Welcome to the EULAR 2019 Report

The Annual European Congress of Rheumatology 2019, hosted by the European League Against Rheumatism (EULAR) and jointly organised with the Paediatric Rheumatology European Society (PReS), once again demonstrated itself as the prime platform for rheumatology information exchange and professional education in Europe and for the world. More than 14,500 attendees from 120 countries came to this year’s EULAR Congress in Madrid to hear the best in rheumatology research and clinical advances. The scientific programme included presentations carefully selected from 4,900 abstracts submitted, including many involving paediatric rheumatic and musculoskeletal diseases.

The EULAR 2019 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 practice medicine. We hope that you will enjoy this synthesis of the latest in rheumatology clinical research.

A number of the research reports that you will find in the EULAR 2019 Report 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 3-6 June in Frankfurt, Germany, for EULAR 2020!

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The EULAR 2019 Report
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EULAR keeps csDMARDs as top PsA drugs

The draft revision of EULAR’s recommendations for managing psoriatic arthritis sticks with the group’s already-existing conviction that psoriatic arthritis treatment best starts with an NSAID, and if that fails follow with a conventional synthetic antirheumatic drug such as methotrexate, a position in stark contrast with the 2018 recommendation from the American College of Rheumatology to first treat with a tumour necrosis factor (TNF) inhibitor.

For patients with psoriatic arthritis (PsA) manifesting with polyarthritis, conventional synthetic disease-modifying antirheumatic drugs (csDMARDs) “should be first,” and should “start rapidly” if brief, initial treatment with an NSAID proves inadequate, Prof. Laure Gossec said while presenting a draft version of an update to the EULAR PsA management recommendations at the European Congress of Rheumatology.

The EULAR recommendations-revision panel had about the same advice for managing PsA patients with oligo- and monoarthritis, or peripheral arthritis. For oligo- and monoarthritis, “consider a csDMARD after failing NSAIDS, but also consider the patient’s prognostic factors,” like structural damage, and dactylitis. For PsA patients with peripheral arthritis, “it still makes sense to keep csDMARDs as the first-line treatment,” said Prof. Gossec, professor of rheumatology at Pitie-Salpetriere Hospital and Sorbonne University, Paris.

The list of csDMARDs she cited included not just methotrexate, still the top csDMARD, but also sulfasalazine and leflunomide as alternatives, she noted, with methotrexate also the preferred csDMARD for patients with skin involvement. When a PsA patient fails at least one csDMARD, then switching to a biologic DMARD is recommended. For a patient with skin involvement, a drug that targets interleukin-17 or IL-12 and -23 is preferred. If skin involvement is not a major issue, then treatment with a TNF inhibitor is equally valid, she said.

The 2018 PsA management guideline from the American College of Rheumatology (ACR) proposed a strikingly different sequence, endorsing initial treatment with a TNF inhibitor first over all other options, including methotrexate and other “oral small molecules” (the ACR term for csDMARD), and also including NSAIDs [Arthritis Rheumatol. 2019 Jan;71(1):5-32].

This schism between EULAR and the ACR could be seen as predictable, given the different constraints the two societies have set for themselves.

“EULAR recommendations take into account drug costs; the ACR guideline is supposed to be agnostic to costs,” explained Dr. Philip J. Mease, a rheumatologist at Swedish Medical Center in Seattle and a member of the ACR panel that wrote the 2018 PsA guideline.

In fact it was a study Dr. Mease recently led and reported results from that provided the most recent and perhaps best assessment of a TNF inhibitor, compared with methotrexate, as initial treatment for PsA, with findings that suggest that, although the advice from the two societies may sharply differ, the viewpoints of both groups are evidence based.

The SEAM-PsA (Study of Etanercept and Methotrexate in Subjects With Psoriatic Arthritis) trial randomised 851 PsA patients receiving their first treatment to methotrexate only, the TNF inhibitor etanercept only, or both drugs. The study’s two coprimary outcomes, the ACR 20 and minimal disease activity responses after 24 weeks, showed that etanercept monotherapy produced these responses in 61% and 36% of patients, respectively, while methotrexate monotherapy produced response rates of 51% and 23%, respectively. Both these differences between etanercept monotherapy and methotrexate monotherapy were statistically significant. Combining methotrexate with etanercept did not produce a significant improvement over etanercept alone.

Interpreting the meaning of this finding for clinical practice “depends on the lens you look through,” Dr. Mease said in an interview. “A lot of patients respond to methotrexate, which is good when treatment resources are challenged. But when there is no resource challenge, the data support going straight to a TNF inhibitor.”
Obesity might be targetable driver of psoriatic arthritis progression

Two sets of data presented at the European Congress of Rheumatology support the potential for weight loss to be a valuable adjunctive strategy for improving outcomes in patients with psoriatic arthritis.

One set, drawn from the ongoing PsABio observational study, correlated increasing body mass index with greater disease activity and greater disability. Another, based on patients followed for 12 months, showed that a weight loss of about 15% is associated with a significant reduction in psoriatic arthritis (PsA) activity.

“As clinicians, we largely focus on drugs in the treatment of PsA, but these data draw attention to obesity as a potential target for improving outcomes in PsA,” said Dr. Stefan Siebert, a rheumatologist at the Institute of Infection, Immunity, and Inflammation at the University of Glasgow.

Dr. Siebert cautioned that his data show association, not causation, but he said these data add to a growing body of evidence that provide compelling support for trials to test the premise that weight loss improves outcomes.

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Prof. Gossec confirmed the importance of the SEAM-PsA findings in the writing panel’s decision during discussion of the draft, replying to a question about consideration of the study’s findings. “We carefully looked at the SEAM-PsA trial results, which provide some of the only data we have on methotrexate” for PsA. “We felt that the results were in favor of methotrexate’s efficacy, and therefore did not go against our proposal to keep a graduated approach starting with a csDMARD.”

Patients who fail to receive adequate relief from a csDMARD could then try a biologic DMARD – a TNF inhibitor, IL-17 inhibitor, or IL-12/23 inhibitor, Prof. Gossec said. When skin involvement is minimal, any of these options are possible, she said. If skin involvement is significant, the panel recommended preferentially using an IL-17 or IL-12/23 inhibitor based on head-to-head trials in patients with psoriasis, she said.

When a biologic DMARD is not appropriate or fails, another option is to then try a targeted synthetic DMARD, such as a Janus kinase inhibitor. When none of these options are appropriate, or they all fail, another option for patients with mild oligo- or monoarthritis or in patients with limited skin involvement is apremilast, a phosphodiesterase-4 inhibitor. The draft recommendations also advise clinicians to be sure to distinguish fibromyalgia pain from enthesitis involvement, and they introduce the possibility of, with “great caution,” tapering down DMARD treatment in PsA patients who show sustained remission.

Prof. Gossec and Dr. Mease have both been consultants to and received honoraria from several companies. SEAM-PsA was sponsored by Amgen.
Unacceptable pain despite inflammation control commonly occurs in PsA patients

A considerable number of patients with psoriatic arthritis starting their first biologic treatment report unacceptable pain throughout the first year of treatment, even when their inflammation is controlled, according to Swedish researchers.

“Despite this often efficient therapy, 40% of patients still had unacceptable pain after 1 year, and pain with features indicative of a non-inflammatory mechanism accounted for more than 60% of this pain load,” senior study author Dr. Tor Olofsson, a rheumatologist and PhD student at Lund (Sweden) University, said in an interview in advance of his presentation at the European Congress of Rheumatology.

“Within rheumatology, today we are generally very good at treating inflammation in many of the arthritides, but we have a lot of patients with persistent pain despite being well treated for their inflammation,” Dr. Olofsson said. “In psoriatic arthritis patients, this remaining pain seems to be even more frequent than in rheumatoid arthritis with the capturing instruments we use here.”

Dr. Olofsson and his colleagues studied prospectively collected records from 352 psoriatic arthritis patients (48% women) participating...
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in the South Swedish Arthritis Group register who started a first anti–tumour necrosis factor (anti-TNF) therapy during 2004-2010. Participants had a mean age of 47 years and a mean disease duration of 10 years. At the start of anti-TNF therapy, 63% of patients were taking methotrexate, and 68% were taking any conventional disease-modifying antirheumatic drug (DMARD).

Based on the Patient Acceptable Symptom State, unacceptable pain was defined as greater than 40 mm on a 0- to 100-mm Visual Analog Scale (VAS). Inflammation control was captured through C-reactive protein level less than 10 mg/L in combination with one or no swollen joints. Assessments were performed at baseline and 1.5, 3, 6, and 12 months after the start of the first anti-TNF agent. Analyses were also conducted in relation to EULAR-defined treatment response after 3 months (good, moderate, or no response).

At the start of anti-TNF therapy, 85% of patients reported unacceptable pain, which declined to 43% after 3 months and then remained stable, reaching 39% at 12 months. The fraction of patients who had unacceptable pain despite inflammation control was largely unchanged over the study period (24% at treatment start, 27% at 3 months, and 26% at 12 months). Unacceptable pain at 3 months was strongly related to EULAR 3-month response (24% of good responders vs. 79% of nonresponders; \( P \) less than .001). This relationship was less pronounced among patients with unacceptable pain despite inflammation control (19% of good responders vs. 37% of nonresponders; \( P = .016 \)). Among EULAR good responders, unacceptable pain despite inflammation control constituted 81% of all unacceptable pain at 3 months.

Dr. Olofsson said he was surprised by the high levels of pain despite inflammation control reported by these patients. A similar study he and others conducted in rheumatoid arthritis patients a year ago, soon to be published, found that only 12% had unacceptable pain despite inflammation control 1 year after start of a first anti-TNF agent, “so captured by the same instruments, it looks like this problem might be even bigger among patients with psoriatic arthritis.”

There is a possibility that psoriatic arthritis patients may have ongoing pain from low-grade inflammation, he said, but another hypothesis is that many psoriatic arthritis patients develop a more generalised pain condition in line with fibromyalgia. It could be that, if inflammation isn’t treated quickly enough in the beginning of the disease, it could sensitise the central pain system, he said, and it may not be reversible after it has developed.

Alternative treatment strategies are often needed in affected patients, Dr. Olofsson added. This could include regular painkillers or medicines used for more generalised, noninflammatory pain states, such as amitriptyline or duloxetine, as well as nonpharmacologic treatment options.

“The bottom line here is that, if patients are treated aggressively early enough, we might be able to prevent development of this sensitisation process,” Dr. Olofsson said. “If we can also do predictive studies to describe which patients have a higher risk of developing this, then maybe we can be even more focused in the initial management before they become centrally sensitised.”

Dr. Olofsson had no financial conflicts to disclose. Two of his co-authors reported relationships with AbbVie, Eli Lilly, Celgene, Novartis, UCB, and Sandoz.
Pending 2019 revisions to the EULAR recommendations for managing rheumatoid arthritis may be most notable for two discussed changes that were tabled: no change to designating methotrexate the first disease-modifying drug to prescribe, before any biologic drug, and no adoption of imaging criteria to determine whether a patient is in remission.

“No imaging with ultrasound or MRI is out” as a remission criterion. “It’s high risk and a waste of resources,” declared Prof. Josef S. Smolen, head of the EULAR writing panel, in the most forceful declaration he made while presenting the pending recommendation revision at the European Congress of Rheumatology.

Prof. Smolen’s strong warning against an imaging parameter when treating RA patients towards a remission target was no surprise, as he had already voiced this opinion in an editorial he coauthored earlier this year (JAMA. 2019 Feb 5;321[5]:461-72) also provided some of the most recent evidence for the second omission from the new revision that Prof. Smolen called out: no change to the recommendation to use methotrexate as initial treatment for any RA patient. “We continue to say that methotrexate is the first treatment strategy. There is no new evidence that any biological treatment is better than methotrexate, so there is no change,” said Prof. Smolen, professor of medicine at the Medical University of Vienna, who also led the EULAR writing panel for the immediately preceding set of RA treatment recommendations first unveiled 3 years before (Ann Rheum Dis. 2017 Jun;76[6]:960-77).

Perhaps the most notable changes to the recommendations are the way they handle targeted synthetic disease-modifying antirheumatic drugs (tsDMARDs), a class that is now synonymous with the Janus kinase (JAK) inhibitors. “Because of new evidence we have lifted up the tsDMARDs,” said Prof. Smolen, “so that no preference is given to biologic DMARDs over the ts class as happened in the 2016 version, he said. Another revision to this recommendation was to change the addition of either a biologic or tsDMARD to a patient not fully responsive to a conventional synthetic (cs) DMARD and with poor prognostic factors from a “should be considered” to a “should be added” recommendation.

