can identify abnormal heart rhythms and should not be overlooked as a part of screening in such patients, according to Dr. Giacomo De Luca and his colleagues at the Institute of Rheumatology in Rome, Italy.

Dr. De Luca presented at the Congress results from a study that used 24-hour electrocardiogram Holter monitoring in 71 selected systemic sclerosis (SSc) patients who presented with signs or symptoms of cardiac involvement such as dyspnea, palpitations, or elevated cardiac enzyme levels. The aim of their study was to assess the ability of 24-hour Holter electrocardiogram monitoring to identify SSc patients at high risk of sudden cardiac death (SCD) or major arrhythmias and in detecting patients in which electrophysiological studies are recommended and an implantable cardioverter defibrillator (ICD) is needed. The primary endpoint was a composite of SCD or need for ICD. The patients were followed for up to 5 years after assessment, with a mean follow-up of 2 years.

The researchers found ventricular or supraventricular ectopic beats, ventricular and/or supraventricular tachycardia, or rhythm alterations in more than half of patients. A total of six patients met the primary composite endpoint: SCD occurred in four patients, while two patients underwent ICD-insertion due to life-threatening arrhythmic events. Importantly, a rate of ventricular ectopic beats (VEBs) higher than 1,280 in a 24-hour period showed a sensitivity of 83.3% and a specificity of 88.7% to predict SCD or the need for ICD insertion (area under ROC curve = 0.94, *P* less than .001).

All six patients who met the primary endpoint presented a number of VEBs greater than 1,280/day. Moreover, they had lower left ventricular ejection fraction on echocardiography and frequently showed an increase in cardiac enzymes.

The finding of VEBs higher than 1,280 as predictive of death sug-



DR. GIACOMO DE LUCA



DR. SILVIA BOSELLO

gests that ECG Holter monitoring should be used at baseline in patients presenting with signs of cardiac involvement, study coauthor Dr. Silvia Bosello said in an interview. ECG Holter monitoring is not currently in wide use as a baseline screening measure.

**'We strongly believe that ECG Holter is just one of the exams to do in this population of patients with signs or symptoms of cardiac involvement.' In selected patients, 'a comprehensive cardiac evaluation consisting also of invasive exams ... should be considered.'**

Dr. De Luca concurred. "We strongly believe that ECG Holter is just one of the exams to do in this population of patients with signs or symptoms of cardiac involvement," he said. In selected patients with suspicious primary heart involvement and with a high rate of VEBs, "a

comprehensive cardiac evaluation consisting also of invasive exams such as electrophysiological studies and endomyocardial biopsy should be considered" to better understand the level and nature of cardiac involvement, he said.

Dr. Bosello noted that not all patients with a high rate of VEBs will yet have severe disease. "This study can help the physician to identify patients at high risk of developing advanced cardiac disease," and help to define treatment options, which include both rheumatic treatments and cardiac medications such as beta-blockers or specific antiarrhythmic drugs.

"With scleroderma, it is helpful to have a multidisciplinary group of clinicians," she said.

"If there is an arrhythmia, we need the help of a cardiologist to determine the best cardiac therapy. But immunotherapy can also be very helpful because, apart from myocardial fibrosis, an important role in arrhythmogenesis could also be played by the inflammatory burden (myocarditis)."

The researchers are currently extending their study of ECG Holter monitoring to an unselected group of scleroderma patients to determine whether cardiac involvement can be discerned even before patients present with cardiac symptoms. And, they said, their current clinical practice incorporates a vigilant outlook toward detecting cardiac involvement early.

"Every time we have a meeting with the patient, we try to find out about cardiac symptoms," Dr. Bosello said. "We suspect that some level of involvement may occur early in the disease, so we have to begin looking quickly and deeply," she said.

Dr. De Luca and Dr. Bosello reported no conflicts of interest related to their findings.



# Tool Predicts Lymphoma, Death in Primary Sjögren's Syndrome Patients

BY KAREN BLUM

**T**he European League Against Rheumatism Sjögren's Syndrome Disease Activity Index measured at the time of diagnosis predicted the development of lymphoma and death in Spanish patients with severe primary Sjögren's syndrome in a large, multicenter registry.

"We identified a specific hematological and immunological profile (cytopenias, hypocomplementemia, monoclonal band, and cryoglobulinemia) as laboratory predictors of hematological neoplasia in these patients," said lead study author Dr. Pilar Brito-Zerón. "If you have an SS [Sjögren's syndrome] patient with these features, you have to be very careful because this patient has a higher probability of developing a lymphoma."

"Physicians have had an activity index tool for other diseases for a long time, but there was nothing for SS until recently," when the EULAR Sjögren's Syndrome Disease Activity Index (ESSDAI) was published in 2010, Dr. Brito-Zerón said. "In Spain, we have one of the largest cohorts of SS patients in the world," so it was a good opportunity to test the ESSDAI.

Dr. Brito-Zerón of Hospital Clinic in Barcelona and her colleagues studied patient records from the GEAS-SS multicenter registry, a cohort of 921 patients with SS from 20 medical centers in Spain, and retrospectively calculated their 2010 ESSDAI. During a mean follow-up period of 75 months, 25 (3%) of 904 patients developed lymphoproliferative disease; 17 were excluded because they had lymphoma before their primary SS diagnosis. Two-thirds were MALT (mucosa-associated lymphoid tissue) lymphomas, 80% of which were located

in the parotid glands.

The investigators found that the following baseline features at diagnosis were most associated with lymphoma development: male gender (hazard ratio, 5.78; 95% confidence interval, 2.14-15.63); cryoglobulins (HR, 4.44; 95% CI, 1.86-10.58); monoclonal serum band (HR, 4.23; 95% CI, 1.38-13.02); C3 values less than 0.82 g/L (HR, 3.75; 95% CI, 1.38-10.19); C4 values less than 0.07 g/L (HR, 3.22, 95% CI, 1.08-9.61); and older age (HR, 1.04; 95% CI, 1.00-1.07). Gender, low C3, monoclonal band, and cryoglobulins were significant independent variables related to lymphoma, Dr. Brito-Zerón reported at the Congress.



DR. PILAR BRITO-ZERÓN

An ESSDAI score of one or greater in the constitutional (HR, 4.06; 95% CI, 1.54-10.70) and hematologic (HR, 2.59; 95% CI, 1.16-5.78) domains was associated with the development of lymphoma, with hematologic activity being independently associated. In the constitutional domain, patients with the highest degree of activity – including fever greater than 38.5° C, night sweats, and/or involuntary weight loss of at least 10% – showed the highest risk of developing lymphoma (HR, 9.11; 95% CI, 2.51-33.12).

At the time of diagnosis with the 2002 primary SS classification criteria, patients had a mean baseline ESSDAI of 5.81. During follow-up, the patients accumulated another mean 3.34 points for a cumulative ESSDAI of 9.15. A large majority of patients were women (94%) and had a mean age of nearly 54 years at the time of diagnosis. Most of the 921 patients in the registry had xerostomia (96%), xerophthalmia (95%), positive ocular tests (93%; 805 of 863), grade 3-4 parotid scintigraphy (88%; 598 of 676), and positive salivary gland

biopsy (88%; 424 of 482). Cytopenias occurred in 34% overall, including anemia (17%), leucopenia (20%), and thrombocytopenia (9%). Immunologic disease characteristics of the patients included positive autoantibody tests for antinuclear antibodies (90%), anti-Ro (73%), rheumatoid factor (57%), and anti-La (46%). Others had low C4 (12%) or C3 (9%) levels and low cryoglobulins (12%) or monoclonal gammopathy (9%).

The investigators also correlated the baseline ESSDAI score with mortality. After an average follow-up of 75 months, 83 (9%) patients had died. Deaths were attributed to causes related to SS (27 patients), cardiovascular disease (20 patients), infections (17 patients), and other causes (11 patients). The cause of death was unknown in eight patients.

The active ESSDAI domains that were associated with death were the constitutional (HR, 2.66; 95% CI, 1.38-5.11), pulmonary (HR, 2.13; 95% CI, 1.09-4.16), and biologic (HR, 3.01; 95% CI, 1.91-4.76), with the pulmonary and biologic domains being independently associated with death.

Further analysis revealed that a score of one or greater in the constitutional, lymphadenopathy, hematologic, and biologic domains was predictive of death related to SS (HRs ranging from 2.59 to 7.88), while activity at the constitutional, cutaneous, pulmonary, renal, neurologic, and hematologic domains predicted mortality related to infection (HRs ranging from 3.7 to 9.29). The investigators found no associations between activity in specific ESSDAI domains and death from cardiovascular disease or other causes.

