

AHRQ Healthcare Horizon Scanning System – Potential High-Impact Interventions Report

Priority Area 01: Arthritis and Nontraumatic Joint Disease

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Statement of Funding and Purpose

This report incorporates data collected during implementation of the Agency for Healthcare Research and Quality (AHRQ) Healthcare Horizon Scanning System by ECRI Institute under contract to AHRQ, Rockville, MD (Contract No. HHS290-2010-00006-C). The findings and conclusions in this document are those of the authors, who are responsible for its content, and do not necessarily represent the views of AHRQ. No statement in this report should be construed as an official position of AHRQ or of the U.S. Department of Health and Human Services.

This report's content should not be construed as either endorsements or rejections of specific interventions. As topics are entered into the System, individual topic profiles are developed for technologies and programs that appear to be close to diffusion into practice in the United States. Those reports are sent to various experts with clinical, health systems, health administration, and/or research backgrounds for comment and opinions about potential for impact. The comments and opinions received are then considered and synthesized by ECRI Institute to identify interventions that experts deemed, through the comment process, to have potential for high impact. Please see the methods section for more details about this process. This report is produced twice annually and topics included may change depending on expert comments received on interventions issued for comment during the preceding 6 months.

A representative from AHRQ served as a Contracting Officer's Technical Representative and provided input during the implementation of the horizon scanning system. AHRQ did not directly participate in horizon scanning, assessing the leads for topics, or providing opinions regarding potential impact of interventions.

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Preface

The purpose of the AHRQ Healthcare Horizon Scanning System is to conduct horizon scanning of emerging health care technologies and innovations to better inform patient-centered outcomes research investments at AHRQ through the Effective Health Care Program. The Healthcare Horizon Scanning System provides AHRQ a systematic process to identify and monitor emerging technologies and innovations in health care and to create an inventory of interventions that have the highest potential for impact on clinical care, the health care system, patient outcomes, and costs. It will also be a tool for the public to identify and find information on new health care technologies and interventions. Any investigator or funder of research will be able to use the AHRQ Healthcare Horizon Scanning System to select potential topics for research.

The health care technologies and innovations of interest for horizon scanning are those that have yet to diffuse into or become part of established health care practice. These health care interventions are still in the early stages of development or adoption, except in the case of new applications of already-diffused technologies. Consistent with the definitions of health care interventions provided by the National Academy of Medicine (formerly the Institute of Medicine) and the Federal Coordinating Council for Comparative Effectiveness Research, AHRQ is interested in innovations in drugs and biologics, medical devices, screening and diagnostic tests, procedures, services and programs, and care delivery.

Horizon scanning involves two processes. The first is identifying and monitoring new and evolving health care interventions that are purported to or may hold potential to diagnose, treat, or otherwise manage a particular condition or to improve care delivery for a variety of conditions. The second is analyzing the relevant health care context in which these new and evolving interventions exist to understand their potential impact on clinical care, the health care system, patient outcomes, and costs. It is NOT the goal of the AHRQ Healthcare Horizon Scanning System to make predictions on the future use and costs of any health care technology. Rather, the reports will help to inform and guide the planning and prioritization of research resources.

We welcome comments on this Potential High-Impact Interventions report. Send comments by mail to the Task Order Officer named in this report to: Agency for Healthcare Research and Quality, 540 Gaither Road, Rockville, MD 20850, or by email to: effectivehealthcare@ahrq.hhs.gov.

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Executive Summary

Background

Horizon scanning is an activity undertaken to identify technological and system innovations that could have important impacts or bring about paradigm shifts. In the health care sector, horizon scanning pertains to identification of new (and new uses of existing) pharmaceuticals, medical devices, diagnostic tests and procedures, therapeutic interventions, rehabilitative interventions, behavioral health interventions, and public health and health promotion activities. In early 2010, the Agency for Healthcare Research and Quality (AHRQ) identified the need to establish a national Healthcare Horizon Scanning System to generate information to inform comparative-effectiveness research investments by AHRQ and other interested entities. AHRQ makes those investments in 14 priority areas. For purposes of horizon scanning, AHRQ's interests are broad and encompass drugs, devices, procedures, treatments, screening and diagnostics, therapeutics, surgery, programs, and care delivery innovations that address unmet needs. Thus, we refer to topics identified and tracked in the AHRQ Healthcare Horizon Scanning System generically as "interventions." The AHRQ Healthcare Horizon Scanning System implementation of a systematic horizon scanning protocol (developed between September 1 and November 30, 2010) began on December 1, 2010. The system is intended to identify interventions that purport to address an unmet need and are up to 3 years out on the horizon and then to follow them up to 2 years after initial entry into the health care system. Since that implementation, review of more than 21,000 leads about potential topics has resulted in identification and tracking of about 2,250 topics across the 14 AHRQ priority areas and 1 cross-cutting area; more than 600 topics are being actively tracked in the system.

Methods

As part of the Healthcare Horizon Scanning System activity, a report on interventions deemed as having potential for high impact on some aspect of health care or the health care system (e.g., patient outcomes, utilization, infrastructure, costs) is aggregated twice a year. Topics eligible for inclusion are those interventions expected to be within 0–3 years of potential diffusion (e.g., in phase III trials or for which some preliminary efficacy data in the target population are available) in the United States or that have just begun diffusing and that have completed an expert feedback loop.

The determination of impact is made using a systematic process that involves compiling information on topics and issuing topic drafts to a small group of various experts (selected topic by topic) to gather their opinions and impressions about potential impact. Those impressions are used to determine potential impact. Information is compiled for expert comment on topics at a granular level (i.e., similar drugs in the same class are read separately), and then topics in the same class of a device, drug, or biologic are aggregated for discussion and impact assessment at a class level for this report. The process uses a topic-specific structured form with text boxes for comments and a scoring system (1 minimal to 4 high) for potential impact in seven parameters. Participants are required to respond to all parameters.

