BUILDING ON SUCCESS: Psoriatic Arthritis Update

NOVARTIS

IL17 Blockers Provide New Option for PsA, AS

For patients with psoriatic arthritis (PsA) or ankylosing spondylitis (AS) who fail to respond or who respond inadequately to biologic drugs that block tumor necrosis factor alpha (TNFa), secukinumab is the first of a new class of drugs that block interleukin (IL)17. This mechanism of action provides new hope for patients with these disabling chronic diseases.

Building on the Success of Secukinumab

Data from long-term extensions of the original U.S. Food and Drug Administration (FDA) Phase 3 trials led to the approval of secukinumab for PsA and AS in early 2016, says Xenofon Baraliakos, M.D. He is a senior consultant at Rheumazentrum Ruhrgebiet Herne and associate professor of internal medicine and rheumatology at the Ruhr-University Bochum in Germany.

"All these studies support treatment with secukinumab in these indications," says Dr. Baraliakos. "Another very important point is that the outcomes we have found were not different from what we have known in patients treated with TNFa blockers. This means that secukinumab appears to be a new mode of action which is equally effective [as TNFa inhibitors] in PsA and AS," he explains. Secukinumab also earned FDA approval for adults with moderate-to-severe plaque psoriasis in January 2015 and European approval for AS and PsA in November 2015.

Unlike rheumatoid arthritis (RA), which has benefited from the advent of several effective new therapies, says Kenneth Saag, M.D., PsA and AS have seen relatively few therapeutic advances in recent years, except for off-label use of some newer psoriasis treatments. Dr. Saag is a rheumatologist and professor of medicine at the University of Alabama at Birmingham.

For both PsA and AS, says Dr. Saag, "The advent of biologic drugs has revolutionized our treatment—starting with the use of anti-TNF therapies. In the case of both diseases, newer biologics, including anti-IL17 agents, have added tremendously to our ability to effectively

improve symptoms and ultimately reduce the disability and destruction that can occur in people who have been inadequately treated with conventional disease—modifying anti-rheumatic drugs [DMARDs] such as methotrexate and, in the case of ankylosing spondylitis, sulfasalazine."

In most inflammatory diseases, notes Dr. Saag, more than 20% of patients do not respond effectively to anti-TNF agents or to more traditional initial treatments such as DMARDs. "In the case of AS, where assessing disease activity is particularly challenging, the proportion may be greater. Secukinumab is a new mechanistic approach to treating psoriatic arthritis and ankylosing spondylitis. There is now a non-anti-TNF therapy that can address the patient who is not responding well to an anti-TNF therapy, or provide an alternative to that approach."

Secukinumab is also the first FDA-approved fully human IL17 inhibitor to demonstrate sustained improvements in PsA signs and symptoms, including patient-reported pain, through 3 years.

Secukinumab selectively binds to and neutralizes IL17A, inhibiting its interaction with IL17 receptors on keratinocytes, fibroblast-like synoviocytes, endothelial cells, chondrocytes, and osteoblasts.[1] Consequently, the drug inhibits downstream inflammatory pathways involved in autoimmune and inflammatory diseases while leaving other immune functions intact.

Addressing Inflammation

While RA seems to be driven by TNFa and IL6, says Gregg J. Silverman, M.D., PsA and perhaps AS are driven by IL17 and IL23. "We believe that this is a distortion of normal immune defenses, where T cells become abnormally activated and secrete these inflammatory cytokines," he explains. Dr. Silverman is a rheumatologist and professor of medicine at New York University in New York City.

Rather than causing cellular infiltrates in the joint linings, as RA does, says Dr. Silverman, inflammatory infiltrates in patients with AS tend to appear where tendons and ligaments insert into bones (entheses). Inflammatory T cells there have receptors for IL23, which is part of the pathogenesis of AS.[2]

"Inflammation at these sites can cause diseases such as plantar fasciitis and Reiter's syndrome," adds Dr. Silverman. "Inflammation can also spur a proinflammatory cascade that results in spondyloarthropathies, including PsA and AS. These researchers further found that this particular kind of T cell normally arises during development of the aortic valve in human beings. That may be why aortic disease also occurs commonly in people with AS and related syndromes. We never understood previously how the syndromes were connected."

Additional pathogenic factors include genetics and the immune system. "In the past," says Dr. Silverman, "people have investigated the role of immunity and inheritance in developing PsA and AS. They are related, although not everyone inherits them, in Caucasian populations." These syndromes occur more commonly in people who have inherited human leukocyte antigen (HLA)-B27, an element of the immune system that is supposed to help it recognize bacteria and viruses, he explains. When researchers genetically engineered mice with this antigen, he says, "the rats got arthritis, psoriasis, and even intestinal disease that was very similar to the kinds of problems that people with AS and PsA develop."[3] When researchers rendered the same genetically modified rats completely free of intestinal bacteria, he adds, they did not develop these conditions.

"HLA-B27 can also determine which bacteria predominate in the gut,"[4] notes Dr. Silverman. "Therefore, we believe that the bacteria that colonize our intestines contribute in some way to the development of these diseases. It may be that in the future, not only will we treat the inflammation, but hopefully, we will also identify the bad bacteria out of the thousand or more that we normally have in our intestines. Perhaps we can adjust them through use of probiotics or other approaches."

Additionally, says Dr. Silverman, several antibodies to IL17 and related IL23 are in development. "It's remarkable that IL17 blockade with the monoclonal antibody appears to have little or no efficacy in rheumatoid arthritis. Yet it can be absolutely miraculous in the treatment of the psoriasis that also occurs in people with PsA." This is another reason that experts have come to believe that PsA and AS are very distinct diseases from RA, he explains. Further, the appearance of psoriasis can alert physicians to the possibility that a patient will be among the 30% overall with psoriasis who eventually develop PsA, he notes. Early detection and treatment are crucial, he says, because this disease can be very deforming and disabling. While secukinumab is still relatively new, says Dr. Saag, who specializes largely in gout and osteoporosis, "Many rheumatologists are now beginning to explore its use in patients with diseases like psoriatic arthritis and ankylosing spondylitis. Most rheumatologists have had preliminary experience with prescribing the drug. I have already had a chance to use this drug in some patients with these diseases."

Cosentyx is the first approved psoriasis medication to selectively bind to IL-17A and inhibit interaction with the IL-17 receptor.[5,6] The approval is based on the efficacy and safety outcomes from 10

1. Miossec P, Kolls JK. Targeting IL-17 and TH17 cells in chronic inflammation. *Nat Rev Drug Discovery.* 2012;11:763-776.
2. Sherlock JP, Joyce-Shaikh B, Turner SP, et al. IL-23 induces spondyloarthropathy by acting on ROR-γt+ CD3+CD4-CD8- entheseal resident T cells. *Nat Med.* 2012;18(7):1069-1076.
3. Taurog JD, Richardson JA, Croft JT, et al. The germfree state prevents development of gut and joint inflammatory disease in HLA-B27 transgenic rats. *J Exp Med.* 1994;180(6):2359-2364.
4. Lin P, Bach M, Asquith M, et al. HLA-B27 and human β2-microglobulin affect the gut microbiota of transgenic rats. *PLOS One.* 2014;9(8):e105684.