"Activity of constitutional and lymphadenopathy domains, closely related to lymphoma, correlated with death caused by SS itself, while activity in the main extraglandular sites of involvement (in which high doses of corticosteroids and immunosup-

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pressive agents are used) correlated principally with death caused by infection,” Dr. Brito-Zerón said. “ESS-DAI is a useful tool to score systemic activity in patients with primary SS not only in prospective studies, but also in clinical trials that evaluate the

efficacy of a specific drug.”

Since the analysis of these 921 patients was completed in January 2013, an additional 124 patients with primary SS have joined the cohort. In this larger cohort, baseline ESSDAI score of 14 or higher and presence of more than one laboratory marker (lymphopenia, low cryoglobulins, hy-

pocomplementemia, and monoclonal band) both were significantly associated with SS-related death.

Dr. Brito-Zerón noted that the investigators have not analyzed whether treatment influenced outcomes in the cohort, but they plan to.

The investigators had no financial disclosures.

## Meta-Analysis Finds Limited Bone Loss With Low-Dose Glucocorticoids

BY MARY JO M. DALES

**B**one loss at 1 year is limited at the low doses of glucocorticoids typically used to treat adults with chronic inflammatory disorders like rheumatoid arthritis, based on a meta-analysis of prospective studies of 1,565 patients with chronic inflammatory diseases (44 studies) and 635 transplant patients (16 studies).

Glucocorticoid treatment at the high doses used in transplantation patients leads to considerable bone loss, especially in the lumbar spine. In contrast, bone loss is limited during glucocorticoid treatment at the lower doses used in chronic inflammatory disease, Dr. Maarten Boers, professor of clinical epidemiology at VU University Medical Center, Amsterdam, reported at the Congress.

All patients in the meta-analysis had at least two bone mineral density (BMD) measurements over at least 8 months. None received bisphosphonates or antiresorptive therapies; only vitamin D3 and calcium were allowed.

Glucocorticoid doses ranged from 1 to 16 mg/day (mean 9 mg/day) in the patients with chronic inflammatory diseases and from 6 to 53 mg/day (mean 20 mg/day) in the transplant patients. In those with chronic inflammatory diseases, bone loss at the lum-

bar spine at 1 year averaged  $-1.7\%$ . For the patients who had measures of femoral neck bone loss, the average loss was  $-1.3\%$ . In the transplantation group, average bone loss was much higher at  $-3.6\%$  in the lumbar spine and  $-3.1\%$  in the femoral neck.

“We sought to quantify the ‘pure’ effect of GC [glucocorticoid(s)], because so little high-quality information is available,” Dr. Boers explained.



DR. MAARTEN BOERS

The data analysis in these studies was limited to 1 year, but about two-thirds of the patients with chronic inflammatory disease were on chronic glucocorticoid therapy and almost all of the transplant patients were just starting glucocorticoids,

Dr. Boers said.

“On average, the yearly loss in a wide range of doses is limited, but starters have more bone loss. The heterogeneity of studies suggests that factors other than GC dose are the main drivers in determining bone loss. Although the data were not available to study these factors, it appears likely that disease activity is very important and acts as a confounder. In other words, disease activity leads to bone loss, and high GC doses lead to bone loss. Effective treatment of high disease activity requires high GC doses, but the interaction of these factors may lead to bone loss comparable to low disease activity being treated with

low doses,” he explained in an interview.

Many rheumatoid arthritis patients are initially treated with “bridge” glucocorticoid therapy for a few months, until the effect of methotrexate is established, he said. “We prefer ‘COBRA [combination therapy for rheumatoid arthritis] light,’ where patients are initially treated with a higher dose of 30 mg, rapidly tapered to 7.5 mg/day, and maintained for at least 6 months. Several groups are advising to treat for longer periods, and observational data suggest many patients are kept on chronic therapy for periods longer than 1 year,” he said.

Local guidelines differ, but all guidelines agree on the necessity of prophylaxis in high-risk situations and on screening for intermediate-risk patients. Unfortunately, many patients requiring antiresorptive treatment according to the guidelines are still not receiving it, with surveys showing about 70% uptake in patients treated by rheumatologists and only about 30% in patients receiving care from other specialists, he said.

“Given the effects of starting GC therapy in our review, we strongly suggest all patients requiring GC therapy for longer than 3 months at any dose should at least be assessed by DXA scan; postmenopausal women, males age 70 or older, and patients with other risk factors should be treated with antiresorptive agents from the start,” Dr. Boers advised.

Dr. Boers and his coinvestigators reported having no financial conflicts.

# Cranial Ultrasound Performs Better Than Temporal Artery Biopsy for GCA

BY MARY JO M. DALES

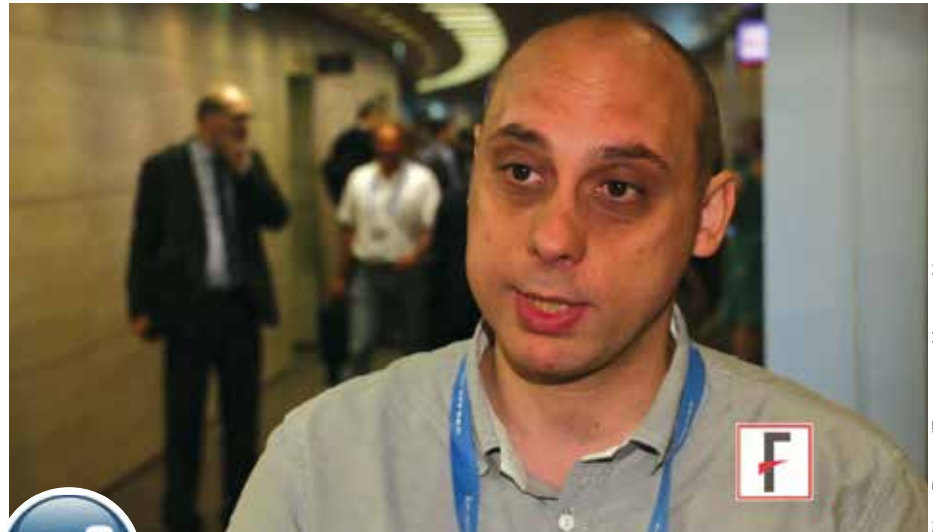
**C**ranial ultrasound was more sensitive and just as specific as was temporal artery biopsy for the diagnosis of giant cell arteritis, based on the results of a retrospective cohort study reported by Dr. Adam Croft at a press conference held during the Congress.

Given that ultrasound is noninvasive, associated with fewer risks, and more sensitive than biopsy, “temporal artery biopsy may now be unnecessary [when] clinical suspicion of GCA [giant cell arteritis] is high or quite low,” said Dr. Croft of the University of Birmingham in England. “Cranial ultrasound may soon replace temporal artery biopsy in the assessment of patients with a suspected diagnosis of GCA in routine clinical practice.”

**Given that ultrasound is noninvasive, associated with fewer risks, and more sensitive than biopsy, ‘temporal artery biopsy may now be unnecessary [when] clinical suspicion of [giant-cell arteritis] is high or quite low.’**

Giant cell arteritis typically is associated with severe headaches and scalp tenderness on the sides of the forehead that must be distinguished from more benign causes of headache. In GCA, these symptoms result from ocular arterial inflammation and narrowing that respond to high-dose steroid therapy.

The findings were seen in a study



Click [here](#) to view a video interview with Dr. Adam Croft.

NICK PIEGAR/FRONTLINE MEDICAL NEWS

of 87 patients who underwent cranial duplex ultrasound for suspected GCA. At 3-month follow-up, 36 patients (41%) had a confirmed clinical diagnosis of giant cell arteritis. Of the 30 patients with a positive cranial ultrasound result, 29 went on to have a confirmed diagnosis. Of the 36 patients with more than three American College of Rheumatology criteria, 21 (58%) had a diagnosis of GCA.

When compared with clinical diagnosis, ultrasound had 81% sensitivity and 98% specificity with a positive likelihood ratio of 41 and a negative likelihood ratio of 0.2. The positive predictive value was 97% and the negative predictive value was 88%, he said. In other words, with a positive ultrasound finding, the probability of giant cell arteritis was 41 times higher.

In contrast, when compared with clinical diagnosis, temporal artery biopsy had a sensitivity of 53% and

a specificity of 100%. The positive likelihood ratio was 2.3 and the negative likelihood ratio 0.2. The positive predictive value was 100% and the negative predictive value was 47%.

