Welcome to the EULAR 2020 Report

This year’s congress was a truly remarkable celebration of scientific and educational excellence in a new online format, keeping faith with EULAR’s commitment to be the prime platform for rheumatology information exchange and professional education in Europe and for the world. The difficult decision to move from a face-to-face format congress in Frankfurt to a virtual format was a necessity placed upon us by the COVID-19 pandemic. The rheumatology community, however, rose magnificently to the occasion and participated with enthusiasm! My thanks to the faculty and speakers from around the globe who contributed in both live and recorded format to give of their expertise and knowledge. My thanks also to the amazing EULAR Secretariat and congress planning team who moved with great agility and ingenuity to create an online congress of excellent quality in a very short time indeed.

More than 18,700 delegates from 138 countries attended this year’s e-congress to inform themselves of the best in rheumatology research and clinical advances. As such, the EULAR Congress has confirmed its global appeal — indeed the virtual format has allowed even greater dissemination of the content with increased value to our community as we collectively seek to improve the lives of people with rheumatic and musculoskeletal diseases.

The EULAR 2020 Report brings you highlights of some of the best presentations, focusing especially on the clinical and therapeutic findings that now, or soon, will change the way physicians and health professionals practice in our most exciting of disciplines.

We hope that you will enjoy this synthesis of the latest in rheumatology clinical and translational research. We missed the personal encounters with you in 2020 but look forward to meeting you in Paris in 2021!

Prof. Iain McInnes
EULAR President
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Thank you and hope to see you in person next year at EULAR 2021 in Paris!

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As might be expected, the “EULAR provisional recommendations for the management of rheumatic and musculoskeletal diseases [RMDs] in the context of SARS-CoV-2” concur with much of the guidance already released on how best to manage patients during the current pandemic.

Highlights of the five overarching principles are that, contrary to earlier expectations, “there is no indication that patients with RMDs have an additional, or have a higher, risk of contracting the virus, or that they face a worse course” than the general population, said the task force convener Prof. Robert Landewé, professor of rheumatology at the University of Amsterdam.

“The second pertinent highlight is that, when it comes to managerial discussions, whether or not to stop or to start treatment for RMDs, rheumatologists should definitely be involved,” Prof. Landewé said during a live session at the congress. “In practice, something that happens very often is that immunosuppressive drugs are stopped by medical specialists involved in the care of COVID but without any expertise in treating patients with rheumatic diseases. We should try to avoid that situation.”

The third highlight, something many rheumatologists may already be well aware of, is that rheumatology drugs are being used to treat COVID-19 patients without RMDs and a shortage of disease-modifying antirheumatic drugs (DMARDs) is a real possibility. As such, the fifth overarching highlight states that the availability of both synthetic and biologic DMARDs is “a delicate societal responsibility” and that “the off-label use of DMARDs in COVID-19 outside the context of clinical trials should be discouraged.”

The EULAR recommendations are now published online in Annals of the Rheumatic Diseases, and they are “what you could call an unprecedented set of recommendations,” Prof. Landewé said. “We have never done this before,” he added, referring to the speed and way in which they had to be put together, remotely, and with little scientific evidence currently available.

There are 13 recommendations that cover 4 themes: general measures and prevention of SARS-CoV-2 infection; the management of RMD patients during the pandemic; the management of RMD patients who have COVID-19; and the prevention of other pulmonary infections in RMD patients.

Highlighting the first three general recommendations, Prof. Landewé said, “Follow the regular guidelines in your country; if a patient with RMD does not have symptoms of COVID-19, simply continue RMD treatments,” albeit with a couple of exceptions.

The next four recommendation highlights are to avoid visits to the hospital or to the office; use remote monitoring via the telephone, for example; and if visits cannot be avoided, then take appropriate precautions. Finally, if you suspect a patient has COVID-19, do a test.

If patients test positive, then the next four recommendations cover what to do, such as continuing use of RMD treatments, but in the case of glucocorticoids this should be the lowest possible dose necessary. There is no consensus on what to do in cases of mild symptoms; the recommendation is to “decide on a case-by-case basis,” said Prof. Landewé. If a patient’s symptoms worsen, then “seek expert advice immediately and follow local treatment recommendations. The rheumatologist is not the expert to treat COVID-19,” he added. That responsibility lies with the pulmonologist, infectious disease specialist, or maybe the intensive care specialist, depending on local situations.

On the whole, the EULAR recommendations are pretty similar to those already released by the American College of Rheumatology, said Dr. Ted Mikuls, of the University of Nebraska Medical Center, Omaha, USA. The ACR recommendations are “slightly more prescriptive”, he suggested, with 25 final guidance statements. For example, general statements focused on the use of not only glucocorticoids, but also other medicines, such as antihypertensives.

“There’s really not a lot of, I would say, major differences in the two efforts and that’s... somewhat reassuring that we’re approaching the unknown from very different parts of the world, and arriving in a very similar place,” commented Dr. Mikuls, who is a member of the ACR COVID-19 recommendations task force.

“I think one of the very important similarities that I would highlight is that, in the absence of known exposure, in the absence of COVID-19 infection, our panel felt very strongly about the importance of continuing rheumatic disease treatments,” Dr. Mikuls observed. The ACR guidelines also touch upon societal perspectives, including “some statements that were made very specific to lupus, and the use of antimalarials, given supply chain issues that we have encountered.”

Dr. Mikuls also said that the American recommendations emphasised that “you really have to manage active inflammatory rheumatic disease. Even in the context of the COVID-19 pandemic, given what we saw as the potential risk of unchecked inflammation and unchecked rheumatic disease.”

One notable difference, however, is that the European recommendations advise on immunisations and pneumonia prophylaxis, saying that all patients without COVID-19 symptoms should make sure they are up to date with any recommended vaccinations, “with a particular focus on pneumococcal and influenza vaccinations,” Prof. Landewé said.

EULAR expects to update its recommendations about every 3 months.

“The current evidence is extremely sparse and fragmented,” Prof. Landewé said. “We, as a task force, are essentially flying blindly. We also have to cover many jurisdictions within Europe, with many conflicting opinions. So the last word to say is that updates are truly necessary, but we have to wait a while.”
Most rheumatology drugs don’t increase COVID-19 hospitalisation risk

The vast majority of patients with rheumatic and musculoskeletal diseases who contract COVID-19 recover from the virus, regardless of which medication they receive for their rheumatic condition, new international research suggests.

“These results provide, for the first time, information about the outcome of COVID-19 in patients with rheumatic and musculoskeletal diseases,” said study investigator Prof. Pedro Machado, of University College London. “They should provide some reassurance to patients and healthcare providers.”

Prof. Machado and his colleagues looked at 600 COVID-19 patients from 40 countries and found that those taking TNF inhibitors for their rheumatic disease were less likely to be hospitalised for COVID-19. However, treatment with more than 10 mg of prednisone daily – considered a moderate to high dose – was associated with a higher probability of hospitalisation.

In addition, hospitalisation was not associated with biologics; JAK inhibitors; conventional disease-modifying antirheumatic drugs (DMARDs), such as methotrexate; antimalarials, such as hydroxychloroquine; or NSAIDs – either alone or in combination with other biologics, such as TNF inhibitors.

The findings were presented at the congress and were published online in Annals of the Rheumatic Diseases. “Initially, there was a huge concern that these drugs could affect the outcome of patients getting COVID-19, but what this is showing is that probably these drugs do not increase their risk of severe outcome,” Prof. Machado, who is chair of the EULAR Standing Committee on Epidemiology and Health Services Research, said in an interview.