Another way in which the pending revision uplifted tsDMARDs was in the wording for the recommendation that deals with patients who do not respond to a first tumour necrosis factor (TNF) inhibitor plus methotrexate or another csDMARD, and now lists as the first option switching to a biologic or tsDMARD with a different mode of action followed by a different TNF inhibitor, a reversal of order from before when a different TNF inhibitor got first mention. This order change was a modest revision that reflected observational evidence that was modestly persuasive that switching to an agent with a different mechanism of action is often the most effective approach, Prof. Smolen said.

The new recommendations also reaffirmed the 11th recommendation from the 2016 version, which called for tapering of the biologic or tsDMARD from a patient in remission while retaining the csDMARD, usually methotrexate. Prof. Smolen cited new evidence in favor of this approach (Ann Rheum Dis. 2019 Jun;78[6]:746-53), which allowed the writing panel to upgrade the evidence supporting this recommendation to the A level. The concept of tapering down the biologic or tsDMARD for a patient in sustained remission while maintaining the csDMARD was “fully confirmed” in a recent report, he added. The writing panel also upticked its rating of the evidence in favor of cautiously tapering the csDMARD in patients who maintain remission on just a csDMARD.
Rheumatoid arthritis management

Two major changes that improved RA management in recent years – the introduction of potent biologic and targeted synthetic drugs to control inflammatory disease, and the treat-to-target strategy – have also produced an unanticipated snag in the care patients receive. Their persistent comorbidities and their more atypical rheumatoid manifestations often go overlooked and untreated.

The situation has been dubbed “DAS blindness,” when clinicians caring for patients with RA are so focused on a patient’s disease activity score (DAS), measured by counting their swollen and tender joints (usually 28 joints to tally the DAS score), that they lose sight of other important features of a RA patient’s disease such as pain and fatigue, Dr. Ruth Williams said at the EULAR Congress.

“There is so much focus on the DAS28 that people are blinded by it. Clinicians concentrate too much on the primary physical condition” of RA, “and they miss important functional, psychological, and social impacts of the disease,” said Dr. Williams, a general-practice physican who is also a long-time RA patient who works as a patient representative and RA researcher at King’s College London.

In Dr. Williams’ extended personal experience as an RA patient (she was first diagnosed in 1966 as a child), management of the disease changed dramatically with the relatively recent, widespread adoption of the DAS28 score in routine clinical practice in Europe and the United States, migrating from its initial use in research studies. Once her clinicians began to use the DAS28 “I felt that perhaps I wasn’t being seen anymore. It was just the biology of my disease being noted rather than me as an individual,” Dr. Williams said in an interview. Clinicians “need to discuss with patients what remission means to them, and their objectives” from treatment, because a patient’s treatment goals may go beyond just reducing the number of swollen or tender joints they total in the DAS28 assessment.

Rheumatologists also have begun to recognise this common disconnect between both the assessment and the antirheumatoid treatment that RA patients routinely receive, and the symptoms that cause problems for RA patients that are not directly tied to their inflammatory disease. Patients can present with remission-level responses in their tender and swollen joint counts and in their serum level of C-reactive protein or erythrocyte sedimentation rate but still score high on the patient global assessment (PGA) scale, a residual consequence of RA that places them out of remission range based on the 2011 “Boolean” criteria for RA remission in trials endorsed by the EULAR recommendations were limited because “the EULAR recommendations have achieved a steady state of the art” for defining whom to treat, treatment targets, and appropriate treatment strategies, he said.

Prof. Smolen had been a consultant to or a speaker on behalf of several drug companies.
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In a review of 411 RA patients who met three of the four ACR/EULAR criteria that collectively define remission, 61% missed on the PGA measure (Ann Rheum Dis. 2012 Oct;71[10]:1702-5), noted Dr. Joan M. Bathon professor of medicine and director of rheumatology at Columbia University, New York, in a talk during the Congress.

Another review of 273 RA patients who missed on one of the four criteria showed 80% missing because of their PGA score (Arthritis Res Ther. 2013;15:R221). The specific clinical features that triggered high PGAs in these patients were things like fibromyalgia, back pain, anxiety, depression, and rheumatoid activity in joints not included in the DAS28 score, Dr. Bathon noted.

The PGA can have poor correlation with the other three measures, but that is a strength because it reflects different dimensions of RA that are important to patients. When the PGA is discordant with the other three measures of remission, it may not make sense to try to improve it by simply using more immunosuppressive treatment.

The solution to the dilemma of what remission target to aim for when treating to target is to apply common sense to existing guidelines and recommendations and tailor management to each patient, she concluded. “The worst thing we can do is to take criteria meant for clinical trials and for patients with average scores and apply them to every individual patient,” she said. Remission guidelines are good for large populations, “but we shouldn’t apply them to every single patient without thinking.”

A similar plea for thoughtful use of the treat-to-target model and immunomodulatory treatment came in a separate talk from Prof. Laure Gossec, a professor of rheumatology at Pitie-Salpetriere Hospital and Sorbonne University in Paris.

The challenge of DAS28 is that it was a remission criteria developed by the ACR and EULAR to use in clinical trials that was coopted for use in routine practice. Despite that, Prof. Gossec believes that DAS28 largely succeeded in this transition. “The DAS28 performs well, it has good prognostic capacity and is widely used.” In her practice, Prof. Gossec relies on the DAS28 score as her primary tool to track disease status in RA patients. “It’s not perfect, but I’m familiar with it, and I work with it,” she said.

It’s undeniable, she acknowledged, that a high PGA often stands between a patient and remission. PGA “is hard to use to guide anti-inflammatory treatment. Many patients have high PGA scores even though they have no inflammation.” Discrepancies like this create a case for dual-treatment targets, both a low swollen and tender joint count and low PGA, as separate and equal treatment goals, Prof. Gossec said, an approach she and her associates proposed in a recent article (Arthritis Care Res. 2018 Mar;709[3]:369-78).

Dr. Williams had no disclosures. Dr. Bathon has been a consultant to AbbVie and has received research funding from Bristol-Myers Squibb and Pfizer. Prof. Gossec has been a consultant to and has received research funding from several companies.
Recognise and assess RA fatigue routinely, rheumatology experts urge

Fatigue is one of the most frequent features of rheumatoid arthritis, and it needs to be assessed and addressed, several leading rheumatology experts urged at the European Congress of Rheumatology.

“Fatigue is an outcome of outstanding importance for patients with rheumatoid arthritis, and therefore it should be an outcome of outstanding importance for clinicians who take care of these patients,” said Prof. José António Pereira da Silva, a professor of rheumatology at the University of Coimbra (Portugal) during a clinical science session dedicated to the topic.

“Fatigue is described as being significant by as many as 40%-80% of all patients with rheumatoid arthritis, and described as being severe by 41%-49% of these patients according to different studies,” Prof. da Silva said.

“The impact upon the quality of life from the patients’ perspective is quite varied but always rather important, if not ‘dramatic,’“ Prof. da Silva said. Fatigue needs to be part of treatment targets alongside disease activity and thus regularly measured, he added.

The problem of fatigue

The problem, however, is that fatigue is such a complex construct, observed Dr. James Galloway, of the Centre for Rheumatic Diseases at King’s College London. “It’s definitely multifactorial in origin; it’s a combination of inflammatory disease, psychosocial situations, and comorbidity.”

Moreover, said Dr. Galloway, “what people describe as fatigue is multidimensional; it’s not just how well you sleep, but how much energy you have, and it’s also how motivated you are.” The fatigue that accompanies RA is different from the fatigue that is experienced in daily life, he noted, and it has a huge impact on patients’ lives.

Determining the cause of fatigue can be challenging, said Prof. Wan-Fai Ng, professor of rheumatology at the Institute of Cellular Medicine at Newcastle (England) University.

“Fatigue is a syndrome that often coexists with other symptoms, and there may be different type of fatigue,” Prof. Ng said. He noted that there were many potential underlying biological mechanisms, but the most studied so far is inflammation. Fatigue is probably driven, at least in part, by “sickness behaviour” and there are frequent associations between fatigue and chronic inflammatory conditions such as RA and Sjögren’s syndrome.

“I think the role of conventional inflammatory mechanisms, at least in chronic fatigue in chronic conditions, remains unclear,” Prof. Ng added.

“The biological systems, for example the vagus nerve, that regulate the immune system may play key roles in fatigue, especially in chronic inflammatory states.”

Whatever the underlying mechanism, it’s clear that there are multiple factors at play that need addressing if fatigue is to be properly addressed in the clinic. Prof. da Silva unveiled a new path analysis model that will be published in a future issue of Clinical and Experimental Rheumatology that showed how disease activity, pain, disability, sleep disturbance, and depression might all interlink to account for fatigue in patients with RA.

Young or old, fatigue is a prominent, persistent symptom

Fatigue is not just a problem in older adults with rheumatic and musculoskeletal diseases, as Dr. Ellen Dalen Arnstad pointed out in a separate session at the congress. Younger adults and adolescents are also often affected, as demonstrated by data she presented from an 18-year follow-up study of individuals with juvenile idiopathic arthritis (JIA).

An oft-used definition of fatigue, she said was “a persistent, overwhelming sense of tiredness, weakness, and exhaustion.” This results in “decreased capacity of physical function or mental work and is unrelieved by sleep or rests.”

Dr. Arnstad, a paediatric rheuma-
tologist at the Hospital of Levanger in Norway and PhD student at the Norwegian University of Science and Technology in Trondheim, presented data from the Nordic JIA study of 377 subjects who were assessed for fatigue. These showed that there were higher levels of fatigue among participants with active disease, pain, and self-reported health problems. The mean Fatigue Severity Scale score was 3.2 overall, with a higher score in females (3.5) versus males (2.5).

“We found highest mean fatigue scores among those with bad physical and mental health,” Dr. Arnstad reported. Just over a quarter (26%) of patients had severe fatigue, which was defined as a score of 4 or more.

“Fatigue is a prominent symptom in JIA after 18 years of disease duration,” and it “should be measured in a long-term follow-up, both in clinical and research settings,” Dr. Arnstad said.

How should fatigue in RA be assessed?
“Fatigue is recognised by OMERACT [Outcome Measures in Rheumatology Clinical Trials group] as being one of the measured outcome factors in rheumatoid arthritis, one that we should all be taking care of,” Prof. da Silva said. It was added alongside the core set of measures that should be used in all trials “wherever possible.”

So how should fatigue be measured in practice? There are lots of instruments available. Indeed, Prof. da Silva and associates recently counted more than 12, but there is no consensus and no guidelines on which should be used.

“We propose to use a single-item instrument as a screening tool, like the BRAF NRS [Bristol Rheumatoid Arthritis Fatigue Numerical Rating Scale] or RAID-F [Rheumatoid Arthritis Impact of Disease–Fatigue domain], which would be supplemented by additional multidimensional assessments if significant levels of fatigue are identified,” he said in an interview. “This will be particularly useful when the aims are to explore causality of fatigue or the efficacy of an intervention.”

Prof. da Silva noted after his presentation that the RAID-F score is routinely used at his practice. “It’s an extremely useful instrument in trying to assess how the patient is dealing with rheumatoid arthritis,” he said. He emphasised that fatigue needed to be considered separately from disease activity and that “it should be part of treatment targets and it should be regularly measured in both research and clinical practice.”

How can fatigue in RA be treated?
When faced with a patient with RA who is experiencing fatigue, it’s important to take a full history and try to determine the cause or contributing factors, Dr. Galloway advised. “I think it’s really important to [take a history of this] specific symptom in the same way you take a history of articular pain.” Consider the onset of fatigue, for example. Is it sudden or linked to a particular stressor or life event, or has its development been more gradual? What’s been the clinical course, duration, and daily pattern? Are there any factors that might alleviate it or exacerbate it? What’s the impact on the patient’s daily life – both in terms of work and social participation?

Treating RA more effectively might help, “but that is unlikely to be sufficient,” Dr. Galloway said, observing that “leaving uncontrolled inflammation is bad, but, in 2019, more inflammation is probably not the solution to fatigue.” Instead, he suggested looking for and treating comorbidities that might be contributing to the fatigue, such as anemia, endocrine or cardiac disease, or perhaps sleep apnea or depression, among others.