Phase II and Phase III studies, including over 3,990 adult patients with moderate-to-severe plaque psoriasis, which demonstrated that Cosentyx resulted in clear or almost clear skin in the majority of patients and had an acceptable safety profile.[7]

Secukinumab is the only IL17A antagonist FDA-indicated for psoriasis, PsA, and AS. In FDA Phase 3 clinical trials, it achieved the following results:

- In PsA, 67% of patients treated with secukinumab 150 mg achieved a 20% reduction in American College of Rheumatology symptom scores (ACR20) after 2 years of treatment.[8] Also at this point, 84% of patients showed no radiographic progression. And 64% of patients sustained improvements seen with the 150 mg and 300 mg doses over one year of treatment.[9] Secukinumab is also the first FDA-approved fully human IL17 inhibitor to demonstrate sustained improvements in PsA signs and symptoms, including patient-reported pain, through 3 years.[10] Response rates were consistent from the first year of follow-up (69.4% achieving ACR20) through the third year (76.8%), whether or not patients had previously received an anti-TNF therapy, as many patients with PsA have.

- In AS, Assessment of SpondyloArthritis international Society (ASAS) 20 response rates at 16 weeks were 60% and 61% for the 75 mg and 150 mg doses, respectively.[11] In a separate analysis, 74% of patients achieved ASAS20 response at one year. Patients sustained improvements in the signs and symptoms of AS through 52 weeks of treatment. Additionally, up to 80% of patients with AS treated with secukinumab showed no radiographic progression in the spine or joints over 2 years.

- Regarding psoriasis, Steven R. Feldman, M.D., Ph.D., says that in pivotal clinical trials, approximately three-fourths of patients reached PASI 75 (a 75% reduction in Psoriasis Area and Severity Index) at the 300 mg dose at 3 months. Specifically, 81% of patients reached PASI 75 in the ERASURE study, versus 77.1% in the FIXTURE study.[12] The 150 mg dose also performed very well, says Dr. Feldman, with around 70% of patients reaching PASI 75 in these studies. The most exciting results, he says, involved the high proportion of patients who reached clear or almost clear (PASI 90) status at week 12: 59% of patients on the 300 mg dose and 39% of the 150 mg dose, respectively. Dr. Feldman is a professor of dermatology, pathology, and social sciences and health policy at Wake Forest University School of Medicine in Winston-Salem, North Carolina.

"Now, there were a lot of common infections in the ERASURE and FIXTURE studies," says Dr. Feldman. "Roughly 20% of the people in the placebo group and 30% in the Cosentyx group had a common infection, which is fascinating because there were fewer serious infections with Cosentyx than with placebo. If there were fewer serious infections, why are there so many more, 50% more, common infections? The common infections were things like nasopharyngitis, diarrhea, upper respiratory tract infection, rhinitis, and oral herpes infections.

"This is especially interesting," Dr. Feldman continues, "because there are people who are born with genetic deficiencies in the IL-17 pathway and what they get is chronic mucocutaneous candidiasis. And those patients, as far as we're aware, don't have increased sensitivity to viruses or upper respiratory tract infection. They just get mucocutaneous – not disseminated – candidiasis and superficial staph infections.

"So why are there so many common viral and other infections with IL17 blockade when we don't see those infections in someone with an IL17 deficiency? Psoriasis, particularly extensive moderate-to-severe psoriasis, is a socially disabling disease. I think what's going on is that patients with severe psoriasis, with an average body surface area of 30% covered with psoriasis, tend to stay home. They watch late-night TV because they're depressed. They don't get out; they don't hang around with friends or relatives.

"If they go on the placebo in the study, they don't change their behavior, but I suspect there's a good chance that when they go on the study drug and their psoriasis clears up and the joint pain gets better and their energy improves that their depression lifts and then they go visit their nephews and nieces and get runny noses and diarrhea; they go to the gym and hang out with people and they get upper-respiratory-tract infection or rhinitis. They go to bars and meet men or women and they get oral herpes virus infections. There are all sorts of behavioral changes that could account for the higher number of common infections in the Cosentyx group compared to the placebo group," Dr. Feldman observed.

Comparative Analysis

Secukinumab also has shown effectiveness comparable to that of TNFa antagonists adalimumab and infliximab. Although a head-to-head clinical trial between secukinumab and adalimumab (EXCEED) was recently announced, currently no such comparisons exist. In the absence of such data, researchers have used math-

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6. Rich PA, Sigurgeirsson B, Thaci D, et al. Secukinumab induction and maintenance therapy in moderate to-severe plaque psoriasis: a randomized, double-blind, placebo-controlled, phase II regimen-finding study. *Brit J Dermatol.* 2013; 168(2): 402-411.
7. Novartis. Cosentyx (secukinumab) draft label. October 2014.
8. Mease PJ, McInnes IB, Kirkham B, et al. Secukinumab inhibition of interleukin-17A in patients with psoriatic arthritis. *N Engl J Med.* 2015;373(14):1329-1339.
9. McInnes IB, Mease PJ, Kirkham B, et al. Secukinumab, a human anti-interleukin-17A monoclonal antibody, in patients with psoriatic arthritis (FUTURE 2): a randomised, double-blind, placebo-controlled, phase 3 trial. *Lancet.* 2015;386(9999):1137-1146.
10. Mease PJ, Kavanaugh A, Reimold A, et al. Secukinumab provides sustained improvements in the signs and symptoms of active psoriatic arthritis through three years: efficacy and safety results from a phase 3 trial [Abstract 961]. *Arthritis Rheumatol.* 2016;68(suppl 10). http://acrabstracts.org/abstract/secukinumab-provides-sustained-improvements-in-the-signs-and-symptoms-of-active-psoriatic-arthritis-through-3-years-efficacy-and-safety-results-from-a-phase-3-trial/. Accessed January 9, 2017.
11. https://www.ncbi.nlm.nih.gov/pubmed/27390130 Deodhar AA, Dougados M, Baeten DL, et al. Effect of secukinumab on patient reported outcomes in patients with active ankylosing spondylitis: a phase III randomized trial (MEASURE 1). *Arthritis Rheumatol.* 2016;68(12):2901-2910.
12. Langley RG, Elewski BE, Lebwohl M, et al. Secukinumab in plaque psoriasis–results of two phase 3 trials. *N Engl J Med.* 2014;371(4):326-338.

ematical models to estimate short- and long-term effectiveness. The technique of matching-adjusted indirect comparison (MAIC) accounts for differences in baseline patient characteristics by employing individual patient data from one or more trials to match the population (appropriately weighted) of another trial.

One ACR 2016 abstract matched patient data from pooled secukinumab 150 mg arms of FUTURE 1 and FUTURE 2 PsA studies against the adalimumab 40 mg arm of the ADEPT study. Patients treated with secukinumab achieved higher ACR20 (representing a 20% reduction in ACR signs and symptoms) and ACR50 response rates at week 16: 66.4% and 45.9%, respectively, versus 55.6% and 32.5% for adalimumab (p = 0.085 and 0.029, respectively). At week 48, 72.2% and 55.1% of secukinumab-treated patients reached ACR20 and ACR50, respectively, versus 56.3% and 43.7% of adalimumab-treated patients (p = 0.010 and 0.029, respectively). Investigators also found evidence of greater improvements in the HAQ-DI score (-0.50 for secukinumab, -0.40 adalimumab, p = 0.0388).[13]

Up to 80% of patients with AS treated with secukinumab showed no radiographic progression in the spine or joints over 2 years.

Vibeke Strand, M.D., who co-authored the abstract, says that essentially, "We took individual patient data and tried to match the population from FUTURE 2 to the population from IMPACT 2, noting that FUTURE 2 is about 3 times as large – 299 patients versus 100 with IMPACT 2." There's also a gap of several years between these 2 studies, she notes. Although mathematical modeling cannot support asserting that secukinumab at either dose is better than infliximab, she adds, the analysis shows that one can expect comparable responses from the 2 drugs. Dr. Strand is an adjunct clinical professor in the Division of Immunology/Rheumatology at the Stanford University School of Medicine in Stanford, California.

