The eular Report 2013

An authorised publication of the European League Against Rheumatism
Welcome to the EULAR Report 2013

The Annual European Congress of Rheumatology hosted by the European League Against Rheumatism (EULAR) is recognized as the primary platform for European rheumatology education and information exchange in the world. This year’s EULAR Congress was no exception. Over 14,000 attendees came to Madrid from 120 countries around the world (60% from Europe) to hear the best in rheumatology research and clinical advances. The scientific program contained presentations selected from 3,889 abstracts submitted.

We hope that this report is of interest and value for those of you who were unable to attend the EULAR Congress in Madrid and for those who did (since nobody can expect to see all of the best of the Congress while there). The EULAR 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 next EULAR Congress, to be held 11-14 June 2014 in Paris, please visit www.eular.org.

PROF. MAXIME DOUGADOS
Past President of EULAR
Professor of Rheumatology at René Descartes University
Chief of the Department of Rheumatology at Cochin Hospital, Paris

PROF. MAURIZIO CUTolo
President of EULAR
Professor of Rheumatology and Internal Medicine
Director of Research Laboratory and Academic Unit of Clinical Rheumatology
Department of Internal Medicine, University of Genova, Italy
Annual European Congress of Rheumatology
Paris, France, 11-14 June 2014

Scientific Secretariat
EULAR Secretariat
Seestrasse 240
CH-8802 Kilchberg / Zurich
Switzerland
Phone +41 44 716 3030
Fax +41 44 716 3039
E-mail: eular@eular.org

Organising Secretariat
EULAR 2014
c/o MCI Suisse SA
Rue de Lyon 75
CH-1211 Geneva 13 - Switzerland
Phone +41 22 33 99 590
Fax +41 22 33 99 601
E-mail: eular2014@mci-group.com
Revised EULAR Rheumatoid Arthritis Guidelines Keep Synthetic DMARDs First

By Mitchel L. Zoler

In a newly updated recommendations for managing rheumatoid arthritis, a EULAR task force retained much from its prior 2010 version but included some significant changes such as elevating the biologic drugs tocilizumab and abatacept to the same status as tumor necrosis factor inhibitors.

The 2013 draft revision may be most notable for what stayed the same from 2010, such as keeping conventional synthetic disease-modifying antirheumatic drugs (DMARDs) as the only first-line interventions for newly diagnosed patients with rheumatoid arthritis (RA). This means the update keeps all biologic DMARDs as secondary treatments reserved for patients who fail to respond adequately to or are intolerant of methotrexate or the other conventional, synthetic DMARDs cited as first-line options: sulphasalazine, hydrochloroquine, and leflunomide.

By maintaining synthetic DMARDs – either methotrexate monotherapy or in combined regimens – as its only first-line options for treating RA, the European League Against Rheumatism (EULAR) Task Force appointed to develop the new revision broke with the 2012 RA management recommendations of the American College of Rheumatology (ACR), which cited treatment with a tumor necrosis factor (TNF) inhibitor as a first-line option, with or without combination with methotrexate, for patients with early RA, high disease activity, and poor prognostic features (Arthritis Care Res. 2012;64:625-39).

The reason to keep all biologic DMARDs as second-line drugs was the evidence that supports the “efficacy of a treat-to-target strategy when adding biologics after insufficient response to methotrexate,” said Dr. Josef S. Smolen, professor of rheumatology at the Medical University of Vienna, who presented the draft update during a session at the Congress. Dr. Smolen stressed that although the EULAR-appointed, 33-member update task force had completed all their votes to approve the draft recommendations, the update was still subject to further review and change before its eventual publication. (See box to read all 14 recommendations.)

The new draft “does not advocate use of biologics as first DMARD strategies because the treat-to-target approach will lead to a similar overall outcome while avoiding the overtreatment of 20%-50% of patients with early RA,” Dr. Smolen explained. The revision also does not endorse monotherapy with a TNF inhibitor or any other type of biologic DMARD.

Another major break from the past in the new revision is its leveling of the role for tocilizumab and abatacept alongside the several TNF inhibitor DMARDs now on the worldwide market. Last year’s

Continued on following page

Summary of EULAR’s 2013 RA Management Recommendations

The draft 2013 EULAR rheumatoid arthritis management recommendations include three overarching principles and 14 recommendations. Here is a summary of the draft recommendations:

1. Therapy with DMARDs should start as soon as rheumatoid arthritis is diagnosed.
2. Treatment should aim to achieve remission or low disease activity.
3. Monitoring should be frequent, and if there is no improvement after a maximum of 3 months or if the target has not been reached by a maximum of 6 months, treatment should be adjusted.
4. Methotrexate should be part of the first treatment strategy.
5. When methotrexate is contraindicated or not tolerated, consider sulfasalazine or leflunomide as part of the treatment regimen.
6. Early treatment with a combination of conventional synthetic DMARDs is a reasonable alternative to initial methotrexate monotherapy.
7. Consider adding a low-dose glucocorticoid as part of initial treatment for up to 6 months; taper down as rapidly as clinically feasible.
8. If the treatment target is not reached, consider changing to another synthetic DMARD regimen; if the patient has poor prognostic features, consider adding a biological DMARD.
9. If a patient does not respond adequately to treatment with conventional, synthetic DMARDs – with or without concurrent treatment with a glucocorticoid – a biological DMARD should be started along with methotrexate. The biological DMARD could be a TNF inhibitor, abatacept, or tocilizumab.
10. Patients who fail to adequately respond to a biological DMARD should be switched to another biological DMARD. Patients who fail a first TNF inhibitor may be switched to a different TNF inhibitor.
11. Treatment with tofacitinib can be considered after patients fail treatment with biological DMARDs.
12. For patients in persistent remission, first taper down the corticosteroid dosage. If remission persists consider tapering down treatment with any biological DMARD, especially if the patient is also receiving one or more synthetic DMARDs.
13. In patients with sustained, long-term remission, consider tapering down the dosage of conventional, synthetic DMARDs as a shared decision between the patient and physician.
14. When adjusting therapy, take into account progression of structural damage, comorbidities, and safety issues, as well as disease activity.

Source: Dr. Smolen
ACR recommendations specified anti-TNF drugs as an option for initial therapy of patients with high disease activity and poor prognostic features, as well as low disease activity patients who get inadequate benefit from synthetic DMARDs. In the ACR recommendations, abatacept as well as rituximab fell lower in the management algorithm, while tocilizumab was completely off the page.

Not only do the new EULAR recommendations place tocilizumab and abatacept on the same level as the TNF inhibitors, the EULAR draft further singles out tocilizumab as the “preferred agent” for patients who must receive a biologic DMARD as monotherapy rather than the preferred way, in combination with methotrexate. “Preference is given to combining all biologicals with methotrexate,” Dr. Smolen said. The revision also cites rituximab as another biologic DMARD to consider, but it’s not ranked as high as the others.

In another change from 2010, the task force specially noted the potential benefit from using multiple conventional synthetic DMARDs for initial treatment. “The 2013 task force reiterates the evidence-based view that conventional synthetic DMARD monotherapy is effective, but based on some newer trial data on conventional synthetic DMARD combination therapy, the task force more explicitly endorses combination of conventional synthetic DMARDs early on. Preference to combination is not given because of possible limitations in the design of these trials and conflicting trial data.”

The 2013 recommendations also specify a role for tofacitinib. Dr. Smolen highlighted that the task force reached a consensus on how to fit tofacitinib into the treatment algorithm in early April, before the European Medicines Agency denied the drug European marketing approval in late April. Despite the drug being turned down as a treatment option for European patients, “the task force was convinced of the clinical, functional, and structural efficacy of tofacitinib based on available evidence.” However, citing a possibly higher risk for flare of herpes zoster, compared with biologic DMARDs, the task force said that tofacitinib should be used only in patients who had failed at least one biologic drug and “preferably two” until more experience and registry data became available.

Dr. Smolen said he has been a consultant to, a speaker for, or has received grant support from 14 pharmaceutical companies. He also said he served as the principal investigator for seven trials that assessed six different biologic agents for the treatment of rheumatoid arthritis.

Continued from previous page

In another change from 2010, the task force specially noted the potential benefit from using multiple conventional synthetic DMARDs for initial treatment. “The 2013 task force reiterates the evidence-based view that conventional synthetic DMARD monotherapy is effective, but based on some newer trial data on conventional synthetic DMARD combination therapy, the task force more explicitly endorses combination of conventional synthetic DMARDs early on. Preference to combination is not given because of possible limitations in the design of these trials and conflicting trial data.”

The 2013 recommendations also specify a role for tofacitinib. Dr. Smolen highlighted that the task force reached a consensus on how to fit tofacitinib into the treatment algorithm in early April, before the European Medicines Agency denied the drug European marketing approval in late April. Despite the drug being turned down as a treatment option for European patients, “the task force was convinced of the clinical, functional, and structural efficacy of tofacitinib based on available evidence.” However, citing a possibly higher risk for flare of herpes zoster, compared with biologic DMARDs, the task force said that tofacitinib should be used only in patients who had failed at least one biologic drug and “preferably two” until more experience and registry data became available.

Dr. Smolen said he has been a consultant to, a speaker for, or has received grant support from 14 pharmaceutical companies. He also said he served as the principal investigator for seven trials that assessed six different biologic agents for the treatment of rheumatoid arthritis.

Continued from previous page

Abatacept, Adalimumab Equivalent for RA in 2-Year Head-to-Head Trial

BY BIANCA NOGRADY

A 2-year head-to-head comparison of abatacept and adalimumab in rheumatoid arthritis patients who were on background methotrexate has found equal improvement with both biologics, according to results from a study presented at the Congress.

The randomized, investigator-blinded AMPLE trial is the first 2-year comparator study of biologics done in biologic-naive rheumatoid arthritis patients.

“Through 2 years of treatment, in this first active comparator study between biologic agents in rheumatoid arthritis patients, the 2013 task force was convinced of the clinical, functional, and structural efficacy of tofacitinib based on available evidence.” However, citing a possibly higher risk for flare of herpes zoster, compared with biologic DMARDs, the task force said that tofacitinib should be used only in patients who had failed at least one biologic drug and “preferably two” until more experience and registry data became available.

Dr. Smolen said he has been a consultant to, a speaker for, or has received grant support from 14 pharmaceutical companies. He also said he served as the principal investigator for seven trials that assessed six different biologic agents for the treatment of rheumatoid arthritis.

Continued from previous page

Abatacept, Adalimumab Equivalent for RA in 2-Year Head-to-Head Trial

BY BIANCA NOGRADY

A 2-year head-to-head comparison of abatacept and adalimumab in rheumatoid arthritis patients who were on background methotrexate has found equal improvement with both biologics, according to results from a study presented at the Congress.

The randomized, investigator-blinded AMPLE trial is the first 2-year comparator study of biologics done in biologic-naive rheumatoid arthritis patients.

“Through 2 years of treatment, in this first active comparator study between biologic agents in rheumatoid arthritis patients, the 2013 task force reached a consensus on how to fit tofacitinib into the treatment algorithm in early April, before the European Medicines Agency denied the drug European marketing approval in late April. Despite the drug being turned down as a treatment option for European patients, “the task force was convinced of the clinical, functional, and structural efficacy of tofacitinib based on available evidence.” However, citing a possibly higher risk for flare of herpes zoster, compared with biologic DMARDs, the task force said that tofacitinib should be used only in patients who had failed at least one biologic drug and “preferably two” until more experience and registry data became available.

Dr. Smolen said he has been a consultant to, a speaker for, or has received grant support from 14 pharmaceutical companies. He also said he served as the principal investigator for seven trials that assessed six different biologic agents for the treatment of rheumatoid arthritis.

Continued from previous page

Abatacept, Adalimumab Equivalent for RA in 2-Year Head-to-Head Trial

BY BIANCA NOGRADY

A 2-year head-to-head comparison of abatacept and adalimumab in rheumatoid arthritis patients who were on background methotrexate has found equal improvement with both biologics, according to results from a study presented at the Congress.

The randomized, investigator-blinded AMPLE trial is the first 2-year comparator study of biologics done in biologic-naive rheumatoid arthritis patients.

“Through 2 years of treatment, in this first active comparator study between biologic agents in rheumatoid arthritis patients, the 2013 task force reached a consensus on how to fit tofacitinib into the treatment algorithm in early April, before the European Medicines Agency denied the drug European marketing approval in late April. Despite the drug being turned down as a treatment option for European patients, “the task force was convinced of the clinical, functional, and structural efficacy of tofacitinib based on available evidence.” However, citing a possibly higher risk for flare of herpes zoster, compared with biologic DMARDs, the task force said that tofacitinib should be used only in patients who had failed at least one biologic drug and “preferably two” until more experience and registry data became available.

Dr. Smolen said he has been a consultant to, a speaker for, or has received grant support from 14 pharmaceutical companies. He also said he served as the principal investigator for seven trials that assessed six different biologic agents for the treatment of rheumatoid arthritis.

Continued from previous page
Researchers recruited 646 patients with active RA and an inadequate response to methotrexate, and randomized them to either 125 mg of abatacept weekly (without an IV load) or 40 mg of adalimumab bi-weekly, with a stable dose of methotrexate.

The data show that both agents have an excellent retention rate, with 79% of the abatacept and 65% of the adalimumab groups completing the 2-year follow-up.