“I would discourage the prescribing, for the large part, of drugs for fatigue; that’s because that’s where the evidence is probably the least strong,” Dr. Galloway said. However, there is much better evidence for the use of exercise training in RA and for combining exercise and psychosocial approaches. Improving sleep hygiene may also be beneficial for some patients.

The bottom line is that “fatigue matters” and should be “talked about more with our patients,” Dr. Galloway said.

Prof. da Silva and Dr. Arnstad had no financial conflicts of interest. Prof. Ng disclosed research collaborations with Resolve Therapeutics, electroCore, GlaxoSmithKline, and AbbVie. He also disclosed acting as a consultant for Novartis, GlaxoSmithKline, AbbVie, MedImmune, Pfizer, and Bristol-Myers Squibb. Dr. Galloway disclosed receiving honoraria for speaking at meetings, support for conference travel, or both from AbbVie, Bristol-Myers Squibb, Celgene, Janssen, Eli Lilly, Pfizer, and UCB.
Putting New Evidence into Clinical Practice in GCA and RA—Together We Dare

This year’s Roche EULAR symposium entitled Putting New Evidence into Clinical Practice in GCA and RA—Together We Dare, addressed the practical applications of new clinical evidence in giant cell arteritis (GCA) and rheumatoid arthritis (RA) to improve patient care. With new clinical evidence, the symposium presenters emphasized how rheumatologists are now better equipped than ever before to manage these conditions.

In his presentation, New Insights into the Treatment of GCA, Dr. John Stone highlighted that since GCA is a chronic, life-altering condition, early recognition and diagnosis is paramount. Using information from his own clinic and the latest GiACTA trial data, Dr. Stone explored new therapeutic strategies to enable sustained disease control, while tapering glucocorticoids, thereby leading to improved patient outcomes.

In his presentation, Strengthening the Treatment Paradigm in RA, Dr. Frank Buttgereit stressed the importance of shared decision-making to improve the treatment of RA and illustrated this point with respect to the use of glucocorticoids and their limitations. Using data from the SEMIRA trial, he explained how rheumatologists can maintain patients in low disease activity and can taper their glucocorticoids.

In a panel discussion, Debating the evidence in RA and GCA, attendees submitted questions to the presenters. Discussions drew upon the parallels and differences between GCA and RA and detailed why and how new data should inspire confidence among rheumatologists about setting more ambitious goals for treating their patients to enable better disease control with less treatment burden.

Following the Roche symposium, Dr. Stone provided a summary of the event and its outcomes.

Roche Satellite Symposium Video
Repeated ANA testing after negative result provides little diagnostic value

Repeated antinuclear antibody testing after a negative result has limited use for the diagnosis of ANA-associated rheumatic conditions, according to data from a multicentre, retrospective analysis that considered a 7-year period.

For more than 7,875 repeated ANA tests in 4,887 patients, “the vast majority of results didn’t change,” Dr. Ai Li Yeo, a PhD candidate, rheumatologist, and infectious disease fellow at Monash University, Melbourne, reported at the European Congress of Rheumatology.

ANA tests were repeated between 2 and as many as 45 times in individual patients, she reported, but the results of 79% of these tests remained unchanged – 45% of tests were persistently negative and 34% persistently positive using a cutoff titer of 1:160.

“Our study showed that there was a very low yield in repeating an ANA test for the diagnosis of ANA-associated rheumatologic conditions unless there was evidence of evolving multisystem clinical features,” Dr. Yeo said.

Indeed, the positive predictive value was just 0.01. “So for a hundred patients starting off with a negative ANA result that on repeat testing became positive, the probability is that one patient will have a new ANA-associated rheumatic condition diagnosis,” Dr. Yeo said.

“ANA testing is frequently performed and is part of the classification criteria for autoimmune conditions such as lupus and scleroderma,” she observed. However, the test provides no information on the severity or activity of the disease, and the value of serial monitoring for such conditions is unclear.

“Minimising unnecessary tests is a global health economic priority,” Dr. Yeo said. She noted that there are multiple initiatives in place to try to open a dialog about using healthcare resources most effectively, such as “Choosing Wisely” set up by the American Board of Internal Medicine Foundation.

The aim of the present analysis was to calculate the cost of repeated ANA testing and to see if any change in the ANA result was associated with new diagnoses of ANA-associated rheumatic conditions.

The analysis considered more than 36,700 tests that were performed on samples from more than 28,800 patients within the Monash Health tertiary health network between 2011 and 2018. Of these, 22,657 (62%) had given a negative result and 14,058 (38%) had given a positive result.

“Not surprisingly, the age of those who tested positive was significantly higher than those who tested negative,” Dr. Yeo said (52.6 vs. 48.9 years; P less than .001). There was also a higher number of women than men tested, and women more often tested positive.

Around one-fifth of tests performed were repeat tests, of which 511 (6.5%) changed from being negative to positive over a median of 1.71 years.

“A small percentage of people alternated between results,” Dr. Yeo acknowledged, with 9.4% of people going from a positive to a negative result, 10.5% moving from a negative to a positive result, and 1.9% going from positive to negative to positive.

With repeated tests, just five new diagnoses of ANA-associated rheumatic conditions were made: two cases of systemic lupus erythematosus, one case of scleroderma, and two cases of undifferentiated connective tissue disease. There was a range of ANA titers and patterns and evolving clinical features of a multisystem disease.

Based on the direct costs of ANA testing in her health care system, not performing repeated tests could yield significant savings, Dr. Yeo said, a 21.4% reduction, in fact, based on this analysis. The cost of an ANA test in Australia ranges from 15 to 46 euros, making the cost of all tests in this analysis 564,745 euros. Taking away the cost of all the single ANA tests performed (443,209 euros) gives a potential cost saving of more than 121,000 euros, she said.

“We now have an opportunity to prevent unnecessary ANA testing, Dr. Yeo said. “Ultimately, our aim is to change behaviour at the start of the ordering cycle by educating medical students and doctors about inappropriate test ordering.”

The majority of repeated tests had been ordered by nonrheumatologists (82% of cases), and Dr. Yeo said that rheumatologists ordered repeat tests in 11% of cases. However, there was little information available in this retrospective analysis as to why the tests had been repeated.

The research was picked as one of the six best clinical abstracts at the congress, out of a total of almost 5,000 submitted abstracts.

Dr. Yeo reported having no conflicts of interest.
Addressing Real-World Practice Gaps in the Management of RA

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ACCREDITATION STATEMENT
An application has been made to the UEMS EACCME® for CME accreditation of this event.
EULAR issues guidelines on managing rheumatic complications of cancer immunotherapies

EULAR has issued recommendations to help rheumatologists address the increasingly common clinical issue of diagnosing and managing rheumatic-related adverse events associated with cancer immunotherapy.

“The rheumatic adverse events associated with immunotherapy represent a spectrum of new clinical entities, and they are challenging because they can be difficult to control while attempting to preserve the antitumour effects of oncologic drugs,” Dr. Marie Kostine, of the Centre Universitaire Hospitalier, Bordeaux, France, explained at the European Congress of Rheumatology.

The recommendations were drawn from the deliberations of an expert task force that identified the clinical issues to address and then developed a consensus about best practice recommendations. In addition to rheumatologists with expertise in this field, the task force included oncologists, allied health personnel, and two patient representatives.

The recommendations include four overarching principles and 10 recommendations.

“One of the overarching principles regards the importance of shared decision making between rheumatologists, oncologists, and patients,” Dr. Kostine said. Because of the expertise of rheumatologists in employing immunomodulatory therapies as they pertain to inflammation of the joints, the recommendations emphasise the value of their collaboration in clinical decisions.

The recommendations address patient referral, the assessment of preexisting rheumatic conditions, diagnosis, and therapeutic strategies.

“Rheumatologists should make themselves aware of the wide spectrum of potential clinical presentations of rheumatic adverse events following the initiation of immunotherapy,” Dr. Kostine said. While rheumatoid arthritis–like symptoms are common, the immune activation produced by checkpoint inhibitors and other immunotherapies can affect nearly every organ in the body, which includes diverse involvement of joint tissues.

In addition to joint pain, which has occurred in up to 40% of patients receiving a checkpoint inhibitor in some series, rheumatic disease–related events can include vasculitis, systemic sclerosis, and lupus. When associated with immunotherapy, these events sometimes develop in the absence of inflammatory markers or autoantibodies.

The new consensus guidelines emphasise that glucocorticoids can be “considered” to control rheumatic-related adverse events despite their immunosuppressive effect. However, because of their potential to attenuate the benefit of immune activation for treatment of the oncologic disease, such drugs, if used, “should be tapered to the lowest effective dose.”

The consensus recommendations were based on an extensive literature review, but Dr. Kostine acknowledged that prospective studies regarding the best practices for managing rheumatic-related adverse events of immunotherapies remain limited. She suggested that this knowledge gap was one reason for creating an expert task force.

“There has been an immunotherapy revolution, such that rheumatologists who have not yet seen these adverse events soon will,” said Dr. Kostine, noting that the number of approved immunotherapies and their clinical indications have been increasing rapidly.

The EULAR recommendations were created specifically for rheumatologists. In addition to guiding them towards best practice, the report from the task force provides background on the clinical issues raised by therapies that cause inflammatory side effects while stimulating immune function to treat malignancy.
Checkpoint inhibitor–induced rheumatic complications have unique features

The musculoskeletal complications of checkpoint inhibitor therapy are sometimes described as RA like, but a detailed analysis of a consecutive series of patients presented at the European Congress of Rheumatology produced the conclusion that the phenotypic expression is unique.

“These manifestations do not necessarily include synovial involvement, so their description as a rheumatoid arthritis–like presentation is not accurate. Rather, our findings suggest the pathology is something completely different and completely new,” said Dr. Alexandra Filippopoulou, a rheumatology resident at the University of Patras (Greece).

This comment was based on a prospective study evaluating musculoskeletal complications in patients treated with checkpoint inhibitors over a recent 2-year period. Of the 130 consecutive patients who received a checkpoint inhibitor in the study period, 10 (7.7%) complained of joint pain and were determined to have an inflammatory complication.

The median time to development of musculoskeletal symptoms in this mostly male patient series was 2.5 months. The site of cancer was lung in four, bladder in three, kidney in two, and skin in one. Nivolumab was the most common checkpoint inhibitor used, but others were represented.

MRI studies were conducted in 8 of the 10 patients. Overall, the MRI studies showed more myofascial than synovial involvement, but Dr. Filippopoulou described three distinct patterns.

In four patients, there was prominent periarticular involvement marked by diffuse swelling in the hands, feet, knees, or a combination of these joints. Synovitis, when observed, was mild, but myositis and fasciitis were common in adjacent tissues.

In three patients with a chief complaint of knee pain, myofasciitis was prominent in the surrounding muscles. Again, synovitis, when observed, was mild. It was unclear whether a partial tear of the quadriceps tendon observed in one patient was checkpoint inhibitor related.

In a third pattern, shared by three other patients, synovitis was prominent, but so was myositis in adjacent muscles. In two of these patients, the inflammatory activity was confined to the hands; in the third, both the knees and the ankle were also involved.

Regardless of these patterns of inflammation, “almost all of these patients continued to show good range of motion, which is not something that is commonly seen in patients with rheumatoid arthritis,” Dr. Filippopoulou observed.

Overall, the joint pain tended to be mild to moderate. They all responded well to low-dose glucocorticoids or analgesics without need to discontinue the anticancer therapy, she reported.

Not least interesting of the findings, half of the patients with musculoskeletal adverse events had a favourable response to the checkpoint inhibitor therapy, compared with just 12.5% of patients without these complaints, a difference that reached statistical significance (P = .0016), according to Dr. Filippopoulou. This observation is consistent with a study published last year that also associated immune-related adverse events with a greater likelihood of an anticancer response (Ann Rheumatic Dis. 2018;77:393-8).

“This is an interesting finding, but the theory that musculoskeletal adverse events predict a better response to checkpoint inhibitor therapy needs to be proven,” she said.

A larger case series is needed to better characterise joint inflammation associated with checkpoint inhibitors, but Dr. Filippopoulou concluded from her series that these adverse events are not accurately described as RA like. Rather, the phenotypic expression appears to be unique, not fully resembling any other joint pathology.

Dr. Filippopoulou reported no potential conflicts of interest.
EULAR School of Rheumatology educates global audience

The EULAR School of Rheumatology continues the EULAR tradition of providing quality educational opportunities in the field of rheumatic diseases, not only for physicians and health professionals but also for patients and their families.

