The Science and Art of Treating Psoriasis

An Update

IL17 DRIVES KEY IMMUNE PATHWAY IN PSORIASIS

>>> As researchers continue to investigate the pathogenesis of plaque psoriasis at the molecular and genetic levels, the interleukin (IL) 17 pathway is receiving more interest. Other pathways that appear to be more heavily involved in acute and pustular psoriasis include interferon and IL36, respectively.

Approximately 80% of patients with psoriasis have plaque psoriasis, notes Michel Gilliet, M.D., chair of the Department of Dermatology at the University Hospital CHUV in Lausanne, Switzerland. "We know its pathogenesis well," he says. "It's due to aberrant activation of dendritic cells, which produce a number of cytokines such as tumor necrosis factor (TNF) alpha and IL23. These cytokines stimulate autoimmune T cells, which are Th17 cells that produce IL17a and IL17f, as well as IL22."

"Pure T-Cell Disease"

James Krueger, M.D., Ph.D., notes that although co-activation of other T-cell subsets plays a role, plaque psoriasis is a polar IL23/Th17 disease. In European-American populations, he says, "Psoriasis is a pure T-cell disease with a highly congruent molecular phenotype across its variants." Dr. Krueger is the D. Martin Carter Professor in Clinical Investigation and head of the Laboratory of Investigative Dermatology at Rockefeller University in New York.

The characteristic thick epidermal hyperplastic reaction of psoriasis is driven not only by hyperproliferation of keratinocytes, explains Dr. Krueger, but also by a reactive epidermal phenotype that spurs keratinocytes into a wound-healing process called regenerative maturation. "That regenerative phenotype is consistently associated with increased infiltration of tissue by T cells, and by myeloid dendritic cells that make IL23," he says.

Under this 20-year-old pathogenic model, adds Dr. Krueger, activated T cells produce cytokines that induce immune-related molecules on keratinocytes, and somehow convert homeostatic growth into the wound-healing or regenerative pathway. When this hypothesis was formulated, "We didn't know what T-cell poles were driving the disease. The main hypothesis at the time was that all cutaneous immunity could be explained by a balance of Th1

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and Th2," he says, with psoriasis exemplifying a Th1-deviated disease like tuberculoid leprosy.

More modern maps of cytokine expression support this theory,[1] notes Dr. Krueger. "But there's a new kid on the block – IL17," which in psoriasis is overexpressed to a higher degree than even gamma interferon. Here we introduce a new subset of T cells – Th17 T cells – that have been known only for the last decade. In mice, he explains, the dimeric cytokine IL23 directs these T cells to make IL17 and IL22 (in humans, most IL22 production occurs in a different subset, Th22 T cells), whereas Th1 is driven by IL12. IL23 binds to receptors, activates STAT3, and drives the IL17 response.

A 2004 study Dr. Krueger co-authored established the first link between this cytokine axis and psoriasis.[2] Using mRNA profiling to measure levels of the 2 subunits of IL23 – p40 and p19 – Dr. Krueger and colleagues showed that in lesional and nonlesional skin from patients with psoriasis, IL23 was consistently upregulated, and linked to an increase in dendritic cells that produce high levels of IL23.

Subsequent genetic data have implicated at least 3 immune axes – interferon-γ, IL17, and IL22 – in psoriasis,[3] says Dr. Krueger. "If one turns off disease with cyclosporine treatment, over a period of 2 months, disease improvement is reflected through keratin 16 reductions. Interferon-γ and IL22 also decrease, but the largest decrease occurs in IL17 expression, which is nearly undetectable at the end of treatment. These data don't say that any of these axes drive psoriasis, specifically. But what does this new IL17 axis add to the immunology of psoriasis that interferon-γ did not?"

> "The complex immune model of psoriasis must be redrawn."

The first clue to the answer came when German researchers added IL22 and interferon-γ to psoriatic keratinocytes and found that only IL22 could induce production of psoriasin.[4] "We did similar experiments with IL17," note the investigators. "We got strong induction of psoriasin. So we have these 2 Th17 or Th17-related cytokines [IL17 and IL22] doing something important that interferon-γ does not."

Blocking IL12 reduces interferon-γ levels, while blocking IL23 reduces IL17 and IL22, explains Dr. Krueger. These findings provide a basis for finer dissection of the pathways in psoriasis using specific antagonists to IL17, IL22, and IL23, he says. "We learned about the outstanding importance of IL17 in psoriasis in 2010" when a small Phase 1 study showed that one injection of an IL17 blocker unexpectedly produced a 75% reduction in Psoriasis Area and Severity Index scores (PASI 75) in 7 of 8 patients, and a physician global assessment of clear or almost clear in all 8 patients.[5]

Gene-expression profiling revealed that within 2 weeks of IL17 inhibitor administration, "A pathological signature of 10,000 genes was turned down to 500, and that was maintained for the 6 weeks of treatment," says Dr. Krueger. "So 95% of the disease transcriptome was turned off specifically by IL17 blockade. That opened the floodgates to this whole class of agents that have been tested."

"We also know from treatment trials using anti-TNF therapy that the first cytokine that decreases in plaque psoriasis is IL17," adds Dr. Gilliet. "So in recent years, there has been the development of anti-IL17 therapy, which is highly efficacious."

Among U.S. Food and Drug Administration (FDA)-approved IL17 blockers for psoriasis, says Dr. Krueger, "Secukinumab has an incredibly good ability to induce PASI 75 responses in patients, with superiority to older agents that we had, including ustekinumab and etanercept."

With secukinumab, notes Dr. Gilliet, "We can reach up to PASI 90 in 70% of cases, and even PASI 100 in 40%,[6] again proving that this pathway, with aberrant dendritic cell activation that stimulates Th17 cells to produce IL17, is very important in plaque psoriasis. (For more information on the efficacy of secukinumab, please see "Insight and Innovation" on page 3.)

Considering what is known to date, says Dr. Krueger, "the complex immune model of psoriasis must be redrawn" with a more central emphasis on IL23, IL17, and the ensuing response that likely feeds back and perpetuates psoriasis.[7] "We now know that there are at least 2 specific autoantigens for psoriasis – LL37 and the melanocyte-related protein ADAMTSL5. They are provided to T cells by antigen-presenting cells, and they drive the activation of a Th17 response. The idea is, you start with IL17 and other cytokines made by Th17 cells that are step one activators. There are major effects on keratinocytes that induce about 20 different immune active inflammatory molecules that can then [provide] feedback and recruit other cell populations, including Th1, into the milieu."

IL17-induced chemokines recruit neutrophils, Dr. Krueger continues. "And with chronicity, IL19, IL36, and other cytokines that are proliferative effectors for keratinocytes can create the epidermal hyperplasia response, leading to dendritic cell infiltration and chronicity of the disease. I believe we can explain virtually all the histopathological features of psoriasis by saying that psoriasis and IL17 are mostly about inducing very high levels of innate defense antimicrobial proteins at the skin surface."

These antimicrobial proteins include human beta defensin 4 and lipocalin, Dr. Krueger adds. "These are essentially antimicrobial shields that would protect against surface organisms. We know that IL17 protects against Candida, which is a surface infection. Even the epidermal hyperplasia response can be viewed as an attempt to eliminate infected surface keratinocytes very quickly. So the fast turnover can be part of a keratinocyte-directed innate immune response – that is the IL17 pathway."