Relying on temporal arterial biopsy results alone leaves “patients at risk of missing out on potentially sight-saving steroid treatment, or of being treated with high-dose steroids unnecessarily,” he said. Further, temporal artery biopsy is not without risks. The biopsy can miss the artery and can result in permanent facial nerve damage. A negative biopsy rarely informs practice.

The availability of cranial ultrasound depends on whether one’s practice is located near facilities with the infrastructure and the availability of well-trained rheumatologists and radiologists who can do the scan rapidly, Dr. Croft said in an interview.

Dr. Croft had no financial disclosure.



# Potentials and Pitfalls of Imaging in Giant Cell Arteritis Examined

BY JENNIE SMITH

Imaging plays a key role in the diagnosis and monitoring of giant cell arteritis, helping clinicians detect inflammatory changes in the temporal arteries, and also, importantly, in large arteries in the body that are difficult to biopsy.

However, imaging of large vessels “is a relatively new field,” said Dr. Nicolò Pipitone of the Istituto di Ricovero e Cura a Carattere Scientifico, in Reggio Emilia, Italy. It is also a field “with little in the way of agreed standards in choosing and interpreting imaging studies, or evidence-based recommendations to guide the use of imaging in patients with large-vessel vasculitis.” Rheumatologists may not be fully aware of the potentials and pitfalls of imaging studies in investigating and monitoring large-vessel vasculitis, he said in an interview.

Color-Doppler sonography (CDS), contrast-enhanced magnetic resonance imaging (MRI), and magnetic resonance angiography (MRA), along with contrast-enhanced computerized tomography (CT) and contrast-enhanced computerized tomography angiography (CTA), can all be used to identify inflammation of the arterial wall and lumen before vascular complications appear, Dr. Pipitone said. 18F-Fluorodeoxyglucose positron-emission tomography (PET) is also used to assess large-vessel inflammation.

At the Congress, Dr. Pipitone brought rheumatologists up to date on the imaging technologies suited to detecting inflammation in superficial and deep vessels of medium to large size. Using the most recent evidence, he showed which techniques

can help ascertain whether a patient has large-vessel vasculitis and which clinical features should dictate the type of imaging to be used.

CDS, for example, is extremely use-



DR. NICOLÒ PIPITONE



DR. HUBERT DE BOYSSON

ful in identifying vessel wall thickening in superficial arteries such as temporal arteries, while MRI/MRA and CT/CTA studies can show changes to deep, large vessels such as the thoracic and abdominal aorta, Dr. Pipitone said.

Dr. Pipitone also discussed ways in which imaging can be used to monitor response to treatment, and how to

being studied as a way to predict vascular complications such as stenoses or aneurysms.

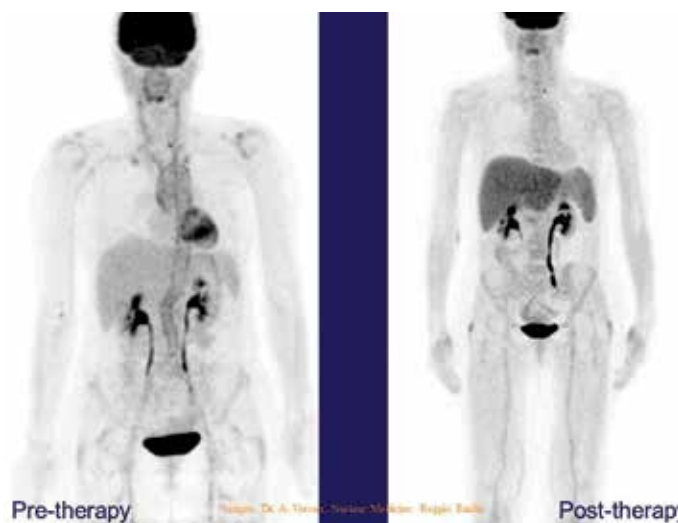
Another speaker at the Giant Cell Arteritis session on Wednesday, Dr. Hubert de Boysson discussed the risk of aortic complications among patients with confirmed GCA. Extracranial involvement of GCA is probably underdiagnosed, and PET is one form of imaging suited to detecting inflammation in the thoracic, abdominal aorta, subclavian, axillary, carotid, iliac/femoral, and upper- and lower-limb arteries.

Dr. de Boysson, of the Centre Hospitalier et Universitaire Côte de Nacre, in Caen, France, conducted a study in which evidence of inflammation in large body vessels in PET scans was associated with increased risk of aortic complications at 3 years' follow-up.

For their study, Dr. de Boysson and his colleagues recruited 133 patients with a GCA diagnosis. PET was performed at diagnosis or during follow-up. PET results were positive in about half of patients, with a median of four body areas involved, and the thoracic aorta was involved in 79% of positive cases.

Patients with positive PET findings had significantly more extra-cephalic manifestations and fewer cephalic symptoms than did patients with a negative PET, the researchers found. Aortic complications were associated with positive PET (hazard ratio, 3.96; 95% confidence interval, 1.1-14.26) and the absence of cephalic manifestations (HR, 0.27; 95% CI 0.09-0.85) at a median follow-up of 35 months.

Neither Dr. Pipitone nor Dr. de Boysson disclosed conflicts of interest.



**This patient's total vascular score was 8 at baseline and dropped to 2.4 on repeat PET scan at 3 months posttherapy.**

differentiate vasculitis from other vessel changes such as atherosclerosis.

In addition to these clinical uses, imaging technologies are increasingly

# Giant Cell Arteritis Patients Face High Aortic Aneurysm Dissection Risk

BY MITCHEL L. ZOLER

**T**he usual rule that the larger an aortic aneurysm grows the greater the risk it will undergo dissection or rupture doesn't work in patients with giant cell arteritis. Their aortic aneurysms appear liable to dissect or rupture at any size after the diagnosis of giant cell arteritis occurs, based on a retrospective study of 195 patients followed at a single U.S. center.

"Aortic size at diagnosis or last follow-up did not predict aortic dissection or rupture," nor were linear, serial measurements of aortic size able to reliably predict risk for these complications in patients with GCA, Dr. Ashima Makol reported at the Congress. Without a reliable way to identify patients with GCA at risk for dissection or rupture, the only management advice remaining is to follow GCA patients annually with imaging, said Dr. Makol, a rheumatologist at the Mayo Clinic in Rochester, Minn.

Positron-emission tomography, CT angiography, or MR angiography seem to be the best ways to follow these patients, but if those are too costly to do annually, then transesophageal echocardiography or a chest x-ray are other options, Dr. Makol said in an interview.

Although 30% of patients with GCA have a vasculitis that involves the aorta and its branches and an increased risk for developing aortic aneurysms, the way these aneurysms change over time and the relationship between aneurysm size and the risk for dissection or rupture in GCA patients were not previously reported. To address this, Dr. Makol and her associates reviewed 195 patients with GCA and an aortic aneurysm seen at the Mayo Clinic during 2000-2012.

The aneurysms occurred in the ascending thoracic aorta in 161 patients (83%), the descending thoracic aorta in 21 (11%), and the abdominal aorta in the remaining 13 patients (7%).

(Percentages total 101% because of rounding.) The patients averaged 74 years old, 62% were women, and 49% had a history of smoking.

During follow-up, 14 patients (7%) had an aneurysm dissection, and 1 patient (1%) had an aneurysm rupture. All of the dissections and the rupture occurred in thoracic aorta aneurysms.

At the time of GCA diagnosis, the average aneurysm size in the 15 patients who developed an aneurysm complication was 51 mm, which was very similar to the average size of 49 mm in the 180 patients who did not have an aneurysm dissection or rupture during follow-up.

Patients also showed no clear link between aneurysm size at the time of dissection or rupture and the aneurysm size during follow-up of patients without these complications. The average maximum aneurysm diameter among the 15 patients with a complication at the time of their event was 54 mm, while the average aneurysm size at last follow-up among those without a dissection or rupture during follow-up was 50 mm, a difference that was not statistically significant, Dr. Makol said.

The average rate of aneurysm growth during 3 years of follow-up for all the GCA patients in the analysis was 1.59 mm/year, a rate "somewhat higher" than the average annual growth rate of 1 mm/year reported for aortic aneurysms in patients without inflammatory disease. The 54-mm average aneurysm diameter at the time of dissection or rupture in the GCA patients was "somewhat lower"

than the 65-mm average aneurysm diameter seen at the time of dissection or rupture in patients without inflammatory disease, she noted.