A similar study matched patient data from the secukinumab 75 mg, 150 mg, and 300 mg arms of FUTURE 2 against the infliximab arm of IMPACT 2. At week 24, patients treated with secukinumab 150 mg and 300 mg showed higher ACR20 response rates – 79.6% and 74.9%, respectively – versus infliximab (54.0%; p = 0.035). At one year, researchers observed a higher ACR20 response rate for secukinumab 150 mg and a higher ACR50 response rate for secukinumab 300 mg than for infliximab.[14]

For rheumatologists, concludes Dr. Saag, "The clinical pearl is that there's an increasing array of therapeutic agents that we can use to effectively manage people who have psoriatic arthritis and ankylosing spondylitis." Because different patients often respond in individual ways to each drug, he says, "It's important to have treatment options for managing these complex diseases."

The approval of secukinumab for the treatment of psoriatic arthritis (PsA) offers patients and clinicians an effective new option for the troublesome symptoms of not only skin and joint issues, but also enthesitis and dactylitis.

Enthesitis refers to inflammation at tendon, ligament, or joint capsule insertions. Dactylitis refers to inflammation of an entire digit, either finger or toe.

13. Nash P, McInnes IB, Mease PJ, et al. Secukinumab for the treatment of psoriatic arthritis: comparative effectiveness versus adalimumab using a matching adjusted indirect comparison [Abstract 1738]. *Arthritis Rheumatol.* 2016;68(suppl 10). http://acrabstracts.org/abstract/secukinumab-for-the-treatment-of-psoriatic-arthritis-comparative-effectiveness-versus-adalimumab-using-a-matching-adjusted-indirect-comparison/. Mp://acrabstracts.org/abstract/secukinumab-for-the-treatment-of-psoriatic-arthritis-comparative-effectiveness-versus-adalimumab-using-a-matching-adjusted-indirect-comparison/. Accessed January 9, 2017.
14. Strand V, Mease PJ, McInnes IB, et al. Secukinumab for the treatment of psoriatic arthritis: comparative effectiveness versus infliximab using a matching adjusted indirect comparison [Abstract 1729]. *Arthritis Rheumatol.* 2016;68(suppl 10). http://acrabstracts.org/abstract/secukinumab-for-the-treatment-of-psoriatic-arthritis-comparative-effectiveness-versus-infliximab-using-a-matching-adjusted-indirect-comparison/. Accessed January 9, 2017.

Secukinumab Attacks Enthesitis and Dactylitis in PsA

Unmet Needs

The results of treating with secukinumab in the FUTURE 1 and FUTURE 2 U.S. Food and Drug Administration (FDA) Phase 3 trials give patients renewed hope for the reduction or resolution of these difficult symptoms, says M. Elaine Husni, M.D., M.P.H., a rheumatologist at Cleveland Clinic in Cleveland, Ohio. "These are very important data, because previous PsA treatments have not been very effective," she says. "Enthesitis and dactylitis represent unmet needs in our patients. Secukinumab has implications to improve quality of life."

In FUTURE 1, researchers randomized a total of 606 patients with PsA into one of 3 treatment arms: secukinumab 10 mg/kg (weeks 0, 2, 4) followed by subcutaneous secukinumab 150 mg or 75 mg every 4 weeks, or placebo. In FUTURE 2, 397 patients were randomized to receive subcutaneous secukinumab 75 mg, 150 mg, 300 mg or placebo once weekly for the first 4 weeks, then every 4 weeks thereafter. At baseline, 51.5% of patients in both treatment arms had dactylitis, compared to between 32% and 46% in the 3 treatment arms of FUTURE 2. Approximately 63% of patients treated with secukinumab in FUTURE 1 had enthesitis, compared to 56% to 69% among treated patients in FUTURE 2.[1,2]

At week 24, a significantly higher proportion of patients in FUTURE 1 (pooled doses) achieved complete resolution of dactylitis and enthesitis with secukinumab compared to placebo. Multiple assessment methods also showed that secukinumab reduced the number of dactylic digits and enthesitis sites at this time point.

Among patients with dactylitis who were symptomatic at baseline, 48.1% and 56.7% in the 150 mg in the 75 mg cohorts, respectively, achieved complete resolution at week 24, versus 15.5% for placebo ($p < 0.0001$). At 52 weeks, the proportion of patients who achieved complete resolution climbed to 87.7% and 89.7%, respectively, for the 150 mg and 75 mg doses, versus 48.5% for both doses at baseline.

Among patients who were treated for enthesitis, 24-week results showed that for the 150 mg and 75 mg doses, 46.0% and 48.8% achieved complete resolution, versus 12.8% for placebo ($p < 0.0001$). At week 52, 81.6% and 79.4%, respectively, at the 150 mg and 75 mg doses experienced complete resolution, versus 37.6% and 36.1%, respectively, at baseline.

Pooled secukinumab results for resolution of dactylitis and enthesitis did not reach statistical significance in FUTURE 2; however, dose-by-dose analysis revealed clinically meaningful improvements in resolution with the 300 mg and 150 mg doses versus placebo at week 24. Among patients with dactylitis, 56.5% and 50% in the 300 mg and 150 mg doses, respectively, achieved complete resolution, compared to 14.8% for placebo. At week 52, 80.2% and 90.9% of patients who had had dactylitis achieved complete resolution, versus 54.0% and 68.0% at baseline.

The treatment of enthesitis by individual doses revealed a similar pattern. At week 24, the proportion of patients in the 300 mg and 150 mg cohorts who achieved full resolution was 48.2% and 42.2%, respectively, versus 21.5% for placebo. For the same doses at week 52, 72.0% and 69.3% of patients, respectively, achieved complete resolution, compared to 44.0% and 36.0% at baseline.

The approval of secukinumab for the treatment of PsA offers patients and clinicians an effective new option for the troublesome symptoms of not only skin and joint issues, but also enthesitis and dactylitis.

"At Least As Effective"

Considering all primary and secondary endpoints in PsA, the authors of a recent review wrote that "Although head-to-head trials would be required to reach definite conclusions, indirect comparisons suggest that secukinumab is at least as effective as currently available therapies mediated via an alternative mode of action."[3]

Dr. Husni adds that in her practice, secukinumab "is still rather new" to her. "I have not been able to establish long-term experience regarding resolution of enthesitis and dactylitis," she says. "I am using secukinumab in my patients with PsA who have more skin disease activity compared to joint activity, and not necessarily switching them to secukinumab if they have enthesitis/dactylitis. With more experience, secukinumab may gain more widespread use for these additional symptoms of PsA."

Going forward, says Dr. Husni, new imaging modalities for examining dactylitis and enthesitis bear watching. "I find that diagnosis of enthesitis can be challenging, as there are several mimickers such as fibromyalgia or myofascial pain syndromes." Recent data suggest that ultrasound and perhaps MRI may be helpful in distinguishing these entities, she adds.

In a recent study conducted at Al-Minia University in Al-Minia, Egypt, investigators examined 50 patients with psoriasis and 20 healthy controls using ultrasound and power Doppler sonography (PDS) for the joints of both hands and feet and the enthesial sites, along with MRI of the lumbosacral spine and sacroiliac joints. Ultrasound documented enthesial abnormalities in 74% of patients with psoriasis, whereas clinical examination detected enthesitis in only 46% of patients.[4]

Overall, these investigators wrote, "A larger number of abnormalities (erosions, synovitis, effusion and PDS signal) that were eventually diagnosed as psoriatic arthritis were found on ultrasound examination than on plain radiographs." Additionally, MRI and radiographs showed evidence of spinal inflammation in 44% and 16% of patients, respectively, and evidence of sacroiliitis in 10% and 6%, respectively, prompting researchers to conclude that using newer imaging modalities allows early diagnosis and early initiation of therapy for spondyloarthropathy in patients with psoriasis.

