Supplement to

December 2019

practical dermatology®

MECHANISM OF ACTION MATTERS: A REVIEW OF NEW AND EMERGING BIOLOGICS

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A CME activity provided by the University of Cincinnati.

Supported by an educational grant from Janssen Biotech Inc., administered by Janssen Scientific Affairs LLC, and Bausch Health US.

Mechanism of Action Matters: A Review of New and Emerging Biologics

Release Date: December 2019
Expiration Date: December 2020

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CONTENT SOURCE

This continuing medical education (CME) activity captures content from a virtual roundtable discussion.

ACTIVITY DESCRIPTION

The term biologic usually refers to the group of complex molecules, such as monoclonal antibodies and receptor fusion proteins, developed to target specific proteins implicated in a variety of immune-mediated diseases, including psoriasis and other cutaneous diseases. Biologic agents have transformed the treatment of psoriasis. This panel discussion focuses on mechanism of action (MOA) of these therapeutic agents and how MOA affects clinical decision-making.

TARGET AUDIENCE

This certified CME activity is designed for dermatologists involved in the management of psoriasis and other cutaneous diseases.

LEARNING OBJECTIVES

Upon completion of this activity, the participant should be able to:

- **Define** biologic therapy.
- **Review** the MOA of approved and emerging biologics for the treatment of moderate to severe psoriasis.
- **Review** the MOA of approved and emerging biologics for the treatment of cutaneous diseases other than psoriasis.
- **Discuss** how the MOA of biologic therapeutics may affect clinical decision-making in dermatologic practice.

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1. Please rate your confidence in your ability to describe the mechanism of action (MOA) of approved and emerging biologics for the treatment of moderate to severe psoriasis (based on a scale of 1 to 5, with 1 being not at all confident and 5 being extremely confident).

a. 1
b. 2
c. 3
d. 4
e. 5

2. Please rate your confidence in your ability to understand how the MOA of biologic therapeutics may affect clinical decision-making in dermatologic practice (based on a scale of 1 to 5, with 1 being not at all confident and 5 being extremely confident).

a. 1
b. 2
c. 3
d. 4
e. 5

3. Which of the following agents is approved by the US Food and Drug Administration (FDA) for the treatment of moderate to severe psoriasis and psoriatic arthritis?

A. Bimekizumab
B. Risankizumab
C. Ustekinumab
D. Tildrakizumab

4. Which of the following biologic agents is a human monoclonal antibody that prevents binding of IL-17A, IL-17F, and IL-25 to the shared IL-17RA receptor?

A. Adalimumab
B. Etanercept
C. Brodalumab
D. Ixekizumab

5. Which of the following agents is a TNF-α inhibitor approved by the FDA for the treatment of hidradenitis suppurativa?

A. Omalizumab
B. Infliximab
C. Dupilumab
D. Adalimumab

6. You are treating a 26-year-old woman with moderate to severe psoriasis affecting 25% of her body surface area, including her scalp and nails. She has a family history of type 2 diabetes and cardiovascular disease. Her body mass index is 30 kg/m^2, and she has a history of optic neuritis. She was treated by her previous dermatologist with topical medications, to which she did not respond. She was then switched to methotrexate, but she could not tolerate the drug. You are considering initiating biologic therapy. Which of the following biologic classes would be a problematic choice given her history of demyelinating disease?

A. Interleukin (IL)-23 agents
B. Tumor necrosis factor-α agents
C. IL-17 agents
D. IL-12/23 agent

7. Which One of the following statements about biologic agents is true?

A. Biologics can be administered orally or subcutaneously.
B. Biologics are able to enter cells easily because they have a low molecular weight.
C. Biologics are proteins with highly specific targets.
D. As of November 2019, there were 8 biologic agents approved for the treatment of moderate to severe psoriasis.

Mechanism of Action Matters: A Review of New and Emerging Biologics

The category of biologics includes a wide range of products of natural origin, including vaccines, blood components, gene therapy, and recombinant therapeutic proteins.[1] Biologics are isolated from a variety of natural sources and produced by biotechnology and other cutting-edge technologies.

Today the term biologic usually refers to the group of complex molecules, such as monoclonal antibodies and receptor fusion proteins, developed to target specific proteins implicated in a variety of immune-mediated diseases, including psoriasis and other cutaneous diseases.[1-3] Biologics are structurally complex, larger molecular weight proteins derived from living cells cultured in a laboratory.[1,3] They must be administered by subcutaneous or intravenous injection because they degrade in the gastrointestinal tract if administered orally.

Biologic agents have transformed the treatment of psoriasis. In the following panel discussion, Joel L. Cohen, MD, FAAD, and Adam Friedman, MD, FAAD, moderate a discussion with Alan Menter, MD, and Joel M. Gelfand, MD, MSCE, about the current role of biologic agents in the treatment of psoriasis, with a focus on mechanism of action (MOA) and how MOA affects clinical decision-making.

WHAT IS A BIOLOGIC?

Q | ADAM FRIEDMAN, MD: Dr. Menter, you've been in the field of psoriasis and biologics since it began. Could you please describe how you discuss biologics with medical students and patients?