Several patients in the series Dr. Makol reviewed who had no aneurysm complications had undergone prophylactic aneurysm repair. Clinicians at the Mayo Clinic follow the usual recommendations, which call for repair of aortic aneurysms when they reach at least 55 mm in diameter in men and 50 mm in women, and repair of thoracic aortic aneurysms that reach at least 55 mm in men and women. Prophylactic repair is also recommended for patients with an aneurysm that grows by more than 5 mm/year or causes symptoms. Many of the GCA patients included in the review therefore did not qualify for repair based on these criteria at the

**'Aortic size at diagnosis or last follow-up did not predict aortic dissection or rupture,' nor were linear, serial measurements of aortic size able to reliably predict risk.**

time of their GCA diagnosis or during follow-up. For now, no recommendations suggest that aortic aneurysms in patients with GCA need a different repair approach than in patients without inflammatory disease.

The study is the first reported to look at the pattern of aneurysm growth and complications in GCA patients, although it is limited to the retrospective experience at one tertiary referral center and so may reflect a referral bias, Dr. Makol said. But the inability of the analysis to identify aneurysm characteristics in GCA patients that can telegraph an increased risk for complications means that all GCA patients with an aortic aneurysm need careful surveillance by annual imaging, she advised.

Dr. Makol said that she had no disclosures.



DR. ASHIMA MAKOL

# Live Births Seen in Half of Pregnancies Exposed to Belimumab

BY MICHELE G. SULLIVAN

**T**he live birth rate among women taking belimumab for systemic lupus erythematosus is similar to the background rate for women with the disorder, according to an analysis of clinical trials.

The study found that women who were taking the drug when they became pregnant had a live birth rate of 48% – in line with studies that place the rate at 55%-88%, Dr. Marcy Powell said at the Congress.

Although the number of pregnancies examined in the studies was small – with 80 exposed to belimumab – the results were echoed by the initial findings in a recently established belimumab pregnancy registry, said Dr. Powell, director of safety evaluation and risk management at GlaxoSmithKline, which manufactures the drug.

More than 3,000 adult patients have been treated with belimumab – many for more than 10 years, but there are scant data on pregnancy outcomes. It's a category C drug; women are advised to avoid pregnancy while taking it and for at least 4 months after stopping it. Thus, the only available pregnancy data are from inadvertent exposures in which the drug was stopped as soon as the pregnancy was discovered.

The data were drawn from the

BLISS 52 and 78 studies, which enrolled more than 1,600 patients, 94% of whom were women. At baseline, the patients' mean age was 38 years. Other medications were common in the cohort: 86% of patients were using corticosteroids, with 58% of those tak-

**Although the number of pregnancies examined in the belimumab clinical trials was small – with 80 exposed to belimumab – the results were echoed by the initial findings in a recently established belimumab pregnancy registry.**

ing a prednisone equivalent of more than 5.7 mg/day. More than half (65%) were using antimalarials, and 49% were taking another immunosuppressant, including azathioprine, methotrexate, or mycophenolate mofetil.

Among the 80 drug-exposed pregnancies, there were 21 elective terminations as well as 20 miscarriages and 1 stillbirth, yielding a total fetal loss rate of 26%. The background miscarriage rate was 12%-22%, and the background stillbirth rate was 2%-5%, both of which are similar to rates observed in the exposed pregnancies. Overall, women tested positive for an-

ticardiolipin antibodies in 20 pregnancies exposed to belimumab, including 21% of the live births and 38% of the fetal losses.

There were 38 live births (48%).

Four neonates had a congenital anomaly:

- ▶ One with Dandy-Walker syndrome.
- ▶ One with an unbalanced translocation (11 and 13) of maternal origin, a strictly genetic anomaly.
- ▶ One born at 27 weeks' gestation with patent ductus arteriosus.
- ▶ One with bilateral enlarged kidneys with abnormal function whose mother was receiving ambrisentan, a known teratogen, for portal hypertension. (The infant was placed on dialysis and had the right kidney removed.)

The stillbirths occurred in conjunction with severe, very early third-trimester preeclampsia, Dr. Powell said. She noted that the sample size is so small that it's unclear whether the results can be extrapolated to larger populations.

However, the Belimumab Pregnancy Registry, established by GlaxoSmithKline, could provide more reliable data, she said. Seven completed pregnancies so far in the registry have included six live births and one miscarriage. Three of the infants were preterm, and there was one birth defect (mild Epstein's anomaly of the tricuspid valve).

## Trial of Sirukumab for Lupus Nephritis Falls Flat

BY MICHELE G. SULLIVAN

**T**he investigational interleukin-6 blocker sirukumab provided no benefit to patients with lupus nephritis but put them at a very high risk of developing a serious infection, investigators found in a small, ran-

domized, placebo-controlled trial.

Based on the study results, the study sponsor, Janssen, has shut down its program for the lupus nephritis indication, Dr. Ronald van Vollenhoven said at the Congress.

"While a few patients did experience a reduction in proteinuria,

we had an unacceptably high rate of adverse events," said Dr. van Vollenhoven, chief of the Unit for Clinical Therapy Research, Inflammatory Diseases, at the Karolinska Institute, Stockholm. "Based on these findings, we will not be advancing any further

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investigation of sirukumab for patients with active lupus nephritis.”

In the trial, 21 patients received intravenous sirukumab 10 mg/kg once every 4 weeks for 24 weeks, and 4 received placebo. During the trial and a 16-week safety observation follow-up period, 48% of those who took the investigational IL-6 blocker developed a serious adverse event, including infections serious enough to require hospital admission.

While not specifying the infections, which occurred in 10 patients, Dr. van Vollenhoven noted that five patients taking the drug discontinued it because of adverse events, which included *Haemophilus influenzae* pneumonia, elevated liver enzymes,

anaphylactic reaction after the first dose, worsening nephritis, and severe neutropenia.

Overall, 19 patients completed the study. In addition to the five who quit because of adverse events, one additional patient withdrew voluntarily. All had active lupus nephritis of about 50 months' duration, with a mean daily proteinuria of more than 2 g; about a third of the group had nephrotic proteinuria. The mean Systemic Lupus Erythematosus Disease Activity Index 2000 was about 16. All were taking concomitant mycophenolate mofetil or azathioprine.



DR. RONALD VAN VOLLENHOVEN

At the end of the treatment period, there was no significant between-group difference in proteinuria, Dr. van Vollenhoven said. Four of those in the active group experienced

at least a 50% reduction in proteinuria over baseline, while none of those in the placebo group experienced this change. However, this difference was not statistically significant. There were no significant changes in the patient or physical global assessment for either group.

Serious adverse events occurred in 48% of those taking the drug, including serious infections (30%) as well as renal/urinary (19%), blood (9.5%), and gastrointestinal (9.5%) events. None occurred with placebo.

Among patients in the sirukumab group, there was one grade 4 lymphocytopenia, one grade 4 neutropenia, and two grade 3 neutropenias. One patient had a grade 2 liver enzyme elevation.

Dr. van Vollenhoven was on the study steering committee and is a consultant and speaker for Janssen, as well as other drug manufacturers. Four coauthors are employees of Janssen.

## Real-World Use Supports Clinical Trial Data for Belimumab

BY MICHELE G. SULLIVAN

**B**elimumab produced significant clinical improvement in 74% of patients with systemic lupus erythematosus who took it over a 6-month period, reducing disease symptoms and steroid use and significantly improving quality of life.

Results from the multicenter German OBSERVE study paralleled – and even exceeded – those of the BLISS randomized trials, Dr. Andreas Schwarting said at the Congress.

“OBSERVE data suggest even greater improvements and lower discontinuation rates in real-world practice,” said Dr. Schwarting of

the Johannes Gutenberg University of Mainz in Germany. “We also saw a lower discontinuation rate than in the BLISS trials, and our study shows that you can identify responders well within 6 months.”



DR. ANDREAS SCHWARTING

Dr. Schwarting was the lead author of the retrospective, observational study, which included 102 patients with active lupus who were treated with open-label belimumab over a 6-month period. In the study, most patients (85%) had moderate or severe disease, and 80% had been on four to five different lupus medications before starting belimumab. The most common reasons for starting belimumab were ineffective prior treatment (88%), worsening

disease (61%), and the need to decrease steroid use (40%).

At baseline, the mean steroid dose was 13.7 mg/day; 62% were taking a high dose, with a mean of 17.5 mg/day.

