The EULAR 2015 Report

An authorized publication of the European League Against Rheumatism

Welcome to the EULAR 2015 Report!

The Annual European Congress of Rheumatology 2015, hosted by the European League Against Rheumatism (EULAR), once again showed its recognition and appreciation as the prime platform for rheumatology information exchange and professional education in Europe and for the world. More than 14,000 attendees from nearly 120 countries came to this year's EULAR Congress in Rome to hear the best in rheumatology research and clinical advances. The scientific program also included presentations carefully selected from more than 4,300 abstracts submitted.

The EULAR 2015 Report brings you highlights of some of the best presentations, focusing on the clinical and therapeutic findings that are able to change the way rheumatologists are practicing medicine. We hope that you will enjoy these accounts and statements of the latest in rheumatology clinical and translational research.

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

For details about the EULAR Congress, please visit www.congress.eular.org.

Best wishes and see you again next June in London for EULAR 2016!

Prof. Gerd Rüdiger Burmester
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EULAR Panel Targets Six Rheumatic Disease Comorbidities

BY MITCHEL L. ZOLER

Clinicians who care for patients with chronic inflammatory rheumatic diseases should consider regularly assessing six potential comorbidities these patients might develop, according to a set of "points to consider" developed by a EULAR task force.

The six comorbidities the working group's report cites are ischemic cardiovascular disease, malignancies, infections, peptic ulcer, osteoporosis, and depression, Dr. Maxime Dougados said at the European Congress of Rheumatology.

This is the "minimum list of comorbidities to systematically check" for patients with inflammatory rheumatic diseases, said Dr. Dougados, professor and chief of rheumatology at Cochin Hospital in Paris.

The task force he heads plans to soon make available on the EULAR Website screening questionnaires for assessing the status of each of these six comorbidities. "We hope you will consider this initiative and implement these points to consider in your practice," he said.

A seventh comorbidity to potentially add to the list for regular assessment is hypertension, said Dr. Deborah P.M. Symmons, professor of rheumatology and musculoskeletal epidemiology at the University of Manchester (England), in a separate talk at the meeting. Roughly 80% of patients with rheumatoid arthritis (RA) have at least one comorbidity, she noted.

MITCHEL L. ZOLER/FRONTLINE MEDICAL NEWS

Dr. Deborah P.M. Symmons

MITCHEL L. ZOLER/FRONTLINE MEDICAL NEWS

Dr. Maxime Dougados

Recent study results have documented the prevalence of comorbidities in patients with RA, Dr. Symmons said. For example, an analysis of data collected during 2011 and 2012 from 3,920 RA patients in 17 countries, including 400 U.S. patients, showed that depression was the most common comorbidity, affecting 15% of patients; other comorbidities included ischemic cardiovascular disease in 6%, malignancy in 5%, and hypertension in 11% (Ann Rheum Dis. 2014;73:62-8). A separate survey of 9,874 RA patients from 34 countries also published last year found patients had a median of two comorbidities each. The most common were hypertension in 32% of patients, osteoporosis in 18%, and osteoarthritis in 16% (Clin. Exp. Rheum. 2014;32:869-77).

"Chronic diseases cluster together, more than you would expect by chance, perhaps because of shared risk factors such as genetic or environmental, the direct impact of inflammation, and because of treatment" patients receive for their rheumatic disease, Dr. Symmons said.

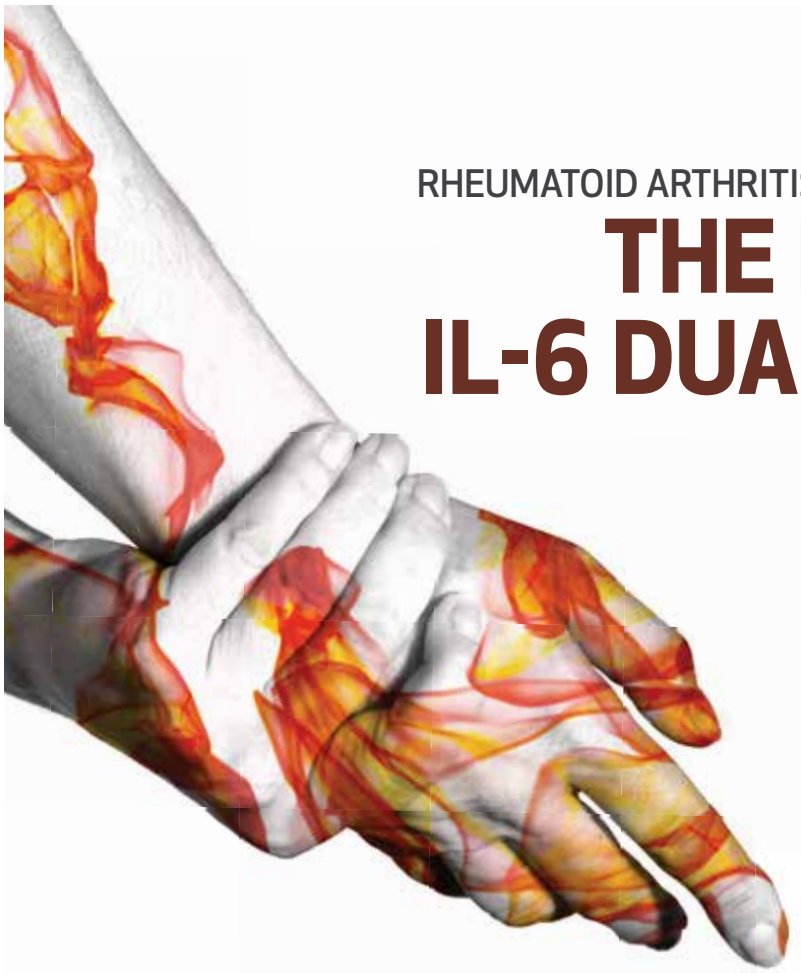
The consequence is that clinicians who manage patients with RA or other rheumatic disease must be on the lookout for comorbidities and take them into consideration when planning management strategies. A rheumatologist might be most concerned about how comorbidities will affect the rheumatic disease, but for patients the overriding concern is how all their chronic diseases, not just their rheumatic disease, will affect their quality of life and physical function, she noted. "We must constantly ask ourselves whether treatment of the RA will worsen the comorbidities, or will treatment of the comorbidities worsen the RA?"

Knowledge of how RA treatments will affect comorbidities is often lacking because patients with comorbidities are usually not enrolled in clinical trials, Dr. Symmons said.

She recommended that rheumatologists systematically screen patients annually for comorbidities and discuss with each patient and with clinicians from other relevant specialties appropriate treatment based on the patient's global status. Steroid treatment should be minimized because of the risk it poses for causing or exacerbating hypertension, hyperlipidemia, diabetes, osteoporosis, and infection.

The rheumatologist does not necessarily need to be the clinician who manages all of a patient's comorbidities, which might be better done by a primary care physician, but the rheumatologist should know that a patient's comorbidities are being managed by someone, and this fact should be documented in the rheumatologist's records for each patient, she said.

Dr. Dougados and Dr. Symmons said they had no relevant financial disclosures. ■



RHEUMATOID ARTHRITIS (RA) AND

THE ROLE OF IL-6 DUAL SIGNALING

Interleukin-6 (IL-6) is a multifunctional cytokine[1]

Under normal physiologic conditions, IL-6 performs many functions, including vital pro-inflammatory roles in response to infection or injury. Due to the presence of both membrane-bound and soluble receptors, IL-6 affects a wide range of biological activity and interacts with a variety of cells and tissues, such as immune cells, synovial fibroblasts, hematopoietic stem cells, hepatocytes, adipocytes, endothelial cells, and pancreatic islets.[1-10]

However, persistently elevated IL-6 levels contribute to chronic inflammation. Elevated IL-6 signaling plays a central role in RA and is associated with both articular and systemic manifestations of the disease. In fact, IL-6 is one of the most abundant cytokines in the serum and synovial fluid of the inflamed joints of patients with RA.[4,11-15]

IL-6 signals through 2 distinct mechanisms[5]

- IL-6 can signal through *membrane-bound* receptors (classical or *cis*-signaling)
- IL-6 can also signal through *soluble forms* of its receptors (*trans*-signaling)
- These 2 distinct signaling mechanisms allow IL-6 to interact with cells that do or do not express the IL-6 membrane-bound receptor (mIL-6R)

In RA, multiple cytokines, including IL-6, TNF-α, IL-1, and IL-17, signal through membrane-bound receptors[1,5,16-18]

- Receptors for tumor necrosis factor-α (TNF-α) or IL-1 are also expressed as membrane-bound and soluble forms[16,17]
- Inflammatory signaling for TNF-α and IL-1 is mediated by the membrane-bound form of the receptor[16,17]

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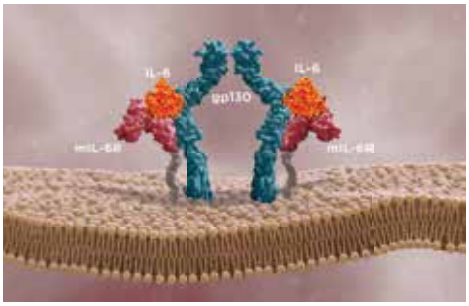
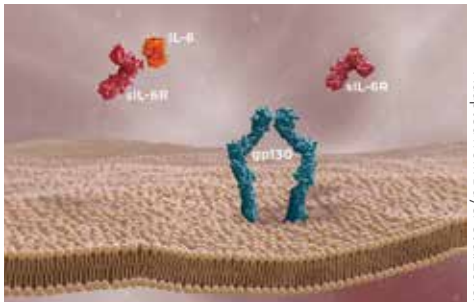
IL-6 signals through classical signaling and *trans*-signaling[1]





Adapted from Dayer et al. 2010.

In classical or *cis*-signaling[1]

- IL-6 binds to mIL-6R
- The mIL-6R complex then binds to glycoprotein 130 (gp130)

In *trans*-signaling

- IL-6 binds to its soluble receptor (sIL-6R)[1] —sIL-6R is present in serum and synovial fluid[19]
- When bound to IL-6, sIL-6R can interact and signal in any cell type that expresses gp130[1,2,5]
- The sIL-6R complex then binds to gp130[1,2]

- These complexes activate the Janus kinase-signal transducer and activator of transcription (JAK-STAT) pathway and the mitogen-activated protein kinase (MAPK) pathway, which induces the expression of pro-inflammatory genes, such as matrix metalloproteinase (MMP) and receptor activator of nuclear factor kappa-β ligand (RANKL)[1,20,21]
- IL-6 signaling is a major contributor to induction of C-reactive protein (CRP) and other acute-phase proteins[1,22,23]
- The acute-phase response changes the concentration of certain plasma proteins, such as CRP, hepcidin, and serum amyloid A (SAA), that are produced in the liver in response to infections, tissue injury, neoplastic growth, or immunological disorder[1,22,23]

When IL-6 levels are persistently elevated, dual signaling may contribute to both articular and systemic manifestations of RA[1,12-15,24-26]

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SANOFI REGENERON

Panel Previews Updated Cardiovascular Disease Recommendations

BY MITCHEL L. ZOLER

The interval for assessing cardiovascular disease risk in patients with at least one inflamed joint can be as long as 5 years, depending on the patient, according to revised recommendations issued by a EULAR expert panel. The first edition of the recommendations called for annual assessment.

"We leave the assessment interval up to each clinician. Annually is very hard to incorporate into clinical practice," said Dr. Michael T. Nurmohamed, convenor of both the initial recommendation panel as well as the group that produced the new revision. He previewed the updated recommendations during a talk at the Congress. The final form of the revised recommendations, which apply to patients with rheumatoid arthritis, psoriatic arthritis, or ankylosing spondylitis, will soon be posted online and published, he said.

The context for cardiovascular disease risk assessment of patients with these rheumatoid diseases who are in primary-prevention mode has changed since the initial version was released in 2009 (Ann. Rheum. Dis. 2010;69:325-31). That changed context led to a rethinking of the appropriate interval for risk-factor assessment, said Dr. Nurmohamed, professor and head of rheumatology research at VU University Medical Center in Amsterdam. "In 2009, tight control of rheumatoid diseases generally did not exist," he said in an interview.

In patients with well-controlled rheumatoid disease, "you can assess their cardiovascular disease [CVD] risk, and if the risk is very low" you can defer the next follow-up assessment for 5 years or longer. But if a patient's CVD risk is high, assess the patient more often, Dr. Nurmohamed suggested. The recommendations also call for an updated CVD risk assessment following a "major change" in antirheumatoid therapy.

MITCHEL L. ZOLER/FRONTLINE MEDICAL NEWS

VIDEO HIGHLIGHTS: Click here to watch a video interview with Dr. Michael T. Nurmohamed.

The updated recommendations include two other notable changes. First, there is now a much deeper evidence base behind the need for CVD risk assessment and management in patients with psoriatic arthritis or ankylosing spondylitis. "We mentioned them before, but the data weren't all that hard. We now have more evidence," he said in an interview.

Second, the revised recommendations say that ultrasound examination of atherosclerotic plaque number and volume in a patient's carotid artery "may be considered." Dr. Nurmohamed acknowledged that carotid examination by ultrasound is very discretionary; it can provide useful risk information, but "not every rheumatologist will do it."

Most other aspects of the revised recommendations remain similar to the 2009 edition. They emphasize controlling inflammation to lower CVD risk, multiplying a patient's CVD risk score by a factor of 1.5 to better estimate their increased risk level due to their rheumatic disease, cautious use of nonsteroidal anti-inflammatory drugs, and minimized use of glucocorticoids. Multiplying a patient's CVD risk score results in a "rough" risk estimate, he cautioned. "The problem is we use 1.5 for all patients, regardless of their rheumatoid-disease duration," he said.

Recommended interventions to reduce a patient's CVD risk include lifestyle steps of healthy diet, regular exercise, and smoking cessation, and the standard drug interventions for reducing CVD risk: antihypertensive medications and lipid-lowering drugs, especially statins. Target levels for treating hypertension and hyperlipidemia remain the same as for primary prevention in the general population, he said. CVD risk assessment and management steps for patients with one of the covered rheumatoid diseases and established CVD are the same as for standard secondary-prevention measures in the general population.

A notable gap in the revision is the continued absence of recommendations for patients with gout. "Gout is on our research agenda, but represents an enormous task," Dr. Nurmohamed said. He anticipates that his panel will eventually develop recommendations for managing CVD risk in gout patients. ■

EULAR's Psoriatic Arthritis Recommendations Gain New Drugs

BY MITCHEL L. ZOLER

Tumor necrosis factor inhibitors remain the mainstay of treatment for patients with psoriatic arthritis who don't fully respond to treatment with a nonsteroidal anti-inflammatory drug and at least one conventional synthetic disease-modifying antirheumatic drug in newly updated treatment recommendations written by a EULAR task force.

The revised recommendations for psoriatic arthritis (PsA) replace what EULAR had last released in 2011 and published in 2012 (Ann Rheum Dis. 2012;71:4-12) and also add three new drug options not mentioned in the 2011 version that the panel now endorsed as alternatives to a tumor necrosis factor (TNF) inhibitor when a TNF inhibitor is not appropriate. The three additions are ustekinumab, which acts by inhibiting interleukin-(IL-)12 and IL-23, secukinumab, which acts by inhibiting IL-17, and apremilast, which inhibits phosphodiesterase-4. Ustekinumab and secukinumab are considered biological disease-modifying antirheumatic drugs (bDMARDs), like the TNF inhibitors, while apremilast occupies a new classification niche as a targeted synthetic DMARD, said Dr. Laure Gossec, convener of the PsA treatment task force, at the Congress.

Although ustekinumab, secukinumab, and apremilast all have a role to play in managing selected PsA patients, they all remain second line to TNF inhibitors, stressed Dr. Gossec, professor of rheumatology at Pierre and Marie Curie University in Paris. A TNF inhibitor is the first agent to turn to when treatment with an NSAID and a conventional synthetic DMARD fails to bring about remission or minimal disease activity essentially because of its much longer track record of safety and efficacy, she said. Specifically, TNF inhibitors have been studied long term and have demonstrated their safety in registries, they have not been surpassed for efficacy by any other agent using indirect comparisons, and now that biosimilar TNF inhibitors have entered the market they also could potentially offer a price advantage, compared with newer agents.

Dr. Laure Gossec

Mitchel L. Zoler/Frontline Medical News

But for some patients, TNF inhibitors are not appropriate, such as a patient with certain comorbidities or a history of infections that would make a TNF inhibitor contraindicated, she said. For these patients, one of the other types of biologic DMARDS now available would be the top alternative. In other patients, a comorbidity profile or a history of infections might make any biologic DMARD contraindicated, in which case the targeted synthetic DMARD apremilast is an appropriate alternative, she said.

The revised recommendations contain several other new items:

- For patients with active enthesitis, dactylitis, or both and an insufficient response to an NSAID or local glucocorticoid injections, then a TNF inhibitor or alternatively an IL-12 and IL-23 inhibitor (currently ustekinumab) or an IL-17 inhibitor (currently secukinumab) may be considered. Conventional synthetic DMARDS are ineffective for these patients, while in contrast all of the biologic DMARDs are effective, but the TNF inhibitors have an edge because of greater experience with the class in this setting.
- For patients with predominantly axial disease that is active and insufficiently responsive to NSAID treatment, a biologic DMARD should be considered, specifically a TNF inhibitor. Conventional synthetic DMARDs also have no efficacy for these patients, and few data exist regarding the efficacy of IL-12 and IL-23 inhibitors or IL-17 inhibitors.
- When patients fail to respond adequately to one biologic DMARD, switching to another biologic DMARD should be considered. This could involve switching from one TNF inhibitor to another, as some evidence exists that this could be effective. Alternatively, it could involve switching to a IL-12 and IL-23 inhibitor, an IL-17 inhibitor, or possibly a targeted synthetic DMARD (currently apremilast). The task force did not endorse any particular order of these drugs when switching occurs.

Dr. Gossec has been a consultant to AbbVie, Bristol-Myers Squibb, Celgene, Chugai, Janssen, Novartis, Pfizer, Roche, and UCB. ■

EULAR Releases First Recommendations for Managing Women's Health in SLE/APS

BY NICOLA GARRETT

For the first time, EULAR has devised recommendations on women's health and the management of family planning in women with systemic lupus erythematosus and antiphospholipid syndrome.

At the Congress, Dr. Laura Andreoli, a member of the EULAR task force on Women's Health and Pregnancy in SLE/APS that developed the recommendations, shared preliminary guidelines that are intended to equip medical specialists involved in the care of these patients with evidence-based recommendations to guide the way they counsel their patients.

Most of the decisions related to pregnancy, contraception, and in vitro fertilization in systemic lupus erythematosus (SLE) and antiphospholipid syndrome (APS) patients are taken in few tertiary level centers.

However, the current feeling is that medical specialists involved in the care of these patients at any level would benefit from recommendations related to these issues so that they can provide proper and timely counseling to their patients, Dr. Andreoli of the University of Brescia (Italy) explained in an interview.

"In an ideal setting, women with SLE/APS should be asked about their reproductive plans at early stages of the disease. Any specialist should be in the position to give first-line information that can be afterwards extended in more specialized centers if needed."

The recommendations are meant to guide clinicians in the management of women with SLE/APS who desire to give birth to a child by counseling them on the prevention of pregnancy-related risks factors for the mother and the baby and maternal disease complications during the postpartum period, as well as possible physical difficulties in parenting. The recommendations also cover the use of contraceptive methods, assisted reproduction techniques, menopause, female tumor prevention, and HPV vaccination.

Specifically the task force advises that:

• SLE/APS patients planning a pregnancy should be counseled and managed after risk stratification by taking into consideration disease activity, serological profile and antiphospholipid antibodies (aPL), hypertension, and use of drugs.

• Women with SLE and/or APS can be candidates for contraceptive measures based on their disease activity and thrombotic risk. Fertility preservation methods, especially gonadotropin-releasing hormone analogues, should be considered prior to the use of alkylating agents.

• Assisted reproduction techniques can be safely used in patients with stable/inactive disease and seem to have efficacy comparable to that of the general population. Patients with positive antiphospholipid antibodies or APS should receive appropriate anticoagulation and/or low-dose aspirin.

• Disease activity, serological markers, and renal function parameters are useful to monitor for obstetrical adverse outcomes and disease flares during pregnancy.

• Fetal monitoring should be conducted in a manner similar to that of a high-risk pregnancy and should include Doppler ultrasonography, particularly after 24-28 weeks of gestation, to screen for placental insufficiency; fetal echocardiography is indicated for suspected fetal dysrhythmia, especially in patients with positive anti-Ro and/or anti-La.