Authors of a recent cross-sectional analysis of 222 patients with PsA noted that although ultrasound is emerging as a preferred method to assess enthesitis, "little is known about the relation between the presence of enthesitis and the severity of joint damage in patients with PsA." Using measures such as the MAdrid Sonography Enthesitis Index (MASEI) and, for radiographic joint damage, the modified Steinbrocker score, the modified New York Criteria for sacroiliitis, and the modified Stoke

1. Mease PJ, McInnes IB, Kirkham B, et al. Secukinumab inhibition of interleukin-17A in patients with psoriatic arthritis. *N Engl J Med.* 2015;373(14):1329-1339.
2. McInnes IB, Mease PJ, Kirkham B, et al. Secukinumab, a human anti-interleukin-17A monoclonal antibody, in patients with psoriatic arthritis (FUTURE 2): a randomized, double-blind, placebo-controlled, phase 3 trial. *Lancet.* 2015;386(9999):1137-1146.
3. Mease P, McInnes IB. Secukinumab: a new treatment option for psoriatic arthritis. *Rheumatol Ther.* 2016;3:5-29.
4. Hamdy M, Omar G, Elshereef RR, Ellaban AS, Amin M. Early detection of spondyloarthropathy in patients with psoriasis by using the ultrasonography and magnetic resonance image. *Eur J Rheumatol.* 2015;2(1):10-15.

Ankylosing Spondylitis Spine Score (mSASSS), these investigators showed that indeed, the severity of sonographic enthesitis is a marker of radiographic peripheral and axial joint damage in PsA.[5] Multivariate regression analyses showed statistically significant associations between higher MASEI scores and peripheral joint damage, elevated modified Steinbrocker scores, joint ankylosis, and arthritis mutilans.

A study comparing ultrasonic imaging of lower-leg enthesopathy in PsA, psoriasis, and other inflammatory arthritis showed that the frequency of enthesopathy in the lower limbs was significantly higher in age- and gender-matched patients with PsA and psoriasis than in healthy controls.[6] In PsA, 345 (78.4%) of 440 enthesial sites were abnormal, compared with 304 (69.1%) in psoriasis and 107 (24.3%) in controls ($p < 0.05$ in all analyses). The presence of erosion and power Doppler (PD) signal in the Achilles tendon was significantly higher in PsA than in psoriasis (9:1, 12:1, respectively; $p = 0.011, 0.002$). Logistic regression analysis showed that along with these symptoms, a longer course of psoriasis may be a risk factor for development into PsA. "Musculoskeletal ultrasound might help to identify enthesial changes in PsA," these authors concluded.

Uncertainties and controversies persist in ankylosing spondylitis

5. Polachek A, Gladman DD, Cook RJ, Chandran V, Eder L. The association between sonographic enthesitis and radiographic damage in psoriatic arthritis [Abstract 3157]. *Arthritis Rheumatol.* 2016;68(suppl 10). http://acrabstracts.org/abstract/the-association-between-sonographic-enthesitis-and-radiographic-damage-in-psoriatic-arthritis/. Accessed January 5, 2017.
6. Sun F, Zhu J. Comparison of ultrasonic imaging of enthesopathy in the lower extremity in patients with psoriatic arthritis, psoriasis, and other inflammatory arthritis [Abstract 149]. *Arthritis Rheumatol.* 2016;68(suppl 10). http://acrabstracts.org/abstract/comparation-of-ultrasonic-imaging-of-enthesopathy-in-the-lower-extremity-in-patients-with-psoriatic-arthritis-psoriasis-and-other-inflammatory-arthritis/. Accessed January 5, 2017.

Secukinumab Prevents and Treats Radiographic Progression in AS

(AS) research and treatment, but recent data provide more evidence that biologic drugs, including secukinumab, represent appropriate choices for long-term treatment. These data increasingly indicate that biologic drugs target not only the clinical symptoms of AS, but also radiographic progression (RP), which refers to axial skeleton bone and joint changes that show up on x-ray.

The established form of spondyloarthritis, AS typically strikes young people. It affects the axial skeleton—the spine and sacroiliac joint (SIJ) —causing pain, inflammation, and, if not successfully treated, fusion, leading to an inability to move the spine over time.

Before the approval of secukinumab, says Xenofon Baraliakos, M.D., potent options for patients with AS included only nonsteroidal inflammatory drugs (NSAIDs) and tumor necrosis factor alpha (TNFa) blockers. Dr. Baraliakos is a senior consultant at Rheumazentrum Ruhrgebiet Herne and associate professor of internal medicine and rheumatology at the Ruhr-University Bochum in Germany.

Phase 3 Results

Many patients do not respond adequately to NSAIDs, says Dr. Baraliakos. And while TNF blockers have shown efficacy in reducing signs and symptoms of AS, none has demonstrated the ability to prevent RP after the first 2 years of treatment.[1-3] In a Phase 3 trial of secukinumab, approximately 80% of patients randomized to this drug at baseline showed no RP after 2 years of treatment (although this analysis did not include a control group).[4] "For the first 2 years, there was no loss of response. Patients maintained their initial response levels," says Dr. Baraliakos.

Phase 3 data also showed that, as was known from treatment with TNF inhibitors, patients who respond well early in treatment tend to be the ones who maintain good responses over time.[5] Many patients achieved noticeable responses after just 2 weeks of treatment, says Dr. Baraliakos. Most (71% and 67%, respectively) of ASAS 20 responders at week 2 or 16 showed improved responses to ASAS 40 by week 16 or 52. And a majority (64% and 84%) of ASAS 40 responders at week 2 or 16 maintained this response by week 16 or 52, respectively. Similar trends occurred in ASAS responses between weeks 16 and 104.

"This pattern of fast response predicting long-term response is also a positive finding because secukinumab has demonstrated the same pattern in response as compared to the gold standard, which so far has been TNFa blockers," says Dr. Baraliakos. "And we didn't see any safety signals that would worry us in short- and long-term treatment so far."

New recommendations by the Assessment of SpondyloArthritis in-

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3. https://www.ncbi.nlm.nih.gov/pubmed/19703304 Van der Heijde D, Salonen D, Weissman BN, et al. Assessment of radiographic progression in the spines of patients with ankylosing spondylitis treated with adalimumab for up to 2 years. *Arthritis Res Ther.* 2009;11(4):R127.
4. Baraliakos X, Deodhar AA, Braun J, et al. Effect of interleukin-17A inhibition on spinal radiographic changes through two years in patients with active ankylosing spondylitis: results of a phase 3 study with secukinumab [Abstract 6L]. *Arthritis Rheumatol.* 2015;67(suppl 10). http://acrabstracts.org/abstract/effect-of-interleukin-17a-inhibition-on-spinal-radiographic-changes-through-2-years-in-patients-with-active-ankylosing-spondylitis-results-of-a-phase-3-study-with-secukinumab/. Accessed December 30, 2016.
5. Baraliakos X, Schiff M, Pavelka K, Martin R, Porter B, Gaillez C. Secukinumab sustains individual clinical responses over time in patients with active ankylosing spondylitis: two year results from a phase 3 randomized placebo-controlled trial [Abstract 695]. *Arthritis Rheumatol.* 2016;68(suppl 10). http://acrabstracts.org/abstract/secukinumab-sustains-individual-clinical-responses-over-time-in-patients-with-active-ankylosing-spondylitis-2-year-results-from-a-phase-3-randomized-placebo-controlled-trial/. Accessed December 30, 2016.

ternational Society (ASAS)/European League Against Rheumatism (EULAR) suggest that rheumatologists should put patients with axial spondyloarthropathy who fail NSAIDs on a biologic drug fairly quickly, says Dr. Baraliakos.[6] In Europe, he says, "The decision of which biologic to use is shared by the physician and patient. We have stated in the recommendations that biologic agents in general, and not limited anymore to TNFa inhibitor therapy, should be considered in patients with persistently high disease activity despite conventional treatments."