“EULAR has traditionally been a preeminent supplier of education in rheumatology for different target populations worldwide,” Prof. Annamaria Iagnocco, EULAR President-Elect, said in an interview.

“The EULAR School of Rheumatology was launched with the aim of offering various types of outstanding educational material for its three pillars: physicians, health professionals in rheumatology, and people with rheumatic and musculoskeletal diseases,” Prof. Iagnocco said.

The EULAR School of Rheumatology’s notable accomplishments for 2018 include administering seven online courses, organising 12 live courses and meetings, updating two publications, and awarding many bursaries and grants for education and further study.

The subject areas for the School of Rheumatology’s online coursework in 2018 included rheumatic and musculoskeletal diseases (RMDs), connective tissue disease, paediatric rheumatology, systemic sclerosis, imaging, ultrasound, and health professionals research.

Overall, India was the top country to use the School of Rheumatology’s online courses as resources in 2018, and most of the participants had a keen interest in RMDs. India also was the top country to use the imaging and paediatric rheumatology courses.

The United Kingdom had the most users of the ultrasound online course, while the systemic sclerosis course was most popular in Italy; Spain and Portugal tied for top users of the connective tissue disease course. The Netherlands was the No. 1 country to use the health professionals research course, followed by the United Kingdom and New Zealand.

RMDs took the top spot overall for textbooks in 2018, followed by ultrasound, paediatric rheumatology, and systemic sclerosis.

Prof. Iagnocco described the development of the EULAR School of Rheumatology as a “complex process” that has involved additions to the rich collection of educational materials already available from EULAR.

“With the support of different teams of experts, the whole system has been changed and enriched. The use of a new learning platform gives facilitated access to the educational material,” she said.

The future of the School of Rheumatology includes use of the app, which allows school members to browse the latest EULAR recommendations, as well as diagnostic tools such as classification criteria, outcome measures, and imaging libraries.

“New materials have been produced in the last year, and they are all of the highest quality,” Prof. Iagnocco said. “All materials were offered following an innovative educational model that reflects the changing needs of the learners, the number of whom is constantly increasing.”

Augmented reality–learning app helps to promote “Don’t Delay, Connect Today” campaign

A new augmented reality (AR) modality has shown effectiveness in increasing rheumatoid arthritis knowledge in a recent study examining the central message of EULAR’s “Don’t Delay, Connect Today” campaign.

“This research aims to find new and exciting forms of media that could be used to put forward the central message of the Don’t Delay, Connect Today campaign,” Louise Bennett, PhD, of the University of Glasgow, said in an interview.

Don’t Delay, Connect Today was created to educate the general public and primary healthcare providers about the importance of recognising the early warning signs of rheumatic and musculoskeletal diseases, such as RA. It also highlights the importance of early diagnosis and treatment for achieving long-term sustained remission, an approach that has been adopted by many countries across Europe.

Dr. Bennett and colleagues participating in the Rheumatosphere public engagement team from the University of Glasgow and Glasgow Caledonian University have worked to develop interesting and effective ways of disseminating the campaign’s message to the public. Although augmented reality has been used successfully as an innovative teaching tool to enhance
The investigators designed the interactive augmented reality application for a lay audience using aspects of RA pathogenesis, along with the concept of the importance of early diagnosis and treatment.

A total of 27 visitors to the Glasgow Science Centre completed a 5-point Likert scale questionnaire before and after interacting with the posters and augmented reality application. The 25- to 34-year-old age range of the majority of participants was a key target audience for the campaign, since this demographic of the population largely believes that they are “too young” to develop arthritis, according to Dr. Bennett.

Participants reported that the application was easy to use, engaging, and enjoyable. Further assessment of the application using a 5-point Likert scale revealed that it successfully raised awareness of RA, with 81% of participants reporting that they felt more aware about the pathogenesis, symptoms, and treatment of RA after using the application. Additionally, 55% of participants said they were inclined to raise awareness about the causes, symptoms, and treatments of RA among friends and family.

“Through our presentation, we demonstrate how newer technology such as augmented reality can be used to explain complex subject matter, such as rheumatic disease states, whilst limiting cognitive overload,” Dr. Bennett said. She and her colleagues “also hope that others may be inspired to invest in these new technologies for the delivery of the Don’t Delay, Connect Today campaign in the future.”

One author disclosed serving on a speakers bureau for AbbVie and receiving grant/research support from AstraZeneca, Bristol-Myers Squibb, Celgene, Janssen, MedAnnex, Pfizer, and UCB.

Dr. Louise Bennett
While there’s no doubt that physical activity can provide a myriad of benefits for patients with rheumatic diseases, there is significant uncertainty around how to help and motivate patients to make it a habit so they can reap its long-term rewards.

At a European Congress of Rheumatology session titled “Exercise – more than a wonder drug,” Dr. Keegan Knittle of the University of Helsinki offered advice on how to help patients maintain physical activity by taking delegates through behavioural science theories on self-determination, self-regulation, and habit formation.

According to Dr. Knittle, rheumatology health professionals can help patients begin on their physical activity journey by helping them to identify the types of physical activities that they most enjoy doing.

“This is easy for some individuals, but it could be a struggle for others. Offering individuals opportunities to try new ways of being active is a good start as people are more likely to maintain behaviours that they enjoy,” he said in an interview.

Helping patients to identify the positive outcomes that they can gain from being physically active – such as feelings of strength, health, and strong social behaviours – can also help them to maintain those activities.

“To be maintained over time, physical activity needs to become habitual and occur almost automatically. Careful planning can help people to strengthen their habits for physical activity behaviour,” he noted.

Dr. Knittle also took delegates through behaviour change techniques that patients can use to help them form a strong physical activity habit.

“While helping patients to maintain physical activity is always a challenge, especially in the face of degenerative or progressive arthropathies, behavioural science can offer health professionals in rheumatology some theory and evidence-based methods to support physical activity maintenance in practice,” he added.

But once patients have established a physical activity habit how do they know how much is optimal for them?

According to Prof. George Metsios of the Faculty of Education Health and Wellbeing at the University of Wolverhampton (England), there is ample evidence to show the benefits of exercise in people with rheumatic and musculoskeletal diseases (RMDs), but a consensus on the “dosage” of exercise is currently missing.

“Similar to receiving the right dosage of medication for alleviating and managing disease symptoms, receiving the appropriate exercise dosage is equally important in people with RMD,” Prof. Metsios said in an interview.

“What is optimal is highly individual, but in our clinical experience, it appears that exercise intensities between 60% and 90% of maximum heart rate elicit beneficial effects in multiple different disease outcomes, which are relevant to RMDs, including reduced fatigue and inflammation, improved cardiorespiratory health, quality of life, and functional ability.

“Exercise is safe, even when progressively higher exercise intensities are applied, this has multiple different benefits in different physiological and psychological outcomes in RMDs. The benefits of using exercise as an adjunct treatment in RMDs are too many to ignore. As such, targeted efforts need to be made to effectively implement physical activity in clinical practice,” he added.
Five reasons why you should offer smoking cessation advice to your patients

There is a pressing need for rheumatology health professionals to educate their patients about the importance of smoking cessation, particularly as patients begin to ask more about the impact of smoking on disease outcomes, delegates learned at the Congress.

In the session titled “How not to smoke like a chimney,” rheumatologist Helen Harris of NHS Lothian's Western General Hospital in Edinburgh presented research to EULAR delegates illustrating that helping smokers with rheumatic and musculoskeletal diseases to quit is achievable and should be considered an essential part of the rheumatology outpatient consultation.

Evidence shows that smoking has a direct effect on inflammatory rheumatic diseases and increases the risk of comorbidities, she said in an interview.

However, research shows that the practice of offering smoking cessation advice is highly variable across practices and countries. For example, a survey of rheumatologists in 25 countries revealed that, although most doctors give advice to quit smoking to most patients, only 20% had a specific protocol for smoking cessation. Nurses also gave cessation advice to most patients in only one-third of departments that had nurses providing patient education.

“There is a pressing and unmet need to improve awareness amongst rheumatologists of the importance of smoking cessation advice for rheumatology patients,” Dr. Harris said.

“Smoking predicts higher incidence, greater severity, and reduced treatment responses in rheumatoid arthritis, lupus, and spondyloarthritis,” she explained.

Furthermore, the most common risk of immunosuppressive therapies used to treat these conditions is infection; and smoking is known to increase the risk and severity of both bacterial and viral infections.

“Counselling smokers to quit at the time of commencing immunosuppressive treatment is therefore imperative,” she stressed.

Smoking cessation advice is particularly important for people with rheumatoid arthritis, as these patients have a different profile of cardiac risk factors compared with the general population, she said.

RA patients are also at a substantially higher risk of lung cancer and other airway diseases, making smoking cessation “essential to effectively lower cardiovascular disease, risk of lung cancer, and other lung conditions in RA patients who smoke.”

Dr. Harris set out her top five reasons to offer brief smoking cessation advice to rheumatology patients:

• Improve chances of response to therapy.
• Reduce infective risks of immunosuppressive therapy.
• Improve success of medication dose reduction.
• Reduce cardiovascular and respiratory diseases and cancer risks.
• Reduce mortality.

“Raising awareness of the harms of smoking for rheumatology patients is the first step in the cessation pathway and can be done effectively using posters or postcards freely available through www.nrars.org.uk,” she added.

At the same session, Ida Kristiane Roelsgaard from the Copenhagen Center for Arthritis Research (COPECARE) in Denmark took delegates through the current state of evidence around the benefits of smoking cessation.

According to Ms. Roelsgaard, smoking cessation interventions have traditionally been designed for people without chronic diseases, which means the literature on smoking cessation interventions in people with inflammatory joint diseases is limited.

“Why there is lack of research on smoking cessation and inflammatory joint diseases is difficult to answer. ... We do know that smoking can worsen the disease outcomes and patient-reported outcomes, so testing the effect of smoking cessation and smoking cessation interventions in this patient group is important,” she said in an interview.

At the moment, there is also no current evidence around whether one smoking cessation intervention works better than another, but the good news is that evidence in the area is increasing, and patients are starting to ask more questions about the impact that smoking can have on their disease, as well as the benefits of quitting. For example, one key finding from her qualitative research was that smokers with rheumatoid arthritis had a strong wish for more of a focus on smoking cessation from their health professional.

People with rheumatoid arthritis who participated in an ongoing randomised, controlled trial testing an intensive smoking cessation intervention felt they had gained more knowledge and acquired tools for changing their smoking behaviour, even though they did not immediately quit.

“They thought that the clinical study was a positive approach from the rheumatology department and saw it as an opportunity to finally quit smoking,” Ms. Roelsgaard explained.

Neither presenter had conflicts of interest to disclose.
Treat-to-target slowly emerging in axial spondyloarthritis

Treating patients with axial spondyloarthritis (axSpA) until a specific target is reached is an emerging concept that has gained a lot of attention in the past few years, Dr. Pedro Machado said at the European Congress of Rheumatology.

“The availability of biologic therapies has improved the clinical outcomes for our patients with axial spondyloarthritis and targeting clinical remission or inactive disease is now an achievable treatment goal in clinical practice,” he observed. “This has triggered the question: Is there a role for ‘treat-to-target’ in axial spondyloarthritis?”

Dr. Machado, an honorary consultant in rheumatology and muscle diseases at University College Hospital and the National Hospital for Neurology and Neurosurgery in London, took a critical look at the treat-to-target approach during a clinical science session at the EULAR congress.

The concept of treat-to-target is not new, he acknowledged, having been imported from other chronic conditions where there is a very specific target to achieve. It is not only well established in nonrheumatic diseases but also has proved to work in patients with rheumatoid arthritis and psoriatic arthritis with evidence from the TICORA (Tight Control of Rheumatoid Arthritis) and TICOPA (Tight Control in Psoriatic Arthritis) trials.

Whether the approach can also work in axSpA is open to debate, and one of the main arguments against using a treat-to-target in axSpA asks, what exactly is the target? While there is no firm agreement yet, Dr. Machado observed that achieving either clinical remission or inactive disease would be the most likely target.

It could be argued this is already being done to some degree, but “we need to be more ambitious,” Dr. Machado said. Indeed, current Assessment of Spondyloarthritis International Society (ASAS)/EULAR recommendations for the treatment of axSpA (Ann Rheum Dis. 2017;76[6]:978-91) note when patients with high disease activity despite sufficient standard treatment should be escalated to treatment with a biologic disease-modifying antirheumatic drug. High disease activity was defined as an Ankylosing Spondylitis Disease Activity Score of 2.1 or more or a Bath Ankylosing Spondylitis Disease Activity Index score of 4 or more.

