

Exclusive Coverage of the

2017 AMERICAN COLLEGE OF RHEUMATOLOGY ANNUAL MEETING

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Federal Agencies Address the Dual Crises of Pain and Opioid Addiction

KELLY DAVIO

During a panel discussion at the American College of Rheumatology's 2017 Annual Meeting in San Diego, California, representatives from the US Department of Health and Human Services (HHS), the National Institutes of Health (NIH), and the Centers for Disease Control and Prevention (CDC) outlined ongoing federal initiatives to address the parallel problems of pain and opioid addiction.

HHS

Vanila M. Singh, MD, MACM, chief medical officer of the Office of the Assistant Secretary of Health at HHS, began her remarks by itemizing the 5 prongs of HHS' plan to address the problem of opioid addiction: improving access to treatment and recovery services;

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American College of Rheumatology and National Psoriasis Foundation Unveil New Clinical Guideline for Treating Psoriatic Arthritis

KELLY DAVIO

At the American College of Rheumatology's (ACR) 2017 Annual Meeting, the ACR and the National Psoriasis Foundation (NPF) presented a draft of their new, jointly developed clinical guideline for treating psoriatic arthritis (PsA).

Development of the Guideline

Alexis Ogdie, MD, MSCE, of the Hospital of the University of Pennsylvania, addressed the method of developing the new approach to PsA, explaining that the ACR and NPF teams evaluated treatments including nonpharmacologic therapies (such as smoking cessation,

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promoting the use of overdose-reversing drugs; strengthening the current understanding of the opioid epidemic through public health surveillance; providing support for research on pain and addiction; and advancing better practices for pain management.

- To address these objectives, HHS convened a conference on pain that developed the National Pain Strategy. The strategy seeks to address the following:
 - The prevention of and care for long-term pain
 - Service delivery and payment. Singh said that there are “treatment modalities right now that would help the experience patients have in the perioperative realm, the acute pain realm...[and the] chronic pain realm” that are difficult to gain reimbursement for. Developing evidence to present to healthcare plans will be key in gaining reimbursement. Additionally, efforts are under way to develop a standardized, consistent, comprehensive pain assessment and outcomes measures across the continuum of pain.
 - Professional education and training. “We want [pain] to be in the purview of our young medical residents,” said Singh. To this end, a pain education portal is under development.
 - Public education and communication. Singh indicated that the public often reports that citizens have little input with policy makers, but that there is “a willing public as well as private sector [wants] to communicate about issues of pain.”
 - Population research. Estimating the prevalence of chronic pain is critical to better understanding pain’s impact.

HHS is assembling a Pain Management Task Force to help implement its strategy, and stakeholders, as mandated by Congress, include prescribers,

“ Estimating the prevalence of chronic pain is critical to better understanding pain’s impact.”

pharmacists, medical organizations, veterans’ organizations, first responders, patients and patient groups, state medical boards, hospital associations, addiction community centers, representatives from rural America, and representatives from minority health populations.

NIH

Linda L. Porter, PhD, director of the Office of Pain Policy at the NIH, explained that the NIH’s current efforts to address pain “...did start because of the opioid crisis, but they’re mostly related to pain, what we know about pain, and how we care for pain. It’s hard to separate the opioid crisis from the pain crisis, but we certainly are riding a wave [of public awareness] right now.”

Together with other government agencies, the NIH released the Federal Pain Research Strategy that is determining priorities for research into pain. Porter reports that the top 5 areas that the NIH deems to be most impactful overall are as follows:

- Determining the association between patient and intervention factors and psychosocial interventions
- Understanding heterogeneity of the circuitry involved in acute pain sensation and modulation
- Understanding and addressing plasticity mechanisms that promote persistent pain and endogenous resolution mechanisms that may reverse persistent pain
- Determining mechanisms that sustain or resolve chronic pain and assessing which elements can be intrinsically and extrinsically modulated

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weight loss, and exercise); symptomatic treatments (including nonsteroidal anti-inflammatory drugs [NSAIDs], glucocorticoids, and local glucocorticoid injections); oral small molecule drugs (OSM, a term synonymous with, but preferred by the panel to, disease-modifying antirheumatic drugs); tumor necrosis factor (TNF) inhibitors; interleukin (IL)-12 and IL-23 inhibitors; IL-17 inhibitors; abatacept; and tofacitinib.

Ogdie explained that the ACR and NPF began by evaluating PICO questions (which consider the **p**atient, **i**ntervention, **c**omparison intervention, and **o**utcome), investigating the level of evidence available to address each of the PICO questions, and making a recommendation that was either strong (based on good evidence) or conditional (based on a lower threshold of evidence). Strong recommendations are those that more than 50% of patients should adopt and that could be adopted by policy makers in most situations.

A patient panel meeting in April 2017, which included 10 patients, addressed patient considerations in selecting a therapy, with patients listing treatment burden, onset of action, side effects, and effectiveness, among others, as key concerns. Finally, a voting panel—comprising 2 patients, 11 rheumatologists, 1 rheumatology physician assistant, 1 dermatologist, and 1 dermatologist/rheumatologist—adopted recommendations that achieved a 70% or greater consensus.

Recommendations for Treatment

Jasvinder Singh, MD, MBBS, MPH, presented a sample of the 80 treatment recommendations established in the new guideline, noting that 94% of the recommendations are conditional while 6% are strong. Among the example recommendations that Singh discussed are the following:

In the case of treatment-naïve active PsA, the guideline recommends starting a TNF inhibitor (instead of an OSM, IL-17 inhibitor, IL-12 inhibitor, or IL-23 inhibitor). An OSM is preferable to other biologics if a TNF inhibitor is not an option. Methotrexate is preferable to NSAIDs, and an IL-17 inhibitor is preferable to an IL-12 or IL-23 inhibitor. This recommendation is conditional and should be discussed with the patient.

Patients with active PsA despite OSM therapy should be switched to a TNF inhibitor rather than another OSM or any other type of biologic. If PsA is still active after the change, an IL-17 inhibitor should be the next step, rather than an OSM or another biologic. Finally, if PsA continues to be active, the patient should be switched to an IL-12 or IL-23 inhibitor rather than an OSM, abatacept, or tofacitinib. This recommendation is also conditional and should be evaluated in light of patient preferences.

A patient who has active PsA spondylitis and axial disease despite treatment with NSAIDs should be switched to a TNF inhibitor rather than another biologic. If the PsA remains active, the patient should then be switched to an IL-17 inhibitor

(rather than an IL-12 or IL-23 inhibitor). Again, this conditional recommendation should be discussed with the patient.

Treat-to-Target and Vaccination

The new guideline recommends a treat-to-target strategy, and that patients initiate biologic treatment and then receive killed vaccines (rather than delaying treatment until after killed vaccines have been administered). It also recommends delaying the start of a biologic if the patient requires a live, attenuated vaccination.

Nonpharmacologic Therapy

The guideline gives a strong recommendation, with a high level of evidence, to smoking cessation in patients with PsA. Conditional recommendations include exercise (with low-impact exercise, such as tai chi, yoga, or swimming, noted as being preferable to high-impact exercise); physical therapy; occupational therapy; weight loss in the case of patients who are overweight or obese; massage therapy; and acupuncture.