This year's ACR abstracts also illuminated subtle differences in imaging technologies used to assess sacroiliac joint changes. One study addressed the question of whether physicians could limit patients' radiation exposure by replacing x-ray and computed tomography (CT) with magnetic resonance imaging (MRI). "We took patients who had ankylosing spondylitis and compared the number of erosions and other structural changes found and missed by the 3 techniques. And we found that there is no superior technique in general,"[7] says lead study author Dr. Baraliakos.

It appears that the slicing techniques (CT and MRI) outperform x-ray (a cumulative technique) overall, he says. "And it seems that in the early stages of the disease, MRI may be better than CT because MRI assesses the cartilage damage more thoroughly. In the later stage of AS, CT might be superior to assess erosions because there, the damage has progressed from the cartilage, which is the first layer of tissue, to the bone. So presently, we can say that x-rays are okay for detecting erosions, but MRI may be an important imaging technique to replace it. It is associated with no radiation exposure, which is a positive for the patient. We need to repeat the data and see that they apply in other patients and other cohorts as well."

For patients with PsA or AS, secukinumab works equally well whether or not patients have previously received biologic therapy with TNFa blockers.

Spontaneous Remission?

Also yet to be settled is the issue of spontaneous remission. "The U.S. Food and Drug Administration [FDA] has been arguing with us about approving some biologic drugs for ankylosing spondylitis because they believe that there's such a thing as spontaneous remission," says Vibeke Strand, M.D. She is an adjunct clinical professor in the Division of Immunology/Rheumatology at Stanford University School of Medicine in Stanford, California.

"It is controversial because people may present with significant pain and discomfort, and they may or may not have changes that show up on an x-ray," says Gregg J. Silverman, M.D. "And because the disease progresses slowly over many years, it is not yet clear whether or not it merits expensive monoclonal antibody therapy," he continues. "It can take 10 years or more to see the gradual progression of destruction." Dr. Silverman is a rheumatologist and a professor of medicine at New York University in New York City.

Dr. Baraliakos says he agrees with the argument that a very small proportion of patients have very mild disease that probably does not progress and may not need continuous treatment. "But if you diagnosed patients properly, this should not be an issue. In my opinion, there are still some issues in understanding this disease that early that we can also predict its long-term outcome. To overcome this problem, the decision must be made that patients with nonradiographic axial spondyloarthritis who are going to be treated with biologics should not only have the disease itself, but also an objective sign of inflammation, such as elevated C-reactive protein (CRP) or a positive MRI of the sacroiliac joints. That way, you avoid the issue of the patient perhaps being misdiagnosed without really having a chronic inflammatory condition."

Among potential treatments for RP, says Dr. Silverman, "The data regarding whether IL17 blockade can interfere with this progression are not yet complete. Presently, we are seeing primarily symptomatic improvements. Studies suggest that there can be clinical benefits with IL17 agents." Trials of oral and other biologic therapies for AS and PsA are ongoing, he adds. But it is too early to say whether these drugs would be effective in preventing RP.

To date, largely on account of ethical concerns, there have been no long-term data regarding inhibition of RP in AS. "We've never had x-ray studies that have shown we have reduced radiographic progression," explains Dr. Strand, "in part because we haven't had long-term controlled studies because it has been considered unethical" to leave patients on placebo for extended periods without treating any RP that may develop during the study.

Several companies have begun long-term placebo-controlled trials in hopes of showing both that biologic drugs can inhibit structural progression and that spontaneous remission does not occur, says Dr. Strand. "That means these studies are going to take a full year of all patients being exposed. It also means that researchers will have to offer rescue therapy for patients who start to progress symptomatically or structurally. I've been very much against these studies, but if this is what it takes to get labeling in the United States commensurate with what we already have in Europe, then we must get it done so that ankylosing spondylitis can be recognized as the disease it is, and treated appropriately."

Previously, she says, longitudinal studies have shown that nonradiographic AS can progress to RP and that aspects associated with

6. Van der Heijde D, Ramiro S, Landewé R, et al. 2016 update of the ASAS-EULAR management recommendations for axial spondyloarthritis. *Ann Rheum Dis.* 2017 Jan 13. pii: annrheumdis-2016-210770. doi: 10.1136/annrheumdis-2016-210770. [Epub ahead of print.]
7. Baraliakos X, Hoffmann F, Deng X, Wang Y, Huang F, Braun J. Which is the most reliable imaging method for detection of structural changes in the sacroiliac joints of patients with ankylosing spondylitis? A cross-sectional study comparing MRI, CT and conventional radiographs [Abstract 682]. *Arthritis Rheumatol.* 2016;68(suppl 10). http://acrabstracts.org/abstract/which-is-the-most-reliable-imaging-method-for-detection-of-structural-changes-in-the-sacroiliac-joints-of-patients-with-ankylosing-spondylitis-a-cross-sectional-study-comparing-mri-ct-and-convention/. Accessed December 30, 2016.

RP include HLA-B27 positivity and poor prognostic factors, such as the presence of many existing spinal manifestations.[8] Dr. Strand adds that the terms "nonradiographic AS" and "AS" should be used only to classify patients with axial spondyloarthritis, not as separate diagnoses. She and co-authors wrote, "We propose that only the term "axial spondyloarthritis" be used to diagnose patients.... The available data justify performing randomized controlled trials designed to obtain regulatory approval for therapeutic agents in patients across the entire spectrum of axial spondyloarthritis."[9]

"In terms of ankylosing spondylitis," says Kenneth Saag, M.D., "one of the big challenges continues to be the difficulty in ascertaining disease activity. It's a disease that doesn't lend itself as easily as psoriatic arthritis or, say, rheumatoid arthritis to a joint examination, whereby it's easy to determine that joints are tender, swollen, or warm. When disease involvement is predominantly in the axial skeleton, namely the spine, the neck, and the sacroiliac joints, it can be challenging to disentangle what's active from what's more damaged and inactive disease or some other concomitant problem that shows osteoarthritis or fibromyalgia. That's what made that disease somewhat challenging. But overall, there's been progress, and we're pleased to have new treatments on the horizon. There continues to be every 2 to 3 years steady improvement in new data that lends itself to clinical advances in disease management." Dr. Saag is a rheumatologist and a professor of medicine at the University of Alabama at Birmingham.

Dr. Strand adds that although psoriatic arthritis (PsA) may carry highly variable peripheral manifestations, including enthesitis and dactylitis (for more information, please see "Secukinumab Attacks Enthesitis and Dactylitis in PsA," on page 4), the effects of spondyloarthropathy can be just as profound. "It occurs at a younger age," she says. "And it can be underdiagnosed." Rheumatologists once believed that AS affected men much more frequently than women, by a ratio of as much as 9 to 1, she notes. But because nonradiographic AS impacts women much more often than men, "Maybe the prevalence of spondyloarthropathy is actually 50-50 women and men."

