Welcome to the EULAR 2016 Report!

The Annual European Congress of Rheumatology 2016, 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. Close to 14,000 attendees from nearly 120 countries came to this year’s EULAR Congress in London to hear the best in rheumatology research and clinical advances. The scientific program also included presentations carefully selected from more than 4,100 abstracts submitted.

The EULAR 2016 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 and other health professionals 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 14-17 June in Madrid for EULAR 2017!

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EULAR recommendations on DMARD use in RA made ‘more concise’

BY SARA FREEMAN

The European League Against Rheumatism recommendations on the use of disease-modifying antirheumatic drugs for the treatment of rheumatoid arthritis have been updated in line with current evidence and made more concise.

Dr. Josef S. Smolen of the department of rheumatology at the Medical University of Vienna (Austria), who presented the 2016 guidelines at the congress, noted that they now consist of 12 rather than the 14 recommendations that were included in the 2013 update (Ann Rheum Dis. 2014;73:492-509) and the 15 recommendations that were in the original 2010 version.

These 12 recommendations cover treatment targets and general approaches in the management of rheumatoid arthritis that incorporate disease-modifying antirheumatic drugs (DMARDs) and the use of glucocorticoids, and present treatment options as a hierarchy to help guide clinicians through appropriate procedures when initial and subsequent treatment fails. All DMARDs are considered in the recommendations, from the long-standing conventional synthetic (cs)DMARDs, such as methotrexate, sulfasalazine, and leflunomide, and the newer biologic DMARDs, such as the anti–tumor necrosis factor (TNF)–targeting drugs, to the newer biosimilar DMARDs, and targeted synthetic (ts) DMARDs, such as the Janus kinase (JAK) inhibitors tofacitinib and baricitinib.

The recommendations have been developed in accordance with EULAR’s standard operating procedure for the development of recommendations, Dr. Smolen observed, and involved three systematic literature reviews and expert opinion garnered from a task force of 50 experts and patients.

“This was the largest task force I have ever convened,” Dr. Smolen said, noting that rheumatologists from outside Europe had been invited to contribute their expertise and knowledge for the first time. Altogether 42 rheumatologists, three clinical fellows, two health professionals, and three patients were involved in revising the recommendations.

There are now four rather than three overarching principles, two of which are shared with early inflammatory arthritis recommendations that were also presented at the congress. The first two principles state that shared decision making is key to optimizing care and that rheumatologists should be the primary specialists looking after patients. The third principle recognizes the high burden that RA can have not only on an individual level but also on health care systems and society in general, which rheumatologists should be aware of. The fourth and final principle states that treatment decisions should be based on patients’ disease activity but that other factors, such as patients’ age, risk for progression, coexisting disease, and likely tolerance of treatment should also be kept in mind.

In an interview, Dr. Smolen highlighted that the EULAR recommendations cover three main phases of DMARD treatment: First is the DMARD-naive group of patients, who may be at an early or late stage of their disease. Second is the group in whom initial treatment has failed, and third is the group for whom subsequent treatment has not worked.

“In all these phases, we have some changes,” Dr. Smolen said. As an example, he noted that in the DMARD-naive setting, the use of csDMARDs has always been recommended but that the prior advice to consider combination csDMARD treatment has been edited out.

“We now say methotrexate should be part of the first treatment strategy, and the treatment strategy encompasses the use of additional, at least conventional synthetic, DMARDs.”

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Glucocorticoids are also more strongly recommended as part of the initial treatment strategy in combination with methotrexate, he said, although there is the proviso to use these for as short a time as possible.

In situations where patients do not respond to methotrexate plus glucocorticoids or they cannot tolerate methotrexate, then the recommendations advise stratifying patients into two groups. Those with poor prognostic factors might be switched to a biologic therapy, such as an anti-TNF agent or a tsDMARD. In regard to the latter, there is now more evidence behind the use of JAK inhibitors, notably tofacitinib, Dr. Smolen observed. Biologic DMARDs should be combined with csDMARDs, but if the latter is not tolerated then there is the option to use an IL-6 pathway inhibitor.

“There is now compelling evidence that all biologic DMARDs, including tocilizumab, convey better clinical, functional, and structural outcomes in combination with conventional synthetic DMARDs, especially methotrexate,” Dr. Smolen observed during his presentation of the recommendations. This may not be the case for the JAK inhibitors based on the current evidence.

When asked how the EULAR recommendations match up to those issued earlier this year by the American College of Rheumatology (Arthritis Care Res. 2016;68:1-25), Dr. Smolen observed that the two had become “much closer.” There remain differences in recommendations on glucocorticoid use, which are “somewhat clearer” in the European than in the American guidelines, and EULAR proposes combining biologic DMARDs with csDMARDs rather than using them as monotherapy. The EULAR recommendations also do not distinguish patients by disease duration but by treatment phase, and use prognostic factors for stratification.

The recommendations are currently in draft format and once finalized they will be published in Annals of the Rheumatic Diseases and also made freely available via the EULAR website, joining the organization’s many other recommendations for the management of rheumatic diseases. Dr. Smolen noted that these are intended as a template to provide national societies, health systems, and regulatory bodies a guide to the best evidence-based use of DMARDS in RA throughout Europe.

Dr. Smolen has received grant support and/or honoraria for consultations and/or for presentations from: AbbVie, Amgen, AstraZeneca, Astro-Pharma, Bristol-Myers Squibb, Celgene, GlaxoSmithKline, ILTOO Pharma, Janssen, Merck Serono, Merck Sharp & Dohme, Novartis-Sandoz, Pfizer, Roche-Chugai, Samsung, and UCB.

### Early identification, treatment still key to early arthritis recommendations

**BY SARA FREEMAN**

Prompt referral to a rheumatologist and early initiation of treatment remain 2 of the 12 key recommendations in the updated EULAR recommendations for early arthritis.

There are now three specific recommendations dealing with referral and diagnosis; four that cover initial drug treatment with disease-modifying antirheumatic drugs (DMARDs), nonsteroidal anti-inflammatory drugs (NSAIDs), and glucocorticoids; two that cover management strategy and monitoring; and three that cover nonpharmacologic interventions, prevention, and patient information and education.

Although many of the recommendations have not radically changed, there have been revisions to the wording. In line with other EULAR recommendations for the management of rheumatic disease, the updated early arthritis recommendations also now contain three overarching principles. The first states that the management of early arthritis should aim to achieve the best possible care and emphasizes the need for shared decision making between rheumatologist and patient. The second states that a rheumatologist should be the main specialist looking after a patient with early arthritis, and the third states that a definitive diagnosis should be made only after a careful medical history and clinical examination have been undertaken.

The EULAR “recommendations deal especially with early-stage inflammatory arthritis,” said Dr. Bernard Combe of Hôpital Lapeyronie in Montpellier, France, who was the convener of the task force behind the updated recommendations. As such, they are universal for all rheumatologic arthritis conditions when diagnosed early, before they differentiate into more specifics, he said in an interview. That includes progression from early inflammatory arthritis to rheumatoid arthritis, psoriatic arthritis, and spondyloarthritis.

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**About Samsung Bioepis**

Samsung Bioepis is actively devoted to developing affordable and high-quality biopharmaceutical and biosimilar products. We strive to become the next global leader in advancing healthcare and people’s wellbeing.

**BIOSIMILARs: Your questions answered**

*Addressing key questions regarding biosimilars and their impact on the management of Rheumatoid Arthritis*

**AGENDA**

*Chairperson: Paul Emery*

- **08.15–08.25** Paul Emery (United Kingdom)
  What do you think about biosimilars?

- **08.25–08.40** Brian Min (Republic of Korea)
  How does Samsung Bioepis rapidly develop and manufacture high-quality biosimilars?

- **08.40–08.55** Michael Rawlins (United Kingdom)
  How are biosimilars regulated and monitored?

- **08.55–09.15** Thomas Dörner (Germany)
  How can clinicians interpret biosimilar studies?

- **09.15–09.35** Paul Emery (United Kingdom)
  What if biologics were readily available?

- **09.35–09.45** Paul Emery (United Kingdom)
  Questions & Answers
Dr. Combe, who is also professor of rheumatology at Montpellier University and head of the bone and joint diseases department at Montpellier University Hospital, presented the updated EULAR recommendations at the congress.

He noted that the recommendations were first written almost 10 years ago (Ann Rheum Dis. 2007 Jan;66[1]:34-45) and so were in need of an update. A task force of 20 rheumatologists, two patients, and one healthcare professional representing 12 European countries was involved in the update that adhered to EULAR standard operating procedure of developing recommendations.

Although EULAR had published recommendations on the management of arthritis in the intervening years, he said, this had focused more on management, and the aim of the early arthritis recommendations was to cover the “entire spectrum of the management of early inflammatory arthritis.”

The updated recommendations start and end with patient-centered statements, he observed. The first notes that patients with any joint swelling associated with pain or stiffness should be referred to and seen by a rheumatologist within 6 weeks of the onset of symptoms. The final recommendation deals with patient information and education about the disease, and programs aiming to help patients cope with pain, disability, and ensure their continued ability to work and participate in their usual social activities.

The concept of early identification and treatment is not new, Dr. Combe observed, but there is so much more evidence in support of initiating DMARD therapy within the first 3 months of referral, even if patients do not fulfill classification criteria for a specific inflammatory rheumatic disease.

In terms of diagnosis, the recommendations now hinge on performing a thorough clinical examination and using ultrasonography to confirm the presence of arthritis if needed. MRI is no longer recommended in this initial diagnostic work-up because of the cost and often lack of widespread access in all European countries, Dr. Combe said. MRI might be considered later, however, if a diagnosis cannot be reached. Assessment of the number of swollen joints, acute phase reactants, and antibody tests (rheumatoid factor and anticitrullinated protein antibody) also might be of use at this point.

Among the various DMARDs, methotrexate is recommended as the “anchor drug”; it should be used as part of the first treatment strategy in patients who are at risk of persistent disease, unless it is contraindicated. The goal of treatment with DMARDs is to achieve clinical remission. Regular monitoring of disease activity, side effects, and comorbidities should be performed alongside their use. Regular monitoring of all pharmacologic therapy should include assessment of tender and swollen joint counts, global health assessments by the patient and the physician, and acute phase reactants.

As for NSAIDs, they are recommended for symptomatic relief, but “at the minimum effective dose for the shortest time possible.” The risks for gastrointestinal, renal, and cardiovascular complications should be carefully weighed against the likely benefits. Glucocorticoids also are recommended for reducing pain and swelling and structural progression, but again these need to be used at the lowest possible dose and for no more than 6 months to avoid potential long-term side effects.

A recommendation on nonpharmacologic interventions also is included, which states that physical exercise and occupational therapy should be considered as adjunctive therapy.

In addition, the task force came up with a list of 10 research questions that need to be answered, which include items on risk prediction, optimal treatment combinations, and dosing regimens.

As with other EULAR recommendations, a flow chart is included that summarizes the recommendations to help guide physicians on when and how to treat, when to adapt dosing or change medication, and other treatments and approaches to consider.

There is a new recommendation on prevention highlighting the importance of smoking cessation, dental care, weight control, vaccination, and managing comorbidities.

Once the recommendations have been finalized, they will be published in the EULAR journal, Annals of the Rheumatic Diseases.

Dr. Combe has received research grants and honoraria from Pfizer, Roche-Chugai, and UCB, and honoraria from Bristol-Myers Squibb, Janssen, Eli Lilly, Merck Sharpe & Dohme, and Novartis.
THE EVOLVING LANDSCAPE OF RHEUMATOLOGY:
BIOSIMILARITY & EXTRAPOLATION

SATELLITE SYMPOSIUM PRESENTED ON THURSDAY 9 JUNE 2016

Chair: Peter Taylor

Welcome and introductions
Peter Taylor (University of Oxford, Oxford, UK)

Laying the foundation: analytical and functional characterisation of protein products and the demonstration of molecular similarity
Emily Shacter (ThinkFDA, Maryland, US)

Building the totality-of-the-evidence: confirming biosimilarity and supporting extrapolation
Craig Leonardi (Central Dermatology, St. Louis, Missouri, US)

Impacting the clinical landscape: the role of biosimilar therapies in rheumatology
Peter Taylor

Panel discussion and summary
Led by Peter Taylor, joined by all
People with rheumatoid arthritis are more likely to receive an early diagnosis and treatment when healthcare professionals across all settings work together, including general practitioners, rheumatologists, physiotherapists, and patients.

Although progress has been made in identifying and treating people with inflammatory arthritis earlier, there is room for improvement across all aspects of the jigsaw puzzle of musculoskeletal care, delegates learned in a session at the congress that introduced EULAR’s “Time Is Joint” initiative to identify and treat rheumatic and musculoskeletal diseases as early as possible.

Prof. Annette van der Helm-van Mil, a rheumatologist at Leiden University Medical Centre in the Netherlands, said that barriers to diagnosis and treatment exist at different levels of patient care. In many countries, patients need to seek medical attention through their general practitioner, who then has to refer them.

This is difficult, however, as general practitioners see many people with a wide range of musculoskeletal symptoms, Prof. van der Helm-van Mil said. She addressed the logistical issues involved in gaining early access to rheumatologic care, as well as the evidence around the benefits of early treatment and how to identify patients with arthralgia who are at high risk of rheumatoid arthritis (RA).

Prof. Christian Mallen, the National Institute for Health Research Professor of General Practice Research at Keele University (United Kingdom), agreed that it is sometimes hard for busy general practitioners to distinguish people with potentially serious pathology, particularly if they do not present with classical symptoms.

He said the absence of diagnostic tests that are useful in community settings adds to the challenge.

“With GPs under increasing pressure not to refer, we need help from our consultant colleagues to help us know who to refer and when,” Prof. Mallen said in an interview. “While some areas have superb ‘fast track’ pathways, these are not the norm and as such we need appropriate care pathways to support and promote diagnosis.

“Being critical of GPs is commonplace but not productive … We need to work together to improve care and support earlier diagnosis,” he said.

According to Prof. Mallen, most examples of successful rapid-access clinics that had improved time to diagnosis always seem to have one thing in common: “A high-quality educational program underpinned by strong relationships between primary and secondary care.”

Working together is a sentiment that physiotherapist Paul Kirwan agrees with. “Whether you are a rheumatologist, orthopedic surgeon, GP, physiotherapist, nurse, or any other allied health professional dealing with patients with joint pain, it is important we all try to identify these patients as early as possible to minimize joint damage and get the optimal treatment for these patients,” he said in an interview.

According to Mr. Kirwan of Connolly Hospital, Dublin, Ireland, physiotherapists are well placed to identify patients with inflammatory arthritis as they are often the first point of contact for patients complaining of joint pain. They also see patients who, over a course of visits, may have presented initially with a single painful joint or tendon that has evolved into multiple joints.

“It is of utmost importance [that physiotherapists be] able to recognize joint pain that is non-mechanical,” he stressed, because “physiotherapists need to arrange for these patients to be assessed promptly by rheumatology.”

Mr. Kirwan took delegates through some simple strategies and clinical tools that physiotherapists can use in their clinical assessment.

The role of the patient also is important in fostering rapid diagnosis, and this could be achieved by raising public awareness around the signs and symptoms of RA and the importance
of early diagnosis, according to Ailsa Bosworth, chief executive and founder of the National Rheumatoid Arthritis Society in the United Kingdom.

This is, however, easier said than done when there are no signs of government funding. “We do what we can … but we do not have the funds to run TV adverts as the government has done, for example, to raise awareness of stroke,” she said in an interview.

Early arthritis clinics (EACs) are also instrumental in ensuring patients are seen earlier because evidence shows they prioritize patients more effectively. “We wish to encourage all rheumatology units where an EAC does not exist, to set one up. … It is possible to do this without a lot of extra funding,” said Ms. Bosworth, who also took delegates through the impact that RA has on people’s lives, with particular reference to the prevalence of depression and anxiety in early RA.

Updated axial SpA recommendations include IL-17 inhibitors

BY MITCHEL L. ZOLER

The option of treating axial spondyloarthritis with an interleukin-17 inhibitor has become an officially recommended option for the first time in a new update to management recommendations for this disease released by a task force assembled jointly by EU-LAR and the Assessment of SpondyloArthritis International Society.

The update replaces recommendations last released by the two groups for managing patients with ankylosing spondylitis in 2010 (Ann Rheum Dis. 2011 June;70[6]:896-904), as well as the prior recommendations from the two organizations for using tumor necrosis factor (TNF) inhibitors on these patients (Ann Rheum Dis. 2011 June;70[6]:905-8).

The new update also broadens the disease spectrum from ankylosing spondylitis to axial spondyloarthritis (SpA).

The latest recommendations continue to place nonsteroidal anti-inflammatory drugs (NSAIDs) as first-line pharmacotherapy for patients with axial SpA to control pain and stiffness, and they continue to place treatment with a biologic disease-modifying anti-rheumatic drug (DMARD) – identified in the recommendations as most typically a TNF inhibitor by current practice – as second-line treatment after NSAIDs.

The recommendations specify that initiation of a biological DMARD should target patients who have both failed treatment with at least two different NSAIDs over the course of at least 4 weeks of treatment and who have active disease documented by either of two standard measures of disease activity in patients with axial SpA: either a score of at least 2.1 on the ankylosing spondylitis disease activity score (ASDAS) or a score of at least 4 on the Bath ankylosing spondylitis disease activity index (BASDAI).