ALAN MENTER, MD: When discussing this topic with medical students as well as patients, I use common English that everyone can understand. I let patients know that we now have 11 US Food and Drug Administration (FDA)-approved biologic agents (Table 1), and I show them the joint guidelines from the American Academy of Dermatology and the National Psoriasis Foundation that came out in April 2019.[4] I use the term "immunomodulator" when discussing biologics, because patients have seen the television advertisements and done Google searches, and they come to us with the idea that biologics suppress the immune system. So I tell them we are no longer suppressing the immune system like we were 20 or 30 years ago with methotrexate, cyclosporine, and other drugs. I let them know we now have specific agents—and I use the term "agents"—that modulate the immune system, bring it back to normal.

DR. FRIEDMAN: I agree that it's so important to change the lexicon. I explain to patients that biologics are protein-based therapies geared to the biological underpinnings of their disease. These are not drugs that are ingested and then broken down through the liver with a lot of off-target effects. These are selective, personalized, focused agents.

JOEL L. COHEN, MD: Dr. Menter, do you have a favorite figure you use to explain the MOAs of biologics to patients or medical students?

DR. MENTER: The figure published in the *New England Journal of Medicine* in 2009 is probably the most frequently cited.[8] I've taken that complex illustration and made it very simple, and I keep it on the wall of my office (Figure 1). I show patients the pathways and explain that by gobbling up the excess amount of this chemical—and I say chemical rather than cytokine—and I point to, for example, tumor necrosis factor (TNF)-α, or interleukin (IL)-17, or IL-23, the immune system is brought back to normal.

DR. COHEN: Dr. Gelfand, what figure do you prefer to illustrate the pathophysiology of psoriasis?

JOEL M. GELFAND, MD, MSCE: I like the illustration from the article by Michelle Lowes and colleagues (Figure 2).[9] It shows how keratinocytes and melanocytes likely stimulate an initial immune reaction that then evolves into a problem of innate and adaptive immunity. It then shows where the targets are along the line: where TNF plays a role, where IL-17 plays a role, where IL-23 plays a role. I find this figure helpful when I explain the targeted, rational design of the therapies we use for psoriasis.

DR. COHEN: To that point Joel, could you discuss pathogenesis from a high-level view? Could you walk us through the pathways of what we see clinically from a biological, cellular perspective?

DR. GELFAND: The first question patients want answered is "Why do I have this disease?" The second question they need answered is "How does the disease work?" so they can understand why we are recommending certain treatments.

I first explain genetic susceptibility, the multiple genes we inherit from our parents that make us potentially more susceptible to develop this type of immunologic reaction. I explain that psoriasis is not inherited like eye color or skin color, it's more complicated in that multiple genes are involved.[10] I explain that roughly 40% of patients have a family history, which means 60% of patients do not.[11] It is not uncommon for patients in my practice to be concerned about having