As in PsA, says Dr. Strand, "Patients with AS tend to get diagnosed late. Many have suffered for many years without adequate treatment." While underdiagnosis, under-recognition, and a lack of treatment options have created challenges, she says, "Having a new class of inhibitors, the IL17 inhibitors, is extraordinarily helpful."

8. Ramiro S, Stolwijk C, van Tubergen A, et al. Evolution of radiographic damage in ankylosing spondylitis: a 12 year prospective follow-up of the OASIS study. *Ann Rheum Dis.* 2015;74(1):52-59.
9. Deodhar A, Strand A, Kay J, Braun J. The term "non-radiographic axial spondyloarthritis" is much more important to classify than to diagnose patients with axial spondyloarthritis. Ann Rheumatol Dis. 2016;75:791-794.

Anti-TNF-Naïve Patients Respond Well to IL17 Inhibition

Pivotal secukinumab trials and extensions studies have shown that for patients with psoriatic arthritis (PsA) or ankylosing spondylitis (AS), secukinumab works equally well whether or not patients have previously received biologic therapy with tumor necrosis factor alpha (TNFa) blockers. This makes secukinumab fully equivalent to this class of biologic drugs for these indications, experts say.

Approved more than a year ago in Europe, secukinumab targets the pathway interleukin (IL) 17A – and in this way, differs from the most commonly used biologic drugs for PsA and AS, which target TNFa, says Xenofon Baraliakos, M.D. He is a senior consultant at Rheumazentrum Ruhrgebiet Herne and associate professor of internal medicine and rheumatology at the Ruhr-University Bochum in Germany.

"And the data say that treatment with secukinumab – both in patients who were naïve to TNF blockers and those who have had TNF blockers before but failed their treatment for any reason – is very effective, similar to what we knew with TNFa blockers. This is important because we need to know all potential aspects of this new treatment. A key aspect would be patients who are naïve to TNF blockers – they received this new drug as their first biologic. We needed to show that this new biologic is as good as the standard that we have had so far." In Phase 3 testing and beyond, continues Dr. Baraliakos, "Secukinumab showed that it is just as good, which is exactly what is expected from new drugs coming into the market."

PsA: FUTURE 1 and 2

In the FUTURE 1 and FUTURE 2 Phase 3 trials in PsA, approximately two-thirds of patients were anti-TNF-naïve. This figure includes 70.8% and 70.3% for the 150 mg and 75 mg doses, respectively, in FUTURE 1; and 67%, 63%, and 66% for the 300 mg, 150 mg, and 75 mg doses in FUTURE 2.[1]

In both FUTURE 1 and 2, significantly more patients achieved primary endpoints with secukinumab than with placebo at 24 and 52 weeks. ACR20 response rates in FUTURE 1 at 24 weeks among anti-TNF-naïve patients at the 150 mg and 75 mg doses were 54.5% and 55.6%, respectively, versus 39.0% and 38.3%, respectively, for these same doses among anti-exposed patients. ACR20 responses in anti-TNF-naïve patients at 52 weeks showed a similar pattern: 75.2% and 73.2% for the 150 mg and 75 mg doses, respectively, compared to 53.3% and 51%, respectively, in anti-TNF-exposed patients.

ACR50 results in this study at 24 weeks were 39.9% and 36.6% among anti-TNF-naïve patients at the 150 mg and 75 mg doses, respectively, versus 22.0% and 16.7% for anti-TNF-exposed patients

1 Mease P, McInnes IB. Secukinumab: a new treatment option for psoriatic arthritis. *Rheumatol Ther.* 2016;3(1):5-29. Review.

at these doses, respectively. At 52 weeks, 56.6% and 42.3% of patients at the 150 mg and 75 mg doses, respectively, achieved ACR 50, compared to 31.1% and 28.6%, respectively, for these doses in patients who had previously taken TNF inhibitors.

In FUTURE 2, 24-week ACR20 responses in the anti-TNF-naïve subgroup were 58.2%, 63.5%, and 36.9% for the secukinumab 300 mg, 150 mg, and 75 mg doses, respectively. The corresponding figures among anti-TNF-exposed patients at these doses were 45.5%, 29.7%, and 14.7%, respectively. At week 52, between 67.9% and 84.7% of anti-TNF-naïve patients who took secukinumab achieved ACR20, versus between 48.3% and 63.2% of anti-TNF-exposed patients.

The highest level of ACR50 response at week 24 was achieved by patients who took secukinumab 150 mg (44.4%), followed by those who took the 300 mg dose (38.8%) and the 75 mg (24.6%) dose. Also at this time point, the percentages of anti-TNF-exposed patients who achieved ACR50 were 27.3%, 18.9%, and 5.9% for the 300 mg, 150 mg, and 75 mg doses, respectively. ACR50 responses among anti-TNF-naïve patients at 52 weeks exhibited a consistent dose response: 59.3%, 52.5%, and 42.9% for the 300 mg, 150 mg, and 75 mg doses, respectively. ACR50 responses at this time point among anti-TNF-exposed patients hovered between 27.6% and 31.6% for all 3 doses.

Based on pivotal trial results out to 52 weeks, "Efficacy was demonstrated regardless of concomitant methotrexate therapy and in both anti-TNF-exposed patients and those naïve to anti-TNF therapies. These results highlight the important role played by IL17A in the pathogenesis of PsA, and together with the positive results from recent studies in AS, suggest that secukinumab will be a valuable addition to the available treatment options for PsA and other chronic and disabling rheumatic diseases."[1]

AS: MEASURE 1 and 2

Of the 371 patients in the pivotal MEASURE 1 clinical trial in AS, 73% were anti-TNF-naïve, as were 61% of the 219 patients in MEASURE 2.[2] Approximately 26% to 39% of patients in each study had inadequate responses to anti-TNF agents.

In MEASURE 1, both the secukinumab 150 mg and 75 mg doses met researchers' primary endpoint – at least 20% improvement in Assessment of SpondyloArthritis international Society scores (ASAS20) at week 16. Overall ASAS20 response rates were 61% (150 mg) and 60% (75 mg). In MEASURE 2, 61% of patients at the 150 mg dose reached ASAS20 at week 16. At week 52, patients randomized to secukinumab at baseline – and those who switched to secukinumab from placebo in MEASURE 2 – maintained clinical responses observed at week 16.

"Although head-to-head trials would be required to fully assess the efficacy and safety of secukinumab versus TNF inhibitors," study authors wrote, "the ASAS20 response rates achieved with secukinumab at week 16 in our studies were similar to those reported in Phase 3 studies of anti-TNF agents in which most patients had not received previous anti-TNF therapy, even though 30% to 40% of the patients in our studies have had no response to previous anti-TNF treatments. Thus, secukinumab not only is effective in patients who have not received TNF agents previously, but also may be effective in patients in whom previous anti-TNF treatment failed."

An abstract comparing 52-week results for anti-TNF-naïve patients versus those of anti-TNF-exposed patients showed that not only did the former group maintain their responses for one year, but also that patients in this group generally responded better than the anti-TNF-exposed patients did. [3]

The abstract showed that the proportion of anti-TNF-naïve patients who reached ASAS20 in MEASURE 1 and MEASURE 2 was between 51.1% and 68.2% for the secukinumab 150 mg and 75 mg doses, respectively, at week 16, and between 71.4% and 82.1% for these doses at week 52. In contrast, ASAS20 response levels among anti-TNF-exposed patients taking the same secukinumab doses in MEASURE 1 and 2 were between 25% and 58.8% at week 16, and between 47.4% and 70.8% at week 52.