Future Research and Added Guidelines

Singh pointed out that many common clinical situations in the management of PsA lack strong evidence in the medical literature. This lack of evidence suggests a need for greater investigation into the following areas:

- Head-to-head comparisons of medications for PsA
- Specific studies devoted to enthesitis, axial disease, and arthritis mutilans
- Randomized trials of nonpharmacologic interventions
- Trials of monotherapy versus combination therapy
- Vaccination trials for live, attenuated vaccines
- Trials and registry studies of patients with common comorbidities
- Studies of NSAIDs and glucocorticoids to define their role in PsA management

Singh also pointed out room for improvement in the guideline, and specified the following as topics that the guideline could address in future revisions:

- Treatment options for patients for whom a biologic is not a viable treatment option
- Use of PsA therapies in pregnancy
- Incorporation of high-quality cost or cost-effectiveness analyses into recommendations
- Other comorbidities, such as fibromyalgia, hepatitis, depression and anxiety, malignancy, and cardiovascular disease

The group hopes to publish the guideline in a peer-reviewed journal and disseminate the document to the medical community shortly. The ACR and NPF will continue to provide periodic literature search updates and annual reevaluations to the guideline. ●

Value-Based Contracting in the “Era of Unknowns”

KELLY DAVIO

During a session at the American College of Rheumatology's 2017 Annual Meeting in San Diego, California, Greg Mertz, MBA, FACMPE, managing director for Physician Strategies Group, LLC, gave a presentation titled “Value Contracting: Opportunities of Fantasy?” in which he outlined the current landscape for performance-based contracting.

What Is Value in Healthcare?

Mertz began by giving his definition of value in healthcare: “a term used to describe the need by governmental and private payers to lower the cost of care...We always have to use quality along with value—we have to say it'll still be quality care.” He added, “You can't call it 'rationing,' because people won't like that.”

“ The cost savings produced do not necessarily merit the heavy investment needed to adapt a practice to ACO guidelines. Medicare paid \$691 million in incentives to the ACOs that saved on costs, creating a loss for the government of \$39 million. ”

Mertz gave a brief overview of the evolution of value in the American healthcare model, saying that, beginning in 2008, reporting certain indicators to the government was “a fishing expedition” designed to help the Centers for Medicare & Medicaid Services understand the key drivers of cost. “They simply began to collect a lot of data at your expense,” he said.

Meaningful use incentives followed for those physicians who implemented certified electronic health records, and meaningful use eventually evolved into the Medicare Access and CHIP (Children's Health Insurance Program) Reauthorization Act of 2015 which includes the Merit-based Incentive Payment System.

The next phase of evolution was the development of accountable care organizations (ACOs), which Mertz described as “these big, amorphous organizations of physicians that are supposedly caring for populations,” followed by bundled payments under Medicare and the chronic care management program.

Value Opportunities For Rheumatologists

Among the top models of value-based contracting—ACOs, bundled payments, and employer-based contracting—Mertz sees ACOs as being the most pertinent to practicing rheumatologists.

Currently, 432 US ACOs are approved by Medicare. However, only 22 of them assume risk; 410 ACOs are “upside only,” meaning they receive incentives if they are successful in reducing costs, but are not subject to penalties if they fail to do so. Among those 410 ACOs, 56% (242) together generated \$652 million in cost savings in the most recently reported data, with an average savings of \$2.7 million per ACO.

“[The] savings per patient is actually kind of modest,” said Mertz, who suggested that the cost savings produced do not necessarily merit the heavy investment needed to adapt a practice to ACO guidelines. Furthermore, Mertz said, Medicare paid \$691 million in incentives to the ACOs that saved on costs, creating a loss for the government of \$39 million.

Upside-only arrangements are unlikely to continue in the long term, Mertz cautioned: “[Medicare] paid out more than they saved. That's government math...even the feds are bright enough to figure out that that's not right.”

Ultimately, Mertz said, the United States may be moving toward a system of global capitation, in which a fixed amount of money is paid to a practice per patient. For now, the government's approach is, according to Mertz, “Throw spaghetti against the wall and see what sticks,” and most commercial payers will follow the government's lead once it makes a decision on the best way to deliver healthcare.

In the current “era of unknowns,” as Mertz called it, rheumatology practices considering joining an ACO should take into account the following as part of the decision-making process:

- **Investment.** Most practices will need to invest in people and technology to meet ACO standards.
- **Cost.** Practices should determine how much it will cost them to join an ACO, and assess whether future savings can be used to cover that initial investment.
- **Alternatives.** In some markets, there are few alternatives to joining an ACO; while in less competitive markets, a practice may not suffer a loss of patients if it decides not to join an ACO.
- **Patient volume.** In some markets, increased patient volume or shared savings may offset the costs of joining an ACO.
- **Patient engagement.** “How does the patient play into this value-based world?” asked Mertz, adding that costs can never truly be reduced unless patients are compliant with their treatments.
- **Data.** Mertz suggested that practices consider whether the data they collect and report will correlate to care, or whether it will simply be “busy work.”

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- Investigating biological, psychological, and social mechanisms that contribute to population group differences in chronic pain

Additionally, these are the 5 areas believed to be of the greatest near-term value:

- Optimizing public health strategies to educate patients on managing pain
- Understanding cellular mechanisms of heterogeneity in acute pain sensation
- Understanding and addressing plasticity mechanisms that promote persistent pain and endogenous resolution mechanisms that may reverse persistent pain, as included in the above list
- Determining optimal safe and effective chronic pain management
- Better defining the epidemiology of pain in disparate populations

“Better-quality pain management is really crucial to helping reduce our reliance on opioids,” said Porter. In global terms, “more than 50% of the global disease burden [has a] contribution of some pain disorder...we have an opioid problem, and we have a pain problem, and we need a balance of how we manage pain and not deny people who need medication for their particular conditions...They need better care and they need safer medications.”

Porter also indicated that the NIH is currently working together with pharmaceutical companies to promote the development of safe and effective pain management therapies.

“ We have an opioid problem, and we have a pain problem, and we need a balance of how we manage pain and not deny people who need medication. ”

CDC

Chad Helmick, MD, medical epidemiologist with the arthritis program at the CDC, said that the opioid crisis is “...really a dysfunctional pain management system. Why focus on pain? The numbers tell the story,” he said, reporting that 25.3 million adults (11.2% of the population) in the United States have daily pain, and 14.4 million have severe pain (6.4% of the population). “The system is not working for these people very well.”

Rheumatologic conditions account for a great many cases of pain, says Helmick, who indicated that 50% of adults who were issued prescriptions for opioids have arthritis. Similarly, current methods of treating pain associated with rheumatic disease are related to the growing problem of opioid addiction: “We have a variety of evidence-based [therapies]” outside of opioids, he said, referring to physical activity, self-management education, and physical therapy, “but we don’t use them.”

The good news, Helmick said, is the growing momentum to address both pain and addiction. The Healthy People 2020 initiative includes developmental objectives for pain, including decreasing the prevalence of adults who have high-impact chronic pain, and the 2016 National Health Interview Survey included 2 questions geared toward better understanding the incidence and impact of chronic pain. ●

Value-Based Contracting (Continued from page 12)

- Compensation. Some practices will have to change the ways in which they pay their employees under an ACO.

If they are ready to join an ACO, practices should ask the organization the following questions:

- What other physicians are in the network?
- Does the payer have good data on the drivers of cost?
- What are the historic care patterns for the population being treated?
- What is the highest cost setting?
- Are the patients coming from other practices or from within the network?
- How are incentives distributed?

Where Is Value Headed?

Looking to the future, Mertz predicted that value models will continue to change and evolve, that commercial payers will wait to see which Medicare-approved models generate success and savings before making their own changes, and that practices may not see any return on value for investing in an alternative model.