The scores and opinions are then synthesized to discern those topics deemed by experts to have potential for high impact in one or more of the parameters. Experts are drawn from an expanding database ECRI Institute maintains of approximately 170 experts nationwide who were invited and agreed to participate. The experts comprise a range of generalists and specialists in the health care sector whose experience reflects clinical practice, clinical research, health care delivery, health business, health technology assessment, or health facility administration perspectives. Each expert uses the structured form to also disclose any potential intellectual or financial conflicts of interest

(COIs). Perspectives of an expert with a COI are balanced by perspectives of experts without COIs. No more than two experts with a possible COI are considered out of a total of the five to eight experts who are sought to provide comment for each topic. Experts are identified in the system by the perspective they bring (e.g., clinical, research, health systems, health business, health administration, health policy).

The topics included in this report had scores *and/or* supporting rationales at or above the overall average for all topics in this priority area that received comments by experts. Of key importance is that topic scores alone are not the sole criterion for inclusion—experts’ rationales are the main drivers for the designation of potentially high impact. We then associated topics that emerged as having potentially high impact with a further subcategorization of “lower,” “moderate,” or “higher” within the high-impact-potential range. As the Healthcare Horizon Scanning System grows in number of topics on which expert opinions are received and as the development status of the interventions changes, the list of topics designated as having potentially high impact is expected to change over time. This report is being generated twice a year.

For additional details on methods, please refer to the full AHRQ Healthcare Horizon Scanning System Protocol and Operations Manual published on AHRQ’s Effective Health Care Web site.

Results

The table below lists the three topics for which (1) preliminary phase III data for drugs were available; (2) information was compiled and sent for expert comment before May 8, 2015, in this priority area; and (3) we received five to seven sets of comments from experts between July 1, 2014, and May 18, 2015. (Fifteen topics in this priority area were being tracked in the system as of May 8, 2015.) Three topics emerged as having potential for high impact on the basis of experts’ comments and their assessment of potential impact. These topics are noted by an asterisk in the table below. The material on interventions in this Executive Summary and report is organized alphabetically by disease state. Readers are encouraged to read the detailed information on the interventions that follows the Executive Summary.

Priority Area 01: Arthritis and Nontraumatic Joint Disease

Topic	High-Impact Potential
1. * Lesinurad for treatment of hyperuricemia and allopurinol-refractory gout	Lower end of the high-impact-potential range
2. * Secukinumab (Cosentyx) for treatment of ankylosing spondylitis	Lower end of the high-impact-potential range
3. * Secukinumab (Cosentyx) for treatment of psoriatic arthritis	Lower end of the high-impact-potential range

Discussion

Arthritis and nontraumatic joint disease is a priority area in which we have identified a moderate number of interventions as meeting criteria for tracking in the Healthcare Horizon Scanning System. Experts deemed three topics as having high-impact potential: An oral drug for treating patients with gout and a monoclonal antibody for treating either ankylosing spondylitis or psoriatic arthritis.

Ankylosing Spondylitis

Ankylosing spondylitis (AS) is a form of chronic inflammatory arthritis affecting the joints in the spine, particularly the sacroiliac joints (intersection of the spine and pelvis), leading to pain and, in more advanced cases, spinal fusion and rigidity. AS occurs in up to about 1% of the general

population, with the highest distribution in people of northern European descent. Men are three times as likely as women to have AS. The disease is thought to be caused by a combination of genetic and environmental factors, most of which remain to be elucidated. Infection or other environmental conditions are thought to trigger AS development. Progressive stiffness in the spine is common, progressing to ankylosis (fusion of some or all spinal joints) after years of disease in many patients. Most patients have mild or moderate disease with intermittent exacerbations and maintain some mobility and independence throughout life. However, up to 70% of patients with severe AS may develop spinal fusion. No cure is available for AS, and treatment focuses on symptom management. Physical therapy is included in any treatment plan to help patients maintain upright posture and spinal mobility, reduce the impact of hip and other joint symptoms, and manage pain and stiffness. Nonsteroidal anti-inflammatory drugs (NSAIDs) are used for first-line therapy to treat AS pain. Additionally, corticosteroids and tumor necrosis factor (TNF)-alpha inhibitors may also be prescribed to reduce inflammation. Surgery could be required in patients with severe pain or joint damage.

Secukinumab (Cosentyx) for Treatment of Ankylosing Spondylitis

- **Key Facts:** AS is an inflammatory form of arthritis that primarily affects the spine and can cause vertebrae to fuse; no cure exists for AS. Treatments focus on reducing inflammation, improving mobility, and decreasing pain; however, available treatment options are not effective for about 40% of patients with AS. Effective treatments are needed. Secukinumab (Cosentyx™) is a monoclonal antibody antagonist targeting interleukin-17A (IL-17A), a cytokine thought to be involved in developing delayed-type hypersensitivity reactions. This effect is reported by investigators to be mediated by increased chemokine production, which promotes the recruitment of inflammatory cells such as monocytes and neutrophils to the local area. By blocking the effects of IL-17A–localized autoimmune reactions, AS pathogenesis could be reduced while minimizing the systemic immunosuppression associated with TNF-inhibitor therapy. Investigators reported top-line data from ongoing phase III clinical trials showing that more patients treated with secukinumab achieved Assessment in Ankylosing Spondylitis 20 (ASAS20) rates than patients given placebo. Patients with AS who did not respond to prior treatment with TNF therapies showed significant improvement in ASAS20 rates, although these rates were significantly lower than in patients who were treatment-naïve. However, patients given secukinumab were more likely to experience adverse events, including serious events, than patients given a placebo.

Five phase III trials on secukinumab for treating AS are ongoing. The company has reported plans to submit global regulatory filings for secukinumab for treating AS and for psoriatic arthritis (PsA) in 2015. In January 2015, secukinumab was approved for treating plaque psoriasis.