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6. 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.
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Other Forms of Psoriasis

Acute forms of psoriasis, including erythrodermic and guttate psoriasis, seem to correspond to an acute inflammatory process that is distinct from chronic plaque psoriasis, says Dr. Gilliet. "And our own work has shown that in fact, these types of psoriasis are characterized by the expression of another cytokine – interferon alpha (IFNa) – which is produced by a unique subset of dendritic cells called plasmacytoid dendritic cells."[8]

Gene-expression analysis in erythrodermic and guttate psoriasis reveals very high levels of IFNa and less IL17 than in plaque psoriasis, explains Dr. Gilliet. "So we believe these are basically 2 extremes of the disease. One is plaque-type psoriasis with production of TNF and IL17, but then there are acute forms such as erythrodermic and guttate psoriasis, which are linked to IFNa production and less to TNFa/IL17 production.

Treating acute forms of psoriasis currently requires cyclosporine, which is known to inhibit T-cell stimulation but can also block interferon production by plasmacytoid dendritic cells, says Dr. Gilliet. "There are currently no available targeted treatments for interferon, but they are being developed."

Paradoxical psoriasis, which occurs in 5% of patients taking anti-TNF drugs, also stems from the IFNa pathway,[9] says Dr. Gilliet. Blocking TNFa favors IFNa production, he explains. "So the message is, we need to stop the anti-TNF treatment in these patients" and treat the underlying psoriasis with an alternative mechanism of action such as blocking IL17 or blocking IL12/23. Meanwhile, says Dr. Gilliet, "We treat the paradoxical psoriasis lesions with topical steroids or cyclosporine in severe cases." Methotrexate and phototherapy are used if the paradoxical psoriasis is pustular, he adds.

Pustular psoriasis includes palmar/plantar pustulosis (PPP), acute generalized pustular psoriasis (GPP), and, affecting the fingers, acrodermatitis continua of Hallopeau. All 3 forms may respond poorly to TNF inhibitors, says Dr. Gilliet, and are driven by the IL36/IL1 pathway.[10] In families with familial GPP, mutations in the IL36 receptor gene cause excess IL36 signaling, which activates NFkB and other signaling molecules, ultimately elevating IL1 levels. An IL36 receptor antagonist is being developed to block IL36 signaling and pustular psoriasis.[10] <<<

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9. Unpublished data.
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INSIGHT AND INNOVATION

>>> In treating psoriasis, success depends on integrating a multifaceted array of considerations, with implications for overall health.

"It's an art in the treatment of psoriasis to find the most optimal treatments in the individual patient," says Peter van de Kerkhof, M.D., chair of the Department of Dermatology at Radboud University Nijmegen Medical Center in the Netherlands.

"First, it is important that the right treatment selection be based on the clinical factors of psoriasis, but also with a view of the patient's comorbidities," he says. With classical systemic treatments, he explains, "it is not so much the efficacy after 12 weeks" but the far more important issue of safe long-term efficacy, which to date has been an unmet need in most patients with psoriasis.

Classical treatments – including dithranol, phototherapy, acitretin, tumor necrosis factor (TNF) alpha blockers, and dimethyl fumarate – are highly effective in psoriasis because they impact the Th1-Th17/Th2 pathway both lesionally and systemically, says Dr. van de Kerkhof. "With respect to cyclosporine A and methotrexate, these treatments have been reported not to influence the Th1-Th2 balance but depress both cytokines equally."[1]

The insight that TNF signaling is of major pathogenetic importance in psoriasis led to a game-changing shift in the form of TNF inhibitors, he says. "Anti-TNF treatments have been a very important innovation in the treatment of psoriasis, providing long-term safety control. Ustekinumab also proved to result in high efficacy and long-term control."[2-5]

Among small-molecule drugs, says Dr. van de Kerkhof, "Apremilast inhibits the phosphodiesterase (PDE) 4 pathway. In this way, it also changes the balance of the Th1 and Th2 pathways." Another small-molecule drug, tofacitinib, targets Janus activated kinase (JAK), he says.

"We used to talk a lot about PASI 75. Increasingly, we're talking about PASI 90. With the more effective treatments such as adalimumab, we're getting PASI 90 results in just over 45%, and with ustekinumab, depending on the dose, between 45% and 50%," says Dr. Richard Warren, F.R.C.P., Ph.D., Reader, University of Manchester, UK, and Honorary Consultant Dermatologist based at Salford Royal NHS Foundation Trust, Greater Manchester, UK.

IL17 inhibition is the next step in therapeutic innovations for psoriasis, says Dr. van de Kerkhof.

In this class of drugs, says Dr. Warren, "Secukinumab has been licensed for the longest period of time, and therefore is the one that we have the most current understanding of in terms of real-world use. Secukinumab

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3. Reich K, Nestle FO, Papp K, et al. Infliximab induction and maintenance therapy for moderate-to-severe psoriasis: a phase III, multicentre, double-blind trial. *Lancet.* 2005;366(9494):1367–1374.
4. Menter A, Tyring SK, Gordon K, et al. Adalimumab therapy for moderate to severe psoriasis: a randomized, controlled phase III trial. *J Am Acad Dermatol.* 2008;58(1):106–115.
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is an IL17A antagonist, and it now has numerous indications [for plaque psoriasis, psoriatic arthritis, and ankylosing spondylitis in Europe and the United States]."

In Phase 3 trials of secukinumab, the proportions of patients reaching PASI 75 at week 12 were 82% and 77% (at the 300 mg dose).[6] "We also have learned that optimal efficacy of these treatments is not expressed after 12 weeks," says Dr. van de Kerkhof. "So we must be a little bit patient, because the efficacy is much better expressed at week 16 [approximately 85% in both studies]." Patients generally maintained these results out to week 52, observed Dr. Warren. During this time frame, he says, "Using 300 mg was significantly better than the 150 mg dose, and much better than using etanercept."[6]

Regarding PASI 90, Dr. van de Kerkhof says that with secukinumab, 72% of patients reached this goal at week 16. Dr. Warren adds that week 52 PASI 90 results (68.5%) have held strong out to 4 years of treatment (66.4%), with a favorable safety profile.[7] "These are observed data," he says. Between week 52 and week 152, he adds, only 39 patients withdrew owing to immunogenicity events: "Even though it's a relatively nonconservative analysis, in the form of observed data, these results are very impressive."

With anti-IL23 treatments, around 80% of patients reached PASI 90 after 28 to 36 weeks of treatment.[8]

The study that set secukinumab apart from the rest of the biologic drugs for psoriasis pitted it head-to-head against ustekinumab, says Dr. Warren. "Ustekinumab is one of the gold standard drugs in psoriasis," he notes. "In this trial, the primary endpoint was set at week 16. The PASI 90 levels were impressive – 80% for secukinumab in the 300 mg dosing schedule" versus 59% for ustekinumab.[9]

"One of the practical things we face in dermatology," notes Dr. Warren, "is that patients will sometimes want a break from treatment," perhaps on account of a problem or because of changing life circumstances such as a pregnancy. "What we need to know is, if you restart that drug, will it work effectively again?"

Investigators took patients from secukinumab's pivotal trials who were PASI 75 responders at week 52 and re-randomized them to placebo or continued secukinumab. "Those in the placebo group gradually lost response," explains Dr. Warren. "When they fell to 50% of their maximum response, investigators put them back on secukinumab." After 12 weeks, the proportion of patients who regained PASI 75 was excellent,"[10] says Dr. Warren.