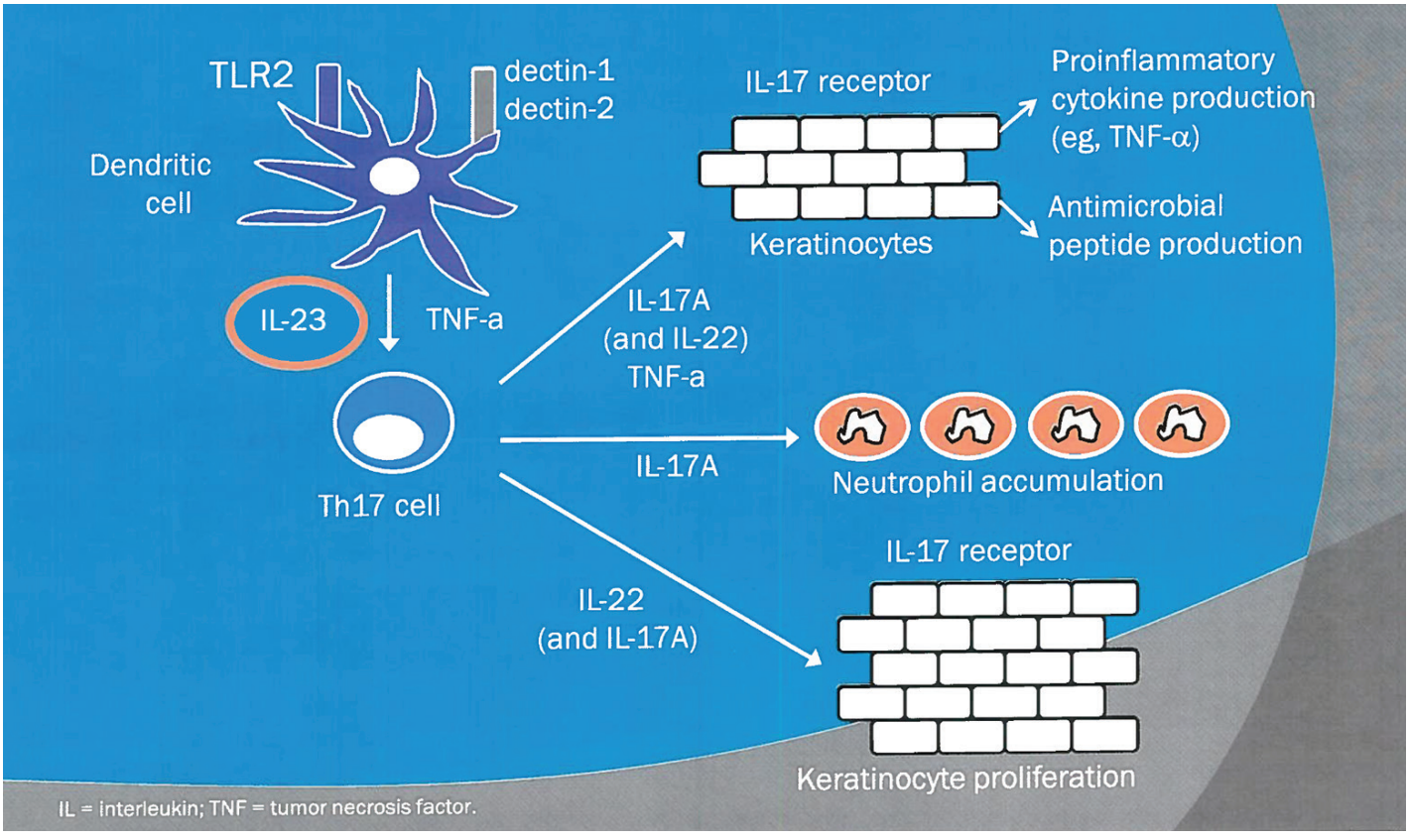

Figure 1. Dr. Menter's favorite illustration to explain the MOAs of biologics to patients.

children or to be anxious that their kids will develop severe psoriasis like they have. I explain that the likelihood is actually pretty low—roughly a 15%-20% lifetime risk when one parent has psoriasis.[10,11]

I then explain what happens biologically: Somehow the immune system got tricked, and over time it recognizes proteins that our skin makes as abnormal when they're actually normal. Physicians should know that there are two major antigens identified. One is keratinocyte-derived, a cathelicidin called LL37, and one is melanocyte-derived, ADAMTSL5 [A Disintegrin-like and Metalloprotease domain containing Thrombospondin type 1 motif-like 5].[12]

I explain to patients that if our immune system thinks there is something wrong with our skin, the body tries to flake it off. That's how we've evolved as humans. A normal skin cell takes about 30 days to be born, but in psoriasis the entire epidermis turns over in a day or two. That is why patients get thick, scaling patches that can crack and bleed.

I then explain that the immune system releases cytokines; that's what makes the cells proliferate so rapidly. I explain that we have three basic flavors: TNF, which is somewhat upstream or nonspecific, IL-23, and IL-17, which are important for the immune function of barrier tissues: the skin, the lungs, and the gastrointestinal tract.

With targeted biologics, we're able to achieve what appear to be better outcomes for patients: greater response rates, more rapid responses, as well as a likely lower risk of adverse effects.

DR. MENTER: I would add one more aspect to the issue of genetics and psoriasis. I tell every patient who asks about the genetics of psoriasis my personal history. I have two brothers with significant psoriasis, both of whom are taking biologic agents. One of them also has Crohn's disease, which is genetically linked to psoriasis. My father had vitiligo, which is also genetically linked to psoriasis. When we started the National Psoriasis Victor Henschel BioBank with Anne Bowcock, I included my whole family.[13] I tell patients that I have every known gene for psoriasis. The big question is, why do my two brothers have psoriasis but I do not? We still don't know in the world of genetics what triggers a genetic predisposition to psoriasis.

DR. FRIEDMAN: Agreed. Nature and nurture, not one or the other. I have a question for Dr. Gelfand. The nomenclature for biologics can be extremely confusing, because not all antibodies are created equal. We have humanized, we have chimeric. Are there any tricks to remembering how the name of the drug is put together, especially in terms of the likelihood of neutralizing antibodies?

DR. GELFAND: I think the trick is that you don't need to know that information. When the biologics first came out, there was all this nomenclature that indicated whether the agent was humanized, or fully human, or chimeric. At this stage of the game, it's not

TABLE 1. CURRENT AND EMERGING BIOLOGIC AGENTS FOR THE TREATMENT OF PSORIASIS.[1,5-7]

Drug	Target	Mechanism of Action	FDA Approval Status in PsO
Etanercept	TNF-α	TNF-α receptor IgG1 fusion protein that binds to soluble TNF-α	Approved 2004 Approved 2016 for patients 4 years of age and older
Infliximab	TNF-α	Chimeric monoclonal antibody that binds to both soluble and membrane-bound TNF-α	Approved 2006
Adalimumab	TNF-α	Human monoclonal antibody that binds to both soluble and membrane-bound TNF-α	Approved 2008
Ustekinumab	IL-12/IL- 23 p40	Human monoclonal antibody that binds to p40 subunit of IL-12 and IL-23	Approved 2009 Approved 2017 for patients 12 years of age and older
Secukinumab	IL-17A	Human monoclonal antibody that binds to IL-17A	Approved 2015
Ixekizumab	IL-17A	Humanized monoclonal antibody that binds to IL-17A	Approved 2016
Brodalumab	IL-17A receptor	Human monoclonal antibody prevents binding of IL-17A, IL-17F, and IL-25 to the shared IL-17RA receptor	Approved 2017
Guselkumab	IL-23 p19 subunit	Human monoclonal antibody binds selectively to the p19 subunit of IL-23 and inhibits its interaction with IL-23 receptor	Approved 2017
Tildrakizumab	IL-23 p19 subunit	Humanized monoclonal antibody binds selectively to the p19 subunit of IL-23 and inhibits its interaction with the IL-23 receptor	Approved 2018
Certolizumab	TNF-α	Chimeric antibody that binds to both soluble and membrane-bound TNF-α	Approved 2018
Risankizumab	IL-23 p19 subunit	Humanized monoclonal antibody binds selectively to the P19 subunit of IL-23 and inhibits its interaction with the IL-23 receptor	Approved 2019
Bimekizumab	IL-17A/F	Humanized monoclonal antibody neutralizes both IL-17A and IL-17F	Phase 3 trials ongoing
Mirikizumab	IL-23 p19 subunit	Humanized monoclonal antibody binds to p19 subunit of IL-23	Phase 3 trials ongoing
M1095	IL-17A/F	Anti-IL-17 A/F bispecific nanobody	Phase 1

