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The National Psoriasis Foundation

Reports on the 2016 AAD Meeting, Supported by Novartis

Volume I

The Role of IL-17 in Psoriasis

IL-17: A Driving Force in the Pathology of Psoriasis

Interleukin17 (IL-17) is produced by Th17 cells, as well as other lymphocytes, mast cells, and monocytes, and is a key cytokine that drives the pathology of psoriasis, psoriatic arthritis (PsA), and ankylosing spondylitis, says Philip Mease, M.D., director of the Rheumatology Clinical Research Division at the Swedish Medical Center in Seattle, WA, and clinical professor at the University of Washington School of Medicine in Seattle. It does so, he says, "by stimulating effector cells such as chondrocytes, fibroblasts, various other immune cells to produce metalloproteinases, and other molecules that lead to destruction of cartilage and bone." He adds that IL-17 also leads to the stimulation and proliferation of keratinocytes, the skin cells that when increased in number lead to the pathology we see in psoriasis—the erythematous, scaly lesions on the skin that can be quite extensive, itchy, and cosmetically embarrassing for patients.[1]

Increased IL-17 Levels in Psoriasis Flare

Dr. Mease notes that both the Th17 and IL-17 cells and the cytokine are prominently a part of the innate immune system. He explains that "when there is an infection or trauma or when there's gut inflammation, there can be initiation of over-production of interleukin,[2,3] which in turn stimulates the differentiation and activation of Th17 cells and then the over-production of IL-17." He goes on to say that "this is one of the explanations for why we see flares of psoriasis."

"This biology of psoriasis—this cascade effect of IL-23, stimulating Th17 cells, stimulating the production of IL-17, for example, in the context of infection or trauma to the skin or changes in the gut microbiome—we know because IL-17 is seen in increased amounts when you do a biopsy of the skin of psoriasis, the synovial tissue of PsA, or some of the tissue in ankylosing spondylitis," Dr. Mease explains.

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Mechanism of Action of IL-17 Inhibitors

What is the outcome when psoriasis is treated with a medication that is known to inhibit IL-17? "By blocking IL-17, you're blocking a fundamental part of the cytokine cascade involved in this disease, ultimately limiting epidermal hyperproliferation, decreasing angiogenesis, and decreasing immune cell activation," says Joel M. Gelfand, M.D., MSCE, associate professor of dermatology and epidemiology, medical director of the Dermatology Clinical Studies Unit in the Department of Dermatology, and director of the Psoriasis and Phototherapy Treatment Center, all at the University of Pennsylvania Perelman School of Medicine in Philadelphia. The result of this activity, Dr. Gelfand says, is rapidly clearing psoriatic skin disease as well as improvement in inflammatory joint disease.

Trial Results of IL-17 Inhibitors

The 2 direct inhibitors of IL-17A that have been approved by the U.S. Food and Drug Administration (FDA) are secukinumab and ixekizumab, notes Dr. Mease. "Secukinumab is now approved for treatment of psoriasis, PsA, and ankylosing spondylitis, and ixekizumab is now approved to treat psoriasis, and it is in development with ongoing studies in PsA and ankylosing spondylitis," he says.

Trials evaluating the effects of the IL-17 inhibitors have shown a striking benefit for psoriasis, says Dr. Mease, with Psoriasis Area and Severity Index (PASI) 75 response rates seen in more than 80% of patients versus less than 60% given placebo, and PASI 90 response rates seen in about 50% of patients versus 5% given placebo.[2] "These are really high levels of response in psoriasis," he says, "and the effect is rather rapid and

Comorbidities Include Migraine, Stroke, and More

As research continues to examine the comorbidities of psoriasis, links to neurological problems and uveitis are emerging. A small study shows that treating psoriasis with biologic drugs may provide protection against cardiovascular disease.

In one study involving a Danish national database, incidence ratios of new-onset migraines among patients with mild psoriasis, severe psoriasis, or psoriatic arthritis (PSA, with or without psoriasis) ranged from 1.37 to 1.92 per 1,000 patient-years.[1] "This is significant because patients with psoriasis have a known risk for stroke. There's also known to be a risk of stroke among patients who suffer from migraine," says Jashin J. Wu, M.D., director of dermatology research at Kaiser Permanente Los Angeles Medical Center in California.

"Uveitis is a known risk for psoriasis, but it's not well studied," adds Dr. Wu. Another study using the Danish database showed incidence ratios for new-onset uveitis of 1.38 ($P = 0.02$), 1.40 ($P = 0.34$), and 2.50 ($P < 0.001$), respectively for patients with mild psoriasis, severe psoriasis, or PSA with or without psoriasis.[2]

A third study using the Danish database revealed that patients with mild or severe psoriasis had incidence ratios for new-onset-multiple sclerosis (MS) of 1.84 and 2.61 per 10,000 patient-years, respectively.[3] "If a patient has a first-degree relative with MS," says Dr. Wu, "that patient should not be given a TNF inhibitor because it could bring on new-onset MS."

These 3 studies add to the already long list of psoriasis comorbidities, he says. "You may not need to screen for them, but at every visit, I ask the patient if he or she is having any new symptoms. Patients with psoriasis could also have something else, like uveitis, migraines, MS, or any of the other comorbidities that we're aware of."

In a prospective pilot study, researchers used echocardiogram results to examine whether biologic drugs impact left ventricular function in 18 patients (14 on adalimumab, 4 on ustekinumab) with severe psoriasis who also had subclinical systolic and diastolic dysfunction. After 3 months of treatment, says Dr. Wu, all 18 patients improved in terms of systolic and diastolic function.[4] "There were no changes in ejection fraction, body mass index, or other markers. Investigators theorized that early treatment possibly may be useful to reverse subclinical myocardial dysfunction, and that if patients are maintained on long-term therapy, this may translate into reduced cardiovascular risk."