The two medications showed similar efficacy for American College of Rheumatology (ACR) 20, 50, 70, and 90 responses and rates of remission on the Disease Activity Score-28 (DAS28), Dr. Schiff said. For ACR 20, the 2-year response rate was 60% in each group. The ACR 50 response rate was 47% for the adalimumab group and 45% for the abatacept group. For the ACR 70, the rates were 29% for adalimumab and 31% for abatacept, and for the ACR 90, the rates were 8% for adalimumab and 15% for abatacept.

The 2-year DAS28 rate was virtually identical in each group, with a mean decrease of about 2.2 from baseline. X-ray nonprogression was seen in 84% of each group at 2 years, Dr. Schiff said.

The study found similar numbers of serious adverse events in both arms (14% of the abatacept group and 17% of the adalimumab group). However, serious adverse events leading to discontinuation of the study medication occurred in 5% of patients taking adalimumab and 2% of those taking abatacept.

There was one death in each group—neither of which was related to the study drugs. There were seven malignancies in each group; four patients in each group discontinued their study medication because of neoplasm.

Infections were the most common serious side effects (31 total), occurring in 4% of the abatacept and 6% of the adalimumab groups. There were eight opportunistic infections—four in each group. The adalimumab group had two cases of pulmonary tuberculosis, one case of disseminated tuberculosis, and one case of disseminated histoplasmosis. There were three cases of pneumonia in the abatacept group and four in the adalimumab group.

Autoimmune events were also relatively common—18 in all, with 12 in the abatacept group (4%) and 6 in the adalimumab group (2%). Dr. Schiff said none of these were serious or clinically important.

During the question-and-answer period, Dr. Schiff said it’s not currently possible to predict which patients would respond to the drugs. “We looked at responders in both groups and were not able to differentiate them based on clinical characteristics,” he said. “We are now analyzing the biomarkers and hope to have that information for EULAR 2014.”

“EULAR/ACR guidelines recommend starting a patient on methotrexate and then optimizing the dose over 3-6 months, and if a patient has an incomplete response to methotrexate, then to add a biological agent,” said Dr. Schiff in an interview.

He noted that anti-tumor necrosis factor (anti-TNF) agents have been the first choice of most rheumatologists, and adalimumab is the most widely chosen anti-TNF agent worldwide, which is why it was selected as one of the agents for the head-to-head trial. Abatacept employs another method of action: T-cell inhibition.

“This paper has important clinical significance because a patient and his or her rheumatologist want to have data to make an informed choice of a biologic agent to add when an incomplete response to methotrexate occurs,” he said.

Dr. Schiff disclosed that he is a consultant and speaker for Bristol-Myers Squibb and AbbVie.
Synthetic Triple Therapy Matches Anti-TNF Therapy in Rheumatoid Arthritis

BY MITCHEL L. ZOLER

When rheumatoid arthritis patients fail initial treatment with methotrexate monotherapy, are they better served by a less expensive step-up treatment or the one that may better slow their radiographic progression and produce faster responses?

That seems to be the choice between step-up from methotrexate monotherapy by adding synthetic disease-modifying antirheumatic drugs (DMARDs) such as sulfasalazine and hydroxychloroquine, or by adding a tumor necrosis factor (TNF) inhibitor such as etanercept.

The RACAT (Rheumatoid Arthritis: Comparison of Active Therapies) trial tested those two options in 353 rheumatoid arthritis (RA) patients at 36 U.S. or Canadian sites between July 2007 and December 2010. The study’s primary endpoint, improvement in average disease activity score in 28 joints (DAS28) from baseline to 48 weeks of treatment, was similar in both treatment arms, proving the noninferiority of the triple synthetic DMARD regimen against the etanercept, biological arm, Dr. James R. O’Dell reported in a poster at the Congress. The results also appeared online simultaneously with Dr. O’Dell’s poster presentation (N. Engl. J. Med. 2013 June 11 [doi: 10.1056/NEJMoai1303006]).

“We showed that starting first with a TNF inhibitor or first with triple therapy resulted in the same outcomes. But costs were not the same. We [successfully] treated another 30% of patients who did not need a biologic” with the synthetic triple therapy. ‘And in the patients where triple therapy doesn’t work, you can change them to a biologic and they have identical outcomes, clinically by DAS28 and radiographically,’ compared with patients who began on etanercept added to methotrexate from the start, he said. Dr. O’Dell is chief of rheumatology at the VA Medical Center in Omaha, Neb., and professor of medicine at the University of Nebraska.

“Nothing is lost for the patient; if they don’t do well on triple therapy they can switch to a biological. The data are persuasive and the economic case is easy to make. You absolutely ought to go with triple therapy,” he concluded based on the study findings.

But “it is very difficult to get physicians to buy into this” strategy, he said in an interview. TNF inhibitors such as etanercept and other biological DMARDs are “seductive,” Dr. O’Dell said, because they are effective, work quickly, and appear more “targeted” than synthetic DMARDs, and they are promoted by well-financed marketing campaigns.

Dr. O’Dell conceded that the study data showed a signal of more radiographic progression with triple synthetic DMARD treatment that could potentially, over time, accrue to more substantial differences. At 48 weeks after the onset of treatment, patients on triple therapy had an average 0.54-point increase (worsening) in their van der Heijde modified Sharp score, compared with an average 0.29-point rise in the patients who received etanercept, a 0.25-point average difference in favor of etanercept that did not reach statistical significance. But this trend toward greater radiographic progression in patients on triple therapy was consistent with the statistically significant, roughly 1-point average additional increased radiographic progression with triple therapy, compared with patients on methotrexate plus etanercept, that was seen after 2 years of follow-up in the TEAR (Treatment of Early Aggressive Rheumatoid Arthritis) trial (Arthritis Rheum. 2012;64:2824-35).

The TEAR study, which enrolled patients with very early RA, included a subgroup with an inadequate response to methotrexate monotherapy, and in that subgroup, patients randomized to triple therapy and those randomized to etanercept plus methotrexate had similar clinical outcomes, consistent with the new study findings.

“It’s hard to say that 1 or 2 units on the Sharp score doesn’t matter much, even if you don’t see the difference for several years,” commented Dr. Daniel Furst, professor of medicine and director of the Rheumatology Clinical Research Center at the University of California, Los Angeles.

“Triple therapy is effective clinically, but it doesn’t do so well for x-rays. There are relationships between a 1 or 2 Sharp score difference and long-term outcomes. Across the board with biologics, the difference is 1 or 2 Sharp units. If one’s philosophy is to hit the RA hard and stop it, then perhaps a biologic is better,” Dr. Furst commented in an interview.

But another view was that triple therapy could play a useful and cost-effective role. The new findings, along with the TEAR results, make “initial treatment of early RA with triple therapy a reasonable approach,” said Dr. Joel M. Kremer, a professor of medicine at Albany (N.Y.) Medical College and director of research at the Center for Rheumatology in Albany. The only clear downside is that if triple therapy doesn’t work, the patient loses time, but that’s true for every treatment option, he noted.

“We don’t usually have the opportunity to hear the data for generic drugs” as much as for brand-name formulations, Dr. Kremer said in an interview. “Will data like this substantially change prescribing patterns? Probably not, but what might happen is that insurers may look at these data and say that patients should fail triple therapy before starting a biologic. That would be a sea change” for rheumatology, he added.

“I have always used methotrexate first, usually in combination with hydroxychloroquine,” Dr. Kremer said. He has not usually also prescribed sulfasalazine, but said he would consider adding it...
The new study enrolled patients with a DAS28 score of 4.4 or higher despite at least 12 weeks of stable methotrexate therapy with a weekly dosage of 15-25 mg. The patients averaged about 57 years old. After the first 24 weeks on randomized treatment, patients who did not have a decrease in their DAS28 of at least 1.2 units switched to the alternative regimens. The primary outcome was change in DAS28 at week 48 according to initial treatment assignment; the researchers collected 48-week DAS28 scores from 309 enrolled patients. The mean change in DAS28 from baseline at 48 weeks was a 2.12-unit reduction in the triple-therapy patients and a 2.29-unit reduction in the etanercept patients, an average 0.17-unit difference between the two treatment arms that was not statistically significant and that fell within the study’s prespecified range for noninferiority for triple therapy.

A similar percentage of patients, 27%, in each of the treatment arms switched to the alternative therapy at 24 weeks because of a lack of an adequate initial response. There were also no statistically significant differences between the treatment arms in their rate of American College of Rheumatology (ACR) 20 and 50 responses at both 24 and 48 weeks.

The results showed significant differences between the treatment arms after the first 24 weeks of treatment for higher-level responses. For example, the percentage of patients achieving an ACR 70 response was 5% in the triple-therapy patients and 16% in the etanercept patients, a statistically significant difference. The rate of patients with a DAS28 score of 2.6 points or less at 24 weeks was 13% in the triple-therapy patients and 22% in those on etanercept, a significant difference.

Based on findings like these, “I would start a biologic in a patient who failed high-dose methotrexate and had poor prognostic factors and highly active disease, because at 6 months etanercept had the edge,” said Dr. Edward C. Keystone, director of the Centre for Arthritis and Autoimmune Disease at Mount Sinai Hospital in Toronto, and a coinvestigator on the new study. But for all the other patients, “why not start on triple therapy first if you can switch them later if needed and the patients do well?” he asked. “The important observation is that the same percentage of patients failed in each arm. That is a huge message.”

The RACAT study received no commercial support. Dr. O’Dell said that he had no disclosures. Dr. Furst has been a consultant to or received grant support from Abbott, Amgen, Bristol-Myers Squibb, and other companies. Dr. Kremer has been a consultant to or received grant support from Pfizer, Abbott, Genentech, and other companies. Dr. Keystone said that he has been a consultant to or has received research grants from Amgen, Pfizer, Merck, and other companies.
Proposed ACR-EULAR Scleroderma Classification Criteria Are More Inclusive

BY SARA FREEMAN

ew classification criteria for scleroderma presented at the Congress correctly identify more patients who could potentially be included in epidemiological studies and clinical trials than is possible with existing classification systems.

The new system is still a proposal and is under review by the European League Against Rheumatism (EULAR) and the American College of Rheumatology (ACR), according to Dr. Frank van den Hoogen, who is the director of the rheumatology center at Sint Maartenskliniek in Nijmegen and head of the department of rheumatology at Radboud University in Nijmegen, both in the Netherlands.

In a validation cohort, the ACR-EULAR criteria had a sensitivity of 91% and a specificity of 92% to correctly identify patients with systemic sclerosis (SSc). By comparison, the 1980 Preliminary ARA Criteria had a sensitivity of 75% and a specificity of 72%.

The whole process of developing the ACR-EULAR criteria has taken about 5 years, Dr. van den Hoogen explained in an interview. “The ARA criteria were not as sensitive as we wanted because they excluded some patients with limited disease and also patients with newly diagnosed disease,” he added.

“The purpose of classification criteria is to include similar patients in research,” Dr. van den Hoogen said. “Classification criteria are not synonymous with diagnostic criteria,” he explained, “[they] are generally more standardized and less inclusive.” This is because physicians will see patients with multiple symptoms and it would not be possible to include every symptom seen in routine practice in a set of classification criteria. Nevertheless, diagnostic criteria do tend to mirror classification criteria.

The process of determining which items to include was driven by both data and consensus. Delphi exercises and a nominal group technique were used to create a set of potential items for SSc classification.

Several patient cases were then reviewed by leading scleroderma experts based in Europe and North America. The cases represented the full spectrum of systemic sclerosis, including those with a low and those with a high probability of having the disease. Experts ranked the importance of the symptoms exhibited by each of these cases, and a whittled down list with a scoring system was obtained. SSc was present with a score of 9 or more.

Skin thickening of the fingers of both hands extending past the metacarpophalangeal (MCP) joints was considered to be indicative of scleroderma, and was given a score of 9. Conversely, patients with skin involvement likely to be due to another scleroderma-like disorder or skin thickening sparing the fingers were not likely to have SSc.

Other items included skin thickening of the fingers, with subitems of puffy fingers (score = 2) and whole finger skin thickening, distal to the MCP (4); fingertip lesions, with subitems of digital tip ulcers (2) and pitting scars (3), telangiectasia (2), abnormal nailfold capillaries (2); pulmonary arterial hypertension, interstitial lung disease, or both (2); Raynaud’s phenomenon (3); and the presence of any scleroderma-related autoantibodies (3).

The ability of these criteria to correctly identify patients with and without SSc was then prospectively tested in a random sample of 200 individuals and further validated in a cohort of 405 individuals that included both early and prevalent cases of scleroderma and its mimics.

“The proposed ACR-EULAR criteria for the classification of [SSc] should allow more patients to be classified correctly as [SSc],” including those with early (less than 3 years) scleroderma and the 20% of patients who have limited disease but who do not meet current classification criteria, Dr. van den Hoogen said.

“New ACR [EULAR] criteria show increased sensitivity in comparison to the old [ARA] criteria,” concurred Dr. Suzana Jordan of University Hospital Zurich. She presented findings on the use of the proposed system in 317 patients mainly with early or mild disease from the Zurich scleroderma cohort.

Applying the criteria to this Swiss patient population, Dr. Jordan noted that “75% of [SSc] patients were correctly identified compared to just over half of all patients (51%) using the ARA criteria.” Furthermore, “50% of early scleroderma patients who did not fulfill the old criteria met the new,” she concluded.