PsO, psoriasis; TNF, tumor necrosis factor; IL, interleukin.

clinically important for prescribers, students, or patients to know.

The only biologic where there is a specific concern of antibodies that commonly develop and can cause clinically significant problems like hypersensitivity reactions is infliximab. For the rest of the biologics, it's not clinically relevant in most cases. An exception is perhaps certolizumab, where it's a Fab fragment and therefore thought to not cross the placental barrier or get into breast milk in clinically significant amounts; therefore, it's generally thought to be a better option when a woman is pregnant or lactating.[14]

TB AND OTHER TESTING

Q | DR. COHEN: Could we talk about the testing you do in your patients with psoriasis?

DR. GELFAND: I think of my patients quite comprehensively. So I discuss with them–especially those with more extensive disease—how people with extensive psoriasis tend to have other problems related to skin inflammation. I mention psoriatic arthritis, and I explain the signs and symptoms so they know what to look out for. I explain that patients with psoriasis tend to have higher rates of cardiovascular disease and diabetes and therefore should be up to date on regular age-appropriate screenings, such as blood pressure checks or screenings for hemoglobin A1C and lipids. If I'm going to order blood work in preparation for a patient initiating systemic therapy and the patient doesn't have a primary care physician or hasn't been screened in a while, I'll include hemoglobin A1C and lipids as part of the evaluation so I can get a baseline. Then I'll identify any other major cardiovascular disease risk factors that are commingling with their disease, because this is very prevalent in our patient population. These include obesity, smoking, hypertension.

From there, my standard work-up is a complete blood count and a comprehensive metabolic panel—liver function, kidney function. I'll also test for hepatitis B, including surface antigen, core antibody, and surface antibody, hepatitis C, HIV, and TB with a QuantiFERON-TB