Because it has been approved for treating plaque psoriasis, cost of the drug is available. Based on a May 2015 query of a U.S.-based, online aggregator of prescription-drug prices, GoodRx, the retail cost of a single 150 mg pen-injector of secukinumab is about \$3,500, which could be administered once every 4 weeks for treating AS. If approved for treating AS, secukinumab would likely be covered for treating patients with active AS who have had an inadequate response to two or more NSAIDs or patients who have had an inadequate response to TNF inhibitors.

- **Key Expert Comments:** Experts commenting on this intervention stated that a significant unmet need exists for patients with AS who do not respond to treatment with existing therapies. However, the experts thought additional clinical studies are needed to compare the efficacy of

secukinumab to TNF inhibitors as well as to determine long-term efficacy of secukinumab. High treatment costs could limit patient access to secukinumab if third-party payers do not cover the drug.

- High-Impact Potential: Lower end of the high-impact-potential range

Gout

Gout is the most prevalent form of inflammatory arthritis and is associated with impaired health outcomes and worsened quality of life. According to data from the U.S. National Health and Nutrition Examination Survey 2007–2008, about 8.3 million adults have gout. Elevated serum uric acid (sUA) levels are thought to be the most important risk factor for developing gout, which can result in monosodium urate crystals forming and depositing in and around joints, leading to acute flares and inflammation. Uncontrolled gout can lead to accumulation of tophi, leading to chronic pain, joint erosion, and limited mobility. Risk factors for developing gout include obesity, hypertension, alcohol consumption, diuretic use, and a diet rich in fructose, meat, seafood, and vegetable purines. Additionally, patients with chronic hyperuricemia have an increased risk of cardiovascular disease, kidney dysfunction, and metabolic syndrome. Current treatment options for reducing hyperuricemia in patients with gout include the xanthine oxidase inhibitors allopurinol and febuxostat, which decrease uric acid production.

Lesinurad for Treatment of Hyperuricemia and Allopurinol-Refractory Gout

- **Key Facts:** Hyperuricemia is believed to be the most important risk factor for developing gout. About 47% of patients with gout do not achieve target goals for sUA levels (<6 mg/dL) with the standard of care, the xanthine oxidase inhibitors allopurinol and febuxostat. Only about 30% of patients achieve overall gout control, so a significant unmet need exists for more effective treatments. About 90% of patients with gout are thought to have insufficient excretion of uric acid due to genetic defects in renal transporters of uric acid, including the human urate transporter 1 (URAT1), which is involved in uric acid reabsorption. By selectively inhibiting URAT1, lesinurad is thought to promote urinary excretion of uric acid leading to improvements in hyperuricemia. In phase III clinical trials, significantly more patients treated with lesinurad in combination with a xanthine oxidase inhibitor achieved target sUA levels than patients given a xanthine oxidase inhibitor alone. Additionally, with lesinurad monotherapy, more patients with gout and an intolerance or contraindication to xanthine oxidase inhibitors achieved target sUA levels than did those given placebo. Patients given lesinurad as monotherapy were more likely to experience serum creatinine elevations and renal adverse events, including serious events, than patients given a placebo. Other adverse events commonly reported in patients treated with lesinurad monotherapy included constipation, diarrhea, and nausea. When lesinurad was combined with xanthine oxidase inhibitors, commonly reported adverse events were arthralgia, back pain, nasopharyngitis, and upper respiratory tract infection.

Five phase III trials on lesinurad have been completed, and two phase III extension trials are ongoing. The company is preparing U.S. Food and Drug Administration (FDA) regulatory submissions for lesinurad (200 mg) as a once-daily combination therapy for treating gout. Lesinurad for treating gout was approved by the European Medicines Agency in January 2015.

Our searches found no information regarding the expected cost of lesinurad. However, one financial analyst predicted annual sales of lesinurad could reach \$582 million by the year 2020. An estimated 10% of patients with chronic gout could be prescribed lesinurad,

according to an April 2012 survey of rheumatologists in the United States performed by health care consultant Decision Resources Group. If approved for marketing, lesinurad would be covered by third-party payers similar to other uric acid–lowering drugs for treating or preventing gout, although if the drug is more costly than alternatives, prior authorization and a tiered approach would likely be used.

- **Key Expert Comments:** Experts commenting on this intervention stated that a significant unmet need exists for new treatment options to help patients with gout improve the management of their sUA levels. However, this need could be overstated by the manufacturer’s estimates. Many treatment options are available to address acute flares and manage chronic gout. However, few agents are available to address the underlying mechanisms leading to gout, the experts thought. Lesinurad demonstrates potential for reducing sUA levels in combination with xanthine oxidase inhibitors or as monotherapy in patients intolerant to xanthine oxidase inhibitors, the experts thought. However, they warned, lesinurad uptake could be limited by adverse events, such as kidney complications, which will continue to be elucidated in ongoing clinical trials.
- **High-Impact Potential:** Lower end of the high-impact-potential range

Psoriatic Arthritis

Psoriatic arthritis (PsA) is a form of chronic inflammatory arthritis that affects people with the skin condition psoriasis. In about 80% of patients, the skin condition develops before arthritis; its exact cause is unknown. The National Psoriasis Foundation estimates about 7.5 million Americans have psoriasis, of whom 10% to 30% will also develop PsA. Risk factors for developing PsA include having a family history of the disease, being between 30 and 50 years of age, and having psoriasis. About 50% of patients with PsA have the HLA-B27 allele. Stress or immunosuppression are also thought to be contributing factors, allowing expression or exacerbation of PsA symptoms. The main symptoms of PsA are joint pain, stiffness, and swelling that can affect any joint. Symptoms worsen over time, with periods of improvement or remission. Severe PsA will develop in a small proportion of patients, appearing in their hands, feet, and spine, which can lead to deformities and disability. In patients with severe PsA, early treatment is essential to achieve optimal pain relief and to prevent joint destruction.