Dr. van den Hoogen said that he had no disclosures, except that this work was funded jointly by EULAR and the ACR.
Patients with systemic sclerosis should undergo annual screening for pulmonary arterial hypertension using a combination of transthoracic echocardiography and pulmonary function tests, an international expert panel said.

These are the first evidence- and consensus-based recommendations for pulmonary arterial hypertension (PAH) screening in patients with systemic sclerosis, and the panel also called for screening patients with mixed or other connective tissue diseases with scleroderma features. “Our hope is that these recommendations will lead to earlier detection of PAH in connective tissue diseases and improve patient outcomes,” Dr. Dinesh Khanna said while presenting the screening recommendations at the Congress.

About 5%-15% of patients with systemic sclerosis develop PAH, and once PAH occurs, up to 30% of patients will die within 3 years, said Dr. Khanna, director of the scleroderma program at the University of Michigan, Ann Arbor.

“Despite having approved drugs available” to treat systemic sclerosis and other scleroderma-spectrum disorder connective tissue diseases, these treatments “have not had a huge impact on survival. The only thing we can offer patients is screening, followed by early diagnosis and treatment,” Dr. Khanna said in an interview.

The new recommendations say that patients with a tricuspid regurgitant velocity measured by transthoracic echocardiography greater than 2.8 m/s require assessment for PAH by right heart catheterization. Right heart catheterization is also needed for patients with a tricuspid regurgitant velocity of 2.5-2.8 m/s if they also have signs or symptoms of PAH such as dyspnea, fatigue, chest pain, dizziness, loud pulmonary sound, or peripheral edema. Another echo finding that should trigger right heart catheterization regardless of signs or symptoms or tricuspid regurgitation is right atrial or ventricular enlargement.

The key measures on pulmonary function tests that trigger right heart catheterization is a forced vital capacity (FVC) to diffusion capacity of lungs for carbon monoxide (DLCO) ratio of more than 1.6, or a DLCO of less than 60% if either appears in the setting of PAH signs or symptoms. Alternatively, meeting either of these pulmonary criteria should lead to right heart catheterization.

Continued on page 12
The first and only selective T-cell co-stimulation modulator approved for the treatment of RA

Now available in both IV and SC formulations

Prescribing Information can be found overleaf.
Continued from page 10

regardless of signs and symptoms if the patient’s most recent blood level of N-terminal pro-brain natriuretic peptide (NT-ProBNP) was greater than twice the upper limit of normal.

The panel also said that patients should undergo right heart catheterization regardless of PAH signs and symptoms if they fulfill the screening algorithm developed for the DETECT study (Ann. Rheum. Dis. 2013 May 18 [doi:10.1036/annrheumdis-2013-203301]).

The panel recommended annual transthoracic echo and pulmonary function test screening, or more frequently if a patient shows new signs or symptoms. Measurement of NT-ProBNP should happen at baseline, and then be repeated if new signs or symptoms of PAH appear. They also recommended applying the full DETECT screening algorithm in patients diagnosed with systemic sclerosis or other scleroderma spectrum connective-tissue disease for more than 3 years and a DLCO that is less than 60%. Right heart catheterization is mandatory to definitively diagnose PAH, Dr. Khanna stressed. The panel also said screening is not needed in patients with mixed- or other connective tissue disorders who did not have scleroderma-like features.

In a separate report at the meeting Dr. Khanna and his associates assessed the ability of transthoracic echocardiography and pulmonary function tests to screen patients with PAH. They used data from 69 patients with PAH in two separate reported series that together had 347 patients with systemic sclerosis who underwent assessment for suspected PAH (J. Rheumatol. 2011;38:2172-9 and J. Rheumatol. 2010;37:2290-8).

The new, retrospective analysis showed that combining transthoracic echo and pulmonary function test screens can have a negative predictive accuracy of 98% for correctly ruling out PAH in patients with systemic sclerosis, reported Dr. Heather Gladue, a rheumatology fellow at the University of Michigan.

The recommendations panel cautioned that its proposals should not substitute for individualized, direct assessment of each patient. The panel also noted that the cost-effectiveness of its recommendations had not yet been assessed. In addition to representatives from the University of Michigan, the task force included members from the University of California, Los Angeles; Massachusetts General Hospital, Boston; Stanford (Calif.) University; the University of Zurich; University Hospital in Lille, France; the University of Paris-South; McGill University, Montreal; Johns Hopkins University, Baltimore; and St. Joseph Hospital, Phoenix.

The task force was supported by the Scleroderma Foundation and the Pulmonary Hypertension Association. Dr. Khanna said that he has been a consultant to several drug companies including Actelion, Bayer, Genentech/Roche, Gilead, Merck, and DIGNA. Dr. Gladue said that she had no disclosures.
More Evidence Shows That TNF Inhibitors Are Associated With Reduced Diabetes Risk

BY JENNIE SMITH

Recent research has suggested that tumor necrosis factor inhibitors can significantly reduce diabetes risk in people with rheumatoid arthritis.

Dr. Siri Lillegraven of Diakonhjemmet Hospital in Oslo presented results from the CORRONA (Consortium of Rheumatology Researchers of North America) study, which Dr. Lillegraven, its lead author, called “the first large study to find the same association” at the Congress. The study used CORRONA registry data from 22,943 patients and about 22,000 RA treatment regimens with a mean duration between 1.5 and 2.4 years.

Dr. Lillegraven and her colleagues found an adjusted hazard ratio for type 2 diabetes of 0.35 for TNF inhibitors (95% confidence interval, 0.13-0.91), compared with a reference group of nonmethotrexate, nonhydroxychloroquine, nonbiologic disease-modifying antirheumatic drugs such as cyclosporine, sulfasalazine, and leflunomide. The disease-modifying antirheumatic drugs (DMARDs) hydroxychloroquine and methotrexate were separately compared with this reference group.

“It was a statistically significant finding, and the model was adjusted for differences between patients who received TNF inhibitors and the patients who received the comparator drugs,” Dr. Lillegraven said in an interview.

One of Dr. Lillegraven’s coauthors on the study, Dr. Daniel Solomon of Brigham and Women’s Hospital in Boston earlier reported a lower risk of type 2 diabetes for individuals taking TNF inhibitors or hydroxychloroquine, compared with nonbiologic DMARDs (JAMA 2011;305:2525-31).

In that study, which enrolled about 14,000 patients and evaluated about 22,000 treatment episodes, the multivariate adjusted hazard ratio for diabetes was 0.62 (95% confidence interval, 0.42-0.91) for TNF inhibitors, compared with other nonbiologic DMARDs. The effect was even greater for hydroxychloroquine, compared with other nonbiologics (HR, 0.54; 95% CI, 0.36-0.80).

Dr. Lillegraven and her colleagues saw a similar effect size for hydroxychloroquine, compared with the nonbiologic DMARDs, but this did not reach statistical significance.

As both studies were observational in design, Dr. Lillegraven noted, the results do not carry the weight of randomized, controlled trial findings. “We would have loved to have a clinical trial that confirmed the findings,” she said, adding that designing such a trial would be difficult. “The outcome is relatively rare, and you will not likely get enough diabetes outcomes to be able to conclude whether an exposure had an effect.” In Dr. Lillegraven and her colleagues’ study, for example, only 84 incident cases of diabetes occurred.

Last year, investigators reported that TNF inhibitors were associated with a halving of diabetes risk, compared with RA patients who had never used them (HR, 0.49; 95% CI 0.24-0.99), in a cohort of 1,587 RA patients without diabetes at enrollment who were followed for 3-4 years (Arthritis Care Res. 2012;64:215-21), and several studies have suggested a relationship between the biologic pathways that TNF inhibitors affect and diabetes.

Dr. Lillegraven also analyzed the impact of body-mass index and steroid dosage on diabetes incidence in these patients. Those with a BMI of more than 30 kg/m² had a statistically significant sixfold increased rate of incident diabetes, compared with patients with a BMI of less than 25 kg/m². Patients with a BMI of 25-30 kg/m² had a significant, nearly twofold increased rate. Patients who received a steroid dose of at least 7.5 mg/day had a statistically significant, twofold increased diabetes incidence, compared with patients who did not receive any steroid treatment.

Dr. Lillegraven said that her study’s findings, added to the earlier findings, support “a potential for tailoring treatment in high-risk individuals.” But it is still too early to draw any definite conclusions regarding how this should be carried out in the clinic, she cautioned.

Dr. Lillegraven declared no conflicts of interest relevant to her study. Dr. Solomon declared unpaid consultancies for Pfizer and Novartis. Three other coauthors reported financial relationships with pharmaceutical firms and CORRONA, a database registry for rheumatologic diseases; one is an employee of CORRONA.
MRI Scoring System for Joint-Space Narrowing Has Research Promise in RA

BY ELIZABETH MECHCATIE

A magnetic resonance imaging scoring system of joint-space narrowing in rheumatoid arthritis showed “a very high” agreement with computed tomography scores and may become a useful tool in rheumatoid arthritis clinical trials after further validation, judging from data presented by Dr. Uffe Møller Døhn.

In a small study, which was conducted to validate the OMERACT-RAMRIS MRI JSN scoring system in the wrists and metacarpophalangeal (MCP) joints, there was a very high agreement between the joint-space narrowing scores on MRI and CT and moderate agreement between scores on MRI and x-ray, said Dr. Møller Døhn of Copenhagen University Hospital at Glostrup at the Congress. In addition, there was “high to very high” inter- and intrareader reliability, particularly for the wrist joints.

An OMERACT (Outcome Measures in Rheumatology) initiative, this scoring system is being developed to provide a more precise and sensitive method of measuring joint space damage in patients with rheumatoid arthritis (RA), but it needs to be validated through comparisons to other imaging methods.

To evaluate the degree of agreement with CT and x-ray scores, this study assessed MRI and CT images of the wrist and second to fifth metacarpophalangeal (MCP 2-5) joints of 14 people with RA and one healthy control, who were from a clinical trial. Three readers assessed the images twice, and a single reader scored x-rays using the Sharp-Van der Heijde method, said Dr. Møller Døhn, who is in the center for rheumatology and spine diseases at the hospital.

The MRI scores of joint space narrowing “were very highly correlated” with CT scores, when comparing the wrist and MCP scores both separately and combined: Using intraclass correlation coefficients (ICCs) as a measure of agreement between scores and scorers, the MRI and CT scores for joint space narrowing were 0.94 for the MCP joints, 0.92 for the wrist, and 0.92 for the wrist and MCP joints combined. But the ICCs for the x-ray joint space narrowing scores were lower: With MRI scores, the ICCs were 0.49 for the MCP 2-5 joints and 0.55 for the wrist. With CT scores, the ICCs were 0.56 for the MCP 2-5 joints and 0.43 for the wrist.

“The most important next step is to test the scoring system in a longitudinal setting, in order to investigate the sensitivity to change,” Dr. Møller Døhn said in an interview. “Before the system can be implemented as an outcome measure in clinical trials, we need to know if it is more sensitive than other methods that are already available. If it turns out that [joint space narrowing] assessment of several joints on x-ray is just as good as – or better than – MRI, then it does not add information to what we already use today.”

Dr. Møller Døhn reported that he had no relevant financial disclosures.
Algorithm Helps to DETECT Pulmonary Arterial Hypertension in Systemic Sclerosis

BY SARA FREEMAN

The use of a two-step algorithm significantly increased the rate at which pulmonary arterial hypertension was diagnosed in patients with systemic sclerosis in a prospective, observational, cross-sectional study.

The results of the DETECT study, presented at the Congress, showed that the two-step algorithm had a sensitivity of 96% for correctly identifying the condition, which was higher than the 71% sensitivity obtained using methods recommended currently by the European Society of Cardiology/European Respiratory Society (ESC/ERS) guidelines. The ESC/ERS recommendations are mainly based on consensus rather than robust evidence, and focus on the use of transthoracic echocardiography.

“DETECT is unique because it shows that if you just do an echocardiogram that you miss 29% of people who subsequently have pulmonary arterial hypertension [PAH], whereas if you apply the DETECT algorithm you miss only 4% of the people,” Dr. Dinesh Khanna, director of the scleroderma program at the University of Michigan, Ann Arbor, said in an interview.

Dr. Khanna, who was a coinvestigator in the study, added: “PAH is a leading cause of mortality; it has high prevalence and it has a median survival of 2-3 years. ... You don’t want to miss these patients.” Dr. Khanna presented recommendations for annual screening of PAH in systemic sclerosis patients at another session at the meeting. (See article on page 8.)

Although 4% of patients are still being missed, this is a dramatic improvement over current clinical practice, said DETECT investigator Dr. Christopher Denton, who presented the findings of the international, multicenter trial. The study was also recently published online (Ann. Rheum. Dis. 2013 May 18 [doi: 10.1136/annrheumdis-2013-203301]).
MRI Detects High Level of Subclinical Small Joint Inflammation in Early Arthritis

BY SARA FREEMAN

A high percentage of patients with early arthritis have inflammation of the small joints that can be detected with MRI but not by physical examination.