Another argument against using the approach concerns the evidence base. There are no prospective, randomised trials supporting the use of treat-to-target over routine care. However, there is a lot of observational evidence, Dr. Machado said in an interview. Such studies have shown that achieving inactive disease may improve structural outcomes and stop the development of radiographic damage of the spine. Importantly, these observational studies also show that achieving inactive disease may also help to improve patients’ functional outcomes and quality of life.

Evidence backing a treat-to-target approach in axSpA from a randomised, controlled trial may currently be lacking, but the TiCOSPA (Tight Control in Spondyloarthritis) trial is in progress and should help change that, Dr. Machado said.

“The missing bit is a randomised trial, but I would say that the observational evidence is almost enough to advocate a treat-to-target strategy in axial spondyloarthritis,” he said. This was also the view of an international task force that recently published recommendations and overarching principles for a treat-target strategy in spondyloarthritis, including axSpA (Ann Rheum Dis. 2018;77:3-17).

Of course, a treat-to-target approach may not be without its pitfalls. There are a limited number of drugs currently that could be used to “hit the target” of disease activity, Dr. Machado said in his presentation. The approach might also lead to “overtreatment,” and more treatment is not always better as it could not only lead to more adverse events, but it also may mean the approach is not cost effective.

Depending on the TiCOSPA study results, which are expected next year, Dr. Machado said that “the feasibility and cost-effectiveness of such a strategy in clinical practice also needs to be tested.”
Referral, treatment, and rapid access to care are three of nine new quality standards developed by a multidisciplinary task force of the Assessment of SpondyloArthritis International Society (ASAS) with the aim of improving the management of adults with axial spondyloarthritis (axSpA).

The other quality standards look at how to improve patient education and self-management and call for annual review, Dr. Uta Kiltz said at the European Congress of Rheumatology.

“Several unmet needs such as delayed diagnosis and restricted access to treatment have been described in patients with axSpA worldwide,” Dr. Kiltz observed in an interview. Results from the ASAS-COMOSPA study (Ann Rheum Dis. 2018;77[3]:405-11), for example, highlighted inequity in the prescription of biologic disease-modifying antirheumatic drugs across the globe.

“The variation in quality of care is noted across rheumatologic diseases,” said Dr. Kiltz, of Ruhr University Bochum and Rheumazentrum Ruhrgebiet in Herne, Germany. “Assessing the quality of care provided to patients with axSpA is important not only to patients and physicians, but also to providers and purchasers of healthcare.”

A major goal of ASAS is to improve quality of care and health outcomes in patients with axSpA. To address the many gaps in current care, the society set out to develop quality standards to optimise patients’ access to care and their overall treatment.

“A quality standard consists of a quality statement accompanied by a measure. The measure can be used to assess the quality of care or service provision specified in the treatment,” Dr. Kiltz explained.

Quality standards are very different from recommendations or guidelines, she stressed. While the latter imply evidence-based actions that should be done to optimally diagnose and treat the disease, quality standards identify resources or processes that need to be optimised in high-priority areas for quality improvement.

The nine ASAS quality standards cover key areas for quality improvement relating to the care of adults with axSpA that need improvement worldwide. The statements were carefully phrased following a consensus, and the tools by which they could be measured agreed.

The first three standards concern the time to referral from primary to specialist care and state that people with a suspicion of axSpA are referred to a rheumatologist within 3 working days, assessed by a rheumatologist within 3 weeks after referral, and have their diagnostic work-up completed within 2 months.

The next two quality standards concern pharmacologic management: Disease activity of people with axSpA is monitored under the supervision of a rheumatologist with validated composite scores at least twice a year, and in people with axSpA and active disease despite conventional therapy, treatment escalation to biologics is discussed.

Nonpharmacologic treatment is also covered, with the sixth quality standard stating: “People with axial SpA are informed about the benefits of regular exercise.”

Quality standard 7 states: “People with axSpA are offered education on the disease including self-management within 2 months of diagnosis,” Dr. Kiltz said. Rapid access to care is the focus of quality statement 8: “People with axSpA and disease flare or possible drug-related side effects receive advice within 2 working days of contacting the rheumatologist.”

The ninth and last quality standard states that people with axSpA should have a comprehensive annual review by a rheumatologist.

“These are the first quality standards applicable worldwide for the improvement of healthcare for adult patients with axSpA. The ASAS quality standards are all measurable and achievable and are intended to minimise variation in quality of care.”

Dr. Kiltz had no relevant conflicts of interest.
Flu vaccine succeeds in TNF-inhibitor users

Influenza vaccination is similarly effective for individuals taking a tumour necrosis factor (TNF) inhibitor and healthy controls, but the number needed to vaccinate to prevent one case of influenza for patients taking a TNF inhibitor is much lower, according to data from a study presented at the European Congress of Rheumatology.

The number needed to vaccinate (NNV) to prevent one case of influenza among healthy control patients was 71, compared with an NNV of 10 for patients taking the TNF inhibitor adalimumab, reported Dr. Giovanni Adami and colleagues at the University of Verona (Italy).

While TNF inhibitors “are known to increase the risk of infection by suppressing the activity of the immune system,” it has not been clear whether the response to vaccination is impaired in patients treated with a TNF inhibitor, Dr. Adami said.

Dr. Adami and colleagues reviewed data from 15,132 adult patients exposed to adalimumab in global rheumatoid arthritis clinical trials and 71,221 healthy controls from clinical trials of influenza vaccines. Overall, the rate of influenza infection was similarly reduced with vaccination in both groups. The rate in healthy individuals went from 2.3% for those unvaccinated to 0.9% for those vaccinated; for TNF inhibitor–treated patients, the rate was 14.4% for those unvaccinated versus 4.5% for those vaccinated.

“It is not surprising that the number needed to vaccinate is dramatically lower in patients treated with immunosuppressors, compared to healthy individuals,” Dr. Adami noted. “As a matter of fact, patients treated with such drugs are at higher risk of infections, namely they have a greater absolute risk of influenza. Nevertheless, [it] is quite surprising that the relative risk reduction is similar between TNF inhibitor–treated patients and healthy controls, mean-

Continued // next page
Booster vaccines found largely safe in children on immunosuppressive drugs

Administration of live attenuated booster of the MMR vaccine with or without varicella (MMR/V) was not associated with serious adverse events in children on immunosuppressive therapy for a rheumatic disease, according to data presented at the European Congress of Rheumatology.

“The study implies that patients can receive booster vaccinations regardless of age, diagnosis, or therapy,” reported Dr. Veronica Bergonzo Moshe, a paediatric rheumatologist at Meir Medical Center, Kfar Saba, Israel.

In the absence of safety data, the vaccination of children with rheumatic diseases taking immunosuppressive therapies has been controversial. Although these children face communicable and sometimes life-threatening diseases without vaccination, many clinicians are not offering this protection because they fear adverse consequences.

Current Paediatric Rheumatology European Society (PReS) guidelines have been equivocal, recommending that vaccines be considered on a “case-by-case basis” in children with a rheumatic disease if they are taking high doses of disease-modifying antirheumatic drugs (DMARDs), glucocorticoids, or any dose of biologics.

“The fear is that a state of immune suppression might decrease response to the vaccine or lead to a flare of the rheumatologic disease,” Dr. Moshe said.

In the retrospective study presented by Dr. Moshe, data were collected on 234 children with rheumatic diseases who received a live attenuated MMR/V booster. The children were drawn from 12 paediatric rheumatology centers in 10 countries.

In this relatively large series, 82% of the children had oligoarticular or polyarticular juvenile idiopathic arthritis (JIA). A range of other rheumatic diseases, including juvenile dermatomyositis, localised scleroderma, and isolated idiopathic uveitis were represented among the remaining patients. All were taking medication, and 48% were in remission.

When broken down by therapy, there were three localised reactions in 110 (2.7%) children who received the booster while on methotrexate. No other adverse events, including disease flare, were observed.

Similarly, six of the seven adverse events observed in 76 (8%) patients who were taking methotrexate plus a tumour necrosis factor (TNF)–inhibitor biologic at the time of vaccination were local reactions. Fever was reported in one patient. All of these events were transient.

In the 39 patients taking a TNF inhibitor alone, there was a single case of transient fever. There were no adverse events reported in the three patients vaccinated while on tocilizumab, seven patients while on anakinra, or five patients while on canakinumab.

Following vaccination, there were no signs of symptoms of the diseases that the vaccines are designed to prevent. In the minority of patients who did develop localised reactions or fever in this series, there was no apparent relationship with disease activity, age, or sex when compared to those who did not develop an adverse event.

These retrospective data are not definitive, but they are reassuring, according to Dr. Moshe. A larger prospective study by the PReS vaccination study group is now planned. The issue of leaving children unvaccinated is topical because of the recent outbreaks of measles in the United States.

“We must have clear guidelines on how to deal with the administration of live vaccines in this patient population so that we can provide the safest and most effective practice,” Dr. Moshe said.

These data are a first step. “This large retrospective study demonstrates that live attenuated booster vaccine is probably safe in children with rheumatic diseases,” said Dr. Moshe, but she deferred to the PReS guidelines in suggesting that the decision to vaccinate still might best be performed on a case-by-case basis.

Continued from // previous page

The researchers also calculated the cost to prevent one case of influenza, using a cost of approximately 16.5 euro per vaccine. Using this method, they estimated a cost for vaccination of 1,174 euro to prevent one influenza infection in the general population, and a cost of about 165 euro to vaccinate people treated with a TNF inhibitor to prevent one infection.

Dr. Adami advised clinicians to remember the low NNV for TNF inhibitor–treated patients with regard to influenza vaccination. “A direct disclosure of the NNV for these patients might help adherence to vaccinations,” he said.

Next steps for research should include extending the real-world effectiveness analysis to other medications and other diseases, such as zoster vaccination in patients treated with Janus kinase inhibitors, Dr. Adami said.

Dr. Adami had no financial conflicts to disclose. Several coauthors disclosed relationships with companies including Abiogen Pharma, Amgen, Grünenthal, Janssen-Cilag, Mundipharma, and Pfizer.
Efforts towards producing CNO/CRMO classification criteria show first results

Surveys and consensus techniques have been instrumental in identifying much needed candidate criteria toward the classification of chronic nonbacterial osteomyelitis (CNO), according to recent findings from international surveys of paediatric rheumatologists that were presented at the European Congress of Rheumatology.

Dr. Melissa Oliver, a paediatric rheumatologist at Riley Hospital for Children, Indianapolis, USA, and colleagues recently undertook the multiphase study as part of an international collaborative effort led by the Childhood Arthritis and Rheumatology Research Alliance to establish consensus-based diagnostic and classification criteria for CNO, an autoinflammatory bone disease of unknown cause that primarily affects children and adolescents. CNO is also known as chronic recurrent multifocal osteomyelitis (CRMO). If this disease is not diagnosed and treated appropriately in a timely fashion, damage and long-term disability is possible. In the absence of widely accepted, consensus-driven criteria, treatment is based largely on expert opinion, Dr. Oliver explained in an interview.

“There is an urgent need for a new and more robust set of classification criteria for CRMO, based on large expert consensus and the analysis of a large sample of patients and controls,” she said.

There are two proposed diagnostic criteria, the 2007 classification of nonbacterial osteitis and the 2016 Bristol diagnostic criteria for CRMO, but both are derived from single-centre cohort studies and have not been validated, Dr. Oliver explained.

The list of candidate items that have come out of the study is moving clinicians a step closer towards the design of a practical patient data collection form that appropriately weighs each item included in the criteria.

The study employed anonymous survey and nominal group techniques with the goal of developing a set of classification criteria sensitive and specific enough to identify CRMO/CNO patients. In phase 1, a Delphi survey was administered among international rheumatologists to generate candidate criteria items. Phase 2 sought to reduce candidate criteria items through consensus processes via input from physicians managing CNO and patients or caregivers of children with CNO.

Altogether, 259 of 865 paediatric rheumatologists (30%) completed an online questionnaire addressing features key to the classification of CNO, including 77 who practice in Europe (30%), 132 in North America (51%), and 50 on other continents (19%). Of these, 138 (53%) had greater than 10 years of clinical practice experience, and 108 (42%) had managed more than 10 CNO patients.