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Dr. Wu has received research funding from AbbVie, Amgen, AstraZeneca, Boehringer Ingelheim, Coherus Biosciences, Dermira, Eli Lilly, Janssen, Merck, Novartis, Pfizer, Regeneron, Sandoz, and Sun Pharmaceutical Industries. He is a consultant for AbbVie, Amgen, Celgene, Dermira, Eli Lilly, Pfizer, Regeneron, and Sun Pharmaceutical Industries.

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it's quite sustained, as patients in these trials have been tracked now over several years of treatment."

"When a person has psoriasis and PsA," says Dr. Mease, "they have a double whammy, which is having both the pain and disability of the arthritis and the socio-embarrassment and discomfort of the psoriasis." In patients with PsA who were treated with IL-17 inhibitors, he says, "we also see the same improvement in the skin manifestations." As for the arthritis, Dr. Mease notes, "we see American College of Rheumatology (ACR) 20 responses that are in the 50% to 60% range and ACR 50 in actually the 40% range."[3,4]

"These levels of responses are similar to what we've seen with previous biologic therapies in PsA," adds Dr. Mease. This is good news, he explains, because it means that the IL-17 inhibitors can be employed as the first biologic that a patient uses and they can be used after a patient has tried an anti-tumor necrosis factor a (anti-TNF-a) agent that either had a good response but lost the response over time or never had a response in the first place.

"The reason why we think IL-17 is so important in psoriasis," says Dr. Gelfand, "is that the studies of the antibodies that block IL-17 have yielded response rates greater than ever seen before, and they're notable not only for their absolute odds of making the skin clear or completely clear but also in how rapidly they work. Within 2 to 4 weeks, many patients are achieving almost clear skin, which is unprecedented."

IL-17 Inhibitor Treatment

The dosing regimen of an IL-17 inhibitor for skin disease is different from that for joint disease, says Dr. Gelfand. "We currently have 2 FDA-approved IL-17 inhibitors for psoriasis of the skin and we have an IL-17 inhibitor approved for the joint disease as well as ankylosing spondylitis; ixekizumab is approved for just the skin currently, although that may change over time, whereas secukinumab is approved for psoriasis, PsA, and ankylosing spondylitis." According to the prescribing information for secukinumab, for psoriasis, 300 mg by subcutaneous injection for the first 5 weeks (0, 1, 2, 3, and 4), followed by 300 mg every 4 weeks, is recommended.

"The bottom line is that the treatment trials validate the mechanism data that we know—that Th17 cells and the products of IL-17 are important in the pathology of psoriasis, psoriatic arthritis, and ankylosing spondylitis—and we see, as a consequence of the inhibition of IL-17, good clinical benefits."

Philip Mease, M.D.
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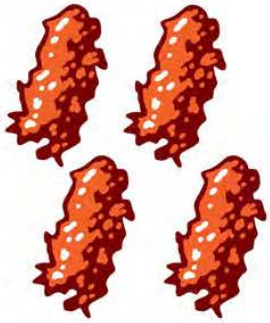
For some patients, this regimen (subcutaneous injections weekly for 5 weeks and then monthly thereafter) with a dose of 150 mg may be acceptable.

For ixekizumab, the recommended dose is 160 mg—two 80-mg injections—at week 0, then 80 mg every 2 weeks for 12 weeks,

INTERLEUKIN 17-A (IL-17A) IN PSORIASIS

A MESSENGER PROTEIN (OR CYTOKINE) FOUND TO PLAY A KEY ROLE IN PSORIASIS AND OTHER AUTOIMMUNE DISEASES[1]

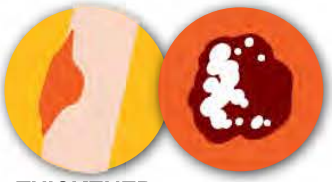
HOW INCREASED LEVELS OF IL-17A AFFECT THE SKIN IN PSORIASIS[2,3]



Increased levels of IL-17A

IL-17A signals to immune cells (keratinocytes), which hyperproliferate

Too many immune cells cause:



THICKENED SKIN

PLAQUES

IL-17A signals to the immune cells to go to infection site

Immune cells cause inflammation leading to:

ITCHING

REDNESS

FEEDBACK LOOP CREATED

The immune cells induce more secretion of IL-17A

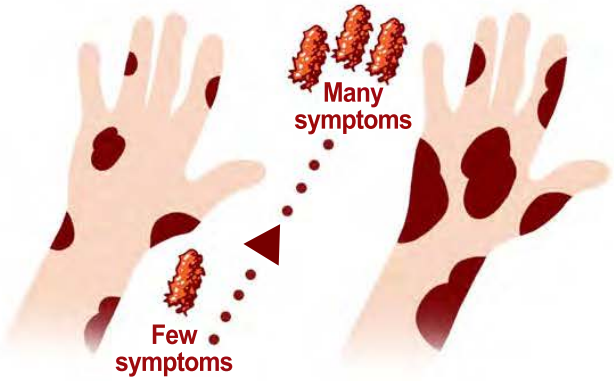
IL-17A wrongly continues to signal that more keratinocytes and immune cells are needed

IL-17A CAN AFFECT OTHER PARTS OF THE BODY[4,5]

JOINTS
Psoriatic arthritis

SPINE
Ankylosing spondylitis

HIGHER IL-17A LEVELS MAY CAUSE MORE SEVERE PSORIASIS SYMPTOMS[6,7]



IL-17A: A NEW POTENTIAL TARGET

Newer, innovative treatments have been developed in response to this unmet need. These treatments specifically target the cytokines that trigger inflammation, such as IL-17A interrupt the inflammatory cycle in psoriasis. They have shown positive results in the treatment and management of psoriasis.[4]

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and then 80 mg once a month. Dr. Gelfand points out that "the advantage of ixekizumab, our newest drug for psoriasis, is that it requires fewer subcutaneous injections than secukinumab does.