Results of a cross-sectional study, presented by Dr. Annemarie Krabben at the Congress, found that 66% of wrist, 27% of metacarpophalangeal (MCP), and 13% of metatarsophalangeal (MTP) joints that were not clinically swollen showed signs of inflammation on MRI. However, inflammation on MRI was present in 92% of wrists, 86% of MCP, and 29% of MTP joints that were clinically swollen.

"You would expect that inflammation on MRI would be present in the clinically swollen joints, but we also saw inflammation in the nonswollen joints," explained Dr. Krabben of Leiden University Medical Center in the Netherlands. Furthermore, "when you look at the joints with MRI-detected inflammation, a lot of these didn't have clinical inflammation," she added.

Clinical joint swelling was absent but signs of bone marrow edema were detected on MRI in 60% of wrist, 53% of MCP, and 78% of MTP joints. If severe MRI-detected edema was considered, joint swelling was absent in 35%, 39%, and 58% of wrist, MCP, and MTP joints, respectively. Joints without clinical swelling showed signs of inflammation on MRI in 61% of wrist, 64% of MCP, and 77% of MTP joints.

The study involved patients with early arthritis who were part of the Leiden Early Arthritis Clinic cohort. Overall, patients had undifferentiated arthritis (37%), rheumatoid arthritis meeting the 2010 American College of Rheumatology-European League Against Rheumatism criteria (36%), or other diagnoses (27%). This cohort was established in 1993 to detect and treat inflammatory disorders early in the disease state (Rheumatology [Oxford] 2011;50:93-100).

Upon entry into the cohort, patients underwent a physical examination that included 68 tender and 66 swollen joint counts and 1.5-Tesla MRI of the wrist, MCP, and MTP joints. The latter were used to determine the presence and extent of synovitis, bone marrow edema, and tenosynovitis.

In total, 1,790 small joints were examined in 179 patients who had a median duration of symptoms of 15 weeks. Overall, 30% of wrist, 15% of MCP, and 11% of MTP joints were swollen at physical examination and the majority also showed inflammation on MRI.

Continued on following page
Rheumatoid Arthritis Remission Similar for Tocilizumab Alone or With Methotrexate

BY MICHELE G. SULLIVAN

Patients with early, active rheumatoid arthritis who took tocilizumab—in either alone or in combination with methotrexate—continued to benefit from it by the end of a 2-year study.

About half of those on either treatment strategy in the study achieved remission by the end of the first year and this did not change appreciably by the end of the second year. There was also a very low rate of radiographic progression, Dr. Tom Huizinga said at the Congress.

The results confirm and extend the earlier findings of ACT-RAY, a 2-year, randomized, placebo-controlled study of tocilizumab employed as a switch or add-on therapy for patients with early, active rheumatoid arthritis (RA). The 24-week data, published earlier this year, showed that tocilizumab was just as effective without methotrexate as with it, suggesting that it could be employed as monotherapy (Ann. Rheum. Dis. 2013;72:43-50).

All 553 patients in ACT-RAY received open-label tocilizumab 8 mg/kg intravenously every 4 weeks. They were randomized to the switch strategy (tocilizumab 8 mg/kg IV every 4 weeks with oral placebo) or the add-on strategy (tocilizumab 8 mg/kg IV every 4 weeks plus 2.5 mg methotrexate), said Dr. Huizinga, head of the department of rheumatology at Leiden (the Netherlands) University Medical Center.

Most of the patients (81%) were women; mean age was 53 years. Patients had a mean disease duration of 8 years and a mean Disease Activity Score–28 (DAS28) of 6.4.

Most of the study group (433) completed the second year of treatment. Reasons for withdrawal included lack of efficacy (2% in the add-on strategy group and 5% in the switch strategy group) and adverse events (10% of add-on patients and 11% of switch). There were three deaths in the add-on group and six in the switch group.

Sustained remission was defined as a DAS28 of less than 2.6 at two consecutive visits separated by 12 weeks. By week 52, about 50% of the overall cohort (53% add-on strategy and 47% switch strategy) had achieved remission and were able to discontinue tocilizumab.

By week 104, 86% of the overall cohort had experienced a flare in disease activity, with a median time of 90 days from tocilizumab discontinuation. Most of those patients restarted tocilizumab. The medication continued to be effective. The mean DAS28 at flare was 4.46, dropping to a mean of 2.99 within 4 weeks of restarting treatment.

The mean DAS28 score at week 104 was unchanged from the score at week 52, decreasing by 3.6 from baseline in both groups. The large majority of each group experienced no radiographic progression during year 2 (94% of the add-on and 91% of the switch groups).

By the end of the study at week 104, 23% of the add-on group and 18% of the switch group were in remission as measured by the Clinical Disease Activity Index—virtually identical to CDAI remission rates at week 52.

The safety results were consistent with previous findings, Dr. Huizinga said. Serious adverse events and infections occurred in 15% of the add-on group and 4% of the switch group.

Liver enzyme elevations were more common among those in the add-on group. Elevations of up to three times the upper limit of normal of alanine amino-transferase occurred in 58% of the add-on group and 40% of the switch group. Elevations of up to five times the upper limit occurred in 13% of the add-on group and 5% of the switch group. Aspartate transaminase elevations of up to three times the upper limit of normal occurred in 51% of the add-on group and 30% of the switch group. Elevations of up to five
A new radiographic scoring method successfully assessed damage in the large joints of patients with rheumatoid arthritis who were being treated with biologic therapy, according to research presented at the Congress.

The ARASHI (Assessment of Rheumatoid Arthritis by Scoring of Large-Joint Destruction and Healing in Radiographic Imaging) method, developed by a team in Japan, was tested over a period of 2 years in 51 patients who were being newly treated with tumor necrosis factor–alpha (TNF-alpha) inhibitors.

“Evaluation of radiographic damage of the small joints in the hands and feet using the van der Heijde total Sharp score in patients with early RA [rheumatoid arthritis] has been established,” said Dr. Isao Matsushita, assistant professor in the orthopedic surgery department at the University of Toyama, Japan.

While the Larsen grade is most often used to assess large joints, this radiographic grading system has several limitations, including a “ceiling effect,” resulting from the substantial variation found within each of the six Larsen grades (scored 0-5), he said in an interview at the meeting. Dr. Matsushita and his colleagues developed the ARASHI method to offer a more sensitive means of determining radiographic progression in the large joints.

The ARASHI method is composed of two parts (Mod. Rheumatol. 2013 April 27 [doi: 10.1007/s10165-012-0823-6]), Dr. Matsushita explained. First, there is a status score, which takes four categories into account: joint space narrowing (scored 0-3), erosion (scored 0-3), joint surface (0-6), and joint stability (0-4).

Second, there is a change score, which assesses the same four categories plus the porosity of the joint.

A total of 57 patients with early RA who were about to be treated with TNF-alpha inhibitors were included in the study, and 51 completed 2 years’ treatment with these agents. The most frequently prescribed TNF-alpha inhibitors were infliximab, in 24 patients, and etanercept, used in 14; another 7 patients switched from infliximab to etanercept, and 6 patients were treated with adalimumab.

The mean age of the patients was 60 years, with a mean RA duration of 10.6 years.

The investigators used the ARASHI status score to assess 96 hip and 86 knee joints at baseline (before TNF-alpha inhibitor treatment was started). They later computed the ARASHI change score for the joints at both 1-year and 2-year follow-up visits. A 1-point or more increase in the ARASHI change score constituted radiographic progression. Higher scores indicated higher levels of joint damage.

All of the hip and knee joints with a status score of greater than 2 showed progression of joint damage under TNF-blocking therapies, Dr. Matsushita said. He added that of the joints with a low baseline ARASHI status score (0-2), only 6.5% showed progressive damage over the course of the study. Furthermore, the joint-space narrowing score was more closely related to the joint damage subsequently seen than was the erosion score.

Taken together, these findings demonstrate that the ARASHI scoring method is useful for the evaluation of radiographic damage in large weight-bearing joints, and to predict the risk for progression in patients with RA,” said Dr. Matsushita, noting that the next step is to look at the utility of the score in other large joints, perhaps the shoulder, elbow, and ankle joints.

Dr. Matsushita said that he had no disclosures.
RoACTEMRA is the only biologic proven superior to a TNF inhibitor (adalimumab) in RA monotherapy.\(^8\)

**ONE BIOLOGIC MONOTHERAPY STANDS OUT**

1 in 3 RA patients receive biologic monotherapy.\(^1\)-\(^7\)

Prescribing Information RoACTEMRA\(^®\) (tocilizumab) in Rheumatoid Arthritis (RA): Please refer to RoACTEMRA SPC for full prescribing information.

**Indication:** RoACTEMRA, in combination with methotrexate (MTX), is indicated for the treatment of moderate to severe active rheumatoid arthritis (RA) in adult patients who have either responded inadequately to, or who were intolerant to, previous therapy with one or more disease-modifying anti-rheumatic drugs (DMARDs) or tumour necrosis factor (TNF) antagonists. In these patients, RoACTEMRA can be given as monotherapy in case of intolerance to MTX or where continued treatment with MTX is inappropriate. RoACTEMRA has been shown to reduce the rate of progression of joint damage as measured by X-ray and to improve physical function when given in combination with MTX.

**Dosage and Administration:** Patients should be given the Patient Alert Card. Infusion iv infusion given once every 4 weeks. Doses exceeding 800mg per infusion are not recommended. Dose adjustments: Dose reduction to 4mg/kg, or interruptions, are recommended in the event of raised liver enzymes, low absolute neutrophil count (ANC) or low platelet count. RoACTEMRA should not be initiated in patients with ANC count below 2x10^9/L.

**Contraindications:** Hypersensitivity to any component of the product, active, severe infections. Precautions: Infections: Cases of serious and sometimes fatal infections have been reported, interrupt therapy until controlled. Caution in patients with recurring/chronic infections, or other conditions which may predispose to infection. Tuberculosis (TB): Screen for and treat latent TB prior to starting therapy. There is a risk of false negative tuberculin skin and interferon-gamma TB blood test results, especially in patients who are severely ill or immunocompromised. Patients should be instructed to seek medical advice if signs/symptoms of a tuberculosis infection occur during or after therapy with RoACTEMRA. Hypersensitivity reactions: Serious hypersensitivity reactions have been reported and may be more severe and potentially fatal in patients who have experienced hypersensitivity reactions with previous infusions even if they have received premedication with steroids and antihistamines. Appropriate treatment should be available for immediate use if anaphylaxis occurs. If an anaphylactic reaction or other serious hypersensitivity reaction occurs, permanently discontinue RoACTEMRA. Hepatic disease/impairment: Use with caution in patients with active hepatic disease/impairment. Transaminase elevations: Not recommended in patients with ALT or AST >5xULN; caution in patients with ALT or AST >1.5xULN. Haematological abnormalities: Caution in patients with platelet count <100x10^9/L. Continued treatment not recommended in patients with ANC <0.5x10^9/L or platelet count <50 x 10^3/µL. Lipid parameters: If elevated, follow local guidelines for managing hyperlipidaemia. Vaccinations: Live and live attenuated vaccines should not be given concurrently. Combined with other biologic treatments: Not recommended. Viral reactivation: Has been reported with biologics. Diverticulitis: Caution in patients with a history of intestinal ulceration or diverticulitis. Patients with symptoms of complicated diverticulitis should be evaluated promptly. Interactions: Patients taking other medicines which are metabolised via CYP450 3A4, 1A2, or 2C9 should be monitored as doses may need to be adjusted. Pregnancy and Lactation: Women should use contraception during and for 3 months after treatment. A decision on whether to continue/discontinue breastfeeding on RoACTEMRA therapy should take into account relative benefits to mother and child. Undesirable effects: Prescribers should consult SPC for full details of ADRs. Very common ADRs (≥1/10); URTI, hypercholesterolaemia. Common ADRs (≥1/100 to <1/10); cellulitis, pneumonia, oral herpes simplex, herpes zoster, abdominal pain, mouth ulceration, gastritis, rash, pruritus, urticaria, headache, dizziness, increased hepatic transaminases, increased weight and increased total bilirubin, hypertension, leukopenia, neutropenia, peripheral oedema, hypersensitivity reactions, conjunctivitis, cough, dyspepsia. Medically significant events: Infections: Opportunistic and serious infections have been reported, some serious infections had a fatal outcome. GI perforations: Primarily reported as complications of diverticulitis. Infusion reactions: Clinically significant hypersensitivity reactions requiring treatment discontinuation were reported and were generally observed during the 2nd – 5th infusions. Fatal anaphylaxis has been reported. Other: Decreased neutrophil count, decreased platelet count, hepatic transaminase elevations, lipid parameter increases, very rare cases of pancreatitis. Legal Category: POM.

**POM Presentations and Basic NHS Costs:** 10mg of tocilizumab in 4mL, (20mg/mL) 1 vial: £102.40, 200mg of tocilizumab in 10mL, (20mg/mL) 1 vial: £256.00, 400mg of tocilizumab in 20mL, (20mg/mL) 1 vial: £512.00. Marketing Authorisation Numbers: EU/1/08/492/01 80mg; EU/1/08/492/03 200mg; EU/1/08/492/04 400mg. Marketing Authorisation Holder: Roche Registration Limited, 6 Falcon Way, Welwyn Garden City, Herts AL7 1XR. RoACTEMRA is a registered trade mark.