Incorporation of the ASDAS as a potential alternative to the BASDAI for assessing disease activity in these patients is another new feature of these recommendations, noted Dr. Désirée van der Heijde, convenor of the update task force, who presented the new recommendations at the congress.

The new recommendations place use of an interleukin (IL)-17 inhibitor as a third-line management option, for patients who fail to adequately respond to a first TNF inhibitor, and they also say that an alternative to starting an IL-17 inhibitor at this stage of management is to instead try treatment with a second type of TNF inhibitor. The IL-17 inhibitor class includes secukinumab, which received approval from the Food and Drug Administration for treating active ankylosing spondylitis in January 2016 and which also has approval for the same indication from the European Medicines Agency.

The updated recommendations leave unchanged from the prior version advice to use biological DMARDs only after failure of other treatments, as well as advocacy of nondrug therapy with regular exercise, smoking cessation, and physical therapy when appropriate as the very first therapeutic step to take, before even starting an NSAID regimen. For patients with axial SpA who have peripheral arthritis, the recommendations say that clinicians can consider treatment with a local injection of a glucocorticoid and...
a treatment course with sulfasalazine. The recommendations do not endorse treatment with a conventional, synthetic DMARD for patients with purely axial disease, and they also recommend against long-term treatment with a systemic corticosteroid. The update calls analgesics contraindicated.

Another new feature of the updated recommendations is endorsement of treating axial SpA patients to a predefined treatment target, although the recommendations left the nature of that target undefined and something for the treating clinician to discuss and tailor to each patient individually, said Dr. van der Heijde, professor of rheumatology at Leiden (the Netherlands) University Medical Center. The update also introduces for the first time the recommendation to consider tapering down treatment with a biological DMARD for patients who achieve remission.

Dr. van der Heijde said that she has been a consultant to 17 drug companies.

IT’S IMPORTANT TO have updated treatment recommendations as we accrue new evidence and treatment options. These recommendations can now address interleukin-17 inhibitors, which were not available for U.S. use to treat ankylosing spondylitis when the American College of Rheumatology and its collaborating organizations released updated recommendations for treating ankylosing spondylitis and nonradiographic axial spondyloarthritis in September 2015 (Arthritis Rheum. 2016 Feb;68[2]:282-98). Having interleukin (IL)-17 inhibitors now available and joining tumor necrosis factor (TNF) inhibitors as a second class of biological drugs to treat these patients is a big step forward.

I do not believe strong evidence exists to make IL-17 inhibitors second-line agents behind TNF inhibitors as was done in the new European recommendations. That was an expert-opinion based decision rather than something based on clear evidence.

Another notable feature of the updated European recommendations is that they anchor several treatment decisions to measuring a patient’s disease activity and comparing the level of activity against defined thresholds. This is very different from the approach generally used in U.S. practice, where it is not required for patients to have a certain level of quantifiable disease activity to either initiate or stop treatment.

The European recommendations also call specifically for considering tapering down a biological drug once a patient achieves remission of active disease. In my experience, when a patient achieves remission it is more often the nonsteroidal anti-inflammatory drug that rheumatologists prefer to taper because they attribute the patient’s good response primarily to his/her biological treatment. And the evidence is good that, when a patient with ankylosing spondylitis stops treatment with a TNF inhibitor, his/her disease tends to reactivate.

During the near future, we can expect an increased focus on diagnosing patients with axial spondyloarthritis and ankylosing spondylitis earlier and starting treatment earlier. I expect that this could lead to improved patient outcomes. I also expect that we will soon see more evidence regarding the effect of drug treatment on extra-articular manifestations of these diseases, and that this evidence will help dictate the specific treatments we choose for each patient. In the future, we will administer more personalized management for these disorders that is better tailored to each individual patient.

Dr. Lianne S. Gensler is a rheumatologist and director of the ankylosing spondylitis clinic at the University of California, San Francisco. She has been a consultant to or has received research support from AbbVie, Amgen, Janssen, Novartis, and UCB. She made these comments in an interview.
The new EULAR recommendations for fibromyalgia incorporate a decade’s worth of new evidence collected since the last edition appeared in 2008.

Although the 2016 recommendations do not reflect a novel understanding of the pathophysiology of fibromyalgia or a radically different approach to managing the disease, compared with those published in 2008, they differ vastly in the level and quality of supporting evidence behind them, said Dr. Gary J. Macfarlane, convener of the fibromyalgia recommendations panel and clinical professor of epidemiology at the University of Aberdeen (United Kingdom).

Dr. Macfarlane said that the past decade has seen “an explosion of evidence from randomized trials” around the management of fibromyalgia. “I think this will be one of the first EULAR guidelines in which all the recommendations are going to be based on systematic reviews or meta-analysis” – 107 altogether, he said in an interview.

Fibromyalgia – a heterogeneous pain condition that involves abnormal pain processing and can affect sleep, function, and quality of life – can be complex to diagnose and treat. Pain is a signature feature of fibromyalgia, but it is not the only treatment target: sleep, ability to function, and quality of life all are important, Dr. Macfarlane said.

The guidelines emphasize that optimal management of fibromyalgia requires not just a prompt diagnosis but “a comprehensive assessment of the patient’s ability to function and about the psychosocial context in which symptoms occur,” he said.

Patient education, including written information, is key and is the first step in management. Initial management should focus on nonpharmacologic interventions, specifically exercise. In patients for whom educational materials alone are insufficient to provide benefit, the next step is enrollment of the patient into a physical therapy program that involves an individualized program of graded physical exercise. Other nonpharmacologic interventions that can be introduced at this stage include hydrotherapy and acupuncture.

If there is insufficient response to these first two intervention steps, the next phase should start with a second round of patient assessment to develop an individualized intervention program. This involves characterizing the dominant features of the patient’s complaints into one of the three main categories: pain-related depression and anxiety, or behavior indicating abnormal coping strategies; severe pain, sleep disturbance, or both; or severe disability or sick leave, Dr. Macfarlane said at the congress.

For patients in the first subgroup – pain-related depression and anxiety, or behavior indicating abnormal coping strategies – the intervention should consist of psychological therapies, primarily cognitive-behavioral therapy (CBT). For patients with more severe depression or anxiety, psychopharmacologic treatment is also an option.

For patients in the second subgroup – those with severe pain, sleep disturbance, or both – the main intervention is pharmacotherapy. For severe pain, this can involve duloxetine, pregabalin, or tramadol either alone or in combination with paracetamol (acetaminophen). For sleep disturbance, recommended drug interventions are low-dose amitriptyline, cyclobenzaprine, or pregabalin administered at bedtime.

For patients in the third subgroup – with severe disability or sick leave – the recommended intervention is a multimodal rehabilitation program.

“We made the decision to consider all therapies whether they were licensed in Europe or not,” Dr. Gary J. Macfarlane said. Continued on following page
have been proposed in the past, but which his working group refrained from recommending because of either lack of demonstrated effectiveness or the poor quality of the studies that appeared to document efficacy. These nonrecommended interventions are biofeedback, capsaicin, hypnotherapy, massage, S-adenosyl methionine or SAMe, and other complementary and alternative therapies.

Dr. Macfarlane noted that, despite a decade’s worth of findings, many questions still hover over the ideal management of fibromyalgia. Although the guidelines strongly promote exercise, “we still don’t have enough information about what specific type of exercise would be most beneficial.”

And while studies show overwhelmingly that CBT is effective, the size of the benefit is modest. Dr. Macfarlane said that it will be important to learn whether combined pharmacologic and nonpharmacologic approaches might be more effective from the get-go for certain patients – in contrast to the stepped approach outlined in the guidelines – and whether there is a way to identify patients for whom such interventions as CBT are most likely to be effective.

Another question still unanswered is whether fibromyalgia should remain primarily the domain of rheumatologists. While this was not a question addressed in the guidelines, the writing committee involved not only rheumatologists but also specialists in pain, internal medicine, occupational health, and nursing – underscoring the multidisciplinary direction that fibromyalgia treatment is taking.

“I think rheumatologists have an important role to play because pain is a dominant feature and because fibromyalgia is often comorbid with inflammatory rheumatic conditions,” Dr. Macfarlane said. “But I think we should be looking at other models of care for these patients as well.”

Because patients are referred in and out of various specialties, “there is no one really looking at the overall management, thinking about them holistically,” he said. “There’s a need for us to organize health care services better, so when we have a patient with fibromyalgia-like symptoms, we manage their journey through the system effectively instead of ping-ponging them around.”

Dr. Macfarlane has given lectures on behalf of Janssen and has received research support from Pfizer.

Updated Behçet’s disease recommendations expand biologic treatment

BY MITCHEL L. ZOLER

EULAR task force issued the first update to recommendations for managing Behçet’s disease since 2008, with revised recommendations that reflect expanded use of biologic agents, and increased evidence to guide management of gastrointestinal involvement, use of anticoagulants in patients with venous involvement, and use of surgical and interventional treatments, Dr. Gülen Hatemi said while presenting the update at the European Congress of Rheumatology.

The task force, which included more than 20 members, identified 304 articles to apply to the update, and produced five overarching principal and 18 specific recommendations divided among six categories of clinical manifestations of Behçet’s disease, said Dr. Hatemi, convener of the task force and a rheumatologist at Istanbul University in Turkey.

For mucocutaneous involvement, the update included five items that all received a “strong” recommendation from the task force: For an oral or genital ulcer, use a topical agent, such as a local steroid. Try colchicine first to prevent recurrent mucocutaneous lesions, especially when the dominant lesion is erythema nodosum or a genital ulcer. Treat papulopustular or acnelike lesions with topical or systemic agents, as when treating acne vulgaris. Coordinate treatment of leg ulcers, which can be caused by venous stasis or obliterative vasculitis, with a dermatologist and vascular surgeon. And azathioprine, thalidomide, interferon-alpha, a tumor necrosis factor (TNF)-alpha antagonist, or apremilast may be necessary for selected patients.

The task force issued two strong recommendations for managing eye involvement along with one conditional recommendation. The first strong recommendation was that managing uveitis requires close collaboration with an ophthalmologist, with the goal of inducing and maintaining remission. Patients with an inflammatory eye disease affecting the posterior segment should receive treatment with azathioprine, cyclosporine, interferon-alpha, or a monoclonal TNF-alpha antagonist. Treatment with a systemic corticosteroid should occur only when combined with azathioprine or another systemic immunosuppressant.

The second strong recommendation was that patients who present with an initial or recurrent acute episode of sight-threatening uveitis should receive treatment with a high-dose glucocor-
ticoid, infliximab, or interferon-alpha. Intravitreal injection with a glucocorticoid as an adjunct to systemic therapy is an option for patients with a unilateral exacerbation. The conditional recommendation was for patients with isolated anterior uveitis. When these patients have markers of a poor prognosis—such as young age, male sex, or early disease onset—systemic treatment with an immunosuppressant is a possible option.

The panel issued three strong recommendations along with one conditional recommendation for managing vascular involvement. One of the strong recommendations called for treating acute deep vein thrombosis with a glucocorticoid as well as an immunosuppressant such as azathioprine, cyclophosphamide, or cyclosporine. A conditional recommendation said patients with refractory venous thrombosis could be considered for treatment with a monoclonal TNF-alpha antagonist, along with an anticoagulant if the patient’s risk for bleeding was generally low and a coexistent pulmonary artery aneurysm was ruled out.

Management of arterial aneurysms received the other two strong recommendations. The panel recommended high-dose glucocorticoid plus cyclophosphamide for a pulmonary artery aneurysm, followed by a monoclonal TNF-alpha antagonist for refractory cases. Patients with these aneurysms who are at high risk for major bleeding should undergo embolization in preference to open surgery. When patients have aortic or peripheral artery aneurysms, treatment should start with cyclophosphamide and a corticosteroid before an aneurysm repair is attempted. But surgery or stenting of the aneurysm should not be delayed when patients are symptomatic.

Gastrointestinal involvement received one strong and two conditional recommendations. The panel strongly recommended confirming gastrointestinal involvement using endoscopy, imaging, or both, while also ruling out treatment with a nonsteroidal anti-inflammatory drug, inflammatory bowel disease, or an infection such as tuberculosis as the cause of gastrointestinal symptoms.

One of the conditional recommendations called for an urgent surgical consult when patients have perforation, major bleeding, or obstruction. The second conditional recommendation called for considering glucocorticoid treatment to treat an acute exacerbation of gastrointestinal involvement. Additional treatment options to pair with a glucocorticoid include a disease-modifying drug such as 5-aminosalicylic acid or azathioprine. For patients with severe or refractory gastrointestinal symptoms or both, a monoclonal TNF-alpha antagonist or thalidomide is another potential option.

The panel issued two strong recommendations for managing nervous system involvement. The top treatment option for parenchymal involvement is a high-dose glucocorticoid followed by slow tapering while also treating with an immunosuppressant such as azathioprine. Treatment with cyclosporine should be avoided, the panel said. Treatment with a monoclonal TNF-alpha antagonist is an option to consider as first-line treatment for patients with severe nervous system involvement or for those with refractory disease. The second strong recommendation was to treat a cerebral venous thrombus with a high-dose glucocorticoid followed by tapering, with short-term anticoagulant treatment as an option. Patients also need screening for the presence of vascular disease at an extracranial location.

The panel’s final recommendation was a strong endorsement of colchicine as first-line treatment for arthritis in Behçet’s patients, although patients with acute monoarticular disease can be managed with an intra-articular injection of a glucocorticoid. For patients with recurrent or chronic arthritis, treatment options include azathioprine, interferon-alpha, or a TNF-alpha antagonist.

Dr. Hatemi has received research support from, received honoraria from, or has been a speaker for AbbVie, Celgene, Merck Sharp & Dohme, and Pfizer.
New fragility fracture recommendations emphasize coordination of care

BY SARA FREEMAN

EULAR and the European Federation of National Associations of Orthopaedics and Traumatology have joined forces to develop recommendations for the prevention and management of fragility fractures.

Such fractures are common in men and women over the age of 50 years and can lead to repeat fracture in some patients. The recommendations are unique as they are the first to consider both acute orthopedic and postfracture rheumatologic care, said Dr. Willem F. Lems of the Amsterdam Rheumatology and Immunology Centre.

At the congress, Dr. Lems provided an overview of the draft recommendations, noting that there would be several overarching principles, one of which recognized the multidisciplinary nature of caring for someone with a fragility fracture. An important point is not who is taking care of the patient, but that the patient is given the best possible care within the multidisciplinary framework.

What constitutes optimal care of course depends on the clinical situation, notably the type of fracture and the age of the patient, and optimal care in all phases of presentation (pre-, peri-, and postoperative) can have an important effect on a patient’s outcome. The prevention of subsequent fractures is a key focus, with the recommendation that all patients should be investigated systematically and those deemed at high risk for another fracture should be prescribed both pharmacologic and nonpharmacologic interventions as appropriate. Patient education is also considered important.

As for all EULAR-developed recommendations, standard procedures were followed that involved convening an expert scientific advisory committee and using the Delphi technique to come up with the most important research questions that would be used to formulate the final 10 recommendations. Four of the recommendations cover the acute care setting and six provide advice on postfracture care.

The first of the acute care recommendations looks at pre- and perioperative management of a fragility fracture and highlights that, within 24-48 hours of admission, patients should receive adequate pain and fluid management and treatment, including early surgery if appropriate. This is based on evidence that better outcomes can be achieved in terms of both morbidity and mortality if patients can be seen and managed quickly.

Another of the acute care recommendations focuses on orthogeriatric care, noting that the orthopedic surgeon and a dedicated orthogeriatric team should work together, particularly for elderly patients who have suffered a hip fracture. Key elements here are the management of and prevention of delirium, deep vein thrombosis, pressure sores, and malnutrition.

As for actual fracture treatment, a balanced approach is advised when deciding upon a surgical or nonsurgical approach, especially because this is likely to be an older population with other comorbidities. Only one in three vertebral fractures are symptomatic and only about 10% of patients will be hospitalized for pain. Analgesics, modifying activities, and bracing can be options here. Surgical options for distal radial fracture, hip fracture, and trochanteric and femoral neck fractures are included.

The fourth recommendation looks at the organization of postfracture care and the need for a systematic approach to identify those who may be at risk for subsequent fractures, starting with the suggestion that any patient older than 50 years with a recent fracture
should be assessed. The fifth recommendation addresses ways to evaluate this risk, such as looking at the clinical risk factors, performing bone scans and imaging, and screening for underlying osteoporosis or metabolic disorders.

Implementation is the next step, and the sixth recommendation suggests ways these recommendations could be integrated into routine practice. Often one of the biggest barriers to effective postfracture care is the lack of patient, and sometimes clinician, awareness of the risk for a subsequent fracture. This recommendation looks at the role of a possible local fracture liaison service or facilitator to coordinate between the various members of the multidisciplinary team from secondary (orthopedic surgeons, rheumatologists, endocrinologists, and geriatricians) to primary care.

The seventh recommendation addresses rehabilitation and the need to initiate physical training and muscle strengthening as early as possible after the initial fracture, with long-term continuation of balance training and fall prevention.