> "It's an art . . . to find the most optimal treatments in the individual patient."

Secukinumab also provides efficacy regardless of patients' previous exposure to biologic drugs. A pooled analysis of 4 Phase 3 trials showed that at week 12, 58.1% of biologic-naïve patients treated with secukinumab 300 mg achieved PASI 90, versus 50.7% of patients who had previous exposure to biologics.[11] Among patients who had previously responded to biologics, 55.2% achieved PASI 90 at week 12, versus 42% of patients who had failed previous biologic drugs.

To characterize secukinumab's safety, researchers pooled all patients from the drug's Phase 2 and Phase 3 psoriasis studies, and found no significant differences in rates of common adverse events (AEs) between secukinumab at either the 300 mg or 150 mg dose and placebo or etanercept, which Dr. Warren says is considered a very safe biologic agent. In 2,725 patient years of secukinumab exposure, incidence rates for common AEs were 236.1 per 100 patient years for secukinumab 300 mg and 239.9 for secukinumab 150 mg, versus exposure-adjusted incidence rates of 351.8 and 243.4 for placebo and etanercept, respectively.[12,13] Among all drugs studied, nasopharyngitis was the most common AE, followed by headache, upper respiratory tract infection, and arthralgia.

"Based on our understanding of immunology," Dr. Warren adds, "IL17 inhibition brings with it specific theoretical issues. For example, it plays a role in host defense against Candida. We are then interested to see what happens with patients who go on to secukinumab in terms of Candida infections." In Phase 2 and Phase 3 studies out to 52 weeks, no significant differences emerged among secukinumab, etanercept, and placebo. Candida infections impacted a slightly higher percentage of patients at the 300 mg secukinumab dose than on etanercept, Dr. Warren says (exposure-adjusted IR per 100 patient years: 3.55 and 1.37, respectively). Nevertheless, "The percentage of patients on secukinumab who got Candida infection was small. The take-home message is that all of the Candida infections were treatable, and the patients were able to remain on therapy without problems."[12,13]

Secukinumab failed to show any advantage in a clinical trial for Crohn's disease, says Dr. Warren, leading some observers to wonder whether the drug might cause problems in the inflammatory bowel disease (IBD) setting. However, in pooled data from all secukinumab psoriasis studies, he says, "There is no signal that inflammatory bowel disease is being induced by this medicine." Only 3 of 1,410 patients on secukinumab developed IBD while on treatment, versus one of 323 patients on etanercept.[12,14]

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11. Blauvelt A, et al. Secukinumab Treatment Maintains Efficacy in Moderate to Severe Plaque Psoriasis Through Second Year of Treatment: A Randomized Extension of the ERASURE and FIXTURE Studies. American Academy of Dermatology Conference. Session F010. March 20-24, 2015; San Francisco.
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"There are certain types of psoriasis that we tend to think of as being harder to treat. One of those is nail disease," says Dr. Warren. Secukinumab is one of a very few biologic drugs for psoriasis to have a randomized controlled trial in nail psoriasis, he notes. This trial showed a 45.3% reduction in Nail Psoriasis Severity Index (NAPSI) scores at week 16 for the 300 mg dose (versus a 10.8% reduction for placebo; $p < 0.01$).[15] Although varying trial designs preclude the possibility of comparing efficacy between trials of different drugs directly, he says, in nail psoriasis, secukinumab performed comparably to adalimumab, which was studied in an open-label 12-week trial.[16]

For plaque psoriasis of the palms and soles (but not palmoplantar pustulosis), Dr. Warren says, "Again, data are somewhat limited." In a randomized controlled trial of secukinumab, 39% of patients achieved physician global assessment (PGA) scores of zero or one (clear or almost clear) after 16 weeks of treatment.[17] At week 80, 57.2% of patients achieved PGA scores of zero or one, "suggesting that perhaps plaques on the hands and soles improve a little more slowly" than those elsewhere, Dr. Warren points out.

He adds, "The take-home message is that there has been a dearth of randomized controlled high-quality data for some of these more tricky-to-control sites. The secukinumab data are a fantastic addition to the data set we have."

Overall, he says, "IL17A antagonism works extremely well for psoriasis. The trials have been well done. They have demonstrated secukinumab's superiority over etanercept and ustekinumab. The long-term data are robust. Importantly, as we have drilled into different data in particular around nail disease and plaque disease of the hands and feet, again we have seen excellent randomized controlled trial data for secukinumab."

"With insight into psoriasis pathogenesis," says Dr. van de Kerkhof, "new treatments are arising. They are not only an academic exercise, but they are truly innovating the treatment of psoriasis – especially long-term treatments, with biologics and small molecules offering a new future for patients with psoriasis." <<<

15. Reich K, Sullivan J, Arenberger P, et al. Secukinumab is Effective in Subjects with Moderate to Severe Plaque Psoriasis with Significant Nail Involvement: 16 Week Results from the TRANSFIGURE Study. Paper presented at 23rd World Congress of Dermatology; June 11, 2015; Vancouver, Canada.
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JUMPSTARTING CLINICAL SUCCESS

>>> Recognizing and treating psoriasis early – with a specific target in mind – can mean the difference between satisfied and unsatisfied patients, and between the avoidance and presence of complications such as psoriatic arthritis (PsA).

With the high volume of patients whom dermatologists see, says April Armstrong, M.D., M.P.H., "Many dermatologists are under time pressure to complete patient visits as quickly as possible. However, it is important to take the time to ask about joint symptoms and signs, because a delay in psoriatic arthritis diagnosis can result in irreversible joint damage." Dr. Armstrong is associate dean for clinical research and vice chair of the Department of Dermatology at the University of Southern California, Los Angeles, Keck School of Medicine; she also directs the Clinical Research Support Office at the Southern California Clinical and Translational Science Institute.

A video she shares emphasizes the personal pain of psoriasis, which some patients call "a nightmare" and "a living hell." The large survey in which these comments emerged revealed that only 45% of patients with psoriasis believe that clear skin is possible, and that those patients who are most likely to believe this are under age 40.[1]

Overall, says Dr. Armstrong, "In the United States, half of psoriasis patients are dissatisfied with their treatment, and nearly half of patients with psoriatic arthritis are also dissatisfied with their treatment."[2]

By intervening early, she explains, "You can get a timely improvement in disease signs and symptoms, and in quality of life. In addition, initiating patients on a highly efficacious medication early on establishes confidence and trust in the provider. So treating psoriasis and psoriatic arthritis adequately at the outset is very important."

The concept of cumulative life course impairment (CLCI) describes the long-term, multifaceted impact of psoriasis,[3] says Dr. Armstrong. "That includes a physical component, a psychological component, and then finally the stigma that can occur with psoriasis."

CLCI comprises comorbidities of psoriasis such as anxiety and depression, cardiovascular disease, psoriatic arthritis, inflammatory bowel disease, metabolic syndrome, sleep apnea, uveitis, and kidney disease, says Dr. Armstrong. (For more information, please see "Focus on Comorbidities" on page 8.)