The primary endpoint was overall clinical response after 6 months of treatment. Most (75) had a disease activity improvement of at least 20%, including 35 who had an improvement of up to 49%, 31 with at least a 50% improvement, and 9 with at least an 80% improvement.

Five patients showed no improvement. Two became worse on the medication, and 14 had less than a 20% improvement. Six patients discontinued the drug: three because of disease progression, one because of an allergic reaction, one as a result of a lack of compliance, and one because of heart failure after hos-

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pitalization. The patient with heart failure died, but Dr. Swarting said there was no apparent causal relationship with belimumab.

The improvement occurred in all lupus manifestations, including arthritis (71% response rate), a high

level of anti-double-stranded DNA antibodies (50%), low complement levels (34%), fatigue (65%), and rash (62%).

The Systemic Lupus Erythematosus Disease Activity Index scores decreased from a mean of 10.6 to 5.6.

Belimumab exerted a steroid-sparing effect, Dr. Swarting noted.

The mean daily steroid dose decreased from 13.7 mg to 7.6 mg. Among those using more than 17.5 mg/day, the dosage decreased to 8.6 mg/day.

GlaxoSmithKline sponsored the study. Dr. Swarting said he has received honoraria, consulting, and speakers fees from the company.

## Three miRNA Biomarkers Predicted Osteoarthritis Severity

BY MARY JO M. DALES

**T**hree microRNAs have been shown to be associated with disease severity in patients with hip or knee osteoarthritis, based on data from a large population-based cohort in Italy.

The presence of three specific miRNAs are biomarkers that might prove to be useful for predicting OA severity if validated in other cohorts and di-

cartilage loss, said Dr. Beyer of the University of Erlangen-Nuremberg in Germany.

For the study, serum samples from 816 cohort members who had osteoarthritis and were followed for at least 15 years were analyzed for the presence of any of the 374 miRNAs. A microarray screening identified 12 candidate miRNAs, validated in the entire cohort. Based on a regression analysis, the 67 cohort members who

Let-7e was a negative predictor for total joint arthroplasty with an adjusted hazard ratio of 0.75 (95% confidence interval, 0.58-0.96;  $P = .021$ ) when normalized to U6, and 0.76 (95% CI, 0.6-0.97;  $P = .026$ ) after normalization to the Ct-average.

However, miR-454 was inversely correlated with severe knee or hip osteoarthritis with an adjusted HR of 0.77 (95% CI, 0.61-0.97;  $P = .028$ ) when normalized to U6. This correlation was lost when data were normalized to Ct-average ( $P = .118$ ).

Finally, miR-885-5p showed a trend toward a positive relationship with arthroplasty when normalized to U6 (HR, 1.24; 95% CI, 0.95-1.62;  $P = .107$ ) or to Ct-average (HR, 1.30; 95% CI, 0.99-1.70;  $P = .056$ ).

If specific miRNAs prove to be biomarkers to predict OA severity, it would offer the ability to use markers that are found in the peripheral circulation, stable over time, and not sex dependent. Such markers also could prove useful for finding new OA therapies, he said.

Next steps for further study include validation of the miRNA biomarkers in other OA cohorts, Dr. Beyer said. The well-defined Bruneck cohort is a stable community that has been extensively studied similar to the Framingham cohort in the United States. The Bruneck cohort is all white, however, and the results of this study need to be validated in diverse populations.

Dr. Beyer declared having no relevant financial disclosures.



Click [here](#) to view a video of Dr. Christopher Sparks (right) interviewing Dr. Christian Beyer.

verse populations of OA patients, Dr. Christian Beyer reported at a press conference during the Congress.

The miRNAs could also be a first step toward finding new OA therapies, such as approaches that avert

went on to have knee or hip arthroplasty were found to differentially express three of the miRNAs: let-7e, miR-454, and miR-885-5p. The most promising of the markers appears to be let-7e.

# Osteoarthritis Biomarkers: Great Potential in Research, Practice

BY SHARON WORCESTER

**O**steoarthritis represents a dynamic process of joint tissue turnover that is associated with release of matrix molecule fragments from articular cartilage, subchondral bone, and synovial tissue. These fragments, when present in blood and/or urine, and when considered in the context of relevant clinical and radiographic osteoarthritis parameters, could serve as useful biochemical markers for osteoarthritis.

Such biochemical markers would have great potential in OA practice and research; they would help to diagnose OA in an early stage, identify important treatment targets, and de-

velop disease-modifying treatments or in multiple joints by assessing biochemical markers? Can we already use biochemical markers to assess treatment efficacy? Do particular biochemical markers differ in this respect? For example, some biochemical marker assays (e.g., deamidated COMP, Coll2-1 NO2) also take into account post-translational modifications of the circulating matrix molecules that may also relate to processes like inflammation and protein aging, he said.

“Better and more consistent performance of systemic biochemical markers of joint

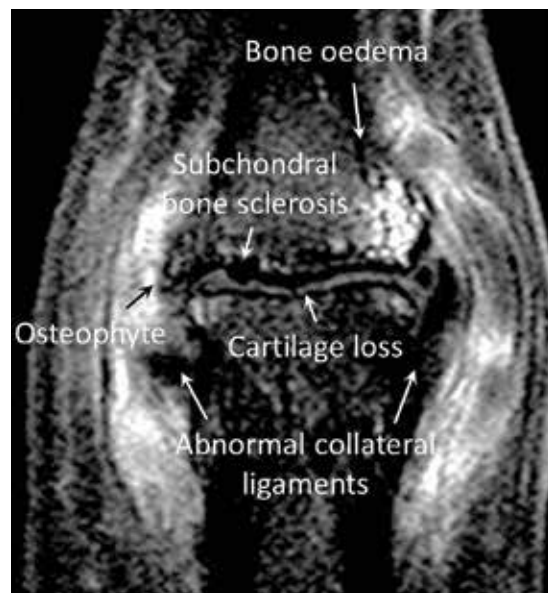
metabolism is needed before widespread implementation in OA research and practice can be fully justified,” he said, adding that markers with higher specificity for OA in general, and maybe even for particular joints, are needed.

That said, currently available biomarkers certainly do have a place in current research. For example, they can be used as secondary endpoints in clinical trials to elucidate mechanisms of action of tested agents and the biomarkers themselves, he noted.

During the same session at the Congress, Dr. Ai Lyn Tan of the University of Leeds, England, reviewed novel imaging markers with respect to their effectiveness and cost-effectiveness.

“Most of the novel work with respect to imaging markers for OA involves magnetic resonance imaging, which in recent years has contributed significantly to improving our understanding of OA pathology and to providing insights regarding diagnosis and monitoring response to therapy,” Dr. Tan said.

MRI is particularly well suited for



DR. AI LYN TAN

**A high-resolution MRI of a proximal interphalangeal joint with osteoarthritis shows various abnormalities that potentially can be imaging markers for osteoarthritis.**



DR. ERWIN VAN SPIL



DR. AI LYN TAN

velop disease-modifying treatments and might prove to be a sensitive way of evaluating treatment efficacy, according to Dr. Erwin van Spil of the University Medical Center Utrecht, the Netherlands.

At the Congress, Dr. van Spil, who performed the first systematic review of biochemical marker performance in OA, illustrated the challenging road of obtaining effective biochemical markers for OA. He addressed where the development of these markers is at the moment by discussing a number of relevant questions: To what extent do biochemical markers reflect specific processes in the pathogenesis of OA? Can we rely on biochemical markers? Can we quantify the extent and severity

of OA, thanks to its ability to visualize all joint structures, including bone, cartilage, meniscus, tendons, ligaments, and synovium, which all can be affected in OA, she noted.

Dr. Tan addressed the various sophisticated novel MRI techniques and scoring systems that have been devised for assessing OA; these techniques mainly focus on measuring and characterizing the morphology and physiology of cartilage changes, she said.

Thus far, MRI as an imaging marker for OA has mainly been explored as a research tool as it is limited by its high cost and the relative complexity of image interpretation, but given the potential development of new disease-modifying OA drugs on the horizon, a reliable, reproducible, validated marker of treatment response is needed, she noted.

Ongoing cohort studies like the Osteoarthritis Initiative provide an opportunity for identifying such markers, she added.

Dr. van Spil and Dr. Tan each reported having no disclosures.



# Effectiveness of Generalized Osteoarthritis Therapies Is a Toss-Up

BY NICOLA GARRETT

**I**ntensive group-based treatment is no more effective than a scaled-down telephone support program in improving the level of daily function in patients with generalized osteoarthritis, according to results from a randomized study.