The final three recommendations focus on how to educate patients about their risk factors, need for follow-up, and the duration of any pharmacologic or nonpharmacologic therapy that they may need. Nonpharmacologic options might include stopping smoking, limiting alcohol intake, as well as taking supplements such as calcium or vitamin D. There will be specific guidance on the use of calcium and vitamin D, which have both pros and cons, but the optimal dosage appears to be 1,000–1,200 mg/day for calcium and 800 IU/day for vitamin D.

Pharmacologic options to prevent subsequent fragility fractures include the bisphosphonates alendronate, rise-dronate, and zoledronic acid, and also the monoclonal antibody denosumab. These are the only drugs that have been shown to reduced the risk for vertebral, nonvertebral, and hip fractures in primary analyses. Adherence, tolerance, and regular monitoring are key, and a five-step plan is suggested to aid clinical decision making that covers case finding, risk evaluation, differential diagnosis, treatment, and follow-up.

The recommendations are being finalized and should be available for publication later this year. The recommendations task force also plans to propose a research agenda.

Dr. Lems had no relevant disclosures.

Continued on following page
A framework for building individualized care

THE PRIOR 2009 EULAR recommendations were very much in need of updating given the plethora of studies in the past 7 years addressing ANCA-associated vasculitis (AAV). The emergence of rituximab as an effective therapy in AAV had to be considered and included in these newer guidelines. Its potential role in both remission induction, as well as remission maintenance of AAV, is addressed.

The recommendations are somewhat complicated, particularly as eosinophilic granulomatosis with polyangiitis (EGPA, previously referred to as Churg-Strauss syndrome) has been included, but most of the well-done prospective clinical trials addressing remission induction and remission maintenance in AAV were limited to patients with granulomatosis with polyangiitis or microscopic polyangiitis and did not include patients with EGPA. The role of plasma exchange is also discussed, but the results of the PEXIVAS trial, which will address that more definitively, are not yet forthcoming. Those results are anticipated in the not too distant future and will much better define that component of management in those most severely ill patients with AAV. These recommendations serve as a framework for helping clinicians understand what is widely accepted as standard of care for these diseases but in no way can define individual treatment decisions, as the authors acknowledge. Such decisions must become very personalized in relation to details of the patient’s individual comorbidities and other features of their medical and even socioeconomic status. For example, when choosing between rituximab and cyclophosphamide for remission induction in a young woman (or man, for that matter), future fertility concerns (which cyclophosphamide could potentially compromise) are very relevant. Moreover, the costs of rituximab are substantial, and the lack of superiority of rituximab over cyclophosphamide in many situations, particularly in patients with new severe disease, could be an important factor to consider when choosing which immunosuppressive will be used.

Many of the unanswered questions await results of ongoing or upcoming trials, including some addressing the relative efficacy of various remission maintenance regimens (rituximab vs. azathioprine) or the role of plasmapheresis. Many questions in AAV are not easily addressable in clinical trials, such as whether there are some groups of patients in whom remission maintenance therapy should never be withdrawn. However, such questions may be addressed through observational studies of the well-defined patient cohorts and registries that have been developed in the United States and Europe.

Dr. Robert F. Spiera is director of the Scleroderma, Vasculitis, & Myositis Center at the Hospital for Special Surgery, N.Y. He is also professor of clinical medicine at Cornell University, N.Y. He has received research funding and consulting fees from Roche/Genentech, which markets rituximab.

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The recommendations now contain one single, simple overarching principle, Dr. Mukhtyar said at the congress. That is, the need for shared decision making between the patient and the clinician. This principle is also included as the first point in many of the other recently updated EULAR recommendations on the management of rheumatic diseases.

Both previous and updated versions of the vasculitis recommendations contain 15 recommendations, with some changed and others combined. One key recommendation is about who should treat patients with AAV; it states that patients “should be managed in close collaboration with, or at, centers of expertise,” Dr. Mukhtyar said.

“Patients with ANCA-associated vasculitis have often very complex presentations that involve several different specialties, and it is always worthwhile that these patients are looked after by people who commonly see them, because these are rare conditions,” he observed.

Deciding when to perform a biopsy is also covered, with the recommendation being that it can be used to establish a new diagnosis and to further evaluate cases of suspected relapsing vasculitis. “When do you do a biopsy?” Dr. Mukhtyar asked. “Well, every time you can; every time it is clinically feasible,” he suggested.

As for treatment, there are different recommendations depending on whether the aim is to induce or maintain remission and whether there has been a major relapse. In patients with organ- or life-threatening disease, for example, the advice is to use glucocorticoids and either cyclophosphamide or rituximab to induce remission, Dr. Mukhtyar said. The specific dosing or
administration of glucocorticoids is not specified as this will depend on the clinical situation, but the advice is to taper down when possible, somewhere between month 3 and 5.

For remission induction in less severe (non–organ threatening) disease, the recommendation is to use glucocorticoids plus either methotrexate or mycophenolate mofetil. Situations when methotrexate or mycophenolate mofetil should and should not be used are specified, notably when cyclophosphamide or rituximab are not available or are contraindicated.

For maintenance of remission, the task force advised using low-dose glucocorticoids plus azathioprine, rituximab, methotrexate, or mycophenolate mofetil.

Guidance on when to use plasma exchange is given for patients with severe disease and options following failure of remission-induction therapy, and when to switch therapy is also covered.

There are also several follow-up recommendations, such as the periodic assessment of cardiovascular risk, and patient-focused recommendations on awareness of the nature, benefits, and risks of therapy.

The recommendations should provide clinicians with reliable guidance on the best approach to treating AAV, according to Dr. Yates. “From the patients’ point of view, these recommendations should provide useful insight into which treatments they are likely to be offered and when. They also emphasize that as a patient, you should have a voice in your treatment and if you have any questions or concerns, be sure to speak with your specialist.”

Dr. Yates and Dr. Mukhtyar did not report having any relevant disclosures.

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**EULAR-PReS recommendations aim to aid pediatric to adult care transition**

By Sara Freeman

The first European recommendations developed to help the transition of young people from pediatric to adult rheumatology care within Europe were announced at the European Congress of Rheumatology.

The key aim of the guidelines, which have been jointly written by EULAR and the Pediatric Rheumatology European Society (PReS), is to make the transition process more consistent across rheumatology practices throughout Europe, which in turn should help to ensure both the continuity and the quality of clinical care, explained Dr. Helen E. Foster of Newcastle University in the United Kingdom.

“There is evidence that there has been a long-standing problem of young people growing up with their condition moving to adult care and either falling between the services or being lost to follow-up, or there has not been continuity of care,” she said in an interview ahead of presenting the new EULAR/PReS recommendations at the congress.

“All in all, that’s translated into poorer health outcomes for young people,” said Dr. Foster, who was one of the main conveners of the EULAR/PReS Working Party for Transitional Care Management for Adolescents and Young People.

The premise is to try to provide practical recommendations that clinicians can use to help young people in their care from the age of 11 years and older as they get ready for the transfer to adult services. The latter process can occur anywhere from 16 to 19 years of age, Dr. Foster said, but it is important to try to start the transition process early and get young people more involved and responsible for their own care.

“The idea is that young people are supported to be in control of their condition, that they can cope with being seen on their own in clinic, that they are getting on with their lives, and ultimately that they have a better outcome, which includes becoming healthy, getting a job, living independently, and having a family,” she said. The age at transfer is flexible and needs to fit with the young person’s home and school life. Ideally, it occurs at a time when their disease and medication are stable, they are attending routine appointments, and generally able to be independent and cope with their condition.

**Developing the recommendations**

Together with Dr. Kirsten Minden of the German Rheumatism Research Centre Berlin (DRFZ), Dr. Foster chaired the international, multidisciplinary EULAR/PReS Working Party to review existing national and international recommendations, consensus statements, and other supporting evidence on transitional care management in childhood-onset rheumatic illness.

The remit was to develop recommendations to facilitate optimal transitional care management in rheu...
matematology across different European countries. As such, the recommendations cover both the ideal situation as well as the bare minimum requirements to hopefully allow widespread adoption. To this end, the working party performed a systematic literature review according to EULAR standard operating procedures. They developed a set of 12 recommendations based on the evidence they reviewed. (See box.)

There are 47 different health systems within Europe, all running according to different health policies set by different governments. Dr. Minden observed. In fact, only a handful of countries have specific transition care policies or pathways, so the aim was to try to develop recommendations that would work across the board while giving some ideas on how to improve existing strategies further.

She noted that some examples of existing transition programs are “Growing up and moving on” in the United Kingdom (Pediatr Transplant. 2005;9:364-72), “On your own feet ahead” in the Netherlands (BMC Health Serv Res. 2014;14:47), and “Devices for Optimization of Transfer and Transition of Adolescents with Rheumatic Disorders (DON’T RETARD)” in Belgium (Rheumatology [Oxford]. 2016;55:133-42). Of these, two are specific to the transition of young people with juvenile idiopathic arthritis (JIA) and one is for rheumatologic conditions in general.

Core elements of these programs are the need to provide written information and have a transition care plan, the allocation of a dedicated transition coordinator, and an individualized transition plan for each patient, Dr. Minden said. These elements are also part of the EULAR/PReS transition recommendations.

One of the issues to be addressed, however, is whether these transition programs actually work in the long term. “Transitional care services in rheumatology are beginning to happen and their further development can surely be facilitated by the provision of tool kits and resources for health care providers and patients,” she noted. Some of the tools already exist, so the challenge now is to get these available to all so that there can be a wider dissemination of knowledge.

The ON TRAC program includes online and mobile-enabled checklists that can be used with young people and their families, although Dr. Tucker noted that the program had perhaps not been as successful as had been hoped. Another Canadian initiative specific to rheumatology practice is the RACER (Readiness for Adult Care in Rheumatology) questionnaire. This was developed to assess how ready young people with chronic health conditions and their families to transition from pediatric to adult care.

The ON TRAC program includes online and mobile-enabled checklists that can be used with young people and their families, although Dr. Tucker noted that the program had perhaps not been as successful as had been hoped. Another Canadian initiative specific to rheumatology practice is the RACER (Readiness for Adult Care in Rheumatology) questionnaire. This was developed to assess how ready young people with chronic ailments were to transition to adult service.

Dr. Tucker also highlighted the YARD (Young Adult Rheumatic Diseases) clinic at her institution, set up for those aged 18 years or older with a definite diagnosis of rheumatic disease. Parent are not allowed within the clinic so as to enable young adults to take responsibility for their overall care and collaborate with their health care providers. The clinic provides education, assistance with separation independence, and other issues pertinent to this young population of patients, and it also aims to encourage adherence to

### The 12 EULAR/PReS transition recommendations

- Access to high-quality coordinated transition care services should be available to all young people.
- Transition should “start early” (11 years of age) or directly after diagnosis.
- Direct communication is needed between young people and their families and pediatric and adult care providers.
- Each young person should have an individualized transition plan.
- There should be a written transition policy within all relevant services; this should be regularly agreed upon and updated.
- The multidisciplinary team involved in transitional care should be clearly defined in a written document.
- Transition services should address the complexity of adolescent and young adult development.
- There must be an agreed-upon and written transfer document.
- Health care teams should be given appropriate training in adolescent and young adult rheumatic diseases.
- Secure funding is needed for uninterrupted clinical care and transition into adult services.
- An open digital platform should host the recommendations and support tools and information.
- More evidence is needed to demonstrate the outcomes of the transition to adult services.
appointments and treatments.

“Collaboration between pediatric rheumatologists and adult colleagues is critical to improve the outcomes of young adults with rheumatic diseases,” Dr. Tucker said. She added, “Better articulated guidelines for transition care and use of new tools have great potential to improve the care of these patients ‘lost in-between.’”

Why the need for the EULAR/PReS recommendations?

Dr. Foster noted that, in many countries, there is a natural break between pediatric and adult care, with young people often moving from one center to another, perhaps in another part of the country. An important part of the transition process is therefore ensuring that there are appropriately trained staff members and good communication between centers to ensure that young people don’t get lost during the move.

“This is everyone’s business,” Dr. Foster said at the congress. “It is a shared responsibility to get it right.” That means adult and pediatric health care teams work together. Care needs to be “holistic,” she added, and cover medical, psychosocial, vocational issues, and be “developmentally appropriate throughout.” Young people also need to be involved from the start of the process, beginning early and continuing into young adulthood.

The recommendations aim to be flexible so that they can be widely implemented by health care teams throughout Europe. “It is not ‘one size fits all,’” Dr. Foster acknowledged in the interview, noting the importance of being realistic and recognizing the differences between health systems, resources, and access across Europe.

Dr. Foster, who trained in adult rheumatology before turning to pediatric rheumatology, noted that there are existing resources that can be used and although funding will be an issue on some levels, there are things that can be done by using existing tools and resources.

“We don’t want to reinvent the wheel. We want to share best practice and resources,” she said. Indeed, one of the recommendations is that all the guidelines and all the resources used to develop them are made publicly available via an electronic platform so that anybody involved in the care of a young person with rheumatic disease, as well as the young person and their family, can access them.

“Transitional care is key to improving long-term outcomes for young people with rheumatic disease,” Dr. Foster concluded. The EULAR/PReS transition care management guidelines have been developed with the engagement of all relevant stakeholders, she said, so they should be widely applicable and “important levers for change” throughout Europe. “Implementation will require funding, but also our will and energy to make them actually work in practice.”

The EULAR/PReS transition recommendations are being finalized and will be published soon in Annals of the Rheumatic Diseases.

Dr. Foster, Dr. Minden, and Dr. Tucker had no disclosures relevant to the development of the recommendations.
European initiative unveils pediatric care recommendations

BY SARA FREEMAN

Recommendations on managing juvenile idiopathic arthritis and connective tissue disorders in children and young people across Europe were unveiled at the European Congress of Rheumatology.

The recommendations, which come from the SHARE (Single Hub and Access Point for Paediatric Rheumatology in Europe) project, cover best practices and provide guidance based on current evidence and expert opinion for the optimal diagnosis and treatment of these rare rheumatic diseases that affect the pediatric population.

It is hoped that the recommendations will be used to improve access to treatment and care within individual countries such that a child in one country will be able to receive the same standard of care as a child in another, Dr. Nico Wulffraat of University Medical Center Utrecht (the Netherlands) said in an interview.

Dr. Wulffraat, one of the driving forces behind the project, noted that the SHARE project was set up to look at making the management of rare pediatric rheumatic diseases more uniform across Europe. It addressed conditions such as juvenile idiopathic arthritis (JIA), childhood-onset systemic lupus erythematosus (cSLE), childhood antiphospholipid syndrome (APS), childhood vasculitis, juvenile dermatomyositis, and pediatric scleroderma. In addition, recommendations on diagnosis and treatment of periodic fever syndromes have been developed in collaboration with experts from the Eurofever Project.

“Our evidence- and consensus-based recommendations will hopefully drive access to uniform and optimal care throughout Europe, including off-label therapy when appropriate according to international consensus-derived expert advice,” Dr. Sebastiaan Vastert, SHARE project co-coordinator, said in an interview. He added: “The SHARE network will be invaluable for further international collaboration, both for optimization of care and for international collaboration in research as well.”

Dr. Wulffraat observed that while the recommendations are primarily directed at health care professionals, they also are of use for other stakeholders such as health authorities and insurance companies, and of course patients themselves to ensure that the best level of care is being achieved throughout Europe.

The process for developing the recommendations was perhaps as important as the recommendations themselves, said Dr. Vastert, also of University Medical Center Utrecht. The process helped to build a network of international experts who could work together to develop future recommendations for improving patient care.

The recommendations for JIA and other pediatric rheumatic diseases included 51 “cross-cutting” statements, Dr. Vastert said. One of these statements was that a pediatric rheumatologist should manage children with signs of rheumatic disease. Another highlighted the members of a multidisciplinary team who should be involved as appropriate, such as a nurse specializing in pediatric rheumatic disease, a physiotherapist or occupational therapist, and a psychologist or psychosocial worker. Dr. Vastert also noted that good communication between team members is essential. In addition, there needs to be clear guidance on when to refer to a pediatric rheumatologist.

The SHARE project JIA recommendations include 10 evidence-based statements on diagnosis, 31 evidence-based statements on treatment, and 17 general statements on specific care for JIA, Dr. Vastert said. A few examples of the latter are that new patients should be seen in a specialist center within 4 weeks of referral; new patients and those starting a new therapy should be reviewed within 2-3 months to check on adherence, tolerance, and disease progression; and monitoring response to ongoing treatment should be every 3-6 months, preferably using existing standardized disease activity tools.

EULAR standard operating procedures were followed when developing the various SHARE recommendations, said Dr. Michael Beresford of the University of Liverpool (United Kingdom) and the lead for the recommendations on childhood connective tissue disorders. Dr. Beresford noted that the latter were a rare, and in some cases extremely rare, complex group of pediatric rheumatic diseases that could lead to significant morbidity and mortality.

“Evidence-based guidelines have been lacking, and management is based mainly on physician experience. Consequently, treatment regimens
vary widely throughout Europe,” Dr. Beresford observed. “These [recommendations] provide evidence-based, internationally agreed-upon standards of optimal care for pediatric connective tissue disorders.”