Initially, Dr. Oliver and colleagues identified 33 candidate criteria items that fell into six domains: clinical presentation, physical exam, laboratory findings, imaging findings, bone biopsy, and treatment response. The top eight weighted items that increased the likelihood of CNO/CRMO were exclusion of malignancy by bone biopsy; multifocal bone lesions; presence of bone pain, swelling, and/or warmth; signs of fibrosis and/or inflammation on bone biopsy; typical location of CNO/CRMO lesion, such as the clavicle, metaphysis of long bones, the mandible, and vertebrae; presence of CNO/CRMO–related comorbidities; normal C-reactive protein (CRP) or erythrocyte sedimentation rate (ESR); and typical MRI findings of CNO/CRMO.

By phase 2, candidate items, which were presented to 39 rheumatologists and seven parents, were refined or eliminated using item-reduction techniques. A second survey was issued to 77 of 82 members of a work group so that the remaining items could be ranked by their power of distinguishing CNO from conditions that merely mimicked the disease. The greatest mean discriminatory scores were identified with multifocal lesions (ruling out malignancy and infection) and typical location on imaging. Normal C-reactive protein and/or an erythrocyte sedimentation rate more than three times the upper limit of normal had the greatest negative mean discriminatory scores.

The next steps will be to form an expert panel who will use 1000minds software to determine the final criteria and identify a threshold for disease. The investigators hope to build a large multinational case repository of at least 500 patients with CNO/CRMO and 500 patients with mimicking conditions from which to derive a development cohort and an external validation cohort. So far, 10 sites, including 4 in Europe, have obtained approval from an institutional review board. The group has also submitted a proposal for classification criteria to the American College of Rheumatology and EULAR, Dr. Oliver said.

Dr. Oliver had no disclosures to report, but several coauthors reported financial ties to industry.
Mechanism does not matter for second-line biologic choice in JIA

When biologic treatment is indicated after initial tumour necrosis factor (TNF)–inhibitor therapy for juvenile idiopathic arthritis (JIA) has failed, the mechanism of action of the second biologic does not appear to matter, according to data presented at the European Congress of Rheumatology.

“There appears to be no difference in effectiveness outcomes or drug survival in patients starting a second TNF inhibitor versus an alternative class of biologic,” said Lianne Kearsley-Fleet, PhD, an epidemiologist at the Centre for Epidemiology Versus Arthritis at the University of Manchester (England).

Indeed, at 6 months, there were no significant differences among patients who had switched from a TNF inhibitor to another TNF inhibitor or to a biologic with an alternative mechanism of action in terms of the following:

- The change in Juvenile Arthritis Disease Activity Score-71 from baseline (mean score change, 7.3 with second TNF inhibitor vs. 8.5 with an alternative biologic class).
- The percentage of patients achieving an American College of Rheumatology Pediatric 90% response (22% vs. 15%).
- The proportion of patients achieving minimal disease activity (30% vs. 23%).
- The percentage reaching a minimal clinically important difference (44% vs. 43%).

There was also no difference between switching to a TNF inhibitor or alternative biologic in terms of the duration of time patients remained treated with the second-line agent.

“After 1 year, 62% of patients remained on their biologic therapy, and when we looked at drug survival over the course of that year, there was no difference between the two cohorts,” Dr. Kearsley-Fleet reported. There was no difference also in the reasons for stopping the second biologic.

“We now have a wide range of biologic therapies available; however, there is no evidence regarding which biologic should be prescribed in JIA, and if patients switch, which order this should be,” Dr. Kearsley-Fleet stated. This current NHS England guidelines recommend that most patients with JIA should start a TNF inhibitor (unless they are rheumatoid factor positive, in which case they should be treated with rituximab), and if the first fails, to switch to a second TNF inhibitor rather than to change class. The evidence for this is limited, she noted, adding that adult guidelines for rheumatoid arthritis now recommended a change of class if not contraindicated.

Using data from two paediatric biologics registers – the British Society for Paediatric and Adolescent Rheumatology Etanercept Cohort Study and Biologics for Children With Rheumatic Diseases – Dr. Kearsley-Fleet and her associates looked at data on 241 children and adolescents with polyarticular JIA (or oligoarticular-extended JIA) starting a second biologic. The aim was to compare the effectiveness of starting a second TNF inhibitor versus switching to an alternative class of agent, such as a B-cell–depleting agent such as rituximab, in routine clinical practice.

A majority (n = 188; 78%) of patients had etanercept as their starting TNF inhibitor and those switching to a second TNF inhibitor (n = 196) were most likely to be given adalimumab (58%). Patients starting a biologic with another mode of action (n = 45) were most likely to be given the interleukin-6 inhibitor tocilizumab (73%), followed by rituximab in 13%, and abatacept in 11%. The main reasons for switching to another biologic – TNF inhibitor or otherwise – were ineffectiveness (60% with a second TNF inhibitor vs. 62% with another biologic drug class) or adverse events or intolerance (19% vs. 13%, respectively).

The strength of these data is that they come from a very large cohort of children and adolescents starting biologics for JIA, with systematic follow-up and robust statistical methods, Dr. Kearsley-Fleet said. However, she noted that JIA was rare and that only one-fifth of patients would start a biologic, and just 30% of those patients would then switch to a second biologic.

“We don’t see any reason that the guidelines should be changed,” Dr. Kearsley-Fleet observed. “However, repeat analysis with a larger sample size is required to reinforce whether there is any advantage of switching or not.”

Versus Arthritis (formerly Arthritis Research UK) and The British Society for Rheumatology provided funding support. Dr. Kearsley-Fleet had no financial conflicts of interest to disclose.
Large-scale juvenile idiopathic arthritis studies assess etanercept safety

By analysing registry data from more than 10,000 patients with juvenile idiopathic arthritis (JIA), two recent studies further characterise the safety of etanercept in real-world practice, with a focus on risks of immune-mediated diseases, malignancies, and infections. The studies, presented at the European Congress of Rheumatology, offer reassurance in some areas, while keeping other safety concerns on the radar.

The first study, conducted by Dr. Roline Krol, of Utrecht (Netherlands) University, and her colleagues, evaluated the association between etanercept exposure in JIA patients and subsequent development of inflammatory bowel disease (IBD), a possible adverse event that has been highlighted by previous research, Dr. Krol said.

“Earlier studies found that etanercept was used more often in [JIA] patients who developed IBD, “ Dr. Krol said, “but also that methotrexate had a protective effect on IBD development. “

To evaluate this possibility, Dr. Krol and her colleagues turned to the Pharmachild JIA registry, the largest international registry of its kind, according to Dr. Krol. “[Pharmachild] gives us the possibility to find out a lot more about adverse events, “ she said, “and I think a lot of research is needed in this area, because there’s quite a lot we don’t know yet. “

The investigators reviewed data from 8,309 patients with JIA, finding that 260 had reported gastrointestinal disorders. Of these, 50 confirmed or suspected IBD cases were identified in 47 patients.

Further data analysis showed that patients who developed IBD were generally older (9.1 vs. 7.1 years; P = .002) and more likely to be male (67.6% vs. 48.9%; P = .011). In the 14 patients who had sufficient data about IBD onset and concurrent medication usage, 10 (71.4%) were taking etanercept and 7 (50%) were taking methotrexate at or within 3 months preceding IBD onset.

In an interview, Dr. Krol said that the first finding, concerning a possible relationship between etanercept and IBD, aligns with previous publications; in contrast, methotrexate did not appear to have a protective effect.

“I think a lot of people were thinking that methotrexate was safer for patients, regarding development of IBD [but] we did not find that. I think that’s important to keep in mind. “

Dr. Krol suggested that future research will also incorporate other biologics, such as adalimumab. “A lot still needs to happen, “ she said.

The second study, presented by lead author Dr. Jens Klotsche, of the German Rheumatism Research Center in Berlin, relied upon the German BiKeR registry and its follow-up registry, JuMBO, to evaluate the risk of malignancies, serious infections, and new-onset autoimmune events in JIA patients receiving etanercept.

“Etanercept was the first approved biologic for the treatment of polyarticular JIA in Germany, “ Dr. Klotsche said. “It is still the most frequently used biologic in JIA and patients may be exposed to etanercept over long periods of time to control the inflammation. “

Although long-term etanercept use is relatively common, Dr. Klotsche noted that concerns remain about adverse events, particularly increased risk of malignancies, which prompted a U.S. Food and Drug Administration black-box warning for all anti-TNF therapies in 2008.

Out of 4,546 patients currently in the BiKeR registry, 2,584 patients with JIA were older than 18 years, and therefore eligible for JuMBO. Of these patients, 1,765 (68%) had received etanercept at some time, and 1,101 had been followed into adulthood. The mean exposure to etanercept was 4.2 years, with 518 patients exposed for more than 5 years.

“Overall, 5.8% of patients had a reported autoimmune event with an average onset of 10.2 years after starting treatment, and 0.4% of patients had a reported, new-onset immune-mediated disorder with an average onset of 6.8 years. In all, 11 malignancies were reported, which represents a rate of 0.10...”
events per 100 person-years, with an average onset of 12.1 years after JIA onset and 7.5 years after first etanercept exposure. Of these 11 patients, 4 developed malignancy in childhood and 7 in young adulthood. Three out of the 11 patients were exposed to at least one other biologic therapy. Dr. Klotsche also pointed out that the data confirm the low risk of serious infections associated with etanercept.

“We have not identified any risk that might have questioned the benefit of a biologic therapy. Most importantly, in patients treated with bDMARDs in childhood or adolescence, we did not find a significantly increased risk of malignancy.”

However, Dr. Klotsche, like Dr. Krol, stressed the importance of monitoring long-term etanercept therapy moving forward. “Despite the available data and long-term use of biologics in children, there are still some concerns about possible long-term consequences of biological DMARDs,” he said. “It is therefore imperative to monitor JIA patients who have been treated with various DMARDs including biologics from childhood and adolescence into adulthood to get more information about the long-term safety of drugs and the risk of malignancies and other serious events in JIA patients.”

Dr. Krol and Dr. Klotsche had no disclosures to report. Several coauthors reported financial relationships with numerous pharmaceutical companies.
EULAR releases first adult antiphospholipid syndrome recommendations

Low-dose aspirin is recommended for the primary prevention of antiphospholipid syndrome (APS) in patients at high risk for developing the condition, according to new recommendations developed by EULAR.

Indeed, the NSAID should be given at a dose of between 75 mg and 100 mg per day, in patients with a “high risk” antiphospholipid (aPL) antibody profile, including asymptomatic aPL antibody carriers, patients with systemic lupus erythematosus without APS, and in women who are not pregnant but who have a history of obstetric APS.

The recommendations, which are the first evidence-based guidelines for adult APS to be produced by EULAR, also cover the secondary prevention of APS and how to manage individuals with recurrent episodes.

The recommendations aim to help guide practice and ultimately to improve the quality of care for patients and their outcomes following treatment, Dr. Maria G. Tektonidou said at the European Congress of Rheumatology.

The guidance is necessary as “clinical practise in APS remains highly variable,” said Dr. Tektonidou of the National and Kapodistrian University of Athens. This is perhaps because APS is a “rare disease and also because it’s a newly recognised disease – it’s only 35 years old – and knowledge about the clinical spectrum, classification, and management is continuously advancing.”

Dr. Tektonidou, who was the convener of the EULAR Task Force that wrote the recommendations, noted that they were now published in Annals of the Rheumatic Diseases, and considered three main groups of patients: those with thrombotic APS, those with obstetric APS, and those with catastrophic APS (CAPS). There are three overarching principles, 12 recommendations, and 29 graded statements, she said.

The three overarching principles concerned risk stratification, general measures for managing patients who test positive for aPL antibodies, and patient education and counseling on various topics, such as treatment adherence, therapeutic drug monitoring, contraceptive use, and lifestyle interventions.

Dr. Tektonidou highlighted how risk stratification was important and that a high-risk aPL profile was defined as the presence of lupus anticoagulant on at least two occasions, measured 12 weeks apart according to International Society on Thrombosis and Haemostasis guidelines, or the presence of two or even three aPL antibodies, or persistently high aPL antibody titers. By contrast, a low-risk aPL profile was defined as the isolated presence of anticardiolipin (aCL) or anti-beta-2 glycoprotein I antibodies at low-medium titers, particularly if transiently positive.

“Risk stratification should include the determination of the high-risk aPL profile; a prior history of thrombotic or obstetric APS; the coexistence of other systemic autoimmune diseases, and the presence of traditional cardiovascular risk factors,” Dr. Tektonidou said.