• Hydroxychloroquine, glucocorticoids (oral/intravenous pulse), azathioprine, cyclosporine-A, tacrolimus, and intravenous immunoglobulin can be used to prevent or manage SLE flares during pregnancy.

• If a patient has stable/inactive disease and is negative for aPL, hormonal replacement therapy can be used for severe vasomotor menopausal manifestations.

• Screening for malignancies is similar to that of the general population, with vigilance for cervical premalignant lesions if a patient has been exposed to immunosuppressive drugs. As with the general population, HPV immunization should be considered in women with stable/inactive disease.

Each item in the recommendations addresses the issue of high disease activity because of its strength as a risk factor for poor pregnancy outcome and also as a potential contraindication to hormonal treatments, Dr. Andreoli said.

The full set of recommendations is expected to be published in 2016. ■

PHOTO BY EVELINE PERROUD

Dr. Laura Andreoli

Updated Scleroderma Guidance Focuses On New Treatments, Approaches

BY SARA FREEMAN

Updated expert recommendations from EULAR for the treatment of systemic sclerosis will focus on several new treatment options, although the use of biologic agents is not included in detail because there are still too few data on these drugs to give firm guidance on their use.

The EULAR Scleroderma Trials and Research group (EUSTAR) recommendations for the treatment of scleroderma were first published 6 years ago (Ann Rheum Dis. 2009;68:620-8) and considered data through December 2006.

"Since then, a number of new drugs have become available and new and important information has been published concerning treatments already known before," said Dr. Otylia Kowal-Bielecka of the Medical University of Bialystok, Poland, who discussed some of the main highlights of the revised recommendations (Ann Rheum Dis. 2015;74:90-1) at the European Congress of Rheumatology.

Photo by Eveline Perroud

Dr. Otylia Kowal-Bielecka

> "Since then, a number of new drugs have become available and new and important information has been published concerning treatments already known before."

Scleroderma experts from all EUSTAR centers were invited to participate in the update and submit questions that could form the basis of the updated recommendations. From a total of 170 questions suggested, 46 questions concerning 23 treatment categories were researched in more depth via a systematic review of the literature that considered papers published through September 2014. A task force of more than 30 experts from Europe and the United States, two patients with scleroderma, and a clinical epidemiologist then met in October 2014 to discuss and formulate the final 16 recommendations.

The guidance covers the same main organ categories as the 2009 iteration – Raynaud phenomenon (RP), digital ulcers, pulmonary arterial hypertension (PAH), skin and lung disease, scleroderma renal crisis, and systemic sclerosis (SSc)-related gastrointestinal (GI) disease – Dr. Kowal-Bielecka observed, but the main difference is that many of the treatment options have been updated or reworded.

For instance, phosphodiesterase (PDE)-5 inhibitors and fluoxetine have been added to the treatment options for SSc-RP, which previously only included dihydropyridine-type calcium antagonists and intravenous iloprost. The latter is recommended after oral therapy. Evidence for the use of fluoxetine is weaker than for the PDE-5 inhibitors, but it might be worth considering in a patient with SSc-RP attacks. PDE-5 inhibitors have also been added to the list of options for digital ulcers. For PAH, where sildenafil was already recommended, tadalafil had been specifically included.

Intravenous iloprost and the endothelin-receptor antagonist (ERA) bosentan continue to be recommended for the management of digital ulcers. The recommendation on bosentan has been amended based on new data from two "high-quality," randomized, clinical trials and now considers the whole patient population rather than just those with disseminated disease, Dr. Kowal-Bielecka noted. The new statement recommends considering bosentan to reduce the number of new digital ulcers, especially in patients with multiple ulcers that might not be responding to calcium-channel blockers, PDE-5 inhibitors, and iloprost.

The area with the most changes is the treatment of PAH, with many new drugs now recommended, including

tadalafil, riociguat, ambrisentan, and macitentan, as well as more intravenous prostacyclin analogues such as epoprostenol.

Hematopoietic stem cell transplantation (HSCT) has been added to the list of options for managing skin and lung disease, which includes methotrexate for skin manifestations of early diffuse SSc and cyclophosphamide for interstitial lung disease. HSCT is only for selected patients who have progressive scleroderma and were at risk of organ failure, Dr. Kowal-Bielecka qualified. "In view of the high risk of treatment-related side effects and of early treatment-related mortality, careful selection of SSc patients for this kind of treatment and experience of medical team are of key importance," part of the draft recommendation reads.

Evidence from several descriptive cohort studies support the use of angiotensin-converting enzyme inhibitors for scleroderma renal crisis, and the expert opinion is that they should be used immediately. The recommendations continue to advise against using glucocorticoids in this patient population, based on retrospective study data. It is important to monitor patients' blood pressure and renal function while on treatment with steroids.

Recommendations have not changed for the management of SSc-related GI disease, but have been reworded slightly to recommend prokinetic drugs and the intermittent or rotating use of antibiotics.

"Several biologics were considered as potentially interesting, we had tocilizumab, rituximab, and TNF-alpha blockers on our list, and they also underwent the systematic literature research and review process," Dr. Kowal-Bielecka said in an interview. "However, the evidence available at the moment was considered by the expert panel to be insufficient to provide any recommendations," she said.

Dr. Kowal-Bielecka also noted that the expert panel had developed a research agenda for a list of drugs that are considered promising and which should be more carefully looked at in future trials.

"We believe that these guidelines provide knowledge to the broad community of rheumatologists who do not always have time to follow new developments in the published literature," she observed. In turn, it is hoped that the recommendations will help rheumatologists to manage their patients with SSc better, based on currently available evidence.

"Several biologics were considered as potentially interesting, we had tocilizumab, rituximab, and TNF-alpha blockers on our list, and they also underwent the systematic literature research and review process. However, the evidence available at the moment was considered by the expert panel to be insufficient to provide any recommendations."

The draft recommendations are close to being finalized and undergoing expert review by the EUSTAR task force before publication hopefully later this year, Dr. Kowal-Bielecka said.

The project is funded by a research grant of EULAR to the EUSTAR SSc recommendation group. Dr. Kowal-Bielecka is a member of speaker bureaus for AbbVie, Actelion, Pfizer, and Roche. ■

Immune Complexes Implicated in Systemic Sclerosis Pathogenesis

BY JEFF EVANS

New evidence from in vitro research suggests that immune complexes containing systemic sclerosis–specific autoantibodies might contribute to the etiopathogenesis of the condition.

The study is the first to demonstrate a pathogenic role for immune complexes (IC) isolated from systemic sclerosis (SSc) patients with different autoantibody specificities in the inductor phase of the disease, noted researchers led by first author Dr. Cecilia Chighizola, a postdoctoral fellow at the University of Milan.

"We believe our findings are rather innovative because, despite the diagnostic and prognostic role of scleroderma autoantibodies, almost no data were available about their pathogenic potential. Antinuclear antibodies are detected in almost all scleroderma patients; therefore, our results allow us to draw a comprehensive etiopathogenic hypothesis. Indeed, scleroderma antibodies might be proposed as novel mediators in the complex pathogenesis of systemic sclerosis," Dr. Chighizola said in an interview.

Because the autoantibodies that have been described as diagnostic and prognostic for SSc (anti-topoisomerase I, anti-centromere, anti-RNA polymerase, and anti-Th/To antibodies) have never been observed to be pathogenic, the researchers instead hypothesized that ICs containing the antibodies might induce a pro-inflammatory and pro-fibrotic signaling cascade in target cells. They incubated skin fibroblasts from healthy subjects with ICs from SSc patients and with ICs from healthy individuals to serve as a negative control. In addition, the agonists of Toll-like receptors (TLRs) 3 and 4 served as positive controls; indeed, the investigators postulated that TLRs might be involved in mediating the effects of ICs from SSc patients because SSc autoantibodies are known to bind to nucleic acids.

Dr. Cecelia Chighizola

ICs from SSc patients upregulated the gene expression levels of both interferon (IFN)-alpha and IFN-beta, but conversely, no modulation in the mRNA levels of type I interferons was reported when fibroblasts were stimulated with control ICs, suggesting that the ICs from SSc patients "specifically exert a pro-interferogenic action," Dr. Chighizola said. The researchers found similar results when they applied TLR agonists.

The investigators also found evidence that the ICs from SSc patients could induce an SSc-like phenotype in fibroblasts from healthy controls based on the upregulation of ICAM-1 (a marker of fibroblast activation), IL-6 (a proinflammatory and profibrotic cytokine), IL-8 (involved in inflammation and endothelial damage), and MMP-2 (an enzyme involved in matrix remodeling). They observed a similar effect with TLR3 and TLR4 agonists but not with control ICs, suggesting the specificity of the response.

Dr. Chighizola noted that all ICs from SSc patients were able to induce the in-study mediators, and there were no significant differences across the various ICs bearing different autoantibodies. Further experiments are warranted, however, to better define the characteristic effects elicited by each of the ICs from SSc patients.

Application of either TLR3 agonist or ICs from SSc patients led to increases in mRNA expression levels of both TLR3 and TLR9 in the normal fibroblasts, which suggests their potential involvement in mediating the cellular effects elicited by the SSc ICs.

"The results emerging from our study might impact the clinical management of systemic sclerosis patients, as scleroderma ICs could provide a novel pharmacological target in the very early stages of the disease. Old drugs such as antimalarials are well known to modulate the functionality of TLRs; their use in the very early stages of systemic sclerosis might impact disease evolution," Dr. Chighizola speculated.

She said that in future studies the researchers "plan to transiently silence skin fibroblasts for various TLRs in order to evaluate their contribution to the upregulation of scleroderma mediators in response to incubation with disease ICs. We would also assess the effects elicited by scleroderma ICs in other cells involved in the pathogenesis of this disease, such as endothelial cells."

Dr. Chighizola and her coauthors had no conflicts of interest to report. ■

Protection Against Primary Sjögren's Syndrome Observed in Smokers

BY WHITNEY MCKNIGHT

Tobacco use was associated with a protective effect against primary Sjögren's syndrome, while smoking cessation was correlated with a higher likelihood of developing the disorder, according to a nested case-control study of longitudinal data from two prospective population-based health surveys in Sweden.

The study confirms earlier retrospective data showing an inverse correlation between focal sialadenitis and primary Sjögren's syndrome (pSS) autoantibody production (anti-Ro and anti-La) and tobacco use (Ann. Rheum. Dis. 2000;59:54-60), said lead author Dr. Elke Theander, who was one of six clinical abstract award winners at this year's Congress. Dr. Theander is an associate professor in the Department of Rheumatology at Malmö University Hospital, Lund (Sweden) University.

In their most recent investigation, Dr. Theander and her associates found former smokers were nearly eight times more likely to have pSS (odds ratio, 8.1; 95% confidence interval, 3.2-21), compared with current smokers. Former smokers showed fourfold greater odds for the condition, compared with those who had never smoked (OR, 4.1; 95% CI, 1.8-10).

Dr. Elke Theander

The data were derived from the 33,346-person Malmö Preventive Medicine Study (1974-1991) and the 30,447-person Malmö Diet and Cancer Study (1991-1996), and included four age- and gender-matched controls for each validated case, also matched for the year of screening. Between 1984 and the present, patients who have been included in the pSS registry had their diagnosis after they were included in either of the two population-based health studies. Information on the time of onset of sicca symptoms had been independently recorded at the time of pSS diagnosis.

> "Pre-primary Sjögren's syndrome patients are, due to some reason, prone to stop smoking, which is reverse causality. We do not know why our patients stopped smoking, but they did it, in most cases, years before their first recognized symptoms of pSS."

Of the 63 control-matched individuals, nearly all of whom were women with a mean age of 51 years when diagnosed with pSS, 73% had positive antinuclear antibodies, 57% tested positive for rheumatoid factor, 59% were positive for anti-Ro antibodies, and 41% were positive for anti-La antibodies. Focal sialadenitis with a focus score of 1 or higher was found in 85%.

There was a significantly higher proportion of nonsmokers among pre-pSS individuals, compared with controls (85% vs. 68%; $P = .004$). Current smoking at inclusion was associated with reduced odds of subsequent diagnosis of pSS (OR, 0.26; 95% CI, 0.11-0.60). The pattern of current to former smokers was different in cases and controls. The ratio of present:former smokers was 0.3 among cases and 1.5 among controls (P less than .001).

It's difficult to say why smoking seems protective against pSS and why smoking cessation may initiate the disease, Dr. Theander said. "Inhaled smoke from cigarettes contains numerous toxic and mutagenic substances. Nicotine is only one of them, and we do not know at the moment if nicotine or anything else exerts the described effects. Smoking may result in a number of immunological aberrations; both up-regulation of cytokine genes, blocking of receptors, and other effects on various immune cells are described," she explained.

One mechanism might be that "smoking suppresses immunological pathways which are reactivated during smoking cessation, and the disease starts after this recovery in predisposed individuals. The IL33-ST2 axis might be one such pathway, which is hypothesized to participate in pSS pathogenesis. Smoking is described as a potential IL33 up-regulator in epithelial cells and at the same time is a down-regulator of immunological responses to IL33."

Alternatively, she said, "pre-primary Sjögren's syndrome patients are, due to some reason, prone to stop smoking, which is reverse causality. We do not know why our patients stopped smoking, but they did it, in most cases, years before their first recognized symptoms of pSS."

The researchers had no conflicts of interest to declare. ■

First Gut Microbiota Alterations Described In Systemic Sclerosis Patients

BY KAREN BLUM

NICK PIEGARI/FRONTLINE MEDICAL NEWS

VIDEO HIGHLIGHTS: Click here to view a video interview with Dr. Elizabeth Volkmann.

Patients with systemic sclerosis have a distinct colonic microbiota, compared with healthy individuals, which could contribute to their immune dysfunction and symptoms, according to a new study.

As with chronic inflammatory states such as inflammatory bowel disease, systemic sclerosis (SSc) patients had decreased commensal gut bacteria such as *Bacteroides* and *Faecalibacterium*, and increased pathogenic genera such as *Enterobacteriales* and *Fusobacterium*, in the cecum and sigmoid, compared with healthy controls.

In addition, SSc patients had increased sigmoid and cecum *Bifidobacterium*, which is typically found in lower abundance in inflammatory bowel disease. Additional taxa alterations also were observed. These differences had never been described in scleroderma before, according to lead study author Dr. Elizabeth Volkmann, a rheumatologist and clinical instructor at the University of California, Los Angeles.

"Gastrointestinal tract dysfunction affects 90% of systemic sclerosis patients and is a leading cause of morbidity and mortality in these patients," Dr. Volkmann said in an interview. "Symptoms such as constipation and fecal incontinence are among the most disruptive physical problems for SSc patients, and we really don't know the cause of them at this point."

Dr. Volkmann and her colleagues studied 17 patients with SSc: Eighty-eight percent were women, the median age was 52 years, and the median disease duration was nearly 7 years. They compared these patients to age- and gender-matched healthy controls.

At baseline, the patients underwent a colonoscopy. Researchers obtained cecum and sigmoid mucosal lavage samples for analysis; they used 16S sequencing to determine the microbiota and the Greengenes database to determine operational taxonomic units, in addition to other tests. Patients also completed the UCLA Scleroderma Clinical Trial Consortium Gastrointestinal Tract (UCLA SCTC GIT) 2.0 questionnaire to assess gastrointestinal symptom severity at the time of colonoscopy. They had a mean total score of 0.7 on the questionnaire, indicating moderate symptom severity, she said at the Congress.

"Even with our small sample size, there were still statistically significant differences, including [in SSc patients] a decrease in normal, healthy bacteria and an increase in more pathogenic bacteria that in other disease states cause inflammation," Dr. Volkmann said.

Comparisons between SSc patients and healthy controls demonstrated numerous differences in the microbial communities in both the cecum and sigmoid, including a much higher abundance of the species *Erwinia* and *Trabulsiella* in patients with the most severe symptoms.

"This suggests not only are there differences in the microbiota composition between SSc patients and healthy controls, but these differences may contribute to clinical symptoms," she said.

The SSc patients had a mean total score of 0.7 on the GIT 2.0, indicating moderate symptom severity. They also had moderate severity on the distension, constipation, emotional well-being, and social functioning domains on the GIT 2.0, and mild symptom severity on the diarrhea and fecal soilage domains.

Replacing healthy bacteria through probiotic supplements may be a potential therapy, she said. However, some SSc patients had an increase in *Lactobacillus* and *Bifidobacterium*, which normally are decreased in patients with inflammation, she said. Probiotic therapy should be used to target only species that are decreased, and many commercial probiotics are rich in *Lactobacillus* and *Bifidobacterium*.

One potential hypothesis for why some SSc patients had higher levels of *Lactobacillus* and *Bifidobacterium* may be because most were using a probiotic, she said. However, they asked patients to stop using a probiotic 3 weeks before their colonoscopy.

Her group is continuing studies in this population to evaluate microbiome changes over the course of a year.

Dr. Volkmann did not report any relevant financial disclosures. ■

VIDEO HIGHLIGHTS

Assessment Tool Rapidly Screens Cognition in Lupus Patients

Mitchel L. Zoler/Frontline Medical News

The Montreal Cognitive Assessment provides a quick and easy-to-use screening tool to identify patients with systemic lupus erythematosus with cognitive impairment, Dr. Zahi Touma reported in a poster at the Congress.

In a consecutive series of 78 patients screened with the Montreal Cognitive Assessment (MoCA), the free, single-page test, which can be administered in about 10 minutes, showed a sensitivity of 69% and specificity of 68%, compared with the current standard, the Hopkins Verbal Learning Test-Revised, said Dr. Touma, a rheumatologist at the University of Toronto.

Other easy-to-use and quick screening tools, such as the Mini-Mental State Examination, had substantially worse performance in the study. He and his associates found a sensitivity of 21% and specificity of 91% using the Mini-Mental State exam. For screening, higher sensitivity is desirable so that fewer patients with potential cognitive impairment are missed, he noted.

"Ease of use and time needed for assessment as well as appropriate psychometric properties make the MoCA the preferential screening test for cognitive impairment in patients with SLE," Dr. Touma said in his poster.

Cognitive impairment is very common among patients with systemic lupus erythematosus (SLE). In this study, Dr Touma found a 47% prevalence using MoCA. Cognitive impairment, however, often goes unidentified in SLE patients, likely because of lack of awareness among rheumatologists as well as the absence of a quick and easily administered screening tool, he said in a video interview.

Dr. Touma said he hopes that the apparent efficacy of an easy-to-use screening tool like MoCA will help boost appreciation for the high prevalence of cognitive impairment in SLE patients. He suggested that clinicians screen for cognitive impairment as soon as SLE is diagnosed and that they perform follow-up screening during subsequent patient encounters with SLE patients who initially present without cognitive impairment.

Dr. Touma had no disclosures.