Finally, Mertz said, the greatest barrier to value in health-care is patient compliance. “We should start educating 6-year-old [children] on lifestyle and diet,” he said, but noted that lifestyle education would, even if effective, take many years to have a sizable effect. “They’re going to hold [practices] responsible for patient compliance,” said Mertz. “Good luck with that.” ●

2017 Sees Progress in Approvals for Antirheumatic Drugs

KELLY DAVIO

Kamala Nola, PharmD, MS, professor at the Lipscomb University College of Pharmacy, in Nashville, Tennessee, provided an overview of the drugs that have been approved in the past year for the treatment of inflammatory conditions during a session at the 2017 American College of Rheumatology's Annual Meeting. Some antirheumatic therapies approved in 2017 are as follows:

Brodalumab (Siliq)

In February, this interleukin (IL)-17 inhibitor was approved to treat moderate to severe plaque psoriasis in patients who are candidates for systemic therapies or phototherapy, and who failed to adequately respond to other systemic therapies. The drug, delivered subcutaneously via a prefilled syringe, is contraindicated in Crohn disease, and carries a warning for suicidal ideation.

Brodalumab is subject to a risk evaluation and mitigation strategy program that requires prescribers to enroll in the program and counsel patients on suicidal ideation and behavior. Pharmacists need certification to dispense the drug and they have to maintain records that are subject to audits. Patients must carry a wallet card noting their therapy.

Methotrexate (Xatmep)

The first oral methotrexate solution, approved in April, is indicated for the treatment of polyarticular juvenile idiopathic arthritis and pediatric acute lymphoblastic leukemia. "This is the first time [methotrexate has] been in an appropriate dosage form" to make the drug palatable to children, Nola said.

Abaloparatide (Tymlos)

This human parathyroid hormone related peptide analogue for subcutaneous injection was approved in April to treat postmenopausal women with osteoporosis who have a high risk for fracture. The once-daily 90-mcg subcutaneous injection, taken with supplemental calcium and vitamin D, has no listed contraindications, although it carries warnings that include orthostatic hypotension after injection and risk for osteosarcoma.

Tocilizumab (Actemra)

"Giant cell arteritis finally has a drug," said Nola of this therapy. Tocilizumab was granted a label expansion in May for the treatment of adults with giant cell arteritis. The drug, administered as a weekly subcutaneous injection, may be given in combination with a tapering course of steroids, and may allow patients to discontinue steroid therapy altogether.

Tocilizumab was also approved to treat adults and children 2 years and older with chimeric antigen receptor T cell–induced severe or life-threatening cytokine release syndrome.

Sarilumab (Kevzara)

This IL-6 receptor antagonist was approved in May to treat adults with moderate to severe active rheumatoid arthritis (RA) who did not respond well or had intolerance to 1 or more disease-modifying anti-rheumatic drugs (DMARDs). "We're finally getting to the point where we can say failure of 1 DMARD [means] you can potentially move on," said Nola.

Sarilumab can be used as monotherapy or in combination with methotrexate or conventional DMARDs. The drug carries warnings and precautions for severe infection, neutropenia, thrombocytopenia, elevated liver enzymes, gastrointestinal perforation, hypersensitivity reactions, and avoidance of live vaccines.

Guselkumab (Tremfya)

Approved in July, this IL-23 blocker is indicated for the treatment of adults with moderate to severe plaque psoriasis who are candidates for systemic therapy or phototherapy. The drug is administered in 100-mg, single-dose, prefilled syringes, and carries warnings for infection, tuberculosis, and avoidance of live vaccines.

Belimumab (Benlysta)

"Good news for our lupus patients," said Nola of this drug approved in July. This therapy is available as a self-injectable drug at a 200-mg weekly dose to treat patients with active, autoantibody-positive, systemic lupus erythematosus. Women who are able to become pregnant should speak to their physicians about using contraception while taking belimumab, and for at least 4 months after discontinuing it. Belimumab's manufacturer has made a pregnancy registry available to patients.

Lesinurad and allopurinol (Duzallo)

This fixed-dose oral combination of 200 mg of lesinurad, a URAT1 inhibitor, and 300 mg of allopurinol, a xanthine oxidase inhibitor, was approved in August to treat hyperuricemia with gout in patients who have not reached target serum acid levels with allopurinol therapy alone. This therapy is not recommended for asymptomatic hyperuricemia, and it has a goal uric acid level of less than 6 mg per dL.

Patients should not take more than 1 tablet per day. They should be counseled not to combine the drug with lesinurad and to take the therapy in the morning with food and water. Clinicians should assess renal function prior to initiation. The drug carries warnings and precautions for renal events, skin rash and hypersensitivity, hepatotoxicity, cardiovascular events, and bone marrow suppression. Listed interactions include mercaptopurine and azathioprine.

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Patients With Rheumatic Diseases Are at Increased Risk for Cardiac Disease

KELLY DAVIO

At a session of the 2017 American College of Rheumatology's Annual Meeting in San Diego, California, a cardiologist joined rheumatologists to give a detailed look at the relationship between rheumatic conditions and cardiovascular disease. Rekha Mankad MD, FACC, director of the Women's Heart Clinic at Mayo Clinic in Rochester, Minnesota, presented "Getting to the Heart of the Matter: the Heart in Autoimmune Diseases."

Mankad began with the sobering statement that increased morbidity and mortality from heart disease is present in all autoimmune diseases. She pointed to recent data demonstrating that patients with connective tissue diseases had a higher rate of coronary artery disease compared with the total population. "All of these diseases should alert you that this patient population needs to be looked at a little differently," she said.

Mankad addressed several areas of concern for the rheumatologist:

Pericardial disease

According to Mankad, approximately 50% to 60% of patients who have systemic lupus erythematosus (SLE) will experience pericardial effusions, most of which are asymptomatic. She recounted the case of a 50-year-old male patient with SLE who was referred to her clinic after his rheumatologist suspected cardiac irregularities. Testing demonstrated pericardial effusion. "His heart [was] kind of swimming inside of this large pericardial effusion," she said. "Obviously this had happened very slowly." Four liters of fluid had to be extracted from the patient's pericardial space.

Pericardial disease also affects patients with rheumatoid arthritis (RA), Mankad said, although pericarditis is typically observed post mortem in this patient population. Treatment for pericardial diseases in patients with rheumatic diseases is typically geared toward the treatment of a disease flare itself, including the use of high-dose steroids to aggressively treat inflammation. "I tell patients it's a yin-yang," Mankad said on the use of steroids, noting that chronic steroid use is associated with increased cardiovascular risk, but that high-dose steroids drive down inflammation.

With respect to other agents for rheumatologic autoimmune inflammation, such as anti-tumor necrosis factor biologics, Mankad noted that although these therapies improve arterial function, there is some concern about whether they increase the risk of heart failure. "The jury is out on whether they cause it," she said.

Valvular Heart Disease

Antiphospholipid syndrome, an autoimmune disease that primarily affects young women and that is often associated with

SLE, can cause cardiac lesions. These lesions are accumulations of immune complexes, fibrin, and platelet thrombi. The lesions often involve the mitral valve, and range from small nodules to large, verrucous lesions that may necessitate valve replacement. The risk factor for patients with SLE developing such lesions "might be somewhere between 10% and 20%," said Mankad, who highlighted that disease activity is not correlated with the risk of developing lesions. To identify these problems early, she said, "we should be doing echoes at baseline" in patients with SLE.