Four of the recommendations focus on the secondary prevention of APS, giving guidance on anticoagulant treatment with definite APS, first provoked or unprovoked venous thrombosis, and how to manage recurrent venous thrombosis. There also is a recommendation for the management of patients with definite APS and a first arterial thrombosis, outlining the type and intensity of anticoagulant therapy that should be given. Another four of the recommendations focus on the management of obstetric APS, with a focus on how to manage the various types of complications seen in pregnant women. Then the final recommendation concerns CAPS, it’s prevention and first-line treatment, and how to manage refractory patients.

With regards to CAPS, Dr. Ricard Cervera of the Hospital Clinic of Barcelona said, this is a “terrible” but...
EULAR overhauls large-vessel vasculitis management recommendations

Ten years after they were last published, a EULAR expert task force has revamped guidance on how to manage patients with large-vessel vasculitis. The “substantial revision” of the 2009 recommendations (Ann Rheum Dis. 2009;68[3]:310-7) was based on two new systematic literature reviews, focusing on general management and treatments, respectively. These were performed “without limits,” task force member Prof. Bernhard Hellmich said at the European Congress of Rheumatology.

The reason for starting from scratch was the amount of “high-impact” data that have been published in the intervening years, including the results of several randomised clinical trials, and also the fact that EULAR had released guidance on imaging in large-vessel vasculitis (LVV) in 2018 (Ann Rheum Dis. 2018;77[5]:636-43).

The new recommendations, which are published in Annals of the Rheumatic Diseases (Ann Rheum Dis. 2019 Jul 3. doi: 10.1136/annrheumdis-2019-215672), now include three overarching principles, said Prof. Hellmich, who is the chief physician of the Clinic for Internal Medicine, Rheumatology and Immunology at Medius Kliniken in Kirchheim unter Teck, Germany.

The first overarching principle says that patients with LVV “should be offered best care which must be based on a shared decision between the patient and the rheumatologist, considering, of course, efficacy, safety, and costs,” he stated.

“Second, patients should have access to education focusing on the impact of LVV, its key warning symptoms, and its treatment, including treatment-related complications,” he added.

“Third, patients with large-vessel vasculitis should be screened for treatment-related comorbidities and also cardiovascular comorbidities, and we recommend prophylaxis and lifestyle advice to reduce cardiovascular risks and treatment-related complications.”

Another key change is that there are 10 rather than 15 recommendations. These include new recommendations on early diagnosis, management, and the treatment of relapse.

The first two recommendations highlight the need for specialist referral and multidisciplinary management of giant cell arteritis (GCA) and Takayasu arteritis (TAK).

Recommendation 3 offers advice on confirming a diagnosis of LVV by imaging and confirms the need for specialist referral and multidisciplinary management of giant cell arteritis (GCA) and Takayasu arteritis (TAK).

The new EULAR 2019 adult APS recommendations now include CAPS and recommendation number 12 is split into two parts. The first, part A, states that prompt treatment of infections is needed in all patients positive for aPL antibodies and that anticoagulation should have minimal interruption or be used at level to help prevent the development of CAPS.

The second, part B, states that the first-line treatment of CAPS should be a triple combination therapy of glucocorticoids, heparin, and plasma exchange, or intravenous immunoglobulins, rather than single-agent treatment. Plus, it says that any triggering factor should be treated accordingly.

“Finally,” Dr. Cervera said, “in patients with refractory CAPS, B-cell depletion with rituximab or complement inhibitors, for example eculizumab, may be considered.”

Dr. Tektonidou and Dr. Cervera reported having no relevant conflicts of interest.
imaging or histology. “If you decide to do it by imaging, you should follow the EULAR recommendations on imaging that say that ultrasound or MRI should be used for temporal or other cranial arteries, or ultrasound, PET-CT, or MRI for the aorta and extracranial arteries,” Prof. Hellmich said. “It’s important to confirm the diagnosis,” he added, cautioning that the speed was important in testing as these imaging tests lose their sensitivity the longer patients have been treated with glucocorticoids or other drugs. Recommendation 4 covers the use of high-dose glucocorticoid therapy when there is active disease. This recommendation also includes advice on how to taper glucocorticoid doses: first to a target dose of 15-20 mg/day within 2-3 months and then how to get the dose down within the year to 5 mg/day or less for GCA and to 10 mg/day or less for TAK.

There has been major revision of the recommendation for adjunctive therapy, Prof. Hellmich observed, with recommendation 5 advising the use of tocilizumab in selected patients with GCA – those with refractory or relapsing disease or who have an increased risk of glucocorticoid-induced adverse effects or complications; methotrexate may be used as an alternative.

Recommendation 6 states that all patients with TAK should be given nonbiologic disease-modifying agents in combination with glucocorticoids. In patients where this treatment fails, tocilizumab and tumour necrosis factor (TNF) inhibitors may be considered.

Recommendation 7 addresses advice on treatment of major and minor relapses. “In case of a major relapse, which we defined as signs or symptoms of ischaemia or progressive vascular inflammation, we recommend a reinstitution or dose escalation of glucocorticoid therapy, as recommended for new-onset disease,” Prof. Hellmich said. For minor relapses, the task force advised increasing glucocorticoid doses to the last effective dose and considering a change to adjunctive therapy.

Guidance on the use of antiplatelet agents has undergone major revision. Recommendation 8 states that antiplatelet agents should not be used routinely unless there is another reason to do so, such as in patients with cardiovascular disease or vascular ischaemic complications. “This is a change from the 2009 recommendations where the use of aspirin was recommended for all GCA patients, but that recommendation in the past was based on one observational study, and the studies later on did not confirm this observation,” Prof. Hellmich said.

The ninth recommendation con-
Experts agree on routine lung disease screening in systemic sclerosis

The first consensus recommendations for the identification and management of interstitial lung disease (ILD) in patients with systemic sclerosis (SSc) place particular emphasis on routine screening in all systemic sclerosis patients for early detection, monitoring, and, when warranted, treatment, Dr. Anna-Maria Hoffmann-Vold reported at the European Congress of Rheumatology.

“Everyone with systemic sclerosis needs to be screened because this is the most important risk factor for ILD,” said Dr. Hoffmann-Vold, a clinical scientist in the division of rheumatology at the University of Oslo and head of scleroderma research at Oslo University Hospital.

Although the frequency of screening is not specified based on the opinion that this should be based on risk factors and other clinical characteristics, there was unanimous agreement that lung function tests do not represent an adequate screening tool or method for assessing ILD severity. Rather, the recommendations make clear that lung function studies are adjunctive to high-resolution computed tomography (HRCT).

“HRCT is the primary tool for evaluating ILD, but there was 100% agreement that assessment should include more than one measure, including lung function tests and clinical assessment,” Dr. Hoffmann-Vold reported.

There was a strong opinion that the numerous potential biomarkers described for ILD, although promising, are not yet ready for clinical use.

In the development of these new recommendations, 95 potential statements were considered by the panel of 27 rheumatologists, pulmonologists, and others with experience in this field. A Delphi process was used for members of the panel to identify areas of agreement to produce consensus statements.

The result has been more than 50 statements issued in six major domains. These include statements on risk factors, appropriate methodology for diagnosis and severity assessment, when to initiate therapy, and when and how to initiate treatment escalation.

“We want to increase clinician awareness and provide standardised guidance for evaluating patients for the presence and medical management of ILD-SSc,” she explained.

ILD occurs in about half of all patients with systemic sclerosis. Among these, approximately one out of three will experience lung disease progression. Although these high prevalence rates are well recognised and associated with high morbidity and mortality, Dr. Hoffmann-Vold said that there has been uncertainty about how to screen systemic sclerosis patients for ILD and what steps to take when it was found. It is this uncertainty that prompted the present initiative.

The consensus recommendations are an initial step to guide clinicians, but Dr. Hoffmann-Vold noted that the many statements are based on expert opinion, suggesting more studies are needed to compare strategies for objective severity grading and prediction of which patients are most at risk for ILD progression.

“There are still huge knowledge gaps we need to fill,” she stated. Still, she believes these recommendations represent progress in this field. While they are likely “to increase the standard of care” for those who develop ILD-SSc, they also have identified where to concentrate further research.

Dr. Hoffmann-Vold reported financial relationships with Actelion, Boehringer Ingelheim, and GlaxoSmithKline.

Concerns surgery. “Elective endovascular interventions or reconstructive surgery should be performed in phases of stable remission. However, arterial vessel dissection or critical vascular ischaemia requires urgent referral to a vascular team for urgent work-up.”

The last and 10th recommendation notes that regular follow-up and monitoring of disease activity in patients with LVV are needed and should be mainly based on patients’ symptoms, clinical findings, erythrocyte sedimentation rate, and C-reactive protein levels. Prof. Hellmich again said to refer to the separate EULAR imaging guidelines as there was “insufficient evidence to recommend the routine use of imaging.”

Prof. Hellmich disclosed receiving honoraria for lectures and advisory services from multiple pharmaceutical companies, including AbbVie, Boehringer Ingelheim, Bristol-Myers Squibb, Celgene, Chugai, Merck Sharpe & Dohme, Novartis, Pfizer, and Roche.
Lowering uric acid improved endothelial function but failed as an antihypertensive

Using allopurinol to reduce hyperuricaemia in young adults with prehypertension or stage 1 hypertension failed to significantly lower blood pressure but succeeded in significantly improving endothelial function as measured by increased flow-mediated arterial dilation in a single-center crossover study with 82 participants.

The finding of improved endothelial function suggests that reducing hyperuricaemia may be a new way to manage hypertension or prevent progression to stage 1 hypertension, improve cardiovascular health, and ultimately cut cardiovascular events, Dr. Angelo L. Gaffo said at the European Congress of Rheumatology.

The results indicated that the BP-lowering effect of allopurinol treatment was strongest in people who entered the study with the highest serum urate levels, greater than 6.5 mg/dL, an indication that the next step in developing this approach should be targeting it to people with serum urate levels in this range, said Dr. Gaffo, a rheumatologist at the University of Alabama at Birmingham.

“It’s just a matter of finding the right population to see the blood pressure reduction effect,” Dr. Gaffo said in an interview.

He and his associates designed the SURPHER (Serum Urate Reduction to Prevent Hypertension) study to assess the impact of allopurinol treatment in people aged 18-40 years with prehypertension or stage 1 hypertension as defined by U.S. BP standards at the time they launched the study in 2016 (Contemp Clin Trials. 2016 Sep;50:238-44). Enrolled participants had to be nonsmokers; have an estimated glomerular filtration rate of greater than 60 mL/min per 1.73 m²; have a serum urate level of at least 5.0 mg/dL in men and at least 4.0 mg/dL in women; and be without diabetess, antihypertensive medications, prior urate-lowering treatment, or a history of gout. The 99 people who started the study averaged 28 years old, nearly two-thirds were men, 40% were African Americans, and 52% were white. The participants’ average body mass index was nearly 31 kg/m², and their average BP was 127/81 mm Hg. Average serum urate levels were 6.4 mg/dL in men and 4.9 mg/dL in women. Participants received 300 mg/day allopurinol or placebo, and after 4 weeks crossed to the alternative regimen, with 82 people completing the full protocol.

While on allopurinol, serum urate levels fell by an average of 1.3 mg/dL, a statistically significant drop; on placebo, the levels showed no significant change from baseline.

The primary endpoint was the change in BP on allopurinol treatment, which overall showed no statistically significant difference, compared with when participants received placebo.

The results also showed that among people with a baseline serum urate level of greater than 6.5 mg/dL (15 of the 82 study completers) systolic BP fell by an average of about 5 mm Hg.

The results suggested that the concept of reducing hyperuricaemia in people with early-stage hypertension or prehypertension might be viable for people with higher serum urate levels than most of those enrolled in SURPHER, Dr. Gaffo said. He noted that prior study results in obese adolescents showed that treating hyperuricaemia was able to produce a meaningful BP reduction (Hypertens. 2012 Nov;60[5]:1148-56).

SURPHER received no commercial funding. Dr. Gaffo has received research funding from Amgen and AstraZeneca.
Trial lends support to EULAR interventional treatment recommendations for hand OA

Data from a randomised, controlled trial of patients with carpometacarpal osteoarthritis support the core interventional treatments of patient education, hand exercises, assistive devices, and orthoses that are found in the most recently updated EULAR treatment recommendations for hand osteoarthritis (OA). The results of the study indicate that these core treatments reduce pain, improve function, and potentially reduce the need for surgery, according to Prof. Ingvild Kjeken, of the national advisory unit on rehabilitation in rheumatology at Diakonhjemmet Hospital in Oslo.