For adult patients with active psoriatic arthritis

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- Otezla was studied in 3 randomized, double-blind, placebo-controlled trials of similar design. A total of 1493 adults with active psoriatic arthritis (≥3 swollen and ≥3 tender joints), despite prior or current disease-modifying antirheumatic drug (DMARD) therapy, were randomized to placebo or Otezla 30 mg twice daily, after a titration period[1]
- Patients who failed >3 small molecules or biologics or >1 biologic TNF blocker were excluded[1]

INDICATION

- Otezla® (apremilast) is indicated for the treatment of adult patients with active psoriatic arthritis

IMPORTANT SAFETY INFORMATION

Contraindications

- Otezla is contraindicated in patients with a known hypersensitivity to apremilast or to any of the excipients in the formulation

Warnings and Precautions

- Depression: Treatment with Otezla is associated with an increase in adverse reactions of depression. During clinical trials, 1.0% (10/998) of patients treated with Otezla reported depression or depressed mood compared to 0.8% (4/495) treated with placebo; 0.3% (4/1441) of patients treated with Otezla discontinued treatment due to depression or depressed mood compared with none in placebo treated patients (0/495). Depression was reported as serious in 0.2% (3/1441) of patients exposed to Otezla, compared to none in placebo treated patients (0/495). Suicidal ideation and behavior were observed in 0.2% (3/1441) of patients on Otezla, compared to none on placebo (0/495). Two patients who received placebo committed suicide compared to none on Otezla
  - Carefully weigh the risks and benefits of treatment with Otezla for patients with a history of depression and/or suicidal thoughts/behavior, or in patients who develop such symptoms while on Otezla. Patients, caregivers, and families should be advised of the need to be alert for the emergence or worsening of depression, suicidal thoughts or other mood changes, and they should contact their healthcare provider if such changes occur
- Weight Decrease: Body weight loss of 5-10% was reported in 10% of patients taking Otezla and in 3.3% of patients taking placebo. Monitor body weight regularly; evaluate unexplained or clinically significant weight loss, and consider discontinuation of Otezla
- Drug Interactions: Apremilast exposure was decreased when Otezla was co-administered with rifampin, a strong CYP450 enzyme inducer; loss of Otezla efficacy may occur. Concomitant use of Otezla with CYP450 enzyme inducers (eg, rifampin, phenobarbital, carbamazepine, phenytoin) is not recommended

Adverse Reactions

- Adverse reactions reported in at least 2% of patients taking Otezla, that occurred at a frequency at least 1% higher than that observed in patients taking placebo, for up to 16 weeks (after the initial 5-day titration), were (Otezla%, placebo%): diarrhea (7.7, 1.6); nausea (8.9, 3.1); headache (5.9, 2.2); upper respiratory tract infection (3.9, 1.8); vomiting (3.2, 0.4); nasopharyngitis (2.6, 1.6); upper abdominal pain (2.0, 0.2)

Use in Specific Populations

- Pregnancy and Nursing Mothers: Otezla is Pregnancy Category C; it has not been studied in pregnant women. Use during pregnancy only if the potential benefit justifies the potential risk to the fetus. It is not known whether apremilast or its metabolites are present in human milk. Caution should be exercised when Otezla is administered to a nursing woman
- Renal Impairment: Otezla dosage should be reduced in patients with severe renal impairment (creatinine clearance less than 30 mL/min); for details, see Dosage and Administration, Section 2, in the Full Prescribing Information

Please see Brief Summary of Full Prescribing Information on the following page.

Reference: 1. Otezla [package insert]. Summit, NJ: Celgene Corporation; 2014.

Rx Only

OTEZLA® (apremilast) tablets, for oral use
The following is a Brief Summary of the Prescribing Information; see Full Prescribing Information for complete product information.

INDICATIONS AND USAGE
OTEZLA® (apremilast) is indicated for the treatment of adult patients with active psoriatic arthritis.

CONTRAINDICATIONS
OTEZLA is contraindicated in patients with a known hypersensitivity to apremilast or to any of the excipients in the formulation [see *Adverse Reactions (6.1)*].

WARNINGS AND PRECAUTIONS
Depression: Treatment with OTEZLA is associated with an increase in adverse reactions of depression. During the 0 to 16 weeks placebo-controlled period of the 3 controlled clinical trials, 1.0% (10/998) of patients treated with OTEZLA reported depression or depressed mood compared to 0.8% (4/495) treated with placebo. During the clinical trials, 0.3% (4/1441) of patients treated with OTEZLA discontinued treatment due to depression or depressed mood compared with none in placebo treated patients (0/495). Depression was reported as serious in 0.2% (3/1441) of patients exposed to OTEZLA, compared to none in placebo treated patients (0/495). Instances of suicidal ideation and behavior have been observed in 0.2% (3/1441) of patients while receiving OTEZLA, compared to none in placebo treated patients (0/495). In the clinical trials, two patients who received placebo committed suicide compared to none in OTEZLA treated patients. Before using OTEZLA in patients with a history of depression and/or suicidal thoughts or behavior prescribers should carefully weigh the risks and benefits of treatment with OTEZLA in such patients. Patients, their caregivers, and families should be advised of the need to be alert for the emergence or worsening of depression, suicidal thoughts or other mood changes, and if such changes occur to contact their healthcare provider. Prescribers should carefully evaluate the risks and benefits of continuing treatment with OTEZLA if such events occur.
Weight Decrease: During the controlled period of the studies, weight decrease between 5-10% of body weight was reported in 10% (49/497) of patients treated with OTEZLA 30 mg twice daily compared to 3.3% (16/495) treated with placebo [see *Adverse Reactions (6.1)*]. Patients treated with OTEZLA should have their weight monitored regularly. If unexplained or clinically significant weight loss occurs, weight loss should be evaluated, and discontinuation of OTEZLA should be considered.
Drug Interactions: Co-administration of strong cytochrome P450 enzyme inducer, rifampin, resulted in a reduction of systemic exposure of apremilast, which may result in a loss of efficacy of OTEZLA. Therefore, the use of cytochrome P450 enzyme inducers (e.g. rifampin, phenobarbital, carbamazepine, phenytoin) with OTEZLA is not recommended. [see *Drug Interactions (7.1)* and *Clinical Pharmacology (12.3)*].

ADVERSE REACTIONS
Clinical Trials Experience in Psoriatic Arthritis: Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trial of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in clinical practice. The majority of the most common adverse reactions presented in Table 2 occurred within the first two weeks of treatment and tended to resolve over time with continued dosing. Diarrhea, headache, and nausea were the most commonly reported adverse reactions. The most common adverse reactions leading to discontinuation for patients taking OTEZLA were nausea (1.8%), diarrhea (1.8%), and headache (1.2%). The proportion of patients with psoriatic arthritis who discontinued treatment due to any adverse reaction was 4.6% for patients taking OTEZLA 30 mg twice daily and 1.2% for placebo-treated patients.

Table 2: Adverse Reactions Reported in ≥ 2% of Patients on OTEZLA 30 mg Twice Daily and ≥ 1% Than That Observed in Patients on Placebo For Up To Day 112 (Week 16)

	Placebo		OTEZLA 30 mg BID	
Preferred Term	**Day 1 to 5 (N=495) n (%)[c]**	**Day 6 to Day 112 (N=490) n (%)**	**Day 1 to 5 (N=497) n (%)**	**Day 6 to Day 112 (N=493) n (%)**
Diarrhea [a]	6 (1.2)	8 (1.6)	46 (9.3)	38 (7.7)
Nausea[a]	7 (1.4)	15 (3.1)	37 (7.4)	44 (8.9)
Headache[a]	9 (1.8)	11 (2.2)	24 (4.8)	29 (5.9)
Upper respiratory tract infection[b]	3 (0.6)	9 (1.8)	3 (0.6)	19 (3.9)
Vomiting[a]	2 (0.4)	2 (0.4)	4 (0.8)	16 (3.2)
Nasopharyngitis[b]	1 (0.2)	8 (1.6)	1 (0.2)	13 (2.6)
Abdominal pain upper[b]	0 (0.0)	1 (0.2)	3 (0.6)	10 (2.0)

[a] Of the reported gastrointestinal adverse reactions, 1 subject experienced a serious adverse reaction of nausea and vomiting in OTEZLA 30 mg twice daily; 1 subject treated with OTEZLA 20 mg twice daily experienced a serious adverse reaction of diarrhea; 1 patient treated with OTEZLA 30 mg twice daily experienced a serious adverse reaction of headache.
[b] Of the reported adverse drug reactions none were serious.
[c] n (%) indicates number of patients and percent.

Other adverse reactions reported in patients on OTEZLA were hypersensitivity, weight decrease, frequent bowel movement, gastroesophageal reflux disease, dyspepsia, decreased appetite*, migraine, cough, and rash.
*1 patient treated with OTEZLA 30 mg twice daily experienced a serious adverse reaction.

DRUG INTERACTIONS
Strong CYP 450 Inducers: Apremilast exposure is decreased when OTEZLA is co-administered with strong CYP450 inducers (such as rifampin) and may result in loss of efficacy [see *Warnings and Precautions (5.3)* and *Clinical Pharmacology (12.3)*].

USE IN SPECIFIC POPULATIONS
Pregnancy: *Pregnancy Category C*: OTEZLA should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. Pregnancy Exposure Registry: There is a pregnancy exposure registry that monitors pregnancy outcomes in women exposed to OTEZLA during pregnancy. Information about the registry can be obtained by calling 1-877-311-8972. **Nursing Mothers:** It is not known whether OTEZLA or its metabolites are present in human milk. Because many drugs are present in human milk, caution should be exercised when OTEZLA is administered to a nursing woman. **Pediatric use:** The safety and effectiveness of OTEZLA in pediatric patients less than 18 years of age have not been established. **Geriatric use:** Of the 1493 patients who enrolled in Studies PsA-1, PsA-2, and PsA-3 a total of 146 psoriatic arthritis patients were 65 years of age and older, including 19 patients 75 years and older. No overall differences were observed in the safety profile of elderly patients ≥ 65 years of age and younger adult patients < 65 years of age in the clinical studies. **Renal Impairment:** OTEZLA pharmacokinetics were not characterized in subjects with mild (creatinine clearance of 60-89 mL per minute estimated by the Cockroft–Gault equation) or moderate (creatinine clearance of 30-59 mL per minute estimated by the Cockroft–Gault equation) renal impairment. The dose of OTEZLA should be reduced to 30 mg once daily in patients with severe renal impairment (creatinine clearance of less than 30 mL per minute estimated by the Cockroft–Gault equation) [see *Dosage and Administration (2.2)* and *Clinical Pharmacology (12.3)*]. **Hepatic Impairment:** Apremilast pharmacokinetics were characterized in subjects with moderate (Child Pugh B) and severe (Child Pugh C) hepatic impairment. No dose adjustment is necessary in these patients.

OVERDOSAGE
In case of overdose, patients should seek immediate medical help. Patients should be managed by symptomatic and supportive care should there be an overdose.

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Survey Finds Young Rheumatologists Confident in Training

BY GREGORY TWACHTMAN

Young rheumatologists believe they are receiving adequate training in most core competencies, according to a survey of trainees in rheumatology and recently certified rheumatologists.

"Our findings show that recently trained rheumatologists are confident in their ability to carry out many of the tasks expected of them, including managing patients with a variety of rheumatic and musculoskeletal diseases [RMDs]," lead researcher Dr. Francisca Sivera said.

The research is based on responses from 1,243 survey participants, which was 28% of the target population consisting of trainees (58% of respondents) and those certified within 5 years of the survey period of June-December 2014. Respondents were from 41 EULAR countries with rheumatology training. A total of 30% of the respondents were male.

Although the rheumatologists were confident with most areas of their training, Dr. Sivera noted in an interview that she and her colleagues were "surprised to find that a significant proportion of the trainees across Europe [less than 10%] managed 10 or fewer patients with specific RMDs during their training period. We believe that managing 10 or fewer patients in most RMDs, given the heterogeneity in clinical presentation many of our diseases have, provides you with very limited practical experience."

Dr. Francisca Sivera

In the survey, the rheumatologists rated their confidence in their ability to perform the tasks outlined in 21 core competencies from the European Union of Medical Specialists European Board of Rheumatology's Curriculum Framework, based on a scale of 0-10. The survey did not evaluate actual training. Most scored themselves in the 7-9 range on each competency. For any given competency, mean confidence was higher when a survey respondent received formal education, compared with those who did not. Both greater patient exposure (more than 10 patients) and longer training periods (internal medicine plus rheumatology) also resulted in higher mean scores.

> "The area of training which clearly needs improvement is the identification of monosodium urate and calcium pyrophosphate dehydrate crystals with an optical microscope and performing a musculoskeletal ultrasound."

The two exceptions in which survey respondents had lower confidence were crystal identifications and ultrasound, scoring on average 5.98 and 5.89, respectively.

"The area of training which clearly needs improvement is the identification of monosodium urate and calcium pyrophosphate dehydrate crystals with an optical microscope and performing a musculoskeletal ultrasound," said Dr. Sivera of the Hospital General Universitario de Elda (Spain). "More than a quarter of the respondents had very low confidence in their ability to identify crystals, and less than half had performed a 'sufficient' number of procedures during their training [less than 10]. This is relevant for the management of patients with gout or other crystal arthritis."

Dr. Sivera was less concerned about the lower confidence in performing ultrasounds. "Even though ultrasound is a very useful technique, it is still debated whether every trainee should be expected to master it."

In the area of specific disease management, "the management of patients with connective tissue disease and vasculitis shows the lowest confidence across most countries," she said. "This could be due to any number of causes – other specialties taking over the management of these patients, a lesser prevalence and therefore experience with these diseases, or the higher complexity of these diseases. If possible, these causes should be analyzed and addressed."

Dr. Sivera hopes the survey results will help to "increase the quality of training across Europe and the degree of harmonization between countries. Up to now, there was no data that allowed comparisons of the training across European countries. … Now that we have the picture, we can work toward improving the national quality and hopefully create a European standard." ■

Young Rheumatologists Embrace Social Media

BY GREGORY TWACHTMAN

Social media is playing a role in the practice of rheumatology, especially among young rheumatologists.

Results from a recent survey by the Emerging EULAR Network (EMEUNET) reveal that social media (SM) is playing a significant role in how rheumatologists communicate, with most in the survey saying they are using the various platforms, including Facebook, Twitter, LinkedIn, Instagram, YouTube, and others, for mostly professional reasons. Dr. Elena Nikiphorou reported at the Congress.

"Social media appears to have an increasing impact in modern rheumatology practice and provides a good source of information for educational purposes and potential for networking," said Dr. Nikiphorou, currently a research fellow on a EULAR-funded initiative in Jyväskylä, Finland. She led the research for this survey, and from it gleaned "insights into the use of SM overall and in a professional manner," she said in an interview.

The survey found that the majority of respondents were active users of at least one social media platform (more than 80%), with Facebook being the most common platform for communications, although LinkedIn was the dominant platform for professional communications. The mean weekly use of social media was 7 hours. Nearly three-quarters of the 233 survey respondents reported using social media in a work-related manner.

"The fact that the majority of people were active SM users will hopefully encourage their more widespread use in a professional manner," Dr. Nikiphorou said.

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Overall, respondents were using social media for communicating with friends and colleagues (79%), news updates (76%), entertainment (69%), rheumatology clinical updates (50%), and research updates (48%).

However, the results also highlight "issues around lack of knowledge on the use of SM and concerns regarding their safety, exposure of private life, and being a time-consuming process; issues that could be actively addressed," said Dr. Nikiphorou of the department of rheumatology at Cambridge (United Kingdom) University Hospitals NHS Foundation Trust.

Indeed, "lack of knowledge on how to use social media and not covering individual needs were among the main reasons for abstaining from social media in a work-related manner," she said, with 1 in 10 respondents also expressing concerns regarding the potential negative impact social media use could have on their reputation.

Thirty percent of non–social media users justified not using social media because of lack of knowledge, while 26% considered it unsuitable for their needs and 41% expressed no interest in it.

"We would like to look into greater detail at the reasons for abstaining from social media use in a professional manner," Dr. Nikiphorou said when asked about the next steps for this research. "It would be interesting to also explore in greater detail the age distribution in social media use. In this survey, almost three quarters of responders were under the age of 40."

She said it would be worthwhile to repeat the survey in the future and hopes to see increased awareness of the positive uses of social media, compared with the results from this initial survey. ■

Obesity Linked With Increased Rheumatoid Arthritis Incidence

BY MITCHEL L. ZOLER

Obese people had a 50% increased rate of developing rheumatoid arthritis compared with normal or underweight people, in a case-control study of more than 2,000 Swedish residents for which researchers used prospectively collected data.

The increased rate of developing rheumatoid arthritis (RA) conferred by obesity occurred in both women and in men, it was greatest in the subgroup of people who developed RA symptoms when they were age 50 years or younger, and it was greatest in the subgroup of people seropositive for anti-citrullinated protein antibodies (ACPA), rheumatoid factor (RF), or both Dr. Lotta Ljung said at the Congress.

The findings add to the growing body of evidence documenting obesity as a risk factor for development of RA, said Dr. Ljung, a rheumatologist at Umeå (Sweden) University.

She and her associates used data collected in two Swedish population-based cohorts followed prospectively, the Västerbotten Intervention Programme and the Northern Sweden portion of the MONICA project. The two databases included baseline and long-term follow-up data during 1985-2013 from more than 110,000 Swedish citizens, average age 52 years at baseline, and average body mass index of 26 kg/m^2. The databases included 557 patients with incident RA, which appeared an average of 6 years following entry into their database, with 83% of the cases showing seropositivity for ACPA, RF, or both. The researchers matched these cases on a 3:1 basis with 1,671 controls without RA by their sex, year of birth, cohort, examination year, and region of residence in Sweden.

In an analysis that controlled for both smoking and education level, people who entered one of the databases with a BMI of 30 kg/m^2 or higher, defined as obesity, had a statistically significant 50% increased rate of developing RA during follow-up, compared with people who entered with a BMI of less than 25 kg/m^2, which corresponded to normal- or under-weight. Those with a BMI of 25-29.99 kg/m^2, the overweight group, had a borderline statistically significant 20% increased rate of developing RA during follow-up, compared with the reference group, Dr. Ljung reported.

An analysis that examined the link between incident RA and baseline BMI as a continuous variable showed a 2% increased rate of incident RA for each 1-unit increase in BMI, but this relationship fell short of statistical significance after adjustment for smoking and education level. A second analysis that looked at waist circumference as a continuous variable showed a statistically significant 2% rise in RA incidence for each 1-cm increase in waist circumference at baseline after adjustment.

Dr. Ljung had no disclosures. ■

VIEW ON THE NEWS

Substantial Evidence Supports an Obesity and RA Link

The new findings reported by Dr. Ljung that show obesity is a risk factor for developing rheumatoid arthritis are very consistent with what my associates and I reported last year using data collected in the Nurses Health Study (Ann Rheum Dis 2014;73:1914-22) as well as findings in several other recent reports (Ann Rheum Dis. 2014;73:1911-3). I think we can now say with confidence that obesity does increase a person's risk for developing rheumatoid arthritis.

This firm link is important because it gives us practical information we can give to family members of patients with rheumatoid arthritis (RA) with implications for disease prevention. First-degree relatives of patients with RA often ask me what they can do to try to prevent themselves from also developing RA. For many years we had to tell them we didn't know what they could do, but recently that's changed. I tell relatives that while they can't change their genes they can lose weight or not gain weight and that will reduce their risk, as well as certain other preventive steps such as not smoking. Many rheumatologists have been advocating smoking cessation for several years as a way to prevent RA onset, but talking about the risk for RA posed by obesity is only now starting to gain a similar place in prevention counseling.

Unfortunately we don't yet have clear evidence that by taking these steps relatives of RA patients will better avoid developing the disease themselves, but nevertheless it is something positive they can do that has a reasonably good chance for success.

My associates and I have launched a pilot trial in which we are evaluating a risk calculator designed to assess the RA risk faced by first-degree relatives of RA patients, and then we are studying the efficacy of different counseling approaches to convey information about this risk. Preventive rheumatology is an exciting new facet of our specialty.

Dr. Karen H. Costenbader *is a rheumatologist at Brigham and Women's Hospital in Boston. She had no disclosures. She made these comments in an interview.*

'COBRA Slim' Tops Other Combination Strategies for Early RA

BY SARA FREEMAN

Strategies that combine conventional synthetic disease-modifying antirheumatic drugs, such as methotrexate, sulfasalazine, or leflunomide, with a tapered glucocorticoid regimen to rapidly induce remission in early rheumatoid arthritis resulted in remission rates of 60% or higher after 1 year in a Belgian study.

"There is ample evidence that combination therapy for early rheumatoid arthritis (COBRA)-like remission-induction are both clinically and cost-effective, but unfortunately this type of therapy is not yet widely used in practice," said lead study author Patrick Verschueren, a rheumatologist at the University Hospital in Leuven, Belgium, and professor at KU Leuven. The typical arguments that rheumatologists use against the strategy are that the dosages of prednisone used are unnecessarily high and that the combinations of disease-modifying antirheumatic drugs (DMARDs) are not ideal in terms of efficacy and safety, he said.

Dr. Verschueren presented some of the results of the CareRA [Care in early RA] study to support this view at the Congress. In this 2-year, prospective, multicenter, randomized, controlled trial, different intensive combination treatment strategies were compared over the course of 52 weeks in patients with previously untreated, early RA (less than 1 year).

Of 400 patients who were screened for entry into the trial, 379 were finally recruited and stratified into high- and low-risk groups based on the presence of the classic prognostic markers of joint erosions, rheumatoid factor, and anticitrullinated protein antibody status, and disease activity according to 28-joint disease activity score based on C-reactive protein (DAS28-CRP). In total, there were 289 patients classified as being at high risk and 90 patients classified as having low risk.