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Noting that the effects of CLCI can grow over time, Dr. Armstrong says that with recently diagnosed patients, "their coping mechanism may be to cover their psoriasis and/or seek care. However, if they don't get the right treatment at the right time and continue to suffer from psoriasis, their impairment accumulates. Why is that important? Because up to a certain point, they no longer have healthy coping mechanisms to deal with their psoriasis. Once they cross that threshold, they turn to unhealthy coping mechanisms; for example, drinking and smoking. It's very important that we intervene early in the disease course when patients believe that it can be helped."

European guidelines define treatment success as at least a 75% decrease in psoriasis area severity index (PASI); PASI reductions of 50% or less require a change in treatment regimen.[4] And research shows that treating psoriatic disease with specific goals in mind boosts results. In one randomized study, researchers found that with a tightly controlled treatment regimen, significantly more patients achieved ACR20, 50, or 70, while their skin outcomes and quality of life also improved significantly more than those of patients who were treated with standard of care.[5]

> "It's very important that we intervene early in the disease course."

However, says Dr. Armstrong, "Most American dermatologists do not track PASI in the clinical setting." The U.S. National Psoriasis Foundation has recently established a consensus goal that after 12 weeks of treatment, affected body surface area (BSA) less than 3%, or at least a 75% reduction from baseline, is "acceptable." The ideal target at 3 months – and during maintenance therapy – is BSA less than 1%.[6]

Once the patient's psoriasis is under control, most dermatologists schedule follow-up visits after 6 months of treatment. During these visits, Dr. Armstrong says, "It's important to ask about psoriatic arthritis, because forgetting to ask patients about their joints, and even a delay of a few months in detection of psoriatic arthritis, can result in the progression of joint disease." One study showed that not asking about joints for one year makes patients 2.28 times more likely to have deformed joints and 4 times more likely to have erosion before their psoriatic arthritis is diagnosed, compared to patients referred to a rheumatologist in a timely fashion.[7]

On the surface, she says, the difference between PASI scores of 75 and 90 may not sound substantial. But in terms of quality of life, "A change between PASI 75 to PASI 90 for our patients leads to about a 50% increase in the likelihood of achieving a dermatology life quality index [DLQI] score of zero or one [nearly no impact on the patient's life]."

In psoriasis clinical trials, 76% of patients on secukinumab (versus 61% on ustekinumab) achieved PASI 90 at 52 weeks.[8] In terms of quality of life, "We saw that 71% of patients achieved DLQI zero or one by week 52. These patients believe that their skin disease has essentially no impact on their quality of life. This is something that you can communicate with your patients." If patients follow the recommended regimen for one year, she says, most can expect psoriasis to have virtually no negative effect on their life.

Secukinumab also can reduce bothersome symptoms like pain, itching, and scaling. In a subanalysis from the study comparing secukinumab and ustekinumab, Dr. Armstrong says, "By week 16, 70% of patients on secukinumab had almost complete resolution of their pain. And 50% of patients will be completely free of itch when they are treated with secukinumab. These treatment effects are maintained over 52 weeks. Scaling is significantly decreased as well."[9]

Dr. Armstrong says she frequently encounters patients who want to work but cannot because their PsA is extremely bothersome, or whose psoriasis prevents them from doing the type of work they want to do. "In our survey, 92% of patients with psoriatic disease do not work because of their psoriasis, their psoriatic arthritis, or both. Now we're not only seeing the impact of psoriasis personally, but this is also having an economic impact that can affect their families."[10]

The Work Productivity and Activity Impairment Due to Psoriasis (WPAI-PsO) questionnaire essentially measures the impact of psoriasis on patients' work productivity and activities outside the family.[11] The concept of absenteeism refers to patients missing work days because of their psoriasis, says Dr. Armstrong. "Presenteeism means they are present at work, but not mentally there because they're suffering from psoriasis."

With secukinumab 300 mg, she says, "There is a 2.5% reduction in absenteeism at week 16, and this reduction is sustained by week 52. And then this effect is replicated in work productivity increase [23%, $p < 0.001$] by these therapies as well as activity increase [more than 30%, $p < 0.05$] in our patients.[12] We will be seeing many of these work-related productivity measures coming up in psoriasis assessment."

In summary, says Dr. Armstrong, "The burden of disease for psoriasis remains high, and the aim of the treatment should be to decrease patients' morbidity and mortality as soon as possible. We want to treat patients early not just to target their symptoms and signs, but also to improve their quality of life so that they're better able to cope with their disease." <<<

4. Mrowietz U, Kragballe K, Reich K, et al. Definition of treatment goals for moderate to severe psoriasis: a European consensus. *Arch Dermatol Res.* 2010;303(1):1-10.
5. Coates LC, Moverley AR, McParland L, et al. Effect of tight control of inflammation in early psoriatic arthritis (TICOPA): a UK multicentre, open-label, randomised controlled trial. *Lancet.* 2015;386(10012):2489-2498.
6. Armstrong AW, Siegel M, Bagel J, Van Voorhees AS, Robertson AD, Yamauchi PS. Treatment targets for plaque psoriasis. *JAMA Dermatol.* 2017;(76):290-298.
7. Haroon M, Gallagher P, FitzGerald O. Diagnostic delay of more than 6 months contributes to poor radiographic and functional outcome in psoriatic arthritis. *Ann Rheum Dis.* 2014;74(6):1045-1050.
8. Blauvelt A, Reich K, Tsai T-F, et al. Secukinumab is superior to ustekinumab in clearing skin of subjects with moderate-to-severe plaque psoriasis up to 1 year: results from the CLEAR study. *J Am Acad Dermatol.* 2017;76(1):60-69.
9. Bruce Strober, poster no. 1973, 25th Annual European Academy of Dermatology and Venereology Congress. September 28-October 2, 2016; Vienna, Austria.
10. Armstrong AW, Schupp C, Wu J, Bebo B. Quality of life and work productivity impairment among psoriasis patients: findings from the National Psoriasis Foundation Survey Data 2003-2011. *PLoS ONE.* 2012;7(12):e52935.
11. Reilly MC, Zbrozek AS, Dukes EM. The validity and reproducibility of a work productivity and activity impairment instrument. *PharmacoEconomics.* 1993;4(5):353-365.
12. Puig L, Sofen H, Augustin M, et al. Secukinumab provides greater 52-week improvements in patient-reported outcomes than ustekinumab in patients with moderate-to-severe psoriasis. Poster P1975. Presented at the 25th Annual European Academy of Dermatology and Venereology Congress. September 28-October 2, 2016; Vienna, Austria.

>>> The potential for paradoxical reactions and for psoriasis mimics complicates diagnosis and treatment. Whenever a patient has an autoimmune disease, says Luis Puig, M.D., "The clinician must exert rigorous care and consideration when initiating biologic treatment, especially with anti-tumor necrosis factor [TNF] alpha agents, because in some cases, infliximab, etanercept, or adalimumab can precipitate or worsen several variants of autoimmune disease, from lupus erythematosus to autoimmune thyroiditis." Dr. Puig is director of the Department of Dermatology at the Hospital de la Santa Creu i Sant Pau in Barcelona and a professor of dermatology at the Universitat Autònoma de Barcelona (UAB) Medical School.

Eczematous reactions during the course of anti-TNF therapy – especially with adalimumab – occur in up to 20% of patients with an atopic predisposition, he says. "This is often associated with Staphylococcus aureus superinfections, which can also occur in patients with asteatotic eczema."