In patients with RA, echocardiographic abnormalities may be present in any valve, and those patients who have the highest erythrocyte sedimentation rates (ESR) tend to have more aortic stenosis. Mankad encouraged rheumatologists who hear a heart murmur to follow these patients more closely.

Heart Failure in RA

Mankad presented data from Mantel et al, published in the *Journal of the American College of Cardiology*, showing that the rate of heart failure overall, per 1000 person years, was 4.1 (range, 3.0 to 5.1) in patients with RA versus 3.2 (range, 2.9 to 3.6), for the general population (HR, 1.22). She said that, in looking at these data, "It wasn't just about coronary heart disease. It had to be this other entity [RA] as well."

She added that inflammatory markers for RA typically peak 6 months prior to a diagnosis of heart failure, the rate of hospitalization for heart failure is approximately 20% higher in patients with RA than in patients without RA (7.4 vs 5.5 hospitalization days per patient per year), and that mortality from heart failure is "substantially higher" in patients with RA.

Ischemic Heart Disease

"So much happens with inflammation," said Mankad, explaining that systemic inflammation in autoimmune conditions leads to endothelial dysfunction, which in turn produces arterial stiffness (associated with ischemic heart disease). "Basically, things are stiff. They don't relax well."

She discussed the case of a 40-year-old female patient with Raynaud syndrome, SLE, and a connective tissue disease who had ongoing atypical chest pain that could not be explained until a computed tomography scan showed coronary calcification. "We know that that this is a real phenomenon," said Mankad. "There is something wrong with their coronary arteries. They were called crazy, and their stress tests were said to be false positives...[but] they're real."

Like those with Raynaud or SLE, patients with RA also have an elevated risk for ischemic heart disease. Somewhat surprisingly, a body mass index (BMI) under 20 is associated with a higher

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MACRA Challenges Lead to New American College of Rheumatology Alternative Payment Model

KELLY DAVIO

A panel discussion, titled, “Holy MACRA! How to Survive and Thrive in the New Era of MACRA, MIPS and APMs,” presented at the 2017 American College of Rheumatology’s (ACR) Annual Meeting in San Diego, California, provided practice managers with key information about keeping pace with the Medicare Access and CHIP (Children’s Health Insurance Program) Reauthorization Act (MACRA) of 2015. The panel also provided the ACR with a prime opportunity to reveal the initial draft of its new MACRA-compliant alternative payment model (APM) for rheumatoid arthritis (RA).

Challenges With MIPS

The panel began with moderator Angus B. Worthing, MD, FACP, FACP, chair of the American College of Rheumatology’s Government Affairs Committee, providing an overview of the challenges that the

“ The APM creates a standard approach to RA management based on ACR guidelines, requires the use of methotrexate and disease-modifying antirheumatic drugs (DMARDs) before the use of biologics, specifies the frequency and type of monitoring for patients, and will be updated regularly by the ACR. ”

merit-based incentive payment system (MIPS) poses for clinicians. Under the 2017 structure for MIPS, the categories of quality (60%), resource use (0%), clinical practice improvement activities (15%), and advancing care information (25%) are combined to create a composite score that determines a practice’s annual adjustment from the Centers for Medicare & Medicaid Services (CMS).

Worthing pointed out 3 key downsides to MIPS:

- The annual adjustment in reimbursement set to reach $\pm 9\%$ in 2022; Worthing noted that most practices have overheads of around 70%, resulting in a physician taking home 30 cents per dollar. Thus, a downward adjustment of -9% would be felt keenly: “If that gets cut from 100 down to 91 cents, you’re taking home 21 cents.”
- MIPS is “a budget-neutral system” in which high-performing practices benefit financially at the expense of low performers. “It’s a zero-sum game,” said Worthing. “The losers pay for the winners.”

- CMS’ final rule, announced last week, includes Medicare Part B drug costs—including the cost of expensive biologic therapies—in adjustments beginning in 2020. If a practice is reimbursed for biologics at a 4% margin, then sustains a -9% adjustment, “you’re underwater,” said Worthing. “This will stop infusion therapy or injection therapy” given in the physician’s office, he predicted, because no practice will be willing to take such a financial risk.

Succeeding With MACRA

Ed Herzig MD, FACP, MACR, who has previously served as chair of RheumPAC, the political action committee of the ACR, gave practical advice to rheumatologists looking ahead to the first adjustment period in 2019. Activities that practices may already be undertaking can be reported as quality performance activities, and Herzig encouraged practitioners to report activities such as documenting current medications in patient records, conducting osteoporosis management in women with fractures, overseeing glucocorticoid management in patients with RA, and evaluating RA functional status.

Herzig also offered global tips for success with MACRA:

- Ensure that the practice’s electronic health record system is certified
- Use the ACR’s Rheumatology Informatics System for Effectiveness registry as a way to reduce administrative burden in reporting
- Establish a point person within the practice to monitor patients who are counted in MIPS populations
- Review data monthly (or quarterly at a minimum)
- Decide whether to report data for 90 days of this year or to report a full year of data
- Pick a pace to achieve full compliance with MACRA
- Join a network to reduce the burden of practice change

An APM For RA

Last to speak was Kwam Houston, MD, who unveiled the ACR’s draft of a new APM for the treatment of patients with RA. The organization hopes to eventually expand the model to other diseases if it is approved by the Physician-Focused Payment Model Technical Advisory Committee and CMS.

The APM creates a standard approach to RA management based on ACR guidelines, requires the use of methotrexate and disease-modifying antirheumatic drugs (DMARDs) before the use of biologics, specifies the frequency and type of monitoring

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2017 Sees Progress (Continued from page 14)

Two antirheumatic drugs were notable disappointments, earning Complete Response Letters (CRLs) from the FDA in 2017, Nola told the audience.

Baricitinib

“Here’s where we hit a hiccup in the year,” said Nola of baricitinib. This janus kinase inhibitor for the treatment of patients with RA received a CRL in August. The drug’s developer, Eli Lilly, indicated in a press release that it plans to file a new application to the FDA in January 2018, and expects a 6-month review period.

Sirukumab

The FDA’s Arthritis Advisory Committee did not recommend

the approval of this IL-6 inhibitor for the treatment of patients with moderate to severe RA. While the committee unanimously supported sirukumab’s efficacy, it had uncertainty about its safety. The FDA issued a CRL for sirukumab in September.

Nola also provided an update on which biosimilars have been approved to date to treat rheumatic diseases:

- Adalimumab-atto (Amjevita) and adalimumab-adbm (Cyltezo), both referenced on Humira
- Etanercept-szsz (Erelzi), referenced on Enbrel
- Infliximab-dyyb (Inflectra) and infliximab-abda (Renflexis), both referenced on Remicade

As of the November meeting, Inflectra and Renflexis have launched in the United States. ●

Patients With Rheumatic Diseases (Continued from page 15)

risk of heart disease and lower survival. Mankad suggests that the “high inflammatory milieu is actually driving the BMI down” in these patients, and that low BMI should not be taken as an indication of low risk in a patient with RA.

Recommendations For Rheumatologists

In offering guidance to the audience, Mankad said, “I don’t expect you guys to do a full cardiovascular assessment with a patient,” but urged rheumatologists to “use a high index of suspicion to perform

[cardiovascular testing],” which might include tonometry and pulse wave velocity testing to assess arterial stiffness, brachial artery testing to check endothelial function, and a carotid ultrasound to detect plaque and assess carotid intima-media thickness.