Dr. Verschueren reported on the 289 patients who were classified as being at high risk. These patients were randomized to one of three treatment strategies:

- COBRA Classic – methotrexate, sulfasalazine, and 60 mg of prednisone tapered weekly, starting at week 7, to 7.5 mg daily.
- COBRA Slim – methotrexate plus 30 mg of prednisone tapered, starting at week 6, to 5 mg daily.
- COBRA Avant-Garde – methotrexate, leflunomide, and 30 mg of prednisone tapered, starting at week 6, to 5 mg daily.

There were 98 patients in each of the first two treatment arms and 93 in the third. Glucocorticoids were tapered in all patients starting at week 28 and stopped at week 34. From week 40 onward, investigators aimed for DMARD monotherapy.

Remission rates, defined as achieving a DAS28-CRP score of less than 3.2, were 64.3%, 60.2%, and 62.8% of patients in the COBRA-Classic, Slim, and Avant-Garde groups, respectively ($P = .840$). Other efficacy outcomes, which included the percentage of patients achieving a good EULAR (European League Against Rheumatism) response and a clinically meaningful (score of zero) response using the Health Assessment Questionnaire, did not differ between groups. Changes in radiographic progression between the groups – measured using the Sharp van der Heijde (SvH) score – were also minimal. SvH scores were 1.3 ± 2.1, 1.3 ± 2.5, and 1.0 ± 1.4 at baseline, and these changed over 52 weeks by 0.3 ± 0.5, 0.4 ± 1.1, and 0.3 ± 0.6 in the Classic, Slim, and Avant-Garde groups ($P = .581$).

At the current time, the COBRA Slim regimen, which consists of methotrexate and tapered prednisone, could be regarded as the ideal remission-induction regimen for all early RA patients, regardless of their prognostic profile, Dr. Verschueren suggested. It had similar efficacy, but fewer adverse events, than did the more complex COBRA strategies, which used higher dosages of glucocorticoids and combinations of DMARDs and with clear advantages over the traditional step-up approach, he said.

There were similar percentages of patients in each of the three groups that experienced at least one adverse event, at 67.3% for the COBRA Classic strategy, 66.3% for the COBRA Slim regimen, and 76.3% for the COBRA Avant-Garde approach. "Certain patients might benefit from DMARD combinations plus step-down glucocorticoids if they can tolerate the treatment schedule and comply with it," Dr. Verschueren proposed.

"There are certainly patients who would benefit more from the DMARD combination schemes, but unfortunately we have no biomarkers to identify these, and a 'light' version of the remission-induction scheme seems to have a better risk-benefit balance," he said in an interview.

Until better biomarkers are available, he said, "COBRA Slim seems an ideal one-size-fits-all option for initial treatment of all patients with early RA, provided they are tightly followed afterward and a treat-to-target approach is applied."

Data on the 90 low-risk patients were presented separately in a poster at the Congress. Patients in this arm included 43 patients who were randomized to receive methotrexate following a tight "step-up" glucocorticoid regimen and 47 patients who were randomized to the COBRA Slim schedule. Results showed that high remission rates were achieved with both regimens, but that the remission-induction achieved with the COBRA Slim strategy was associated with more rapid and sustained disease control. The safety of the two regimens was again comparable.

Dr. Verschueren holds the Pfizer Chair for Early Rheumatoid Arthritis Management at KU Leuven. The study was conducted in partnership with various rheumatology centers in Flanders (Belgium) and benefited from the support of a Flemish governmental grant. ■

Imaging Suggests Early Cardiomyopathy Accompanies Early RA

BY MICHELE G. SULLIVAN

Patients with newly diagnosed rheumatoid arthritis already show increased aortic stiffness as well as lower left and right ventricular, end-systolic, and end-diastolic volumes, Dr. Maya Buch reported at the Congress.

The imaging findings lend support to a growing view that inflammation may underlie cardiovascular as well as rheumatic disease, Dr. Buch said in an interview.

"Rheumatoid arthritis is associated with increased cardiovascular disease and death. This is thought to be due to the inflammatory drive as well as traditional risk factors," said Dr. Buch of the University of Leeds (England). "There is also a significant literature base suggesting atherosclerosis is inflammation driven, thus, shared mechanisms are likely."

Dr. Buch and her colleagues conducted cardiac magnetic resonance imaging studies on 66 patients with early rheumatoid arthritis; all were treatment naive and had symptoms of less than 1 year in duration. They were matched for age, gender, and blood pressure with 30 healthy controls.

Patients had a mean age of about 48 years; mean systolic blood pressures were similar – 122 mm Hg for patients and 126 mm Hg for controls.

In the patients, the median erythrocyte sedimentation rate was 39.5 mm/hour; C-reactive protein was 18.9 mg/L. The mean Disease Activity Score 28 was 5.65. Most (82%) were positive for anticitrullinated protein antibodies; 73% were positive for rheumatoid factors.

Dr. Maya Buch

Patients showed significantly reduced aortic distensibility, compared with controls. Aortic compliance and aortic strain were also significantly lower in patients, while aortic stiffness was significantly higher.

Evidence of early cardiac remodeling was present. Left ventricular and right ventricular end-systolic and end-diastolic volumes were all lower in the patients. A trend for lower left ventricular mass index seemed to be associated with seropositivity, Dr. Buch noted. Four patients showed evidence of overt inflammation or fibrosis with focal nonischemic patterns of late gadolinium enhancement.

These changes suggest an early cardiomyopathy, Dr. Buch said, and could imply a higher risk for cardiovascular morbidity and mortality at time of diagnosis. She added that the next steps in learning about this association will be to clarify its natural history, clinical implications, and the potential to modify outcomes with effective therapy. Although these new data are striking, they aren't enough to recommend that newly diagnosed patients get routine cardiac imaging, Dr. Buch said.

"The study clearly implies that subclinical cardiovascular pathology exists at the early stage. Screening wouldn't be appropriate at this stage – the clinical outcome and relevance of subclinical disease is not yet clear. However further evaluation will clarify whether additional benefits of RA disease control – for example, improving the cardiovascular risk and abnormalities seen here – are possible. This could influence future management approach."

Dr. Buch had no financial disclosures. ■

> "Rheumatoid arthritis is associated with increased cardiovascular disease and death. This is thought to be due to the inflammatory drive as well as traditional risk factors."

Biologic Tapering in Rheumatoid Arthritis Shows Cost Efficacy

BY MITCHEL L. ZOLER

Patients with rheumatoid arthritis in sustained remission on a biologic drug successfully remained in remission most of the time while gradually stepping down to a longer dosage interval or eventually going off the biologic entirely in a controlled, multicenter French trial with 98 patients followed for 18 months.

The results also showed that while patients who were maintained throughout 18 months on full biologic-drug dosage fared slightly better clinically, the taper-down strategy saved an average 53,417 euro for each quality-adjusted life-year (QALY) decrement caused by the step-down treatment, Dr. Antoine Vanier reported at the Congress. The actual decrement in QALYs among the 44 patients randomized to the step-down arm during the 18 month study averaged 0.158 QALYs, compared with the 54 patients maintained on full dose. The actual cost savings over 18 months averaged 8,440 euro per patient, said Dr. Vanier, a rheumatologist and biostatistician at Pierre and Marie Curie University in Paris.

Mitchel L. Zoler/Frontline Medical News

Dr. Antoine Vanier

In addition, a numerically larger percentage of patients in the step-down arm, 61%, rated their health status "acceptable," compared with 44% among those in the maintenance arm, although this difference was not statistically significant.

The Spacing of TNF-blocker Injections in Rheumatoid Arthritis Study (STRASS) enrolled adult rheumatoid arthritis patients on subcutaneous treatment with either 40 mg adalimumab every 14 days or 50 mg etanercept every 7

VIEW ON THE NEWS

RA Biologic Step-Down Becomes Routine

Increasingly, the treatment model for rheumatoid arthritis patients in stable remission on treatment with a biologic drug includes considering an increase of the interval between doses. At the center where I work we already do this for a majority of our RA patients. Most patients are not able to completely stop their biologic, but they often can extend the dosing interval without flaring.

In my experience, many RA patients are savvy enough to gradually find their own biologic sweet spot, the between-dose time interval that leaves them feeling good and keep them in remission, while also cutting down on their drug expense. Roughly half the RA patients in my practice who are on a biologic drug take it at a prolonged interval, compared with the label's dosage.

Mitchel L. Zoler/Frontline Medical News

Dr. James R. O'Dell

I'm not surprised that quality-adjusted life years were slightly reduced in this study among the patients randomized to the step-down arm because it is hard for each patient in a tightly structured trial to find their dosing-interval sweet spot, compared with patients in a routine-practice setting. The step-down strategy approach mandated in this study eliminated the flexibility that is possible in the real world because it applies a one-size-fits-all approach. It is much easier for patients and clinicians to find the optimal dosing interval for each individual patient when tweaking of the interval can be tailored individually.

***Dr. James R. O'Dell** is professor and chief of rheumatology at the University of Nebraska Medical Center in Omaha, U.S.A. He has been an advisor to Medac, Antares, AbbVie, Lilly, and Bristol-Myers Squibb. He made these comments in an interview.*

days for at least a year and who maintained a 28-joint disease activity score (DAS28) of 2.6 or below for at least 6 months and had no radiographic joint progression for at least a year. Patients could be on either monotherapy with one of these biologic drugs or on a stable regimen that also included either methotrexate or leflunomide, and patients could also receive up to 5 mg/day prednisone.

The researchers randomized patients to either maintain their entry regimen or start on a program that serially increased the time between biologic injections every 3 months. The adalimumab dosing interval increased to a 40-mg injection every 21 days, 28 days, 42 days, and then patients who remained in remission with an injection every 42 days for 3 months stopped adalimumab treatment entirely. Among the etanercept patients, the between-dose intervals increased to 10 days, 14 days, 21 days, and then a complete stop. Patients who experienced a flare, with their DAS28 rising above 2.6, returned to a more frequent dosing interval until they were able to lower their DAS28 to 2.6 or less once again and regain remission.

After 18 months, 8 (18%) patients in the step-down arm remained on their entry-dosage interval, 19 (43%) patients maintained remission on a lengthened-dosing interval, 15 (34%) patients completely stopped their biologic, and 2 (5%) patients had left the study. In the maintenance arm, all 54 patients remained in the study and in remission on their entry-dosage schedule.

Mitchel L. Zoler/Frontline Medical News

Dr. Bruno Fautrel

The results also showed that while patients who were maintained throughout 18 months on full biologic-drug dosage fared slightly better clinically, the taper-down strategy saved an average **53,417 euro** for each quality-adjusted life-year (QALY) decrement caused by the step-down treatment.

A majority of the patients in the step-down arm remained on their reduced- or no-dose regimen after the trial completed, noted Dr. Bruno Fautrel, senior investigator of STRASS and professor of rheumatology at Pierre and Marie Curie University, Paris. The researchers have so far not been able to identify any patient-specific features to prospectively identify the patients most likely to successfully undergo biologic step-down, Dr. Fautrel added.

Despite this uncertainty as to which patients are best suited to a step-down strategy, the possibility of successfully stepping-down biologic treatment for most RA patients to save on drug costs without compromising patient outcomes makes it "worth considering" on a case-by-case basis, Dr. Vanier said.

Dr. Vanier had no disclosures. Dr. Fautrel has been a consultant to nine drug companies. ■

Polyarthritis Patients' Adaptive Traits Examined

BY JEFF EVANS

Polyarthritis patients can be classified into three different subgroups with a different pattern of strategies to meet personal goals, each of which is associated with different levels of adaptive ability over the course of 1 year, according to new research presented at the Congress.

Lead investigator Roos Arends, a PhD candidate in the department of psychology, health, and technology at the University of Twente, Enschede, the Netherlands, and her colleagues wanted to determine how patients' natural courses of adaptation to polyarthritis interrelate with patterns of goal management over time to build on previous cross-sectional research that related higher levels of goal management strategies to lower levels of distress and higher levels of well-being.

The investigators recruited 331 patients with polyarthritis who had a mean age of 62 years and mean disease duration of 14 years. A total of 61% of participants were women who had rheumatoid arthritis (58%), and only 29% were working. They filled out a questionnaire at baseline that examined patients' different patterns of goal management (goal maintenance, goal adjustment, goal disengagement, and goal re-engagement) and then retook the survey at 6 months and 12 months. The researchers also asked about concepts related to adaptation (depression, anxiety, purpose in life, positive affect, and social participation).

Ms. Arends and her associates identified three goal management patterns: "moderate engagement" (44%), "broad goal management repertoire" (35%), and "holding on" (21%). 'Holding on' included high goal maintenance and low levels of the other strategies, whereas "moderate engagement" included high goal disengagement, average goal re-engagement, and low levels of both other strategies. Patients characterized by a 'broad goal management repertoire' pattern had high levels of goal maintenance, goal adjustment, and goal re-engagement and average goal disengagement.

Ms. Roos Arends

The "holding on" pattern was identified as the most unfavorable in terms of successful adaptation. Patients characterized by the 'broad goal management repertoire' pattern had the highest level of successful adaptation.

Over the course of 1 year, the patterns differed in levels of adaptation, which largely remained stable, even after controlling for demographic and disease-related factors. For example, the "holding on" pattern was related to the highest levels of distress (anxiety and depression), and people characterized by this pattern experienced high levels of distress over time, said Ms. Arends, who received a Health Professionals in Rheumatology abstract award for the study.

The 'broad goal management repertoire' pattern was related to successful adaptation: Levels of successful adaptation were significantly higher over time among patients with this pattern, compared with patients who exhibited the other two goal management strategies. In addition to earlier results, Ms. Arends noted, "this finding underlines the necessity to possess a combination of goal management strategies for successful adaptation."

There's a need for greater assistance to patients who may not know how best to live with their arthritis and the many possible ways they can manage the difficulties it brings, Ms. Arends said in an interview. "Our suggestions are that people with a 'holding on' pattern of goal management might need additional support and guidance to learn more flexible ways for dealing with threatened goals. Despite having a greater variety of goal management when compared to patients with the 'holding on' pattern, patients characterized by the 'moderate engagement' pattern might also profit from additional guidance to strengthen and deploy the various strategies and react in more flexible ways to threatened goal attainment." Based on these results, the intervention "Right on target!" was developed and underwent evaluation in a study including 86 patients with polyarthritis.

Ms. Arends also separately presented the results of a process-evaluation of a goal management group intervention ("Right on target!") given by rheumatology nurses. The intervention intended to support patients with polyarthritis in coping with the disease and its consequences and was focused on the threatened goals of patients. The effectiveness of the intervention in increasing the adaptation of participants is still under study, but it might be a promising way to increase adaptation of patients, she said.

Ms. Arends and her coauthors had no financial conflicts to disclose. ■

Ultrasound-Detected Tenosynovitis Signals Early Rheumatoid Arthritis

BY SARA FREEMAN

A quick ultrasound scan of the hand may be all that is needed to help determine if a patient with early inflammatory arthritis will go on to develop rheumatoid arthritis (RA).

Adjusted odds ratios (OR) for making a diagnosis of RA were 7.1 for having cyclic citrullinated peptide or rheumatoid factor antibodies (*P* less than .0001), 7.9 for having 10 or more joints involved (*P* less than .0001), and 6.6 for having tenosynovitis in the hand or wrist (*P* less than .0001). The association held in patients with seronegative disease, with an OR of 7.6 for having 10 or more involved joints (*P* less than .0001) and 4.8 for hand/wrist tenosynovitis ($P = .003$).

Rheumatologists are challenged to diagnose rheumatoid arthritis early, particularly in patients who may have had symptoms for only a few weeks, said Dr. Andrew Filer, senior lecturer at the University of Birmingham (England).

"One of the problems is that, in the first 3 months of the disease, it really is undifferentiated in a lot of patients, even using the 2010 [American College of Rheumatology/European League Against Rheumatism response] criteria for rheumatoid arthritis," he said. While about a third of patients with inflammatory arthritis will go on to develop RA, the net has been cast so wide that there are patients whose inflammatory arthritis will resolve without treatment, he added.

Dr. Filer and his associates have been working for the past 15 years to find ways to help clinicians identify RA as early as possible. Some of their most recent research has focused on using musculoskeletal ultrasound to examine the small joints (Ann. Rheum. Dis. 2011;70:500-7) and has already shown that it is more accurate than traditional clinical assessment at predicting patient outcomes in very early arthritis.

NICK PIEGARI/FRONTLINE MEDICAL NEWS

VIDEO HIGHLIGHTS: Click here to watch a video interview with Dr. Andrew Filer.

Results from the Birmingham Early Arthritis Cohort (BEACON) presented at the Congress show that ultrasound-detected tenosynovitis can independently identify patients who will go on to develop RA.

The study involved 107 patients with at least one swollen joint whose symptoms had started in the last 3 months. Of these, 43 developed very early RA, 20 had non-RA persistent disease, and the remaining 44 had resolving disease at 18-month follow-up.

Although a wide variety of tendons throughout the body was examined, including those in the shoulders, ankles, hands, and wrists, it was the extensor carpi ulnaris (ECU) tendon in the wrists and flexor tendons in the fingers that were found to be the most important to examine. The ECU tendon is responsible for straightening and rotating the wrist, as well as integral for gripping and pulling.

"Looking at the tendons was a new area for us, and it's taken a while for organizations like OMERACT [Outcome Measures in Rheumatology] to come up with some usable criteria and grading," Dr. Filer observed. Now that these exist and show that ultrasound is a reproducible tool for evaluating tenosynovitis in RA (Ann. Rheum. Dis. 2013;72:1328-34), it was possible to conduct the current prospective study.

Dr. Filer discussed the findings in a press briefing ahead of their scientific presentation by clinical research fellow Dr. Ilfita Sahbudin and noted that tenosynovitis was more difficult to assess clinically than joint inflammation as it was more "hidden."

"Even if it's really established rheumatoid disease it's quite difficult for even experienced rheumatologists to detect swelling of tendons; [we] really have to use imaging like ultrasound or MRI to detect this reliably," he said at the briefing. "Scanning of wrist ECU and finger flexor tendons adds robust diagnostic data for RA in that first window of very early disease."

Dr. Filer suggested that early arthritis clinics should start to integrate these scans into their protocols to validate the findings.

He reported having no financial disclosures. ■

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Hypersensitivity to the active substance or to any of the excipients, pregnancy, women of childbearing potential who are not using reliable contraception, breastfeeding, patients with severe hepatic impairment (with or without cirrhosis), baseline values of hepatic aminotransferases (AST and/or ALT > 3 × ULN).

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Pregnancy: Opsumit is contraindicated during pregnancy.

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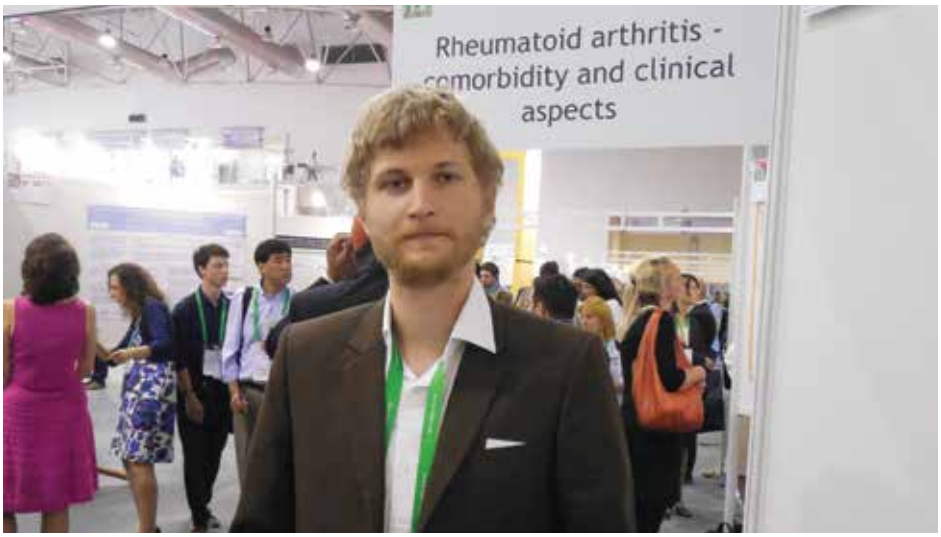
Women With RA Have Increased Cervical Neoplasia Rates

BY MITCHEL L. ZOLER

Women with rheumatoid arthritis who have never been treated with a biologic drug had a modest but statistically significant increased rate of cervical intraepithelial neoplasia in a case-control study with more than 335,000 women.

The analysis showed an adjusted excess hazard for developing cervical intraepithelial neoplasia (CIN) I of 53%, compared with the general population, and an excess 39% rate of CIN II or III, both statistically significant differences, Dr. Hjalmar Wadstrom reported in a poster at the Congress.