In fact, says Dr. Puig, a personal history of atopy appears to increase the risk nearly 4-fold in patients with eczema, usually superinfected with *S. aureus.* "And infliximab has been reported to be more frequently associated with the development or exacerbation of preexisting eczema."[1]

Psoriasiform Dermatitis

Up to 5% of patients treated with anti-TNF agents for psoriasis, psoriatic arthritis, or inflammatory bowel disease (IBD) may develop a psoriasiform dermatitis (also called paradoxic pustular psoriasis) that is often characterized by plaques, pustules, and hyperkeratosis on the palms and soles,[2] notes Dr. Puig. "In these cases, the interleukin (IL) 17 and IL23 pathways seem to be important. IL23 antagonists have been reported to help improve these patients, and IL17 antagonists might also be helpful in patients with psoriasis or psoriatic arthritis, since the skin lesions are characterized by infiltrates of IL17A/IL22-secreting T helper 17 (Th17) cells."[3]

In some instances, he says, IL23 blockade has led to complete remission of skin manifestations and satisfactory control of either psoriatic arthritis or IBD. Such cases appear to support the approach of blocking one of the involved pathways, he says, adding that he would first try ustekinumab because he has more experience with it. "But there is initial evidence suggesting an anti-IL17 drug might be useful, especially in patients with psoriasis, psoriatic arthritis, or ankylosing spondylitis, which are approved indications for one of these agents [secukinumab] but probably not in patients with IBD, whose disease might be worsened by these agents.[4] In a patient with psoriatic arthritis who develops a paradoxic pustular reaction, perhaps I would first try an anti-IL17 drug such as secukinumab, which is also approved for the treatment of psoriatic arthritis and ankylosing spondylitis."

Recent evidence suggests that owing to the presence of IL36 receptors in keratinocytes, IL36 might be another important driver of paradoxic skin reactions.[5]

Paradoxic Reactions to TNF Inhibitors

Treatment with TNF blockers also can fuel paradoxic arthritis. "Several recent publications suggest that rheumatologic manifestations can appear in a significant proportion of patients treated with, for instance, infliximab, in the context of IBD," says Dr. Puig. "Even though it is well known that IBD-associated arthropathy should also respond to anti-TNF agents, this has been described to worsen in patients with IBD under treatment with anti-TNF agents. This is also the case with psoriatic arthritis" in patients using TNF blockers.

"Any kind of disease which can be improved by anti-TNF agents can also be the manifestation of these paradoxic reactions," notes Dr. Puig. In addition to paradoxic arthritis, he says, some patients on TNF blockers may develop paradoxic pyoderma gangrenosum, hidradenitis suppurativa, or even IBD.

> "The evolution of the patient's disease . . . might lead us to change our diagnosis."

"We don't know the mechanism," says Dr. Puig. "The most commonly seen paradoxic manifestations in clinical practice are skin manifestations. And in this case the diagnosis and adequate treatment of paradoxical psoriasis can be very helpful to our gastroenterologist colleagues because they don't have many therapeutic alternatives." If dermatologists can provide a therapeutic alternative, such as cyclosporine or another biologic drug such as ustekinumab that may control the paradoxic manifestations with no effect or even amelioration of the bowel disease, he says, "This can be very helpful for our colleagues and patients."

In other cases, says Dr. Puig, patients with psoriasis being treated with biologics can experience worsening, with confluence of lesions and interspersed islands of spared skin. "There may or may not be palmar or plantar hyperkeratosis. When you see this kind of rash – which can appear following exposure to photodynamic therapy, and in some other cases [from] infliximab or other treatments – one might suspect a drug reaction, but a diagnosis of pityriasis rubra pilaris [PRP] must be entertained, especially

1. Nakamura M, Lee K, Singh R, et al. Eczema as an adverse effect of anti-TNFα therapy in psoriasis and other Th1-mediated diseases: a review. *J Dermatolog Treat.* 2016;15:1-5.
2. Puig L, Morales-Múnera CE, López-Ferrer A, Geli C. Ustekinumab treatment of TNF antagonist-induced paradoxical psoriasis flare in a patient with psoriatic arthritis: case report and review. *Dermatology.* 2012;225(1):14-17.
3. Tillack C, Ehmann LM, Friedrich M, et al. Anti-TNF antibody-induced psoriasiform skin lesions in patients with inflammatory bowel disease are characterised by interferon-γ-expressing Th1 cells and IL-17A/IL-22-expressing Th17 cells and respond to anti-IL-12/IL-23 antibody treatment. *Gut.* 2014;63(4):567-577.
4. Hueber W, Sands BE, Lewitzky S, et al. Secukinumab, a human anti-IL-17A monoclonal antibody, for moderate to severe Crohn's disease: unexpected results of a randomised, double-blind placebo-controlled trial. *Gut.* 2012;61(12):1693-1700.
5. Friedrich M, Tillack C, Wollenberg A, Schauber J, Brand S. IL-36γ sustains a proinflammatory self-amplifying loop with IL-17C in anti-TNF-induced psoriasiform skin lesions of patients with Crohn's disease. *Inflamm Bowel Dis.* 2014;20(11):1891-1901.

when the typical follicular accentuation can be seen."

In these cases, a biopsy can confirm this diagnosis. "Some variants of PRP – especially familial PRP – can be considered nowadays to be related to some monogenic forms of psoriasis,"[6] explains Dr. Puig.

Diagnosing psoriasis is not always a straightforward process, he adds. "Sometimes, the evolution of the patient's disease – while it can be morphologically quite characteristic – might lead us to change our diagnosis. In some cases, the mistake in the original diagnosis can lead to treatment that causes worsening of the disease, which leads us to the correct diagnosis."

In one case he treated, a female patient with apparently typical plaque psoriasis of the forearms, arms, back, and feet responded partially to methotrexate, he says. "But then we started narrowband UVB and there was extension and worsening of the lesions, and a suspicion of subacute cutaneous lupus erythematosus was confirmed by a biopsy. This case proves that a complete history should be taken. And despite that, you can still make a mistake."

Hydroxychloroquine, he notes, which is frequently used to treat cutaneous lupus erythematosus, can worsen psoriasis.

"Even worse, in some patients, psoriasis may coexist with lupus erythematosus. In any patient, correct screening and a laboratory workup are in order before starting ultraviolet [UV]-B or psoralen plus UVA [PUVA] therapy. A special variant of bullous pemphigoid may also coexist with psoriasis vulgaris and be triggered by phototherapy," he adds.

Additional psoriasis mimics that may warrant consideration include the following:

- Candidiasis – In the flexural areas, says Dr. Puig, candidiasis can be very difficult to differentiate histopathologically from psoriasis due to psoriatic pustules in the flexors. "It also can be considered a coexistence because in some situations the superinfection is the Koebner factor that leads to the appearance of psoriasis."
- Contact dermatitis – In palmoplantar eczema, especially the chronic hyperkeratotic variant, contact sensitization might be the Koebner factor that drives the appearance of psoriasis. "In these cases, it is important to look at the knuckles and extension areas because if there is erythema and desquamation, this is unlikely to be provoked by contact dermatitis."
- Mycosis fungoides – When in doubt, says Dr. Puig, "Perform a skin biopsy." <<<

6. Fuchs-Telem D, Sarig O, van Steensel MA, et al. Familial pityriasis rubra pilaris is caused by mutations in CARD14. *Am J Hum Genet.* 2012;91(1):163-170.