**Date of preparation:** February 2013 RCU/KMED00022

REFERENCES


Date of preparation: September 2013 – Zinc code: GL/ACTE/1309/0014

**WHEN COMBINATION IS NOT AN OPTION**
Ultrasound Speeds New Rheumatoid Arthritis Diagnoses and Treatment

BY MITCHEL L. ZOLER

Routine joint scans by ultrasound in patients with suspected rheumatoid arthritis led to faster diagnoses and quicker initiation of disease-modifying treatment in a multicenter-study of more than 250 patients.

But the results did not address whether this earlier diagnosis and treatment produced better outcomes. “While earlier diagnosis and treatment is known to lead to better outcomes, a large, prospective study is required to explore the long-term clinical impact and cost-effectiveness of wider routine use of ultrasound by rheumatologists,” Dr. Stephen Kelly said at the Congress.

Despite this current limitation of the available evidence, Dr. Kelly is convinced of the value of routine ultrasound examinations for joint assessment in patients with possible rheumatoid arthritis (RA). “You can see raging inflammation in joints that are not swollen or tender,” he said in an interview. The discrepancy between clinical symptoms and the ultrasound appearance can be “surprising,” said Dr. Kelly, a rheumatologist at Milen End Hospital in Barts Health NHS Trust in London.

The current study involved observation of patients referred by primary care physicians to rheumatologists at four U.K. hospitals. Each of the four sites selected included some rheumatologists who routinely used ultrasound and others who did not.

By the end of the study, 134 patients had been assessed with ultrasound joint examinations and 124 had been assessed without ultrasound. All patients were initially seen in the referral rheumatology clinics an average of 5 months after symptom onset. They had a mean age of about 53 years, and about 70% were women.

Among the 134 patients assessed initially with ultrasound, the average time to a formal RA diagnosis was 2.24 months, and the median time was 0.89 months. Among the patients not examined with ultrasound, a formal RA diagnosis was made at a mean of 2.76 months and a median of 2 months. These differences were statistically significant.

The investigators eventually diagnosed RA in 54 of the patients assessed with ultrasound and in 58 patients assessed without ultrasound. The median time to the start of treatment with a disease-modifying antirheumatic drug (DMARD) was 0.62 months among patients routinely examined with ultrasound and 1.41 months among those not.

VIEW ON THE NEWS

Ultrasound Helps Early Diagnosis in Challenging Cases

The main issue when imaging joints in patients with suspected rheumatoid arthritis (RA) or early disease is: What does imaging add to a standard clinical examination? Standard x-rays do not show many erosions in patients with early disease; ultrasound, as well as MRI, are much more sensitive. Both ultrasound and MRI can be very helpful for difficult-to-diagnose cases. In my experience, about 5%-10% of early-diagnosis cases benefit from using ultrasound or MRI imaging of joints.

Ultrasound is more widely used than MRI is and also costs less. You can examine multiple joints with ultrasound, you don’t need to inject contrast, and you can also use the ultrasound to guide injections. For all these reasons, ultrasound has rapidly become widely used to aid early diagnoses. But not every clinician has the expertise to perform ultrasound examinations, and it has not yet been definitively proven that using ultrasound routinely for diagnostically challenging cases is cost effective. I suspect it is cost effective to perform ultrasound examinations fairly broadly on patients suspected of having RA, compared with the financial and social costs of delayed RA diagnosis in which the patient goes untreated for an added period of time, but study results are still needed to prove this.

In June, I chaired a task force that issued the European League Against Rheumatism’s first recommendations on using joint imaging in the management of RA (Ann. Rheum. Dis. 2013;72:804-14). The 10 recommendations made by the task force include several that support and encourage the use of ultrasound or MRI for both the initial diagnosis of RA as well as subsequent management. However, because evidence is currently lacking to fully document the feasibility, cost, and training required to use methods like ultrasound in routine practice, our recommendations could not be unqualified. For example, our first recommendation says, “When there is diagnostic doubt, conventional radiography, ultrasound, or MRI can be used to improve the certainty of a diagnosis of RA above clinical criteria alone.” The level of evidence for this recommendation is level III, which is not the highest level. In addition, note that the recommendation says “can be used” rather than mandating the use of ultrasound or another imaging method. In the same way, our third recommendation says, “Ultrasound and MRI are superior to clinical examination in the detection of joint inflammation; these techniques should be considered for more accurate assessment of inflammation.” Again, the level of evidence, III, precluded us from saying anything more definitive than “should be considered.”

Philip G. Conaghan, M.B., Ph.D., is a professor of musculoskeletal medicine at Leeds (England) University. He said that he is a speaker on behalf of or an advisor to Bristol-Myers Squibb, Pfizer, and Roche. He made these comments in an interview.
Continued from previous page

examined without ultrasound.

Put another way, among the patients eventually diagnosed with RA, 67% were diagnosed within a month of initial referral when their rheumatologists routinely used ultrasound, compared with 37% of the RA patients diagnosed within the first month when ultrasound wasn’t used.

Initiation of DMARD treatment for the subgroup eventually diagnosed with RA happened in the first month for 63% of the patients routinely assessed by ultrasound, and in 32% of those worked-up without ultrasound.

In a further analysis, the rheumatologists who assessed 134 patients with ultrasound were asked whether their use of ultrasound made a difference. Fifty-three percent said that the first scan they obtained was instrumental in making their diagnosis, and 39% said that a subsequent ultrasound exam was critical in their diagnostic process.

The researchers also asked the rheumatologists who used ultrasound whether the ultrasound results played an important role in management decisions. Thirty-eight percent of the rheumatologists said that the first ultrasound scan they obtained played an important role in their management decisions, and 57% said that a subsequent ultrasound scan affected management.

The study was sponsored by AbbVie. Dr. Kelly said that he had no personal disclosures.

Biologics Reduced Sick Leave in RA Patients

BY BIANCA NOGRADY

Biologics and improved strategies for their use have significantly reduced the relatively high rate of sick leave among patients with rheumatoid arthritis, but more efficient, multiprofessional intervention strategies are still needed to reduce its incidence, Mathilda Björk, Ph.D., reported at the Congress.

Dr. Björk, of Jönköping University, Sweden, conducted a subanalysis of the Swedish Early Rheumatoid Arthritis cohort study (Swedish acronym – TIRA). The study included patients with early rheumatoid arthritis, and was designed to calculate direct and indirect costs of the disease over a 3-year period. There have been two TIRA cohorts – one in 1996-1998 and one in 2005-2008. All had early disease; they were a mean of 62 years at baseline.

At all follow-up visits, the patients met with a multidisciplinary team including a physician, an occupational therapist and a physiotherapist, and were given individual treatment based on their needs.

Those in the more recent cohort were treated more aggressively with disease-modifying antirheumatic drugs (DMARDs), mainly methotrexate, starting at their first visit. They also received biologics when required.

Dr. Björk’s study examined sick leave rates between the two TIRA cohorts: 1996-1998 and 2005-2008. The comparison found that sick leave rates in the newer cohort declined about 50% compared to those in the older cohort.

In the early cohort, sick leave rates were stable over the 3-year study period. At baseline, 60% of the patients were taking sick leave due to their RA; that number was unchanged at 3 years.

In the newer cohort, the baseline sick leave rate was similar, with 55% taking leave due to their disease. But at the 3-year follow-up, only 30% were on sick leave.

“I think it’s good news,” Dr. Björk said in an interview. Since both groups were making use of the multidisciplinary team treatment, DMARD treatment appeared to be the main driver behind the difference. “They are being used more frequently and in higher doses, and it’s working.”

Dr. Björk said the study came about not only because RA is associated with such high indirect costs for sick leave, but also because of the direct treatment costs of new medications such as biological agents.

“The rationale behind the study was to explore whether more effective disease control reduces sick leave in a post-biologic cohort compared to a prebiologic cohort, with the potential for compensating some of the increased treatment cost.”

The researchers suggested that changes in political policies and the sickness insur-

Continued on following page
Continued from previous page

...tmall for greater patient outcomes. Ms. Anink and her associates therefore set out to determine how prescription trends had changed in Holland since biologic agents became available and how such trends might have influenced patient outcomes. The team used data from the Dutch National Arthritis and Biologics in Children Register, which is an ongoing, multicenter, prospective, observational initiative that began in 1999 with the aim of including all patients with JIA who are treated with a biologic agent for their condition.

Upon inclusion in the ABC Register, key patient characteristics are collected, including age, gender, JIA category, age at diagnosis, disease duration, and prior medication use. Patients are also assessed for current medication use, adverse events of treatment, and a host of laboratory and disease activity parameters, which are assessed again 3 and 6 months after inclusion, and then annually.

A total of 429 cases were included in the current analysis, of which 343 patients had nonsystemic and 86 had systemic disease. Patients had started treatment with at least one biologic agent between 1999 and 2010. There were 82 prescriptions for biologic agents in 2010 for both systemic and nonsystemic JIA, compared with only 12 during 1999-2000. Biologic agents were prescribed after shorter disease durations in 2008-2010, compared with 1999-2001, dropping from 3.3 years to 3.0 years, respectively, in nonsystemic JIA and from 3.5 years to 0.4 years, respectively, for systemic disease, Ms. Anink reported.

Non-systemic JIA patients with lower disease activity at baseline were also being treated with these drugs. Indeed, the median number of active joints at baseline fell from 18 before biologic therapy was given to 5. The median number of joints with limited motion decreased from 12 to 3, and Childhood Health Assessment Questionnaire (CHAQ) scores fell from 1.8 to 1.1 over the same time periods.

Importantly, the proportion of patients with inactive disease after 3 months of therapy increased dramatically, from 0% in 1999-2001 to 34% during 2008-2010 for nonsystemic disease and from 0% to 64% for systemic disease. “We saw the threshold for prescription decreased, which was earlier in the disease course and in patients with lower disease activity,” Ms. Anink summarized. “With these trends, we say the short-term treatment outcomes improved in all JIA categories.”

Similar findings were presented separately at the meeting by a German team. Dr. Kirsten Minden of the German Rheumatism Research Centre, Berlin, and her associates reported that the use of traditional and biologic disease-modifying agents for the treatment of polyarticular JIA rose and occurred earlier over a 12-year period (Ann. Rheum. Dis. 2013;72:731). Improved patient health status, including functional capacity measured by the CHAQ score, disease activity measured by the 10-joint Juvenile Arthritis Disease Activity Score, and pain and overall well-being, coincided with treatment changes.

The ABC Register was financially supported by the Dutch Board of Health Insurances (from 2003 to 2006), Pfizer (formerly Wyeth International, since 2007), and Abbott (since 2010). Ms. Anink had no disclosures to report.

Biologic agents are increasingly being used in the treatment of juvenile idiopathic arthritis, earlier in the course of the disease and in less severe cases, according to longitudinal data from the Dutch National Arthritis and Biologics in Children Register.

Etanercept, which blocks tumor necrosis factor (TNF), was the first biologic agent to be registered in Holland in 1999, Ms. Anink noted. Additional anti-TNF therapies, such as infliximab and adalimumab, became available in 2007-2008, followed by the interleukin (IL-1) blockers canakinumab and anakinra in 2009-2010, and, more recently, the IL-6 blocker tocilizumab in 2011.

Alongside the availability of these novel drugs, treatment goals have changed, from the prevention of long-term joint damage and disability to achieving inactive disease through more aggressive and earlier therapy, Ms. Anink said at the Congress (Ann. Rheum. Dis. 2013;72:154). It’s not known, however, whether the use of these drugs actually leads to better patient outcomes.

With Juvenile Idiopathic Arthritis

Earlier Biologic Use Is on the Rise in Patients With Juvenile Idiopathic Arthritis

BY SARA FREEMAN

The impact of rheumatoid arthritis on an individual’s ability to work is a complex interaction of biological, psychological, social, and occupational factors,” she said. “The interventions need to have a wider perspective than the disease process.”

Dr. Björk had no conflicts of interest relevant to the study.

The median number of active joints at baseline fell from 18 before biologic therapy was given to 5. The median number of joints with limited motion decreased from 12 to 3, and Childhood Health Assessment Questionnaire (CHAQ) scores fell from 1.8 to 1.1 over the same time periods.

Importantly, the proportion of patients with inactive disease after 3 months of therapy increased dramatically, from 0% in 1999-2001 to 34% during 2008-2010 for nonsystemic disease and from 0% to 64% for systemic disease. “We saw the threshold for prescription decreased, which was earlier in the disease course and in patients with lower disease activity,” Ms. Anink summarized. “With these trends, we say the short-term treatment outcomes improved in all JIA categories.”

Similar findings were presented separately at the meeting by a German team. Dr. Kirsten Minden of the German Rheumatism Research Centre, Berlin, and her associates reported that the use of traditional and biologic disease-modifying agents for the treatment of polyarticular JIA rose and occurred earlier over a 12-year period (Ann. Rheum. Dis. 2013;72:731). Improved patient health status, including functional capacity measured by the CHAQ score, disease activity measured by the 10-joint Juvenile Arthritis Disease Activity Score, and pain and overall well-being, coincided with treatment changes.

The ABC Register was financially supported by the Dutch Board of Health Insurances (from 2003 to 2006), Pfizer (formerly Wyeth International, since 2007), and Abbott (since 2010). Ms. Anink had no disclosures to report.

Biologic agents are increasingly being used in the treatment of juvenile idiopathic arthritis, earlier in the course of the disease and in less severe cases, according to longitudinal data from the Dutch National Arthritis and Biologics in Children Register.