Finally, Mankad suggested that statins might be initiated as adjunctive RA therapy, pointing to results of the Trial of Atorvastatin in Rheumatoid Arthritis, in which atorvastatin was associated with significant improvements in disease activity score, C-reactive protein level, ESR, and cholesterol levels in patients with RA. ●

MACRA Challenges Lead (Continued from page 16)

for patients, and will be updated regularly by the ACR. An adherence rate of 75% for reporting will provide flexibility to provide care to patients whose circumstances require deviation from the standard approach, Huston said.

The model recognizes 4 phases of RA care:

- Diagnosis and treatment planning. This stage will trigger a one-time payment to cover evaluation, testing, diagnosis, and treatment planning, inclusive of lab testing, imaging, communication with other physicians, and shared decision making.
- Support for primary care physicians (PCP) in evaluating joint symptoms. Communication with a PCP who has an agreement with a rheumatology network to work collaboratively triggers 1 payment for discussion regarding a specific patient (including discussion of prereferral testing and expediting the referral of high-risk patients).
- Initial treatment of RA. When a patient agrees to a treatment plan, a monthly payment is triggered for 6 months, which

allows flexibility for non-face-to-face communication and advanced services for those who need them. Payments are stratified based on patient characteristics.

- Continued care of RA. Continued care will trigger monthly payments, not tied to office visits, again with stratified payments.

For accountability, clinicians must meet in person with patients at least once every 6 months, document disease activity using a validated scale, maintain a written RA treatment plan consistent with the ACR pathway, follow-up within 2 weeks of a medication change, complete a functional assessment, conduct a tuberculosis screening, and create a steroid plan.

Practitioners who follow the treatment pathway 75% of the time will be exempt from penalties. Those who fall short of 75% compliance will be subject to adjustments from –2% to –8%. The pathway, said Huston, provides adequate payment for high-value services, avoids MIPS penalties, reduces documentation, keeps physicians from being responsible for the high cost of drugs, and gives clinicians more control over performance measures. ●

Rheumatologists' Frustrations With Pharmacy Benefit Managers Take Center Stage

KELLY DAVIO

The title “Reshaping the Relationship Between Physicians and PBMs” suggested that the Sunday session at the 2017 American College of Rheumatology (ACR)'s Annual Meeting in San Diego, California, would focus on reconciling the goals of providers and pharmacy benefit managers (PBMs), but physicians' challenges in dealing with PBMs quickly became the primary focus of the panel discussion.

The session, moderated by Colin Edgerton, MD, a member of the ACR Committee on Rheumatologic Care, kicked off with a presentation by Dan Kelly, PharmD, a representative of

“ PA poses 'high' or 'extremely high' burden on practices and [physicians] reported an average of 36.6 authorizations—requiring an average of 16.4 hours total—per week.”

the prior authorization (PA) software company CoverMyMeds. Kelly acknowledged that PA for medicines is a burden for all healthcare stakeholders, including pharmacists, who must engage in additional communication with prescribers; drug makers, who see sales numbers decrease; and payers and PBMs, who undertake a labor-intensive review process and face patient frustration.

Yet, prescribers may shoulder the bulk of the work related to PAs. Kelly stated that in a 2016 survey of an undisclosed number of physicians, 75% of respondents said that PA posed “high” or “extremely high” burden on their practices, and reported an average of 36.6 authorizations—requiring an average of 16.4 hours total—per week. Perhaps most concerning, 90% of respondents reported that PAs delay access to necessary care.

“We have no evidence to suggest that PA is going to go away or decline in volume,” said Kelly, who pointed to the increasing volume of specialty drug prescriptions, steeper renewal requirements, insurance expansion, new therapeutics, and formulary updates as drivers of increased PA volume. Furthermore, decreasing efficiency—which Kelly blamed on the need to fill out manual forms with complex clinical criteria, the number of different insurance plans, regulatory variance, and lengthy review times—can delay approvals.

Kelly proposed that electronic PAs could help reduce the burden presented by PAs by initiating the process at the point of prescribing, and by cutting down on the time needed to achieve a decision from the payer.

Rheumatologists who commented on Kelly's presentation during the question-and-answer period were skeptical of the willingness of PBMs to engage with a system that would speed patient access to drugs if shareholders benefit financially when access is delayed or denied. One clinician noted that his practice has experienced a marked increase in requirements for PA, not only for expensive biologics to treat rheumatic diseases, but also for older, less-expensive medications such as steroid therapies or methotrexate.

Brent Clough, chief executive officer of Trio Health, a company that collects healthcare data and publishes its findings, also shared a critical view of PBMs and payers. In fact, he said that his presentation was “about throwing payers and PBMs under the bus.” Clough used Trio Health's data on Harvoni, a hepatitis C drug, as an illustration of what he views as a PBM blockade to patient access to medicines. Although Harvoni has a notably high list price at approximately \$90,000 for a 12-week course of therapy, Clough pointed to Gilead Sciences' disclosed data that Harvoni's current average price to Medicaid is less than \$10,000 per course after negotiations (and approximately \$30,000 to commercial payers), making Harvoni a far less costly therapy than indicated by its list price.

However, Clough says, denials of coverage of the drug have been steadily increasing even as the price of Harvoni drops—in 2014, approximately 7% of patients were denied the therapy, and that proportion of patients grew to 37% in 2016. “They've hoodwinked different payers and different plans into denying these patients,” said Clough, who added that, on average, patients had to wait 147 days, due to numerous denials from PBMs, to initiate therapy with Harvoni.

Medicaid recipients also experience wide disparities in access according to location in the United States, with initiation rates ranging from approximately 0% in Alabama to over 90% in Connecticut. “With the current administration, there's talk about further cuts to Medicaid,” Clough added, “Quite frankly, the situation is going to get worse.”

Finally, Sean M. Fahey, MD, chair of ACR's insurance subcommittee, provided a glimpse into how ACR has been engaging with PBMs to date, and noted the discrepancy in objectives: while the goal of the PBM is to generate revenue, he said, ACR wants to preserve patient access to necessary drugs. ACR's insurance subcommittee communicates with payers and PBMs on coverage policies that relate to some of the most expensive drugs prescribed: originator biologics and biosimilars. “We've tried the honey approach, and we've tried the vinegar approach,” said Fahey, but “our comments rarely if ever seem to influence their final decisions, and we have

(Continued on page 20)

In Debate Over Biosimilar Switching, Cost Is Key

KELLY DAVIO

Among the most anticipated sessions at the 2017 American College of Rheumatology's Annual Meeting in San Diego, California was "The Great Debate: Biosimilars...to Switch, or Not to Switch? That Is the Question." Moderated by Daniel E. Furst, MD (a rheumatologist at The Scleroderma Center at Arthritis Associates in Los Angeles, California), and Daniel Solomon, MD, MPH (Professor of Medicine at Harvard Medical School and Chief of the Section of Clinical Sciences in Rheumatology at Brigham & Women's Hospital in Boston, Massachusetts), the debate featured Jonathan Kay, MD, arguing in favor of switching patients from reference products to biosimilars, and Roy Fleischmann, MD, arguing against the practice.

Switching for the Greater Good

Kay, a rheumatologist affiliated with UMass Memorial Health Care in Worcester, Massachusetts, began by framing his remarks with a play on the famous "to be or not to be" question asked by Shakespeare's *Hamlet*. In Kay's version, the lines that follow are "Whether 'tis better for bones and joints to suffer the stings and burden of outrageous prices, or try changing to a biosimilar, and by converting save costs."