Secukinumab (Cosentyx) for Treatment of Psoriatic Arthritis

- **Key Facts:** Current treatments for PsA focus on reducing inflammation, improving mobility, and decreasing pain. Some patients’ symptoms do not respond adequately to treatment with NSAIDs, disease-modifying anti-rheumatic drugs (DMARDs) or TNF inhibitors; suggesting other treatment options are needed. Secukinumab (Cosentyx™) is a monoclonal antibody antagonist for interleukin-17 (IL-17A). IL-17A is a cytokine believed to be involved in developing delayed-type hypersensitivity reactions by increasing chemokine production, which promotes the recruitment of inflammatory cells such as monocytes and neutrophils to the local area. By blocking the effects of IL-17A–localized autoimmune reactions, PsA symptoms may be limited while minimizing the systemic immunosuppression associated with TNF blockers. In phase III trials, patients treated with secukinumab had a significant improvement in American College of Rheumatology criteria for 20% improvement (ACR20) responses versus patients treated with placebo. This improvement was observed in both TNF-naïve and TNF-refractory populations. However, patients given secukinumab were more likely to experience adverse events, including serious adverse events, than patients given a placebo. The most common adverse events

reported in patients with PsA taking secukinumab were headache and upper respiratory tract infection.

Four phase III trials on secukinumab for treating PsA are ongoing. FDA approved it in January 2015 for treating plaque psoriasis; global regulatory filings for secukinumab treating PsA are expected in 2015.

Because secukinumab is approved for treating plaque psoriasis, its cost is available for that indication. Based on a May 2015 query of GoodRx, the retail cost of a single 150 mg pen-injector of secukinumab is about \$3,500, which could be administered once every 4 weeks for treating PsA. If approved for treating PsA, secukinumab would likely be covered by third-party payers similar with prior authorization requirements, which may include patients with PsA who have had an inadequate response to methotrexate, or another nonbiologic DMARDs.

- **Key Expert Comments:** Overall, experts commenting on secukinumab stated that the drug could potentially fill an unmet need for patients with PsA whose disease does not respond to available therapies. However, the experts thought that more clinical studies are needed to determine the long-term efficacy of secukinumab, as well as to compare its efficacy to that of existing therapies such as TNF inhibitors. High cost could be prohibitive and limit patient access to drug if third-party payers do not cover the majority of treatment costs. However, these costs may be offset by decreased use of other health care resources.
- **High-Impact Potential:** Lower end of the high-impact-potential range

Ankylosing Spondylitis Intervention

Secukinumab (Cosentyx) for Treatment of Ankylosing Spondylitis

Unmet need: Ankylosing spondylitis (AS) is a form of autoimmune arthritis that primarily affects the spine and can cause vertebrae to fuse. Up to about 1% of the general population is affected by AS, with a higher distribution in people of European descent.¹ No cure exists for AS. Up to 70% of patients with severe AS can develop spinal fusion, and up to 40% of patients do not respond to the treatment options of nonsteroidal anti-inflammatory drugs (NSAIDs), disease-modifying anti-rheumatic drugs (DMARDs), or tumor necrosis factor (TNF) inhibitors, representing a substantial unmet need for additional therapeutic options for patients with AS.²

Intervention: Secukinumab (Cosentyx™) is a fully human monoclonal antibody antagonist for interleukin-17 (IL-17A). IL-17A is a cytokine believed to be involved in developing delayed-type hypersensitivity reactions. These effects are thought to be mediated by increased chemokine production, which promotes the recruitment of inflammatory cells such as monocytes and neutrophils to the local area. By blocking the effects of IL-17A–localized autoimmune reactions, AS pathogenesis could be purportedly reduced while minimizing the systemic immunosuppression associated with TNF blockers, which are the only biologic agents used for reducing inflammation in patients with AS.² In phase III trials, secukinumab was administered as three loading doses of an intravenous (IV) infusion 10 mg/kg at baseline, 2 weeks, and 4 weeks, followed by one subcutaneous (SC) injection (75 mg) every 4 weeks;³ or secukinumab was administered as three weekly loading doses (75 mg) administered subcutaneously at weeks 1, 2, 3, and 4 followed by a dose every 4 weeks.⁴

Clinical trials: Preliminary data are available for two ongoing clinical trials evaluating secukinumab in patients with active AS. In the phase III MEASURE 1 trial, patients (n=371) with active AS who were intolerant of or did not respond to NSAIDs, DMARDs, or TNF inhibitors, were treated with secukinumab. The drug was administered in three loading doses as an IV infusion, 10 mg/kg, at baseline, 2 weeks, and 4 weeks, followed by one SC injection (75 or 150 mg) every 4 weeks. Patients receiving secukinumab 75 mg SC and 150 mg SC had significantly higher Assessment in Ankylosing Spondylitis 20 (ASAS20) response rates (59.7% and 60.8%, respectively) versus placebo (28.7%; p<0.01) at 16 weeks. Patients who had never received treatment with TNF inhibitors had ASAS20 response rates of 60.0%, 66.3%, and 32.6%, and patients whose symptoms did not respond to previous TNF treatment had ASAS20 responses of 58.8%, 45.5%, and 18.2%, when treated with 75 mg SC, 150 mg SC, or placebo, respectively (p<0.01 versus placebo). At week 16, 66.9% of patients in 75 mg SC group and 69.6% in the 150 mg SC group experienced an adverse event, versus 55.7% given placebo; serious adverse event rates were 1.6%, 2.4% and 4.1%, respectively.⁵

In the phase III MEASURE 2 trial, patients (n=219) with active AS who were intolerant to or did not respond to NSAIDs, DMARDs, or TNF inhibitors were given secukinumab administered as one SC loading dose of 75 or 150 mg once weekly for 4 weeks, followed by one SC injection every 4 weeks. Patients given secukinumab 150 mg had significantly higher ASAS20 response rates than patients given placebo (61.1% vs. 27.0%; p<0.01) at week 16. Higher ASAS20 rates were reported for secukinumab 150 mg versus placebo in patients who had never received TNFs or patients who did not respond to previous TNF therapy (68.9% vs. 31.1% and 48.1% versus 20.7%, respectively; both p<0.05). Improved ASAS40 rates were also reported (44.4% vs. 17.8% and 22.2% vs. 0%, respectively; both p<0.05) at 16 weeks. At 16 weeks, patients who received secukinumab 75 mg did not have significant improvements in ASAS20 or ASAS40 responses compared with patients who received placebo. Similar adverse event rates were reported for secukinumab 75 mg (57.5%), 150

mg (62.5%), and placebo (63.5%) groups up to week 16. Serious adverse events were reported in 5.5% of the secukinumab 75 mg group, 5.6% of the 150 mg group, and 4.1% of the placebo group.⁶