FOCUS ON COMORBIDITIES

>>> While researchers continue to explore associations between psoriasis and established comorbidities, additional comorbidities are emerging. And the many publications that are investigating both established and emerging comorbidities are perhaps raising more questions than there are answers for to date.

"It's very important to realize that psoriasis is not only a disease of the skin. We should realize that psoriatic arthritis occurs in about a third of patients with psoriasis. This is a huge figure. Psoriasis also has been associated with increased risk of cardiovascular disease. We may argue whether this is an independent or dependent risk factor. But it is quite clear that there is a shortening of life expectation due to comorbidities" for patients with psoriasis, says Peter van de Kerkhof, M.D., chair of the Department of Dermatology at the Radboud University Nijmegen Medical Center in the Netherlands.

In addressing comorbidities, says Dr. van de Kerkhof, "It is very important to provide a personalized approach, to look more deeply than the skin, to participate in prevention programs, and not to view dermatologists exclusively as skin doctors."

A growing number of meta-analyses support associations between psoriasis and well-established comorbidities such as coronary artery disease[1] and depression,[2] says Matthias Augustin, M.D., director of the Institute for Health Services Research in Dermatology and Nursing at the University Medical Center Hamburg-Eppendorf in Hamburg, Germany.

"We also have data showing that on the one hand, depression can exacerbate psoriasis. On the other, there is evidence that psoriasis leads to depression. It's probably true, and there are data on this as well, saying that this is an interaction rather than one-directional," says Dr. Augustin.

Recent research further delineates associations between psoriasis and additional comorbidities, ranging from chronic obstructive pulmonary disease[3] to abdominal aortic aneurysms.[4] Studies using a large Danish database have shown that rates of multiple sclerosis[5] and migraine[6] rise as psoriasis severity increases.

Emerging comorbidities identified by a Brazilian review include celiac disease, Parkinson's disease, and erectile dysfunction.[7]

Epidemiologic data must be interpreted with a degree of caution, notes Dr. Augustin. "I believe these associations are mostly true, as far as we have seen them, but we must consider that data from the literature stem from different sources." These sources range from government-mandated health insurance records and registries, with fairly tight inclusion

1. Horreau C, Pouplard C, Brenaut E, et al. Cardiovascular morbidity and mortality in psoriasis and psoriatic arthritis: a systematic literature review. *J Eur Acad Dermatol Venereol.* 2013;27 Suppl 3:12-29.
2. Dowlatshahi EA, Wakkee M, Arends LR, Nijsten T. The prevalence and odds of depressive symptoms and clinical depression in psoriasis patients: a systematic review and meta-analysis. *J Invest Dermatol.* 2014;134(6):1542-1551.
3. Li X, Kong L, Li F, et al. Association between psoriasis and chronic obstructive pulmonary disease: a systematic review and meta-analysis. *PLoS One.* 2015;10(12):e0145221.
4. Khalid U, Egeberg A, Ahlehoff O, Smedegaard L, Gislason GH, Hansen PR. Nationwide study on the risk of abdominal aortic aneurysms in patients with psoriasis. *Arterioscler Thromb Vasc Biol.* 2016;36(5):1043-1048.
5. Egeberg A, Mallbris L, Gislason GH, Skov L, Hansen PR. Risk of multiple sclerosis in patients with psoriasis: a Danish nationwide cohort study. *J Invest Dermatol.* 2016;136(1):93-98.
6. Egeberg A, Mallbris L, Hilmar Gislason G, Skov L, Riis Hansen P. Increased risk of migraine in patients with psoriasis: a Danish nationwide cohort study. *J Am Acad Dermatol.* 2015;73(5):829-835.
7. Oliveira Mde F, Rocha Bde O, Duarte GV. Psoriasis: classical and emerging comorbidities. *An Bras Dermatol.* 2015;90(1):9-20.

criteria, to online polls and telephone surveys that rely solely on patient reporting. (For more information on psoriasis epidemiology, please see "Closing the Epidemiology Gap" on this page.)

To address these limitations, Dr. Augustin and colleagues seek to cross-validate their data whenever possible. In studying epidemiology, for example, this group used company surveys and public polls to cross-check information gleaned from a large German database. Ultimately, they found an overall psoriasis prevalence of 2.5% in Germany, peaking in the 60-to-70-year-old age bracket at 4.15%.[8]

A subsequent study tracked comorbidities by ICD-10 diagnoses within German health insurance records. In all age groups, patients with psoriasis had significantly more comorbidities than did patients with atopic dermatitis (AD).[9] For patients with psoriasis, says co-author Dr. Augustin, "There's a pattern that includes hyperlipidemia, obesity, diabetes, and ischemic heart disease." Compared to patients with AD, those with psoriasis had prevalence ratios between 1.74 and 1.94 for arterial hypertension, hyperlipidemia, obesity, and diabetes.

> "Psoriasis is more than a disease of the skin."

While the debate surrounding statistical associations and causality continues, he says, the clinical ramifications of the above findings are that "We should check for and try to detect comorbidities early because it may help patients to get proper treatment sooner."

In this regard, Dr. Augustin says, current German guidelines incorporate simple screening procedures that provide early detection, to be used merely for screening purposes, not for dermatologists to diagnose or treat comorbidities themselves.[10] "All dermatologists are asked to screen for 12 comorbidities – arterial hypertension, dyslipidemia, obesity, diabetes, metabolic syndrome, nonalcoholic steatohepatitis, depression, nicotine abuse, alcohol abuse, inflammatory bowel disease, psoriatic arthritis, and malignant lymphoma." If a brief screening yields positive findings in any of these areas, "Any further work must be done by a specialist or general practitioner. This is very simple, but I believe it's very useful."

Study authors wrote, "The present recommendations for comorbidities screening ... represent the first step in bridging the gap from epidemiological and pathogenetic data to the development of concrete recommendations for action" in support of nationwide health goals.[10]

Despite the abundance of research into psoriasis comorbidities, says Dr. Matthias, "Surprisingly, there have not yet been evaluations of the impact of screening on long-term outcomes." But evidence has indicated that TNF blockers may reduce cardiovascular risk. Similarly, a well-implemented study has shown that long-term immunosuppression with methotrexate may reduce cardiovascular events over time.[11]

Dr. van de Kerkhof says that dermatologists are fortunate because methotrexate, anti-TNF drugs, and anti-IL17 drugs work well on both psoriasis and psoriatic arthritis. Still, "We must reconcile that many treatments affecting the immune system may also be contraindicated in several situations, as in patients with cancers or a tendency for developing chronic infections. Then it is important to avoid treatments with an immunosuppressive or immunomodulatory potential."

Often, he adds, "The discussion that I hear is, we have enough treatments for psoriasis. There will be no room for any new treatments. This is absolutely wrong. Psoriasis is a very heterogeneous disease with respect to the skin itself. Every patient has his or her own psoriasis. But also, with respect to the comorbidities, we must consider that in our treatment selection, we need to address the inner organs, the comorbidities," wherever possible. <<<

8. Augustin M, Reich K, Glaeske G, Schaefer I, Radtke M. Co-morbidity and age-related prevalence of psoriasis: analysis of health insurance data in Germany. *Acta Derm Venereol.* 2010;90(2): 147-151.
9. Radtke MA, Schäfer I, Glaeske G, Jacobi A, Augustin M. Prevalence and comorbidities in adults with psoriasis compared to atopic eczema. *J Eur Acad Dermatol Venereol.* 2017;31(1):151-157.
10. Radtke MA, Mrowietz U, Feuerhahn J, et al. Early detection of comorbidity in psoriasis: recommendations of the National Conference on Healthcare in Psoriasis. *J Dtsch Dermatol Ges.* 2015;13(7):674-690.
11. Ahlehoff O, Hansen PR, Gislason GH, et al. Myocardial function and effects of biologic therapy in patients with severe psoriasis: a prospective echocardiographic study. *J Eur Acad Dermatol Venereol.* 2016;30(5):819-823.