Kay outlined his position by first defining a biosimilar as a molecule that has undergone rigorous analytical and clinical assessment and has been approved by a regulatory agency. He reminded the audience that the FDA reviews analytical comparisons between the reference biologic and biosimilar along with nonclinical data, clinical pharmacology, and clinical studies in a risk-based, totality-of-the-evidence approach.

He went on to argue that all biologic drugs, including reference products, are subject to variability due to protein folding variance, misfolding, aggregation, enzymatic cleavage, and degradation, and that all biologics have batch-to-batch variability. Proven acceptable ranges are established during product development, and variability within that range does not pose safety or efficacy risks. Furthermore, "drift," or unintended alterations caused by manufacturing practices over time, and intended and regulated alterations created by manufacturing changes, can create variability in reference biologics.

While Kay allowed that variation may have consequences that we do not yet realize, variation is to be expected in biologics. It can be so substantial, Kay said, that the same drug may be considered a biosimilar of other batches of the same product. Variability has an impact on the extrapolation of clinical data from a study in one indication to other indications, said Kay. "We don't ask each batch of a reference product to be tested in large clinical trials in all indications."

He went on to argue that trials such as PLANETAS and PLANETRA in ankylosing spondylitis and rheumatoid arthritis

(RA), respectively, point to the feasibility of switching patients from reference infliximab to its biosimilar.¹ He also highlighted the NOR-SWITCH trial (a 52-week, phase 4 study in patients with Crohn's disease, ulcerative colitis, spondyloarthritis, RA, psoriatic arthritis, or plaque psoriasis) which met its primary end point of noninferiority in patients who were switched from the reference infliximab to a biosimilar.²

While Kay acknowledged that NOR-SWITCH's open-label extension showed losses in patient global assessment (PSA) scores among switched patients, he says that the PSA "reflects nocebo effect," or a misattribution of bodily symptoms to a drug in patients who expect to experience side effects or other poor outcomes. Kay also attributed patient discontinuation of biosimilars in other studies, such as BIO-SWITCH,³ to the nocebo effect.

“Variation is to be expected in biologics...the same drug may be considered a biosimilar of other batches of the same product.”

Given evidence of similar safety and efficacy, Kay argued, a cheaper biosimilar should be used instead of a reference biologic "So that medications are more widely available to all members of society." Any potential risk from switching should be weighed against potential benefits for all patients who need access to biologics.

But Where Are the Cost Savings for Patients?

Fleischmann, a Clinical Professor in the Department of Internal Medicine at the University of Texas Southwestern Medical Center and in private practice at Rheumatology Associates, Dallas, Texas, in arguing against switching patients to biosimilars, did not challenge Kay's comments on the nature of biosimilarity or the approval pathway for biosimilars, which have been well defined. However, Fleischmann took issue with switching biosimilars based on data from NOR-SWITCH, saying, "The assumption was difficult. How do you define 30% [disease] worsening? It couldn't really be accurate." He also questioned the veracity of attributing patients' poor outcomes to the so-called nocebo effect. "Nocebo's a word that comes up when you don't get what you want to see," he said. "[Do] you want to call it nocebo, or you want to call it the data?"

More importantly, Fleischmann framed the issue of switching to biosimilars differently: "If it isn't considerably cheaper to the

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Rheumatologists' Frustrations (Continued from page 18)

not been approached by the PBMs as much as we have [been by] individual payers.”

Among the concerns that the subcommittee is attempting to address with PBMs and payers are the following:

- Formulary issues. Some patients report receiving notices from PBMs warning them that their therapies will no longer be on formulary, and that they must switch therapies. Fahey called these notices a “scare tactic” that can often be resolved via a PA.
- Step edits. Fahey points out that, because there is little data to document the effect of step edits on patients, it can be difficult for clinicians to push back against policies that force patients to fail to respond to a cheaper therapy

before initiating a more expensive one, such as a biologic.

- Nonmedical switching. “More and more, payers and PBMs are trying to shift from one [tumor necrosis factor, TNF] inhibitor to another, more so in the past 6 months, we’ve seen policies asking patients to switch from a TNF inhibitor to a non-TNF inhibitor, even if they’re stable on therapy,” said Fahey, who added that, with biosimilar therapies, “the lines are blurry,” as some emerging data suggest that switching to a biosimilar of a reference therapy may be feasible.

Looking ahead, Fahey said that he hopes alternative payment models could help eliminate some of the burdens PAs and step edits, and that collecting greater real-world data to present to payers and PBMs will be critical. ●

In Debate (Continued from page 19)

patient and society, there is no value in using a biosimilar. This is where I start: cost.” “This is truly the question,” Fleischmann went on. “Are there real, considerable cost savings realized with the use of biosimilars, which accrue to the patient, and therefore [allow them to] have greater access to biologics? If the patient doesn’t have better access, you don’t need a biosimilar.”

Despite the fact that patients and payers have seen cost savings from biosimilars, in the European experience—where single-payer systems are in place—Fleischmann said that his remarks would be grounded in “the realities of our current knowledge of biosimilars and the medical system in the United States, good or bad.” Fleischmann referenced his own experience as a partial owner of an infusion center where no biosimilars have been used to date; insurance plans have requested physician appeals before biosimilars can be approved, he said, and patients would be responsible for roughly the same costs of treatment.

Taking aim at pharmaceutical companies, Fleischmann pointed to the recent AbbVie and Amgen settlement on Humira that will allow a biosimilar adalimumab to enter the US market in 2023. “The deal suggests that the industry’s long-standing strategy of using patents to ward off cheaper competition for brand-name drugs is extending into the era of biosimilars. AbbVie will grant patent licenses for the sale of the biosimilar, so when is Humira going to be cheaper?” He added that AbbVie has substantially raised adalimumab’s list price over time—the price increased by 68% between 2013 and 2016—although AbbVie says it provides rebates and discounts that lower the cost for insurers. But “what about the patient?” Fleischmann asked.

Fleischmann also criticized pharmacy benefit managers (PBMs) for their role in keeping costs high for patients: “We

“ If it isn't considerably cheaper to the patient and society, there is no value in using a biosimilar. If the patient doesn't have better access, you don't need a biosimilar. ”

have a unique system in the [United States] which governs the choice of medications. It’s called the rebate system, and it’s a very sad system,” referring to the arrangement in which PBMs negotiate for lower prices while patients have co-payments on list prices for drugs.

Regardless of the European experience with biosimilars, Fleischmann said, “I live in the [United States]. I don’t get any benefit; my government get any benefit [from biosimilars].” The only entity that has a true advantage from biosimilars, he says, is the payer. Fleischmann underscored this position by citing an article published in *The Center for Biosimilars*[®] reporting that 58% of US health plans do not cover biosimilar infliximab.⁴ ●

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Research Documents Real-World Experience With Biosimilar Infliximab and Etanercept

JACKIE SYROP

Three presentations at the 2017 American College of Rheumatology's Annual Meeting in San Diego, California, covered research on the real-world treatment of patients with rheumatic disease with originator infliximab therapy and biosimilar infliximab (CT-P13; Inflectra and Remsima) and etanercept (Benepali) therapy.

Patients Maintained on Originator Infliximab Showed Greater Adherence

Patients with rheumatic diseases maintained on originator infliximab had greater adherence to therapy than those who initiated the originator and switched to biosimilar infliximab CT-P13, according to results from a Turkish study conducted by Ellis et al.¹ Additionally, CT-P13 discontinuation resulted in originator reinitiation in the majority of patients. The reasons for discontinuation in this study are unknown, but regional differences in practice patterns were observed.