Patients who received more intensive support face to face in a group had no better daily function than did patients who had less intensive interaction by telephone in the study of 158 patients with generalized osteoarthritis (OA) who participated in either intervention over 6 weeks.

Instead, in order to actually improve daily function, the key may be to focus support programs on exercise therapy, said lead author Nienke Cuperus, who presented the findings at the Congress.

Ms. Cuperus explained that before now, most research had focused on the effectiveness of nonpharmacological interventions in patients with localized OA, despite generalized OA patients representing a large subgroup of patients.

Rectifying this gap in the research, Ms. Cuperus and colleagues randomized pa-

tients to group or telephone therapy and measured patient outcomes at 6 weeks and 6 months using the Health Assessment Questionnaire-Disability Index (HAQ-DI) score and the Patient Specific Functioning Scale.

Patients allocated to group therapy had six face-to-face sessions supervised by a physical therapist, with the involvement of an occupational therapist, rheumatology nurse, and a dietician.

The sessions lasted 2-4 hours and focused on education, self-management, and goal setting, with patients also taking

part in a tailored exercise program.

Patients randomized to the telephone program had two face-to-face group sessions followed by four phone calls up to 30 minutes long from a rheumatology nurse, with the involvement of a physical therapist.

Results showed no differences between the treatment groups on the HAQ-DI scores, but after 6 weeks there was a small, but significant, reduction in pain that favored the face-to-face group-based treatment. Within groups, significant improvements were seen on the Patient Specific Functioning

Scale and acceptance after 6 months for both treatment groups. In addition, the face-to-face group showed significant improvements in pain and fatigue after 6 months.

The results were a surprise, said Ms. Cuperus, a PhD student and human movement scientist in the department of rheumatology at Sint Maartenskliniek, in Nijmegen, the Netherlands.

“We expected the group-based treatment to be more effective than the telephone group because of the higher intensity of the face-to-face treatment, the higher number of sessions – including an exercise program – and the fact that more disciplines were involved,” she said in an interview.

The face-to-face group had significant improvements in pain and fatigue, not observed in the telephone group. This difference was likely explained by the fact that the face-to-face patients had more exercise sessions and more time to learn about physical activity, pain management, and activity pacing.

The results suggested that the “choice of mode of treatment delivery could be based on patients’ preferences and costs,” she said, adding that most patients preferred face-to-face treatment and were reluctant to be contacted by telephone.

The researchers declared having no conflicts of interest.



MS. NIENKE CUPERUS

## Different Triggers Found for Knee and Hand Osteoarthritis

BY KAREN BLUM

**M**echanical stress is the most important underlying mechanism in osteoarthritis of the knees, while systemic processes may contribute most to hand osteoarthritis, Dutch researchers have found.

“How obesity results in osteoarthritis [OA] is not quite clear, but several

mechanisms are thought to play a role, such as increased mechanical stress and systemic processes that are associated with adipose tissue,” said senior study author Dr. Margreet Kloppenburg, professor of rheumatology at Leiden University Medical Center in the Netherlands.

“Adipose tissue is known to be a source of active mediators, proinflam-

atory proteins and hormones, influencing inflammation, lipids, glucose metabolism, and insulin resistance,” she said. “These systemic processes also could result in the development of OA. Our aim was to understand more about the link between obesity and OA because this insight could help us reach our ultimate goal: to im-

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prove treatment for OA patients.”

Dr. Kloppenburg and her colleagues reviewed records from 6,628 participants in the Netherlands Epidemiology of Obesity (NEO) study, a population-based cohort of adults aged 45-65 years that is designed to investigate pathways leading to common diseases and conditions in overweight and obese individuals. Participants had a mean age of 56 years and a body mass index of 26 kg/m<sup>2</sup>; 56% were women. The estimated prevalence of OA was 10% in the knee, 8% in the hand, and 4% in both.

Researchers measured weight and fat mass and calculated fat-free mass. They also calculated odds ratios (ORs) to test for associations between surrogates for mechanical stress (weight and fat-free mass) and systemic pro-



DR. MARGREET KLOPPENBURG

cesses (metabolic syndrome) with OA in knees alone, hands alone, or both knees and hands. Adjusted ORs were calculated for each OA type in three weight categories: less than 75 kg, 75-90 kg, and more than 90 kg.

After adjustment for metabolic factors, knee OA was significantly associated with weight (OR, 1.49) and fat-free mass (OR, 2.05). Similar results were observed for OA in both the knees and hands. In hand OA, however, investigators found the opposite: Hand OA was significantly associated with metabolic syndrome, independent of weight (OR, 1.46), and had no associations with weight and fat-free mass, Dr. Kloppenburg reported at the Congress.

“As we hypothesized, knee OA was predominantly associated with surrogates for mechanical stress, whereas hand OA was predominantly associated with surrogates for systemic pro-

cesses,” she said. “But what we had not expected was that surrogates for mechanical stress were predominantly associated with OA in both the knees and hands. This suggests that the co-occurrence of knee and hand OA may not be based on a common underlying pathogenic mechanism, but may represent the presence of two different types of OA.”

Adjusted ORs for knee OA and for OA of both the knees and hands were greater in the higher weight categories, but, in hand OA, ORs did not increase with weight.

“Our study supports findings from clinical trials in obese patients with knee OA demonstrating that weight loss, together with exercise, which can potentially modify mechanical stress, is beneficial,” she said. “It would be worthwhile to investigate whether weight loss also is beneficial in hand OA.”

The NEO study is supported by the Dutch Arthritis Association, Leiden University Medical Center, and Leiden University. The investigators had no conflicts of interest to declare.

## Eurofever Project Takes Aim at Rare Autoinflammatory Disorders

BY MICHELE G. SULLIVAN

**A** large international registry aims to gather extensive data on the presentation, complications, and treatment response of rare autoinflammatory diseases in both children and adults, according to principal investigator Dr. Marco Gattorno.

Launched in 2009, the Eurofever Project is being conducted in 67 rheumatology centers across 31 countries. So far it has accumulated nearly 3,000 patients, about 70% of whom are children. The registry has thus far generated 10 papers that involved more than 50 centers and many more studies are in the offing, Dr. Gattorno said at the Congress.

“The Eurofever registry gives an

epidemiological overview of the distribution and prevalence of these rare disorders in Europe and other countries,” he said in an interview.

“The aim was to understand who the patients are and who is following them. The registry is also collecting information on the clinical manifestations and complications associated with different diseases and on the response to treatment from disease onset to enrollment.”

An online survey collects information on 15 of these rare diseases. Several present very early in life as sudden-onset, recurrent fever, often accompanied by rash, serositis, lymphadenopathy, or arthritis. Disease flares are usually separated by symptom-free intervals of variable duration, characterized by com-

plete well-being, normal growth, and normalization of acute phase reactants. This cycle can result in a considerable delay in diagnosis, the project has determined – from 5 years for children with FMF (familial Mediterranean fever) to “an incredibly astonishing delay of 18 years” for children with TRAPS (tumor necrosis factor receptor-associated periodic syndrome), CAPS (cryopyrin-associated periodic syndrome), and MKD (mevalonate kinase deficiency), said Dr. Gattorno, a pediatric rheumatologist at the IRCCS Institute Giannina Gaslini in Genoa, Italy.

Fortunately, he noted, a recent paper drawn from Eurofever data has found that these delays are shortening. Although patients born in the 1970s and 1980s typically faced decades of diagnostic confusion, children born in

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the 1990s and early in this century are being diagnosed much sooner – often within 5 years, he noted.

The creation of new, evidence-based diagnostic and classification criteria is also the direct result of the Eurofever registry. A paper in process is building such systems for MKD, TRAPS, CAPS, and FMF.

Primary investigator Maria Pia Sormani, Ph.D., of the University of Genoa and her colleagues have created scoring systems for each disorder based on the presence and absence of specific demographic and clinical

characteristics. Meeting or exceeding the predetermined cutoff point for each will provide a “gold standard” for diagnosis, Dr. Gattorno said.

As the Eurofever registry continues to grow, it is adding other rare disorders, he said. These include deficiency of interleukin-36 receptor antagonist (DITRA); chronic atypical neutrophilic dermatosis with lipodystrophy and elevated temperature syndrome (CANDLE); Schnitzler syndrome (chronic, nonpruritic urticaria in association with recurrent fever, bone pain, arthralgia or arthritis, and a low-level monoclonal immunoglobulin M gammopathy); and ADA2 de-

ficiency, a rare syndrome of sporadic fevers, skin rashes, and recurring strokes that begins early in childhood.