The analysis also showed a small increase in the relative rate of invasive cervical cancers among the women with rheumatoid arthritis (RA) on treatment with conventional disease-modifying drugs, such as methotrexate, who never received a biologic disease-modifying drug. The 9% relative increase in the rate of invasive cancer, compared with the general population, did not achieve statistical significance, reported Dr. Wadstrom, a clinical epidemiology researcher at the Karolinska Institute in Stockholm.



Mitchel L. Zoler/Frontline Medical News

Dr. Hjalmar Wadstrom

The "moderately but not dramatically" increased rate of CIN "is not a reason for big concern or alarm," but highlights that women with RA should comply with local cervical cancer–screening recommendations and programs, said Dr. Johan Askling, professor of rheumatology and clinical epidemiology at Karolinska and senior author of the study.

"It would be a shame if these RA patients with a small increased risk did not attend the [cervical screening] programs we have set up. Clinicians should make sure that women with RA attend to screening because nonattendance is their major risk factor," he said in an interview. "Our findings don't call for a change in screening recommendations, they just highlight the importance of attending to screening" in women with RA, Dr. Askling said.

Mitchel L. Zoler/Frontline Medical News

Dr. Johan Askling

The researchers ran a linkage analysis of Swedish registries and identified 34,984 adult women with RA and matched them with 300,331 women drawn from the general Swedish population. Age of the RA patients ranged from 18 to 97 years with a median age of 62 years, and they selected general-population controls who matched this group. In the regression analyses they ran to calculate hazard ratios they adjusted for age, education, prior cervical screening, comorbidities, marital status, and time hospitalized during prior 5 years. The analysis included CIN and invasive cancer cases during 14 years of follow-up, 1999-2012.

Both Dr. Wadstrom and Dr. Askling cited two potential factors behind the increased rates of CIN I, II, and III in women with RA: the inflammatory state of RA and treatment with immunosuppressive nonbiologic agents, such as methotrexate.

The increased CIN rates found in this analysis were also "seen in other patients treated with potent immunosuppressive drugs," like organ transplant patients, Dr. Askling noted.

The current study serves as prelude to an analysis he and his associates are now running to assess cervical neoplasia and cancer rates among women with RA treated with biologic disease-modifying drugs.

Dr. Wadstrom had no disclosures. Dr. Askling has received research support from eight drug companies. ■

Usual Physiotherapy Remains Best Approach in Knee Osteoarthritis

BY SARA FREEMAN

There was no advantage to individually prescribed exercises for knee osteoarthritis over usual physiotherapy in a multicenter, longitudinal, randomized study reported at the Congress.

Indeed, the results of the United Kingdom–based Benefits of Effective Exercise for Knee Pain (BEEP) study showed that all of three of the interventions tested improved patients' pain and physical function to a similar degree over the 18-month follow-up period.

Three different interventions were compared: usual physiotherapy care consisting of up to four treatment sessions over 12 weeks (176 patients), an individually tailored and supervised exercise (ITE) program consisting of six to eight sessions over 12 weeks (178 patients), and a targeted exercise adherence (TEA) program consisting of 8-10 sessions over 6 months (172 patients). Data were collected at 3, 6, 9, and 18 months via postal questionnaires.

Participants in all groups received an advice booklet outlining the benefits of exercise and exercises to perform.

> "Clearer identification of those who respond to exercise, rather than changing the characteristics of exercise programs, is needed in future research."

"Clearer identification of those who respond to exercise, rather than changing the characteristics of exercise programs, is needed in future research," suggested the presenting author Emma Healey, Ph.D., of Keele University, Staffordshire, England.

The aim of the BEEP was to see if changing the characteristics of exercise programs could improve patients' outcomes when compared with usual physiotherapy. A total of 65 general practices, five National Health Service physiotherapy services, and 47 physiotherapists took part in the study and recruited 526 adults aged 45 years or older with knee osteoarthritis (OA) from a total of 1,530 who had been screened.

Exercises were focused on the lower limb and selected from a template in the usual care group but individually prescribed and supervised in the other two groups. Patients in the TEA group also had exercises aimed at improving their overall fitness. An exercise diary was completed by those in the ITE group and an 'adherence-enhancing toolkit' was used by the TEA group.

The primary outcome measure used was change in the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) pain and function scales at 6 months. On a scale of 0-20, no clinically or statistically significant differences were seen between the groups, with pain scores of 6.4, 6.4, and 6.2 for the usual care, ITE, and TEA groups, respectively. A similar pattern was seen for function scores (21.4, 22.3, 21.5, respectively) assessed on a scale of 0-68. These findings didn't change over time, with all patients doing well with longer follow-up, Dr. Healey observed.

Clinical effectiveness was also evaluated according to Outcome Measures in Rheumatology–Osteoarthritis Research Society International (OMERACT-OARSI) responder criteria, but again no differences between the groups were found, with around half of the study population fitting responder criteria at 6 months.

Although patients' self-reported adherence to their exercise was high at the 3-month assessment (75%-77%), it gradually declined over the course of the follow-up period. "Exercise behavior was back to baseline levels by 18 months," Dr. Healey noted. Self-reported adherence appeared to remain higher for longer in the TEA group, but differences between treatment groups were again not statistically significant upon closer evaluation.

Usual physiotherapy had an edge over the other interventions in terms of both effectiveness measured in quality-adjusted life-years and knee OA–related resource use at 18 months' follow-up, according to an economic evaluation.

"Economic analysis suggests usual care is 'treatment of choice,'" Dr. Healey said.

The research was funded by the National Institute for Health Research and Arthritis UK. Dr. Healey reported having no financial disclosures. ■

Erosive Hand Disease Is Likely a 'More Severe Form of OA'

BY SARA FREEMAN

Erosive hand osteoarthritis is probably a more severe form of the disease, rather than a separate clinical entity, a team of Norwegian researchers has suggested.

Dr. Alexander Mathiessen and associates from Diakonhjemmet Hospital in Oslo found that synovial inflammation was more common in patients with erosive disease. However, when they stratified the 293 patients studied according to the degree of structural joint damage, they found that the differences disappeared.

"Modern imaging techniques such as MRI and ultrasound have shown high prevalence of synovitis in hand osteoarthritis," they explained in a poster presentation at the Congress.

Although erosive hand osteoarthritis (OA) is often considered a more inflammatory phenotype, with more pain and disability and a more aggressive disease course, "it has been debated whether erosive hand OA is an inflammatory subset with more synovitis than conventional OA, or just a severe form of the disease" they observed.

Although a recent study (Ann. Rheum. Dis. 2013;72:930-4) had found a higher frequency of inflammation in patients with erosive hand OA versus nonerosive hand OA, the study had not adjusted for the severity of structural damage. Dr. Mathiessen and coworkers therefore set out to examine whether the higher prevalence of synovitis that had been seen in patients with erosive hand OA was linked to the extent of joint disease according to the Kellgren-Lawrence (KL) scale.

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The team used data from the Musculoskeletal Pain in Ullensaker Study (MUST) cohort (BMC Musculoskelet. Disord. 2013;14:201), an observational study comprising 630 participants with self-reported OA. Their analysis used data on 293 patients who reported having hand OA and who fulfilled American College of Rheumatology criteria, with no other inflammatory joint disease.

The majority (76%) of patients with hand OA studied were women, with a mean age of 64.9 years. There were over 4,000 joints examined using both ultrasonography and radiography, of which 359 (7.9%) were erosive.

"We focused mainly on the proximal and distal interphalangeal joints, since radiographic erosions occur in these joints mainly," the researchers said.

Just fewer than 30% (n = 86) partici pants had at least one erosive interphalangeal joint. The median number of finger joints involved was five, ranging from 0 to 15.

Grey scale (GS) and power Doppler (PD) synovitis was seen in 18.9% and 1.8% of patients with erosive hand OA and 11.1% and 0.4% of those with nonerosive hand OA, respectively (*P* less than .001 for both comparisons).

Patients with erosive disease were more likely to have greater joint damage on the KL scale than patients with nonerosive disease, with 41.7% versus 4.5%, respectively, having a KL grade of 3-4 and 26.7% versus 64% having a KL grade of 0-1.

The team reported that the prevalence of both GS and PD synovitis increases with more structural joint damage irrespective of erosive status and that there was a similar level of joint inflammation when data were stratified according to KL grade.

Somewhat paradoxically, they said, "erosive joints actually have less inflammation than nonerosive joints."

The investigators did not report having any disclosures. ■

Steroid Injection Accuracy May Not Matter for OA Knee Pain Relief

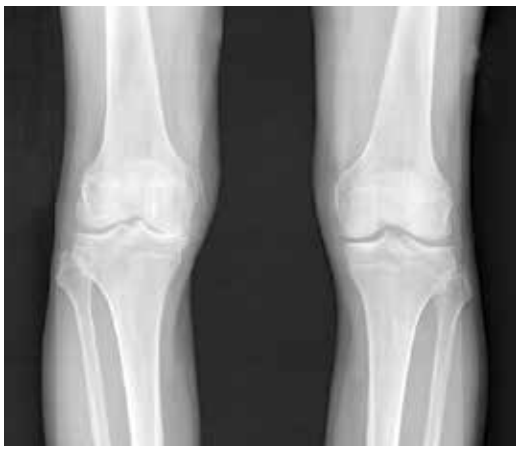
BY SARA FREEMAN

Ensuring that intra-articular injections are correctly placed does not appear to result in better pain management for knee osteoarthritis, according to research presented at the Congress.

"Accurate injection neither resulted in higher rate of response to treatment than inaccurate injection nor greater mean pain reduction," said George Hirsch, Ph.D., of the Institute of Inflammation and Repair at the University of Manchester (England) and the Dudley Group NHS Foundation Trust.

Dr. Hirsch and his associates defined response to treatment as at least a 40% reduction in pain on the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC), and the percentages who met that definition were similar among patients who had their injections correctly placed and those who did not at 3 weeks (57.7% vs. 63.4%, respectively; $P = .0355$) and 9 weeks (39.3% vs. 51.4%; $P = .0148$).

There also were no differences between mean pain reduction at 3 weeks (–110.7 mm vs. –116.9 mm on a visual analog scale; $P = .781$) and 9 weeks (–65.2 mm vs. –92.8 mm; $P = .247$) between the patients with accurate and inaccurate intra-articular injection placement.



Courtesy National Institute of Arthritis and Musculoskeletal

The researchers aimed to determine if injecting accurately into the knee could have an effect on patients' pain outcomes because, despite the effectiveness of intra-articular corticosteroid injections (IACIs) for pain in knee OA, "responses to treatment vary." In the poster presentation, Dr. Hirsch noted that uncertainty remained as to whether structural factors including accurate intra-articular placement mattered in regards to pain reduction.

> "These results raise potential questions about the routine use of [ultrasound] to enhance or predict response to IACI in knee OA."

The practical, prospective, observational study included 141 men and women with a mean age of 63.8 years who had been referred for IACI for their knee OA in a routine practice setting.

Before aspiration and injection into the affected knee(s) based on clinical examination, patients underwent careful x-ray and ultrasound assessment. Following injection, an air arthrosonogram was used to see if injections had entered the joint cavity.

Overall, just over half (53%) of patients were classed as responders at 3 weeks and 44% at 9 weeks, and a positive arthrosonogram was seen in 98 (70%).

In addition to no advantage for accurate injection placement on pain outcomes, there was no indication that individual physical factors mattered either. Mean measurements of sonographic effusion and synovial hypertrophy did not differ between responders and nonresponders at either time point assessed.

Similar findings also were seen for mean scores for power Doppler signal and individual radiographic features of osteoarthritis that included joint-space narrowing and presence of bone spurs.

"These results raise potential questions about the routine use of [ultrasound] to enhance or predict response to IACI in knee OA," Dr. Hirsch said.

The authors reported having no financial disclosures. ■

Tai Chi Equivalent to Physical Therapy For Knee Osteoarthritis

BY SARA FREEMAN

Tai chi is as effective as standard physical therapy in reducing pain and improving physical function and quality of life in patients with knee osteoarthritis, according to the results of a randomized, single-blind study reported at the Congress.

The primary outcome of change in the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) pain subscale score from baseline to 12 weeks was –167.2 mm in the patients randomized to the tai chi group vs. –143.0 mm in those who completed a standard physiotherapy program ($P = .16$).

"Future studies of 'Eastern' complementary medicine will further inform 'Western' medical treatment guidelines," said Dr. Chenchen Wang, director of the Center for Complementary and Integrative Medicine at Tufts Medical Center in Boston. She noted that the study findings showed that tai chi could be a viable alternative to physical therapy for knee osteoarthritis (OA), which she called "a chronic disabling disease."

Dr. Wang and her associates have previously shown that the classic Yang-style tai chi results in clinically important improvements in patients with fibromyalgia (N. Engl. J. Med. 2010;363:743-54). They have also previously reported beneficial effects in small numbers of patients with knee OA (Arthritis Rheum. 2009;61:1545-53). The present study findings replicate these results in a larger group of patients followed up for a longer period of time.

"This is the longest follow-up of tai chi for knee osteoarthritis to date," Dr. Wang observed. It is also representative of a racially diverse population, she said. The study is ongoing but not recruiting participants and will continue to compare the effectiveness and cost-effectiveness of the Chinese martial art vs. standard-of-care physiotherapy for 1 year (BMC Complement. Altern. Med. 2014;14:333).

Of 204 randomized patients with a mean age of 60 years and disease duration of 8 years, 167 (82%) completed the tai chi sessions and 12-week evaluation for the primary endpoint. In addition, three-quarters of patients completed 24 weeks and 69% completed 1 year of the intervention, showing the sustainability of the exercise program. Overall attendance was similar between the groups, at 74% for tai chi and 81% for physical therapy.

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The 106 patients randomized to the tai chi group performed the martial art twice a week for 12 weeks while the 98 patients in the physical therapy group underwent twice-weekly sessions for the first 6 weeks, then continued with "rigorously monitored" exercises at home for 12 additional weeks. Patients knew to which group they had been randomly assigned, but the study physician and outcomes assessments were blinded to the treatment allocation.

Similar benefits were seen with both strategies for the secondary endpoints of physical function subscale of the WOMAC ($P = .08$), Patients' Global Assessment ($P = .06$), and chronic pain self-efficacy ($P = .22$). There were also similar improvements in 6-minute ($P = .76$) and 20-meter ($P = .40$) walking tests.

Health-related quality of life measured using the Short Form 36 suggested a possible statistical advantage of tai chi over physical therapy for the physical but not mental component summary, with mean differences between the groups of 3.2 (P less than .01) and 1.6 ($P = .08$), respectively. There was also a statistical difference in depression scores between the groups, but this may not be clinically significant, Dr. Wang observed.

"This study provides evidence to support both tai chi and physical therapy improve pain and physical function for patients with knee osteoarthritis," she said. "Interestingly, we didn't see any differences in effectiveness attributable to the four individual tai chi instructors."

The National Center for Complementary and Integrative Health of the National Institutes of Health supported the study. Dr. Wang reported no relevant conflicts. ■

Vitamin D Supplementation Fails to Reduce Knee Osteoarthritis Pain

BY SARA FREEMAN

Vitamin D supplementation did not ease osteoarthritic knee pain measured using the Western Ontario and McMaster Universities Osteoarthritis Index in a 2-year, randomized, double-blind, placebo-controlled trial.

Results of the VIDEO (Vitamin D Effect on Osteoarthritis) study in patients with symptomatic knee osteoarthritis (OA) and low vitamin D levels also showed that replenishing vitamin D also had no effect on the loss of cartilage volume, although there might be a marginal benefit on bone marrow lesions (BMLs) and pain assessed using a visual analog scale (VAS).

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"Vitamin D at 50,000 IU/month over 2 years did not meet the primary endpoint in this randomized, controlled trial," said Jason Jin, a Ph.D. candidate at the Menzies Research Institute, University of Tasmania in Hobart, Australia, who presented the VIDEO study findings at the Congress.

He cited a recent commentary published in the Journal of the American Medical Association (JAMA 2015;313:1311-12) that looked at vitamin D research and clinical practice in which the authors said that "clinical enthusiasm for supplemental vitamin D has outpaced available evidence." This seems to be true considering the results of this and other previous randomized trials, Mr. Jin observed.

"The background of this study is that, in the last decade, vitamin D has become a hot topic in osteoarthritis research and epidemiologic studies have found that vitamin D deficiency is very common in knee osteoarthritis patients," he said. Low levels of vitamin D have been linked to increased knee pain, radiographic progression, and increased cartilage loss in OA.

Two prior randomized, controlled trials provided conflicting evidence, he highlighted, with one study showing that supplementation of 2,000 IU/day of vitamin D for 2 years had no effect on symptoms or knee structure (JAMA 2013;309:155-62) while another showed that a monthly dose of 60,000 IU for 1 year may be beneficial in terms of relieving pain and functional outcomes but longer follow-up was required (Clin. Orthop. Relat. Res. 2013;471:3556-62).

The VIDEO study was therefore designed to try to resolve some of the controversy and look at a larger group of patients for a longer period of time. The study's hypothesis was that vitamin D might ease knee pain and perhaps effect structural changes in patients with symptomatic knee OA who had low vitamin D levels. A low vitamin D level was defined as a serum measurement of 25(OH) D of 12.5-60 nmol/L (5-24 ng/mL) at baseline.

Of almost 600 patients screened, 413 were randomized, with 209 randomized to the oral vitamin D supplementation group and 204 to the matched placebo arm. Patients in each group had comparable characteristics at baseline, with a mean age of around 62 to 63 years. Half the patients were female. Baseline serum vitamin D levels were about 43 nmol/L (17.2 ng/mL). Virtually all (96%) of patients had radiographic evidence of knee OA, 97% had cartilage defects, and 80% had bone marrow lesions.

While serum levels of 25(OH)D were successfully increased in the supplemented patients over the course of the study, this did not translate into an improvement in the coprimary endpoint of a change in Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) knee pain over 24 months. The difference in WOMAC pain between the vitamin D and placebo groups was a nonsignifcant –14.8 (–49.9 vs. –35.1; $P = .102$). Vitamin D–supplemented patients did, however, report marginally less VAS pain (–14.8 vs. –9.4; $P = .038$).

Total tibial cartilage volume loss, the second coprimary endpoint, was not significantly different between the vitamin D and placebo groups, at around 121 and 150 mm^3 per annum, with 2-year changes of –3.44% vs. –4.23% per annum ($P = .132$). The secondary endpoints of changes in tibiofemoral cartilage defects (0.29 vs. 0.47; $P = .159$) and tibiofemoral BMLs (–0.59 vs. –0.21; $P = .087$) were also not significantly different, but patients randomized to vitamin D supplementation had fewer increases in BMLs (17% vs. 27%; $P = .03$).

There was no concern over the safety of vitamin D supplementation, although more general side effects were noted in the vitamin D vs. the placebo group.

Commenting on the strengths and weaknesses of the study, Mr. Jin noted it was a large, multicenter, randomized, double-blind, placebo-controlled trial with a reasonably long follow-up. The patient group studied has good generalizability to those seen in everyday practice, he suggested, noting that the main limitation was the number of patients lost to follow-up because of noncompliance: 21 patients in the vitamin D group vs. 8 patients in the placebo group.