"An advantage of secukinumab is that it does have a currently FDA-approved label for other indications, including PsA," says Dr. Gelfand. "For insurance reasons, for example," he says, "secukinumab may be easier to obtain in those circumstances and also there could be a little more flexibility in the dosing." For instance, if a patient is completely clear with 300 mg monthly, lowering the dose to 150 mg monthly can be considered, because the injections are divided, explains Dr. Gelfand. And that's important, he notes, because in clinical trials, there was a slightly higher risk of infection in patients receiving the higher dose of secukinumab compared to its lower dose.[5]

Risk of Infection: IL-17 Antagonists Versus Other Biologics

The safety profile of the IL-17 inhibitors is quite acceptable, says Dr. Mease. "There is a slight increase in risk for serious infection, but it's no more of an increase than we've seen with other biologic medications," he notes, "and also there is no specific signal that there is an increase in opportunistic infections like tuberculosis."

Results from a study presented at the 73rd Annual Meeting of the American Academy of Dermatology showed that, as a group, biologics do not increase the risk of infection compared to nonbiologic agents. Among the different biologic agents, higher rates of serious infection were seen with the TNF-a inhibitors infliximab (2.5%), adalimumab (2%), and etanercept (1.5%) than with ustekinumab (0.8%).[6]

"The reason why we think IL-17 is so important in psoriasis is that the studies of the antibodies that block IL-17 have yielded response rates greater than ever seen before."

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Candida Infections

"Since IL-17 is important for protection against surface fungal infection like Candida infection," says Dr. Mease, "it is one of the adverse effects we were watching for in the clinical trials." Studies have reported "a handful of cases of mild to moderate Candida infections[5]—for example, what we call oral thrush or sometimes mucocutaneous candida—but the infections generally were pretty easily treated with topical medications and did not need discontinuation of therapy," he explains. In clinical practice, Dr. Gelfand has found that some patients say, "I've been getting more colds. Is it related to my biologic?" In his experience, the types of infections associated with biologic therapy (common colds and conditions of that nature) usually do not require drug discontinuation and tend to be a minor problem.

"The bottom line," says Dr. Mease, "is that the treatment trials validate the mechanism data that we know—that Th17 cells and the products of IL-17 are important in the pathology of psoriasis, psoriatic arthritis, and ankylosing spondylitis—and we see, as a consequence of the inhibition of IL-17, good clinical benefits."

Other Potential Benefits of IL-17 Inhibitor Therapy

IL-17 inhibitor therapy may also improve other clinical domains, such as tendonitis of the Achilles tendon or the plantar shaft and dactylitis, in which a whole digit is swollen, says Dr. Mease. "We know from the trials involving ankylosing spondylitis that back inflammation may improve, and this may be seen not only in ankylosing spondylitis but also in PsA." Dr. Mease notes that "as a consequence of this, other important measures, like quality-of-life function, have been shown to be improved as well."

Outside of psoriasis and PsA, "at this point in time, we don't know if IL-17 inhibitor therapy has additional treatment benefits," says Dr. Gelfand. "For example, observational studies involving TNF-a inhibitors suggest they are associated with a decrease in the risk of cardiovascular disease. It's unknown what the effects of IL-17 inhibitors are on cardiovascular disease."

Some research suggests a protective effect of IL-17 inhibition on certain cancers,[7] and in some mouse models, it may be helpful in reducing breast-cancer-associated metastasis,[8] says Dr. Gelfand. However, he notes that "we don't have enough data yet to really know for certain if IL-17 inhibitors meaningfully alter the risk of cancer."

For more information, please visit:
www.aad.org

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Psoriasis Treatments Grow Increasingly Targeted

The growing availability of genetic and other information about psoriasis and the patients it affects is helping clinicians to target psoriasis treatments more effectively than ever.

Christopher Griffiths, M.D., is Foundation Professor of Dermatology on the Faculty of Medical and Human Sciences and NIHR Senior Investigator at the University of Manchester Health Science Center in the U.K., and president of the International Psoriasis Council. He says that in response to technological advances and rising healthcare costs, healthcare systems worldwide are moving toward the "4 Ps":

- Preventing disease
- Predicting outcomes and disease progression
- Personalizing treatments, and
- Participation by patients in healthcare decision making

This trend is newly underway in the approach to inflammatory skin disease and inflammatory disease overall, Dr. Griffiths says. In breast cancer, he adds, it is known that cancers that strongly express the human epidermal growth factor (HER-2) respond best to Herceptin (trastuzumab, Genentech). Given the high cost of such drugs, he says, most new cancer therapies come with a companion diagnostic he describes as "a bedside test that tells whether a patient will respond to a particular drug."

The introduction of new biologic therapies, says Dr. Griffiths, has brought about transformational change for patients with psoriasis, particularly for those whose psoriasis is severe. However, he points out, these therapies can be un-

predictable. "We know that not all people with severe psoriasis who go on biologic drugs respond. Some don't respond well. Some have side effects. Some respond initially but lose their response over time. We'd like to be able to use clinical, genetic, and immunological information before we put a patient on a biologic therapy to predict and then stratify the patient's response to that particular drug."

Rather than embark on a costly 3- to 6-month trial of a biologic drug that may fail, "Wouldn't it be nice if we could figure out the appropriate treatment for a particular patient initially?" asks Wilson Liao, M.D., associate professor of dermatology and director of the Psoriasis and Skin Treatment Center at the University of California, San Francisco (UCSF) School of Medicine.

Researchers have found that people with certain genetic variants either have a better or worse response to particular medications, says Dr. Liao. He notes that preliminary studies suggest that variants in 3 genes—TNFAIP3, TNFRSF1B, and CARD14—can predict a stronger or weaker response to TNF inhibitors. Patients with the human leukocyte antigen (HLA)-Cw6 variant tend to respond better to ustekinumab,[1,2] which targets interleukin (IL)-12 and IL-23, adds Dr. Griffiths. "There are a handful of other examples," but he says because these studies were smaller, it's difficult to draw robust conclusions from them.

Researchers have long known that genes play a role in psoriasis, says Dr. Liao. While 3% of the U.S. population has psoriasis, 33% of patients with psoriasis have a relative who has the disease. Among identical twins, he adds, the ratio is even higher. Because psoriasis is a complex genetic disease, he explains, "it's typically not one gene that gives you psoriasis or doesn't. It's a combination of genes plus environment," as is the case with eczema, vitiligo, lupus, and alopecia areata.