Similar patterns emerged in ASAS40 results. Among the anti-TNF-naïve group in both studies, between 31.1% and 48.9% of patients on all secukinumab doses achieved ASAS40 at 16 weeks. Between 47.6% and 67.1% of patients on all doses reached this level at week 52. Among anti-TNF-exposed patients, between 17.9% and 29.4% of patients on all doses reached ASA40 at week 16; between 26.3% and 50.0% reached this level at week 52.

ASAS20 response rates at 2 years (104 weeks) in MEASURE 1 were 73.7% and 68.0% for the secukinumab 150 mg and 75 mg groups, respectively.[4] At this time point, 85.5% and 72.3% of anti-TNF-naïve patients reached ASAS20 in the 150 mg and 75 mg cohorts, respectively. In anti-TNF-exposed patients at 2 years, 55.6% and 71.4% achieved this response level in the 150 mg and 75 mg cohorts, respectively. Moreover, 69.6% and 52.3% of anti-TNF-naïve patients at the 150 mg and 75 mg doses, respectively, reached ASAS40 at 2 years, versus 44.4% and 57.1% of anti-TNF-exposed patients at these same doses, respectively.

According to study authors, "This analysis demonstrates that secukinumab improves the clinical signs and symptoms of AS through 2 years of continued therapy. Secukinumab was effective in both anti-TNF-naïve and anti-TNF-exposed patients, although absolute response rates were generally higher in anti-TNF-naïve patients."[4]

1. Mease P, McInnes IB. Secukinumab: a new treatment option for psoriatic arthritis. *Rheumatol Ther.* 2016;3(1):5-29. Review.
2. Baeten D, Sieper J, Braun J, et al. Secukinumab, an interleukin-17A inhibitor, in ankylosing spondylitis. *N Engl J Med.* 2015;373(26):2534-2548.
3. Baeten D, Blanco R, Geusens P, et al. Secukinumab provides sustained improvements in the signs and symptoms of active ankylosing spondylitis in anti-TNF-naïve patients and those previously exposed to anti-TNF therapy: 52 week results from two randomized, double-blind, placebo-controlled phase 3 trials [Abstract 2890]. *Arthritis Rheumatol.* 2015;67(suppl 10). http://acrabstracts.org/abstract/secukinumab-provides-sustained-improvements-in-the-signs-and-symptoms-of-active-ankylosing-spondylitis-in-anti-tnf-naive-patients-and-those-previously-exposed-to-anti-tnf-therapy-52-week-results-from/. Accessed January 6, 2017.
4. Braun J, Baraliakos X, Deodhar A, et al. Effect of secukinumab on clinical and radiographic outcomes in ankylosing spondylitis: 2-year results from the randomised phase III MEASURE 1 study. *Ann Rheum Dis.* 2016 Dec 13. pii: annrheumdis-2016-209730. doi: 10.1136/annrheumdis-2016-209730. [Epub ahead of print.]

PsA Delivers Deep Quality-of-Life Impact

Research indicates that patients can experience an emotional toll from the physical, economic, and social impact of psoriatic arthritis (PsA). "We know that psoriatic arthritis is profoundly problematic for patients, maybe to some extent even more so than rheumatoid arthritis [RA]," says Vibeke Strand, M.D. Dr. Strand is an adjunct clinical professor in the Division of Immunology/Rheumatology at Stanford University School of Medicine in Stanford, California.

More troublesome potentially than RA, PsA goes beyond the peripheral joints, sometimes involving the spine, Dr. Strand explains. Likewise, "It can involve the entheses – the insertions of tendons into the bone. Dactylitis occurs when an entire finger – all the joints of a finger – are massively swollen and painful," she says. (For more information, please see "Secukinumab Attacks Enthesitis and Dactylitis in PsA," on page 4.) "Believe it or not," Dr. Strand continues, "that can impair function almost as much as, if not more than, just having the proximal interphalangeal [PIP] and metacarpophalangeal [MCP] joints of the hands involved [as in RA]. These are very much issues for psoriatic arthritis. It is the variability, and the multiple manifestations that psoriatic arthritis demonstrates, which are much more heterogeneous than RA. Because many patients do not get diagnosed early, this is a major problem."

There is a growing understanding of the effects of PsA on patients' home, work, and emotional lives. A survey involving 1700 patients from 16 countries showed that many patients with PsA cannot undertake everyday activities that would allow them to lead a normal life.[1] Researchers grouped patients who said they had been happy "all" or "most of the time" during the previous week into a "happy" cohort; patients who answered "a little" or "none" to this question were defined as "not happy." When researchers considered physicians' and patients' perceptions of health status and clinical characteristics, the unhappy group had worse health outcomes (in terms of pain, afflicted joint counts, and psoriasis area and severity index/PASI scores). Only 56.9% of patients in the unhappy group reported satisfaction with their current treatment, versus 83% in the happy group ($p < 0.001$).

As the number of treatments and measuring tools available for PsA increases, so does the importance of establishing a consensus on key clinical trial outcomes.

"We were looking at how patients in the real world report the impact of their disease," says survey co-author Dr. Strand. "We know that it impacts their ability to work, and whether they work within or outside the home. Many patients take lower-paying jobs because they want to do some type of work but they know they can't do as much as they would like to. Psoriatic arthritis also impacts their social, family, and leisure activities." Authors of this abstract suggested that proactively treating PsA to reduce severity should improve important components of health-related quality of life.

A similar survey involving nearly 1500 patients with PsA assessed the relationship between physical functioning and work. This analysis confirmed a strong inverse relationship between physical functioning, employment levels, and work productivity in patients with PsA.[2] Greater disease severity correlated with worse physical function, in terms of higher Health Assessment Questionnaire Disability Index (HAQ-DI) scores ($p < 0.0001$). As HAQ-DI scores increased so did unemployment and retirement owing to PsA ($p < 0.0001$).

For employed patients, the percentage of work time missed owing to PsA significantly rose as HAQ-DI scores climbed; the same was true for patients' percentage of impairment while working and overall work impairment. (In the latter area, patients with HAQ-DI scores between 2 and 2.6 reported a 76.9% overall productivity loss, versus just 16.6% for patients with HAQ-DI scores less than 0.6.) Taken together, authors concluded, this study's findings suggest that strategies to reduce disability in patients with PsA will not only benefit patients, but will also bring a positive societal and economic impact.

In a Danish cohort study co-authored by Dr. Strand, researchers matched 10,525 patients with PsA and 20,777 matched patients from the general population and found that at all time points studied (January 1998 through December 2014), patients with PsA had higher total health care costs, lower income ($p < 0.001$), and a $12,024 higher average societal cost per patient in comparison with matched controls.[3]

Additionally, patients' relative risk (RR) of being on disability pen-

1. Alten R, Strand V, Conaghan PG, et al. Psoriatic arthritis limits patients' abilities to undertake activities crucial for normal daily life and impacts happiness, results from a multinational real-world sample [Abstract 2770]. *Arthritis Rheumatol.* 2016;68(suppl 10). http://acrabstracts.org/abstract/psoriatic-arthritis-limits-patients-abilities-to-undertake-activities-crucial-for-normal-daily-life-and-impacts-happiness-results-from-a-multinational-real-world-sample/. Accessed January 3, 2017.
2. Conaghan PG, Alten R, Strand V, et al. The relationship between physical functioning and work for people with psoriatic arthritis: results from a large real-world study in 16 countries [Abstract 1712]. *Arthritis Rheumatol.* 2016;68(suppl 10). http://acrabstracts.org/abstract/the-relationship-between-physical-functioning-and-work-for-people-with-psoriatic-arthritis-results-from-a-large-real-world-study-in-16-countries/. Accessed January 3, 2017.
3. Kristensen LE, Jørgensen TS, Christensen R, et al. Societal costs and patients' experience of health inequities from psoriatic arthritis: a Danish cohort study [Abstract 3187]. *Arthritis Rheumatol.* 2016;68(suppl 10). http://acrabstracts.org/abstract/societal-costs-and-patients-experience-of-health-inequities-from-psoriatic-arthritis-a-danish-cohort-study/. Accessed January 4, 2017.

sion versus the RR experienced by controls increased over time, from 1.36 at 5 years before diagnosis to 1.60 at the time of diagnosis, and 2.69 at 10 years after diagnosis. At the latter time point, 21.8% of patients with PsA received disability pensions. The study also showed significantly higher comorbidity burdens for patients with PsA. In comparison with controls, patients with PsA had baseline odds ratios between 1.25 and 2.03 for neoplasms, cardiovascular disease, respiratory disease, infectious disease, and hematological disease.