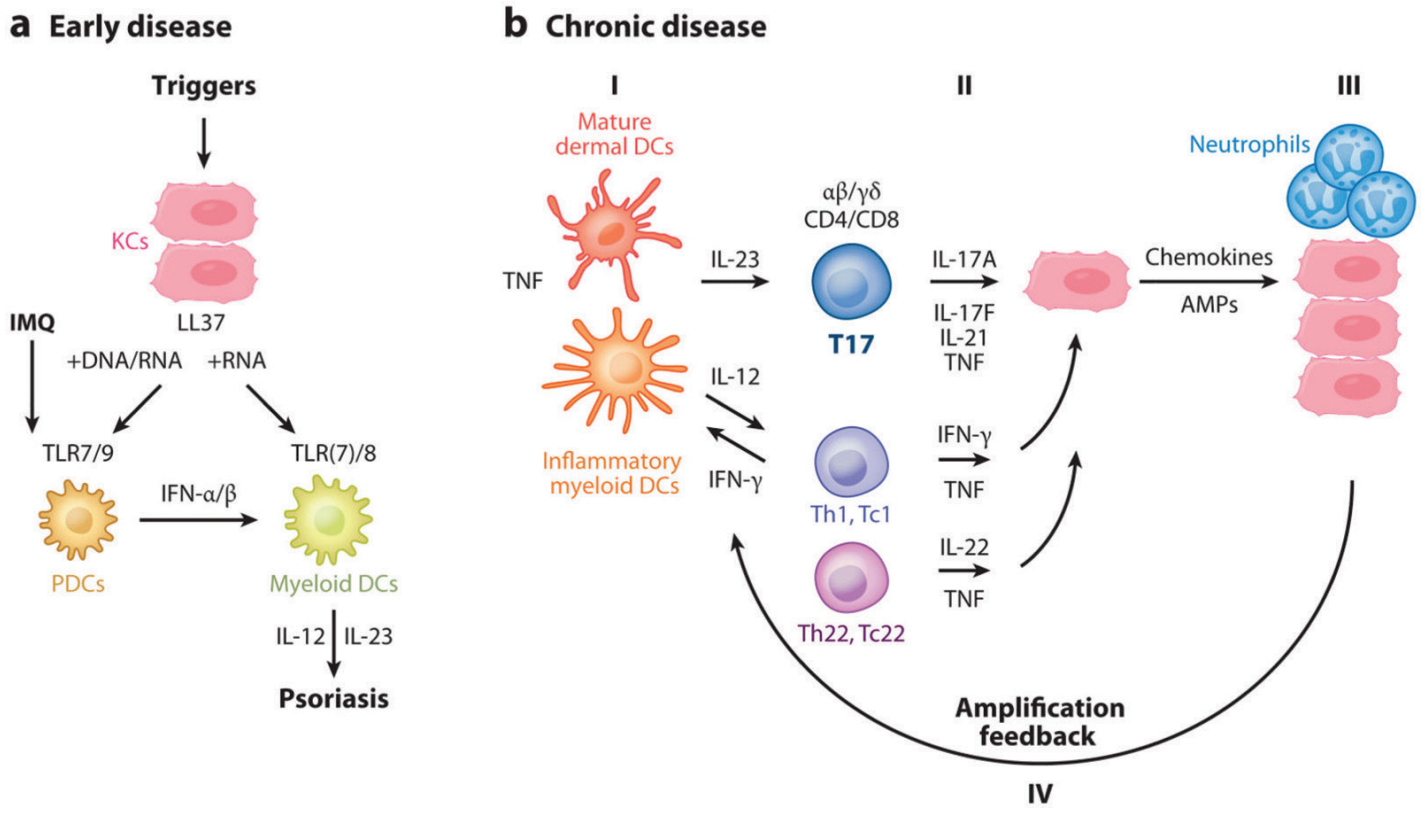

Figure 2. Dr. Gelfand's preferred illustration to show the pathophysiology of psoriasis, which can be initiated by endogenous factors, including drugs like imiquimod, but the disease pathophysiology remains the same. (a) Early disease: Imiquimod (IMQ), a TLR7 agonist, can activate plasmacytoid dendritic cells (pDCs) to produce interferons (IFN). LL37, a peptide derived from cathelicidin, may have an important role in the initiation of psoriasis lesions via this pathway. LL37 released from keratinocytes (KCs) can bind to nucleic acids to activate pDCs to release IFN-α/β. LL37/RNA complexes can also activate resident myeloid DCs to produce IL-12 and IL-23, key psoriatic cytokines. (b) Chronic disease: The major pathogenic pathway in psoriasis occurs when (I) mature dermal DCs and inflammatory myeloid DCs produce cytokines such as IL-23 and IL-12. (II) These cytokines activate T17 (Th17 and Tc17), Th1, and Th22 cells to contribute to the cytokine milieu and further act on keratinocytes. (III) Keratinocytes can produce chemokines and antimicrobial peptides (AMPs) to (IV) augment cutaneous immune responses. (Originally published in *Annu Rev Immunol.* 2014;32:227-255. Reprinted with permission.)

Gold test. In some patients, I may go so far as to order uric acid or C-reactive protein (CRP) tests. I more frequently order tests for those markers in patients who are on the fence about going on systemic treatment. I'm trying to better understand how well the patient's body is dealing metabolically with psoriasis. Some patients will have elevated uric acid levels related to chronic accelerated epidermal cell turnover, which puts them at greater risk for gout. Other patients may have elevated CRP. If those levels are already trending up, I let the patient know that these are signs that the body is not adapting well to the inflammation going on in the skin.

DR. MENTER: We did some studies on granulomas: TB granulomas, histoplasmosis granulomas, coccidioidomycosis granulomas.[15] It's fascinating that a granuloma, be it an infectious granuloma or a noninfectious granuloma, such as a sarcoid granuloma or granuloma annulare, needs TNF-α stable within it to maintain its structure. So if you take out the TNF-α with an anti-TNF-α agent, that granuloma is going to collapse. If there's a tuberculous bacillus within that granuloma or a Histoplasma species, you are going to activate the bacteria or fungus that's within the granuloma. We've had many patients on TNF-α agents with disseminated granuloma annulare or disseminated sarcoidosis, and those granulomas collapse within weeks because of the TNF-α within the granuloma.

The risk of TB activation with a non-TNF-α agent is incredibly lower than with a TNF-α agent, because of the nature of a granuloma.[16] I explain to patients who are about to start one of the newer agents that drug labeling says they need a TB test. But these drugs have a far lower likelihood of activating or precipitating TB than a TNF-α agent has.

DR. FRIEDMAN: I think that's a significant point. The class labeling for all biologics stipulates screening for latent TB infection even though the risk is quite low. Even if you were thinking about a TNF blocker, the current dogma is to treat the TB for between six and eight weeks (depending on which infectious disease person you speak to) and then, even though the duration of treatment for the infection is much longer, you can actually start therapy at that point. So I think the risk has been grossly overstated.

DR. GELFAND: Based on the new American Academy of Dermatology guidelines, there really isn't a medical need to screen people annually

CASE 1: UNSUCCESSFUL TREATMENT WITH METHOTREXATE, ETANERCEPT, AND ADALIMUMAB

Dr. Cohen: We have two cases that illustrate some of the issues we've been discussing. Dr. Friedman, would you like to present your case?

Dr. Friedman: I think the most difficult questions we face when using biologic agents are: a) Do they act the way we anticipate they'll act, and b) If they do, for how long will they act that way? I'd like to discuss the concept of treatment failure, switching, and cycling with a recent case of mine. I'd like to walk through the case and get the panelists' takes on what you would do if presented with a similar situation. Also, full disclosure, I want to pick your brains because this complicated case is ongoing.

The patient is a 43-year-old woman who has had psoriasis for more than 20 years but is in otherwise good health. When she first presented to me, she had skin disease affecting her scalp, trunk, and groin. She reported that she had been unsuccessfully treated with methotrexate, etanercept, and adalimumab. What would be your first step with this patient?