Dr. Liao says researchers interested in studying the genetics of psoriasis during the past decade at UCSF (including himself) have enrolled about 1,000 patients in a complex database that holds a broad range of information, from patients' type of psoriasis to their DNA data. In this project, he says, UCSF works with around a dozen collaborators worldwide that include, for example, institutions like Washington University in St. Louis, Missouri, and Anhui Medical University in Hefei, China, as well as individual researchers in Sweden, Scotland, and Barcelona.

Underscoring the importance of such comprehensive teamwork, Dr. Liao says, "Genetic advancement these days requires collaboration with other programs and universities. The more patients you have to study, the more precise you can be in locating psoriasis genes." Whereas earlier gene chip technology could examine 100 to 500 gene variants, he explains, today's gene chips can analyze up to 1 million variants—for just $50 to $100 per chip. "As of 2008, we had identified 3 psoriasis genes. Today, over 65 genes are known."

These genes tend to cluster in and affect certain pathways, mostly in the immune system, Dr. Liao continues. They include the NF-kB pathway, which impacts inflammation; the Th17 pathway, which drives processes ranging from angiogenesis to skin thickening and inflammation; and pathways that govern antigen presentation and innate immunity.

"We're starting to develop a picture of what's going wrong in psoriasis. Tiny parts of the immune system are a little bit off. That's exciting because it allows us potentially to target those pathways using drugs," says Dr. Liao.

"We've had secukinumab on the market [in the United States] for about a year," says Jeffrey M. Weinberg, M.D., associate clinical professor of dermatology at Mount Sinai School of Medicine in New York. This drug, he says, has recently been approved for psoriatic arthritis (PSA) and ankylosing spondylitis by the U.S. Food and Drug Administration (FDA). It was joined by ixekizumab in March 2016, when that drug earned FDA approval for moderate to severe plaque psoriasis. Dr. Weinberg notes that both secukinumab and ixekizumab have very high efficacy rates. "This class of medications gives us numbers we have not seen" with previous generations of biologics, he says.

In Phase III trials of all the IL-17 drugs, says Dr. Weinberg, 82% to 89% of patients achieved a 75% reduction in psoriasis area and severity index scores (PASI 75). With secukinumab, 59% of patients reached PASI 90, and 28.6% achieved PASI 100, or complete clearance. With ixekizumab, 68% to 70% achieved PASI 90, and 40.5% achieved PASI 100. Brodalumab is another drug in development that acts on the IL-17 signaling pathway by targeting the IL-17 receptor. In brodalumab Phase III trials, 72% to 75% of patients reached PASI 90, and 38% to 62% reached PASI 100, he says.

Overall, he says, "Safety has remained very strong with this class of drugs. New drugs need to be monitored carefully, but there's no major reason to believe we're going to see any particular toxicity" with IL-17 drugs, which he says provide faster responses, on average, than older biologics.

"Even though we know that many genes correspond to certain pathways," says Dr. Liao, "there are still perhaps 20 to 30 genes where we're not sure what pathway they belong to or what they do" in the pathogenesis of psoriasis. "That could lead us to a new pathway that could be targeted in the future with a new drug."

Of the 65 psoriasis genes, says Dr. Liao, the genomic region with the greatest impact is the human leukocyte antigen (HLA) region. "By knowing which HLA molecules are associated with psoriasis, researchers have been able to hunt down psoriasis autoantigens," including LL37 (cathelicidin, which resides in various cell types, among them keratinocytes).[3] "It's always been a mystery: What is that initial trigger in the skin that sets off the fire? Genetics has been giving us some helpful hints."

The impact of these mutations is usually subtle, Dr. Liao cautions. "It turns out that 85% of psoriasis variants impact gene expression; they don't directly affect the protein. It's not that having one mutation has a dramatic effect in causing the problem. It's the incremental buildup of many small mutations."

An exception is pustular psoriasis, which Dr. Liao estimates accounts for less than 5% of all psoriasis cases. "It is a very severe type of psoriasis—many of these patients must be hospitalized because they have severe skin inflammation and potentially skin breakdown. As opposed to typical psoriasis, pustular psoriasis potentially is caused more by these protein-changing mutations." Specifically, he says, exome sequencing, which allows sequencing of all 20,000 human genes in one experiment, has revealed that mutations affecting the protein-coding region in at least 5 genes appear to cause pustular psoriasis.[4]

"As we're learning more about the genes, we're starting to be able to tease out how a person's genes might influence age of onset and where on the body the psoriasis tends to manifest."

Wilson Liao, M.D.
University of California
San Francisco School of Medicine

Genetic research also is beginning to identify not only who may get psoriasis, but when and how it will develop. "Of the 65 psoriasis genes," says Dr. Liao, "the more variants you have, the younger you tend to develop psoriasis."[5] Additionally, it appears that mutations in HLA-Cw6 predispose patients to developing facial lesions at between 10 and 20 years of age.[6]

"As we're learning more about the genes, we're starting to be able to tease out how a person's genes might influence age of onset and where on the body the psoriasis tends to manifest," he says.

PSORTing Out Psoriasis

Dr. Griffiths has established Psoriasis Stratification to Optimize Relevant Therapy (PSORT), a Manchester-led consortium of U.K. scientists, clinicians, and pharmaceutical industry representatives working to elucidate which markers will predict response to psoriasis therapies—in this case, biologics. It is funded by the Medical Research Council, a publicly financed government agency responsible for coordinating and funding medical research in the U.K.

According to Dr. Griffiths, much of the study data will come from the British Association of Dermatologists Biologic Interventions Register (BADBIR), a national registry that comprises more than 11,000 patients taking biologic and conventional systemic medications for psoriasis. "Close to 40% of them also have biological information as well—DNA and/or serum samples—and we have detailed information on those patients at baseline. The registry was set up to examine the safety of biologic medicines, but simultaneously, it's a very powerful resource that allows us to track information on patients over many years," he says.