As of 1 June, 1,061 patients from 28 participating countries had been entered into the EULAR COVID-19 database, which was launched as part of the international Global Rheumatology Alliance registry. Patient data are categorised by factors such as top rheumatology diagnosis, comorbidities, top-five COVID-19 symptoms, and DMARD therapy at the time of virus infection.

Prof. Machado’s team combined data from the EULAR and Global Rheumatology Alliance COVID-19 registries from 24 March to 20 April. They looked at patient factors – such as age, sex, smoking status, rheumatic diagnosis, comorbidities, and rheumatic therapies – to examine the association of rheumatic therapies with hospitalisation rates and COVID-19 disease course.

Of the 277 patients (46%) in the study cohort who required hospitalisation, 55 (9%) died. But this finding shouldn’t be viewed as the true rate of hospitalisation or death in patients with rheumatic disease and COVID-19, said Prof. Gerd Burmester of Charité–University Medicine Berlin. “There’s tremendous bias in terms of more serious cases of COVID-19 being reported to the registries,” he explained, “because the mild cases won’t even show up at their rheumatologist’s office.”

“This can skew the idea that COVID-19 is much more dangerous to rheumatic patients than to the regular population,” Prof. Burmester said in an interview. “It scares the patients, obviously, but we believe this is not justified.”

The study can only highlight associations between rheumatic drugs and COVID-19 outcomes. “We cannot say there is a causal relationship between the findings,” Prof. Machado said.

Longer-term data, when available, should illuminate “more granular” aspects of COVID-19 outcomes in rheumatic patients, including their risks of requiring ventilation or developing a cytokine storm, he noted.

Prof. Burmester and Prof. Machado agree that research needs to continue as the pandemic rages on. But so far, “there are no data suggesting that, if you’re on a targeted, dedicated immunomodulator, your risk is higher to have a worse course of COVID-19 than the general population,” Prof. Burmester said.

“We simply didn’t know that when the pandemic started, and some patients even discontinued their drugs out of this fear,” he added. “It’s more reassuring than we originally thought.”
Among patients with ankylosing spondylitis or undifferentiated spondyloarthritis, risk for anterior uveitis may hinge on the choice of biologic disease-modifying antirheumatic drug (bDMARD), a large Swedish cohort study suggests.

Study results were reported in the opening plenary abstract session at the congress. “Randomised, controlled trials indicate that compared to tumour necrosis factor (TNF) inhibitors, secukinumab has similar efficacy regarding axial inflammation in spondyloarthritis and better efficacy regarding cutaneous psoriasis, but is inferior in inflammatory bowel disease,” noted lead investigator Dr. Ulf Lindström, of the department of rheumatology and inflammation research in the Institute of Medicine at the University of Gothenburg (Sweden). “However, the efficacy of secukinumab, compared to TNF inhibitors, in anterior uveitis has not been extensively studied.”

The investigators used national registry data to study 3,568 patients with ankylosing spondylitis or undifferentiated spondyloarthritis who started bDMARDs in 2005-2018. They considered four agents: the anti–interleukin-17A antibody secukinumab, adalimumab, and infliximab.

Analyses based on 4,523 treatment episodes showed that after excluding the 23% of patients who had previously experienced anterior uveitis, merely 0.9% of patients experienced new-onset anterior uveitis while on their bDMARD, Dr. Lindström reported.

There was confounding by indication, whereby patients with previous anterior uveitis were channeled toward adalimumab and infliximab, and away from secukinumab and etanercept. In addition, there was confounding by line of treatment, with secukinumab usually used in the third line.

After excluding patients who had experienced anterior uveitis in the past year to partly address confounding, the adjusted risk for first on-treatment anterior uveitis was about twice as high with secukinumab and with etanercept as compared with adalimumab. After additionally excluding all biologic treatment episodes beyond the third line, elevation of risk remained significant only for etanercept.

“There is probably a higher occurrence of anterior uveitis on treatment with secukinumab, compared to adalimumab, but there may still be residual confounding and bias that we need to consider,” Dr. Lindström concluded.

**Findings in context**

“These results are not surprising as we have known that secukinumab and etanercept are not good for controlling recurrent and chronic uveitis,” Dr. Nigil Haroon commented in an interview. However, “a single episode of uveitis or infrequent episodes are not usually considered a contraindication to starting these drugs.”

Study caveats included lack of adjustment for uveitis severity and potentially missed uveitis episodes in patients who treated it themselves with steroid eye-drops, he said. “Standard practice is to keep drops with them to start at the earliest possible time point.”

“It would be useful to know the number of patients who stopped medications as a result of uveitis,” added Dr. Haroon, who is codirector of the spondylitis program at the University Health Network and associate professor of medicine and rheumatology at the University of Toronto. “Time-to-event analysis may also be interesting.”

“The study raises an important point regarding channeling bias, and this is important to consider when interpreting clinical trial data as well. Investigators are unlikely to include patients with history of uveitis (or strong family history of inflammatory bowel disease or personal history of gut symptoms) in studies with IL-17 inhibitors and etanercept. Hence, the results have to be interpreted with caution.”

**Study details**

Dr. Lindström and coinvestigators assessed incidences of any anterior uveitis (ascertained from outpatient ophthalmology visits having this diagnostic code) and of anterior uveitis flares (the subset occurring after a gap of at least 90 days without the diagnosis).

When they excluded patients who had experienced anterior uveitis in the year before starting therapy, secukinumab and etanercept carried the highest incidences of anterior uveitis (6.8 and 7.5 per 100 patient-years, respectively) and anterior uveitis flares (2.8 per 100 patient-years for each), he reported.

With adalimumab as the comparator, adjusted risk for first on-treatment anterior uveitis in this population was significantly higher with secukinumab (hazard ratio, 2.23) and etanercept (hazard ratio, 1.80).

When the investigators additionally excluded episodes of therapy beyond the third line, only etanercept carried notably higher incidences of anterior uveitis (7.0 per 100 patient-years) and anterior uveitis flares (2.6 per 100 patient-years). “This could imply that some of the higher incidence rate seen for secukinumab could be due to the fact that these patients are harder to treat and have received more biologics before,” Dr. Lindström proposed.

With adalimumab again as the comparator, the adjusted risk for first on-treatment anterior uveitis in this population was significantly higher only with etanercept (hazard ratio, 1.85).

A final analysis included all patients who started adalimumab in 2004-2018 and then switched to one of the other agents, dramatically reducing confounding by indication. In this population, the incidence rate ratio of anterior uveitis flares was 3.05 for secukinumab, 1.79 for etanercept, and 0.53 for infliximab, compared with adalimumab.

Dr. Lindström disclosed that he had no relevant conflicts of interest. The study did not receive any specific funding. Dr. Haroon disclosed consulting for Amgen, AbbVie, Janssen, Lilly, Novartis, and UCB.
TNF inhibitors don’t quell opioid use for inflammatory arthritis

Opioid use does not decline after patients with inflammatory arthritis start tumour necrosis factor (TNF) inhibitor therapy; in fact, average use appears to increase, according to findings from a study presented at the congress.

“Starting a TNF inhibitor, you would think the pain would go down, and we were hoping the dose of opioids would go down with it,” said investigator Dr. Olafur Palsson from the University of Iceland in Reykjavik and Lund University in Sweden.