Specifically, the connective tissue disorder recommendations cover when to refer and how to diagnose, treat, and monitor cSLE (including neuropsychiatric SLE), childhood APS, and juvenile vasculitides, including rare pediatric vasculitides such as Takayasu arteritis. The SHARE recommendations for the management of juvenile dermatomyositis were recently published in Annals of the Rheumatic Diseases (Ann Rheum Dis. 2016 Aug 11. doi: 10.1136/annrheumdis-2016-209247).

Giving a few examples of recommendations for cSLE, Dr. Beresford noted that one of the challenges is to try to prevent delay in diagnosis. The expert panel decided that the 2012 Systemic Lupus International Collaborating Clinics (SLICC) criteria could be used for diagnosis. A referral to a pediatric rheumatologist is warranted, they determined, when a child has a positive antinuclear antibody (ANA) test and meets two clinical SLICC criteria.

Dr. Beresford conceded that antibody testing might not be available because of cost in all countries, but they “decided to draw a line in the sand” to say that it is important that it is routinely done in order to come closer to a definitive diagnosis.

The aim of treatment for cSLE, the recommendations advise, is to optimize control and prevent damage caused by both the disease and by its treatment. For example, all children should be on hydroxychloroquine, and if tapering of prednisone is not possible, a disease-modifying antirheumatic drug should be added. It’s also important to actively check compliance with therapy, Dr. Beresford said.

The SHARE project was initially funded by a grant from the European Agency for Health and Consumers between 2012 and 2015 and now continues under the auspices of the Paediatric Rheumatology European Society. All speakers reported having no relevant disclosures.

TNF inhibitors improved refractory skin disease in juvenile dermatomyositis

BY JEFF EVANS

Tumor necrosis factor–inhibitor treatment improved refractory skin disease in juvenile dermatomyositis patients in the largest observational study of its kind from the United Kingdom and Ireland Juvenile Dermatomyositis Research Group.

Muscle disease in the juvenile dermatomyositis (JDM) patients largely had already improved with conventional therapies prior to treatment with anti–tumor necrosis factor (TNF)-alpha agents, but it did improve further with anti-TNFs.

The effect of TNF inhibitors was most notable for those with skin calcinosis, lead author Dr. Raquel Campanilho-Marques reported at the European Congress of Rheumatology on behalf of her colleagues in the Juvenile Dermatomyositis Research Group.

Some evidence suggests that TNF-alpha might be involved in the pathogenesis of idiopathic inflammatory myopathies, particularly in more prolonged courses of JDM.

But there is limited prior evidence for the efficacy of TNF inhibitors in JDM patients, where small observational studies and case series have shown improved core-set measures of disease activity in patients treated with anti-TNF agents, noted Dr. Campanilho-Marques, a pediatric rheumatologist in the infection, inflammation and rheumatology section at the University College London Institute of Child Health and the Great Ormond Street

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Hospital for Children NHS Trust in London.

The 67 patients in the study involved those who were enrolled in the JDM Cohort and Biomarker Study, met Bohan and Peter criteria for JDM, and were on anti-TNF therapy at the time of analysis because of nonresponse to conventional therapy, active skin disease, calcinosis, or muscle weakness. They had at least 3 months of anti-TNF therapy and received either infliximab 6 mg/kg every 4 weeks (after a standard initial induction regimen) or adalimumab 24 mg/m² every other week.

A majority of the patients in the study were female (n = 41) and white (n = 54), with a mean age at disease onset of about 5 years. At the time of first use of anti-TNF agents, the patients had a mean age of about 10 years and a mean disease duration of about 3.2 years. Treatment with TNF inhibitors lasted for a mean of about 2.5 years.

Of the 67 patients, data were not analyzed for 4 patients; there was insufficient information for 1 patient, while 3 patients had allergic reactions to their anti-TNF therapy on the first or second infusion. The remaining 63 patients included 43 who received infliximab, 4 on adalimumab, and 16 who used both.

Prior to anti-TNF treatment, 52 of 53 patients (98%) were taking methotrexate, azathioprine, hydroxychloroquine, or a combination of those. That declined to 45 of 56 (80%) at the start of anti-TNF therapy and then increased to 44 of 49 (89%) after 12 months of using an anti-TNF agent.

The use of cyclophosphamide declined markedly, from 26 of 65 patients (40%) to 3 of 65 (5%) at the start of TNF inhibition, and then to none after 12 months of anti-TNF therapy. Immunoglobulin therapy also declined, from use in 10%-12% of patients before and at the start of anti-TNF treatment to just 1 of 41 patients (2%) after 12 months of TNF inhibitor therapy.

The median modified Disease Activity Score for skin involvement significantly improved over the course of 12 months of treatment with infliximab, decreasing from 4 to 1. That was also the case for Physician Global Assessment score, as well as muscle outcome measurements on the Childhood Myositis Assessment Scale (CMAS) and the 8-item Manual Muscle Testing (MMT8).

For the 31 patients in the study who had calcinosis, lesions improved (reduced in number and/or size) in 17 patients, including 8 with complete resolution of their lesions.

The investigators did not examine treatment response in relation to muscle-specific antibodies, but Dr. Campanilho-Marques said that it is something they would like to do in the future.

The main indication for anti-TNF agents was active skin disease that had not responded to conventional treatment, noted Dr. Campanilho-Marques, who is also with the departments of rheumatology at the Santa Maria Hospital and the Instituto Português de Reumatologia, both in Lisbon.

For 16 patients who switched from infliximab to adalimumab, the changes in outcome measures were not statistically significant. The switches occurred at a median of 2.35 months after starting infliximab; 10 patients switched because of inefficacy, 4 because of adverse events, and 2 because of patient preference.

After 12 months of anti-TNF therapy, the median prednisolone dose declined from 6 mg to 2.5 mg, but the decline appeared to be driven by five patients who sharply decreased their dose. Seven patients successfully stopped anti-TNF therapy after improvement occurred, Dr. Campanilho-Marques said.

Serious adverse events occurred 12 times during the year-long study period, including nine allergic reactions and three hospitalizations because of infection. Another 19 mild to moderate adverse events took place, which involved 15 infections and three local site reactions and skin rash, which led five patients to discontinue the biologic.

Overall, adverse events occurred at a rate of 13.3/100 patient-years, including 5.2 serious events/100 patient-years. One patient died because of a small bowel perforation that was probably secondary to disease-related damage. There were no malignancies or tuberculosis cases.

The researchers had no relevant disclosures.
Depression worsens newly diagnosed juvenile idiopathic arthritis

BY MITCHEL L. ZOLER

Depression is relatively common among teenagers newly diagnosed with juvenile idiopathic arthritis, and adolescents with both disorders appeared to have a less complete response to their treatment in a study of 102 patients.

Juvenile idiopathic arthritis (JIA) that first manifests when a patient is a teenager comes at a “vulnerable time” that can drive the development and worsening of depression, and depression can potentially exacerbate inflammation and also interfere with treatment compliance, Dr. John Ioannou said at the congress.

Depression and JIA can produce a “vicious cycle in which depression exacerbates the disease and the disease exacerbates depression,” explained Dr. Ioannou, who is a rheumatologist at University College Hospital in London.

Although no study results have yet identified an effective intervention for depression identified in teenagers with newly diagnosed JIA, the immediate message from these new findings is that clinicians must assess the psychological health of adolescents with JIA both when they are first diagnosed as well as at subsequent visits, and if depression is found it requires some sort of intervention, Dr. Ioannou said in an interview.

He and his associates studied 102 patients from the United Kingdom, who were newly diagnosed with JIA and were 11-16 years old at baseline and enrolled in the Childhood Arthritis Prospective Study (CAPS), a nationwide cohort of patients with childhood-onset arthritis of various types. The average age of the group they studied was just under 13 years old, 57% were girls, 52% had persistent oligoarticular arthritis, 30% had polyarticular arthritis, and 18% had enthesitis-related arthritis.

All patients underwent assessment at baseline for depression using the Mood and Feelings Questionnaire and 15 (15%) had a score that flagged them as having “probable” depression.

This depression prevalence is about three- to fourfold higher than for an otherwise healthy group of similarly aged adolescents, Dr. Ioannou commented.

At baseline, the subgroup of teens with depression had a significantly higher number of inflamed joints, restricted joints, and also more overall pain and disability as measured on the Childhood Health Assessment Questionnaire.

The 102 teens with JIA underwent follow-up assessment 1-3 years later, after they had received ongoing treatment for their JIA. At follow-up, standard JIA treatment had largely resulted in resolution of joint inflammation and movement restriction among all patients, including those with depression at baseline. However the adolescents who had both JIA and depression at entry continued to have significantly more pain and disability at follow-up than did the nondepressed JIA patients, suggesting a link between depression and refractory pain and disability in JIA patients, the researchers reported.

“We need to ensure that psychological assessments and support are available to all young people diagnosed with JIA, and that this is fully integrated into routine care” for newly diagnosed JIA patients, Dr. Ioannou said. He had no disclosures.
Patients with psoriatic arthritis appear less likely to achieve a good response to their first anti–tumor necrosis factor (anti-TNF) therapy if they are obese, according to data taken from two Nordic registries.

In a large observational cohort study, obese individuals with psoriatic arthritis (PsA) were significantly less likely than their nonobese counterparts to achieve a European League Against Rheumatism (EULAR) good or moderate response at 6 months (35% vs. 65%, $P = .02$). The overall odds ratio for achieving a good or moderate response was 0.47 when comparing obese with nonobese individuals.

The findings are potentially important because, with the exception of infliximab, anti-TNF therapy is not currently adjusted according to body weight, said presenting study author Pil Højgaard in an interview at the European Congress of Rheumatology.

Ms. Højgaard, who is an MD PhD student at the department of rheumatology, Copenhagen University Hospital Gentofte, Rigshospitalet, and the Parker Institute in Copenhagen, noted that obesity was a frequent comorbid condition in patients with PsA and that it is a known proinflammatory condition. As such, obesity could potentially affect immunologic processes, the pharmacokinetics of treatments, and ultimately patient outcomes.

Since TNF-alpha inhibitor (TNFi) treatment fails in around half of all patients with PsA treated in routine care, Ms. Højgaard noted that the aim of the cohort study was to investigate whether obesity could be having any influence on this.

Data on baseline characteristics, EULAR response rates, and drug adherence were obtained for 1,943 patients with PsA prescribed their anti-TNF therapy from two nationwide registries of disease-modifying therapies being used to treat rheumatic conditions in Denmark and Iceland, DANBIO (Rheumatology, 2011;50:69–77) and ICEBIO, respectively.

At baseline, body mass index (BMI) data were available for 1,271 patients and 408 (32%) of these had a BMI of 30 kg/m² or more and were classed as being obese. The majority (39%) had received a first prescription for adalimumab, with around a quarter each prescribed etanercept (26%) or infliximab (24%), and the remainder prescribed golimumab (7%) and certolizumab (4%).

Compared with the 863 (68%) nonobese individuals, the obese patients were older (47 vs. 49 years, $P = .01$), less likely to smoke (30% vs. 23%, $P = .01$), and had higher disease activity measured on the Disease Activity Score 28 (DAS28) (4.4 vs. 4.6, $P = .01$). Health Assessment Questionnaire scores were also higher in obese than in nonobese individuals (1.1 vs. 0.9, $P$ less than .01), and there were higher tender joint counts (6 vs. 5, $P = .01$), and higher pain levels assessed on a visual analog scale (VAS). Obese patients also had higher scores on a VAS patient global scale. The median follow-up time was 1.5 years.

Patients who were obese were found to adhere to TNFi treatment for shorter periods of time than nonobese patients, with median durations of 1.76 and 3.08 years, respectively ($P$ less than .001). This discrepancy was most pronounced among men, a finding that may account for the fact that they were less likely to achieve a good EULAR response than their nonobese counterparts ($OR = 0.5$).

Being obese versus not being obese independently predicted TNFi withdrawal overall (hazard ratio, 1.6), especially in men (HR, 1.8; HR, 1.5 in women). TNFi withdrawal was more likely in obese than in nonobese patients even when individual treatments were considered; adalimumab: HR, 1.6; etanercept: HR, 2.0; infliximab: HR, 1.6.

An association between obesity and reduced response to anti-TNF therapy has also been observed in patients with rheumatoid arthritis, Ms. Højgaard acknowledged.

There have also been a few studies of PsA and psoriasis “but to my knowledge, I think in the field of psoriatic arthritis, we are one of the few that have been looking at long-time drug survival,” she said. “We also include quite a lot of patients.

“Of course this is not a randomized clinical study, so there could be residual confounding factors,” Ms. Højgaard cautioned. “It is always a bit difficult to say something about causality when it is a database study,” she added. “I think what we can see here is that there is an association, but in order to recommend weight loss we need some prospective studies.”

She noted that there was one published clinical study (Ann Rheum Dis. 2014;73:1157–62) that had looked at the benefit of a weight reduction program started at the same time as TNFi initiation in patients with PsA.
Secukinumab may slow structural ankylosing spondylitis progression

BY MITCHEL L. ZOLER

Long-term treatment with the interleukin-17A inhibitor secukinumab showed suggestive evidence of inhibiting structural progression of spinal disease in 168 patients with ankylosing spondylitis, the first time any evidence for an effect like this has been seen with a biologic drug or any other agent used to treat ankylosing spondylitis.

However, the effect occurred in uncontrolled, 2-year open-label treatment of patients originally enrolled in one of the secukinumab pivotal trials, and the analysis did not include comparison against a historical control group, caveats that demand confirmation of this effect in additional studies, Dr. Jürgen Braun said at the European Congress of Rheumatology.

The open-label secukinumab extension study involved patients who had been enrolled in the MEASURE 1 study, one of the pivotal trials that had established secukinumab as safe and effective for improving the clinical status of patients with active AS. The primary endpoint of MEASURE 1 had been the percentage of patients achieving at least a 20% improvement in their Assessment of Spondyloarthritis International Society (ASAS20) response after 16 weeks of treatment (New Engl J Med. 2015 Dec 24;373[26]:2534-48).

Based in part on these data the European Medicines Agency approved secukinumab for the treatment of ankylosing spondylitis in October 2015.

The new data reported by Dr. Braun assessed the level of spinal pathology in a subgroup of the MEASURE 1 patients when measured by radiography using the modified Stoke Ankylosing Spondylitis Spine Score (mSASSS) at baseline and after 104 weeks on secukinumab treatment.

Patients in MEASURE 1 who began on active treatment received 10 mg/kg intravenous secukinumab for 4 weeks, followed by subcutaneous dosages of either 75 mg or 150 mg every 4 weeks for 104 weeks. His analysis also included some patients who entered MEASURE 1 in the placebo group and then switched to open-label, subcutaneous secukinumab treatment after 16 or 24 weeks on placebo.

Analysis of 168 patients who started on intravenous secukinumab and later received any subcutaneous secukinumab treatment out to 104 weeks showed an average increase in mSASSS of 0.30 after 104 weeks when compared against their baseline scores, reported Dr. Braun, professor and medical

The change in progression was monitored over a 2-year period, Dr. Jürgen Braun said.

Continued on following page
Among an additional 89 patients who began in the placebo group and then switched to subcutaneous secukinumab, the average change in mSASSS from baseline to 104 weeks was 0.54. By comparison, Dr. Braun noted that AS patients treated with a tumor necrosis factor inhibitor have shown 2-year progression in their mSASSS of about 0.8-0.9, and AS patients not treated with an active biologic drug have shown 2-year mSASSS progression of about 1.0.

Dr. Braun has been a consultant to Novartis, and several other drug companies, and three of his coauthors are Novartis employees.

**VIEW ON THE NEWS**

**Evidence for AS structural control needs confirmation**

The results on radiographic progression in ankylosing spondylitis patients who continued on secukinumab treatment for 104 weeks suggest for the first time that a biologic drug can reduce radiographic progression of ankylosing spondylitis. This effect has not been seen in patients treated with a tumor necrosis factor inhibitor. The results showed that roughly 80% of the patients maintained for 2 years on secukinumab did not have radiographic progression, although the results also showed that about 20% of these patients did have detectable radiographic progression.

This analysis has several limitations and caveats. The study did not include a control group, not even a historical control group, and it involved open-label treatment. In addition, the treatment effect observed was very close to the level of a measurement error. It would help to compare these results with a historic control group, or to run a new study that compares the effect of secukinumab on long-term radiographic progression directly with the effect of treatment with a tumor necrosis factor inhibitor.

Because of these limitations the results of this analysis are of limited immediate value. Prior results have shown that clinically the efficacy of secukinumab for treating ankylosing spondylitis is more or less the same as the efficacy of various tumor necrosis factor inhibitors. If an additional effect from secukinumab on slowing radiographic progression in these patients were proven, it would be of clear added value, but further study is needed to show this.

Dr. Denis Poddubnyy is a professor of rheumatology and head of rheumatology at the Benjamin Franklin campus of Charité Medical University in Berlin. He made these comments in an interview. He has been a consultant to Novartis and several other drug companies.
Anti-infliximab originator antibodies also cross-react with infliximab biosimilar

BY AMY KARON

Antibodies to the originator biologic infliximab (Remicade) cross-reacted with the infliximab biosimilar CT-P13, marketed as Remsima or Inflectra, according to a multicentre, controlled study of patients with rheumatoid arthritis and spondyloarthritis presented at the congress.