Manufacturer and regulatory status: Novartis International AG (Basel, Switzerland) is developing secukinumab for treating active AS in patients who are intolerant to or have had an inadequate response to NSAIDs, DMARDs, or TNF inhibitor therapy.⁷ The company has announced plans for regulatory submissions for an AS indication in 2015.^{2,8}

In January 2015, the U.S. Food and Drug Administration (FDA) approved secukinumab for treating adults with moderate-to-severe plaque psoriasis, and the company has also announced plans for regulatory submissions for a psoriatic arthritis (PsA) indication in 2015.⁸

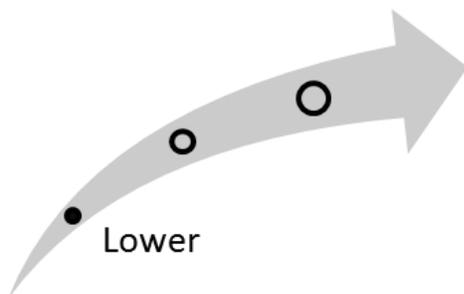
Diffusion and cost: According to GoodRx, the retail cost of a single carton (1 preloaded pen-injector) of secukinumab 150 mg/mL is about \$3,500, which would be administered once every 4 weeks for treating AS.⁹

Because secukinumab is not yet approved by FDA for treating AS, no specific coverage, coding, or payment information is available. However, third-party payers would likely consider coverage in appropriate patients. For example, one third-party payer, Aetna, covers the TNF inhibitor adalimumab (Humira[®]) for treating AS in patients who have an inadequate response to two or more NSAIDs.¹⁰ Payers are likely to cover secukinumab for treating active AS in patients who have had an inadequate response to two or more NSAIDs or patients who have had an inadequate response to TNF inhibitors.

Clinical Pathway at Point of This Intervention

AS treatment focuses on physical therapy and exercise to preserve range of motion and manage pain and stiffness, combined with NSAIDs to reduce inflammation and slow disease progression.¹¹ Some patients may also be prescribed the immunosuppressive therapies sulfasalazine or methotrexate to suppress long-term inflammation in joints other than the spine. Corticosteroids may be used intermittently to control inflammation. Patients whose symptoms do not respond to conservative therapy or have a higher level of spinal inflammation may be prescribed a TNF inhibitor to decrease inflammation and improve spinal mobility.¹¹ Secukinumab could be used in place of a TNF inhibitor or in patients whose condition does not respond to therapy with a TNF inhibitor.

Figure 1. Secukinumab (Cosentyx) for treatment of ankylosing spondylitis



Experts commenting on this intervention stated that a significant unmet need exists for patients with AS whose disease does not respond to existing therapies. However, the experts thought that long-term efficacy data are needed to determine secukinumab's true treatment value. The experts also called for randomized controlled trials to compare secukinumab and existing therapies, such as TNF inhibitors. They thought high treatment costs would limit patient access to secukinumab if

third-party payers do not cover the drug, of it is covered as a step-therapy. Based on this input, our overall assessment is that this intervention is in the lower end of the high-impact-potential range.

Results and Discussion of Comments

Six experts, with clinical, research, and health systems backgrounds, offered perspectives on this intervention.¹²⁻¹⁷ We have organized the following discussion of expert comments according to the parameters on which they commented.

Unmet need and health outcomes: An unmet need exists for patients with treatment-refractory AS, stated the experts. Basing their opinions on the available data, the experts generally thought that secukinumab could address this unmet need. However, some experts were concerned about the adverse event rates reported.^{12,15} Some experts also noted that additional clinical studies are needed to directly compare secukinumab to other agents, such as TNF inhibitors, as well as long-term functional outcomes.^{12,14,15}

Acceptance and adoption: Clinicians are likely to accept secukinumab as a new treatment option for AS, the experts opined. Patients with refractory AS are also likely to accept a new treatment option; one research expert noted that patients may even accept long-term adverse events to avoid AS disease progression.¹⁴

Health care delivery infrastructure and patient management: As a self-injectable medication, secukinumab is not expected to cause a significant shift in health care delivery infrastructure or patient management. The experts commented that the estimated costs for the drug were substantial; however, better AS management could reduce the need for clinician visits and physical therapy. Reduced hospitalizations, surgical procedures, rehabilitation, and reduced use of orthotics could also provide cost offsets from secukinumab treatment.¹⁶

Health disparities: Experts offered mixed comments on the impact of secukinumab on health disparities. Secukinumab could be more expensive than existing options, which may render the drug inaccessible to some patients with AS, some experts thought. Additionally, two research experts noted that the initial use of secukinumab as an IV infusion would require regular clinical visits, which could limit some patients' access to care.^{13,14} However, some experts thought that third-party payers would cover the drug, which would not affect health disparities unless patients have high co-pays or inadequate insurance coverage.^{15,16}

Gout Intervention

Lesinurad for Treatment of Hyperuricemia and Allopurinol-Refractory Gout

Unmet need: Hyperuricemia is thought to be the most important risk factor for developing gout.¹⁸ About 47% of patients with gout do not achieve target goals for serum uric acid (sUA) levels (<6 mg/dL) with the standard of care, the xanthine oxidase inhibitors allopurinol and febuxostat. About 90% of patients with gout are said to have insufficient excretion of uric acid, which could be due to genetic defects in renal transporters of uric acid.¹⁹ About 70% of uric acid excretion occurs in the kidney.¹⁸ Human urate transporter 1 (URAT1) is an organic anion transporter involved in controlling the reabsorption of uric acid from the proximal renal tubules. Also, only about 30% of patients achieve overall gout control, suggesting an unmet need exists for additional options for gout control.²⁰