“But this research shows that the insertion of a TNF inhibitor has only a minor effect on that,” he said in an interview.

The findings are an “important reminder” to rheumatologists that they should broaden their consideration of other pain treatments and techniques for patients with inflammatory arthritis, Dr. Palsson said. “They should focus on trying other tactics to get patients’ pain and stiffness under control; there may be some underlying factors.”

The investigators compared opioid prescription rates in 940 patients with rheumatoid arthritis, psoriatic arthritis, ankylosing spondylitis, and undifferentiated arthritis with a control group of 4,700 matched subjects.

The team assessed nationwide databases that capture all patients taking biologics for rheumatic diseases and more than 90% of all drug prescriptions. They found that patients with inflammatory arthritis in Iceland were more likely to have received at least one opioid prescription than were control subjects (75% vs. 43%).

During the study period, average yearly opioid dose rose much more in the patient group than in the control group. And 2 years after the initiation of TNF inhibitors, the number of patients taking opioids was unchanged from baseline, at about 40%.

Overall, the patient group was prescribed nearly six times more opioids than the control group. The investigators used a bootstrapping analysis to obtain a reliable confidence interval.

“In a way, the data are extremely skewed,” Dr. Palsson explained. “Most patients were taking very low doses of opioids and a few were taking extremely high doses. It’s hard to do a statistical analysis.

“With bootstrapping, you don’t detect small fluctuations in data,” he said, acknowledging this study limitation. Also, “prescription data don’t necessarily reflect consumption of a drug. People prescribed high doses may not necessarily be consuming high doses.”

Dr. Palsson has disclosed no relevant financial relationships.
A treat-to-target strategy for managing patients with axial spondyloarthritis failed to meet its primary efficacy endpoint but still showed several suggestive indications of benefit compared with usual care in a multicentre, randomised study with 160 patients.

The treat-to-target management strategy tested in the Tight Control in Spondyloarthritis (TICOSPA) study aimed to get patients to an Ankylosing Spondylitis Disease Activity Score (ASDAS) of less than 2.1, as recommended for patients with axial spondyloarthritis (axSpA) by an international task force (Ann Rheum Dis. 2018 Jan;77[1]:3-17). Also notable about the study was its primary endpoint, at least a 30% improvement in the Assessment of Spondyloarthritis International Society Health Index (ASAS HI) (Clin Exp Rheumatol. 2014 Sep-Oct;32[5, Suppl 85]:S-105-8), a measure of health-related quality-of-life that the study organisers selected in part because of its distinction from the treatment target.

“For the first time in rheumatology, we targeted inflammation to have an impact on another domain of the disease. Despite not reaching statistical significance, we see a difference between the groups,” Dr. Anna Moltó said at the congress. After 12 months in the study, the 80 axSpA patients assigned to the treat-to-target regimen had a 47% rate of attainment of the primary endpoint, compared with 36% of the 80 patients assigned to usual care, an 11% absolute between-group difference with a P value that came close to but failed to achieve the conventional standard of statistical significance after adjustment for potential confounders (P = .09). Six secondary outcomes showed statistically significant improvements compared with the control patients, including the Bath Ankylosing Spondylitis Disease Activity Index (BASDAI), the ASAS 20, and ASAS 40. Five additional metrics showed nominal between-group improvements with the treat-to-target strategy that were not statistically significant, including various forms of the ASDAS.

One additional notable finding came from a cost-efficacy analysis run by Dr. Moltó and associates, which showed that the treat-to-target strategy was “dominant” over usual care by producing both better outcomes as well as a lower total cost, compared with control patients, even though twice as many patients on the treat-to-target strategy received a biologic disease-modifying antirheumatic drug (bDMARD) compared with patients in the usual care group. The incremental cost utility ratio for treat-to-target was 19,430 euros per quality-adjusted life-year gained, putting the strategy into the range of a “cost-effective” approach, and the two treatment arms also had comparable safety, said Dr. Moltó, a rheumatologist at Cochin Hospital in Paris.

The 11% increase in treat-to-target patients achieving at least a 30% improvement in their ASAS HI score “is potentially clinically relevant” because the comparator arm in the study received “very active” usual care and was not by any measure a true placebo control group, noted Prof. Maxime Dougados, a rheumatologist and professor of medicine at Cochin Hospital and senior investigator for the study. In general, in treatment studies of rheumatologic diseases a 10% or greater absolute increase in the incidence of a beneficial outcome is considered clinically meaningful when compared with an actively treated control arm, he noted.

“Using the ASAS HI score was very ambitious for the study, and it’s a very relevant outcome,” said Dr. Sofia Ramiro, a rheumatologist at Leiden (Netherlands) University Medical Centre who was not associated with the study and chaired the session where Dr. Moltó gave her report. “We have had treat-to-target trials that showed benefit when disease activity was the endpoint.”

But when a study “targets treatment to [reducing] disease activity and then uses disease activity as the outcome measure you expect to see an effect, but it is circular reasoning and we are left with challenges in interpreting the results. Now we have a trial that is formally [neutral] but with a different, more ambitious endpoint. All the indications are for benefit from treat-to-target for both the primary endpoint and for all the other endpoints.”

“We were in a difficult situation when choosing the outcome. We didn’t know whether a 30% improvement in the ASAS HI was really relevant, but it seems to be,” said Prof. Désirée van der Heijde, a rheumatologist and professor of medicine at Leiden University Medical Centre and a collaborator on Dr. Moltó’s study. “I’d choose ASAS HI again as a primary endpoint” for a treat-to-target study in patients with axSpA, she said, but added that a 30% improvement in this score as the response threshold may warrant reconsideration. Both Prof. van der Heijde and Prof. Dougados agreed that at least one additional study with a somewhat similar design is needed to better document and confirm a role for a treat-to-target strategy in axSpA patients.

The TICOSPA study ran at 10 French centres and 4 centres each in Belgium and the Netherlands. The study enrolled adults with rheumatologist-diagnosed axSpA with an ASDAS score greater than 2.1 who had not yet received a bDMARD, had not yet maxed out on their dosage of NSAIDs, and had certain baseline immunologic and
TNF inhibitors cut odds of VTE in RA patients

The risk for venous thromboembolism (VTE) is almost 50% lower in patients with RA taking tumour necrosis factor (TNF) inhibitors than it was in those taking conventional synthetic disease-modifying antirheumatic drugs (DMARDs), according to data from the German RABBIT registry.

“Some rheumatologists have thought TNF inhibitors could increase the risk for venous thromboembolism events, but we don’t think this is true, based on our findings,” said investigator Dr. Anja Strangfeld, who presented the findings at the congress.

The risk is more than one-third lower in RA patients treated with other newer biologics, such as abatacept, rituximab, sarilumab, and tocilizumab.

However, risk for a serious venous thromboembolism is twice as high in patients with C-reactive protein (CRP) levels above 5 mg/L and is nearly three times as high in patients 65 years and older.

For the study, Dr. Strangfeld, of the German Rheumatism Research Center in Berlin, and her colleagues followed about 11,000 patients for more than 10 years.

“Patients with RA have a greater risk for venous thromboembolism compared with the general population, but we didn’t know the risk conveyed by different DMARD treatments,” Dr. Strangfeld said in an interview. “It is also evident that higher age and lower capacity for physical function increase the risk, which was not so surprising.”