PSORT first will examine the HLA-Cw6 biomarker in relation to ustekinumab response, as well as predictors of low serum drug levels with various biologics. "These data will start to emerge over the next few months," says Dr. Griffiths.

Previous research has shown that 75% of patients with chronic plaque psoriasis develop it before age 40; the remainder develop it after age 40, says Dr. Griffiths. "Clinically, their diseases look very similar, but we know there are genetic differences." Patients with early-onset psoriasis are much more likely to be HLA-Cw6 positive, for example. However, Dr. Griffiths says that in all large psoriasis studies to date, the average patient age is the mid- to early 40s. "That means that the vast majority have early-onset psoriasis. We have no idea whether we can extrapolate the findings from early-onset psoriasis to late-onset psoriasis with any drug," he notes. To address this data gap, Dr. Griffiths stratified all patients in Pfizer's etanercept registry according to age of onset. "We showed that people with early-onset psoriasis

are much more likely to respond to etanercept than those with late-onset psoriasis.[7] By putting all this information together—age of onset, genetics, biomarkers in the skin, and blood—you can build up a picture of each individual patient."

Such data also could help identify which patients will progress to developing PSA. Physicians could then target these patients with earlier, more aggressive treatments to prevent joint destruction, says Dr. Griffiths. Treatment choices would depend on the individual circumstances, he says, but earlier use of methotrexate or anti-TNF biologic therapy would be indicated. All patients with psoriasis should be screened for PSA using an instrument such as the Psoriasis Epidemiology Screening Tool (PEST),[8] he adds.

"Many psoriasis genes have also been found to affect other autoimmune and cardiovascular diseases," says Dr. Liao. A UCSF study showed that 3 genes that contribute to cardiovascular issues such as heart attacks, high blood pressure, and coronary artery disease—FUT2, UBE2L3, and SH2B3—are increased in patients with psoriasis.[9] "The degree of overlap that we found was modest," he reports. "The reason that patients with psoriasis are getting heart problems is not purely from genetics, but more so because of systemic inflammation. If you have inflamed skin and an inflamed immune system, that inflammation essentially spills over into the blood vessels to cause heart problems." (For the latest information on psoriasis comorbidities, please see sidebar article "Comorbidities Include Migraine, Stroke, and More.")

Clinically, says Dr. Griffiths, "We know that patients with nail disease are less likely to have a fast or good response to adalimumab. We don't know why." With biologics in general, he says, patients who have high blood levels 4 weeks into treatment are much more likely to respond, and vice versa.

Pushing Patient Participation

"Think not what disease the person has, but what person the disease has." This ancient insight from the Greek physician Hippocrates is relevant to the treatment of psoriasis today, suggests Dr. Griffiths. "Managing psoriasis is not just managing the skin—it's identifying the psoriasis subtype and identifying and preventing PSA and cardiovascular disease. Lifestyle change and behavior modification are all parts of managing the patient." Getting patients to lose weight, exercise, stop smoking, or reduce alcohol consumption will improve their overall health, he says, and also may boost their response to treatment.

As the availability of healthcare data grows, says Dr. Griffiths, patients are becoming much more knowledgeable about their disease, and much more able to participate in disease management. "That might require using apps or other technology that allows them to track their disease remotely or receive reminders about taking their medications. Patients are much more engaged in the process now than they were in the past. That close association, or 'contract,' between physician and patient probably increases the chance that the patient will adhere to the prescribed regimen."

Patients appear ready for this transition, he says. The PSORT initiative has involved the Psoriasis Association of the U.K. every step of the way. "The patients themselves told us they didn't like trying various drugs until they found one that works for them. They wanted the opportunity—even if it may involve having a small punch biopsy, blood test, or buccal smear—to get on the best drug for them the first time, in a much more targeted manner."

Looking perhaps 10 to 20 years in the future, Dr. Griffiths says, "When someone with psoriasis presents to a dermatologist, the patient will have come the week before and had some blood tests, will have given some demographic information, and had a small skin biopsy." That information will allow the dermatologist to identify the patient's type of psoriasis.

"What we currently call psoriasis is not just a single disease; it's many very similar clinical diseases. But we will be able to discriminate between them using molecular markers or genetic tests, which will allow us to target patients' treatment much more precisely than we can at the moment," he says. Data gathered from patients also will help dermatologists identify which drug or drugs will work best, and most safely, for each patient. "I'm certain that's the way we're going to manage not only psoriasis, but also other inflammatory skin diseases, in the future."

For more information, please visit:
www.aad.org
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International Efforts Address Treatment Challenges

In many regions, dermatologists struggle to obtain the most effective treatments for their patients with psoriasis. In the Middle East and Latin America, obstacles include lack of awareness as well as lack of funding for psoriasis research and treatment, along with the high prevalence of endemic infectious diseases.

According to the World Health Organization (WHO), psoriasis impacts more than 100 million people worldwide, imposing significant physical, financial, and social burdens. These problems will require concerted, multifaceted efforts to combat, according to WHO.[1]

"Everyone involved with the disease has to pitch in and help to the level of their capacity," says report reviewer Mahira El Sayed, M.D., professor of dermatology and venereology at Ain Shams Universities in Cairo, Egypt. Dr. El Sayed is forming a new patient association to battle local financial, logistical, and cultural challenges to psoriasis treatment.

Devastating Burden

In Egypt, says Dr. El Sayed, psoriasis carries a particularly devastating impact for young women. Social stigma and ignorance often prevent women with psoriasis from marrying. Married women who develop psoriasis are frequently divorced by husbands who worry that their children will contract the disease. Some patients—including many children—are prohibited from eating with their families and schoolmates for fear of contagion.

A young male lawyer under Dr. El Sayed's care suffers from severely incapacitating hand and foot psoriasis. "His father is desperate for any improvement," she says, because coworkers and clients will not accept the patient in the workplace.

"I rarely see a patient with psoriasis who is not upset or psychologically distressed about the disease and having problems living a normal life [in Egypt]," says Dr. El Sayed. I spend a lot of time to counsel each patient and make them understand the disease." For the young lawyer, she is also working to get access to biologic drugs.