Intervention: Lesinurad is a selective inhibitor of URAT1 intended to promote urinary excretion of uric acid leading to improvements in hyperuricemia.²¹ Because lesinurad purportedly improves sUA excretion, it is thought to complement use of xanthine oxidase inhibitors, which decrease uric acid production.¹⁹ In phase III trials, lesinurad was administered 200 or 400 mg, once daily, orally, in combination with allopurinol or febuxostat,^{22,23} or 400 mg, once daily, as monotherapy in patients with an intolerance or contraindication to xanthine oxidase inhibitors.²⁴

Clinical trials: Four phase III trials have been completed that evaluated lesinurad in combination with allopurinol or febuxostat or as monotherapy in patients unable to tolerate xanthine oxidase inhibitors.

In two replicate phase III trials, CLEAR 1 (n=603) and CLEAR 2 (n=610), patients received lesinurad 200 mg or 400 mg or placebo daily in combination with allopurinol. Patients had sUA levels of 6.5 mg/dL or higher at screening, were on stable allopurinol doses (≥ 300 mg or ≥ 200 mg in patients with moderate renal impairment), and had a history of at least 2 gout flares in the prior 12 months. In the CLEAR1 trial, patients were given lesinurad 200 mg or 400 mg, and 54% and 59%, respectively, achieved the sUA target of less than 6.0 mg/dL by month 6, compared with 28% of patients treated with allopurinol and placebo ($p < 0.0001$).²² In the CLEAR 2 trial, patients were also treated with lesinurad 200 mg or 400 mg, and 55% and 67%, respectively, achieved the sUA target by month 6, compared with 23% of patients treated with allopurinol and placebo ($p < 0.0001$).²² Combination therapy in both trials did not significantly reduce the reported number of gout flares or number of patients with complete tophus resolution.²⁵

In the phase III, randomized, double-blind CRYSTAL trial (n=324), patients with gout, sUA levels of 6.0 mg/dL or more, and at least one measurable tophus received lesinurad 200 mg or 400 mg in combination with oral febuxostat (80 mg) or febuxostat with placebo. Data reported by the manufacturer showed that more patients treated with lesinurad and febuxostat achieved the target sUA-level goal of less than 5.0 mg/dL at month 6 than did patients treated with febuxostat alone ($p < 0.0001$). Patients treated with lesinurad 200 mg and febuxostat did not achieve a statistical improvement at month 6 ($p = 0.13$).²³

In the phase III, randomized, double-blind LIGHT trial (n=214), patients with gout, sUA levels of 6.5 mg/dL or higher, and an intolerance or contraindication to a xanthine oxidase inhibitor were given lesinurad 400 mg or placebo, once daily. Data from the manufacturer showed a significantly higher proportion of patients receiving lesinurad achieved the sUA-level goal of less than 6.0 mg/dL at 6 months than did patients given a placebo.²⁴ Use of lesinurad alone resulted in more patients experiencing elevated serum creatinine levels and renal adverse events, including serious events, than patients given placebo. Other adverse events commonly reported in the lesinurad monotherapy group included constipation, diarrhea, and nausea.²⁴ Some preliminary evidence suggests lesinurad

could increase the risk of renal complications.²⁶ The most common adverse events reported in the CLEAR1 and CLEAR2 studies were back pain, nasopharyngitis, and upper respiratory tract infection.²³ The most common adverse events reported in the CRYSTAL trial were arthralgia, nasopharyngitis, and upper respiratory tract infection.²³

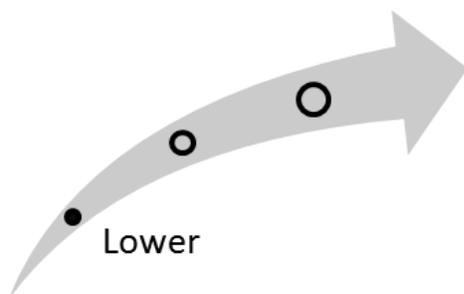
Manufacturer and regulatory status: The Ardea Biosciences subsidiary of AstraZeneca (London, UK), makes lesinurad. It could be used in combination with xanthine oxidase inhibitors to treat hyperuricemia. Lesinurad could also be used as monotherapy in patients with gout who are intolerant of or who have contraindications for xanthine oxidase inhibitors.²⁷ The company is preparing regulatory submissions for lesinurad (200 mg) as a once-daily, chronic, combination therapy for treating gout.²⁵

Diffusion and cost: Our searches found no information about the expected cost of lesinurad, should it be approved. However, according to one financial analyst, annual sales of lesinurad could reach \$582 million in the year 2020.²⁵ About 10% of patients with chronic gout could be prescribed lesinurad, according to an April 2012 survey of U.S. rheumatologists conducted by health care consultant Decision Resources Group.²⁸ If approved for marketing, lesinurad will probably be covered by third-party payers similarly to other uric acid-lowering drugs for treating or preventing gout, although if the drug is more costly than alternatives, prior authorization and a tiered approach could be used.