A total of 697 adult patients with 1 or more rheumatoid arthritis (RA) diagnosis codes who were taking reference infliximab were identified in a Turkish national healthcare database. Eligible patients initiated and continued the reference in the continuer cohort (CC) (n = 605) or initiated the reference and switched to CT-P13 in the switch cohort (SC) (n = 92) during the study period. Mean duration of originator infliximab therapy during the baseline period was 422 days (CC) and 438 days (SC). Average duration of follow-up was 16 months (CC) and 15 months (SC).

During the combined baseline and postindex periods, median time on any infliximab therapy was 1080 days (CC) and 540 days (SC). Discontinuation occurred in 19% (CC) and 87% (SC) of patients; mean time from index to originator discontinuation was 276 days (CC), while mean time from index to CT-P13 discontinuation was 132 days. Switching from originator infliximab to CT-P13 occurred in 13% of all originator initiators on the index date, and an additional 10% of the CC switched to a noninfliximab antitumor necrosis factor medication post index. The majority of the SC (82%) switched again post index (away from CT-P13) and 88% of those reinitiated originator infliximab therapy.

Regional variation in switching was noted: switching from originator infliximab to CT-P13 occurred most frequently in Central Anatolia. Switching from CT-P13 occurred in more than 75% of SC patients in all regions, except for the Aegean.

US Biosimilar Infliximab Not Significantly Affecting Reference Infliximab

The US adoption of biosimilar infliximab (Inflectra) so far has been low and has not yet significantly impacted reference infliximab (IFX), according to an analysis by Radtchenko et al.²

Longitudinal prescription and medical claims from Symphony Health were used to evaluate the uptake of biosimilar infliximab relative to reference infliximab from the time of the FDA's approval of biosimilar infliximab in April 2016 through the first quarter of 2017. The database contained claims records for 279 million patients representing an estimated 63% of specialty prescriptions, 58% of medical claims, and 25% of hospital claims in the United States.

Of the 78,481 patients who initiated a biologic or biosimilar therapy for RA since the approval of biosimilar infliximab, 0.1% were treated with the biosimilar and 6.6% were treated with reference infliximab. The first patient began treatment with the biosimilar in May 2016 and 78 patients started receiving the biosimilar during the first quarter of 2017. Claims records show the following for patients treated with the biosimilar:

- 73.3% were female
- 64.4% were 65 years or older
- 1 patient was commercially insured, the rest had unknown insurance status
- 34.4% were previously treated with reference infliximab
- 62.2% received the biosimilar as their first biologic
- Mean age for patients receiving the biosimilar was 65.9 years compared with 55.0 years for patients receiving reference infliximab ($P < .0001$)
- Mean number of prior biologics was 0.5 for patients receiving the biosimilar and 0.5 for patients receiving reference infliximab
- Median (mean) duration was 1.0 (4.5) days for the biosimilar and 60.0 (101.2) for reference infliximab due to late biosimilar adoption.

The investigators concluded that the infliximab biosimilar has not significantly affected the use of the reference biologic. "Duration of therapy on [the biosimilar] is relatively short due to its delayed launch," they note. The majority of patients treated with biosimilar infliximab received it as their first biologic, but one-third of these patients switched from the reference. Future monitoring of biosimilar infliximab uptake is warranted, especially as other approved biosimilars prepare for launch.

Biosimilar Use in Children and Young People With Juvenile Idiopathic Arthritis in a Real-World Setting

A study of biosimilar use in children and young people with juvenile idiopathic arthritis (JIA) in the United Kingdom shows that these drugs are used as both first-line and subsequent-line

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Research Is Presented on 4 Proposed Etanercept Biosimilars

JACKIE SYROP

Four presentations at the 2017 ACR Annual Meeting in San Diego, California, covered research comparing reference etanercept to 4 proposed biosimilars: SB4, LBEC0101, CHS-0214, and GP2015.

Antidrug Antibodies and Injection Site Reactions

Significantly fewer patients taking the etanercept biosimilar SB4 developed antidrug antibodies (ADAs) or experienced injection site reaction (ISRs) compared with those taking reference etanercept ($P < .0001$), according to the results of a phase 3, randomized, double-blind study of patients with moderate to severe rheumatoid arthritis (RA) who received either SB4 or reference etanercept with background methotrexate for 52 weeks.¹ Efficacy was comparable between SB4 and reference etanercept in patients without detectable ADAs and in patients who did not experience ISRs, Vencovsky et al reported.

The study was carried out in 595 patients (299 received SB4; 296 received reference etanercept). At week 24, among those given SB4, 2 patients were ADA-positive and 297 patients were ADA-negative. For those given reference etanercept, 39 patients were ADA-positive and 257 patients were ADA-negative. At week 24, ISRs occurred in 9 patients given SB4 and 48 patients given reference etanercept.

Due to the low incidence of ADA in the SB4 treatment group, the impact of ADAs on efficacy could not be evaluated. Within the reference group, there was a trend toward increased efficacy in patients without detectable ADAs compared with patients with ADAs. In both the SB4 and reference groups, patients without ISRs tended to experience greater efficacy than patients with ISRs. There was no reported correlation between the presence of ADAs and ISRs.

Efficacy of LBEC0101 Equivalent to Reference Etanercept

The clinical efficacy of the proposed etanercept biosimilar LBEC0101 was equivalent to that of reference etanercept, was well tolerated, and had a comparable safety profile to the reference, according to a phase 3 trial in patients with active RA inadequately responding to methotrexate.²

Matsuno et al followed 374 patients for 52 weeks in the multicenter, randomized, double-blind, parallel-group, reference product-controlled study conducted in Japan and Korea. Patients with active RA for 6 months or more who had an inadequate response to methotrexate were randomly assigned to receive weekly doses of LBEC0101 ($n = 187$) or the reference ($n = 187$) administered subcutaneously for 52 weeks. The primary efficacy end point was mean change from baseline in disease activity score in 28 joints based on erythrocyte sedimentation rate

(DAS28-ESR) at week 24. Efficacy, safety, and immunogenicity outcomes were assessed up to week 52.

Least-squares mean changes from baseline in DAS28-ESR score at week 24 in the per-protocol set were -3.009 in the LBEC0101 group and -2.859 in the reference group. The estimated treatment difference in change from baseline to week 24 in DAS28-ESR score between the 2 groups was -0.150 (95% CI, -0.3768 to 0.0775), completely within the pre-specified equivalence margin of -0.6 to 0.6 , indicating that equivalence in efficacy between LBEC0101 and the reference was proven.

The secondary end point, change in RA symptoms on the ACR20 scale (20% improvement in tender or swollen joint counts and similar improvement in 3 of the other 5 criteria from the ACR) at week 24, was similar between the 2 groups. Incidence of adverse events (AEs) up to week 52 was comparable except for ISRs, which were reported in 34.3% of patients in the reference group and 10.2% of the LBEC0101 group. ADAs developed in 1.6% and 9.6% of patients in the LBEC0101 and reference groups, respectively, by 52 weeks.

CHS-0214 Well Tolerated, Efficacious in Extension Study

The majority of patients in an open-label safety extension study of the proposed etanercept biosimilar CHS-0214 maintained an efficacious response to treatment with the biosimilar and tolerated the treatment well, with no increase in treatment-emergent AEs (TEAEs) with ongoing drug exposure, according to Louw et al.³ The investigators noted that there were no new safety signals identified in these patients, with an average of 80 weeks of treatment.