"In our country, we are unable to supply our patients with new drugs, including biologics, which are becoming more of a habit in the West—especially in the United States and Europe." Biologics are extremely expensive, she explains, and the government does not provide any funding for psoriasis care and research, although diseases such as cancer and heart disease receive some government funding.

Noting that in the tropics, the skin is much more exposed because of all the outdoor activities, Brazil-

ian dermatologist Ricardo Romiti, M.D., Ph.D., says patients with psoriasis may avoid public beaches and pools.

"We're trying to make people understand that patients really need help, and that new medications should be available to all of them."

Mahira El Sayed, M.D.
Ain Shams Universities, Cairo

Dr. Romiti, who practices in the Department of Dermatology at the Hospital das Clínicas of the University of São Paulo (USP) in Brazil, says access for Brazilian patients to biologic drugs differs depending on the disease being treated and where the patient lives. "In some states, biologics for psoriasis are paid for by the government. For example, in São Paulo, the state government pays for this kind of treatment. In other states, such as Rio de Janeiro, the government does not pay. It's different from rheumatological or gastroenterological diseases, where biologic drugs are generally paid for by the federal government in Brazil. For psoriasis, it varies from state to state," he explains.

Biologic drugs approved for psoriasis in Brazil include adalimumab, etanercept, infliximab, ustekinumab, and more recently, secukinumab. "For patients with moderate to severe psoriasis, we have a treatment algorithm that was developed by the Brazilian Dermatological Society [SBD],"[2] explains Dr. Romiti. These guidelines recommend phototherapy as a first-line treatment. "If patients don't respond or are not able to undergo phototherapy because they live at a long distance, you should initiate systemic treatment such as methotrexate or a retinoid. If these medications have a contraindication, do not work for the patient, or the patient experiences side effects, then biologics are indicated."

Spreading the Word

Access to information about treatment, says Dr. Romiti, is a problem throughout Latin America, as well as Brazil, which has more than 200 million residents. "It's most important that patients become aware that nowadays we have very effective and safe therapeutic possibilities for moderate to severe psoriasis. Patients who live far from large academic centers don't have this information. Sometimes their disease is neglected due to ignorance."

It is for this reason, he says, that the SBD publishes treatment guidelines[2] and promotes campaigns to raise awareness about psoriasis "not just for patients but also for their families, friends, and non-dermatologists who may treat psoriasis." Several patient advocacy groups also help in this regard, he says.

To deal with this issue in Egypt, Dr. El Sayed says, "We are working to set up a patient association. It will be very important in helping patients talk about the disease. We're trying to make people understand that patients really need help, and that new medications should be available to all of them."

Ultimately, she says, "we need a national strategy for psoriasis that will involve all the health sectors. We are gathering a number of eminent professors from around the country to formulate guidelines for these patients." This group plans to present the guidelines and the scope of the psoriasis problem to Egypt's minister of health this fall.

For the past year, Dr. El Sayed has been recruiting patients to tell their stories. "It's not something that patients do easily," she notes. To help them, the association holds workshops. To raise public awareness, Dr. El Sayed has organized a fundraising run held on Egypt's National Psoriasis Day, along with a press conference to educate the media and the public about the importance of psoriasis treatment. She also has a weekly psoriasis clinic in Cairo, with help from several patient volunteers. "I treat and talk to patients, giving them encouragement to discuss their disease and bring their families," she says.

To educate younger dermatologists and doctors in small rural villages, Dr. El Sayed periodically travels throughout Egypt. "We tell them how to evaluate patients using assessment tools, how to treat patients, how to prescribe the right treatment, and when to hospitalize or refer the patient to a more specialized center. We need to do this for all healthcare providers and primary care physicians." She also invites young dermatologists from all over Egypt for similar education in her clinic.

Of the more than 7,500 dermatologists in Brazil, says Dr. Romiti, only about 10% treat moderate to severe psoriasis, which requires systemic therapies. "These patients are more time-consuming. You must ask for a lot of exams and follow-up. It's very hard work. Often, a specialist who doesn't deal specifically with more severe psoriasis on a daily basis prefers to refer the patient to a colleague with more experience in this area."

Studying Local Populations

Dr. El Sayed has conducted a study to better understand psoriasis in Egypt. "I've studied around 1,000 patients," she says, "trying to determine the types of psoriasis we have in Egypt, and

PSORIASIS

Nearly **3%** of the world's population is living with psoriasis[1]

More than **1/3** of patients with plaque psoriasis suffer from its moderate-to-severe form[2,3]

MORE THAN

125 MILLION[1]

PEOPLE ARE AFFECTED WORLDWIDE

EFFECT ON QUALITY OF LIFE[4-7]

PHYSICAL SYMPTOMS[8]

Thick, red skin · Scaling · Itching · Pain

COMORBIDITIES[4]

Depression · Diabetes · Psoriatic arthritis · Heart disease

UP TO 30% OF PEOPLE WITH PSORIASIS ARE AFFECTED BY PSORIATIC ARTHRITIS[8]

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NOVARTIS PHARMACEUTICALS

how different we are" from other ethnic groups, based on factors such as psoriasis severity and age of onset. This study identified 6 different psoriasis phenotypes in Egypt.[3] "Phenotypes are a way to differentiate patients from each other," she explains, providing a framework to determine what sort of treatment and budget each group requires.

Noting that mild disease is often easily treated with topical creams or ointments, Dr. El Sayed says this is not the case with more severe forms, especially in patients with comorbidities. "A large percentage of the population has moderate to severe disease, which takes longer to treat and is usually associated with many comorbidities, such as hypertension, diabetes, liver disease, heart disease, and atherosclerosis." (She is conducting a separate 500-patient study to assess the extent of heart disease in Egyptian patients with psoriasis.) "Many of our patients are smokers, and smoking is known to aggravate psoriasis."