Etanercept, which blocks tumor necrosis factor (TNF), was the first biologic agent to be registered in Holland in 1999, Ms. Anink noted. Additional anti-TNF therapies, such as infliximab and adalimumab, became available in 2007-2008, followed by the interleukin (IL-1) blockers canakinumab and anakinra in 2009-2010, and, more recently, the IL-6 blocker tocilizumab in 2011.

Alongside the availability of these novel drugs, treatment goals have changed, from the prevention of long-term joint damage and disability to achieving inactive disease through more aggressive and earlier therapy, Ms. Anink said at the Congress (Ann. Rheum. Dis. 2013;72:154). It’s not known, however, whether the use of these drugs actually leads to better patient outcomes.

Ms. Anink and her associates therefore set out to determine how prescription trends had changed in Holland since biologic agents became available and how such trends might have influenced patient outcomes. The team used data from the Dutch National Arthritis and Biologics in Children (ABC) Register, which is an ongoing, multicenter, prospective, observational initiative that began in 1999 with the aim of including all patients with JIA who are treated with a biologic agent for their condition.

Upon inclusion in the ABC Register, key patient characteristics are collected, including age, gender, JIA category, age at diagnosis, disease duration, and prior medication use. Patients are also assessed for current medication use, adverse events of treatment, and a host of laboratory and disease activity parameters, which are assessed again 3 and 6 months after inclusion, and then annually.

A total of 429 cases were included in the current analysis, of which 343 patients had nonsystemic and 86 had systemic disease. Patients had started treatment with at least one biologic agent between 1999 and 2010. There were 82 prescriptions for biologic agents in 2010 for both systemic and nonsystemic JIA, compared with only 12 during 1999-2000.

Biologic agents were prescribed after shorter disease durations in 2008-2010, compared with 1999-2001, dropping from 3.3 years to 3.0 years, respectively, in nonsystemic JIA and from 3.5 years to 0.4 years, respectively, for systemic disease, Ms. Anink reported.

Non-systemic JIA patients with lower disease activity at baseline were also being treated with these drugs. Indeed, the median number of active joints at baseline fell from 18 before biologic therapy was given to 5. The median number of joints with limited motion decreased from 12 to 3, and Childhood Health Assessment Questionnaire (CHAQ) scores fell from 1.8 to 1.1 over the same time periods.

Importantly, the proportion of patients with inactive disease after 3 months of therapy increased dramatically, from 0% in 1999-2001 to 34% during 2008-2010 for nonsystemic disease and from 0% to 64% for systemic disease. “We saw the threshold for prescription decreased, which was earlier in the disease course and in patients with lower disease activity,” Ms. Anink summarized. “With these trends, we say the short-term treatment outcomes improved in all JIA categories.”

Similar findings were presented separately at the meeting by a German team. Dr. Kirsten Minden of the German Rheumatism Research Centre, Berlin, and her associates reported that the use of traditional and biologic disease-modifying agents for the treatment of polyarticular JIA rose and occurred earlier over a 12-year period (Ann. Rheum. Dis. 2013;72:731). Improved patient health status, including functional capacity measured by the CHAQ score, disease activity measured by the 10-joint Juvenile Arthritis Disease Activity Score, and pain and overall well-being, coincided with treatment changes.

The ABC Register was financially supported by the Dutch Board of Health Insurances (from 2003 to 2006), Pfizer (formerly Wyeth International, since 2007), and Abbott (since 2010). Ms. Anink had no disclosures to report.
Coping Strategies Put OA Pain in CHECK

BY MICHELE G. SULLIVAN

Patients with knee osteoarthritis who “retreated” into a passive coping strategy and engaged in an unhealthy lifestyle were likely to develop more long-term pain than were patients who stayed physically healthy and emotionally strong, in a large Dutch cohort study.

“To diminish pain in patients with early symptomatic OA [osteoarthritis], attention should be given not only to pain complaints, but also to effective use of coping strategies and unhealthy lifestyle factors,” said the lead author of the study, Janet Wesseling, Ph.D., of University Medical Center, Utrecht, the Netherlands. “This is a further argument to take coping and lifestyle factors into account in the management of early OA.”

Her findings were extracted from data in the CHECK (Cohort Hip and Cohort Knee) study, a 10-year prospective cohort study with a mirror cohort in the United States. It’s following 1,002 patients with early OA-related complaints of hip and/or knee pain (Ann. Rheum. Dis 2013;72[Suppl. 3]:152).

The study’s pain trajectory subanalysis included 5-year data on 705 patients with symptomatic knee OA. Dr. Wesseling identified three trajectories in these patients: good, moderate, and poor pain outcomes.

Patients with a good outcome trajectory (n = 222) had over time a slight decrease in pain severity and ended up with low pain severity. Those with a moderate outcome trajectory (n = 294) had a stable course of moderate pain over time. The poor outcome trajectory group (n = 189) had an increase in pain severity over time and ended up with severe pain.

Over time, these patients also experienced significantly more osteophyte enlargement than did patients in the moderate- and good-outcome groups, with a mean growth of 5.2 mm, compared with 3.4 mm and 2.9 mm, respectively.

Surgical outcomes were significantly different in the poor-outcome group, Dr. Wesseling said. There were 12 total knee replacements in the poor-outcome group, compared with 4 in the moderate-outcome group and just 1 in the good-outcome group.

Distinguishing different trajectories could have implications for treatment, Dr. Wesseling noted in an interview. Clinicians can suggest improvements in the way patients choose to deal with their condition – beginning with an up-front conversation.

“At the very least, the topic should be discussed during counseling on OA. Physicians should be alert to increasing stress levels in their patients. Sometimes, physicians can help counsel patients about managing stress, but a psychological consult might also be useful. And self-management programs can help patients manage and tolerate their pain.”

The CHECK study is supported by the Dutch Arthritis Association. Dr. Wesseling and her colleagues had no disclosures to report.
Symptomatic Hand Osteoarthritis Linked to Increased Heart Disease Risk

BY BIANCA NOGRADY

Symptomatic hand osteoarthritis is associated with a significant increase in the risk of coronary heart disease events, although the association was not significant for asymptomatic hand osteoarthritis, according to results from a study presented at the Congress.

A population-based cohort study of 1,348 participants from the Framingham Heart Study found more than double the incidence of coronary heart disease among individuals with symptomatic hand OA, compared with those without hand OA (hazard ratio, 2.26; 95% confidence interval, 1.22-4.18), Dr. Ida K. Haugen reported.

The study defined symptomatic hand OA as one or more hand joints with Kellgren-Lawrence grade of 2 or above and pain in the same joint. The definition excluded individuals with rheumatoid arthritis (RA).

The association persisted even after adjustment for lower limb pain (HR, 2.00; 95% CI, 0.96-4.15), to account for the physical inactivity potentially associated with OA in lower limb joints, according to Dr. Haugen from Diakonhjemmet Hospital in Oslo, and her associates.

However, individuals with radiographic but not symptomatic hand OA showed a nonsignificant increase in the risk of coronary heart disease (HR, 1.60; 95% CI, 0.96-2.66).

The study set out to examine a possible association between hand OA and cardiovascular disease, based on the premise that hand OA is especially likely to be related to metabolic rather than mechanical causes.

“We hypothesized that the association between hand OA and coronary heart disease could be mediated through metabolic or radiographic only – and cardiovascular events, overall mortality, heart failure, and atherothrombotic stroke."

“We hypothesize that the varying associations may be due to different risk factors for coronary heart disease versus cerebrovascular disease and congestive heart failure; for example, hypertension seems to be more important for cerebrovascular disease than for coronary heart disease,” Dr. Haugen said.

While further research is needed to explore the mechanisms of the association, Dr. Haugen suggested that clinicians note that patients with hand OA may be at greater risk of coronary heart disease, and preventive strategies may therefore be of greater importance in this group.

Dr. Haugen reported having no relevant financial disclosures.
Ustekinumab Benefits in Psoriatic Arthritis Preserved Through 1 Year

BY ELIZABETH MECHCATIE

The lessening of the signs and symptoms of psoriatic arthritis that occurs during the first 6 months of ustekinumab treatment persisted and improved further at the end of 1 year, with a favorable safety profile, according to 52-week data from the PSUMMIT II trial.

The sustained benefits in American College of Rheumatology (ACR) 20 responses and other efficacy endpoints were evident even in patients who had been treated previously with anti–tumor necrosis factor (anti-TNF) agents and among those who were anti-TNF naive, although the benefits were greater in the latter group patients, according to Dr. Christopher T. Ritchlin, a professor in the department of medicine, allergy/immunology, and rheumatology at the University of Rochester (N.Y.). This includes beneficial effects on skin and enthesitis, Dr. Ritchlin said at the Congress.

The PSUMMIT II study is a follow-up to the PSUMMIT I study, the findings of which showed that ustekinumab, a human interleukin (IL)-12 and IL-23 antagonist, showed significant effectiveness in patients with psoriatic arthritis (PsA) who had not been exposed to anti-TNF drugs.

Ustekinumab is currently approved for treating moderate to severe plaque psoriasis in adults who are candidates for phototherapy or systemic therapy in the United States, or those who have failed to respond to, have a contraindication to, or are intolerant of other systemic therapies in Europe. In December 2012, the manufacturer, Janssen, announced that it had filed for further approval for ustekinumab in both the United States and Europe for the treatment of active disease.

The PSUMMIT II study enrolled 312 patients with active PsA who had five or more tender and five or more swollen joints, and a C-reactive protein level of 0.3 mg/dL or higher. Patients who had been treated previously with anti-TNF therapy (n = 180) and those naive to anti-TNF therapy (n = 132) were included and randomized to one of two doses of ustekinumab (45 mg or 90 mg) or placebo administered at week 0, 4, and 12. At 16 weeks, patients with less than a 5% improvement in tender and swollen joint counts on placebo were switched to active treatment, those on 45 mg ustekinumab had their dose upped to 90 mg, and those on 90 mg remained on that dose.

At 6 months, significantly more patients treated with ustekinumab than placebo achieved the primary endpoint of an ACR 20, and more patients on active treatment had an ACR 50, and at least a 75% improvement in the Psoriasis Area and Severity Index (PASI 75).

These results were sustained at 1 year, with 47%-48% of those on 45 mg and 90 mg, and 56% of those who switched from placebo to the 45-mg dose, achieving an ACR 20. In addition, 26%-29% achieved an ACR 50 (29% for those switched from placebo), and 13%-18% achieved an ACR 70 (15% for placebo).

There were also improvements associated with treatment in HAQ-DI (Health Assessment Questionnaire-Disability Index) scores at week 52, according to Dr. Ritchlin. The mean change in HAQ-DI scores from baseline to week 52 were –0.21 for placebo, –0.20 for the 45-mg dose of ustekinumab, and –0.28 for the 90-mg dose.

Among those who had not been treated before with an anti-TNF agent, 59%-60% of those on ustekinumab (73% for those switched from placebo) achieved an ACR 20 at week 52, compared with 37%-41% of those who had taken an anti-TNF agent previously before being treated with ustekinumab (30% for placebo). Although responses among anti-TNF naive patients were superior, the responses among those who had been treated with these agents previously were still significantly improved, an indication that ustekinumab “offers an alternative for patients who cannot take... Continued on following page
or fail anti-TNF agents,” Dr. Ritchlin said in an interview. Treatment was “very effective” for skin symptoms and for enthesitis, he noted. Compared with baseline, dactylitis was improved by a median of 95% among those on the 45-mg dose, 91% among those on the 90-mg dose, and 100% in those who switched from placebo to the 45-mg dose of ustekinumab. Similar improvements in enthesitis were seen, with the highest improvement (60%) seen with the highest dose of ustekinumab.

PASI scores at baseline ranged from 11 to 13 and improved by 56%-64% by follow-up at week 52.

In general, ustekinumab was well tolerated, with no deaths or cases of tuberculosis reported and with similar rates of adverse events and serious adverse events between the two doses (just under 6%). There were two malignancies: one breast cancer and one squamous cell carcinoma in two patients taking the 90-mg dose of ustekinumab, who had both been treated with anti-TNFs previously. The rate of serious infections was less than 1% among those treated with ustekinumab. Through 60 weeks of treatment, there were three major adverse cardiovascular events, all myocardial infarctions, in patients treated with ustekinumab. These patients all had multiple cardiovascular risk factors, Dr. Ritchlin said. They had also been exposed previously to anti-TNF treatment.

Radiographic data from the trial are expected and likely to be available by the end of the year for presentation at the annual American College of Rheumatology meeting.

Dr. Ritchlin disclosed having received grant and research support from Janssen. Four of the nine remaining authors are Janssen employees and shareholders of Johnson & Johnson, Janssen’s parent company.

Sara Freeman contributed to this report.

Effects of Apremilast Sustained at 1 Year in Psoriatic Arthritis Patients

BY SARA FREEMAN

Apremilast improves the signs and symptoms of psoriatic arthritis in about 60% of patients at 1 year, according to long-term data from the PALACE 1 trial.

At week 52, a 20% improvement in disease symptoms according to American College of Rheumatology (ACR 20) response criteria was achieved by 57%-63% of patients treated with apremilast, providing evidence of sustained treatment effects.