Dr. Menter: Given that the patient has received multiple drugs previously, I do believe we need to jump into the new drugs, IL-17s and IL-23s, that have significantly higher response rates than our traditional drugs, the IL-12/23 and TNF-α drugs. But I'd like to make the point that my final decision about which drug to use for which patient is not driven by what I believe the patient requires but by third-party payers who tell you and me what we have to use.

Dr. Gelfand: I would second what Alan said. This patient is new, and all my new patients get a full-body skin exam, head to toe. I want to make sure they don't have skin cancer or melanoma, and I'm also looking for any hidden signs of psoriasis that the patient may not be aware is psoriasis. I've had patients with genital psoriasis who weren't aware of it or didn't think it was psoriasis. I think it's important that patients be educated about what is going on with their bodies, which can help reduce stigma and dispel misconceptions about the disease. Also, understanding their disease helps patients be partners in shared decision-making. It's so important to engage with the patient, understand her preferences, and then help her make a decision about what will be best for her.

With your patient, I would want to know a bit more about her experience with TNF-α agents. Did she do well and then lose response or did she never really respond? If the former is the case, she could be a candidate for another TNF-α inhibitor. If the latter is the case and she really didn't respond at all, I would give preference to other therapies—given insurance limitations.

She's still within child-bearing potential, so I would ask her if she's on birth control or if she's planning on having children. I would also try to understand if she has any signs of inflammatory arthritis whatsoever in her peripheral or axial joints—spine or sacroiliac joint.

Dr. Friedman: I'm so glad you asked what treatment failure meant for her. She did not respond at all to the TNF agents. She had no joint stiffness at rest and no lower back pain—but the story continues and that does change.

At this point, which was 2015, I started her on ustekinumab. She took ustekinumab for about eight months, during which time she had no cutaneous improvement. However, she did start to develop morning joint stiffness toward the end of the 8 months, and she was diagnosed with psoriatic arthritis. I then started her on secukinumab, and she did wonderfully for about 3 years. Then, in the summer of 2019, she came back with worsening skin and joint symptoms. Now I'll stop the story so you can jump back in.

Dr. Gelfand: This is a pretty common scenario in my clinical practice. Not to oversimplify, but patients tend to fall into one of two categories: those who do well on a biologic and continue to do well and those who have more stubborn disease. I use the phrase "stubborn disease" with patients because it's a term they can relate to. Those with stubborn disease need extra attention from us. For this patient, given that she did well on an IL-17 inhibitor and is now having some signs of recurrence, I would probably move to another IL-17 inhibitor, probably ixekizumab, which has good efficacy in both the skin and joints.

Dr. Menter: I fully agree with what you've all said. How many of us have had patients who have failed three or four biologics? Do you change the nature of the biologic from TNF-α, to IL-12/23, IL/23, IL/17? Can you go back to a TNF-α? I think the most important point is that we cannot predict which agent works best for which patient. Yes, we now have 90 percent PASI 75 scores for our IL-17 and IL-23 agents, but it still means that 10% to 15% of patients will not get an appropriate, quick response and maintain that response. Safe, long-term control is my goal for my patients.

Dr. Friedman: I have a bit of a curve ball now for the story. Obviously, switching is in order, and I chose to switch her to brodalumab. Surprisingly, she decompensated very quickly, and her skin and joints significantly worsened in a matter of weeks. I then switched her to ixekizumab.

Have either of you witnessed a change in agent that you anticipated would be better but instead actually resulted in the opposite outcome?

Dr. Gelfand: Your experience with her not responding to brodalumab and then responding to ixekizumab is certainly unusual. But it is not in the realm of the unexpected, which shows how complicated this disease is and re-emphasizes Alan's point that, despite all our progress, there is still a degree of trial and error.

I'd want to know more details about your patient's medication history. Is it possible we're dealing with a drug-induced or drug-aggravated variant of psoriasis? I often co-manage my patients with rheumatologists, and because the joints are an important part of her symptomatology, I would probably engage with my rheumatology colleagues and try to home in on whether this is truly an inflammatory arthritis or if there is a mixed picture. Gout, fibromyalgia, and osteoarthritis can all comingle with psoriatic arthritis and complicate the clinical picture.

Dr. Friedman: All great points. In odd cases like this one I work closely with a rheumatologist to help potentially tease out if there is more going on than psoriasis and psoriatic arthritis. Fortunately for this patient, she is doing quite well with ixekizumab. Let's move on to the next case.

CASE 2: A 20-YEAR HISTORY OF PSORIASIS

Dr. Gelfand: My patient is a 35-year-old woman with psoriasis affecting most of her scalp, elbows, knees, and fingernails, which have subungual debris. Body surface area (BSA) affected is five percent, and the physician global assessment is 4. Disease onset was at age 15. She experiences mild itching. She notes that all her joints hurt all the time. She also experiences severe embarrassment, and she spends a great deal of time trying to conceal her skin involvement. Her skin improves during the summer. She has used only topical treatments. She hates needles and once passed out during a blood draw.

In terms of medical history:

- Polycystic ovary syndrome, obesity (body mass index = 31 kg/m2), depression, history of urinary tract infections, optic neuritis (1 episode in college). Blood pressure in the office was 140/90 mm Hg, but she doesn't have a history of high blood pressure.
- Medications: Sertraline
- Social history: No tobacco use, two glasses of wine per night. Works as a social media coordinator. She is engaged, and the wedding is in 6 months.
- Family history: Paternal grandfather had psoriasis. Father died at age 52 of a myocardial infarction. Brother has Crohn's disease.