CLOSING THE EPIDEMIOLOGY GAP

>>> A Global Psoriasis Atlas under development aims to increase understanding of the epidemiology and natural history of psoriasis by narrowing knowledge gaps and standardizing research and reporting methods to facilitate between-study comparisons.

The International League of Dermatological Societies (ILDS) has joined with the International Federation of Psoriasis Associations (IFPA) and the International Psoriasis Council (IPC) to establish the Global Psoriasis Atlas. "This atlas will enable us to build an evidence base and begin benchmarking some of these comparisons between countries and within countries. Several work programs should get under way in 2017," says Darren Ashcroft, Ph.D., a professor of pharmacoepidemiology and founding director of the Centre for Pharmacoepidemiology and Drug Safety Research at the School of Pharmacy and Pharmaceutical Sciences, both at the University of Manchester, UK.

A systematic review of global psoriasis epidemiology that Dr. Ashcroft co-authored found 53 psoriasis studies eligible for inclusion, he says, "and several important gaps in our knowledge about not only the epidemiology, but also the natural history of psoriasis.[1] For example, we know far more about the epidemiology of psoriasis in adults than in children. The review also highlighted a number of methodological issues in the work that has been undertaken to date." Some studies relied on patient-reported diagnoses of psoriasis, he says, while other studies employed diagnoses by dermatologists or other physicians. "The lack of standardization within this body of literature has limited our ability to compare disease prevalence between different studies in a meaningful way," notes Dr. Ashcroft.

Psoriasis incidence studies suffer from similar limitations, he adds. "There are no studies at the moment that simultaneously compare incidence,

1. Parisi R, Symmons DPM, Griffiths CEM, et al. Global epidemiology of psoriasis: a systematic review of incidence and prevalence. *J Invest Dermatol.* 2013;133:377-385.

prevalence, and mortality longitudinally in patients with psoriasis." Some studies suggest that the prevalence of psoriasis is growing over time, he says. "If so, is this being driven by changes in incidence rates or the number of new cases presenting? Or is it driven by patients nowadays living much longer with psoriasis due to reductions in early mortality?"

To begin answering such questions, Dr. Ashcroft and colleagues used the UK's Clinical Practice Research Datalink (CPRD) to investigate incidence, prevalence, and mortality over a 15-year period in the UK. "At any point in time, CPRD has more than 5 million patients registered, and over 21 million lives over the 28 years that these data sets have been running," says Dr. Ashcroft.

The study found a steady increase in psoriasis prevalence, from approximately 2.3% of patients in 1999 to 2.8% in 2013.[2] In 10-year age bands between 20 years and 90 years, "We saw 50% to 150% increases in prevalence," says Dr. Ashcroft. However, he adds, incidence appeared to be relatively stable overall: "If anything, we saw a slight decline over that 15-year period."

As with the general population, notes Dr. Ashcroft, patients with psoriasis are living longer. "This seems to be the key driver that's pushing the prevalence rate up. What's also striking is that there's a persistent premature mortality gap" that did not narrow during the period studied. Between ages 60 and 79, the hazard ratio (HR) for mortality in patients with psoriasis, compared to those without it, is 5.6, and for patients over age 80 with psoriasis, the HR is 25.2 ($p < 0.0001$ in both analyses).

The study also highlighted differences between early-onset and late-onset psoriasis. While data revealed no gender differences in incidence rates of psoriasis that begins after age 40, explains Dr. Ashcroft, incidence of early-onset rates appears to peak in females during the early 20s, compared to the early 30s for males.

"These findings raise the question, do early-onset and late-onset psoriasis represent 2 distinct conditions?" says Dr. Ashcroft. "Growing evidence suggests that people with early psoriasis suffer more severe psoriasis, require systemic treatments, and are more likely to have a family history of psoriasis.[3] In terms of clinical phenotypes, guttate and erythrodermic psoriasis appear to occur much more frequently in patients with early-onset psoriasis." <<<

2. Springate DA, Parisi R, Kontopantelis E, Reeves D, Griffiths CEM, Ashcroft DM. The incidence, prevalence and mortality of patients with psoriasis: a UK population-based cohort study. *Br J Dermatol.* 2016 Aug 31.
3. Theodorakopoulou E, Yiu ZZ, Bundy C, et al. Early- and late-onset psoriasis: a cross-sectional clinical and immunocytochemical investigation. *Br J Dermatol.* 2016;175(5):1038-1044.

THERAPEUTIC SYNERGY FOR PsA

>>> Dermatologists may have an advantage in early detection of psoriatic arthritis (PsA), but the complexities of PsA are bringing together dermatologists and rheumatologists in managing patients with PsA and psoriasis.

"The syndrome of psoriatic arthritis involves several tissues," including the synovium, the gut, and the insertions of tendons into bones, says Iain McInnes, M.D., Muirhead Professor of Medicine; Arthritis Research UK (ARUK) Professor of Rheumatology; and director of the Institute of Infection, Immunity and Inflammation at the Glasgow Biomedical Research Centre at the University of Glasgow, UK.

"There are at least 2,500 ligament-tendon or joint capsule insertions holding the muscles and ligaments to the skeleton. All these structures are called entheses," says Dennis McGonagle, M.D., Ph.D., a professor of investigative dermatology at the Leeds Institute of Rheumatic and Musculoskeletal Medicine, University of Leeds, and the Clinical Lead at the Welmec-EPSRC Centre for Medical Engineering.

The hallmark of PsA is inflammation evident on MRI, ultrasound, or both, at attachment sites on the adjacent bone in florid PsA, says Dr. McGonagle. "And in animal models that have features of PsA, the disease typically starts in the attachment sites, then spreads to the adjacent soft tissue, leading to swelling and bone inflammation or osteitis." Together, these joint linings and attachments comprise the synovio-enthesial complex.[1]

"It is the soft tissue-tendon complex that becomes dactylitis," adds Dr. McInnes. (Dactylitis is the swelling of all digital joints, also called "sausage" fingers.) PsA can impact the axial skeleton, skin, and nails as well, says Dr. McInnes. The skin and gut might respond very differently to an immunologic threat, he notes, compared to the eye, which cannot afford a destructive response, because this would lead to blindness. "So you should not assume that the same pathway inhibitor will necessarily operate with the same magnitude of effect and therapeutic utility if you're comparing the skin, joint, eye, and gut," he says.

Yet dermatologists may be able to spot PsA early in patients with psoriasis by focusing on attachment sites or entheses, says Dr. McGonagle. Ultrasound scanning shows that 50% of patients with psoriasis who do not have clinical arthritis have evidence of enthesopathy or enthesitis.[2] "So in psoriasis clinics," he says, "up to half of patients who don't have any PsA symptoms have abnormalities at their attachment sites. This means that when patients come to dermatology with early PsA there will be no joint swelling. Dermatologists need to look out for abnormalities and insertion sites including painful heels, knees, bones, and back pain or chest wall pain. These disparate features occur because there are multiple insertion sites holding all the joints and the skeleton together."