Prof. Kjeken said the researchers at Diakonhjemmet Hospital encountered the question of whether occupational therapy helps delay thumb carpo-metacarpal (CMC1) surgery when meeting with occupational therapists who work with these patients. “They experienced that surgeons increasingly referred patients with CMC1 osteoarthritis for provision of orthoses and hand exercises,” she said. “They also got positive feedback from patients that these interventions reduced pain and helped them to manage their daily activities, but as we know, such feedback may not give the whole picture, as patients who are satisfied are more prone to give feedback than those who are not.”

In a randomised, controlled trial presented at the congress, 180 patients from three Norwegian rheumatology departments received information on hand OA, while 90 participants in the occupational therapy group additionally received a hand exercise programme, day and night orthoses, and assistive devices. They also registered days of exercise and use of orthoses into a treatment diary. Patients had a follow-up visit at 4 months, 18 months, and 24 months.

“Prof. Kjeken noted that the results may not have been statistically significant because of lack of data from studies on how many referrals led to surgery. The assumption of a 70% surgery rate used in the sample size calculation was therefore based on surgeons’ assumptions rather than facts,” she said. “As the results show, a much lower proportion had received surgery after 2 years. Thus, even if the dropout rate in our study was lower than expected, it was probably underpowered to detect the suggested 20% difference between groups with the assigned power and significance level.”

The median time to surgery in the occupational surgery group was longer (350 days; interquartile range, 210-540), compared with the control group (297 days; IQR, 188-428 days). Predictors of surgery included a higher motivation for surgery (odds ratio, 1.22; 95% confidence interval, 1.07-1.38) and previous nonpharmacologic treatment (OR, 2.70; 95% CI, 1.16-6.27). Hand pain, reduced function, or degree of CMC1-OA were not predictors.

In secondary analyses at 4 months, there were significant betweengroup differences in pain at rest, grip strength, pain after grip, in patient-reported measure activity performance of the hand (MAP-Hand) and in Quick Disabilities of the Arm, Shoulder, and Hand Score (QuickDASH), with the occupational therapy group showing greater improvement, which for most outcomes was clinically relevant (P less than .01).

The results also showed a gap between treatment recommendations for hand OA and clinical practice, Prof. Kjeken said, as only 21% of the participants had received nonpharmacologic treatment before being referred to surgical consultation.

“The updated EULAR treatment recommendations for hand OA states that patient education, hand exercises, assistive devices, and orthoses are the core interventional treatments for people with hand OA, and that surgery should only be considered when other treatment modalities (including medication) have failed,” she said. “This study thereby supports that the recommended core treatment reduces pain and improves function, and potentially reduces the need for surgery, which is a more costly intervention.”

One of the authors reported grant or research support from Pfizer and being a consultant and on the advisory board for AbbVie. The other authors reported no relevant conflicts of interest.
Bisphosphonate before denosumab may avert BMD rebound

Results from an ongoing study of postmenopausal women who discontinue osteoporosis treatment with denosumab so far support the use of denosumab as a second-line therapy after a bisphosphonate, unless otherwise indicated, in order to reduce the loss of bone mineral density (BMD) after its discontinuation and also to support treatment to reduce bone turnover biomarkers as much as possible after stopping denosumab.

“We saw in our study that, even if you give bisphosphonates after denosumab discontinuation, [patients] could lose bone, and the group that controlled the loss of bone had very high control of bone turnover markers,” study author and presenter Dr. Bérengère Rozier Aubry said in an interview at the European Congress of Rheumatology.

She and her colleagues at the Center of Bone Diseases at Lausanne (Switzerland) University Hospital are conducting the ReoLaus (Rebound Effect Observatory in Lausanne) Bone Project to determine whether giving a bisphosphonate to postmenopausal women with osteoporosis after they have discontinued denosumab can stop the loss of BMD observed in many patients up to 2 years after stopping denosumab. This postdenosumab BMD loss has also been observed to occur with multiple spontaneous vertebral fractures.

Nearly half of patients who start denosumab discontinue it within 1 year, and 64% by 2 years, according to U.S. administrative claims data (Osteoporos Int. 2017 Apr. doi: 10.1007/s00198-016-3886-y), even though it can be taken for up to 10 years. The discontinuation is either because the patient wishes to do so or there’s a medical indication such as stopping aromatase inhibitor treatment, resolution of osteoporosis, or side effects, Dr. Rozier Aubry said in a press conference at the congress.

Upon discontinuation of denosumab, there’s a marked rebound effect in which levels of bone turnover markers rise for 2 years, and some multiple spontaneous vertebral fractures also have been reported when raloxifene, ibandronate, or alendronate have been given after stopping denosumab, she said.

In the ReoLaus Bone Project, Dr. Rozier Aubry and associates are following 170 postmenopausal women with osteoporosis at Lausanne University Hospital who are taking denosumab therapy. At the congress, she reported on the first 71 women in the cohort with 1 year of follow-up. They had a mean age of 64 years, had fewer than one prevalent fracture before starting denosumab, and stopped denosumab after a mean of 7.7 injections. Overall, 8% took glucocorticoids, and 22% took aromatase inhibitors.

Recommendations from other groups advise giving antiresorptive treatment (bisphosphonates, hormone therapy, or selective estrogen-receptor modulators) but do not say which one, in what dose, when, or for how long, she noted.

Treatment with zoledronate 6 months after the last denosumab injection achieves partial preservation of BMD, but multiple vertebral fractures have still been reported when raloxifene, ibandronate, or alendronate have been given after stopping denosumab, she said.

“Our proposition is to start with 1 or 2 years of bisphosphonates, and if the osteoporosis is severe, to switch to denosumab treatment for 4, 6 years.”

or all of the BMD that was gained is lost (J Clin Endocrinol Metab. 2011 Apr. doi: 10.1210/jc.2010-1502). Multiple spontaneous vertebral fractures also have been reported in 5%-7%, as Dr. Rozier Aubry and colleagues first described in 2016 (Osteoporos Int. 2016 May. doi: 10.1007/s00198-015-3380-y) and others have reported subsequently.

Recommendations from the Endocrine Society in March 2019, a 2017 position statement from the European Calcified Tissue Society, and guide-lines from other groups advise giving antiresorptive treatment (bisphosphonates, hormone therapy, or selective estrogen-receptor modulators) but do not say which one, in what dose, when, or for how long, she noted.

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The investigators collected data on what treatment was used after denosumab, how bone turnover markers
The advantages of a virtual RMD conference for patients

A virtual conference organised by ReumaNet in Brussels reached far more patients than did its traditional physical conference, broadened ReumaNet’s social media visibility, and raised patient awareness of rheumatic and musculoskeletal diseases (RMDs) on a broader scale, according to a presentation at the Congress that described the event and its impact.

“If we want to reach a lot of patients, we should use more digital solutions to do so, such as a virtual conference,” said presenter Mitchell Silva, PhD, M-Health coordinator at ReumaNet.

ReumaNet hosted the virtual conference in place of its biennial physical conference for patients that addresses various RMD topics. About 200 people generally attend the traditional event. For the virtual conference, ReumaNet created an online system that included more than 20 prerecorded presentations on subjects such as the medical evolution of RMDs; the psychological, vocational, social, and physical aspects of having an RMD; and changing technology in healthcare and sustainability of the healthcare system. ReumaNet also offered partner organisations “virtual booths” that enabled them to provide educational material in PDFs or video formats.

“More than 1,300 people registered for the virtual event and more than 140,000 people were reached on social media, according to ReumaNet. On the platform itself, the content received more than 5,000 video views and the virtual booths received more than 3,000 visits. In addition, the virtual conference achieved high patient satisfaction rates and also raised the visibility of ReumaNet’s Facebook page.

The fact that the virtual conference was a temporary event, meaning it had a start and end date, gave a sense of urgency to visit the event online, Dr. Silva said.

“After the end date, the content was taken offline,” he noted. “Having credible information, prescreened and validated, in one place was a big asset for visitors. A similar approach will be repeated this year, however, with a simple website that does not require preregistration in contrast to the technology that was used in this pilot.”

The new approach demonstrated that it is possible to expand the reach of lay public to such information, compared with traditional face-to-face events, by using virtual conference technology, Dr. Silva said.

“This concept can be repeated by other patient organisations across Europe and serve as an inspiration,” he said. “By using this approach, high-quality educational content can be provided to anyone who has an interest in learning more on a variety of topics. Even more interesting, you will learn more about the profiles of the patients who have an interest in such educational content. ReumaNet is open to share this concept with other patient organisations in Europe.”

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changed 1-3 months after the last denosumab injection and then regularly afterward, how bone mineral density changed after 1 year, and any new osteoporotic fractures.

At the time of denosumab discontinuation, 59% received zoledronate, 24% alendronate, 3% other drugs, and 14% nothing. At a mean of about 17 months after the last denosumab injection, the investigators classified 30 patients as BMD losers (losing at least 3.96%), and 41 had stable BMD. The researchers found that BMD losers were younger (61.4 years vs. 65.5 years), were less likely to use zoledronate before starting denosumab (0% vs. 12%), and had greater serum CTX (C-telopeptide cross-linked type 1 collagen) levels at denosumab initiation (644 ng/mL vs. 474 ng/mL) and 12.8 months after stopping denosumab (592 ng/mL vs. 336 ng/mL) than did those with stable BMD. All differences were statistically significant.

“Our results support the use of denosumab in second line after bisphosphonate treatment to restrain the BMD loss at its discontinuation ... and a strategy to maintain the bone turnover marker serum CTX as low as possible after denosumab discontinuation;” she concluded.

“Our proposition is to start with 1 or 2 years of bisphosphonates, and if the osteoporosis is severe, to switch to denosumab treatment for 4, 6 years. ... We can use denosumab for 10 years without side effects, and after that we give bisphosphonates to consolidate the treatment,” she said.

Dr. Rozier Aubry and her associates plan to follow patients in their study for 2 years. She disclosed serving on speakers bureaus for Eli Lilly, Pfizer, Amgen, and Novartis.
Getting patients involved in research agenda setting

More and more researchers in the Netherlands are finding their way to patient organisations for collaboration. The patient’s voice is becoming a more integral part of the healthcare landscape. The National Association ReumaZorg Nederland wants to take this voice of patients to the level where it helps set the agenda.

Patricia Pennings of ReumaZorg Nederland presented research at the congress on the top five patient problems and wishes for research into rheumatic and musculoskeletal diseases (RMDs) that she hopes will help to influence researchers and those who provide research funding to be more patient driven at the beginning of the research agenda–setting process, rather than relegating it to an obligatory (last) part at the end of the submission process of their research proposal.

“Patients want their voice to be heard from the very start of a research project, even before the first research proposal is actually written, even before research funds decide what to use their funding for.”

Ms. Pennings wants to inspire people to get the patient’s voice into the discussion at the very beginning of the research agenda–setting process.

“Something interesting with regards to the top five of wishes is the wish about exercising,” she said. “More than two-thirds of respondents in our research project found exercise to be one of the main things for further development because they would really like to see an accessible and affordable network of physical exercise activities under professional supervision, more investigation on the cause of inflammatory RMDs, more investigation on the cause of fatigue with RMDs and how to cope, and research on alternative forms of therapy and their effects on specific types of RMDs.

“Fatigue is still one of the main problems of people with RMDs, along with learning how to cope with fatigue and finding out what causes fatigue in RMDs,” she noted. “This goes for people with all types of RMDs;” she said. “Although the abstract nature of fatigue makes it difficult to study, it absolutely remains a wish for further investigation.”

Another conclusion she got from the research is that fatigue remains a consistent problem.

“Patients want their voice to be heard from the very start of a research project, even before the first research proposal is actually written, even before research funds decide what to use their funding for.”

The other standout to Ms. Pennings was the desire for more research on alternative therapies.

“We learned in this project that many people with RMDs turn to alternative medication or alternative forms of therapy as well because they feel they are not completely helped by the regular medication that is available,” she said, emphasising the need for more research on alternative therapies to actually determine scientifically if they work. “Researchers need to focus more on that!”

What I really hope is that, with this research agenda, researchers and other patient organisations are inspired to initiate projects on things that matter most to people with RMDs,” she said. “That we put the focus in research and development on where it is needed most – on the needs of patients. Because only then we can make a difference:”