Mr. Jin reported having no conflicts of interest to disclose. ■

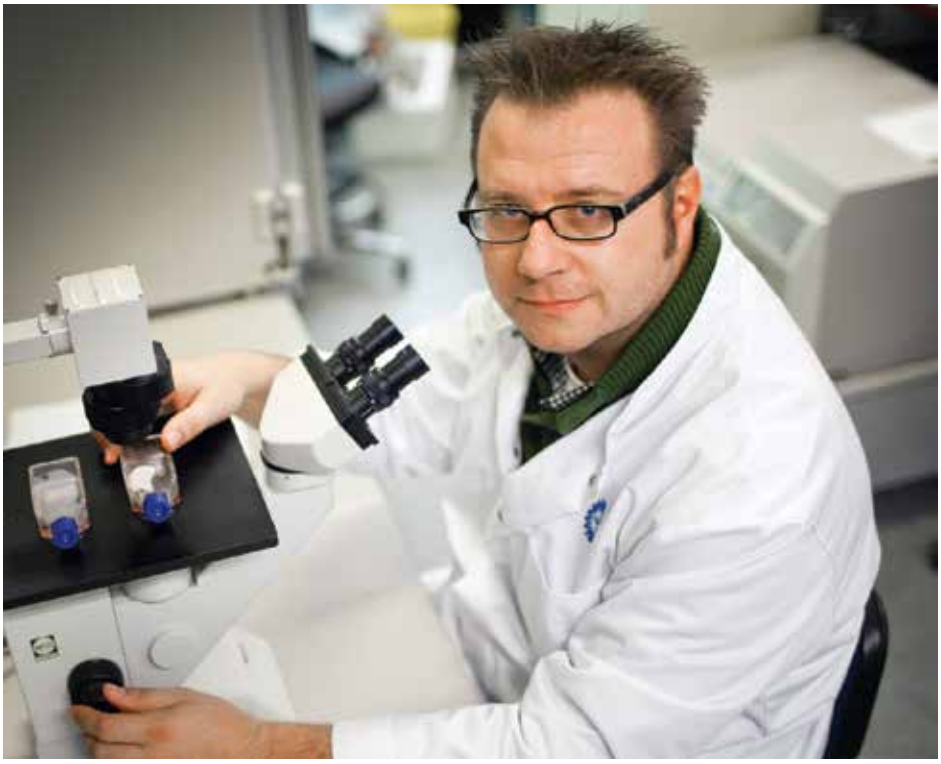
Joint Distraction Could Preempt Knee Replacement for Osteoarthritis

BY SARA FREEMAN

Knee joint distraction – a method of relieving mechanical stress on the joint by temporarily pinning it – could help some patients with osteoarthritis avoid the need for a knee prosthesis, judging from preliminary findings from a randomized, controlled, comparative trial.

At 1-year follow-up, all subscales of the Knee Injury and Osteoarthritis Outcome Score (KOOS) and the Total KOOS score were significantly and progressively improved from baseline in patients who underwent knee distraction (*P* less than .001). Overall, the mean change in the Total KOOS score was not significantly different from that in the group of patients who underwent total knee replacement (TKR); although the KOOS subscale of quality of life did show greater improvement with the prosthesis than with distraction ($P = .027$), it was felt that this will "level out" when data on all 60 patients included in the trial are available.

This research, performed at the UMC [University Medical Center] Utrecht and Sint Maartenskliniek in Woerden in the Netherlands, highlights how knee distraction may offer a valuable alternative to TKR, particularly in younger patients with OA, according to Simon Mastbergen, Ph.D., who studies tissue degeneration and regeneration in the department of rheumatology and clinical immunology at UMC Utrecht, and associates (Ann. Rheum. Dis. 2015;74:359-60).



Dr. Simon Mastbergen

Dr. Floris Lafeber

SARA FREEMAN/FRONTLINE MEDICAL NEWS

"When you have a total knee prosthesis at a relatively young age, the outcome is not as successful as most people think," Dr. Mastbergen said in an interview during a poster session at the Congress.

Around 40% of TKRs are performed in people under the age of 65 years, he observed, and younger patients have a higher risk of revision failure because of mechanical failure as they tend to be more active than elderly patients with knee OA. Indeed, it's been estimated that around 44% of younger patients who have TKR will need revision surgery at some point, and as secondary procedures are more difficult to perform and can be much more disabling "we need a joint-saving treatment."

Joint distraction is a surgical procedure that aims to gradually separate the two bony ends of a joint for a certain length of time. The method used by the Dutch team involved patients wearing an external frame bridging the knee that consisted of two long tubes with coiled springs inside with pins coming out that are inserted into the opposing soft tissue and bones and moved by about 5 mm each time. Patients wear the frame for 6-8 weeks and are encouraged to try to bear weight on the affected knee, with the aid of crutches if needed. The idea behind the method is that it will allow the joint to repair itself, and the team

has already shown that cartilaginous tissue repair does indeed seem to occur (Cartilage 2013;21:1660-7).

Dr. Mastbergen noted that patients who underwent knee joint distraction in the study directly comparing it to TKR exhibited significant widening in the joint space, which is good because it indicates that cartilage has been regained. "We feel that knee joint distraction is an alternative for those [patients] who are ready for total knee prosthesis but are actually too young for [it]," he said.

Other randomized controlled trial data from the team were presented during an oral abstract session at the meeting (Ann. Rheum. Dis. 2015;74:108) and showed that knee joint distraction is also as good as high tibial osteotomy, which is another method aimed at relieving mechanical stress on the knee joint. The senior author of the team, Floris Lafeber, Ph.D., who presented data on behalf of colleague Dr. Jan Ton van der Woude, noted that there were several similarities between the two procedures in that they were both joint saving and could potentially postpone TKR and had been shown to improve bone turnover and cartilaginous tissue repair.

Sara Freeman/Frontline Medical News

Dr. Natalia Kuchuk

To compare the two methods, the researchers studied almost 70 patients aged 65 years or younger with medial compartment knee OA who were indicated for high tibial osteotomy. Patients were randomized 2:1 to the two procedures, with 45 undergoing osteotomy and 22 knee joint distraction. Significant improvements in total Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC), visual analog pain, and quality of life (EQ-5D) scores were seen in both groups when compared with the preoperative values (*P* less than .05). None of the parameters showed any statistically significant difference between the two procedures at 1-year follow-up. The data led to the conclusion that knee joint distraction had a clinical benefit that was comparable to osteotomy.

However, both the minimum and mean joint space width showed a steeper increase in patients randomized to the knee joint distraction group, suggesting that cartilaginous tissue repair might be better with the latter method.

> "When you have a total knee prosthesis at a relatively young age, the outcome is not as successful as most people think."

The potential clinical benefit of knee joint distraction was further highlighted in another poster from the team, presented by Dr. Natalia Kuchuk, which showed the effects of the procedure were maintained at 5-year follow-up. Importantly, 80% of the 20 patients studied in this open study still had their own knee joint. The mean age of patients at the time of distraction was 48.5 years. "In young patients, knee joint distraction effectively postpones total knee arthroplasty and is the only treatment which allows regeneration of cartilage," she said in an interview.

Dr. Lafeber also commented in an interview on the practicalities of the procedure, which is still in its experimental phases. "It's a rather invasive procedure, but if you compare it to a total knee replacement or high tibial osteotomy it's less invasive," he said.

"The surgical procedure takes about half an hour, we place a few pins through soft tissue and bone and the distraction tubes are placed mediolaterally to these pins, so in fact it's less invasive than many of the other surgical techniques." The distraction itself is not painful, he added, and actually alleviates OA pain, but patients may need painkillers and perhaps antibiotics for short periods during the method.

Next steps for the team are to follow up patients in the randomized trials for a longer period of time and refine the distraction device. "This is an off-the-shelf, 'proof-of-concept' device, and we are now developing a more patient-friendly, smaller, lighter frame device which is also easier to place by orthopedic surgeons," Dr. Lafeber said. "Then we will do a comparison with the proof-of-concept device."

Reumafonds (the Dutch Arthritis Foundation), ZonMw (The Netherlands Organization for Health Research and Development), UMC Utrecht, and Sint Maartinskliniek funded the research. Dr. Mastbergen, Dr. Lafeber, and Dr. Kuchuk had no disclosures to report. ■

Hydroxychloroquine Shows No Benefit In Hand Osteoarthritis

BY SARA FREEMAN

Hydroxychloroquine should not be prescribed for patients with mild to moderate hand osteoarthritis, according to data from a 24-week, randomized, multicenter, placebo-controlled trial.

The results of the Dutch study, presented at the Congress by Dr. Natalja M. Basoski of Maasstad Hospital, Rotterdam, the Netherlands, showed that hydroxychloroquine was no better than placebo at reducing patients' pain and disability, or for improving their physical, social, or emotional well-being.

The primary outcome measure used was reduction in osteoarthritis (OA) hand pain in the preceding 24 hours measured using a 100-mm visual analog scale (VAS) at the end of the study. The mean change in pain using the VAS over 24 weeks was a reduction of 1.3 mm in the hydroxychloroquine-treated patients versus a 0.10-mm rise in the patients who received placebo ($P = .82$).

There also was no change in the two secondary endpoints of change in total score of the Australian/Canadian Hand Osteoarthritis Index (AUSCAN) and the Arthritis Impact Measurement Scale 2 SF (AIMS2-SF) by the end of the treatment period. Mean changes in AUSCAN total scores were –0.42 and –0.25 ($P = .49$) and mean reductions in total AIMS2-SF scores were –0.17 and –0.076 ($P = .68$), comparing hydroxychloroquine with placebo, respectively.

"Osteoarthritis of the hand is one of the most common types of osteoarthritis, leading to pain, stiffness, and loss of function," Dr. Basoski explained during a clinical science session looking at manifestations of the disease beyond the knee. "Unfortunately, current pharmacological treatment options are limited," she added.

The underlying pathophysiological mechanisms of OA that primarily affect the hand are not clear, although inflammation is known to have a role, as in knee OA. Hydroxychloroquine is an established disease-modifying antirheumatoid drug that has shown benefit in patients with mild rheumatoid arthritis, which has led many rheumatologists to prescribe off label for the treatment of hand OA as well, Dr. Basoski observed in an interview. Data to support this are lacking, however, so this trial aimed to look at the potential symptom-modifying effects of the drug specifically in OA.

Dr. Natalja Basoski

Over a 3-year period starting in July 2010, 202 patients with symptoms of primary mild to moderate hand OA of at least 1 years' duration were recruited at six hospitals in the Netherlands and randomized to hydroxychloroquine 400 mg/day or matching placebo for 24 weeks. Six patients were lost to follow-up early on in the study, leaving 98 patients in each study arm who could be included in the intent-to-treat analysis. Of these, 22 hydroxychloroquine-treated and nine placebo-treated patients discontinued treatment, 10 and 5 in each group, respectively, because of adverse effects.

Dr. Basoski noted that patient characteristics were similar at baseline. Mean age was 57 years, and about 86% of participants were women. Hand OA was defined via American College of Rheumatology criteria and 86% and 91% of hydroxychloroquine- and placebo-treated patients had at least one joint with radiographic evidence of joint disease defined as a Kellgren-Lawrence score of 2 or greater.

"This is one of the studies that does not support the use of hydroxychloroquine in patients with OA of the hands and mild complaints," she said in an interview. "It means that you should not prescribe it anymore, at least based on the results of this study."

Further research is needed to see if there are some patients who might benefit or if it applies to other OA phenotypes, such as erosive hand OA. "More studies should be done, although in our second analysis after the study we tried to differentiate between very low pain and high pain and we still didn't really see a difference," she observed.

Erosive hand OA could be a different case, and results of an ongoing UK study should provide insight on whether hydroxychloroquine could be beneficial in these patients.

Although a similar number of patients treated with hydroxychloroquine or placebo in the trial experienced adverse events (21 vs. 24, respectively), there was an increase in allergic reactions (3 vs. 0) and rash or itching (8 vs. 3) with the active treatment.

With hydroxychloroquine seemingly out of the picture, at least in mild to moderate cases, Dr. Basoski advised on how she might treat a patient with primary hand OA. "I would try to start with paracetamol [acetaminophen] at the dose that is currently recommended, like 4 g/day, then eventually try to use opioids, as NSAIDs are not such a good thing to use in the long term."

Dr. Basoski did not have any conflicts of interest to disclose. ■

Counseling Key to Guiding Rheumatic Disease Treatment During Pregnancy

BY SARA FREEMAN

New therapies introduced over the past 15 years have vastly improved the lives of patients with rheumatic diseases but are also creating complex treatment scenarios as more female patients consider starting a family or become pregnant while taking medication. At the Congress, experts discussed the importance of contraceptive counseling, pregnancy planning, and how to treat pregnant women with rheumatic diseases.

"Nowadays we have such better treatments for our patients that sexuality and contraception is becoming more and more important," said Dr. Eliza Chakravarty of the Oklahoma Medical Research Foundation in Oklahoma City, U.S.A. Yet contraception is "quite underused in our patients," she observed.

Indeed, in one study looking at the risk of unintended pregnancy in women with lupus, over half (55%) of the 212 women surveyed admitted that they had unprotected sex at least once, with almost a quarter (23%) saying that this was usually in the preceding 3 months (Arthritis Care Res. 2008;59:863-6).

This underuse of contraception is not unique to lupus patients, and there are many reasons why women with rheumatic diseases who are sexually active may not always use adequate contraception. One of these reasons was the lack of time during consultations, which tend to focus on disease management rather than issues such as contraceptive counseling. Other reasons may be misconceptions on fertility or a lack of understanding of the teratogenicity of medications or the effect that hormones may have on disease activity. Women also may be reluctant to take additional medicines or feel uncomfortable discussing the topic with their rheumatologists.

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"Patients see their rheumatologist more frequently than any other [health care] provider," Dr. Chakravarty said, adding that continual follow-up appointments over time provide an opportunity to discuss fertility and changing contraception needs. "Contraception is a component of effective disease management for young women," she said.

There are many contraceptive methods available, each with pros and cons and varying efficacy, so women have multiple options to choose from to suit their personal preferences and lifestyles. Dr. Chakravarty suggested that, of all the available methods, long-acting reversible contraceptive methods, such as the subdermal implant or intrauterine device, were perhaps the best choice for many women with rheumatic diseases since they are associated with a low rate of accidental pregnancy and after insertion there is little or nothing to do or remember until the devices needed replacing after 3-10 years.

Dr. Monika Østensen of the Norwegian National Advisory Unit on Pregnancy and Rheumatic Diseases at St. Olavs Hospital-Trondheim University Hospital, echoed the need for repeated family-planning advice. Of course,

pregnancies occur even with the best planning, she said, and the question then is how to manage the rheumatic disease.

The need for treatment will depend on the type of disease, she said, noting that the need generally decreased during pregnancy in women with rheumatoid arthritis (RA) but increased in those with ankylosing spondylitis, most notably in the first and second trimesters (Ann. Rheum. Dis. 2004;63:1212-7). The ideal situation would be to adjust disease-directed therapy if needed before conception, although methotrexate is the only drug with proven teratogenicity that is used for RA and ankylosing spondylitis and that should definitely be stopped, she said.

There is a lot of evidence that methotrexate needs to be stopped before pregnancy. One recent prospective study (Arthritis Rheumatol. 2014;66:1101-10) looked at pregnancy outcomes and methotrexate use and found a high rate of spontaneous abortions if it was used within 10 weeks of conception (14.4%) or in the first trimester (42.5%). The rate of major birth defects was 6.6% if methotrexate was used in early pregnancy, versus 2.9% for women without rheumatic disease or 3.5% in women with rheumatic disease who were not taking the disease-modifying antirheumatic drug (DMARD).

Dr. Østensen advised that, when stopping methotrexate, women should be counseled to wait for one menstrual cycle before attempting to conceive and not to stop therapy without perhaps checking for fertility or switching to another pregnancy-compatible drug. She also stressed that patients who want to become pregnant or who do become pregnant should not immediately stop taking their medication without consulting a rheumatologist. Such an action could result in disease flares, and the aim of therapy should always be to keep the patient in remission or low disease activity and continue drugs that support remission while trying to minimize any likely effects on the fetus.

Leflunomide, rituximab, abatacept, and newer biologics such as tocilizumab, ustekinumab, and tofacitinb are contraindicated because of lack of data on whether they are safe for the fetus. If a woman did become pregnant while taking any of these drugs or even methotrexate, then taking a careful history and performing fetal ultrasound and amniocentesis may be the best approach to determine what action to take and if pregnancy termination should be considered.

> "Nowadays we have such better treatments for our patients that sexuality and contraception is becoming more and more important. Yet contraception is quite underused in our patients."

Tumor necrosis factor-alpha inhibitors (TNFi), the best-studied biologic DMARDs, can be given before conception and during the first and early second trimester; however, use in late pregnancy requires different considerations because transplacental passage varies based on differences related to their structure. Some TNFis, such as certolizumab pegol, have small affinity to the fetal Fc receptor or no Fc part and show low transplacental passage to the fetus. TNFis that possess an Fc part of immunoglobulin G1, however, allow high amounts of transfer and should be avoided in the third trimester whenever possible, Dr. Østensen said.

Data are sparse on human pregnancy exposure and fetal side effects and outcomes for most other biologics, so decisions to use biologics targeting B-cells, T-cell activation, or cytokines like interleukin (IL)-6, IL-23, IL-17, or IL-1beta must be based on the severity of maternal disease and reserved for cases in which no other safe options are available, Dr. Østensen cautioned.

So how can acute arthritis be treated during pregnancy? Options in RA include NSAIDs, short-term oral prednisone with rapid tapering, or intramuscular injection of triamcinolone. Intra-articular steroid injection also might be considered, and TNFi in patients with severe polyarthritis. Spondyloarthritis might be treated with NSAIDs, intramuscular triamcinolone, or intra-articular steroid injection, with TNFi in severe cases.

Newer approaches to managing arthritis during pregnancy are to perhaps prescribe a TNFi with a low propensity for transplacental passage or to use a flexible regimen of TNFi by reducing the dose or prolonging the interval between administrations.

Continuing medications such as hydroxychloroquine, sulfasalazine, or azathioprine might be in some patients' best interests to support remission and keep disease activity low, Dr. Østensen suggested. She noted that prednisone should be used at a low (5-7.5 mg) dose during pregnancy and that the aim should be to try to slowly reduce the use of pregnancy-compatible medications that are not necessary for continued remission, keeping a close eye on patients' disease activity to ensure that no flares occur.

Dr. Chakravarty had no financial disclosures. Dr. Østensen reported receiving speaker fees and honoraria from UCB, Roche, AbbVie, MSD, Pfizer, and New Bridge. ■

MAPPING THE IMPACT OF CHRONIC INFLAMMATION IN RHEUMATOID ARTHRITIS (RA):

From Molecular Triggers and Disease Pathophysiology to Patient Quality of Life

Faculty: Prof. Gianfranco Ferraccioli, Prof. Peter Taylor, Prof. Tom Huizinga, Prof. Bruno Fautrel

This symposium, which took place during the morning of Friday, 12 June 2015, was opened by Prof. Gianfranco Ferraccioli, who provided an excellent overview of the recent developments in pharmacotherapy for RA.

He stressed that the goal of antirheumatic therapy is "to restore the homeostatic balance between pro- and anti-inflammatory cytokines." Prof. Ferraccioli reminded the audience that auranofin, an old gold complex antirheumatic agent, inhibited Janus kinase (JAK) activity; and concluded by indicating that "JAK inhibitor may well prove to be the new frontier for antirheumatics."

Following the opening remarks, Prof. Ferraciolli introduced the first speaker, Prof. Peter Taylor from Oxford University, who presented BIOLOGY OF SIGNALING PATHWAYS IN INFLAMMATORY ARTHRITIS. Prof. Taylor's presentation focused on the dysregulated homeostasis underlying autoimmune rheumatic disorders at the cellular, intercellular, and intracellular levels, as well as its clinical implications.

Prof. Taylor provided an overview of the mechanisms by which effector cells communicate with one another, reminding the audience that "a dynamic network of cytokines affects both healthy and dysregulated immune system homeostasis." Since no single molecular target appears to be capable of eliciting all the desired therapeutic effects, signal transducers that, like the Janus kinases, act as intracellular signal transduction hubs constitute appealing potential targets.

The second presentation, IMPACT OF CHRONIC INFLAMMATION ON COMORBIDITIES, was given by Prof. Tom Huizinga, who began with cardiovascular (CV) comorbidities in inflammatory disorders. He stated that "there are ample data attesting increased CV risk in RA and other inflammatory rheumatic disorders, such as SLE," and explained that this also holds true for patients presenting with traditional CV risk factors, such as comorbid T2DM, who are at higher risk than patients with T2DM without RA, prompting the recommendation to raise the suspicion index for CV risk: "one should clearly address traditional factors for CV risk in these patients, but one should remember that RA disease activity is also an important contributor."

After addressing the underlying pathophysiology of inflammation-triggered CV risk factors, such as modifications in platelets characteristics, liver physiology, and lipidemic profile, Prof. Huizinga concluded that "strong epidemiological evidence indicates that whenever inflammation is lowered, there is a concomitant decrease in CV risk" and "inhibition of signs and symptoms of RA together with management of traditional factors reduces CV risk over time."

The last presentation of this program, LIVING WITH CHRONIC INFLAMMATORY DISEASE: THE PATIENTS' PERSPECTIVE, was by Prof. Bruno Fautrel. He stated that we have powerful treatments, but no cure for RA, and since "patient-centric care is fast becoming a reality, additional outcomes should be taken into account, such as quality of life, and especially, fatigue."