Based on the findings, patients with antibodies to Remicade should not be switched to Remsima or Inflectra because cross-reactivity will increase clearance of CT-P13, thereby potentially eroding therapeutic response and heightening the risk of infusion-related reactions, said senior author Dr. Daniel Nagore of the molecular biology testing company Progenika-Grifols in Derio, Spain, and his colleagues. These results should “help physicians better understand the implications of drug switching in the context of infliximab immunogenicity, and increase the awareness of biologic drug monitoring in patients with rheumatic diseases,” Dr. Nagore added in an interview.

Infliximab is a tumor necrosis factor (TNF)–alpha blocker used in the treatment of rheumatoid arthritis (RA), spondyloarthritis (SpA), plaque psoriasis, psoriatic arthritis, and inflammatory bowel disease (IBD). CT-P13 is the first anti-TNF-alpha biosimilar and was approved for the same indications as Remicade in 2013 by the European Medicines Agency. In a prior study, antibodies to Remicade cross-reacted with CT-P13 in patients with IBD (Gut. 2015 Apr 20. doi: 10.1136/gutjnl-2015-309290). To explore Remicade antibody cross-reactivity in other rheumatic diseases, Dr. Nagore and his colleagues retrospectively selected 250 patients who were currently receiving Remicade for RA or SpA, and 77 infliximab-naive control patients, about one-quarter of whom were healthy and three-quarters of whom had rheumatic diseases. Patients who tested positive for antibodies had undetectable serum levels of infliximab, while those testing negative had a median infliximab concentration of 1.7 mg/mL. The researchers uncovered no links between the presence of infliximab antibodies and the type of rheumatic disease, or the use of concomitant immunosuppressive therapies, such as methotrexate.

“Although additional epitopes may be present in the biosimilar, results suggest that epitopes influencing the immune response to [infliximab] are also present in the biosimilar,” they wrote in a short report published online in Annals of the Rheumatic Diseases (2016 Mar 10. doi: 10.1136/annrheumdis-2015-208684).

Dr. Nagore and five coauthors are full-time employees of Progenika Biopharma, which makes the Remicade assay used in the study. He and his coinvestigators had no other relevant financial disclosures.
A single, intravenous infusion of 1,000 mg of rituximab to people with arthralgia and a high risk for developing rheumatoid arthritis cut the subsequent rate of rheumatoid arthritis development roughly in half during more than 18 months of follow-up in a proof-of-concept, placebo-controlled study that randomized 81 people.

“This is the first study to evaluate the effects of a biopharmaceutical in subjects at risk of developing RA [rheumatoid arthritis],” Dr. Daniëlle M. Gerlag said at the congress. “These results strongly support the rationale for future clinical trials aimed at prevention of RA by a targeted intervention,” added Dr. Gerlag.

Additional studies are needed to confirm this effect and to examine whether the period of protection against RA development can be extended by administration of additional rituximab doses. In the current study, the protective effect from the single dose administered appeared to wane over time, she noted.


The researchers found these participants largely through screening sessions run at health fairs and by publicizing the study during television appearances, Dr. Gerlag said. About three-quarters of the participants were first-degree relatives of patients already diagnosed with RA, but this was not a criterion for enrollment. The participants averaged about 53 years old, and nearly two-thirds were women.

Among the 81 people who underwent treatment, 41 received a single, 1,000-mg infusion of rituximab, and 40 received a placebo infusion. The researchers then followed the participants with scheduled, periodic examinations during a median of 29 months.

During follow-up, 16 of the 40 people in the placebo group (40%) developed RA after a median of 12 months, and 14 of the 41 in the treated arm (34%) developed RA after a median of 17 months. The researchers performed two different statistical analyses on these outcomes. They used a Kaplan-Meier survival analysis to determine the time until 25% of people in each arm developed RA. Among the placebo patients, this occurred after 12 months, while in the intervention arm, it did not occur until 24 months, a statistically significant doubling of the time to this outcome with rituximab treatment, Dr. Gerlag reported.

The second analysis calculated a Cox proportional hazard ratio based on the time to development of rheumatoid arthritis among those in each of the treatment groups. This determined a 55% reduced hazard ratio after 12 months among people treated with rituximab, compared with the placebo-treated controls, and a 53% reduced hazard after 18 months, both statistically significant differences. A safety analysis showed that some people treated with rituximab had mild infusion-related symptoms, but no participants had serious infections. Serious adverse events occurred in 11 people in the rituximab group and in 3 in the placebo arm, but none of these serious adverse events was judged to be related to treatment by the study’s data safety monitoring board, said Dr. Gerlag, who is also on the staff of GlaxoSmithKline in Cambridge, England.

The PRAIRI study received no commercial funding. Dr. Gerlag is also a shareholder in GlaxoSmithKline, but the company played no role in the study.
Subcutaneous methotrexate may help RA patients avoid biologics

BY MITCHEL L. ZOLER

Subcutaneous methotrexate monotherapy may be more effective at helping recently diagnosed patients with rheumatoid arthritis avoid biologic therapy, compared with similar patients on oral methotrexate, based on an analysis of data collected from 483 Canadian patients in routine care and enrolled in a national registry.

“This is a signal for improved efficacy with subcutaneous methotrexate, compared with oral methotrexate,” said Dr. Stephanie Gottheil, who reported these results at the congress.

“In general, as long as patients with rheumatoid arthritis are under good control without a biologic drug, that is preferable” to initiating biologic treatment, said Dr. Gottheil, a researcher at Western University in London, Ont. Delaying the start of biologic treatment saves money, avoids the increased risk of infection that comes with biologic treatment, and defers a patient’s immune response to a biologic drug that can eventually compromise the biologic’s efficacy, she said in an interview.

“These data did not come from a randomized trial and so are by no means conclusive, but this is a signal that supports other data that subcutaneous methotrexate potentially puts patients into remission faster, and we know that earlier remission predicts more sustained remission,” she said.

“The biggest barrier to subcutaneous administration of methotrexate is patient preference to not inject themselves, but results from some studies have also shown that subcutaneous methotrexate is better tolerated,” compared with oral dosing, she added.

The study used data collected in the Canadian Early Arthritis Cohort (CATCH), which enrolls patients at several centers throughout Canada diagnosed with rheumatoid arthritis for less than 12 months. Dr. Gottheil and her associates particularly focused on 1,189 early RA patients with moderate to severe disease activity enrolled in CATCH during 2007-2012 who received methotrexate and had never previously received a biologic drug. The study’s primary endpoint was time to first treatment with a biologic during 3 years of follow-up after entry into the registry.

The patients’ average age at enrollment was 56 years, more than two-thirds were women, and their average methotrexate dosage was 20 mg/week. The cohort included 483 patients on methotrexate monotherapy – with virtually equal numbers on oral methotrexate and subcutaneous methotrexate – and 706 on a regimen that combined methotrexate with one or more additional (nonbiologic) drugs at baseline. The patients in each of the methotrexate monotherapy subgroups were very similar in their demographic and clinical profiles.

The analysis showed no statistically significant difference in time to first biologic use between the patients on a combination regimen and those on oral methotrexate monotherapy.

But when the researchers compared the time to first biologic among those on subcutaneous methotrexate monotherapy with those on oral methotrexate monotherapy, the subcutaneous patients showed a statistically significant, 47% reduced rate of starting any biologic drug during follow-up in an analysis that controlled for age, sex, education, comorbidities, disease duration, baseline disease activity, baseline corticosteroid use, joint erosions at baseline, and score on the health-assessment questionnaire at baseline, Dr. Gottheil reported. The analysis also revealed three other variables that significantly linked with a slower progression to biologic treatment: older age, no use of corticosteroid treatment at baseline, and lower disease activity at baseline.

The CATCH registry research program is sponsored by AbbVie, Amgen, Bristol-Myers Squibb, Hoffmann-La Roche, Janssen, Pfizer, and UCB. Dr. Gottheil had no relevant disclosures.
Nanoparticle targeting may open new RA diagnosis, treatment opportunities

BY SHARON WORCESTER

Targeted biodegradable nanoparticles show potential as a new platform for early detection and effective treatment of inflammatory arthritis, based on a study in two different animal models of the disease.

In an effort to develop the targeted biodegradable nanoparticles (tBNPs) to enable the delivery of drugs or diagnostic tracers specifically into inflamed synovial tissue—an approach that usually allows for enhanced efficacy with limited side effects—Federico Colombo, a PhD student at the University of Trieste (Italy), and his colleagues used polymeric biodegradable nanoparticles to target only inflamed synovial tissue.

The nanoparticles, which had a diameter of 170 nm with a low negative charge, were made of polylactic acid, polycaprolactone, and polyethylene glycol, and were coated with a peptide characterized for its ability to target only inflamed synovial tissue. Immunofluorescence was used to assess the ability of the tBNPs to preferentially target the tissue, and toxicity was assessed by in-vitro assay and in vivo.

The tBNPs were shown to specifically bind inflamed synovial tissue both in vitro and in vivo in a rat model of antigen-induced arthritis. Of note, the targeting was dependent on the degree of inflammation, which “highlights the potentiality of the tBNPs as an early diagnostic tool,” Mr. Colombo said in an interview.

“A single tBNP injection loaded with methotrexate completely abrogated the inflammatory process in the acute antigen-induced arthritis rat model while the same dose of free methotrexate was ineffective,” he said.

Similar effects were seen in the mouse model of chronic collagen-induced arthritis.

“No toxic effect was documented when methotrexate was loaded in nanoparticles in these animals,” Mr. Colombo said. “Our results demonstrated that tBNPs can efficiently and selectively deliver drugs and diagnostic probes to inflamed synovial tissue, providing a new platform for early detection and efficient chronic treatment of inflammatory arthritis, with minimal side effects.”

Such targeting approaches were first studied to drive antibodies, and currently there are several targeted therapies that have been approved by the U.S. Food and Drug Administration for use in cancer patients. Examples include antibodies that are able to target the human epidermal growth factor receptor 2 to treat certain breast cancers and stomach cancers, he noted.

“On the contrary, this is one of the projects aiming to target inflamed synovial tissue,” he said of his work. “Up to now, nanoparticles have been used passively, exploiting only their physiochemical properties and the enhanced permeability and retention effect, while the novelty of our work is the use of an active targeting to drive nanoparticles for RA.”

The nanoparticles could be used as a targeted contrast agent in fluorescence-based or x-ray imaging and computed tomography, because a specific contrast agent or mixture of contrast agents can be loaded in the system, aiming to increase the contrast of the image in the inflamed synovial tissue, he added.

Mr. Colombo and all but one coauthor reported having no relevant financial disclosures. Coauthor Luis Núñez, PhD, is an employee of BioTarget.
B-cell clusters in synovial tissue predict joint damage in early, untreated RA

BY NICOLA GARRETT

The presence of clusters of B cells in synovial tissue can predict which patients with early rheumatoid arthritis are most at risk of developing joint damage, according to research presented at the congress.

The results of the study, which examined synovial biopsies at baseline from 135 patients with early RA who had not taken disease-modifying antirheumatic drugs previously, are clinically significant because they suggest that integration of synovial molecular markers into clinical algorithms might significantly improve patient outcomes, lead author Dr. Frances Humby said in an interview.

“Although outcomes for patients with RA have improved dramatically in the past decade, we are still unable to reliably predict disease prognosis at baseline,” said Dr. Humby, senior lecturer and honorary consultant rheumatologist in the department of experimental medicine and rheumatology at Queen Mary University in London. “If we can use synovial tissue to stratify patients according to best drug, we can move towards an era of personalized medicine for patients with RA.”

Based on the biopsies, Dr. Humby and her associates classified patients into lymphoid, myeloid, or fibroid synovial pathotypes according to the degree of synovial infiltration of CD20+ B cells, CD3+ T cells, CD68+ macrophages, and CD138+ plasma cells. The patients were participating in the Pathobiology of Early Arthritis Cohort at Barts Health NHS Trust in London.

At 12 months of follow-up, the researchers discovered that baseline lymphoid pathotypes were significantly associated with anticitrullinated protein antibody (ACPA) positivity ($P = .017$) and highly active disease as measured by the 28-joint Disease Activity Score, C-reactive protein, erythrocyte sedimentation rate, and swollen joint count ($P$ less than .01).

Furthermore, a significantly higher number of patients with a baseline lymphoid pathotype developed radiographic progression, compared with those stratified as myeloid or fibroid pathotypes (9 of 26 vs. 5 of 53; $P = .026$).

The results shed some light on disease pathogenesis because they begin to explain the clinical observations of disease heterogeneity in rheumatoid arthritis.

“The significant association observed between a lymphoid pathotype and a severe clinical phenotype/seropositivity for ACPA supports a direct role for synovial lymphoid structures in disease pathogenesis,” the researchers said.

“They strongly support the concept that B-cell activation and proliferation within the synovial tissue equate to poorer outcomes and drive ongoing joint damage,” Dr. Humby explained.

It has been known for some time that the synovial cellular infiltrate in RA organizes into lymphocytic aggregates, Dr. Humby said. Previous research suggested the cells were immunologically competent and could support chronic inflammation.

However, she maintained that the results from the current study were of particular significance because of the size of the cohort, the inclusion of patients with only small joint involvement because of the biopsy technique used, and the fact that patients were treatment naive.
obacco use and excess weight can make it harder to achieve sustained remission in the treatment of early rheumatoid arthritis, according to findings from more than 1,000 patients in the Canadian Early Arthritis Cohort (CATCH) multicenter, prospective study.

Aggressive treatment that starts soon after diagnosis of rheumatoid arthritis (RA) is important for the absence of disease activity, which is the hallmark of sustained remission. But the reality is a success rate of less than 50% in the first 3 years with physical deterioration continuing thereafter. "Excess weight and smoking are two risk factors for developing RA. We were interested in seeing if they might also affect how well people responded to treatment," said Susan Bartlett, PhD, a clinical psychologist at McGill University in Montreal.

At the congress, Dr. Bartlett and colleagues reported on a cohort of 1,008 early RA patients who were enrolled in the Canadian Early Arthritis Cohort (CATCH) multicenter, prospective study and followed from around the time of diagnosis through the first 3 years of treatment to estimate the time it took until they achieved sustained remission, defined as having a 28-joint Disease Activity Score less than 2.6 for two consecutive visits.

Mean age of the patients (72% female, 81% white) was early 50s. Overall, 30% of females and 47% of males were overweight, one-third of both genders were obese, and 15%-20% smoked. Treatment at entry included methotrexate in mono- or combination therapy in about three-quarters of the patients, with steroids used in about half and biologics used sparingly.

The proportion of patients in sustained remission was 38% at 3 years, with a median time to remission of 11.3 months. "That finding wasn’t surprising because that is generally what is found in most studies of early RA. However, when we looked more closely at who was and wasn’t achieving remission, we found that people who smoked and those who were overweight or obese were much less likely than their nonsmoking, normal-weight peers to be in sustained remission," Dr. Bartlett said in a pre-congress interview.

After adjustment for factors that could affect response to treatment – including age, race, disability status, pain, and early medications used – smoking ($P = .046$) and excess weight ($P = .003$) were associated with a poorer likelihood of achieving sustained remission. While more men than women were overweight or obese, the effects of weight and smoking appeared to be more problematic for women ($P = .02$).

An average nonsmoking male with a healthy body mass index (BMI; 25 kg/m² or less) had about a 41% probability of achieving sustained remission within 3 years, compared with 15% for an obese male smoker. A nonsmoking female with a healthy BMI had a 27% probability of achieving sustained remission within 3 years, compared with 10% for an obese female smoker. Probabilities of sustained remission were also lower for overweight men and women, Dr. Bartlett reported.

Smoking and obesity have already been linked with an increased likelihood of developing RA, which in turn increases the risk of cardiovascular disease and premature death. The latest data suggest that both smoking and extra weight – including overweight and obese as defined by BMI – may also independently influence the success of treatment. "Our data suggest that if you have RA, it’s important to take the medications that your doctor has prescribed. If you smoke, you need to stop. And if you’re carrying extra weight, not only is that placing a
greater demand on already vulnerable joints, it may also be making your RA treatment less effective,” Dr. Bartlett said.

These lifestyle modifications can be challenging for some people with RA, she said. Clinicians can help by considering lifestyle behaviors that lead to chronic diseases and poorer outcomes in addition to their more traditional view of diagnosis and treatment, she said, adding that patients and clinicians should know that even a small amount of weight loss can improve health and may improve response to therapy.

Well-controlled clinical trials will be needed to better understand the benefits of weight control and smoking cessation for response to RA treatment. Also, why women who smoke and are overweight are at more of a disadvantage than their male counterparts is unknown. “As we begin putting these pieces together, we may learn valuable information that helps us to better control and ultimately cure RA,” Dr. Bartlett said.

The researchers had no conflicts of interest to declare.

Simplify cardiac risk assessment for rheumatologic conditions

BY KAREN BLUM
AND SARA FREEMAN

Cardiovascular disease (CVD) risk assessment for patients with rheumatic diseases can be simple and integrated into general practice or rheumatology clinics, experts said during an Outcomes Science Session at the congress.

Patients with rheumatoid arthritis have a 50% higher risk of heart disease than do their counterparts without the disease, but “just having RA on its own isn’t sufficient to render that individual at high risk,” Dr. Naveed Sattar, professor of metabolic medicine at the University of Glasgow’s Institute of Cardiovascular and Medical Sciences in Scotland, said in an interview.