Clinical Pathway at Point of This Intervention

Patients with gout are treated with a goal of ending the pain of acute flares, preventing future attacks, and preventing formation of tophi and kidney stones. Therapy for acute flares consists of NSAIDs, steroids, and colchicine. Diet and lifestyle modifications (e.g., reducing alcohol and dietary purine intake as well as weight loss) may help prevent future attacks. Preventive therapy with the xanthine oxidase inhibitors allopurinol or febuxostat to lower blood sUA levels is also used in patients with recurrent acute flares or chronic gout.²⁹ Lesinurad could be used in combination with xanthine oxidase inhibitors for patients in whom sUA levels are inadequately reduced despite therapy or as monotherapy for patients who cannot tolerate or have contraindications to xanthine oxidase inhibitors.²²⁻²⁴

Figure 2. Lesinurad for treatment of hyperuricemia and allopurinol-refractory gout



Experts commenting on this intervention stated that a significant unmet need exists for new treatment options to help patients with gout improve their sUA levels, even though many treatment options are available to address acute flares and manage chronic gout. Still, few agents are available to address the underlying mechanisms leading to gout, the experts thought. Lesinurad demonstrated potential for reducing sUA levels in combination with xanthine oxidase inhibitors or as monotherapy in patients intolerant to xanthine oxidase inhibitors. The experts noted that lesinurad uptake could be limited by adverse events such as kidney complications, which ongoing clinical

trials are intended to provide additional data on. Based on this input, our overall assessment is that this intervention is in the lower end of the high-impact-potential range.

Results and Discussion of Comments

Six experts, with clinical, research, health systems, and health administration backgrounds, offered perspectives on this intervention.³⁰⁻³⁵ We have organized the following discussion of expert comments according to the parameters on which they commented.

Unmet need and health outcomes: A moderate unmet need exists for treatments to enable patients with gout to reach sUA level goals, stated the experts. However, one clinical expert noted the unmet need was overstated by the manufacturer, citing 72% of patients in febuxostat clinical trials and 45% of patients on allopurinol achieved desired sUA levels, making the addressable population 28% to 55%.³⁴ Based on the available data, experts generally thought that lesinurad could address the unmet need by significantly lowering sUA levels when used in combination with febuxostat or allopurinol or as monotherapy.

Acceptance and adoption: Clinicians are likely to accept lesinurad as a new option to help patients with gout lower their sUA levels, the experts opined. However, one clinical expert and a health systems expert stated that similarities between lesinurad and marketed drugs such as probenecid could reduce lesinurad adoption.^{34,35} Patients would likely accept a new treatment option that could help them reduce their sUA levels if the drug is effective and tolerable and cost to the patient is similar to other agents, the experts thought.

Health care delivery infrastructure and patient management: As an oral medication, lesinurad is not expected to cause a significant shift in health care delivery infrastructure or patient management. However, better gout management could reduce hospitalizations and renal or cardiovascular complications from acute gout flares, reducing demands on the system. Reduced hospitalizations could also provide cost offsets from treatment with lesinurad.³⁵ One research expert noted concerns over renal adverse events, which could require additional adverse-event monitoring while patients are taking lesinurad.³¹

Health disparities: Experts offered mixed comments on the effect of lesinurad on health disparities. Some experts thought that as a new drug, lesinurad could be more expensive than existing options, and patients who have trouble affording existing gout treatments would have trouble paying for lesinurad, or payers may not cover a newer, more expensive drug, adding to disparities.^{31,32,34,35} However, some experts think third-party payers will cover the drug, which would not exacerbate disparities.^{33,35} Additionally one expert stated that because a higher incidence of gout is observed in black males, lesinurad could reduce racial health disparities if it provided a more effective treatment option.³⁰

Psoriatic Arthritis Intervention

Secukinumab (Cosentyx) for Treatment of Psoriatic Arthritis

Unmet need: In a subset of patients with psoriatic arthritis (PsA), the disease can progress to severe and painful symptoms that, without effective treatment, can lead to deformity and disability of the hands and fingers. Some patients' symptoms do not respond adequately to NSAIDs, disease-modifying anti-rheumatic drugs (DMARDs) or tumor necrosis factor (TNF) inhibitors; thus, additional treatments options are needed to manage PsA in these patients. In a small proportion of patients, severe disease develops in their hands, feet, and spine, which can lead to deformities and disability.

Intervention: Secukinumab (Cosentyx™) is a fully human monoclonal antibody antagonist for interleukin-17 (IL-17A). IL-17 is a cytokine purportedly involved in developing delayed-type hypersensitivity reactions. These effects are thought by investigators to be mediated by increased chemokine production, which promotes the recruitment of inflammatory cells such as monocytes and neutrophils to the local area. By instead blocking the effects of IL-17–localized autoimmune reactions, PsA pathogenesis could be limited while minimizing the systemic immunosuppression associated with TNF blockers, a class of biologic agents that are part of standard of care for PsA.² In phase III clinical trials, secukinumab was administered by SC injection 75, 150, or 300 mg, once every 4 weeks,³⁶ or as three loading doses by IV infusion 10 mg/kg, at baseline, 2 weeks, and 4 weeks, followed by one SC injection 75 mg, every 4 weeks.³⁷

Clinical trials: Data are available for a completed phase III trial (FUTURE 1) and an ongoing phase III clinical trial (FUTURE 2) evaluating secukinumab in patients who have PsA.

In the phase III FUTURE 1 trial, patients (n=606) with active, moderate-to-severe PsA, including those who were intolerant to or did not respond to TNF inhibitors, were given secukinumab as an IV infusion 10 mg/kg, in three loading doses, at baseline, 2 weeks, and 4 weeks, followed by one SC injection (75 or 150 mg) every 4 weeks. Patients receiving secukinumab 75 mg and 150 mg SC had significantly higher American College of Rheumatology criteria for 20% improvement (ACR20) response rates (50.5% and 50.0%, respectively) versus placebo (17.3%; $p < 0.0001$) at 24 weeks. Using an observed analysis, patients treated with secukinumab 75 mg had ACR 20/50/70 responses of 66.9%, 38.4% and 25.6%, respectively; and patients treated with secukinumab 150 mg SC has response rates of 69.5%, 50.0% and 28.2%, respectively, at 52 weeks. Secukinumab demonstrated superiority to placebo in ACR20/50/70 in patients naïve to TNF-inhibitors or patients whose symptoms did not respond to previous TNF-inhibitor therapy at week 24 and the effect was maintained through week 52. Adverse events/nonfatal serious adverse events rates were 78.1%/8.6% and 82.4%/12.9% in patients who received secukinumab 75 mg or 150 mg, respectively, at any point in the study.³⁷

In the phase III FUTURE 2 trial, patients (n=397) with active PsA, including those who were intolerant to or did not respond to TNF inhibitors, were given secukinumab as one SC loading dose of 75, 150, or 300 mg at baseline, then once weekly for 4 weeks, followed by one SC injection every 4 weeks.