Importantly, patient/physician discrepancies persist, as exemplified by near-remission assessment. Differences between Boolean remission and Simplified Disease Activity Index remission rates are explained by the inclusion in the first of a Patient Global Assessment (PGA) score because "for the patient, impact on daily life is key and the point of comparison is the time preceding symptoms onset," while the physician's assessment is driven by disease markers.

As the field stands today, it appears that patient reported outcomes are important for adherence, and patient empowerment in particular and should be integrated into the therapeutic algorithm together with physicians' disease assessment.

The symposium concluded with an engaging question and answer (Q&A) session.

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Anti-TNF Therapy Carries Low Congenital Malformation Risk

BY SARA FREEMAN

Reassuring new data from the German biologics registry RABBIT presented at the Congress indicate that exposure to biologic therapies around the time of conception does not increase the risk of malformations or other harmful neonatal consequences.

Observational studies suggest that biologic disease-modifying antirheumatic drugs (DMARDs) are safe to use in patients with rheumatoid arthritis until conception, but questions remain about their influence on birth outcomes, Dr. Anja Strangfeld of the German Rheumatism Research Center, Berlin, and one of the principal investigators for RABBIT (Rheumatoid Arthritis Observation of Biologic Therapy), said in an interview. Dr. Strangfeld also noted that questions remained on the course of RA during pregnancy in women who stopped biologic therapy in the first trimester, and how to treat high disease activity, including the use of glucocorticoids.

Dr. Anja Strangfeld

Her coprincipal investigator, Dr. Angela Zink, also of the German Rheumatism Research Center, presented the new findings during the scientific sessions, which considered 106 pregnancies in 88 women aged 45 years or younger that had occurred between 2001 and the end of 2014. Of these, 42 had occurred in the preceding 3 years.

Among the 38 women who stopped biologics before conception, therapies included rituximab (n = 13), etanercept (n = 12), adalimumab (n = 9), tocilizumab (n = 2), and infliximab (n = 2). Etanercept and adalimumab were the most common therapies among those using biologics at conception, administered in 29 and 11 patients, respectively.

The study identified five spontaneous abortions in 38 pregnancies (13%) in which biologic DMARD infusions or injections were stopped at least 4 weeks before conception and 11 spontaneous abortions among 57 pregnancies (19%) exposed to biologic DMARDs at conception. A total of 11 patients were biologic naive, and no spontaneous abortions were observed. Reassuringly, the rates of spontaneous abortions were within the range of about 15%-20% observed in the general public.

Induced abortions were decided on in 4 of the 106 pregnancies. Three occurred in the 38 women who stopped biologic therapy before conception, including one abortion due to trisomy 21, and the other one was in a woman who had been taking biologic DMARD therapy at conception.

The live birth rate was 100% for the biologic-naive women, and 79% for both women who stopped biologic DMARDs before conception and those who had been taking them at conception.

Four congenital defects were reported in live-born children: one anal atresia with urogenital malformation (last adalimumab injection 4 weeks before conception), one congenital nystagmus after preterm birth (last adalimumab injection greater than 6 months before conception), and one case of spina bifida (last etanercept injection greater than 9 months before conception). There was also one case of talipes in a child whose mother reported also having talipes and had been taking adalimumab at time of conception.

Although the analysis includes a limited sample of pregnancies, these data confirm previous reports and show no increased risk of major malformations or other harmful consequences in patients exposed to biologic therapy around conception.

"We found that, in patients with long-standing rheumatic disease, remission during pregnancy is rarely reached," Dr. Zink observed. In fact, "disease activity increased during pregnancy in a considerable proportion of the patients," she added. This is in contrast to other studies and experience, however, she acknowledged, where disease activity has been shown to decrease during pregnancy.

Of 23 patients who were already in remission before conception, 10 (43%) remained in remission during their pregnancies. Of the 49 patients who had not been in remission before

Dr. Angela Zink

pregnancy, only seven (14%) went into remission during pregnancy.

Dr. Zink noted that a new German pregnancy registry, RHEKISS, started recruitment in July 2015 to observe treatment needs from the first desire to conceive or early pregnancy (first trimester) until the child's second birthday. This register will initially include women with any inflammatory rheumatic disease but will later also include male patients whose partner is pregnant.

In a separate presentation, Dr. John J. Cush of Baylor Research Institute and Baylor University Medical Center in Dallas, U.S.A., reported other data on the safety of tumor necrosis factor inhibitors (TNFis) in pregnancy. He presented prospectively collected data on pregnancy outcomes in 78 women with rheumatic disease and 148 women with other inflammatory diseases, such as Crohn's disease, who were exposed to certolizumab pegol from the manufacturer UCB Pharma's global safety database.

He observed that because certolizumab's structure lacks an Fc region, it was potentially a more favorable anti-TNF therapy to use during pregnancy than etanercept, infliximab, adalimumab, or golimumab because it was thought to be less likely to cross the placental barrier and affect the developing fetus.

"Live births were reported for the majority of pregnancies of women with rheumatic diseases following maternal certolizumab exposure," Dr. Cush said.

Almost three-quarters (73.1%) of the 78 women with rheumatic disease had a live birth with no congenital malformations. Around 5% of live births were associated with congenital malformations, and the rates of spontaneous and induced abortions were a respective 11.5% and 14.1%.

Dr. John J. Cush

In the 132 women with nonrheumatic inflammatory diseases, there were 86.6% live births without and 4.4% with congenital abnormalities and 9.1% and 5.3% spontaneous and induced abortions.

For all indications, there were 12 congenital malformations from 254 live births. These included anal fistula, polydactyl left hand, posterior ankyloglossia, renal cyst for which no treatment was needed, pyloric stenosis, club foot, and left-sided vesicoureteral reflux.

Dr. Cush noted that one neonate in a set of premature twins delivered at 26 weeks died due to brain damage and pneumoperitoneum.

Importantly, the data were "encouraging," he said, and "suggest that certolizumab exposure in utero, including the first trimester of exposure, does not adversely affect pregnancy outcome."

> "We found that, in patients with long-standing rheumatic disease, remission during pregnancy is rarely reached." In fact, "disease activity increased during pregnancy in a considerable proportion of the patients."

The German biologics registry RABBIT is supported by grants from AbbVie, BMS, Celltrion, Hospira, MSD, Pfizer, Roche, and UCB. Dr. Strangfeld reported having no disclosures. Dr. Zink has received speaker fees from AbbVie, BMS, MSD, Pfizer, Sanofi Aventis, Roche, and USB. Dr. Cush disclosed receiving research grants from Pfizer, Celgene, CORRONA, Amgen, the National Institutes of Health, Novartis, and UCB. ■

New Juvenile Systemic Sclerosis Registry Seeks Better Knowledge, Therapies

BY KAREN BLUM

A prospective international registry for patients with juvenile systemic sclerosis could pave the way toward new treatments and new understanding for this orphan disease, according to the researcher leading the effort.

"We want to learn how the disease develops, determine when the fastest progression of disease occurs and the ideal time point to start treatment, learn what medications seem to be most effective, and establish reasonable primary and secondary outcome measures," said lead study author Dr. Ivan Foeldvari, director of the Hamburg Centre for Pediatric and Adolescent Rheumatology. "This disease runs a little bit differently than it does in adults. Around 75% of patients have diffuse subset, compared with around 40% in adults, and around one-third of patients have overlap features. The mortality is, fortunately, significantly lower at 5 years with a 5-year survival in pediatric patients around 90%-95%. There is an urgent need to develop treatments to prevent mortality in juvenile systemic sclerosis [jSSc]."

Dr. Ivan Foeldvari

> "We want to learn how the disease develops, determine when the fastest progression of disease occurs and the ideal time point to start treatment, learn what medications seem to be most effective, and establish reasonable primary and secondary outcome measures."

The incidence of jSSc is approximately 0.27 per million children. The mean age of onset is around 8 years of age, and a lesser percentage of juvenile than adult patients have gastrointestinal and renal involvement (45% vs. 65%), Dr. Foeldvari said.

He shared clinical features of the registry's first 39 patients in a presentation at the Congress. The patients were enrolled at onset of disease and are reassessed every 6 months using a standardized clinical protocol. So far, he and his colleagues are finding that patients with the diffuse subtype (djSSc) were younger at onset and had more frequent capillary changes and active ulcerations, pulmonary hypertension, and renal involvement than did those with the limited subtype (ljSSc).

Of the 39, 29 have djSSc and 10 have ljSSc. Five of the diffuse subtype (17%) and 3 of the limited subtype (30%) had an overlap feature. The mean follow-up of patients in the cohort was 6.4 years for those with djSSc and 5.3 years for those with ljSSc. The majority of patients in both groups were female. The mean age at the onset of Raynaud's phenomenon was 8.7 years for djSSc and 12.9 years for ljSSc, while the mean age of the first non-Raynaud presentation was 9.1 years in djSSc and 13.8 years in ljSSc.

At the time of inclusion in the registry, the mean modified Rodnan Skin Score was 19.6 in the djSSC group and 7.5 in the ljSSc group. A total of 70% of patients in both groups already had capillary changes, but 67% in djSSc and 33% in ljSSc had a history of ulcerations; 32% of the djSSc group but none of the ljSSc group presented with active ulceration. In addition, 72% of djSSc and 50% of ljSSc had cardiopulmonary involvement; the two patients with pulmonary hypertension had djSSc. About 28%-30% of patients in both groups showed signs of interstitial lung disease on imaging. All three patients with renal involvement had djSSc.

Dr. Foeldvari and his colleagues also noted that in both groups, 30% had gastrointestinal involvement, and around 80% of both groups had musculoskeletal involvement. Anti-Scl 70 positivity was found in 40% of djSSc and 37.5% of ljSSc. Only one patient in the djSSc group had anticentromere antibody.

Researchers worldwide are encouraged to contribute to the registry, details of which are available online at www.juvenile-scleroderma.com, Dr. Foeldvari said. Those interested also may contact him directly at foeldvari@t-online.de.

Dr. Foeldvari is a consultant for Chugai, Novartis, and Pfizer. ■

New Juvenile Dermatomyositis Disease Activity Tool Developed

BY AMY KARON

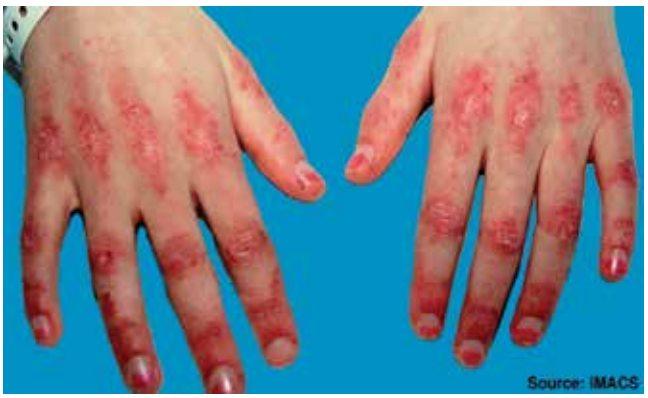
A tool for assessing juvenile dermatomyositis that incorporates perspectives from patients, parents, and physicians showed excellent discriminant ability and good construct validity and responsiveness to change, based on results of a multicenter study presented at the Congress.

The findings reveal the new instrument "to be a simple, but reliable, tool to assess the level of disease activity in a complex disease, as is juvenile dermatomyositis," Dr. Alessandro Consolaro of the University of Genova and Istituto Giannina Gaslini in Genova, Italy, said in an interview.

Juvenile dermatomyositis (JDM) is a rare autoimmune vasculopathy and inflammatory muscle disorder that causes rashes, calcinosis cutis, and proximal muscle weakness in children aged 18 years and younger. Tools to measure disease activity in JDM tend to be long and complicated, and to reflect only physicians' assessments, not those of patients or parents, according to Dr. Consolaro and his colleagues.

The investigators therefore have developed the Juvenile Dermatomyositis Activity Index (JDMAI), which incorporates physician evaluations of disease activity, reports of well-being from patients and parents, and objective measures of muscle strength and cutaneous disease. They tested four versions of the tool on 140 patients whom they saw in their offices within a 6-month period.

Three versions included the hybrid Manual Muscle Testing/Childhood Myositis Assessment Scale (CMAS) and one of three skin measures: the cutaneous domain of the Disease Activity Score (DAS, range 0-9), a cutaneous visual analogue scale (VAS, range 0-10), or the skin involvement type and distribution items of the DAS (range 0-7). The fourth version included the head lift, sits-up, and floor rise parts of the CMAS (range 0-20), and the skin involvement and distribution items of the DAS.



Elizabeth M. Dugan, Adam M. Huber, Frederick W. Miller, Lisa G. Rider / CC-BY-SA-3.0

All four versions of the JDMAI correlated strongly with total DAS results, with Spearman's rank correlation coefficients ranging between 0.80 and 0.90, Dr. Consolaro and his colleagues reported. All four versions also correlated strongly with parents' VAS assessments of disease activity (r values, 0.73-0.80), and with results for the Child Health Assessment Questionnaire (0.72-0.80), they said. The tool correlated moderately with the CMAS, the pain VAS, and the fatigue VAS; it correlated poorly with lactate dehydrogenase (0.27-0.32) and erythrocyte sedimentation rate (0.35-0.38), they said.

When measuring responsiveness to change between two consecutive visits, standardized response means ranged between 0.72 and 0.78. Furthermore, all versions of the JDMAI discriminated among patients who were in remission, had active disease, or were experiencing flares as determined by physicians (*P* less than .001) and parents (*P* less than .001). All versions of the instrument also distinguished among patients with high, moderate, or low disease activity as assessed by physicians (*P* less than .001), Dr. Consolaro and his colleagues said.

"In contrast to the score tools currently available, JDMAI is an easy-to-use tool for the routine assessment of disease activity in JDM," Dr. Consolaro said. The tool enables clinicians to compare disease activity levels at different time points for the same patient and among different patients, he added. As a next step, he and his colleagues plan to use the JDMAI in treat-to-target studies of patients with JDM, he said.

The investigators did not have any relevant disclosures. ■

New Pediatric and Adult Myositis Criteria Quantify Improvement During Treatment

BY MICHELE G. SULLIVAN

New criteria for measuring improvement in pediatric and adult patients with myositis will use cut points to define minimal, moderate, and major levels of treatment response, according to new consensus definitions.

The criteria – jointly developed by EULAR and the American College of Rheumatology – will be based on absolute changes in the measurements of improvement, rather than relative changes, according to Dr. Jiri Vencovsky, a coauthor of the document. Evaluating change this way more accurately identifies improvement in patients and should ease the task of accurately stratifying research cohorts, said Dr. Vencovsky of the Institute of Rheumatology, Prague, Czech Republic.

"The document increases the sensitivity of detecting levels of improvement and will reduce the number of patients necessary to enroll into the clinical trials," Dr. Vencovsky said in an interview. "This is significant, because myositis is a rare and heterogeneous disease, and it is not always easy to perform the trials with numbers of patients that are required by power calculation."

Dr. Jiri Vencovsky

Evaluating change this way also unifies the guidance for both pediatric and adult patients, although each group will have somewhat different thresholds for qualifying for minimal, moderate, and major improvement.

"Generally, to evaluate improvement we use change in six core set measures," he said. "These are somewhat different for adult and pediatric patients."

> "I think it is necessary to acknowledge that this is a large, collective work of many rheumatologists, neurologists, dermatologists, and specialists from other disciplines who provided data on cases and on clinical trials and participated in many rounds of assessments."

For adult patients, the measures include an assessment of activity on a visual analogue scale (VAS) by physician and patient; a measurement of muscle strength by a manual muscle test; a measurement of physical function with the Health Assessment Questionnaire; level of muscle enzymes, such as creatine kinase; and assessment of extramuscular disease activity on a VAS.

For pediatric patients, there are also six core measures, but instead of the manual muscle test, the Childhood Myositis Assessment Scale is used. Also, Dr. Vencovsky said, the global Disease Activity Score replaces the extramuscular disease activity score, and the Health-Related Quality of Life measure replaces muscle enzyme measurements.

The new system is much more data driven and has been validated in research cohorts, he added. "The old definition of improvement was based on the expert consensus, and other expert definitions of improvement. "They all seemed not to be very sensitive, and they were not properly validated. We needed definitions that would be more sensitive and more specific and would give us an opportunity not only to say that patients improved or not, but also how much they improved. Ideally, it would be good to get the same definitions for all patients with idiopathic inflammatory myopathies – adults and children."

The process of creating the new criteria was complicated and rigorous, Dr. Vencovsky said. Several drafts emerged, and each was tested for sensitivity and specificity using results from two large, randomized, controlled trials. There were 31 candidate definitions evaluated (17 for adult patients and 14 for pediatric patients).

The definitions of improvement that performed best in testing were selected for final consideration at a 28-member consensus meeting, which occurred in Paris last year, shortly before the EULAR 2014 Congress. Panel members included experts in rheumatology, neurology, and dermatology.

"In a final round, the experts agreed to use separate threshold cut points for minimal, moderate, and major improvement for adult dermato- and polymyositis vs. juvenile dermatomyositis. The definition is the same, but the cut points

are different for minimal, moderate, and major improvement since the magnitude of response in children is higher than in adult patients."

The definition measures absolute percent change in each core set measure and is based on a conjoint analysis hybrid model," Dr. Vencovsky explained. The absolute change is calculated as start value, minus the end value, divided by range.

In most of the criteria in other diseases, a relative percent change is used. The preliminary criteria that we had also used this, Prof. Vencovsky said, but "it was felt and agreed that absolute percent change is more appropriate to evaluate change in individual core set measures for patients with idiopathic inflammatory myopathies."

The category of "major improvement in adult patients" is considered preliminary, he cautioned, because there were not sufficient numbers of patients for the statistical assessment in either the profiles or in the clinical trial.

Determination of Minimal, Moderate, and Major Improvement

Profile	Improvement category	Cut point on total improvement score
Adult	Minimal	≥20
	Moderate	≥40
	Major	≥60
Pediatric	Minimal	≥30
	Moderate	≥45
	Major	≥70

Note: The new criteria were developed by EULAR and the American College of Rheumatology.

Source: Dr. Vencovsky

The new criteria are not yet available; publications are being prepared. Also, the new definitions of improvement will have to be approved by both ACR and EULAR committees. "Hopefully, the new definition of improvement with a calculator will be available online in autumn 2015."

"I think it is necessary to acknowledge that this is a large, collective work of many rheumatologists, neurologists, dermatologists, and specialists from other disciplines who provided data on cases and on clinical trials and participated in many rounds of assessments," Dr. Vencovsky noted. "The work was organized by a steering committee led by Lisa Rider, Nicola Ruperto, Rohit Aggarwal, Fred Miller, and myself. The ACR and EULAR supported the work. Patients' organizations and the National Institutes of Health also contributed to the criteria development." ■

Serious Adverse Events Rise With Number of Biologics Used in JIA

BY JEFF EVANS

Nick Piegari/Frontline Medical News

VIDEO HIGHLIGHTS: Click here to watch a video interview with Dr. Joost F. Swart.

Biologic drug use in combination with methotrexate appears to carry the greatest risk for serious adverse events in patients with juvenile idiopathic arthritis when different biologics are tried sequentially, according to findings from a study of nearly 6,000 patients in the Pharmachild registry.

The results from the registry, the largest international pharmacovigilance juvenile idiopathic arthritis (JIA) database in the world, showed that patients who had used more than one biologic while on methotrexate had nearly twice the rate of adverse events as did those on methotrexate alone and more than three times the rate of serious adverse events, Dr. Joost F. Swart reported at the Congress.

Dr. Swart is a pediatric rheumatologist/immunologist in the department of pediatric immunology and rheumatology in the Wilhelmina Children's Hospital at University Medical Center Utrecht (the Netherlands). He received a clinical research abstract award for the research at the Congress.

The study involved 5,862 JIA patients in the registry who continued methotrexate and either stayed on it alone (1,674) or also added one (3,025) or more biologics over time (1,163). The registry includes 93 centers of the Paediatric Rheumatology International Trials Organization from more than 30 countries.

Most of the patients who had been treated with one biologic in addition to methotrexate had taken etanercept (66%), followed by adalimumab (19%), infliximab/tocilizumab (about 5% each), and other biologic agents (5%). Treatment experience with multiple biologics was most often with etanercept (30%), adalimumab (27%), infliximab (14%), tocilizumab (9%), abatacept (7%), anakinra (4%), golimumab (4%), and other biologic agents (5%). A total of 40% of children also were treated with corticosteroids (82% of those with systemic JIA); another 20% received other disease-modifying antirheumatic drugs. The patients' JIA subtypes were systemic (10%), persistent oligoarticular (20%), polyarticular rheumatoid factor positive or negative (50%), and other JIA categories (20%).