It’s simple enough to use traditional CVD risk factors in an RA population by including a patient’s age, gender, smoking status, and family history of heart disease, in addition to measuring blood pressure and blood lipid levels. Most risk scores will compile those features into a 10-year risk of a fatal CVD event. To account for the contribution of RA, Dr. Sattar said, simply multiply that score by 1.5.

While “there’s a fixation in some parts of Europe for [measuring] fasting lipids,” it is not necessary, Dr. Sattar said. The two lipid parameters that go in risk scores tend to be cholesterol and HDL cholesterol, he said, which change only minimally in fasting versus nonfasting states.

“The evidence overwhelmingly shows that nonfasting lipids, which can be done easily on the same sample as other clinic tests, are just as predictive of CVD risk as fasting lipids,” he said. “That really matters because many of our patients with RA or other conditions come to the hospital when they’re not fasting, and we shouldn’t be sending them away to come back fasting to do risk scores for CVD. That just doesn’t make sense.”

Updated guidelines from the European Society of Cardiology and guidelines soon to be released from the European League Against Rheumatism suggest that risk scores can be calculated every 5 years for most patients, a change from previous recommendations to calculate risk annually. Risk scoring is not perfect, however, and there is some debate about whether additional blood tests or ultrasound scanning of the carotid artery could augment the ability to predict heart
disease risk. “We’re not quite there yet,” Dr. Sattar said. “I think we should do the simple things first and do them well.”

**CV risk raised in all inflammatory arthritic diseases**

During the same session, Dr. Paola de Pablo of the University of Birmingham, United Kingdom, focused on how immune-mediated diseases predispose to premature, accelerated atherosclerosis and subsequent increased cardiovascular morbidity and mortality.

Cardiovascular risk is not only elevated in those with RA, she observed, but also in those with systemic lupus erythematosus, ankylosing spondylitis, psoriatic arthritis, vasculitides, and inflammatory myopathies. The risk varies but as a rule is more than 50% higher than the rate seen in the general population.

The underlying mechanisms are not clear, but chronic inflammation is closely linked with atherosclerosis, which in turn ups the risk for myocardial infarction and cerebrovascular accident.

Despite treatment, the risk often remains, Dr. de Pablo said. She highlighted how treatment with methotrexate and anti–tumor necrosis factor (TNF)–alpha drugs in RA had been associated with a reduction in the risk for heart attack of 20% and 40%, respectively (Ann Rheum Dis. 2014;74:480–89) so targeting inflammation with these drugs may have positive effects, at least in RA.

Managing traditional cardiovascular risk factors remains important, Dr. de Pablo said. That was a sentiment echoed by Dr. Sattar and by rheumatologist Dr. Michael Nurmohamed of the VU Medical Center in Amsterdam.

Dr. Nurmohamed, who was involved in the 2015 update of the EULAR recommendations on cardiovascular risk management, noted that traditional risk factor management in patients with arthritis in current clinical practice is often poor and that strategies to address this were urgently needed.

Although treating to target and preventing disease flares in the rheumatic diseases is important, it lowers but does not normalize cardiovascular risk.

“‘This appears to be irrespective of the drug used,’” Dr. Nurmohamed said. Rheumatologists need to be careful when tapering medication, particularly the biologics, as these are perhaps helping to temper cardiovascular inflammation, which could worsen when doses are reduced. “Antirheumatic treatment only is not good enough to decrease or normalize the cardiovascular risk of our patients,” he emphasized.

**Norwegian project shows how to integrate CVD assessment into routine practice**

In a separate presentation, Dr. Eirik Ilkahl, a PhD student at Diakonhjemmet Hospital in Oslo, discussed how some rheumatology clinics in Norway are successfully incorporating CVD risk screening.

Through the Norwegian Collaboration on Atherosclerotic disease in patients with Rheumatic joint diseases (NOCAR), which started in April 2014, annual cardiovascular disease risk evaluations of patients with inflammatory joint diseases are being implemented into the practices of 11 rheumatology outpatient clinics. While waiting for clinic appointments, patients are given electronic devices through which they can report cardiovascular risk factors via an electronic patient journal program called GoTreatIt Rheuma. From there, the clinic can order nonfasting lipid measurements and nurses can record patients’ blood pressure.

Then, using the ESC Systematic Coronary Risk Evaluation (SCORE) algorithm, the program automatically calculates a patient’s 10-year risk of a fatal CVD event. If the SCORE estimate is 5% or greater, the rheumatologist forwards a note to the patient’s primary care physician or cardiologist saying there is an indication for initiation of CVD-preventive measures such as medication or lifestyle changes.

Rheumatologists and rheumatology nurses also deliver brief advice regarding smoking cessation and healthy diet.

“The main aim of the project is to
raise awareness of the cardiovascular burden that these patients experience, and to ensure that patients with inflammatory joint diseases receive guideline-recommended cardiovascular preventive treatment,” Dr. Ikdahl said.

Of 6,150 patients defined as eligible for the NOCAR project in three of the centers, 41% (n = 2,519) received a CVD risk assessment during the first year and a half of the program, officers found in a recent review. Of those, 1,569 had RA, 418 had ankylosing spondylitis, 350 had psoriatic arthritis, and 122 had other spondyloarthritides.

Through the program, “a large number of high-risk patients have received screening that they would not otherwise have been offered,” Dr. Ikdahl said.

The major obstacles to successful implementation were time scarcity, defining a date for annual CVD risk assessment among patients who visit the clinics multiple times per year, and making sure lipids were measured before seeing the rheumatologist, he said. “We acknowledge there is room for improvement. It is challenging to implement new work tasks in an already busy rheumatology outpatient clinic, and since the project does not offer financial incentives to the participating centers, we rely on a collective effort and voluntary work based on resources already available.”

**Remember CVD, but don’t forget other comorbidities**

Other research presented by Dr. Laure Gossec, professor of rheumatology at Pitie-Salpétrière Hospital and Pierre & Marie Curie University in Paris, highlighted the importance of identifying all comorbidities and their risk factors in patients with rheumatic diseases, and not just cardiovascular disease.

Dr. Gossec presented the results of an initiative aiming to make the collection and management of comorbidities easier in routine rheumatologic practice. The aim was to develop a simple, more pragmatic form that could be used to help rheumatologists manage selected comorbidities, and know when to refer for other specialist assessment. The focus was on ischemic cardiovascular disease, malignancies, infections such as chronic bronchitis, gastrointestinal disease such as diverticulitis, osteoporosis, and depression.

A committee of 18 experts, both physicians and nurses, was convened to examine the results of a systematic literature review of recommendations on comorbidity management and come up with concise recommendations for rheumatologists. Each of their recommendations covered whether or not the comorbidity was present (yes/no/don’t know) and if screening had been undertaken, such as measurement of blood lipids, and when this had occurred if known. There was then guidance on how to interpret these findings, calculate risk, and what to do if findings were abnormal.

The project is ongoing, and so far the expert panel has developed a pragmatic document with forms to help collect, report, and manage each specific comorbidity and its known risk factors. But it is still perhaps too long to be feasibly used in everyday practice, Dr. Gossec conceded. So the aim is to create a short, 2-page form that could summarize the recommendations briefly, and also develop a questionnaire for the patient to fill out and understand how to self-manage some comorbidities.

“We feel that this is a way to disseminate and adapt to the national context for France the EULAR comorbidities initiative,” Dr. Gossec said. “It also defines exactly what rheumatologists should be doing and when they should refer, hopefully to the benefit of our patients.”

Dr. Sattar has participated in advisory boards for Amgen, AstraZeneca, Boehringer Ingelheim, Eli Lilly and UCB. He has also consulted for Merck and is a member of Roche’s speakers’ bureau. Dr. de Pablo and Dr. Nurmo-hamed reported no relevant financial disclosures. Dr. Ikdahl has received speaker’s honoraria from Pfizer. Dr. Gossec and coauthors have received honoraria from AbbVie France.
Anti-TNF agents may slow erosive hand osteoarthritis

BY KAREN BLUM
AND SARA FREEMAN

Tumor necrosis factor may play a role in erosive hand osteoarthritis, and treatments such as etanercept that target this cytokine may help prevent progression of the condition, according to the results of two studies presented at the congress.

In one of the studies, immunoscintigraphic detection of radiolabeled certolizumab pegol was used to show that tumor necrosis factor (TNF) was present in swollen finger joints. In another study, researchers looked to see if treatment with etanercept would have any specific effects on the joints of patients with erosive hand osteoarthritis (OA) and performed a separate analysis of the potential effect on synovitis and the effect on bone marrow lesions.

“We previously had the idea that TNF is an important cytokine in the pathogenesis of erosive [hand] osteoarthritis; but there have been no animal studies, and it’s very difficult to take biopsies or fluid aspiration from these small finger joints,” Dr. Ruth Wittoek, a staff rheumatologist at Ghent University Hospital in Belgium and a coauthor of all three studies, explained in a precongress interview. “We needed to look for other possibilities to really identify the presence of TNF in those affected joints.”

Dr. Wittoek and her associates used immunoscintigraphy to take static images of both hands of five patients with erosive OA immediately (less than 15 minutes) after administration of radiolabeled certolizumab pegol (early phase) and 4-6 hours following the injection (late phase).

The patients studied had erosive OA for a median of 8.4 years, and their median age was 55.6 years. All patients underwent clinical examination for presence of tenderness and palpable swelling of the joints and ultrasound 1 day prior to undergoing immunoscintigraphy.

All 18 interphalangeal (IP) finger joints were scored according to the anatomical phase scoring system on x-ray, and 90 IP finger joints were studied in total. The uptake of radiolabeled certolizumab pegol was semiquantitatively described as being absent, weak, or strong.

During the early phase following administration, uptake of the radiolabeled TNF inhibitor was seen in seven (7.8%) joints, although the uptake was described as weak in all cases. The radiolabeled TNF inhibitor was seen in 24 (26.7%) joints during the late phase following administration, with five instances described as strong uptake and the remaining 19 instances being weak uptake. No uptake of the radiolabeled TNF inhibitor was seen in metacarpophalangeal joints.

Uptake of the radiolabeled TNF inhibitor was linked to signs of disease activity, including tender, swollen, and radiographically active joints.

Late uptake was present in 12 (36.4%) of 33 tender joints and in 12 (21.1%) of 57 nontender joints (odds ratio, 2.1; 95% confidence interval, 0.8-5.6; P was nonsignificant).

The relationship was most pronounced with palpable joint swelling: Late uptake was present in 14 (61%) of 23 swollen joints and 10 (14.9%) of 67 nonswollen joints (OR, 8.9; 95% CI, 3.3-26.0; P less than .001).

Late uptake was present in 18 (29%) of 62 sonographically active joints (defined as any presence of effusion or synovial proliferation) but just 6 (21.4%) of 28 noninflamed joints (OR, 1.5; 95% CI, 0.5-4.3; P was nonsignificant).

Uptake of the radiolabeled TNF inhibitor was observed in all anatomical phases of erosive hand OA, Dr. Wittoek noted, but the strongest association was found during the final remodeling (R) phase.

“Soft-tissue swelling strongly correlated with uptake of certolizumab, meaning in these joints a lot of TNF was present,” Dr. Wittoek said. “These data further solidify the rationale for cytokine-directed therapies in erosive OA.”

Although the data provide proof of concept that TNF may be involved in erosive hand OA, the lack of a control tracer was noted as a limitation of the study after the presentation. Dr. Wittoek said that it would be interesting to examine that in a future study.

So, if TNF is present, what effect does anti-TNF therapy have on the joints in erosive hand OA?

That question was addressed in a multicenter, double-blind, randomized, placebo-controlled trial involving 90 patients who were randomized to receive either 50 mg of subcutaneous etanercept weekly for 24 weeks, then 25 mg weekly for the remainder of 1 year (45 patients), or placebo (45 patients). Participants were a mean age of 60 years, 81% were women, and 96% fulfilled the American College of Rheumatology hand OA criteria.

“Synovial inflammation is often present in erosive hand OA; moreover, synovitis is associated with pain and with structural damage after around 2 and a half years,” the lead study author, Dr. Margreet Kloppenburg, a professor of rheumatology at Leiden University Medical Center in the Netherlands, said in an interview.
“Therefore, we wanted to know whether blocking of synovial inflammation by a well-known drug such as etanercept would also have a positive effect on outcomes in erosive hand OA,” Dr. Kloppenburg explained.

The primary outcome measure was the level of OA pain assessed on a visual analog scale (VAS) at 24 weeks.

Secondary endpoints included assessment of hand function, quality of life, the number of tender joints, and grip strength after 4, 8, 12, 24, and 36 weeks, and after 1 year. Radiographic progression of IP joints was scored blindly at baseline, 24 weeks, and 1 year following the quantitative Ghent University Scoring System (GUSS). VAS pain was compared between treatment groups at 24 weeks and 1 year in intention-to-treat analyses.

Although etanercept was not superior to placebo on VAS pain at 24 weeks, it was superior to placebo both on pain and structural damage assessed by GUSS in the symptomatic and inflammatory patients who completed the study. The drug was especially effective in joints with signs of inflammation.

Overall, VAS pain in all patients decreased by 24.8 mm (95% CI, –29.2 to –20.5; P < .001) at 24 weeks. In intention-to-treat analysis, differences in pain between the groups were in favor of etanercept but did not reach statistical significance.

The inhibitory effect of etanercept on BMLs was more pronounced in joints with severe synovitis, was associated with being in the erosive and remodeling anatomical phases of erosive hand OA. Synovitis was not associated with those phases.

“We think that TNF-alpha plays a role in the pathophysiology of erosive OA via an effect on the subchondral bone,” Ms. Kroon said. “Because we saw that the beneficial effect of etanercept on BMLs was more pronounced in joints with synovitis at baseline, we think that, in an inflamed synovial hand joint, an interaction takes place between synovium and subchondral bone, which could be influenced by blocking TNF.”

Pfizer and UCB supported the investigator-initiated studies and provided the study drugs. Dr. Kloppenburg has received lecturing, consultancy, and investigator fees or grants from AbbVie, APPROACH, GlaxoSmithKline, Levicet, Pfizer, Servier, and UCB, all paid to her institution. All other authors declared no conflicts of interests.
Study examines predictors of nonresponse to viscosupplementation in knee OA

BY AMY KARON

Higher body mass index and radiologic severity were associated with lack of response to viscosupplementation in patients with knee osteoarthritis, according to a post hoc analysis of a multicentre, double-blind trial presented at the congress.

“This finding may impact our daily practice and help in considering viscosupplementation in future international recommendations. A more stringent selection of patients who are eligible for hyaluronic acid injection could optimize the effectiveness of treatment and limit injections in patients with risk factors for poor outcomes,” said Dr. Florent Eymard, who led the study and presented the findings.

Intra-articular hyaluronic acid injections are used worldwide to improve pain and function in patients with mild to moderate knee osteoarthritis, but response rates in most viscosupplementation trials have been 60%-70% at best, and predictors of treatment success are unclear, said Dr. Eymard, a rheumatologist at AP-HP Henri Mondor Hôpital in Créteil, France.

To explore risk factors for lack of response, he and his associates studied 166 patients with complete clinical and radiologic data who had participated in a trial of 205 patients with symptomatic knee osteoarthritis. The trial compared HANOX-M (HAppyVisc, LABRHA SAS, Lyon, France) – which combines sodium hyaluronate (1-1.5 megadaltons, 31 mg/2 mL) and mannitol 3.5% – with BioHA (Euflexxa, Ferring Pharmaceuticals, Parsippany, New Jersey, USA, 2.4-3.6 megadaltons, 20 mg/2 mL). Patients received three weekly intra-articular injections, and those who fulfilled the OMERACT-OARSI criteria 6 months later were classified as responders. The two study arms resembled each another clinically and demographically, enabling the data to be pooled for the secondary analysis, Dr. Eymard and his associates noted.

The average age of the patients in the subgroup was 65 years. They had about a 49-month history of knee osteoarthritis, and were typically overweight, with a mean body mass index (BMI) of nearly 28 kg/m², according to Dr. Eymard and his colleagues. At month 6, 68% of patients were considered responders, and average pain and total scores on the Western Ontario and McMaster Universities Arthritis Index had fallen by more than 40%. High BMI and severe radiographic narrowing of the tibiofemoral joint predicted lack of response in both the univariate and multivariate analyses. Older age and history of viscosupplementation or intra-articular corticosteroid injections showed the same trend, but did not reach statistical significance. However, when combined, these four risk factors showed “a strong cumulative impact” on lack of response, the researchers reported. Notably, patients who lacked these risk factors all met the criteria for response to viscosupplementation, but those with two risk factors had less than a 70% response rate, and those with all four risk factors had less than a 30% response rate.

Currently, viscosupplementation is commonly used in both obese patients and patients whose osteoarthritis is severe enough to merit total knee replacement, Dr. Eymard noted. Deciding whether to use viscosupplementation in these patients can be difficult, “but we can reasonably propose that patients older than 65 years, with severe radiological and symptomatic osteoarthritis, and no contraindication for surgery or anaesthesia, could be referred to a surgeon without prior viscosupplementation,” he added.