Dr. El Sayed says many patients also have arthritis, which is often undiagnosed until very late in the disease course. One such patient, she says, was "a young boy with psoriatic arthritis so severe his fingers are deformed." Although he is now improving, thanks to twice-weekly treatment with etanercept subcutaneously, she says early diagnosis is important. "We will need to raise physician awareness about early detection and diagnosis of psoriasis so we can manage those patients before they advance to severe disease." Treating severe psoriasis in obese patients can prove very challenging, she adds. "Some of those patients don't respond to anything." In one such patient, "we started with methotrexate, but she did not respond. Then she developed hepatitis C virus (HCV)." Egyptian patients with psoriasis often have HCV, which Dr. El Sayed notes is highly prevalent in the region. To treat HCV, she says, the drug most often used in Egypt is methotrexate, because it's inexpensive and relatively safe, although it's contraindicated for patients with liver disease. Other treatments used for HCV, such as interferon, she adds, may aggravate psoriasis. Fortunately, she says, these patients can tolerate phototherapy, which is readily available at most academic medical centers.

Noting problems with complex patients such as the obese patient with psoriasis, she says, "We had to stop methotrexate and give her cyclosporine. She improved for a while, then rebounded again. Cyclosporine gives a very quick response, but a very quick rebound as well. We had to stop it because her kidney function declined. She had high blood pressure and diabetes. This is the type of patient I get—so complicated that I must play with the cocktail of drugs I have, trying one drug, then another, until something works. I depend on charities and the pharmaceutical industry."

Latent Tuberculosis

"Among the main concerns in tropical countries, not only in Latin America, but also in Africa and southern Asia, are specific infections," says Dr. Romiti. "Tuberculosis is very prevalent in these countries, so it's a big concern that patients taking biologics may activate latent tuberculosis." To avoid this problem, he says, dermatologists must carefully screen these patients before starting them on TNF blockers, in particular.

In Brazil, he explains, this involves following the international guidelines, which recommend taking an adequate patient history and performing an exam, a tuberculin-purified protein derivative (PPD) skin test, and a chest x-ray. Patients who show any signs of latent tuberculosis infection (LTBI), he adds, should be treated prophylactically using isoniazid 5 mg/kg or maximum 300 mg/day for 6 to 9 months in adults.

Yet, because LTBI is endemic in Latin America "even when you screen accurately, patients also may develop active tuberculosis" despite having no signs of LTBI before treatment," says Dr. Romiti. This was the case with a 26-year-old female patient he treated. "She had moderate to severe psoriasis for many years, and she had already been through phototherapy and methotrexate.

"These therapies didn't work after a time, so she started on anti-TNF treatment." After 4 months on this therapy, he says, she developed very widespread, disseminated tuberculosis that affected her skin as well as her kidneys and liver; she also had ocular symptoms. It was therefore necessary to discontinue the anti-TNF drug and have her undergo treatment for tuberculosis under the care of an infectious disease specialist. After completing treatment for TB, she was able to start systemic psoriasis therapy again, with ustekinumab. Three years later, he says, the patient showed no further psoriatic plaques (Psoriasis Area Severity Index/PASI=0) and no side effects related to the anti-IL12/23 therapy.

People with LTBI generally face a 5% to 10% risk of developing active TB, says Dr. Romiti. Those with LTBI who go on anti-TNF drugs face up to a 9-fold higher risk,[4] although drugs that block interleukin (IL)-12 and IL-23 have shown a lower risk concerning TB.[5] "It's a big concern for physicians dealing with anti-TNF drugs to advise the patient that in case of any atypical signs or symptoms of infection to call their physician or go to an emergency unit for an accurate diagnosis."

Increasingly, says Dr. Romiti, Brazilian dermatologists see associations between psoriasis and metabolic syndrome. "Many studies show that in Latin America, the incidence of metabolic syndrome is now equivalent to what we see in the United States and Europe.[6] We must check our patients with psoriasis for specific concerns such as hypertension, dyslipidemia, diabetes, and obesity." Considering the risk of high blood pressure, cardiovascular disease, and other diseases, he maintains, it's important to make a diagnosis of metabolic syndrome in psoriatic patients with these problems.

Dr. Romiti specifies medications that are contraindicated for patients with metabolic syndrome. Systemic retinoids including acitretin—which dermatologists commonly prescribe for moderate to severe psoriasis in Brazil—may elevate serum triglyceride and cholesterol levels; and because methotrexate can impact the liver, he adds, it's important to make sure that patients who take this drug do not have functional abnormalities due to fatty liver before initiating treatment. "You must screen your patients thoroughly before indicating any systemic therapy," he urges.

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Disclosures
Dr. Romiti is a consultant and investigator for AbbVie, Janssen, Leo, Eli Lilly, Novartis, and Pfizer. Dr. El Sayed has been an advisory board member and speaker for AbbVie, Janssen, Leo, Novartis, and Pfizer.

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Hand and Foot Psoriasis Poses Unique Problems

The unique nature of acral skin can thwart the diagnosis and treatment of palmoplantar psoriasis. Fortunately, this type of psoriasis often responds to appropriately selected systemic treatments.

Differential Diagnosis

The morphology of commonly seen dermatoses varies on the palms and soles owing to the distinctive characteristics of palmoplantar skin, says Robert Bissonnette, M.D., president of Innovaderm Research in Montréal, Canada, and a Montréal-based dermatologist in private practice. Dr. Bissonnette stresses characteristics that hinder the diagnosis of hand and foot psoriasis. "Sometimes it's very typical, with silvery, well demarcated plaques. But when it's on the palmar and plantar areas, it's often more difficult."

Plaques on the hands and feet are often less well demarcated than plaques elsewhere, he explains. "There can be erythema, and it can be difficult to determine if it's associated with psoriasis or with a variant clinical presentation. Some patients tend to have feet and hands that are redder than others." Additionally, patients can have hyperkeratosis on the feet due to friction created by footwear.