The extension study was conducted in 359 patients (225 with RA, 134 with psoriasis) who had completed 48 weeks of a prior CHS-0214 equivalence trial and had an additional mean duration of treatment of 31.45 weeks with open-label CHS-0214. Durable response was achieved in 87.5% of patients with RA and 90.1% of patients with psoriasis at the data cut-off date. Loss of efficacy was a factor in study discontinuation for 5 patients. TEAEs were reported in 60.5% of patients, serious AEs were reported in 3.9% of patients, and 4 patients (1.1%) had a TEAE leading to study drug discontinuation.

Phase 3 Study Shows Equivalence of GP2015 to Reference

The proposed etanercept biosimilar GP2015 demonstrated equivalent efficacy to the reference in patients with RA who had an inadequate response to methotrexate, and the overall safety profile of the biosimilar was comparable to the reference, according to the 24-week results of the phase 3 EQUIRA study, reported by Kavanaugh et al.⁴

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Research Documents Real-World Experience (Continued from page 21)

biologic therapies, despite these indications having not been approved for such a use, according to De Cock et al.³

Unlike the situation with RA, in which the majority of patients receiving biosimilars to date have switched from originator biologics, this initial finding in JIA suggests that biosimilars are being considered frontline therapy (as alternatives to the originator drugs) as a cost-savings measure, the investigators hypothesize. "Further follow-up of these children will assess the safety and effectiveness of biosimilars in pediatric use," they concluded.

The Biologics for Children with Rheumatic Diseases (BCRD) study was launched in 2010 as an ongoing, prospective UK study of children with JIA who started biologic therapies other than etanercept. Follow-up data are collected at 6 months, 1 year, and annually thereafter. Since September 2015, data have been captured on 3 biosimilars available in the United Kingdom: 2 of infliximab (Inflectra and Remsima) and 1 of etanercept (Benepali). As of May 2017, 26 patients have started a biosimilar:

- 81% Remsima
- 12% Inflectra
- 8% Benepali

Of these, 35% started a biosimilar as their first biologic therapy. Only 1 patient starting Remsima switched directly from the originator product, Remicade; 62% switched from an alternative, non-originator biologic.

Reasons for switching from alternative biologics were related to efficacy (50%), safety (31%), combined efficacy and safety (13%), and needle phobia (6%). No serious adverse events have been reported to date, and all of the children and young people studied are still receiving their biosimilar drugs. ●

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Research Presented (Continued from page 22)

Adult patients with active RA who had an inadequate clinical response to methotrexate were randomized 1:1 to self-administer GP2015 (n = 170) or the reference (n = 156) subcutaneously once weekly for 24 weeks. All patients continued to receive concomitant methotrexate at a stable dose throughout the study and folic acid.

The primary end point was change from baseline in disease activity score in 28 joints based on C-reactive protein (DAS28-CRP) at week 24. In the per-protocol set, GP2015 was equivalent to the reference in least-squares mean change from baseline to week 24 in DAS28-CRP (95% CI within the prespecified equivalence margin of -0.6 to 0.6). At week 24, the ACR 20/50/70 response rates (20%, 50%, or 70% improvement in tender or swollen joint counts and similar improvement in 3 of the other 5 criteria from the ACR) and the mean change from baseline in DAS28-CRP scores were comparable between GP2015 and reference groups.

In the GP2015 versus reference group (safety set), TEAEs occurred in 43.5% and 49.5% of patients, respectively; serious AEs occurred in 0.5% and 3.2% of patients, respectively; and 1 patient died in the reference group. ISRs, as a part of all AEs, were reported in 7.0% of the GP2015 group and 17.9% of the

reference group. Using a very sensitive assay, very low titers of ADAs were transiently detected; however, at week 24 none of the patients had significant levels. ●

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Research Analyzes Safety, Efficacy of Sarilumab in Patients With Rheumatoid Arthritis

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The results of 3 studies presented at the ACR 2017 Annual Meeting demonstrated the efficacy and safety of sarilumab in patients with rheumatoid arthritis (RA).

The first study¹ showed that switching tocilizumab non-responders to sarilumab may be associated with favorable efficacy outcomes. ASCERTAIN was a 24-week, randomized, double-blind, double-dummy, parallel-group, 3-arm, safety study in patients with RA who had inadequate response to or intolerance of tumor necrosis factor (TNF) inhibitors and were receiving background therapy of conventional synthetic disease-modifying antirheumatic drugs (csDMARDs). The post hoc analysis assessed outcomes among patients who completed ASCERTAIN and who switched to sarilumab 200 mg every 2 weeks subcutaneously in an open-label extension study (EXTEND).

Improvements observed in the Disease Activity Score 28 joints C-reactive protein (DAS28-CRP) and clinical disease activity index (CDAI) in ASCERTAIN were maintained after the switch to

“Improvements in remission and LDA were shown with ongoing sarilumab treatment in patients with RA in 2 phase 3 studies.”

open-label sarilumab in EXTEND through week 84. Regardless of initial treatment in ASCERTAIN, the percentage of patients who achieved ACR 20/50/70 response (20%, 50%, or 70% improvement in tender or swollen joint counts and similar improvement in 3 of the other 5 criteria from the American College of Rheumatology), DAS28-CRP and CDAI remission, and low disease activity (LDA) increased after switching to sarilumab 200 mg every 2 weeks in EXTEND. The greatest increase in patients meeting definitions of remission and LDA was observed in patients initially receiving tocilizumab. A substantial proportion of nonresponders who switched from sarilumab 150 mg every 2 weeks to 200 mg every 2 weeks achieved ACR20/50/70 response, DAS28-CRP and CDAI remission, and LDA compared with nonresponders who were maintained on 200 mg every 2 weeks.

Improvements in remission and LDA were shown with ongoing sarilumab treatment in patients with RA in 2 phase 3 studies.

The 52-week MOBILITY² study included patients with inadequate response to methotrexate and the 24-week TARGET study included patients with inadequate response to or intolerance of TNF inhibitors. A post hoc analysis examined the benefit

of sarilumab treatment by analyzing the proportion of patients who achieved treat-to-target goals of remission or LDA by 1 year in MOBILITY and 6 months in TARGET.

Results showed that in both studies, a greater proportion of sarilumab-treated patients achieved remission and LDA versus placebo-treated patients. Efficacy was evident as early as week 4, and the number of patients who achieved remission or LDA increased through week 24 with ongoing sarilumab treatment in both studies. Further increases were observed up until week 52 in MOBILITY.

Lastly, patients with active RA who switched from adalimumab to sarilumab showed improvements in physical function and signs and symptoms of RA in an open-label extension of a phase 3 trial.³

In the MONARCH study, adults intolerant of, inappropriate for, or who experienced inadequate response to methotrexate received subcutaneous sarilumab 200 mg every 2 weeks or adalimumab 40 mg monotherapy for 24 weeks. Sarilumab monotherapy was more effective than adalimumab monotherapy in reducing disease activity and improving physical function in patients with active RA.

The patients in MONARCH who completed the initial double-blind phase then entered the open-label extension, in which all patients received sarilumab monotherapy at a dose of 200 mg every 2 weeks. The results showed that patients who switched from 40 mg of adalimumab monotherapy to open-label 200 mg of sarilumab every 2 weeks monotherapy showed improvements in physical function and in the signs and symptoms of RA, which became proportional to patients who were initially randomized to 200 mg of sarilumab every 2 weeks in MONARCH. ●

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