This case raises a lot of issues. As an aside, when I see that one of my patients is wearing an engagement ring, I always ask about wedding plans. For many patients, planning a wedding is a stressful time. It's important to determine family planning concerns and how important it is for the patient to be clear on the wedding day so we can address the patient's treatment goals.

The first issue raised by this case is when to start thinking about a systemic agent. The patient is almost treatment naïve. Her BSA is only five percent but she has involvement on hard-to-treat areas like the scalp and nails. Topical agents have not worked for her. The scalp is notoriously difficult to manage with topical medications, her fingernails are not going to respond well to topicals, and phototherapy is usually not particularly helpful in nail disease. So I'm already moving toward an oral or injectable medication for this patient.

All her joints hurt all the time. Joint complaints are common in people in general as well as in people with psoriasis. I have to have a differential diagnosis, and her history is leading me to fibromyalgia or osteoarthritis rather than an inflammatory joint disease. I'll examine her joints and palpate her metacarpophalangeal, proximal interphalangeal, and distal interphalangeal joints to see if there is any swelling or tenderness. I'll try to understand if the joint pain is worse in the morning and if it gets better with activity. Depending on where that information leads me, I might do a workup for inflammatory arthritis. I might get a rheumatoid factor, an anti-CCP antibody test, a uric acid test, and a CRP to get a sense if there is any evidence of inflammatory arthritis or, potentially, rheumatoid arthritis (RA) or gout. Over the years I've had two or three patients who actually had RA when they had a diagnosis of psoriatic arthritis.

She has important comorbidities. The history of optic neuritis was picked up because I specifically asked the question. In my experience, you need to ask very specific questions to elicit accurate information from patients about other medical problems.

Methotrexate would be challenging in this woman: she's of child-bearing potential, her BMI is 31 kg/m^2, and she drinks alcohol regularly.

When considering biologics for this patient, the history of optic neuritis would shift me away from TNF inhibitors because they aggravate optic neuritis (Table 2).[4] This patient doesn't have any history of bowel disease, but her brother has Crohn's disease. That's important to know because the IL-17 inhibitors can aggravate Crohn's disease, and there are rare reports of people developing inflammatory bowel-like symptoms or disease while on IL-17 inhibitors.[23,24] So that information would make me more cautious about using IL-17s in this patient. However, an IL-17 agent wouldn't be an unreasonable choice if that's what the insurance company approves or if that's what the patient prefers. But it's something to think about when selecting among biologics with different MOAs.

That would lead me to the IL-23 pathway. Whether it be ustekinumab, which is an IL-12/23, or the IL-23 inhibitors: guselkumab, tildrakizumab, risankizumab. Ustekinumab had been a great medication for many years, but it has no advantage over the IL-23s and potential disadvantages since it's a little less targeted, so I generally use an IL-23 over ustekinumab unless the insurance company will not approve an IL-23.

Dr. Menter: I'd like to make two points. Your patient has nail involvement. Alice Gottlieb, Craig Leonardi, Jim Krueger, and I did a statistical analysis of outcome measures, and the only time nails were a marker for joint disease was in the distal interphalangeal joint.[25] Second, as much as we all enjoy the IL-12/23 ustekinumab, the ACR 20 score for ustekinumab is

(Continued on page 11)

for TB if they don't have risk factors for exposure.[4] I ask my patients if they have been exposed to anyone with TB or if they have traveled outside the United States, and then I determine if they have traveled to areas that are endemic for TB. If the answers to those questions are negative, I offer them to opt out of annual screening. Probably 90% or more of my patients opt out of annual blood work.

WHICH BIOLOGIC?

Q | **DR. FRIEDMAN:** Dr. Menter, you mentioned that we now have 11 approved biologics. One of the biggest elements of confusion for physicians is which biologic to prescribe. How do you approach the different categories?

DR. MENTER: That's an incredibly complex and important question. We in dermatology were late to the biologic revolution. All the TNF-α agents were approved for joint disease before they were approved for skin disease. Now we have leapt ahead, and dermatology has more biologics than any other specialty.

We do not have biomarkers that can predict which drug will work best in an individual patient with classic plaque psoriasis. I'm still most comfortable with the TNF-α agents and with ustekinumab because we have long-term safety data.[17-19] Perhaps I'm being a bit conservative, but my background makes me more conservative. Patients in clinical trials are not the same as patients in clinical practice, so I like 5 to 10 years of safety data in clinical practice to

CASE 2: A 20-YEAR HISTORY OF PSORIASIS

(Continued from page 10)

47%, whereas it is 30% higher for TNF and IL-17 agents.[26] The IL-23 agents are not yet approved for joint disease. We cannot predict when a patient is going to get joint disease, but if one out of three is going to get joint disease 10 to 15 years after the onset of skin disease, I want to have a drug that works well for joints and skin, if possible.

Dr. Gelfand: That's a great point, Dr. Menter. And that's what this case is trying to get at: What's this patient's joint pathology, what's driving it? She has nail involvement, so it's important to look at the distal interphalangeal joints, examining them with enough pressure to make the top third of your thumb turn white, which is enough pressure to elicit tenderness in those joints if they are affected by inflammatory arthritis.