Chronic inflammation in RA patients elevates the risk for deep vein and pulmonary thrombosis by two to three times, said Prof. John Isaacs of Newcastle University in Newcastle Upon Tyne, United Kingdom, who is chair of the EULAR Scientific Programme Committee.

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Among the supporting studies Prof. Isaacs discussed during an online press conference was a Swedish trial of more than 46,000 RA patients, which had been presented earlier by Viktor Molander, a PhD candidate from the Karolinska Institute in Stockholm (abstract OP0034).

Mr. Molander’s team showed that 1 in 100 patients with high disease activity will develop venous thromboembolism within a year, which is twice the number of events seen among patients in remission.

Combined with the RABBIT data, both studies show that, “if you can control their disease in the right way, you’re not only helping rheumatoid arthritis patients feel better, but you could be prolonging their lives,” Prof. Isaacs said.

The prospective RABBIT study followed RA patients who began receiving a new DMARD after treatment failed with at least one conventional synthetic DMARD, such as methotrexate or leflunomide. At baseline, those taking TNF inhibitors or other biologics had higher CRP levels on average, as well as a higher rate of existing cardiovascular disease. They also received glucocorticoids, such as prednisone, more often.

The observational nature of the RABBIT TICOSPA was sponsored by UCB. Dr. Moltó has been a consultant to and received research funding from AbbVie, Bristol-Myers Squibb, Merck, Pfizer, and UCB.

The TNF inhibitors are actually reducing the inflammation and, therefore, reducing the risk,” Prof. Carmona said in an interview. “It could be an effect of using the drugs on people with higher levels of inflammation. It’s an indirect protective effect.”

The study was funded by a joint unconditional grant from AbbVie, Amgen, Bristol-Myers Squibb, Fresenius-Kabi, Hexal, Lilly, Merck Sharp & Dohme, Mylan, Pfizer, Roche, Samsung Bioepis, Sanofi-Aventis, and UCB. Dr. Strangfeld is on the speakers’ bureau of AbbVie, Bristol-Myers Squibb, Pfizer, Roche and Sanofi-Aventis. Prof. Isaacs is a consultant or has received honoraria or grants from AbbVie, Amgen, Merck, Pfizer, Roche, and UCB.

The RABBIT data can help shape treatment decisions, said Prof. Loreto Carmona of the Musculoskeletal Health Institute in Madrid, who is chair of the EULAR Abstract Selection Committee.

For a woman with RA who smokes and takes oral contraceptives, for example, “if she has high levels of inflammation, I think it’s okay to use TNF inhibitors, where maybe in the past we wouldn’t have thought that,” she said.

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Prof. Carmona has disclosed no relevant financial relationships.

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The researchers randomised 160 patients to either treat-to-target or usual care management by the centre they attended to prevent cross contamination of management strategies. The treat-to-target regimen involved office examinations and consultations every 4 weeks rather than every 3 months with usual care, and also required a predefined management strategy with treatment prompts based on the strategy sent to the treating clinicians via the electronic medical record. The average age of the patients was 38 years, they had been diagnosed with axSpA for an average of just under 4 years, and their mean ASDAS score at entry was 3. During the 12 months of management, 56% of the patients in the treat-to-target arm initiated treatment with a bDMARD, compared with 28% among the controls. Use of NSAIDs was similar between the two study subgroups.

TICOSPA was sponsored by UCB. Dr. Moltó has been a consultant to and received research funding from AbbVie, Bristol-Myers Squibb, Merck, Pfizer, and UCB. Prof. Dougados has had financial relationships with AbbVie, Bristol-Myers Squibb, Janssen, Lilly, Novartis, Merck, Pfizer, and UCB. Prof. van der Heijde has had financial relationships with more than 20 companies including UCB. Dr. Ramiro had been a consultant to or received research funding from AbbVie, Lilly, Merck Sharp & Dohme, Novartis, and Sanofi.
Patients with RA have an elevated risk of interstitial lung disease (ILD), but methotrexate does not accentuate that risk and may in fact be protective, new data show. These were among key findings of a pair of studies reported at the congress.

Although a guideline-recommended cornerstone in the management of RA, methotrexate has been associated with both hypersensitivity pneumonitis and diffuse lung disease. However, its involvement in the development of ILD among patients with RA is unclear.

A Danish study of more than 30,000 RA patients reported at the congress found that their risk of ILD was about three to five times that of the general population. However, risk did not differ significantly whether they had filled a methotrexate prescription or not.

In addition, a multinational case-control study of more than 1,000 RA patients also reported at the congress found that, compared with never-users of methotrexate, ever-users actually had a 59% lower likelihood of developing ILD.

However, both studies were limited by their retrospective design, Dr. Elizabeth R. Volkmann, codirector of the connective tissue disease–related interstitial lung disease program at the University of California, Los Angeles, cautioned in an interview. Hence, there was likely systematic bias and confounding.

“I would interpret the conclusions of both studies with caution,” she maintained. “To understand how a particular intervention, such as methotrexate use, affects the outcome of ILD development, a prospective design is needed, which adequately adjusts for known ILD risk factors, such as male sex and smoking.”

As to whether the new findings are practice-changing and how they might affect patient counseling, “the answers to these questions are not straightforward and depend on other patient-related factors,” according to Dr. Volkmann.

Danish nationwide study
Dr. René Cordtz, a clinical research assistant at the Center for Rheumatology and Spine Diseases, Rigshospitalet-Gentofte, Copenhagen, and colleagues conducted a nationwide population-based cohort study using 1997-2015 registry data to assess lung disease among patients with RA by prescriptions filled.

Results based on 30,512 RA patients showed that, compared with peers filling no methotrexate prescriptions, patients filling at least one did not have a significantly elevated risk of ILD at either 1 year of follow-up (hazard ratio, 1.03) or 5 years of follow-up (HR, 1.00).

In addition, patients with RA had a similarly sharply elevated 5-year risk of ILD relative to the general population regardless of whether they had filled neither methotrexate nor sulfasalazine prescriptions (standardised incidence ratio, 3.38) or had filled prescriptions for methotrexate only (SIR, 3.63), sulfasalazine only (SIR, 4.12), or both (SIR, 5.45).

“RA patients have an increased risk of ILD, compared to the general population, which was not surprising, but very importantly, that risk was not further exacerbated in those treated with methotrexate,” Dr. Cordtz concluded. “We do acknowledge that purchasing your medicine is different from taking your medicine, which is why we found it extra reassuring that when requiring at least two methotrexate prescriptions to be considered exposed, it did not change our results.”

Multinational study
Dr. Pierre-Antoine Juge, a rheumatologist at Bichat-Claude Bernard Hospital, Paris, and colleagues performed a case-control study among 482 RA patients with ILD and 741 RA patients without ILD in three cohorts: a French discovery cohort, a multinational (Brazil, Italy, Mexico, United Kingdom, and United States) replication cohort, and a combined cohort. Those with methotrexate hypersensitivity pneumonitis were excluded.

Results showed that relative to peers without ILD, patients with ILD had a lower prevalence of ever having used methotrexate and had received a lower cumulative methotrexate dose, findings that were consistent across all three cohorts.

Methotrexate ever-use was associated with a significantly lower adjusted likelihood of ILD in the discovery cohort (odds ratio, 0.46), the replication cohort (OR, 0.38), and the combined cohort (OR, 0.41). Furthermore, ever-users were less commonly represented among patients with ILD regardless of chest high-resolution CT pattern (usual interstitial pneumonia pattern vs. not).