The PALACE 1 trial’s primary endpoint of an ACR 20 at 16 weeks, already reported last year, was achieved by 31% of patients treated with apremilast 20 mg and 40% of those given apremilast 30 mg, compared with 19% of those given placebo.

“Oral apremilast demonstrated long-term efficacy, including improvement in signs and symptoms and physical function, and skin manifestations,” Dr. Arthur Kavanaugh, professor of medicine at the University of California, San Diego, said at the Congress.

Apremilast is an oral phosphodiesterase 4 inhibitor under investigation as a treatment for active psoriatic arthritis (PsA). It is being evaluated as a possible treatment for skin psoriasis, ankylosing spondylitis, rheumatoid arthritis, and Behçet’s disease.

PALACE 1 was a phase III, multicenter, double-blind, placebo-controlled study of apremilast for the treatment of active PsA. A total of 504 patients with a documented diagnosis of PsA for at least 6 months were recruited into the study (Ann. Rheum. Dis. 2013;72(Suppl. 3):163).

Functional outcomes improved

Physical function improved according to measurements on the Health Assessment Questionnaire–Disability Index (HAQ-DI).

At baseline, HAQ-DI scores were 1.21, and “we saw that patients improved by –0.35, which is certainly the level that patients can say, ‘I feel better and I can do my daily activities better,’ ” Dr. Kavanaugh said.

Continued on following page
Patient-Relevant Outcomes

New Spondyloarthritis Index Measures Patient-Relevant Outcomes

BY SARA FREEMAN

An international team has developed a new composite health index specifically for use in patients with ankylosing spondylitis.

The Assessment of SpondyloArthritis International Society Health Index (ASAS HI) is based on the ICF (International Classification of Functioning, Disability and Health) and includes 17 dichotomous items that ask about patients’ levels of pain, emotional functioning, sleep habits, sexual function, mobility, self-care, life in the community, and employment. The ICF is a comprehensive and already well-recognized and validated means of classifying and describing functioning, disability, and health in a systematic way.

The tool has yet to be “field tested” to see if it can measure changes in health status in response to treatment. Dr. Uta Kiltz said at the Congress, where she won a clinical science abstract award for her research.

Dr. Kiltz, of Rheumazentrum Ruhrgebiet, Herne, Germany, noted that the development of the tool involved five key stages. These have been outlined previously (Rheumatology 2011;50:894-8), and included a preparatory stage in which potential items for inclusion were identified. Dr. Kiltz and her colleagues considered a total of 251 items obtained from more than 60 existing questionnaires, such as the Bath Ankylosing Spondylitis Functional Index, the Dougados Functional Index, and the AS Quality of Life Questionnaire.

The investigators then conducted an

Continued from previous page

Additionally, 25% and 37% of patients treated with apremilast 20 mg and 30 mg, respectively, achieved a 75% improvement in the Psoriasis Area and Severity Index at 52 weeks, which is a “very high bar” to achieve, he noted.

The main side effect seen was diarrhea, affecting 11%-19% of patients given apremilast and 2.4% given placebo. However, diarrhea occurred mainly in the first 6 months of therapy and could be managed by taking appropriate measures on an individual patient basis, Dr. Kavanaugh said. This might include prescription of an antidiarrheal agent.

“Prolonged exposure to apremilast did not result in any unexpected increased incidence of adverse events or laboratory abnormalities,” he noted. The latter could mean that, if approved, apremilast might not need routine laboratory monitoring.

The PALACE development program

PALACE 1 is one of several clinical trials that have investigated the efficacy and safety of apremilast in active PsA. In these studies, 24 weeks’ treatment with one of two oral doses (20 mg or 30 mg twice daily) of apremilast was compared to placebo. The primary endpoint of the studies was the percentage of patients achieving ACR 20 at 16 weeks.

The trial’s inclusion criteria required patients to have active disease despite prior therapy with disease-modifying antirheumatic drugs (DMARDs), biologic agents, or both. Dr. Kavanaugh noted that the majority of patients had failed DMARD therapy in PALACE 1, with almost one-quarter receiving prior biologic therapy.

Patients who had a less than 20% reduction from baseline in swollen/tender joint counts at 16 weeks were re-randomized to receive apremilast 20 mg or 30 mg if they had originally been treated with placebo, while patients originally randomized to active treatment stayed on their initial dose if they failed to respond significantly. At the end of the planned 24-week treatment period, all remaining patients on placebo were re-randomized to apremilast 20 mg or 30 mg until 1 year of follow-up.

PALACE 3 data also reported

The results of PALACE 3 and combined 6-month safety data from the PALACE 1, PALACE 2, and PALACE 3 trials were also reported at the Congress.

In PALACE 3 (Ann. Rheum. Dis. 2013;72[Suppl. 3]:685), significantly more patients achieved the primary endpoint of an ACR 20 at 16 weeks if they were treated with either the 20-mg dose (29.4%, P = .02) or 30-mg dose (42.8%, P less than .0001) of apremilast, compared with those given placebo (18.9%). There was also statistically significant and “clinically meaningful” improvement in physical function and pain. The results of PALACE 3 support the efficacy and safety findings of the PALACE 1 study and help establish the profile of apremilast in PsA,” the PALACE 3 investigators concluded.

The pooled safety findings revealed no new safety concerns and showed apremilast was generally well tolerated (Ann. Rheum. Dis. 2013;72[Suppl. 3]:85). Rates of diarrhea at 24 weeks were 12.6% and 16.5% for the 20-mg and 30-mg doses of apremilast, and 2.8% for placebo, respectively. Other side effects of note included nausea (10% and 16.1% vs. 4.6%), headache (8.4% and 11.5% vs. 4.6%), and upper respiratory tract infection (7% and 6% vs. 3%).

Time for regulatory approval

Based on the positive findings of the PALACE 1, 2, and 3 studies, apremilast’s developer, Celgene, is expected to file for regulatory approval in the treatment of active PsA. In doing so, apremilast will join another novel agent, ustekinumab, in the queue for approval for this indication.

Ustekinumab is a human interleukin-12 and -23 antagonist produced by Janssen that is already approved in Europe and in the United States for skin psoriasis. One-year data also show that it is effective and well tolerated for PsA. It is given subcutaneously, whereas apremilast is an oral agent.

Dr. Kavanaugh has provided expert advice to and/or received research grants from the following companies: Astra-Zeneca, Bristol-Myers Squibb, Celgene, Centocor-Janssen, Pfizer, Roche, and UCB.

Continued from following page
Exercise Program Improved Strength and Walking for Ankylosing Spondylitis Patients

BY ELIZABETH MECHCATIE

Patients with ankylosing spondylitis who participated in a progressive muscle strengthening program gained significant improvements in muscle strength and walking performance after 4 months, compared with those who did not participate, Dr. Fabio Jennings reported at the Congress.

The exercise program, which involved resistance training with the Swiss ball, was also well tolerated and was not associated with negative effects on disease activity, said Dr. Jennings of the rheumatology division at the Federal University of Sao Paulo, Brazil.

Dr. Jennings and his colleagues performed a randomized, controlled, single-blind, prospective trial of 60 patients with ankylosing spondylitis (AS).

Exercise is recommended for people with AS, but the benefits of a specific exercise program have not been well defined, Dr. Jennings noted.

In the study, 30 patients were randomized to the supervised exercise program, which entailed eight resistance exercises using free weights on a Swiss ball twice a week for 16 weeks, with increases in load every 4 weeks. The 30 patients in the control group continued regular treatment with medications, with no exercise. Demographics, clinical features, and medications were similar in the two groups at baseline.

The impact of the exercise on functional capacity, quality of life, muscle strength, and mobility was evaluated using the BASFI (Bath Ankylosing Spondylitis Functional Index), HAQ-S (Health Assessment Questionnaire for Spondyloarthropathies), the 6-minute walk test, and other assessment tools, every 4 weeks. Disease activity was measured with the BASDAI (Bath Ankylosing Spondylitis Disease Activity Index), erythrocyte sedimentation rate (ESR), and C-reactive protein levels.

After 4 months, there were statistically significant differences between the two groups in the strengths of the muscles used in performing the exercises (abdominal, squat, triceps, reverse fly, and rowing exercises), favoring the intervention group. These patients also had significant improvements in the 6-minute walk test; and they were satisfied with the treatment, as reflected by significant differences between the two groups in the Likert scale used to assess patient satisfaction at all time points measured.

Dr. Jennings had no conflicts of interest.

Use of a Swiss ball to perform the exercise program was “beneficial and safe,” Marcelo Cardoso de Souza said.

Continued on following page
ured by BASDAI, ESR, and C-reactive protein – did not worsen among those who participated in the exercise program.

The study showed that this type of exercise program, using a Swiss ball to improve muscle strength, “is a beneficial and safe intervention” in people with AS, lead author Marcelo Cardoso de Souza, a physiotherapist and member of a multidisciplinary rehabilitation team at the university, said in an interview.

For these patients, improvement in muscular performance and functional capacity is important, Mr. de Souza said, noting that before clinicians refer patients to such a program, patients should undergo a medical evaluation, and the program should be provided by an experienced professional.

None of the investigators had relevant financial conflicts of interest.

Evidence Grows for Use of TNF Inhibitors in Axial Spondyloarthritis

BY MITCHEL L. ZOLER

Tumor necrosis factor inhibitors are further solidifying their position as the go-to drug class for patients with spondyloarthritis who fail to adequately respond to treatment with nonsteroidal anti-inflammatory drugs.

Results from a series of reports at the Congress gave further support for the safety and efficacy of tumor necrosis factor (TNF) inhibitors for treating axial spondyloarthritis (SpA), and another report at the meeting provided some of the first evidence for efficacy of the TNF inhibitor class in patients with the less-studied variant, peripheral SpA.

TNF inhibitors “work well for symptoms, and are the gold standard for treating active axial SpA,” said Dr. Philip J. Mease, a rheumatologist at Swedish Medical Center in Seattle. He reported evidence for the efficacy of a TNF inhibitor in patients with peripheral SpA without psoriatic involvement, a form of SpA that he said is increasingly being diagnosed after it was first defined a few years ago. The study that Dr. Mease reported on was the first to use the diagnostic criteria for peripheral SpA published by the Assessment of Spondyloarthritis (ASAS) in 2011 (Ann. Rheum. Dis. 2011; 70:25-31).

The ABILITY-2 (Study of Adalimumab in Subjects With Peripheral Spondyloarthritis) study enrolled patients in the United States, Canada, and several European countries. Patients either had an inadequate response to at least two different nonsteroidal anti-inflammatory drugs (NSAIDs) or were intolerant of or had contraindications for these drugs. Study participants received either 40 mg of adalimumab (Humira) subcutaneously every other week or placebo for 12 weeks.

The study’s primary endpoint was the percentage of patients achieving the peripheral SpA response criteria 40 at 12 weeks, a composite endpoint that requires at least a 40% improvement on each of three measures: patient global assessment of disease activity; patient global assessment of disease pain; and swollen and tender joint count, enthesitis count, or dactylitis count.

The rate of patients fulfilling the primary endpoint was 39% in 84 patients treated with adalimumab and 20% in 81 patients on placebo, a significant difference. Treatment with adalimumab also was linked to “substantial” and statistically significant improvements after 12 weeks in physical function, health-related quality of life, and work productivity, Dr. Mease reported.

Reports on using TNF inhibitors to treat axial SpA at the congress included results from the first randomized, controlled, phase III trial of a TNF inhibitor to enroll patients from the full range of axial SpA, including roughly equal numbers of patients with ankylosing
Panel Sets Broad SpA Treat-to-Target Goals

BY MITCHEL L. ZOLER

A panel of clinicians with expertise in the management of patients with spondyloarthritis took another step toward better defining this disease category and the goals of its treatment by producing the first “treat-to-target” recommendations for spondyloarthritis.

The new recommendations will “guide physicians, patients, and other stakeholders on how to optimize reduction of signs and symptoms and, ideally, outcomes, and will drive” the current research agenda. Dr. Josef S. Smolen said while presenting the panel’s recommendations at the Congress.

“Treat to target proposes a stepwise approach to achieving optimal outcomes based on available evidence and expert opinion. Treat to target has been successfully applied to management of diabetes, hypertension, hyperlipidemia, and...”

Continued on following page
Continued from previous page

rheumatoid arthritis,” and the new task force set out to address whether it could be used when treating patients with spondyloarthritis (SpA), a question that required the expert task force to review the evidence for setting specific treatment goals for patients with SpA, said Dr. Smolen, professor of medicine at the Medical University of Vienna.

The task force eventually decided that the treat-to-target concept was applicable to SpA, but that the data available so far prevented the task force from setting specific treatment goals. While the recommendations underscore the importance of treating SpA patients with a goal of remission or inactive disease, and failing that, at least low disease activity, they fall short of giving clinicians guidance on how to best measure and define remission or low disease activity or how to achieve these goals.

For example, for axial SpA – the subtype that received the most specific recommendations – the panel advised clinicians to guide treatment decisions by using a “validated composite measure of disease activity” such as the Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) plus acute phase reactants, or the Ankylosing Spondylitis Disease Activity Score (ASDAS) with or without functional measures such as the Bath Ankylosing Spondylitis Functional Index (BASFI). But the recommendations say nothing about what scores by these measures would define remission or low disease activity. The recommendations also talk about using other factors to further gauge axial SpA disease activity such as MRI analysis of inflammation and radiographic progression, but again Dr. Smolen provided no specific targets when using these measures.