Dr. Swart and his coauthors determined that the overall adverse event incidence rate per 100 patient-years was lowest in JIA patients who took methotrexate alone (10.7), intermediate in those who took methotrexate plus one biologic (13.9), and highest among patients who took methotrexate in combination with more than one biologic in sequence over time (19.5). Lower rates and a similar trend were observed for serious adverse events.

Although the infection rate was higher for patients who took one biologic (4.6) in comparison with methotrexate alone (2.9), the rate did not increase significantly with more than one biologic (4.8). The same trend applied for serious infections (0.7, 1.4, and 2.0, respectively).

The median disease duration increased from methotrexate-only users (3.6 years) to those who used one biologic with methotrexate (5.4 years) and those who used more than one biologic (7.6 years). The investigators tracked more patient-years of use of one biologic (about 9,000) than two (about 2,800). The number of patient-years on methotrexate for those who took a biologic were not counted in the study.

The proportion of patients who discontinued treatment because of an adverse event or drug intolerance rose along with exposure to greater numbers of drugs, from 4% of methotrexate-only users to 16% of those exposed to a single biologic and 18% of those who took more than one biologic.

The group treated with more than one biologic had higher incidence rates for injury, poisoning and procedural complications, blood and lymphatic system disorders, and eye disorders than did the other groups, whereas methotrexate-only users had a higher incidence of hepatobiliary disorders.

Analyses are in progress for determining the relationships between individual biologics and adverse events and for differences in adverse events according to geographic area, Dr. Swart said.

Dr. Swart had no conflicts of interest to disclose, but many of his 28 coauthors disclosed relationships with companies that market the drugs used by patients in the registry. ■

Anti-TNFs Help Psoriatic Arthritis Patients Get Back to Work

BY SARA FREEMAN

Anti–tumor necrosis factor agents have a slight edge over conventional disease-modifying antirheumatic drugs when it comes to helping psoriatic arthritis patients who are having work issues, according to a large British observational study presented at the Congress.

Among 236 of 400 subjects working at baseline, presenteeism improved from 30% to 10% and productivity loss improved from 45% to 10% among patients who started taking anti-TNF (anti–tumor necrosis factor) agents. Gains were more modest when patients were started on DMARDs, with presenteeism improving from 30% to 20% and productivity loss from 40% to 25%. The difference in change of presenteeism between the two treatment groups became statistically significant at 2 weeks and remained so at 24 weeks.

"Work disability is a continuum," said the presenting author, Dr. William Tillett of the Royal National Hospital for Rheumatic Diseases in Bath, England. It starts with the normal situation then graduates from presenteeism, where the individual is sick but still attends the workplace, to absenteeism, where the individual is sick and no longer attends the place of work, and eventual unemployment, he explained. "This study suggests that work disability is reversible in the real-world setting," he added.

Dr. William Tillett

The study is from the Long-term Outcomes in Psoriatic Arthritis (LOPAS II) working group, a 2-year, multicenter, prospective, observational cohort study of work disability in psoriatic arthritis.

The group has previously reported that unemployment in psoriatic arthritis is associated with older age, disease duration of 2-5 years, and worse physical function, but that employer awareness and helpfulness enabled patients to stay on the job. Higher levels of global and joint-specific disease activity and worse physical function were associated with greater levels of reporting to work sick (presenteeism) and productivity loss (Rheumatology. 2015;54:157-62).

> "Work disability is a continuum. This study suggests that work disability is reversible in the real-world setting."

The latest study by Dr. Tillett and his team is a follow-up to see how treatment affects work performance. At baseline, before treatment with anti-TNF agents or DMARDs, the LOPAS II team of investigators found that 164 (41%) of their 400 subjects were unemployed. Unemployed patients tended to be older (median of 59 years vs. 49 years) and to have worse physical function (a median score of 1.4 on the Health Assessment Questionnaire vs. 1.0). Subsequent treatment with anti-TNF agents or DMARDs didn't change overall employment levels.

Patients who started on anti-TNF drugs tended to have a longer disease duration (median of 11 vs. 5 years) and a greater median number of tender (16 vs. 11) and swollen (7 vs. 5) joints, but otherwise there were no significant differences in demographic or clinical measures between the two treatment groups.

Median scores on the Disease Activity Index for Psoriatic Arthritis (DAPSA) improved over 24 weeks from 53 to 14 among anti-TNF patients, which is considered a good response, but only improved from 39 to 30 in the DMARD group, which is considered a poor response. All of the findings were statistically significant.

The results revealed a "surprisingly poor clinical response to synthetic DMARDs on clinical outcomes … as opposed to good response amongst patients commenced on TNF inhibitors," Dr. Tillett said in an interview. The improvement in work disability and disease activity seen also was greater and more rapid among those who started on an anti-TNF agent rather than a synthetic DMARD.

Dr. Tillett reported receiving grant/research support from AbbVie and speaker or advisory board fees from UCB, Pfizer, and AbbVie. The other authors said they have no disclosures. ■

Large-Scale Psoriasis Study Links Trauma to Arthritis

BY SARA FREEMAN

Patients with psoriasis were more likely to develop psoriatic arthritis if they had experienced physical trauma, based on data from a large, population-based study.

The crude incidence of psoriatic arthritis was 30 per 10,000 person-years in psoriasis patients exposed to trauma, compared with 22 per 10,000 person-years in those who were not.

The hazard ratio (HR) for increased psoriatic arthritis risk with any trauma was 1.32 after adjusting for multiple factors, including patient age, gender, and the duration of psoriasis, senior study author Dr. Thorvardur Löve said during a press briefing at the Congress.

"Patients with psoriasis are an easily identifiable group [to study] as they have skin disease on their body," he noted. They also have a high risk of developing arthritis, at around 10%-30% of patients. This makes them an ideal population to study to try to find factors that might mitigate the risk and potentially have a large impact in clinical practice.

NICK PIEGARI/FRONTLINE MEDICAL NEWS

VIDEO HIGHLIGHTS: Click here to view a video interview with Dr. Thorvardur Löve.

"Patients with psoriasis are an easily identifiable group [to study] as they have skin disease on their body," he noted. They also have a high risk of developing arthritis, at around 10%-30% of patients. This makes them an ideal population to study to try to find factors that might mitigate the risk and potentially have a large impact in clinical practice.

"The idea that trauma precipitates psoriatic arthritis is not new," observed Dr. Löve of Landspitali University Hospital in Reykjavik, Iceland. "It comes a little bit from the Koebner phenomenon, which is when psoriasis patients develop a new lesion in the skin where an injury has been."

A few small studies had given rise to the idea that trauma could perhaps trigger a deep Koebner phenomenon in patients with psoriasis, and so the aim of the present analysis was to look at this idea in a larger population.

Electronic health records of more than 10 million individuals living in the United Kingdom between 1995 and 2013 were analyzed from the Health Improvement Network (THIN) database. Of 70,646 patients with psoriasis who were identified, 15,416 had been exposed to some form of trauma, which was stratified as trauma involving the joints, bones, nerves, or skin.

After 425,120 person-years of follow-up, 1,010 incident cases of psoriatic arthritis had been recorded.

Having bone or joint trauma was found to increase the risk for psoriatic arthritis by 46% (HR, 1.46; 95% confidence interval, 1.13-1.54) and 50% (HR, 1.50; 95% CI, 1.19-1.90), respectively. This was after adjusting for age, gender, date of entry into the THIN database, duration of psoriasis, body mass index, smoking, alcohol consumption, and the number of visits to the general practitioner.

Neither nerve nor skin trauma was associated with an increased risk for psoriatic arthritis. Dr. Löve and his fellow researchers also looked to see if patients with psoriasis had an increased risk of rheumatoid arthritis but found no significant association (HR, 1.04; 95% CI, 0.99-1.10).

"The conclusion is that physical trauma is a risk factor for psoriatic arthritis among patients with psoriasis," Dr. Löve said. "We believe this is very important as the baseline risk is so high."

The effect is specific to psoriatic arthritis, as it is not seen in rheumatoid arthritis, which might provide clues for further research, he added. Why trauma might up the risk for developing psoriatic but not other types of inflammatory arthritis remains unclear, but the hypothesis is that patients would need to have a genetic predisposition and the "right types" of T cells in and around the joint that get disturbed in some way, perhaps by infection or by trauma.

"I think it's important to note that at this point we are not making any recommendations to the psoriasis community," Dr. Löve said. He suggested that, before any recommendations could be made, there needed to be a "really robust" conversation between patients, researchers, and physicians to determine exactly what these findings might mean. Certainly more research is needed before suggesting any lifestyle modifications that might help avoid situations associated with certain types of trauma, he said.

A literature review in the journal Clinical Rheumatology provided additional explanation of the deep Koebner effect. The investigators noted in their abstract that "the role of neuropeptides such as substance P and vasoactive intestinal peptide has been highlighted in the synovium after trauma."

An editorial in the Journal of Rheumatology also suggested areas for additional research. Dr. Ignazio Olivieri of San Carlo Hospital in Potenza, Italy, wrote that "criteria of imputability" that should be met include "single and significant trauma; absence of joint lesion before trauma; localization of arthritis in the area of trauma; and absence or short delay between trauma and onset of arthritis."

"You might envision treating [psoriasis] patients early [for psoriatic arthritis] if they break a leg or get a joint dislocation, but we are not there yet," Dr. Love stressed. "This is an idea of where we could take this and where we might actually be able to have an effect."

> "The conclusion is that physical trauma is a risk factor for psoriatic arthritis among patients with psoriasis," Dr. Löve said. "We believe this is very important as the baseline risk is so high."

The research was performed by researchers at the University of Iceland (Reykjavik) in collaboration with researchers at Harvard Medical School in Boston and the University of Pennsylvania in Philadelphia. It was partially funded by the Icelandic Centre for Research (RANNIS) and the National Institutes of Health. Dr. Löve's associate, Dr. Stefan Thorarensen of the division of public health at the University of Iceland, presented the findings during the clinical science session at the Congress.

Dr. Löve and his coauthors reported having no financial disclosures. ■

NSAID Dosing Frequency Matters Little In Ankylosing Spondylitis

BY SHARON WORCESTER

Radiographic progression occurs at similar rates in the spines of ankylosing spondylitis patients treated over 2 years with either continuous or on-demand diclofenac, according to results from a randomized, prospective multicenter trial presented at the European Congress of Rheumatology.

In the ENRADAS (Effects of NSAIDs on Radiographic Damage in Ankylosing Spondylitis) trial, Dr. Joachim Sieper of Charite-Universitätsmedizin Berlin and his colleagues compared continuous treatment with at least 50% of the maximum 150-mg daily dose of the NSAID diclofenac and on-demand treatment with diclofenac. During the entire 2 years of the study, no patient received treatment with a tumor necrosis factor blocker or any other drug other than diclofenac.

The investigators measured radiographic spine progression using the modified Stoke Ankylosing Spondylitis Spinal Score (mSASSS). At baseline, patients randomized to continuous treatment who had complete radiographic follow-up had a mean mSASSS of 10.9, while those randomized to the on-demand arm had a mean mSASSS of 16.4. After 2 years on treatment, the average change in mSASSS from baseline was 1.28 for the 62 patients in the continuous-treatment group and 0.79 for the 60 patients in the on-demand group, a difference that was not statistically significant, Dr. Sieper said.

There also was no statistically significant between-group difference when the analysis focused on the subgroup of patients who were C-reactive protein positive at baseline, 55% and 58% of patients in the groups, respectively, who had their average mSASSS increase by 1.68, compared with 0.96. Similarly, when the analysis focused only on patients who had syndesmophytes at baseline, 53% and 62% of patients, respectively, the average increases in mSASSS were 2.11 and 0.95, a difference that was not statistically significant. Presence of C-reactive protein and syndesmophytes are both known risk factors for radiographic progression.

Mitchel L. Zoler/Frontline Medical News

Dr. Joachim Sieper

Patient characteristics were similar in the two groups. NSAID intake over the 2-year study period, measured using a 0-100 composite score based on treatment duration and NSAID doses and intervals, was a mean of 76 vs. 44 for the continuous and on-demand groups, respectively. At the study's end, 77% of patients remained on diclofenac and had not switched to another NSAID.

Side effects were similar in both groups, with 19 serious adverse events in the continuous-treatment patients and 21 serious adverse events in the on-demand patients.

Previous studies have suggested that NSAIDs given continuously over 2 years reduce radiographic progression, compared with on-demand therapy, in ankylosing spondylitis patients. Similar effects were seen in a prospective cohort.

"In our study, continuous vs. on-demand treatment … did not prevent radiographic progression in [ankylosing spondylitis]. It is highly unlikely that the results would have been different with a higher number of patients, because we found a trend for less progression in the on-demand group," Dr. Sieper said.

Additional study is needed to determine whether an NSAID other than diclofenac, specifically a COX-2 selective drug, would have a different effect on radiographic progression, he said. ■

Epigenetics Points to Anti-TNF Efficacy in Psoriatic Arthritis

BY KAREN BLUM

Tumor necrosis factor–alpha (TNF-alpha) inhibitors are well established as a treatment for psoriatic arthritis patients, but efficacy can vary greatly within that population. New work from Canadian researchers demonstrates that the global DNA methylation pattern differs between TNF-alpha–inhibitor responders and secondary failures, which could help explain the variability in medication success rates.

"Although TNF inhibitors [TNFi] work very well in certain individuals with psoriatic arthritis [PsA], up to 40% of individuals receiving this treatment fail to achieve a therapeutic response, and 20%-50% of individuals who have an initial response to treatment become refractory weeks or months after receiving therapy." lead study author Darren O'Rielly, Ph.D., said at the Congress.

The preliminary study findings eventually could lead to the identification of biomarkers that would indicate patients who are not good candidates for TNFi medications, said Dr. O'Rielly of Memorial University, St. John's, Canada.

Given recent advances in epigenetics and that the epigenetic signature is affected by environmental factors, the investigators set out to determine if methylation alterations could help explain why PsA patients respond or fail with TNFi. The researchers performed genome-wide DNA methylation profiling on blood samples from 41 PsA patients, using machinery that measures about 480,000 CpG sites per sample and covers 96% of RefSeq genes. A total of 21 patients were considered TNFi responders, of whom 13 were treated with etanercept and 8 with adalimumab; median follow-up duration was 18 months. Twenty patients were considered secondary TNFi failures, of whom 15 were treated with etanercept and 5 with adalimumab; median follow-up duration was 36 months.

Nick Piegari/Frontline Medical News

VIDEO HIGHLIGHTS: Click here to view a video interview with Dr. Proton Rahman, a coauthor on the study with Dr. Darren O'Rielly.

Dr. O'Rielly, a senior research scientist at Memorial and director of the Molecular Genetics Laboratory at Eastern Health in St. John's, and his associates measured the methylation level at CpG sites using a genome-wide approach and selected regions of interest based on functional relevance to TNF-mediated signaling pathways with methylation level differences of 5% or greater and an adjusted *P* value less than .05.

After quality-control filtering, investigators evaluated 384,599 CpG sites for TNFi responders and 368,863 CpG sites for TNFi failures. Researchers found 72 CpG sites of interest in the TNFi responder group and 91 CpG sites of interest in the TNFi failure group. Top candidate genes for TNFi responders included TRAPPC9 (which functions as an activator of NF-kB), CCR6 (which regulates the migration and recruitment of dendritic and T cells), and PSORS1C3 (psoriasis susceptibility 1 candidate 3), while top candidate genes for TNFi secondary failures included CD70 (an encoded protein that is a ligand for TNFRSF27/CD27) and TNFRSF1B (a member of the TNF receptor "superfamily" that mediates most of the metabolic effects of TNF-alpha).

"We are very encouraged by these findings," Dr. O'Rielly said. "We were a little surprised that several of our best candidate genes, such as TNFRSF1B and CD70, appear to play a role in TNF-alpha signaling, and that their methylation change occurs in a gene region that is consistent with a possible functional effect. We were expecting to find some methylation changes in genes but not necessarily in pathways with a direct connection with TNF-alpha–mediated signaling."

The group plans to confirm these findings for the best candidate genes using other methylation-specific polymerase chain reaction technology, he said, and will investigate additional CpG sites adjacent to the region of interest, including promoters and enhancers, in the best candidate genes to better characterize the full extent of methylation changes in these regions. They also would like to replicate the findings in a prospective, independent cohort.

Dr. O'Rielly reported no relevant financial conflicts. ■

Smoking Hurts Odds for Sustained Remission in Anti-TNF–Treated AS

BY KAREN BLUM

Smoking is a major factor that prevents patients with ankylosing spondylitis on anti–tumor necrosis factor therapy from attaining sustained remission, according to a new study presented at the Congress. The research, conducted in more than 300 Canadian patients, also found that younger patients with shorter history of disease and those who achieved normalized C-reactive protein levels soon after treatment were more likely to have sustained remission.

"We were particularly interested in understanding what factors affect sustained remission," said senior study author Dr. Walter P. Maksymowych, a professor of medicine at the University of Alberta in Edmonton, Canada. "Sustained remission has not really been explored in the field to date, and there are no set definitions of what it is. These are expensive therapies, and we wanted to know which patients do well on biologics and remain well." Investigators also wanted to better understand whether MRI measures of inflammation and structural damage at baseline, or after treatment, might play a role in predicting sustained remission in ankylosing spondylitis (AS) patients, he said.

As part of a cohort study called FORCAST (Follow-up Research Cohort in AS), AS patients from Northern Alberta attending community and academic practices have been assessed for clinical and laboratory values every 6 months; received radiography at baseline and at 2 years; and received MRI at baseline, at 3-6 months for patients starting anti–tumor necrosis factor (anti-TNF) therapy, and annually. The researchers assessed MRI inflammation using the Spondyloarthritis Research Consortium of Canada (SPARCC) sacroiliac joint (SIJ) and spine scores. They

Dr. Walter P. Maksymowych

measured structural change using the SPARCC structural scores (SSS) for fat metaplasia, erosion, backfill, and ankylosis, as well as the Fat Spondyloarthritis Spine Score (FASSS) for fat metaplasia in the spine. They defined sustained clinical remission as an Ankylosing Spondylitis Disease Activity Score (ASDAS) less than 1.3 at two consecutive 6-month visits. Investigators also assessed patient demographics, smoking, HLA-B27 status, nonsteroidal anti-inflammatory drug utilization, baseline C-reactive protein (CRP) level, ASDAS, modified Stoke Ankylosing Spondylitis Spinal Score (mSASSS), SPARCC scores, SSS, and FASSS, as well as early post-treatment attainment of CRP less than 6 mg/L; ASDAS less than 1.3; and SPARCC score less than 2 as predictors of future remission.

In total, Dr. Maksymowych and his colleagues assessed 323 AS patients on anti-TNF therapy. Seventy-five percent (242) were males. They had a mean age of 41 years, mean symptom duration of 18.1 years, and mean follow-up duration of 40.3 months. MRI evaluation was completed in 161 patients.

Seventy (21.7%) patients attained ASDAS remission after an average follow-up of 30.4 months. Patients attaining ASDAS remission were younger (P less than .0001) and were not current smokers ($P = .009$). They had shorter disease duration ($P = .019$), lower mSASSS ($P = .021$), lower baseline ASDAS ($P = .006$), and minimal evidence of spinal fat metaplasia (FASSS less than 5; $P = .043$). They also had post-treatment scores indicating remission of MRI inflammation (SPARCC spine score less than 3 and SIJ less than 2; $P = .033$), and normalized CRP ($P = .002$).

In multivariate analyses, age, smoking status, baseline ASDAS, and normalized CRP were the strongest clinical predictors of sustained remission, Dr. Maksymowych said. MRI parameters were not statistically significant, although the sample size was small.

Smoking "is related to more severe disease in ways we don't yet understand," Dr. Maksymowych said. It could relate to smokers being less tolerant of anti-inflammatory drugs and/or their being less likely to exercise and maintain a healthy lifestyle.

"The implication for clinicians is if you have an AS patient who is a smoker on anti-TNF therapy, that patient needs to be counseled in a variety of ways," he said, including about smoking cessation, healthy eating, and weight management. "It's sort of a red warning flag that this patient is less likely to respond, and it needs to be addressed very early in the treatment course, using all available resources to maximize responses to biological therapy."

Dr. Maksymowych has served as a consultant for AbbVie, Amgen, Eli Lilly, Janssen, Merck, Pfizer, and UCB. ■

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