Finally, methotrexate use appeared to delay the adjusted time to onset of ILD by 3.5 years in the discovery cohort ($P = .001$), by 3.2 years in the replication cohort ($P < .0001$), and by 3.5 years in the combined cohort ($P < .0001$).

“Outside of methotrexate hypersensitivity pneumonitis, methotrexate was not a risk factor for RA-associated ILD in our study. We observed an inverse relationship that was similar whatever the high-resolution CT pattern,” Dr. Juge commented. “But this possible protective effect should be confirmed through a dedicated prospective, randomised, controlled trial.

“Methotrexate should not be considered as a causal factor for RA-associated ILD, and its [discontinuation] should be discussed through a multidisciplinary discussion,” he recommended. In addition, “this study does not investigate the impact of methotrexate use on RA-associated ILD prognosis.”

The Danish study did not receive any specific funding, and none of its authors reported having any financial disclosures. The multinational study did not receive any specific funding. Dr. Juge disclosed that he had no relevant conflicts of interest, but many of his coauthors reported financial relationships with industry. Dr. Volkmann disclosed consulting for Boehringer Ingelheim and Forbiiiis, and receiving grant support from Corbus and Forbiius.
Patients with osteoarthritis treated with tramadol had a 20%-50% higher risk of dying during the first year of treatment than did patients who were treated with NSAIDs, according to the results of a large, population-based study performed in British Columbia, Canada.

Within 1 year of starting treatment, 296 of 13,798 patients treated with tramadol had died, compared with 246 of 13,798 treated with naproxen, giving a death rate of 21.5 versus 17.8 per 1,000 person-years, and representing a 20% increase in all-cause mortality versus the NSAID (hazard ratio, 1.2).

Similar results were seen comparing tramadol with diclofenac and tramadol with cyclooxygenase (COX)-2 inhibitors, but with increasing death rates of 24.8 versus 19.5 per 1,000 person-years (hazard ratio, 1.3) and 23.6 versus 15.7 per 1,000 person-years (HR, 1.5), respectively.

However, all-cause mortality was lower with tramadol than with the opiate pain-killer codeine (21.5 vs. 25.5 per 1,000 person-years; HR, 0.8), Lingyi Li, a PhD student from the University of British Columbia, Vancouver, reported at the congress.

This is not the first time that tramadol’s excess mortality risk has been highlighted. Indeed, just last year (JAMA. 2019;321[10]:969-82), researchers using The Health Improvement Network database reported found that tramadol was associated with higher all-cause mortality than two COX-2 inhibitors, celecoxib (31.2 versus 18.4 per 1,000 person-years) and etoricoxib (25.7 versus 12.8 per 1,000 person-years).

Ms. Li and associates’ data not only now add further weight to those findings, but also go a step further by looking at other serious risks associated with tramadol’s use among patients with OA.

“The objective of this study is to compare tramadol with other commonly prescribed pain-relief medications on the risk of several severe outcomes, including mortality, cardiovascular diseases [CVD], venous thromboembolism [VTE], and hip fracture,” she said during her virtual presentation.

Using sequential propensity score matching, the researchers compared data on patients in British Columbia during 2005-2014 with a first prescription of tramadol (n = 56,325), the NSAIDs naproxen (13,798) or diclofenac (17,675), COX-2 inhibitors (17,039), or codeine (7,813).

“For CVD, we found that there is a higher risk among tramadol users, compared with diclofenac [HR, 1.2] and COX-2 inhibitors [HR, 1.2], but not with naproxen [HR, 1.0] and codeine [HR, 0.9] users,” Ms. Li reported.

Similarly, the 1-year risk of VTE was significantly higher among tramadol users...
Self-management app may positively impact the health of osteoarthritis patients

Use of a self-management smartphone app may positively impact the health of older patients with self-reported knee and/or hip OA, according to research findings presented at the congress.

Health Professionals in Rheumatology abstract award winner Tim Pelle of Sint Maartenskliniek, Nijmegen, Netherlands, and coinvestigators conducted a randomised, controlled trial that found that use of the dr. Bart smartphone app had positive effects on activities of daily living, pain, and symptoms for individuals with knee and/or hip OA aged 50 years and older.

Despite observing these positive effects, the same benefit was not observed for the primary outcome of the study, the number of knee/hip OA–related secondary health care consultations, compared with usual care in the previous 6 months. “We were slightly disappointed, because we hypothesised that dr. Bart app would result in better self-management which we assumed to result in change in healthcare utilisation patterns; for example, optimal use of primary care services and less use of secondary health-care services,” Mr. Pelle said in an interview.

Self-management is of most importance in the nonsurgical treatment of patients with knee and/or hip OA, and modern technologies offer the potential to support self-management 24/7, he said.

The randomised study included 427 participants with self-reported knee and/or hip OA aged 50 years and older. Study participants were randomly assigned to either the dr. Bart app (n = 214) or usual care (n = 213) for a total of 6 months.

Study subjects completed online questionnaires at the start of the intervention and at 3 and 6 months follow-up. Various secondary clinical endpoints were also evaluated, including functional limitations, pain, symptoms, self-management behaviour, and others.

Even though, the majority of study participants were women (72%), with a mean age of 62.1 years (range, 7.3 years), and most had symptoms primarily in their knee(s) (73%).

After analysis, the investigators found that app use did not significantly lower the number of secondary healthcare consultations, compared with usual care (incidence rate ratio, 1.20; 95% confidence interval, 0.67-2.19).

In contrast, a positive overall treatment effect was observed for some clinical outcomes.

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only when compared with diclofenac (HR, 1.5) and COX-2 inhibitors (HR, 1.7).

"For hip fractures, tramadol initiation was associated with an increased risk of hip fractures, compared with all NSAIDs, but not with codeine,” she said. The risk of hip fractures was 40%-50% higher with tramadol versus naproxen (HR, 1.4), diclofenac and COX-2 inhibitors (both HR, 1.5).

“Our results suggest an unfavourable safety profile of tramadol use,” Ms. Li said, suggesting that “several guidelines on tramadol use in clinical practice might need to be revisited.”

According to a recent Cochrane review (Cochrane Database Syst Rev. 2019 May 27. doi: 10.1002/14651858.CD005522.pub3) there is "moderate-quality evidence" that tramadol “has no important benefit on mean pain or function in people with osteoarthritis.”

The authors of the review wrote that, while some patients might glean a benefit from treatment, the evidence suggests that “adverse events probably cause substantially more participants to stop taking tramadol.”

Current guidance on the use of tramadol varies. The American Academy of Orthopaedic Surgeons guidelines recommend its use in patients with symptomatic knee OA on a par with NSAIDs (J Bone Joint Surg. 2013;95:1885-6) while the American College of Rheumatology guidance (Arthritis Care Res. 2020;72[2]:149-62) conditionally recommends that it be used only if there is no real alternative, such as a contraindication to NSAIDs or pain relief is ineffective.

Patients with rheumatic disease are increasingly taking opioid painkillers such as tramadol, with other data reported at the EULAR 2020 E-Congress (Ann Rheum Dis 2020;79[suppl 1]:174, Abstract OP0280) showing a rise from 15% in 2007 to 25% in 2016 in the Catalonia region of Spain alone. A rise from 5% to 10% has previously been reported in the United States from 2003 to 2009 (Arthritis Care Res. 2014;66[10]:1489-95).