Many PsA screening questionnaires are available online, Dr. McGonagle says. "About one in three people who have a positive screening questionnaire actually has PsA." Other causes of joint pain could include osteoarthritis, mechanical issues, or fibromyalgia, he says. Because the entheses are relatively difficult to image, "It's hard to prove beyond doubt whether the pain is due to inflammation or other issues. If there's any doubt, when treating the skin, pick a drug that has approval for arthritis to see if the joint component can be reversed." According to a recent study conducted at the University of Leeds, treating severe psoriasis with ustekinumab causes the subclinical arthritis present in up to half of patients with psoriasis to regress.[3] "So dermatologists are not only well placed to

1. McGonagle D, Lories RJU, Tan AL, Benjamin M. The concept of a "synovio-entheseal complex" and its implications for understanding joint inflammation and damage in psoriatic arthritis and beyond. *Arthritis Rheum.* 2007;56(8):2482-2491.
2. Gisondi P, Tinazzi I, El-Dalati G, et al. Lower limb enthesopathy in patients with psoriasis without clinical signs of arthropathy: a hospital-based case-control study. *Ann Rheum Dis.* 2008;67(1):26-30.
3. Savage L, Goodfield M, Hensor EMA, et al. Ultrasonic improvement of peripheral subclinical enthesopathy in therapy-naïve patients treated with ustekinumab for chronic plaque psoriasis: a 52-week, prospective, open label, controlled cohort study. [Abstract 960.] *Arthritis Rheum.* 2016; 68(Suppl 10). http://acrabstracts.org/abstract/ultrasonographic-improvement-of-peripheral-subclinical-enthesopathy-in-therapy-naive-patients-treated-with-ustekinumab-for-chronic-plaque-psoriasis-a-52-week-prospective-open-label-controlled-coho/. Accessed February 16, 2017.

treat psoriasis, but there's evidence emerging that they may actually be preventing psoriatic arthritis by treating the skin disease."

The most recent PsA recommendations by the Group for Research and Assessment of Psoriasis and Psoriatic Arthritis (GRAPPA) suggest considering a patient's previous treatments, preferences, and comorbidities, and choosing treatments that address as many afflicted domains as possible.[4] For example, nonsteroidal anti-inflammatory drugs (NSAIDs) are first-line therapy for axial disease, enthesitis, and dactylitis.

"For axial, peripheral articular, and enthesial disease, the best evidence supports the use of biologics," says Dr. McInnes. In Phase 3 clinical trials, tumor necrosis factor (TNF) alpha inhibitors achieved 20% reductions in American College of Rheumatology scores (ACR20) in 50% to 60% of patients.[5-9] "TNF blockers revolutionized therapy 15 years ago," says Dr. McInnes. Although they are effective drugs with satisfactory safety profiles that rheumatologists and dermatologists are very comfortable using, he adds, "The problem is that over time, people will discontinue their TNF blocker. After 5 years, in most of our registries, about half of patients will no longer be on the drug they started" because they have lost response to it. And when patients subsequently try different TNF inhibitors, "The magnitude of response diminishes."[10-12]

> "The secret is communication and partnership."

Biologic drugs with new modes of action have been very welcome, he says. With IL17 blockers such as secukinumab, "We're moving progressively downstream in the pathogenesis of psoriatic arthritis. The IL17A cytokines belong to the wider IL17 superfamily that mediates many of the effector responses driven by IL12 and IL23. In the FUTURE 2 trial, 50% to 55% reached ACR20 at week 24, and maintained this level through one year.[13,14] In ACR50 responses, he says, "There is no real difference between 150 and 300 mg exposure," with 35% of patients at either dose reaching ACR 50 at week 24, versus 44% (300 mg) and 39% (150 mg) at week 52. TNF-naïve patients exhibited slightly higher week 52 ACR50 response rates (79.4% and 68.7% for secukinumab 300 mg and 150 mg, respectively) than those who had previous TNF exposure (54.5% and 37.8% for secukinumab 300 mg and 150 mg, respectively).

Encouraging results emerged in the treatment of enthesitis and dactylitis, says Dr. McInnes. "Over one year of therapy for the 300 mg and 150 mg doses, a very satisfactory proportion of patients resolved these highly troublesome clinical features, which often are present in the absence of other musculoskeletal manifestations." Enthesitis resolved in 53.6% of patients on the 300 mg dose and in 48.4% on the 150 mg dose; the corresponding figures for dactylitis were 69.6% and 65.6%.[13,14]

Thanks to earlier recognition and treatment of PsA, continues Dr. McInnes, only about 10% of patients who present at his practice suffer from joint erosion visible on x-rays (radiographic progression [RP]). "Nevertheless, it is an important regulatory requirement that we show that interventions stop erosions." In the FUTURE trials, patients on placebo progressed slightly, while those on secukinumab experienced virtually no RP.[15] "This tells us that the drug is anti-erosive," says Dr. McInnes.

Safety findings in the FUTURE trials mirrored those of secukinumab trials in psoriasis.[16,17] In FUTURE 2, adverse event rates of secukinumab and placebo were similar in number and nature at week 16, with nasopharyngitis and headache topping the list. By week 52, these AEs occurred less frequently for secukinumab users (nasopharyngitis, 13.5% at 300 mg dose, 12.3% at 150 mg) than for patients on placebo (24.2%). Headaches impacted 5.9% and 6.5% of secukinumab users taking 300 mg and 150 mg, respectively, versus 14.9% for placebo. Because Candida infections occurred more frequently with secukinumab than with placebo, study authors wrote that "Continued vigilance for such infections will be needed during assessment of inhibitors of this pathway."[13] An integrated review of safety in all secukinumab studies for PsA mirrored these findings.[18]

Logistically, Dr. McInnes says, when managing patients with psoriasis and PsA, "The secret is communication and partnership. Once monthly, we run a combination clinic – dermatologists and rheumatologists seeing patients together. It makes an extraordinary difference for patients. We do not say, 'Your joints are wonderful, but your skin is awful. The dermatologist will see you in 6 weeks,'" or vice versa. Although psoriasis and PsA affect heterogeneous tissues, he says, "The responsibility for managing the totality of the syndrome lies with us as a team."

The same approach applies to comorbidities, he says. "Our patients face a multiplicity of challenges beyond the skin and joints. They're more likely to die of vascular disease. They are far more likely to have metabolic

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syndrome. And we have recently published research showing that they have direct abnormalities of the hippocampus. They are more likely to be depressed than healthy controls, and they're not depressed simply because they have psoriatic arthritis. They seem to be depressed in addition because they have an inflammatory-like disease of the hippocampus with abnormalities of serotonergic signaling."[19] (For more information, please see "Focus on Comorbidities" on page 8.)

To manage comorbidities, "We measure blood pressure and body mass index (BMI) at every visit. We measure cholesterol once a year," says Dr. McInnes. "And even if we don't prescribe statins or blood pressure medications, we insist that they are prescribed, and we monitor and follow that prescription. Diabetologists take responsibility for diabetic nephropathy and retinopathy. Why should we not as physicians take responsibility for the comorbid complications of our disease?" <<<

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