Patients receiving secukinumab 75, 150, or 300 mg SC had significantly higher ACR20 response rates (29.3%, 51.0%, and 54.0%, respectively) than did patients treated with placebo (15.3%; $p < 0.05$ for 75 mg; $p < 0.0001$ for 150 and 300 mg) at 24 weeks. Efficacy was observed with secukinumab 150 mg and 300 mg irrespective of prior TNF inhibitor treatment. Patients treated with secukinumab or placebo reported similar rates of overall adverse events: 53.8% of patients in the pooled secukinumab group and 58.2% of patients in the placebo group reported an adverse event. Serious adverse events were reported in 3.3% and 2.0% of patients, respectively, up to week 16.³⁶

Manufacturer and regulatory status: Novartis International AG (Basel, Switzerland) is developing secukinumab for treating patients with active PsA who are intolerant to or have had an inadequate response to NSAIDs, DMARDs, or TNF inhibitor therapy.⁷ The company plans regulatory submissions for a PsA indication in 2015. The company has also announced plans for regulatory submissions for an ankylosing spondylitis (AS) indication in 2015.⁸

In January 2015, FDA approved secukinumab for treating adults with moderate-to-severe plaque psoriasis.⁸

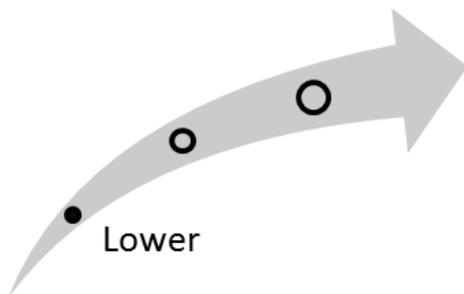
Diffusion and cost: According to a U.S.-based, online aggregator of prescription-drug prices, GoodRx, the retail cost of a single carton (1 preloaded pen-injector) of secukinumab 150mg/ml is about \$3,500, which could be administered once every 4 weeks for treating PsA.⁹

Because secukinumab is not yet approved for treating PsA, no specific coverage, coding, or payment information is available for this indication; however, the drug would likely be available for coverage under Medicare Part B benefits once approved. Private third-party payers would likely consider coverage in appropriate patients. For example, one third-party payer, Aetna, covers TNF inhibitors apremilast (Otezla[®]) and ustekinumab (Stelara[®]) for treating patients with active nonaxial psoriatic arthritis who have had an inadequate response to methotrexate, or if methotrexate is contraindicated or not tolerated, or who have had an inadequate response to another nonbiologic DMARD. Aetna also considers these treatments medically necessary for patients with active axial psoriatic arthritis whose symptoms have not responded adequately to two or more NSAIDs. However, the use of two or more biological therapies in combination for treating psoriatic arthritis is considered investigational. Additionally the payer covers secukinumab for adults with moderate-to-severe chronic plaque psoriasis who meet specified treatment criteria.³⁸

Clinical Pathway at Point of This Intervention

No cure is available for PsA; treatment focuses on controlling symptoms. Treatment typically consists of NSAIDs, DMARDs, immunosuppressant medications, and, commonly, TNF inhibitors.³⁹ Up to 45% of patients with PsA do not respond to their current treatments.⁴⁰ Secukinumab could be used in place of a TNF inhibitor or in patients whose condition does not respond to therapy with a TNF inhibitor.

Figure 3. Secukinumab (Cosentyx) for treatment of psoriatic arthritis



Overall, experts commenting on secukinumab stated that the drug could potentially fill an unmet need for patients with PsA who do not respond to available therapies. However, the experts thought that longer term efficacy data are needed, as well as direct comparisons to existing therapies such as TNF inhibitors. The drug's high cost could limit patient access if third-party payers do not cover the majority of treatment costs. However, these costs may be offset by decreased use of other health care resources. Based on this input, our overall assessment is that this intervention is in the lower end of the high-impact-potential range.

Results and Discussion of Comments

Six experts, with clinical, research, and health systems backgrounds, offered perspectives on this intervention.⁴¹⁻⁴⁶ We have organized the following discussion of expert comments according to the parameters on which they commented.

Unmet need and health outcomes: An unmet need exists for patients with PsA whose disease is refractory to existing therapies, stated the experts. Based on the available data, experts generally thought that secukinumab could address this unmet need. However, some experts thought that more clinical data directly comparing secukinumab to competing TNF inhibitors are needed.⁴²⁻⁴⁴

Acceptance and adoption: Clinicians are likely to accept secukinumab as a new option to help patients with PsA manage their disease, the experts opined. The experts thought that patients with PsA would accept this option, especially those whose disease has not responded to other therapies.^{43,45} Patients are also likely to accept secukinumab because of the simple self-administration of the drug.^{42,44}

Health care delivery infrastructure and patient management: As a self-injected medication, secukinumab is not expected to significantly shift health care delivery, or change infrastructure or patient management. The experts commented that the estimated costs were substantial, especially if secukinumab is effective in patients who do not respond to other treatments. However, one clinician noted that better PsA management could reduce the need for clinician visits, other prescriptions, inpatient stays in rehabilitation facilities, and use of orthotics, offsetting the direct cost of secukinumab.⁴⁴

Health disparities: Experts offered mixed comments on the impact of secukinumab on health disparities. One clinical expert noted that he had been analyzing Medicare data on patients with psoriasis and indicated that the data suggest that African Americans with PsA may be less likely to use a biologic drug than Caucasians; however, no reason was provided for this observation.⁴¹ Otherwise, experts thought that treatment with secukinumab would not exacerbate health disparities unless patients have high out-of-pocket costs and/or inadequate insurance coverage.^{44,45}

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