International Effort Streamlines Clinical-Trial Outcome Reporting

As the number of treatments and measuring tools available for PsA increases, so does the importance of establishing a consensus on key clinical trial outcomes.

Outcome Measures in Rheumatology (OMERACT) is an international organization of rheumatologists, dermatologists, radiologists, nurses, methodologists, and patients whose aim is to develop consensus on outcome measurements in rheumatologic diseases and to include trainees. A recent reevaluation of OMERACT standards for disease-specific core sets,[1] along with the recognition of a critical aspect of the patient perspective, prompted the update of the 2007 PsA Core Domain Set, explains Ana Maria Orbai, M.D., M.H.S. The growth in treatment options over the past decade also fueled the reevaluation, she notes. Dr. Orbai is an assistant professor of medicine and director of the Psoriatic Arthritis Program at Johns Hopkins University School of Medicine in Baltimore, Maryland, and she co-chairs the Group for Research and Assessment of Psoriasis and Psoriatic Arthritis (GRAPPA)-OMERACT PsA Core Set Working Group.

"The GRAPPA-OMERACT Working Group is tasked with the Psoriatic Arthritis Core Domain Set Update," says Dr. Orbai. "Our objective is to update what is currently being measured in psoriatic arthritis clinical trials. The first step was to update the PsA Core Domain Set, which represents what should be measured in every future PsA clinical trial.[2] The Core Domain Set now includes the patient perspective, because patients who participated in international focus groups in 7 countries [131 participants in all, from the United States, the United Kingdom, Australia, Brazil, France, Netherlands, and Singapore] told us what is important to them. The next step we have embarked on is to develop the PsA Core Outcome Measurement Set – the set of outcome measures that need to be collected in PsA clinical trials to adequately measure the updated PsA Core Domain Set."

When researchers began evaluating the rheumatologic aspects of psoriatic arthritis, explains Vibeke Strand, M.D., "We essentially borrowed outcome instruments from rheumatoid arthritis. We have now developed good measures for enthesitis and dactylitis, so in fact we're doing a better job of assessing both spinal manifestations and the other articular manifestations of psoriatic arthritis. Both of those contributed to this reevaluation, as well as having many more patients with psoriatic arthritis involved in the effort." Dr. Strand is an adjunct clinical professor in the Division of Immunology/Rheumatology at Stanford University School of Medicine in Stanford, California.

In 2007, says Dr. Strand, OMERACT had established a solid consensus on a Core Domain Set for use in randomized controlled trials. But since then, "We understand more about the heterogeneity of psoriatic arthritis that has skin and musculoskeletal manifestations. And we know that there is a delay in diagnosis. Many patients have psoriasis as well as musculoskeletal complaints, but they're not recognized as having psoriatic arthritis when the diagnosis should have been made years before. Psoriatic arthritis in general has been under-recognized and/or undertreated for a long time."

To update relevant measurements, says Dr. Orbai, "We started by asking patients what is important to them. We constructed an international focus-group study in 7 countries representing 5 continents. We extracted domains that are important to patients, then reviewed the literature to see what was measured before. Then we put those things together, yielding a total of 39 unique PsA domains. We surveyed patients and physicians separately to prioritize those domains." Ultimately, researchers and patients used these data to agree upon 10 domains for inclusion in PsA clinical trials.

"Fatigue was added to the required outcomes in clinical trials because it is very important to patients," continues Dr. Orbai. "And we redefined musculoskeletal disease activity into a more comprehensive definition for PsA. It used to include just joint activity; now it is more comprehensively defined to include not only joint counts, but also enthesitis, dactylitis, and spine symptoms."

1. Boers M, Kirwan JR, Wells G, et al. Developing core outcome measurement sets for clinical trials: OMERACT filter 2.0. J *Clin Epidemiol.* 2014;67(7):745-753.
2. Orbai AM, de Wit M, Mease P, et al. International patient and physician consensus on a psoriatic arthritis core outcome set for clinical trials. *Ann Rheum Dis.* 2016 Sep 9. pii: annrheumdis-2016-210242. doi: 10.1136/annrheumdis-2016-210242. [Epub ahead of print.] PMID: 27613807.

In 2016, OMERACT endorsed the following updated PsA Core Domain Set:[3]

- Musculoskeletal disease activity (peripheral arthritis, enthesitis, dactylitis, and spine symptoms)
- Skin disease activity (skin and nail disease)
- Pain
- Patient global health
- Physical function
- Health-related quality of life
- Fatigue
- Systemic inflammation

"The effort is half done in that we picked the domains that we believe are important and should be evaluated in all trials," notes Dr. Strand. "Now we must pick the preferred instruments for those particular domains. That work is ongoing, and we expect to have that completed in the next couple of years."

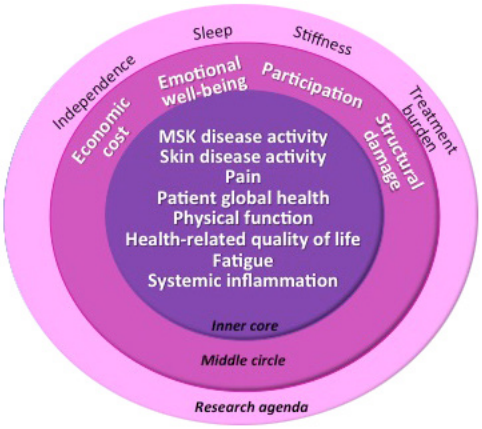

Figure Legend: Updated 2016 PsA Core Domain Set: Musculoskeletal (MSK) disease activity includes peripheral joints, enthesitis, dactylitis, and spine symptoms; skin activity includes skin and nails; patient global health is defined as patient-reported disease-related health status. The inner circle (core) includes domains that should be measured in all PsA randomized controlled trials (RCTs) and longitudinal observational studies (LOS). The middle circle includes domains that are important but may not be feasible to assess in all RCTs and LOS. The outer circle, or research agenda, includes domains that may be important but that need further study.2 Reproduced with permission from Orbai AM., et al. Ann Rheum Dis. 2016. ARD Online First published on December 3, 2016 as 10.1136/annrheumdis-2016-210242, Figure 3, Page 6 (72).

3. Orbai AM, de Wit M, Mease PJ, et al. International patient and physician consensus on psoriatic arthritis outcomes for clinical trials [Abstract 957]. *Arthritis Rheumatol.* 2016;68(suppl 10). http://acrabstracts.org/abstract/international-patient-and-physician-consensus-on-psoriatic-arthritis-outcomes-for-clinical-trials/. Accessed January 4, 2017.

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