Eurofever is sponsored by the Executive Agency for Health and Consumers of European Union and other EU grants, as well as unrestricted grants by Novartis and SOBI, from which Dr. Gattorno has received speakers fees. The technical expertise is provided by the Paediatric Rheumatology International Trials Organisation.

*The registry is actively enrolling patients. Information on the registry and how to participate can be found at [www.printo.it/eurofever/](http://www.printo.it/eurofever/)*

## Juvenile Idiopathic Arthritis Response Predicted After Start of Therapy

BY JEFF EVANS

**T**hanks to microarray analysis of gene expression in patients with juvenile idiopathic arthritis, response to treatment at 12 months can be predicted after just 4 months of therapy, based on a longitudinal analysis of whole blood samples from children participating in the TREAT study.

The prediction of active versus inactive disease could be made even more strongly when stratifying patients based on the presence of rheumatoid factor (RF), which is an “exciting” finding, study investigator Dr. James Jarvis said in a video interview. “We’ve known for a long time that children with rheumatoid factor-positive disease are just harder to treat,” he said at the Congress.

The U.S. National Institutes of Health-funded TREAT (Trial of Early Aggressive Drug Therapy in Juvenile Idiopathic Arthritis) study compared treatment with metho-



Click [here](#) to view a video interview with Dr. James Jarvis.

trexate alone against methotrexate plus etanercept for children with newly diagnosed juvenile idiopathic arthritis. The current analysis found that treatment in RF-positive patients led to changes in fewer genes than in RF-negative patients, and also

changed the expression of different genes than in those with RF-negative disease. Dr. Jarvis is chief of allergy/immunology and rheumatology in the pediatrics department at the University at Buffalo, The State University of New York.



# Rationale for New Classification of Juvenile Idiopathic Arthritis Articulated

BY JENNIE SMITH

**A**s in adult arthritis, several different disease pathways are known to be involved in juvenile idiopathic arthritis.

Results of research in gene expression, epigenetics, proteomics, immunology, and clinical responses to biological agents point to several existing juvenile idiopathic arthritis (JIA) categories as distinct diseases with counterparts in adult forms. Indeed, with the exception of early-onset antinuclear antibody-positive (ANA-positive) arthritis, which occurs only in children, most appear to have parallels in adult diseases.

It's time, therefore, to revisit the JIA nomenclature and classification, according to Prof. Alberto Martini of the University of Genova and Istituto G. Gaslini in Genova, Italy. At the Congress, he put forward several of ideas on which he hopes new JIA classification criteria can eventually be built.

A main goal of revisiting the current International League of Associations for Rheumatology criteria is to “finally differentiate those forms that are observed only in children from those that represent the childhood counterpart – although with different frequency and possibly phenotypes – of diseases also observed in adults,” Prof. Martini said.

Now that certain categories of JIA such as rheumatoid factor-positive (RF-positive) polyarthritis and enthesitis-related arthritis have been shown

to have pathways and disease features similar to those of adult RF-positive rheumatoid arthritis and undifferentiated spondyloarthritis, it is worth considering these as juvenile forms of the adult disorders and renaming them accordingly, argues Prof. Martini, chair of the EULAR Standing Committee on Paediatric Rheumatology.



PROF. ALBERTO MARTINI

Systemic JIA, rather than being a homogenous disease, is more likely a syndrome that includes a heterogeneous group of disorders causing a persistent activation of the innate immune system, Prof. Martini said. While the category remains valid as a whole, a large portion of sJIA patients may be better considered to have a childhood

form of Still's disease. The subset of patients with sJIA systemic features who do not develop arthritis may also be classified as having juvenile-onset Still's, following diagnostic criteria for adult-onset Still's.

Psoriatic arthritis (PsA) is a heterogeneous JIA category comprising two patient groups – one with disease analogous to adult PsA and another with characteristics of ANA-positive early-onset oligoarthritis, which is a disease of children. However, Prof. Martini argued, current International League of Associations for Rheumatology classification makes it difficult for clinicians to identify patients with disease similar to that seen in adults.

Another JIA category Prof. Martini advocated reconsidering is RF-negative polyarthritis, whose ANA-positive

subset shares much in common with ANA-positive oligoarthritis.

Early-onset, ANA-positive oligoarthritis is a well-defined entity observed only in childhood. “Some patients with this disease are nowadays wrongly classified as [having] RF-negative polyarthritis just because of a difference in the spread of arthritis, or as [having] PsA because of the presence

**A main goal of revisiting the international criteria is to ‘finally differentiate those forms that are observed only in children from those that represent the childhood counterpart ... of diseases also observed in adults.’**

of psoriasis or of some psoriatic features. It would be advisable to group all these patients together in the new category of ANA-positive, early-onset arthritis independently from the number of joints involved or the presence of psoriasis,” Prof. Martini said.

Even the broad term JIA itself might be better off abandoned, Prof. Martini argued, because it suggests a single disease with various phenotypes, as rheumatologists once understood JIA to be. Prof. Martini stressed that his recommendations are only the beginning of a process that will take years. Any new criteria “must be the result of an expert consensus of doctors and validated prospectively on a cohort of patients to see if in fact they identify more homogeneous entities.”

Prof. Martini had no disclosures.

# Little Risk Found With Biologics for JIA

BY MICHELE G. SULLIVAN

**E**tanercept, adalimumab, and methotrexate used alone appear to confer very little risk of serious infections upon children who take them for juvenile idiopathic arthritis.

The risks are significantly higher when methotrexate is combined with either of the biologics, but overall the drugs' safety profiles are good, according to the results of a study that Dr. Gerd Horneff, a pediatric rheumatologist at Asklepios Children's Hospital, Sankt Augustin, Germany, presented at the Congress.

At the same time, he said in an interview, the best way to reduce opportunistic infections in children treated for juvenile idiopathic arthritis (JIA) is to limit drug exposure by achieving good disease control.

In his multivariate analysis of 3,350 treated children with a total of 5,929 exposure-years, only disease activity level and combination therapy showed independent, significant associations with an increased risk of infections.

There were 28 serious infections – a rate of 4.7 per 1,000 person-years. The multivariate analysis showed that the use of adalimumab and etanercept significantly increased this risk, compared with methotrexate. For every increase in class on the 10-joint Juvenile Arthritis Disease Activity Score, the risk of serious infection increased by 12%, suggesting that lowering disease activity “is not only improving the quality of life but also possibly

lowering infection risk,” he said.

Dr. Horneff was a coinvestigator on another study involving 2,263 patients with 4,500 patient-years of exposure on etanercept, 500 patient-years on adalimumab, and 2,900 patient-years on methotrexate.

There were 75 serious adverse events among those taking methotrexate (2.6 per 100 person-years), 199 among those taking etanercept (4.5 per 100 person-years), and 23 among those taking adalimumab (4.6 per 100 person-years).

The rates of malignancies between the groups did not significantly differ.

Dr. Horneff has received grants from AbbVie, Pfizer, and Roche.



DR. GERD HORNEFF

# Gout Triggers Often Differ in Men, Women

BY MICHELE G. SULLIVAN

**W**omen have different predisposing risk factors for gout than do men, who more often fit the stereotypical profile of patients with gout who consume foods that increase the risk of the disease.

In the study based on data collected from participants in the Consortium of Rheumatology Researchers of North America (CORRONA) gout registry, women with gout were more likely to have taken predisposing medications and to have more gout-associated comorbidities, whereas men were more likely to consume foods linked to the disorder, such as alcohol and red meat, according to Dr. Leslie Harrold, scientific director of the CORRONA gout registry.

“We live in an era of personalized medicine,” she said in an interview. “These findings speak to the need to

tailor our evaluations and treatments based on the patient. There cannot be a one-size-fits-all approach. We need to approach women with gout differently than men with gout.”

Patients in the gout study were enrolled in 2012-2013. Data gathered from patients and their rheumatologists at study enrollment included demographics, predisposing factors (comorbid conditions, medications, diet), gout disease characteristics, current treatments, and physical exam findings.

The 54 participating rheumatologists enrolled 1,167 gout patients (239 women). Women were significantly older than men (71 years vs. 61 years) and had higher body mass index (34 kg/m<sup>2</sup> vs. 23 kg/m<sup>2</sup>). They also were significantly more likely to have hypertension (77% vs. 57%), diabetes (28% vs. 17%), and renal disease (25% vs. 14%).