For other, less well studied types of SpA, the new recommendations were even more nebulous. For psoriatic arthritis, the panel indicated that “validated measures of musculoskeletal disease activity” should be “performed and documented regularly” as should other factors such as spinal and extraarticular manifestations, imaging findings, and comorbidities, but the recommendations gave no specifics on what any of these measures might be or what level might equal remission or low disease.

The same held true for peripheral SpA. Other factors touched on by the new recommendations include the need for individualized and shared decision making between physicians and patients, the need for coordination of care among rheumatologists and other medical specialists who treat SpA patients (dermatologists, gastroenterologists, and ophthalmologists), and the need to take into account extraarticular manifestations of SpA diseases, comorbidities, and treatment risks along with the goal of low disease activity.

“I think it was important to document that there is a paucity of trials that have looked at strategies to treat” SpA. “For rheumatoid arthritis we have strategies, but not in spondyloarthritis, and I think it is important to say that,” said Dr. Jürgen Braun, medical director of Rheumazentrum Ruhrgebiet in Herne, Germany.

SpA also lags behind rheumatoid arthritis by not having any treatments proven to slow radiographic progression. “Although we say that it is presumably important to treat inflammation [in patients with SpA], we are not sure,” said Dr. Braun, who served as a member of the treat-to-target task force.

Even though the task force’s report highlights the absence of evidence for most facets of SpA management, “in the absence of evidence you need eminence, and that’s what was produced.” Dr. Braun predicted that rheumatologists and other clinicians who care for patients with SpA would welcome these new recommendations despite their shortcomings. “What we say is what clinicians feel: If a patient’s CRP is elevated we must do something about it, but the evidence supporting this is limited. Presumably, it is important to treat inflammation, but we are not yet sure,” he said in an interview.

“We don’t have trial results yet where you set up a quantifiable endpoint as your target, but that is coming,” said Dr. Philip J. Mease, director of the rheumatology clinical research division at Swedish Medical Center in Seattle and a member of the task force. For example, the results from the Tight Control of Psoriatic Arthritis (TICOPA) trial “will tell us whether more aggressive treatment to a quantifiable target is appropriate and makes a difference. We anticipate that it will, but evidence is currently lacking.” The primary endpoint of the TICOPA trial is change in the ACR20 response, but the trial includes several other clinical measures as secondary endpoints, including the Assessment in Ankylosing Spondylitis (ASAS), the BASDAI, and the psoriasis area severity index (PASI).

“The rheumatoid model is prompting us to develop quantifiable measures like the ASDAS and the new Psoriatic Arthritis Disease Activity Score (PASDAS) that we’ll start to see used. I just spoke with a colleague about the need to also develop a similar measure for peripheral SpA,” Dr. Mease said in an interview.

The task force that developed the treat-to-target recommendations included 16 physicians and patients on its steering committee and 16 on an advisory committee. The majority came from various European locations, but about a quarter of the task force members were from the United States. To arrive at its recommendations, the task force used a comprehensive literature review that identified 22 published reports that addressed treatment targets for SpA (Ann. Rheum. Dis. 2013 June 10 [doi: 10.1136/annrheumdis-2013-203860]). The treat-to-target recommendations were published online a few days before Dr. Smolen’s presentation at the meeting (Ann. Rheum. Dis. 2013 June 8 [doi:10.1136/annrheumdis-2013-203419]).

Dr. Smolen, Dr. Braun, and Dr. Mease said that they had no disclosures relevant to the topic.
Serum Biomarker Predicts Radiographic Progression in Spondyloarthritis

BY SARA FREEMAN

Elevated serum levels of vascular endothelial growth factor may be predictive of radiographic progression in the spine, according to data from a German study of patients with spondyloarthritis.

The cutoff point appears to be at 600 pg/mL, with the effects particularly strong in patients who also develop syndesmophytes, which are bony growths that develop within ligaments.

“In patients with syndesmophytes, VEGF [vascular endothelial growth factor], as a predictor of radiographic progression, performed better than CRP [C-reactive protein],” reported Dr. Denis Poddubny at the Congress (Ann. Rheum. Dis. 2013;72:125).

“We all know that radiographic progression varies substantially among patients with spondyloarthritis,” Dr. Poddubny observed. “Until recently there was only one strong predictor of radiographic progression: the presence of syndesmophytes at baseline,” he added.

Last year, however, Dr. Poddubny of Charité Universitätsmedizin Berlin and his associates published the findings of a study involving 210 patients with early axial spondyloarthritis (axSpA) who were recruited from the German Spondyloarthritis Inception Cohort (GESPIC). This study looked at baseline predictors of spinal radiographic progression over 2 years and found that in addition to radiographic damage, elevated CRP levels and cigarette smoking were independently predictive (Arthritis Rheum. 2012;64:1388-98).

The team’s research also suggested that there could be a few serum biomarkers, including VEGF, that could be predictive, so the investigators conducted a larger study in 172 patients with definite (n = 95) or nonradiographic (n = 77) axSpA to look specifically at the possible association.

Radiographs of the spine taken at baseline and at 2 years’ follow-up were reviewed independently by two readers, who used the modified Stoke Ankylosing Spondylitis Spinal Score (mSASSS) to record the extent of radiographic progression. If there was a worsening of 2 units or more in mSASSS and the formation of new or increased growth of syndesmophytes, radiographic progression had occurred.

In total, 22 patients had radiographic progression, including 18 with new formation or growth of syndesmophytes.

Baseline VEGF was measured in the serum at baseline and was significantly higher in patients who developed radiographic progression at 2 years than in those who did not (357 pg/mL vs. 402 pg/mL; P = .027).

Serum VEGF levels were also significantly higher in the patients who had developed new syndesmophytes at 2 years when compared with those who had not (386 pg/mL vs. 309 pg/mL; P = .041).

“Patients with elevated VEGF had an odds ratio of 2.9 for [radiographic] progression and 3.1 for syndesmophyte formation,” Dr. Poddubny said in an interview. This was a little disappointing, he noted, as CRP and the erythrocyte sedimentation rate had similar predictive power.

However, in patients at high risk of progression, namely those with syndesmophytes already present at baseline, VEGF was significantly better than CRP at predicting both radiographic progression and new syndesmophyte formation or growth.

Patients with elevated VEGF at baseline were 36.6 times more likely to have radiographic progression and 13.6 times more likely to have new syndesmophyte formation or growth at 2 years than those with levels below 600 pg/mL. In comparison, elevated CRP levels increased the risks by only 2.4 and 2.5 times, respectively.

VEGF is an essential mediator of angiogenesis and endochondral ossification, Dr. Poddubny observed. It’s been shown to have “a chemoattractive effect on osteoblasts and mesenchymal progenitor cells,” he added, and also stimulate osteoblast differentiation and bone turnover.

While the results are very promising, further research is of course required. The possible predictive value of VEGF in relation to spinal radiographic progression in patients treated with tumor necrosis factor–alpha inhibitors remains to be seen, for example, and future studies should perhaps look at this question.

“With VEGF we are probably able to improve our prediction of spinal progression in patients with axSpA,” Dr. Poddubny said in an interview. This is addition to assessing “classical factors,” such as syndesmophytes, CRP, and smoking status.

Dr. Poddubny had no disclosures.
Spinal MRI Adds Little Value in Diagnosis of Spondyloarthropathy

BY SARA FREEMAN

There is no added benefit of performing spinal MRI in the diagnosis of spondyloarthritis, the results of an international, multicenter study suggest.

Around one-quarter of patients with nonradiographic axial spondyloarthritis (nr-axSpA) who had a negative MRI scan of the sacroiliac joints (SIJs) were reclassified as having SpA. This false-positive result balances out the value of combined spinal and SIJ MRI.


Although you get about 20% more patients – which is the good news – we found about the same magnitude of false-positive controls," he said in an interview. He added that he was very disappointed with this result, and these data need confirming. Dr. Weber collected data for the study while at the Balgrist University Clinic in Zurich, and also as a visiting professor in the rheumatology department at the University of Alberta, Edmonton.

The present or absence of SpA was determined in these scans, and comparisons were made between the results for MRI of the SIJ alone versus spinal MRI alone, as well as for the SIJ alone versus a combined read of both the spinal and SIJ MRI scans.

Dr. Weber noted that he would not recommend changing current practice as a result of this study. Further data are eagerly awaited from an ongoing Danish initiative that hopes to scan and assess around 2,000 whole-body MRIs in patients with suspected spondyloarthropathy by the end of the year. "This study will be very informative and very important for us because this is a large sample size. Preliminary data on about 1,000 MRIs point in the same direction," he observed.

Other data from the study, which Dr. Weber presented separately at the meeting, looked at the frequency and possible reasons for false-positive results with spinal MRI in the control groups (Ann. Rheum. Dis. 2013;72:125).

"Patients with mechanical back pain and healthy volunteers may show spinal MRI lesions suggestive of spondyloarthropathies, such as corner inflammatory lesions or corner fat lesions," he explained. "We found that about 30% of those controls were misclassified as having spondyloarthropathy by evaluation of the spinal MRI alone, so without SIJ MRI," said Dr. Weber. Bone marrow edema and fat infiltration were the MRI lesions largely responsible for this misclassification.

Dr. Weber had no disclosures.

Arimoclomol Eased Inclusion Body Myositis In Small Trial of Older Adults

BY SARA FREEMAN

Arimoclomol showed promise as a treatment for the most common type of inflammatory myopathy in adults over age 50 in a 1-year, phase IIa, "proof-of-concept" study.

Not only was the novel oral agent well tolerated, which was the study’s main objective to assess, but it also showed early signs that it could be effective in the treatment of patients with sporadic inclusion body myositis (IBM). Indeed, there was a trend toward slower deterioration in physical function, muscle strength, and right-hand grip muscle strength for arimoclomol when compared against placebo at 8 months’ follow-up.

"IBM is an enigmatic disease," study investigator Dr. Pedro Machado said at the Congress. "IBM muscle tissue displays [both] inflammatory and degenerative features."

Dr. Machado, a senior clinical research associate at the MRC Centre for Neuromuscular Diseases at University College London (UCL), explained that arimoclomol targets the heat shock response, amplifying the expression of heat shock protein. As such, it potentially targets both the degenerative and inflammatory components of the disease. Previous studies have only involved agents directly purely at the inflammatory component of IBM pathology, and all were Continued on following page
ineffective,” the researcher observed.

For the double-blind study, teams based at UCL and the University of Kansas, Kansas City, collaborated to recruit 17 men and 7 women (mean age, 67 years) who had had IBM for an average of about 8 years. These patients were randomized in a 2:1 ratio to receive active therapy with arimoclomol 100 mg three times daily or matching placebo for 4 months, with follow-up lasting for 12 months (Ann. Rheum. Dis. 2013;72:164).

The investigators assessed patients for the development of adverse events, physical function using the IBM functional rating scale (IBMFRS), and muscle strength via manual muscle testing and maximum voluntary isometric contraction testing (MVICT) at 4, 8, and 12 months. They also measured the patients’ fat-free mass percentage with dual-energy x-ray absorptiometry at 4 and 12 months, and took muscle biopsies to assess the levels of heat shock protein 70 in muscle tissue before and after 4 months of treatment.

Fourteen of the 16 patients randomized to arimoclomol completed 4 months of treatment; 1 patient returned for final assessment at 12 months’ follow-up. All eight placebo patients completed 12 months of follow-up.

“The drug was very safe and well tolerated. Compliance was, on average, 99%, and we also performed ophthalmological assessment, and there were no ophthalmological problems,” Dr. Machado said.

The most common adverse events were gastrointestinal problems, infections, and falls, although there was no difference between the arimoclomol and placebo groups in terms of the frequency, type, or severity of these or other adverse events.

“We have to remind ourselves that this is an elderly population,” Dr. Machado said, noting that the infections seen all responded to standard antibiotic therapy.

There was one case of hypertension requiring prolonged hospitalization in a patient given arimoclomol. “There were also two cases of hyponatremia in the arimoclomol group, but this was mild, transient, and asymptomatic, and it resolved without treatment.”

At 4, 8, and 12 months after baseline, scores on the IBMFRS in the arimoclomol versus the placebo arm changed by a respective –0.34 vs. –0.88 (P = .239), –0.68 vs. –2.50 (P = .055), and –2.03 vs. –3.50 (P = .538). These data suggest that less deterioration in physical function occurred with arimoclomol than with placebo, Dr. Machado said.

Muscle strength appeared to improve with active treatment, as did right-hand grip strength based on MVICT results at 8 months that approached significance (1.26 vs. –0.54; P = .064).

“A trend towards a slower deterioration was observed in the arimoclomol group for the IBMFRS, for the [muscle] strength score, and for the quantitative muscle assessment only for the right-hand grip assessment at 8 months,” Dr. Machado said.

“We believe that these data support further research of arimoclomol in inclusion body myositis,” he concluded.

The study was funded by Arthritis Research UK, a University of Kansas Neurology Ziegler Grant, and a University of Kansas General Clinical Research Center CReFF Grant. Dr. Machado had no disclosures.
Medical news tailored exclusively for rheumatologists.

Look for your monthly newsletter edition of Rheumatology News International.