“However, we can continue to consider viscosupplementation in patients with severe radiological osteoarthritis if they are young, have many comorbidities, or refuse surgery.”

Dr. Eymard had no disclosures.
No major malformations ascribed to bisphosphonate use in pregnancy

**BY JEFF EVANS**

One of the largest studies of pregnancy outcomes after bisphosphonate exposure has found no evidence for major teratogenic effects in women with inflammatory diseases and glucocorticoid-induced osteoporosis and women with bone diseases.

The investigators for the French case-control study did find higher rates of neonatal complications and spontaneous abortion among infants of mothers with systemic inflammatory diseases and bisphosphonate use, but the higher rates could be the result of confounding because of the severity of underlying disease and exposure to other medications.

“I think if a woman is worried about bisphosphonate exposure during pregnancy, this study can bring her some reassuring news,” although it does not necessarily mean that bisphosphonates are safe during pregnancy, first author Aurélien Sokal said in an interview at the congress. He is a medical student at Beaujon Hospital, Clichy, France, but conducted the study with colleagues during his time in training in the rheumatology department at Paris-Sud University.

“Very little is known about the effect of bisphosphonates on pregnancy outcomes and fetal development,” Mr. Sokal said, and they are feared for possible teratogenic effects in pregnancy because of their long half-life in bone – where they can be released even 1 year after their administration – as well as their ability to cross the placenta and high affinity for high-turnover bones, such as those in a growing fetus. He also noted that abnormalities in bone length, low birth weights, and bone diseases have been observed in rats exposed to bisphosphonates during gestation.

The study compared 23 patients with inflammatory diseases and bisphosphonate exposure during pregnancy against 92 controls with inflammatory diseases but no exposure, and 16 with bone diseases and exposure to bisphosphonates against 64 healthy controls with no underlying disease or bisphosphonate use. The patients came from a database assembled by the French Reference Center of Teratogenic Agents (CRAT) in Paris that has collected information since 1975 on patients referred for any drug exposure during pregnancy and followed their care through the end of pregnancy.

The 39 patients who were exposed to bisphosphonates took the drugs during 1987-2014 within the 6 weeks preceding (n = 6) or during pregnancy (n = 33). They had a mean age of 33 years.

Systemic inflammatory diseases

The systemic inflammatory diseases found in women in the study included systemic lupus erythematosus (SLE), rheumatoid arthritis, antiphospholipid syndrome, systemic vasculitis, and other diseases. Of the 23 cases with systemic inflammatory diseases, 16 took risedronate, 5 took alendronate, 1 took etidronate, and the bisphosphonate was unknown in 1. Bisphosphonate exposure occurred before pregnancy in 1, during the first trimester in 21, second trimester in 4, third trimester in 4, and in all trimesters in 1.

Other types of medications were used significantly more often by patients with systemic inflammatory diseases than by controls: steroids (78% vs. 47%), methotrexate (26% vs. 5%), colchicine (17% vs. 2%), proton pump inhibitors (22% vs. 5%), and reproductive hormones (17% vs. 2%). Controls took antimalarials significantly more often (50% vs. 22%).

Voluntary abortions occurred at a similar rate in both exposed and unexposed women (12% vs. 9%), whereas significantly more therapeutic pregnancy terminations occurred among women exposed to bisphosphonates. 

**VIDEO HIGHLIGHTS:** Click here to watch a video interview with Aurélien Sokal.
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(17% vs. 1%). Live births occurred in 94% of the remaining exposed pregnant women, compared with 80% of controls.

Newborns were delivered at a mean of 38 weeks in both cases and controls, “I think if a woman is worried about bisphosphonate exposure during pregnancy, this study can bring her some reassuring news,” although it does not necessarily mean that bisphosphonates are safe during pregnancy.

and there were no differences in birth weight, length, or rate of congenital malformation.

The two malformations in neonates from exposed women had an uncertain link to bisphosphonates. One involved a neonate with severe malformative syndrome who had a mother with SLE but who was without exposure to known teratogenic drugs, and another with convulsant encephalopathy whose mother had systemic sclerosis and took pentoxifylline, cisapride, dihydroergocryptine, and colchicine.

However, cases had a 25% rate of neonatal complications, compared with a significantly lower 5% in controls. No infants had hypocalcemia.

Bone diseases

The 16 women with bone diseases included 9 with osteoporosis, 3 with malignancy, and 4 with miscellaneous bone conditions. A total of 5 received intravenous bisphosphonates and 11 received oral drugs (9 alendronate, 2 other). Most received a bisphosphonate in the first trimester (9 patients), but also 4 received it before pregnancy and 3 in the second trimester. More pregnancy terminations (voluntary or therapeutic) occurred among women with bone disease when compared with controls (19% vs. 3%), but the difference was not statistically significant. However in the remaining patients, live births occurred significantly less often in cases than in controls (69% vs. 100%). Birth weight, length, gestational age at birth, and the rates of congenital malformation and neonatal complications were otherwise similar.


The study is ongoing and continues to collect data on the follow-up of children, Mr. Sokal said.

The study had no specific funding, and none of the investigators had disclosures to report.
Website provides guide to keep people with RMDs working

BY KARI OAKES

An Irish website with a comprehensive suite of guides and a brand new e-learning program will help individuals with rheumatic and musculoskeletal diseases remain in the workforce, while also helping their employers and health care providers.

Fit for Work Ireland, launched in 2011 by Arthritis Ireland, offers a comprehensive suite of guidelines and trainings for those affected by rheumatic and musculoskeletal diseases (RMDs). This offering helps address a huge unmet need, according to Gráinne O’Leary of Arthritis Ireland, who talked at the congress about the impact the website has had.

In Ireland, approximately 7 million workdays per year are lost because of RMDs, according to a 2009 report by the Work Foundation. This represents about half of the total lost workdays in this small country of 4.5 million people, and means that the disease burden brings a huge personal and national cost, she said.

In her role as head of education and support services, said Ms. O’Leary, “My whole remit is developing and providing services and programs for people to enable them to live with the best quality of life that they can.”

Part of that remit was accomplished in 2011, when Ms. O’Leary and her Arthritis Ireland colleagues launched Fit for Work Ireland (www.arthritisireland.ie/go/fit_for_work), described as “a coalition of stakeholders including employer and employee representatives and health professionals with the key goal of improving employees’ ability to work with RMDs and reducing the impact of RMDs on workplace absenteeism.”

Fit for Work Ireland, said Ms. O’Leary, pulled together the employers’ representatives, one of the largest unions, and various medical associations, including the Irish Society for Rheumatology, representatives from physiotherapy and occupational therapy, and insurers.

The tripartite approach that underpins Fit for Work Ireland provides information and tools for employees, employers, and health care professionals. This comprehensive mindset is the only way to adequately address the difficulties faced by those with RMDs, Ms. O’Leary said. “Many people with RMDs are struggling to maintain and retain their work,” and work is not only an economic necessity, but a key component of personal identity for many, she said.

“One of the things that we did is we put together two guides,” Ms. O’Leary said; one for the employee and one for the employer. Although the employee with an RMD may know that he or she is struggling at work, or that frequent appointments may require an altered work schedule, that individual may not know what creative solutions may be feasible, or even what accommodations are legally available.

Similarly, an employer may not understand that accommodations could help a valued employee retain a position. “Employers are in a very difficult position, and very often they don’t understand what RMDs are ... and they’re unsure about the type of support that their workers need.” Ms. O’Leary said that the employer guide outlines specific aspects of the support that an employer might consider for an individual with an RMD. The accommodations required may actually be quite simple, such as a flexible schedule, or ergonomic adaptations, but they can be key in enabling workers to stay employed, she said.

The general practitioner is an important player in helping individuals with RMDs maintain employment and receive reasonable accommodations. “If an individual goes to them with a complaint, and may be signed out of work for a period of time, what does that interaction consist of? Is there a dialogue about the person’s ability to do their job ... is there any kind of solution proposed? Very often there isn’t, so we began to look at these interrelationships,” Ms. O’Leary said.

Ms. O’Leary said that Arthritis Ireland just finalized a Fit for Work online program that provides video training and scenarios for employers, employees, and health professionals. “It provides a comprehensive package not only to employees, but to employers and health care professionals.”

Ms. O’Leary reported no conflicts of interest. Fit for Work Ireland is supported by AbbVie and by Irish Life, an Ireland-based insurance company.
Online tools seek to engage young patients with RMDs

BY GREGORY TWACHTMAN

As more young patients are getting diagnosed with rheumatic and musculoskeletal diseases (RMDs), the need to engage them with online resources has become more important, particularly with resources such as online forums.

Wendy Olsder of Youth-R-Well.com of Schiedam, the Netherlands, presented information on the guide that Youth-R-Well.com developed with a decade of experience in the Netherlands to help other countries establish online communities to serve youth with RMDs. The organization is in the early stages of testing its guide in three participating countries (Romania, Poland, and Italy) and early results show a promising start.

“On the forum, people can ask questions and others can answer them,” Ms. Olsder said in an interview. “It is really an interactive site” that also features cartoons, photos, monthly columns, and relevant information about diseases.

“I think for youth it works better to have an online youth platform. They want to chat more online instead of meetings,” Ms. Olsder said. For example, in the Netherlands, we have meetings with older people and I think for youth, they are really boring. It’s also really easy to go online. For some people, it’s hard to talk about their disease and go to certain meetings, and [with] the online platform, you can just read things about your disease and [it becomes easier to relate to].”

Similarly, Petra Balazova of Young PARE and the Slovak League Against Rheumatism presented the EULAR Young PARE network’s new online resource that launched in March 2016, the Virtual Knowledge Centre, which provides tools to youth groups to help build online resources.

“We created this toolbox because we wanted to establish a database with information,” Ms. Balazova said. “We would like to create a European network of RMD youth groups.”

The goal of this network ultimately would be to establish a database about national youth organizations; create a European network of RMD youth groups to exchange best practices; provide support to national youth organizations; and ensure that these organizations remain in contact to allow for knowledge to continually transfer.

There is a role for physicians to play, even though these tools and resources are primarily designed for patients and are not necessarily clinical in nature but are more about peer support and lifestyle, according to the presenters. They noted the importance of alerting physicians to these resources so that they may be able to tell their patients about them.

“This specific subgroup of patients is often not recognized as having specific priorities compared to other patients,” said Dr. Alessia Alunno of the University of Perugia, Italy. “So the effort should be first to build strong relationships with patients and make them believe that any concern they have should be raised so they should feel free to discuss any problems they may have, any questions regarding treatment, regarding the disease, regarding any information they may need.”

Dr. Alunno discussed the role of health professionals in improving shared decision making with young RMD patients.

She noted that there is a lot of misinformation about diseases on the Internet, and she encourages doctors to learn about trustworthy resources to guide their patients to.

“We should provide them with the tools to access the information. The same for social media or for other platforms. We need to be sure that patients can have access to a wide range of information that may be beyond the hospital or the outpatient clinic,” Dr. Alunno said.

None of the presenters have relevant financial disclosures.
Success in health technology development requires collaboration

BY NICOLLA GARRETT

The creation of health technology apps must involve the collaboration of developers with end users on their design if improved patient outcomes are to be achieved, according to three speakers at the congress who took attendees through their experience collaborating to develop technology designed to improve patient outcomes.

Involving the end user in the design of a physical activity self-management app for people with rheumatoid arthritis (RA) called tRAp not only improved its effectiveness and usability, said Dr. Asa Revenäs of the department of neurobiology at the Karolinska Institute in Stockholm, but it also gave it more credibility.

“People living with a chronic disease have expert knowledge important for health care to use in the development and improvement of health care services,” she said in an interview.

By collaborating with future users, Dr. Revenäs and her colleagues were able to refine the service, as well as learn what was important for people with RA when it came to maintaining a physically active lifestyle.

Speaker Karin Håkansson of Stocksund, Sweden, who gave input into the development of tRAp, agreed that to produce an app, the developer needs to truly understand what it is like to live with the condition.

By sharing their experiences, people living with the disease can provide a greater insight into what will, and what will not, be successful and useful as an end product.

“Working alongside the scientists and developers, I believe we create a more patient-friendly outcome empowering the patients in the process,” Ms. Håkansson said in an interview.

However, collaboration involving many different perspectives can also raise unique challenges, such as finding the time and resources to incorporate the opinion of end users during the development stage.

Dr. Sanne van der Weegen, an eHealth researcher from Maastricht University in the Netherlands, discussed how developers could engage the perspectives of different end users in the various stages of development.

Dr. van der Weegen said that because end users sometimes find it difficult to come up with ideas on the spot, a solution is to use probe kits that allow end-users to take their time to come up with answers.

Ms. Håkansson suggested managing the end user input session by using a moderator who is able to encourage and bring out the best from the group.

“When I participated, I was happy to do so and share my experience, but it took time to form trust within the group and create a good environment,” she said.

It was also a good idea for developers to limit the target group to those patients whose symptoms have a large impact on their daily lives, she added.
Cost, access, and lack of knowledge remain barriers to measuring physical activity in patients with rheumatic diseases, according to international surveys of patients and health providers that were presented at the congress.

“From our clinical practice, we know that assessing physical activity and aerobic capacity is important to managing inflammatory arthritis,” said Bente Appel Esbensen, PhD, research manager and associate professor at Glostrup Hospital and the University of Copenhagen. But few studies have characterized baseline knowledge or use of these physical activity tools, or associated barriers and motivators, she added. Therefore, she and her associates conducted an online survey of approximately 300 nurses, physiotherapists, and occupational therapists from Sweden, Denmark, Belgium, and Ireland. They also surveyed nearly 800 patients from these countries who had rheumatoid arthritis, ankylosing spondylitis, or psoriatic arthritis.

Most health professionals agreed that measuring physical activity is important, in keeping with current practice recommendations. “But the use of physical activity tools in clinics was low, as was confidence in using them,” said Birgitta Nordgren, PhD, a physiotherapist with the Karolinska Institute in Solna, Sweden. Health professionals need to support and encourage each other to use physical activity tools in practice, and also need more education about these tools, she added.

Likewise, the study found that patients understood the value of objectively measuring physical activity, but usually were unfamiliar with options for doing so. “There is a strong need for further education around measuring physical activity and aerobic capacity,” Dr. Esbensen said.

Some providers and patients are already using wearable sensors and smartphone applications to measure physical activity, noted Thijs Swinnen, a physiotherapist and researcher at University Hospitals Leuven in Belgium. “But it is important to scrutinize these novel tools in the same way as any other outcome measure in rheumatology,” he emphasized. He discussed how to use Outcome Measures in Rheumatology, or OMERACT, to determine which physical activity tools are most reliable, responsive, and feasible for clinical use.

“Research specifically in this patient group is generally lacking,” he noted. “An international initiative to allow for head-to-head comparisons of devices is mandatory, but challenging, given the high cost and constantly changing market of devices.”

It is also unclear how best to translate scientific evidence on physical activity into rheumatology practice, Mr. Swinnen said. Physical activity needs to be considered alongside other lifestyle factors, and simple tools that pass the OMERACT filter and motivate patients to live healthily, despite their challenges, are very much needed, he added.

Even if they are reliable in clinical trials, self-reported measures of physical activity tend to be unreliable and inaccurate when used in clinical settings, Mr. Swinnen noted. On the other hand, “the most sophisticated devices to measure physical activity are too expensive and require too much data for easy clinical use,” he said. “For patients, single-sensor devices are affordable, best known, and most easily adopted. But because they are only valid for certain physical activities, such as counting steps during walking, a skilled health professional needs to guide the choice of device in combination with the best physical activity for that particular patient.”

The researchers had no disclosures.
Study identifies postgraduate health professional education shortcomings

BY DOUG BRUNK

With the notable exception of nurses, postgraduate rheumatology education for health professionals in most European countries is lacking, results from a new study suggest.

“There is a considerable need for postgraduate rheumatology education for health professionals in Europe,” said Prof. Theodora Vliet Vlieland, who presented the study at the congress. “As time and financial constraints were identified as important barriers, educational offerings in people’s home countries and online education were very much desired. The English language was found to be an important barrier to take part in educational offerings for health professionals in many countries, indicating a need for innovative solutions.”

In a project that received financial support from EULAR, Prof. Vliet Vlieland, of the department of Orthopaedics, Rehabilitation and Physical Therapy at Leiden University Medical Centre, the Netherlands, and her associates from the EULAR Standing Committee of Health Professionals in Rheumatology set out to assess the availability of postgraduate education for rheumatology health professionals in Europe, to define their educational needs, and to identify potential barriers.

There were two components to the study: in-person and telephone interviews with representatives of rheumatology health professional organisations, plus an online survey for individual health professionals. On a scale of 0-10, respondents were asked to answer questions on availability of postgraduate education, familiarity with EULAR and its educational offerings, needs regarding contents and mode of education delivery, and potential barriers to education.

The researchers conducted interviews with representatives from 17 countries. Of these, the number of countries where postgraduate rheumatology education was reported to be available was highest for nurses (13 countries), followed by physical therapists (8 countries), occupational therapists (7 countries), and professionals in other disciplines (3 or fewer countries).

Prof. Vliet Vlieland reported that 1,041 respondents from 19 countries completed the online survey, which was translated into eight different languages. “The number of respondents was overwhelming, indicating that the topic is extremely relevant,” she said.