Dr. Bissonnette suggests looking for clues on other body areas normally impacted by psoriasis. "The scalp, nails, and skin folds are often overlooked by patients. Often patients have the typical signs of psoriasis in these areas, but they've never noticed," he says. Somewhat similarly, he notes, around 30% of psoriatic patients also have psoriatic arthritis. "The presence of an inflammatory arthritis and some skin lesions suggestive of psoriasis makes that

diagnosis a higher possibility." When patients present with scaly, erythematous skin problems of the hands and feet, he says, dermatologists typically think of psoriasis and dermatitis. "Consider a broader differential diagnosis that includes common skin diseases such as allergic contact dermatitis, atopic dermatitis (AD), or irritant contact dermatitis (ICD)," he suggests.

Hand dermatitis is even more common than hand and foot psoriasis, says Dr. Bissonnette, and he recommends being alert to clues that can steer the diagnosis toward dermatitis, including poorly demarcated plaques. Contact dermatitis, he says, often affects skin between fingers. "Fissures can be seen in psoriasis, but only in very hyperkeratotic plaques."

In rare cases, he says, the morphology of a patient will fluctuate between psoriasis and dermatitis. "It's hard to tell if it's the morphology that changes from one month or year to another, or the disease changing from a mostly interleukin (IL) 17/Th1-driven disease (psoriasis) to a more Th2-driven disease (AD). Occasionally, we see patients who have typical psoriasis morphology that evolves over time into a more dermatitis-like morphology. Then it can revert back to psoriasis." The systemic retinoid alitretinoin is approved in Canada and many other countries for hand dermatitis, but this is not yet the case in the United States, he says.

Less common diseases not to be overlooked in the differential diagnosis of palmoplantar psoriasis include syphilis, which can induce small papulosquamous lesions on the hands and feet, and T-cell lymphoma, says Dr. Bissonnette.

"In my experience, skin biopsy is not very helpful in confirming a diagnosis of psoriasis in cases where I'm not sure. But it is useful to exclude other diagnoses, such as T-cell lymphoma. And a scraping would be useful to exclude a dermatophyte infection," he advises.

Treating Hand and Foot Psoriasis

With palmoplantar psoriasis, Dr. Bissonnette says, "Do not hesitate to use systemic therapy. Even with potent topical corticosteroids, results are usually disappointing."

Dr. Bissonnette notes that a "dermatologist's first line of therapy is usually topical therapy," especially when lesions affect small skin areas. However, he points out, the thicker stratum corneum and lack of pilosebaceous units on the palms and soles limit penetration of topical agents, to the point that these agents often work only for mild and sometimes moderate hand and foot psoriasis.

"Even with our most efficacious treatments, efficacy on the hands and feet falls far below what it is elsewhere," he says. For example, for moderate to severe psoriasis, biologic drugs typically achieve physician assessments of clear or almost clear for 70% to 85% of patients after 12 weeks' treatment. When the same agents are used for a trial of hand and foot psoriasis, he explains, "only about 30% of patients are clear or almost clear."

Among systemic treatments, Dr. Bissonnette says that phototherapy is often disappointing when used for palms and soles due to poor penetration and poor patient compliance. He says he usually considers acitretin his first choice in patients with hand and foot psoriasis—"especially males and postmenopausal female patients who have no contraindications." He generally starts with 10 mg daily, or even every other day, and slowly increases to 20 mg daily for palmoplantar psoriasis (versus 25 mg daily or more for generalized psoriasis). Other options are methotrexate and biologics.

Palmoplantar Pustulosis

Also in the differential diagnosis, Dr. Bissonnette says, dermatologists should consider palmoplantar pustulosis (PPP)—by far the most common pustular presentation of hand and foot disease seen by dermatologists. "There's a controversy: Does PPP exist as a standalone entity, or is it a variant of palmoplantar psoriasis? Some authors believe these are 2 different diseases. I believe that either they are the same disease, or there's significant overlap."

While the pathophysiology of PPP remains poorly understood, Dr. Bissonnette points to recent evidence showing that cathelicidins could be involved in PPP.[1] He notes another recent study showing that loss-of-function mutations in IL36RN have been associated with generalized pustular psoriasis but not with PPP.[2] "This is the best study, to my knowledge, which has explored the role of IL36RN variants in PPP. It compares more than 250 patients with PPP to patients without PPP."

There may be a genetic component to PPP, says Dr. Bissonnette. Among Japanese women 55 to 59 years old, he explains, PPP affects 300 per 100,000 population, a prevalence rate almost as high as that of psoriasis vulgaris in the same Japanese population. Further, he says, "Many publications in the Japanese literature report an association between PPP and recurrent tonsillitis or gingivitis. There are reports of patients with PPP who have improved significantly or even cleared after a tonsillectomy."[3]

A key difference between PPP and palmoplantar psoriasis is that almost all patients with PPP tend to be smokers or ex-smokers. "There's evidence that stopping smoking improves the disease,[4] so it's always something I try with my patients who are smokers. I've seen good improvement, but it doesn't tend to cure the disease," he says. For these patients, he notes, potent topical steroids combined with smoking cessation often suffice to control residual PPP.

Because PPP has been associated with hypothyroidism, he adds, "This is something that should be investigated in these patients. Its prevalence in patients with PPP is as high as 25%."

For treating PPP, Dr. Bissonnette finds that acitretin tends to work very well in low doses. "I start at 10 mg daily or even every other day," he says. "I go very slowly, specifically for the first month, because patients tend to be scared of the side-effect profile they find on the Internet or in the package insert," which includes alopecia, cheilitis, and, rarely, liver toxicity and increased cholesterol. Acitretin is also highly teratogenic.

Starting conservatively usually shows patients they can tolerate the drug, Dr. Bissonnette says. "I increase the dosage progressively" after the first month, he says. "As soon as I see some efficacy, I stop increasing doses and wait." Most patients are controlled with doses between 10 and 20 mg daily. Doses above 30 mg daily often induce too many side effects, he says, so patients prefer to explore other treatment alternatives.

Because acitretin works more slowly than biologics, Dr. Bissonnette tells individuals receiving care that "they need to be patient, whether you're treating PPP or palmoplantar psoriasis." For PPP, he maintains the highest dose tolerated by the patient through the third and fourth month of treatment, or until response plateaus.

For more information, please visit:
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