With increasing rates of tramadol prescribing, the worry is that perhaps tramadol is not as safe a people think it is, as Dr. Thomas Schwenk pointed out when he reviewed the previous research showing excess mortality with tramadol (NEJM Journal Watch, March 2019).

“The opioid agonist tramadol often is prescribed for patients with osteoarthritis pain because it is thought to be safer than opioids or nonsteroidal anti-inflammatory drugs,” he observed. Dr. Schwenk, who is dean of the University of Nevada school of Medicine, Reno, USA, added that the “results [of that study] suggest that tramadol is not as safe as some people believe.”

He suggested cautious prescribing: “Tramadol might be an option for patients in whom NSAIDs are contraindicated, but it should be prescribed as judiciously as traditional opioids.”

Responsible prescribing to avoid opioid misuse in patients with rheumatic diseases was also advocated in a EULAR press release from the congress. A study from Iceland (See page 7; Ann Rheum Dis. 2020;79[suppl 1]:58, Abstract OP0088) was highlighted that found patients with inflammatory arthritis frequently did not stop taking opioids after the source of their pain had gone; in fact, their use went up despite being treated with tumour necrosis factor inhibitors.

The study authors had no conflicts of interest.

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Efforts towards identifying health-literacy profiles fill an important need in rheumatology

Health literacy is a term that practitioners increasingly use but rarely define. For patients with rheumatoid arthritis (RMDs), health literacy — or, actually, a lack of health literacy — can manifest in different ways, and addressing these deficiencies is not a one-size-fits-all approach.

At this year’s congress, Mark Bakker, a doctoral student at Maastricht (Netherlands) University, explained how identifying different profiles of health literacy may help to break through these health-literacy barriers.

“Health literacy is so much more than just being able to read and write,” Mr. Bakker said. “It’s so much more than just health behaviour. It’s often misunderstood.”

Mr. Bakker and his research team took a multidimensional approach to health literacy. “It involves personal competencies,” he said. “It also involves situational resources in which people might need to find, appraise, and understand information, but also to access services in health, to make health decisions.”

Health literacy also involves interactive skills, a capacity to critically appraise care, and having a social support structure, he said. Different estimations of limited health literacy in the Netherlands point towards a prevalence of about 30%, which, he said, is a lot higher than many might realise.

Patients with low health literacy may use disproportionate amounts of health resources, Mr. Bakker noted. These patients may display poor decision-making about their own health, lack medication adherence, and use emergency services and specialised care more frequently while using preventive services less. “There is an increasing amount of literature available associating limited health literacy to a number of worsening outcomes,” he said. Sometimes, these patients have difficulty asking the right questions. “They may not even know where to begin,” Mr. Bakker said.

Healthcare professionals may feel like they don’t have enough time to probe these issues deeper with patients. “They might not have the tools to provide patients with the right information in the right way,” he said. “And it might be very hard for professionals to even recognise limited health literacy in the clinical setting.”

Mr. Bakker and his colleagues evaluated 895 patients with rheumatoid arthritis, spondyloarthritis, or gout at three outpatient clinics in the Netherlands. The patients completed the Health Literacy Questionnaire (HLQ), which, according to Mr. Bakker, was specifically designed to evaluate the multidimensional nature of health literacy.

The researchers identified 10 distinct health-literacy profiles, each depending on average scores across nine different health-literacy domains ranging from provider support to the patient’s ability to understand health information. The highest health-literacy scores across all domains comprised profile 1, and the lowest scores represented profile 10. However, rather than categorising patients in “high” and “low,” Mr. Bakker noted that the approach allows for diverse patterns in scores across domains. These diverse patterns should be of note, he said.

The goal is to enhance the capacity of health systems and professionals to respond to the health-literacy needs of patients with RMDs, he said. This can be of benefit to all patients in the clinic and specifically for patients with a particular profile. The approach his team has taken to identify tools that could address local health-literacy needs is known as the Ophelia approach, which stands for OPTimising HEalth Literacy and Access (BMC Public Health. 2014;14:694. doi: 10.1186/1471-2458-14-694).

“Our patients have different health-literacy profiles, and our work can inspire the healthcare system to think about these different health-literacy profiles that you see in your own clinical context,” he said.

The idea, Mr. Bakker explained, is for rheumatologists to consider health-literacy challenges in the context of their own setting, and to collaborate with local experts, including both professionals and patients, to develop methods for addressing those health-literacy shortcomings systematically.

Mr. Bakker and colleagues have no relevant conflicts to disclose.

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comes, including activities of daily living (2.9; 95% CI, 0.2-5.6), pain (3.5; 95% CI, 0.9-6.0), and symptoms (2.6; 95% CI, 0.4-4.9) among participants in the dr. Bart group versus usual care. Nonsignificant differences between the groups were observed for health-related quality of life, self-management behavior, illness perceptions, and physical activity.

“Use of the dr. Bart app results in small but positive effects on symptoms, pain, and activities of daily living,” he said.

Overall, the findings suggest that the self-management app may positively impact the health of individuals with knee/hip OA, the researchers explained.

“No future studies are planned yet, but we are [currently] performing an economic evaluation of the dr. Bart app,” Mr. Pelle noted.

No funding sources were reported. The authors reported having no conflicts of interest.

New EULAR recommendations for the intra-articular (IA) treatment of arthropathies aim to facilitate uniformity and quality of care for this mainstay of rheumatologic practice, according to a report on the new guidance that was presented at the congress.

Until now there were no official recommendations on how best to use it in everyday practice. “This is the first time that there’s been a joint effort to develop evidence-based recommendations,” Dr. Jacqueline Usón, associate professor of medicine at Rey Juan Carlos University in Madrid, said in an interview. “Everything that we are saying is pretty logical, but it’s nice to see it put in recommendations based on evidence.”

IA therapy has been around for decades and is key for treating adults with a number of different conditions where synovitis, effusion, pain, or all three are present, such as inflammatory arthritis and osteoarthritis, Dr. Usón observed during her presentation. “Today, commonly used injectables are not only corticosteroids but also local anaesthetics, hyaluronic acid, blood products, and maybe pharmaceuticals,” she said, adding that “there is a wide variation in the way intra-articular therapies are used and delivered to patients.” Health professionals also have very different views and habits depending on geographic locations and healthcare systems, she observed. Ironing out the variation was one of the main objectives of the recommendations.

As one of the two conveners of the EULAR task force behind the recommendations, Dr. Usón, herself a rheumatologist at University Hospital of Móstoles (Spain), pointed out that the task force brought together a range of specialties – rheumatologists, orthopaedic surgeons, radiologists, nuclear medicine specialists, among others, as well as patients – to ensure that the best advice could be given.

The task force followed EULAR standard operating procedures for developing recommendations, with discussion groups, systematic literature reviews, and Delphi technique–based consensus all being employed. The literature search considered publications from 1946 to 2019. “We agreed on the need for more background information from health professionals and patients, so we developed two surveys: One for health professionals with 160 items, [for which] we obtained 186 responses from 26 countries; and the patient survey was made up of 44 items, translated into 10 different languages, and we obtained 200 responses,” she said.

The results of the systematic literature review and surveys were used to help form expert consensus, leading to 5 overarching principles and 11 recommendations that look...
Five overarching principles
The first overarching principle recognises the widespread use of IA therapies and that their use is specific to the disease that is being treated and “may not be interchangeable across indications,” Dr. Usón said. The second principle concerns improving patient-centered outcomes, which are “those that are relevant to the patient,” and include the benefits, harms, preferences, or implications for self-management.