DR. LESLIE HARROLD

Women also had a shorter duration of gout when enrolled (6 years vs. 11 years) and were less likely to have a crystal-proven diagnosis (26% vs. 35%).

Medication risk factors for gout, such as diuretics, were more common in women (49% vs. 22%), while dietary risk factors were more frequent in men, who consumed significantly more beer, hard liquor, beef, and pork, Dr. Harrold reported at the Congress.

Although the clinical features of gout were similar between the genders at the time of initial diagnosis, women reported more frequent disability. Women were more likely to have contraindications to treatment with NSAIDs or colchicine, but women with tophi or active disease – defined as two or more flares per year – used urate-lowering therapy at a rate that was not statistically different from men (78% vs. 84%).

A number of pharmaceutical companies have financially supported the CORRONA registry. In the last 5 years, Dr. Harrold has received research funding from Takeda and has a pending grant with AstraZeneca.

# Consider Ultrasound to Follow Gout Patients' Progress

BY KAREN BLUM

**U**ltrasound can be helpful in assessing treatment progress in gout patients, according to a study that Dr. Sébastien Ottaviani presented at the Congress.

Although ultrasound is successfully used to diagnose gout, "data are lacking on its place in follow-up of gout deposition after the initiation of urate-lowering therapy," Dr. Ottaviani of Hopital Bichat in Paris said in an interview.

His team studied 16 men with a mean age of 61 years and an average 7-year history of gout. Gout was diagnosed by the presence of crystals in synovial fluid and ultrasound evidence of urate deposits (double contour

sign and/or tophi) prior to the start of urate-lowering therapy.

A trained ultrasonographer assessed the knee joint and the first metatarsophalangeal (MTP1s) joint at baseline and 6 months after starting urate-lowering therapy. Serum uric acid levels were taken at baseline as well as at 3 and 6 months after starting treatment.



DR. SÉBASTIEN OTTAVIANI

Tophi were found on clinical exam in 56% of patients. Baseline serum uric acid levels were an average 688 micromol/L.

Ultrasound revealed tophi or a double contour sign among 63%-75% of patients in knees and 88% of patients in MTP1s.

In the 75% of patients who achieved the objective serum uric acid level of less than 360 micromol/L, ultrasound features disappeared or decreased in

all but one with a stable double contour sign in one MTP1.

Among three of the four patients not achieving the objective serum uric acid level, the ultrasound features did not disappear. Dr. Ottaviani and his colleagues called the correlation between the whole ultrasound exam and serum uric acid level "excellent."

"Ultrasound is an easy and feasible imaging procedure which can help the physician to follow gouty patients after introducing urate-lowering therapy," Dr. Ottaviani said. "The double contour sign can disappear within 3-6 months in patients achieving a low serum uric acid level."

While these findings are "promising," he said, "future randomized studies with a large number of patients are required to definitively validate ultrasound assessment for gout treated with urate-lowering therapy."

The investigators reported no relevant conflicts of interest.

# Meta-Analysis Compares Latent Tuberculosis Screening Tests

BY JENNIE SMITH

**P**atients scheduled to receive anti-tumor necrosis factor medicines must first be tested for latent tuberculosis infection and treated with a prophylactic course of antibiotics if appropriate. But "there's still no gold standard for the screening of latent TB," according to Dr. Marie Locci of the Centre Hospitalier Universitaire Nimes (France).

The tuberculin skin test (TST), in longtime use, frequently results in false-positive results, usually because

of previous vaccination with Bacillus Calmette-Guérin (BCG) or environmental mycobacterial exposures. False positives can lead to unnecessary and prolonged exposure to antibiotics. False-negative TST results also can occur in patients with immune-mediated inflammatory diseases or who are taking immunosuppressive drugs.



DR. MARIE LOCCI

In recent years, interferon-gamma-release assays (IGRAs) have been shown to have a higher specificity in detecting latent TB, as they are not affected by BCG vaccination. How-

ever, Dr. Locci and colleagues found that these may have some drawbacks as well.

At the Congress, Dr. Locci presented results from a meta-analysis of 44 studies enrolling nearly 10,000 patients with rheumatic disease or inflammatory bowel disease who were tested prior to biologic treatment. Dr. Locci and colleagues' analysis revealed poor correspondence between IGRA and TST results, which they expected. However, there was only moderate correspondence between the results of two commercially available assays, QuantiFERON TB Gold (QFT-Gold) and T-Spot. Kappas ranged from 0.28 to 0.71 in seven studies: poor in one

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study, moderate in four studies, and good in only two studies.

Both tests are designed to evaluate the interferon-gamma release in vitro, upon contact with tuberculosis antigen. However, Dr. Locci said, it has been theorized (if not proven) that one of the tests might be less affected by a low CD4 lymphocyte count in HIV patients. And the two tests are analyzed differently: One must be evaluated by laboratory technicians while the other is evaluated by an automated process.

While the meta-analysis showed that the IGRA is not affected by im-

munosuppressive drugs, corticosteroid therapy significantly decreased the rate of positivity in the T-Spot test, and showed results close to statistical significance in decreasing positivity in the QFT-Gold test. Other studies have also determined that corticosteroid therapy is associated with indeterminate results in the IGRA, Dr. Locci said. It is thought that corticosteroid treatment may be the main risk factor for an indeterminate result in these assays.

Dr. Locci said that in clinical practice, the cheaper TST remains useful as a first screening measure, because “a negative result means that latent tuberculosis infection is very unlikely.”

For example, in the case of a positive result in a patient with hepatic comorbidities, “we can then propose an IGRA test to confirm the positive result.”

Other studies recommend beginning with QFT-Gold, and if results are indeterminate, using the T-Spot test, followed by TST if required. Dr. Locci called this pathway valid, citing the cost of testing as the main limitation.

Currently, the TST test is widely reimbursed in France, while IGRA, if used from the outset, may come at a cost to patients.

Dr. Locci and colleagues disclosed no conflicts of interest relating to their findings.

## Early Methotrexate Didn't Help in Polymyositis or Dermatomyositis

BY WHITNEY MCKNIGHT

**E**arly adjunctive treatment with methotrexate and glucocorticoids in patients with either polymyositis or dermatomyositis offered no significant benefit in a multicenter, single-blind, open-label, randomized, placebo-controlled study.

When patients with polymyositis (PM) or dermatomyositis (DM) who were naive to methotrexate initially were given either glucocorticoid 1 mg/kg with or without methotrexate 20 mg/week, both groups did not differ in the total dose of the steroids (calculated by mg/kg of body weight) given between baseline and the end of the 48-week treatment course, which was the trial's primary endpoint.

At the Congress, Prof. Jiri Vencovsky of the Institute of Rheumatology, Prague, presented the results of the study of 31 patients: 17 with PM and 14 with DM. The rarity of PM/DM – which is estimated to have a prevalence of 2-10 per 100,000 individuals – has left researchers with a lack of controlled,

high-powered data, so the investigators sought to determine the actual merits of the commonly accepted clinical practice of combining immunosuppression with steroids and to establish standardized assessment methods, if necessary. Patients

were enrolled relatively early after the onset of disease, with a mean disease duration of 9.8 months.

The study, called PROMETHEUS (Polymyositis and Dermatomyositis Research on Methotrexate in European Study), was conducted across five European sites. For the study, 15 patients were randomly assigned to receive

methotrexate in combination with prednisone; 16 were thus assigned to receive only prednisone. The steroid was initially administered at 1 mg/kg and tapered according to the dosing schedule, but only if the improvement criteria recommended by the International Myositis Assessment and Clinical Studies Group (IMACS) were fulfilled.

There was no significant difference in the total prednisone dose between

the groups: 135 plus or minus 14 mg/kg in the combination therapy group, and 124 plus or minus 16 mg/kg in the group treated with steroids alone ( $P = 0.6$ ). During the study, three participants in the steroid arm dropped out, and one dropped out of the combination therapy group.

A similar percentage of patients treated with or without adjunctive methotrexate during steroid therapy for PM/DM met the IMACS definition of improvement (86% vs. 85%).

The patients' maximum duration of previous glucocorticoid treatment was 8 weeks. Patients were monitored every month for the 48-week duration of the trial.

The study's secondary endpoints were individual disease activity parameters as determined by core set measures according to IMACS and also muscle endurance, functional disability, and drug side effects.

The number of adverse events in the groups was similar, with 92 such events reported overall. Five steroid-related adverse events were reported in the steroid-alone group, while two such events were reported in the adjunct group.

The investigators reported having no relevant disclosures.



PROF. JIRI VENCOVSKY