Their mean age was 41 years, 86% were female, 56% reported being familiar with EULAR, 21% had attended one or more EULAR annual conferences, and 14% were familiar with EULAR’s online course offerings. Educational need scores related to content were highest for “inflammatory arthritis” and “connective tissue diseases,” while scores related to desired mode of delivery were highest for “courses in English organised in own country” and “EULAR online course.” The most commonly cited perceived barriers to participate in educational offerings were “lack of resources,” “lack of time,” and “lack of mastery of the English language” (the latter limited to participants who completed the translated survey).

Prof. Vliet Vlieland acknowledged certain limitations of the study, including the fact that, since a link to the survey was distributed by national presidents of rheumatology health professional organisations, “we do not exactly know how large our target population of health professionals was, and thus, to what extent the respondents were representative of all health professionals in Europe. In particular from Eastern European countries, the response was relatively low.”

Prof. Vliet Vlieland reported having no financial disclosures.
Outcome Measures Library sees success in its first 2 years

BY NICOLA GARRETT

The first 2 years of the EULAR Outcome Measures Library’s existence has demonstrated its value to many users, including a network of individuals who have used it to increase awareness of and interest in patient-reported outcome measures in the rheumatology community, according to Dr. Isabel Castrejón.

The Outcome Measures Library (OML) was created in November 2013 in direct response to the increasing importance placed on rheumatology patients’ perceptions of health and their priorities and preferences in making therapeutic decisions, said Dr. Castrejón, who is an assistant professor in the division of rheumatology at Rush University Medical Center in Chicago.

Patient-reported outcomes (PROs) can distinguish active from control treatment as efficiently as other conventional measures, such as swollen joint counts or laboratory tests, and they “allow patients to get involved in their own care,” Dr. Castrejón said in an interview. “But despite being increasingly recognised as important measures, there is great heterogeneity in their use.”

In response to this situation, EULAR sought to develop the OML as a database that standardised and enhanced validated PROs in rheumatic and musculoskeletal diseases. The OML includes 138 generic and disease-specific patient-reported outcomes (PROs) for some of the most common rheumatological diseases such as rheumatoid arthritis, osteoarthritis, spondyloarthritis, fibromyalgia, systemic lupus erythematosus, low back pain, osteoporosis, and gout. It includes a detailed description of each instrument as well as recommendations and rules for use, information about its validation and the instrument itself, and versions in several EU languages.

The library is continually evolving and since its creation has been increasingly used and updated by collaborators, Dr. Castrejón said. For instance, in its first 2 years, the OML has received over 41,000 page views and almost 26,000 visits. The PROs that are downloaded most frequently are the Evaluation of Ankylosing Spondylitis Quality of Life (EASI-QOL), the Multidimensional Health Assessment Questionnaire (MDHAQ), the RA Quality of Life scale (RAQoL), and the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC).

Interestingly, users tend to prefer accessing the library through mobile devices such as the iPad, Android, and iPhone. France and Germany top the list of most frequent users, followed by the United Kingdom, Ukraine, and Spain. The library is also popular with non-European countries, with the United States making up almost 20% of total users.

According to Dr. Castrejón, perhaps the OML’s biggest success to date is the creation of a network of PROs users who have ultimately improved the rheumatology community’s knowledge and interest in PROs and validation.

Terms like “patient-reported outcome measures” and “validation” are often thought to be the domain of researchers only. However, the library was created with both rheumatic and musculoskeletal disease researchers and clinicians in mind.

“We are convinced that this dynamic library with a structured access to a growing database of validated PROs is going to be a useful tool for many researchers and clinicians,” Dr. Castrejón said.

“In the era of ‘treat to target,’ clinicians need to get familiarised with measurement tools, and PROs are the ones more feasible for routine care,” she said.

The library is freely available online (oml.eular.org) and EULAR encourages anyone with an interest in PROs to collaborate and get involved.
FDG-PET/CT useful for finding cause of fever, inflammation of unknown origin

BY BRIAN HOYLE

The use of combined modality imaging with 18F-fluorodeoxyglucose-PET/CT (FDG-PET/CT) may provide enough information to make a definitive diagnosis in patients who present with fever or inflammation of unknown origin, particularly in those who are aged 50 years or older, have elevated C-reactive protein, and have no fever, according to findings from a single-center study of 240 cases.

The retrospective study of patients seen at the University Clinic of Erlangen (Germany) during 2007-2015 found that FDG-PET/CT was helpful in finding a diagnosis for a majority of patients with fever of unknown origin (FUO) and inflammation of unknown origin (IUO).

In an interview prior to his presentation at the congress, the study’s senior investigator Dr. Georg Schett said that “By implementing a single FDG-PET/CT scan in a structured diagnostic approach for patients with FUO or IUO we were able to catch the underlying disease in the majority [79%] of the 240 patients studied. In the FUO group the leading diagnosis was adult-onset Still’s disease, and in the IUO group it was large-vessel vasculitis and polymyalgia rheumatica.”

FUO was defined about 50 years ago as several episodes of temperature exceeding 38.3°C that accompany an illness lasting more than 3 weeks, with no diagnosis after a week of testing following hospital admittance. If inflammation but no fever is involved, the condition is termed IUO.

FUO and IUO are severe, sometimes even life-threatening conditions, in which the cause of fever and inflammation, respectively, has not been defined using standard diagnostic approaches. This makes diagnosis challenging and requires a costly and complicated work-up. A delayed diagnosis can be serious, resulting in severe organ damage in patients with FUO and IUO due to the underlying, and uncontrolled, inflammatory disease.

The current diagnostic approaches for FUO and IUO include a thorough medical history, physical examination, laboratory testing, and imaging. FDG-PET/CT imaging could be potentially useful for the diagnosis of FUO/IUO because of its high-resolution detection of inflammation and malignancy. Dr. Schett and his colleagues explored this potential and examined clinical markers that would increase the likelihood of accurate FDG-PET/CT-based diagnosis in patients presenting with FUO or IUO.

The 240 patients in the study included 72 with FUO and 142 with IUO; the remaining 26 no longer fulfilled the criteria for either condition when they presented to the clinic (“ex-FUO/IUO” patients). The diagnostic work-up included FDG-PET/CT scans. Scans were considered to be positive when uptake of the tracer occurred at foci in addition to the other expected locations. The investigators explored whether the scans aided the final diagnosis, with multivariable regression analysis clarifying clinical parameters that aided the success of the scans in patients with and without FUO or IUO.

The mean age was 52 for FUO patients, 61 for IUO, and 51 for patients who no longer had IUO or FUO symptoms at presentation. These patients had mean C-reactive protein (CRP) levels of 95, 48, and 2 mg/L, respectively. Males comprised 64% of FUO, 40% of IUO, and 58% of ex-FUO/IUO patients.

FDG-PET/CT was helpful in finding the diagnosis in 57% of all patients and 72% of the patients with a later diagnosis. A definitive diagnosis was not reached in 29% of patients with FUO and 17% of patients with IUO. Predictive markers for a diagnostic FDG-PET/CT for FUO and IUO were...
age over 50 years (P = .002 and P = .005, respectively), CRP level over 30 mg/L (P = .003 and P = .005, respectively), and the absence of fever (both P = .003). If all three parameters were fulfilled, FDG-PET/CT was diagnostic in nearly 80% of the cases, while it was successful in only 8% of cases where none of the three parameters was met.

The latter finding is particularly important, according to Dr. Schett, as it “indicates which patient subgroup is profiting the most from FDG-PET/CT.”

“FUO and IUO patients should be referred to specialized centers where FDG-PET/CT scanning is available to improve diagnosis. Simple clinical parameters such as age, CRP-level, and presence/absence of fever can guide targeted use of FDG-PET/CT,” said Dr. Schett, director of the department of internal medicine III and the Institute for Clinical Immunology at the University of Erlangen-Nuremberg (Germany).

False-positive results with FDG-PET/CT – when patients had tracer uptake that did not lead to diagnosis of the underlying diseases – are a challenge. “False-positives happen quite often due to activation of bone marrow and lymph node metabolism during inflammation, which does not support diagnosis,” Dr. Schett said. He added that, when tracer uptake associated with systemic inflammation was not considered, false positives were much less common. False-negative results – when FDG-PET/CT was negative but a diagnosis was made using other approaches – were rare, occurring in only 12 out of the 240 patients.

The research will support establishing recommendations for the use of FDG-PET/CT in FUO and IUO patients. Other patients could benefit as well. “It may be important to investigate also those patients who were referred for FUO or IUO but do not show fever or inflammation at time of admission,” Dr. Schett said. Of these ex-FUO/IUO patients, four were diagnosed with IgG4-related disease and three with familial Mediterranean syndrome by applying FDG-PET/CT.

Dr. Schett and the other authors had no disclosures.
Giant cell arteritis survival doubled in the past 2 decades

BY SARA FREEMAN

The survival of patients with giant cell arteritis has more than doubled in the past 20 years, according to the results of a population-based study presented at the congress.

Comparing two cohorts of patients with giant cell arteritis (GCA) – one diagnosed between 1997 and 2004 and the other between 2005 and 2012 – researchers supported by Arthritis Research Canada found that the adjusted relative risks for death over the two time periods were 3.62 (95% confidence interval, 3.04-4.32) and 1.41 (95% CI, 1.15-1.74), respectively, when compared against individuals in the general population.

“The risk of death from GCA over time has decreased,” noted principal study investigator Dr. J. Antonio Aviña-Zubieta in an interview ahead of the congress.

“We were not expecting such high mortality in the earlier GCA cohort [almost five times the general population]. GCA is a disease of older individuals, therefore the background risk for the individuals without GCA is already high, making it difficult to find statistically significant differences. In addition, we were not expecting such a dramatic improvement in the recent cohort, where the risk of death is approaching the baseline risk of the general population,” he observed.

Dr. Aviña-Zubieta, who is in the department of medicine at the University of British Columbia in Vancouver, and a scientist at Arthritis Research Canada, noted that improved mortality also was seen in individuals without GCA over the two time periods, but this was not as dramatic as in the GCA cohorts.

“This suggests that at least some of the improvement in the GCA cohort is likely related to better care in general.”

Improved survival over time has been noted recently in several rheumatic diseases, such as systemic lupus erythematosus and rheumatoid arthritis, and Dr. Aviña-Zubieta’s research group wondered if the same might be true in systemic vasculitis.

“Given that GCA is the most frequent adult systemic vasculitis, we decided to test this question. Furthermore, given that our cohort is a population-based study, we thought that our result could be generalizable to the general population,” he said.

The study, which was funded by the Canadian Institutes of Health Research, involved obtaining data from an administrative health database on all newly diagnosed cases of GCA (n = 1,009) occurring between 1997 and 2012 in British Columbia, Canada. Cases were each matched by age, gender, and time of entry into the database to 10 non-GCA cases as controls (n = 10,009).

The mean age of participants in the GCA and non-GCA groups was 76 years, and 73% of participants in each group were female. As expected, individuals with GCA were more likely than those without the disease to have preexisting diseases such as hypertension (48.5% vs. 43.5%, P = .001), chronic obstructive pulmonary disease (15% vs. 11.4%, P less than .001), or angina (11.6% vs. 7%, P less than .001); to be taking medications; and to use health care resources to a greater extent.

The definition used to define a case of GCA was quite strict according to Lindsay Belvedere, a research assistant at Arthritis Research Canada and a master in public health student at Brigham Young University in Provo, Utah, who presented the study’s findings. Cases were required to have one ICD-9 or ICD-10 code for GCA given to them by a rheumatologist or after hospitalization or two ICD-9 or ICD-10 codes given on two separate occasions by a nonrheumatologist physician, and also they had to have received at least one prescription for glucocorticoids.

“This definition has been used in previous studies and been found to have a positive predictive value of 91%,” she observed. “To further increase the specificity of our case definition we excluded those who, following their diagnosis for GCA, received a diagnosis for another type of inflammatory arthritis such as psoriatic arthritis.” In addition, to ensure only incident cases were included in the cohort, patients with a GCA diagnosis prior to 1996 were also excluded from the dataset.

The early (1997-2004) versus the late (2005-2012) GCA cohort was found to have “considerably higher” mortality, with 373.7 versus 87.5 cases per 1,000 person-years. By comparison, there was a much smaller improvement in mortality during the two periods in the non-GCA cohort (75.9 vs. 48.6 cases per 1,000 person-years).

“These findings suggest that health

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care in general has improved, but more 
so in individuals with a serious disease 
such as GCA,” Dr. Aviña-Zubieta ob-
serve.d. Whether this is related to pa-
tients being diagnosed earlier, different 
treatment approaches, better manage-
ment of complications, or better strat-
egies to prevent complications remains 
to be tested, he said.

What is certain is that, “in a publicly 
funded health care system, this is good 
news.” Dr. Aviña-Zubieta additionally 
commented: “We need to find out what 
were the cause-specific outcomes which 
have improved – for example, cardio-
vascular disease, infections, or perhaps 
cancer – and which ones did not, so we 
can plan how to tackle them.”

Histologic pattern on biopsy 
linked to survival
Also at the meeting, Dr. Pierluigi Mac-
chioni of Arcispedale S. Maria Nuova 
– IRCCS in Reggio Emilia, Italy, pre-

The EULAR 2016 Report

Lupus may confer higher risk for cervical cancer

BY SARA FREEMAN

Women with systemic lupus ery-

The study’s results indicate that the 
the highest risk for cervical dysplasia or in-
vasive cancer occurred among women 
with SLE who were using immuno-

The results highlight the importance 
of women with SLE attending cervi-
cal cancer screening appointments, 
according to the researchers, who are 
from the Karolinska Institute in Stock-
holm, Linköping (Sweden) University, 
and Stanford (Calif.) University.

“At this time, we cannot comment 
on whether changes to screening pro-
grams are necessary, especially given 
there are considerable differences in 
cervical screening between countries,” 
lead study author Dr. Hjalmar Wad-
ström said in an interview ahead of 
the study’s presentation at the congress.

Dr. Wadström, who is an MD-PhD 
student at the Karolinska Institute 
working under the supervision of Dr. 
Johan As Kling, explained that SLE is 
associated with various immunologic 
aberrations and is typically treated with 
immunomodulatory regimens. These 
regimens, however, have been linked to 
an increased risk of cervical neoplasia.

“Therefore, determining the risk 
among women with SLE is of direct 
clinical relevance,” he said. “Cervical 
cancer screening is important in 
the prevention of cervical cancer.”

To date, there have been few studies 
looking at the topic, and, as SLE is a 
relatively rare disease and the devel-

outcome, the study aimed to better 
estimate the risk.

Data from national Swedish patient 
and pharmacy registers were used 
to assemble a cohort of almost 5,000 
women with SLE and a matched 
cohort of more than 28,000 women 
without SLE from the general Swedish 
population. The average age at the 
start of follow-up was 51 years, and 
about 40% of women were taking oral 
corticosteroids.

A total of 121 events occurred in the 
4,550 women with SLE over the course 
of 23,136 total follow-up years. In com-
parison, there were 336 events in the 
28,113 women without SLE from the 
general population over the course of 
155,543 total years of follow-up.

This produced a hazard ratio for 
cervical neoplasia in women with SLE 
versus those without of 2.12 (95% 
confidence interval, 1.65-2.71). The 
analysis was adjusted for multiple
confounding factors, including family history of cervical cancer and prior cervical screening in the 5 years before the start of follow-up.

Dr. Askling, who presented the findings during a press conference at the meeting, noted that just 5 of the 121 events seen in the overall SLE cohort were invasive cancers and the other events were premalignant changes, which included cervical intraepithelial neoplasia (CIN) stage 1, 2, and 3. “This is as it should be in the population; most events that you pick up in a screening program are premalignant,” he said.

Within the SLE cohort, two subcohorts of women also were identified: those taking hydroxychloroquine (n = 1,783) and those taking immunosuppressive drugs (n = 1,981). One of the reasons for looking at this is that treatment may serve as a proxy for the severity of disease, Dr. Wadström explained.

“SLE is a heterogeneous disease with numerous phenotypes that span from mild to life-threatening systemic disease,” he said. “Patients treated with an antimalarial, with or without oral steroids exclusively, tend to represent less severe cases, while more severe manifestations and organ involvement may necessitate potent cytotoxic immunosuppressive therapy.”

Adjusted HRs for cervical neoplasia comparing women with SLE taking immunosuppressive drugs with those taking antimalarial medication was 1.83 (95% CI, 1.15-2.91).

So what does this mean for clinical practice?

“We think it’s important that women with SLE, especially those with severe disease who are being treated with systemic immunosuppressants, attend cervical screening,” Dr. Wadström said.

Dr. Askling commented that, thankfully, women with SLE seemed to be just as adherent to attending cervical screening appointments as women in the general population. He noted that it was important for clinicians to recognize that women with SLE do appear to have an increased risk for cervical changes and to ensure that they understand the need for continued adherence. “We don’t think at this stage that any additional measures should be taken,” he said.

But should all women with SLE be vaccinated against infection with the human papillomavirus, a known cause of cervical cancer? Dr. Askling said that since the women in the current study were in their 50s, it is not clear if such a move would be of benefit, certainly not when compared with vaccinating younger women. “Yes, we remember vaccination,” he said. “No, it doesn’t solve the problem for now, it solves the problem for the future.”

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