“Contextual factors are important and contribute to the effect of IAT [intra-articular treatment],” she said, discussing the third principle. “These include effective communication, patient expectations, or settings [where the procedure takes place]. In addition, one should take into account that the route of delivery has in itself a placebo effect. We found that in different RCTs [randomised controlled trials], the pooled placebo effect of IA saline is moderate to large.”

The fourth principle looks at ensuring that patients and clinicians make an informed and shared decision, which is again highlighted by the first recommendation. The fifth, and last, overarching principle acknowledges that IA injections may be given by a range of healthcare professionals.

Advice for before, during, and after injection
Patients need to be “fully informed of the nature of the procedure, the injectable used, and potential effects — benefits and risks — [and] informed consent should be obtained and documented,” said Dr. Usón, outlining the first recommendation. “That seems common,” she said in the interview, “but when we did the survey, we realise that many patients didn’t [give consent], and the doctors didn’t even ask for it. This is why it’s a very general statement, and it’s our first recommendation. The agreement was 99%!"

The recommendations also look at the optimal settings for performing injections, such as providing a professional and private, well-lighted room, and having a resuscitation kit nearby in case patients faint. Accuracy is important, Dr. Usón said, and imaging, such as ultrasound, should be used where available to ensure accurate injection into the joint. This is an area where further research could be performed, she said, urging young rheumatologists and health professionals to consider this. “Intra-articular therapy is something that you learn and do, but you never really investigate in it,” she said.

One recommendation states that when intra-articular injections are being given to pregnant patients, the safety of injected compound must be considered, both for the mother and for the fetus. There is another recommendation on the need to perform IA injections under aseptic conditions, and another stating that patients should be offered local anaesthetics, after explaining the pros and cons.

Special populations of patients are also considered, Dr. Usón said. For example, the guidance advises warning patients with diabetes of the risk of transient hyperglycaemia after IA glucocorticoids and the need to monitor their blood-glucose levels carefully for a couple of days afterward.

As a rule, “IAT is not a contraindication to people with clotting or bleeding disorders, or taking antithrombotic medications,” she said, unless they are at a high risk of bleeding.

Importantly, the recommendations cover when IAT can be performed after joint replacement surgery (after at least 3 months), and the need to “avoid overuse of injected joints” while also avoiding complete immobilisation for at least 24 hours afterward. The recommendations very generally cover reinjections, but not how long intervals between injections should be. When asked about interval duration after her presentation, Dr. Usón said that the usual advice is to give IA injections no more than 2-3 times a year, but it depends on the injectable.

“It wasn’t our intention to review the efficacy and the safety of the different injectables, nor to review the use of IAT in different types of joint diseases,” she said. “We do lack a lot of information, a lot of evidence in this, and I really would hope that new rheumatologists start looking into and start investigating in this topic,” she added.

Recommendations will increase awareness of good clinical practice
“IAT injections are commonly administered in the rheumatology setting. This is because IA injection is often a useful treatment for acute flare of arthritis, particularly when it is limited to a few joints,” observed Dr. Ai Lyn Tan, associate professor and honorary consultant rheumatologist at the Leeds (United Kingdom) Institute of Rheumatic and Musculoskeletal Medicine.

IA injection “also relieves symptoms relatively quickly for patients; however, the response can be variable, and there are side effects associated with IA injections,” Dr. Tan added in an interview.

There is a lack of universally accepted recommendations, Dr. Tan observed, noting that while there might be some local guidelines on how to safely perform IA injections, these were often not standardised, and were subject to being continually updated to try to improve the experience for patients.

“It is therefore timely to learn about the new EULAR recommendations for IA injections. The advantage of this will be to increase awareness of good clinical practice for performing IA injections.” Dr. Tan had no relevant conflicts of interest.
A total of 30%-80% of patients who have rheumatic and musculoskeletal diseases (RMDs) are thought to not take their medications according to their physicians’ instructions. New research offers more comprehensive insights into addressing adherence issues with nonpharmacologic interventions — an area not comprehensively addressed by EULAR until now.

“The problem of poor adherence is addressed in some EULAR recommendations/points to consider on the management of specific health conditions or on the role of professionals,” first author Valentin Ritschl of the Medical University of Vienna said in an interview. “However, all these recommendations focus on limited aspects of nonadherence and do not cover the multifaceted nature of this phenomenon.”

Mr. Ritschl and colleagues conducted an extensive systematic literature review, the results of which they presented to a task force consisting of a panel of international experts hailing from 12 different countries. The task force included rheumatologists and other health professionals in rheumatology, as well as patient representatives.

The collaboration resulted in investigators crafting a definition of adherence in addition to drafting four overarching principles and nine points to consider, which Mr. Ritschl presented at the congress.

They defined adherence as “... the extent to which a person’s behaviour corresponds with the agreed prescription.”

The four overarching principles emphasise the following concepts:

- That adherence affects outcomes in people who have RMDs.
- The importance of shared decision-making, with the understanding that the adherence describes the patient’s behaviour “... following an agreed prescription.”
- That numerous factors can affect adherence.
- The notion of adherence being a dynamic process that, consequently, requires continuous evaluation.

Among the nine points to consider, Mr. Ritschl and coauthors encourage all healthcare providers involved in caring for RMD patients to assume responsibility for promoting adherence. Practitioners should also strive to create an ongoing, open dialogue to discuss adherence, especially in cases in which the patient’s RMD is not well controlled. The patient-centred recommendations include taking into account the patient’s goals and preferences because these greatly contribute to the patient’s ability to adhere to any medication regimen. Another arm of that exploration also requires the medical professional to evaluate any circumstances that could bear a negative effect on the patient’s adherence — whether it be medication access issues related to cost or availability, or functional challenges such as memory, motivation, or complexity of the medication regimen.

Mr. Ritschl believes his team’s study will add value and help improve overall outcomes in RMD population management.

“Until today, there are no recommendations or points to consider developed in order to support our patients to be adherent to the agreed treatment plan,” he said. “In our project/initiative, we therefore developed for the first time points to consider to detect, assess, and manage nonadherence in people with RMDs.”

Additionally, the study offers some strategic insights to help improve clinical trials because the deleterious effects of nonadherence also affect study results.

Looking ahead, Mr. Ritschl said randomised, controlled trials are necessary to test strategies that might improve adherence. He strongly emphasised the importance of designing future research studies that are heavily patient-centred and effective for shared decision-making.

The project was funded by EULAR. Mr. Ritschl reported having no disclosures, but many of his coauthors reported financial relationships with pharmaceutical companies.
Updated guidance on lupus nephritis focuses on treatment targets

As many as 40% of patients with systemic lupus erythematosus (SLE) develop kidney disease, which remains a major cause of morbidity, according to Dr. Antonis Fanouriakis of Attikon University Hospital, Athens, who presented new guidelines on the treatment of lupus nephritis from EULAR and the European Renal Association–European Dialysis and Transplant Association (ERA-EDTA).

The researchers followed the EULAR standardised operating procedures for treatment recommendations, which were published in Annals of the Rheumatic Diseases. They used Delphi-based methodology to develop 15 questions for a systematic literature review on which to base the recommendations.

Key changes from the 2012 recommendations include ones for treatment targets, use of glucocorticoids and calcineurin inhibitors, and management of end-stage kidney disease (ESKD).

The target of therapy is complete response proteinuria less than 0.5-0.7 g/24 hours with near-normal glomerular filtration rate by 12 months. This can be extended in patients with baseline nephrotic-range proteinuria.

The recommendations also call for long-term treatment with hydroxychloroquine with regular ophthalmologic monitoring.

For patients with active proliferative lupus nephritis, the recommendations call for initial treatment with mycophenolate mofetil (2-3 g/day, or mycophenolic acid at equivalent dose) or low-dose intravenous cyclophosphamide (500 mg x 6 biweekly doses), both combined with glucocorticoids (pulses of intravenous methylprednisolone, then oral prednisone 0.3-0.5 mg/kg per day).

Alternative treatments for patients with nephrotic-range proteinuria and adverse prognostic factors include a combination of mycophenolate mofetil and calcineurin inhibitors (especially tacrolimus), as well as high-dose cyclophosphamide.

The recommendations advise on subsequent long-term maintenance treatment with mycophenolate mofetil or azathioprine with no or low-dose glucocorticoids (less than 7.5 mg/day). “The choice of agent depends on the initial regimen and plans for pregnancy,” the guidelines committee said. “In nonresponding disease, switch of induction regimens or rituximab are recommended.

In pure membranous [lupus nephritis] with nephrotic-range proteinuria or proteinuria greater than 1 g/24 h despite renin-angiotensin-aldosterone blockade, [mycophenolate mofetil] in combination with glucocorticoids is preferred.”

Patients should be regularly assessed for both renal and extra-renal disease activity, with repeat kidney biopsy considered in cases of incomplete response or nephritic flares, the authors said. Additionally, comorbidities should be managed throughout a patient’s lifespan.

For patients with ESKD, the recommendations favor transplantation as the preferred kidney replacement option, “with immunosuppression guided by transplant protocols and/or extra-renal manifestations,” the committee said.

“Since the publication of the first set of joint EULAR/ERA-EDTA recommendations in 2012, new evidence has emerged in lupus nephritis, including the use of calcineurin inhibitors and ‘multitarget’ therapy, disease monitoring and treatment targets,” Dr. Fanouriakis said in an interview. “To this end, it was deemed appropriate to update these recommendations at this time.”

Dr. Fanouriakis noted that the COVID-19 pandemic has imposed “unprecedented changes” in the practice of medicine.

“Lupus nephritis is a condition which requires a multidisciplinary approach involving physicians of different specialties, while at the same time these patients may carry an increased risk for infections, owing both to their disease and medications,” he said. “To this end, face-to-face examinations for diagnosis, treatment, and regular patient monitoring should be performed in a protected setting; alternatively, if telemedicine services are to be applied, this should try to involve different medical disciplines,” including rheumatology and nephrology.

The take-home message for clinicians about the recommendations is that “optimal outcomes in lupus nephritis are more a matter of a long-term therapeutic strategy, rather than individual drugs,” Dr. Fanouriakis explained. “An early response in proteinuria [within 12 months] is the best prognostic factor for a favourable outcome; nevertheless complete response may require more time in patients with significant baseline proteinuria.

“A repeat kidney biopsy should be considered prior to labeling a patient as ‘refractory’ or in case of nephritic flares,” he said.

The next steps for research in lupus nephritis management include “aspects of diagnosis and patient stratification towards personalised treatment, prognostic biomarkers, novel synthetic and biologic treatments, as well as optimisation of clinical trial design,” Dr. Fanouriakis noted.

Dr. Fanouriakis disclosed relationships with companies including Amgen and Enorasis. He is a paid speaker for Genesis Pharma, Mylan, and Roche.
New recommendations from EULAR on interpreting the results of antinuclear antibody (ANA) testing advised taking the test methodology into account because of differences in performance.

ANA results vary not only by the test being used but also by the underlying disease they are being used to assess, warned Prof. Pier Luigi Meroni, director of the Immunorheumatology Research Laboratory at the IRCCS Istituto Auxologico Italiano in Milan.

“Antinuclear antibody testing is a known diagnostic tool. But the recent advances in methodologies strongly suggest that we have to update our knowledge for a better interpretation of the results,” Prof. Meroni said in his presentation at the congress.

There is “no doubt that ANA testing is useful,” he continued, adding that ANA is used as a primary screening tool in many rheumatic diseases, notably systemic lupus erythematosus (SLE), primary Sjögren’s syndrome, and systemic sclerosis. It’s also recently been suggested as an important entry criterion for the classification of SLE.

In fact, the 2019 SLE classification criteria – developed by EULAR in collaboration with the American College of Rheumatology (ACR) – state that “testing by immunofluorescence on HEp-2 cells or a solid-phase ANA screening immunoassay with at least equivalent performance is highly recommended,” Prof. Meroni said.

The ideas underpinning that recommendation was that “ANA expression is invariable in SLE, and that ANA-negative lupus is quite rare,” he explained. Also, as SLE expression persists over time, ANA testing could be used for classification at any point in the disease course. These assumptions have been borne out in several studies, with very small percentages of patients (6% or less) having ANA-negative lupus, and more than 80% having a positive HEp-2 test over time, even with immunosuppressive treatment.

**Which test methodology to use?**

There are several methods that can be used to detect ANA, including the preferred HEp-2 indirect fluorescence assay (IFA), several solid-phase assays (SpA), and line- or dot-blot immunoassays. The issue is which assay should be used in which disease?

The performance of a particular assay can depend on the disease in which they are used. For instance, while the HEp-2 IFA and SpA are equivalent in SLE and in other connective tissue diseases, “this is not the case for other autoimmune diseases in which basically we don’t know exactly all the autoantigens,” Prof. Meroni explained. “Most of the autoantigens are undefined. They cannot be found in solid-phase kits, and we have to use the IFA for detecting all these autoantibodies.”

Importantly, neither the IFA nor the SpA is superior to the other. “We just say that one technique can detect relevant antibodies that are not detectable by the other one, and maybe the combination of the two techniques can be the right strategy to get the highest sensitivity,” Prof. Meroni said.

“Clinicians should be aware of the type of assay used for ANA detection,” he said, “because there are strong differences in the performance, for example between IFA and SpA, and such differences can have important clinical and relevant consequences.”

The test selected will depend on if the aim is to exclude or confirm a disease, and the optimal strategy will depend on pretest probability. For instance, IFA is more sensitive than SpA for SLE and scleroderma, whereas IFA is less sensitive than SpA for Sjögren’s. For SLE, it is suggested to use both the IFA and SpA. A combination of both tests is also considered optimal for scleroderma. SpA testing offers the best sensitivity for Sjögren’s.

“The story is a little bit more complicated for inflammatory myopathies in which we don’t have assays able to detect all the autoantibodies,” Prof. Meroni said. In that situation, several different techniques have to be used to check if the SpA results fit with the IFA pattern.

In 2019, the ACR released its own position statement on ANA testing, highlighting that it supported the use of the HEp-2 IFA assay as the preferred option for ANA testing and that labs should specify the methods being used to test for ANA when reporting their results. The ACR position statement also noted that “ordering healthcare professionals should select specific ANA subserologies based on a patient’s signs and symptoms and when there is a high pretest suspicion for a specific condition.”

Prof. Meroni disclosed serving as a consultant to AbbVie, Inova Diagnostics, Merck Sharp & Dohme, Pfizer, Thermo Fisher Scientific, and UCB.