American College of Rheumatology (ACR) guidelines list TNF inhibitors as first line for psoriatic arthritis, taking over the old standard bearer methotrexate.[27] Interestingly, ACR guidelines, which are already a bit outdated, don't list IL-17s as first line, but I think data have now emerged showing they probably work about as well as TNF inhibitors, and they are a perfectly reasonable alternative as first-line therapy for the joints in my opinion.[28-31] Ustekinumab does not work in axial disease, so would not be a good option for that type of arthritis. None of the IL-23s are currently approved for psoriatic arthritis, and it will take some time before we know what role they'll play in that common psoriasis comorbidity.

Dr. Friedman: I love this case because it's a medical mine field. There are more red herrings here than in a fish market. You brought up every possible pitfall associated with almost every biologic—even the fact that she hates needles and almost passed out. I have to say that I probably would lead with an IL-17 blocker. She's had psoriasis for 20 years, her psoriatic lesions are on tough locations, the disease is affecting her quality of life. Her family history of Crohn's disease is concerning but not as concerning as the history of optic neuritis. I have to say that I probably would lead with an IL-17 blocker. Now it came up that she has a history of depression, which is a common comorbidity with psoriasis, and pushes some away from considering brodalumab given the boxed warning for suicidal ideation. The post-marketing literature suggest that this concern may be overstated, but the Risk Evaluation and Mitigation Strategy program is still required for use of this biologic.[31]

ensure that rare side effects don't come to the surface years after the drug reached the market.

DR. GELFAND: I share Dr. Menter's conservatism. From my point of view, we have three excellent MOAs to use for patients. I try to explain to patients that despite all the progress we've made, there's still some degree of trial and error in terms of knowing which is the right drug for a patient at a given time. Based on the patient's health profile and comorbidities, I try to figure out the right approach, whether it be an oral drug, or phototherapy, or an injectable biologic.

If we're in the realm of biologics, I talk with the patient about the three classes of agents and explain that the one we use will often be based on what their insurance company will allow. If a patient doesn't have any contraindications to any of the classes of biologics, we'll have a hard time arguing for one over another, because the reality is that all three classes are excellent options for most patients. Personally, I tend to prefer agents that target the IL-23 pathway, primarily because they have the advantageous dosing profile of every two to three months. They tend to have very high efficacy rates, and although we don't have long-term safety data

Biologics for the Treatment of Dermatologic Diseases Other than Psoriasis

Many dermatologic disorders are mediated by a dysregulated cutaneous immune response, and biologic agents are used in many cutaneous diseases other than psoriasis.[1] The treatment of atopic dermatitis has been revolutionized by biologic therapy in the past decade, much as the treatment of psoriasis was revolutionized by biologics in earlier decades. Dupilumab, an IL-4 receptor α-antagonist that inhibits IL-4 and IL-13 signaling through blockade of the shared IL-4 subunit, is FDA-approved for the treatment of moderate to severe atopic dermatitis in patients 12 years of age and older whose disease is not adequately controlled with topical prescription therapies or when those therapies are not advisable.[2] Other biologics for the treatment of atopic dermatitis are in development.

Adalimumab is approved for the treatment of moderate to severe hidradenitis suppurativa in patients 12 years of age and older.[3] Omalizumab is a humanized anti-IgE monoclonal antibody approved for the treatment of chronic idiopathic urticaria in patients 12 years of age and older.[4]

Many biologic agents have been used off-label to treat dermatologic disease. Etanercept, infliximab, and adalimumab have been used for neutrophilic dermatoses such as aphthous stomatitis and pyoderma gangrenosum; bullous dermatoses such as bullous pemphigoid and pemphigus vulgaris; granulomatous dermatoses, such as generalized granuloma annulare; immune connective tissue diseases, such as dermatomyositis and scleroderma; and other diseases such as pityriasis rubra pilaris.[5]

More than 100 articles have been published on the off-label uses of biologic agents.[1] As clinical trials and clinical experience progress, clinicians can expect to see more FDA-approved biologics in their therapeutic arsenal.

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TABLE 2. TREATMENT OPTIONS: BIOLOGICS

TNF agents
-Advantages: Good efficacy, certolizumab has data suggesting it doesn't cross the placenta, gold standard for PsA.
-Disadvantages: TNF agents have class warning for demyelinating diseases, eg, optic neuritis, multiple sclerosis. Patient has history of optical neuritis.

IL 12/23, IL/23 agents
-Advantages: Good to superior efficacy, favorable dosing regimen, ustekinumab approved for Crohn's disease.
-Disadvantages: IL-12/23 thought to have lower efficacy for psoriatic arthritis, IL-23s not approved for psoriatic arthritis, IL-12/23 not recommended for axial disease.

IL-17 agents
Advantages: Superior efficacy, rapid onset.
Disadvantages: Patient has family history of colitis, brodalumab has boxed warning for suicidal ideation (patient is being treated for depression).

Mariette X, et al. *Ann Rheum Dis.* 2018;77:228-233; Singh JA, et al. *Arthritis Care Res (Hoboken).* 2019;71: 2-29; Menter A, et al. *J Am Acad Dermatol.* 2019;80:1029-1072.

with IL-23s, ustekinumab has very good long-term safety data and also very good long-term persistence data.[19-22]

Psoriasis is a marathon, not a sprint, and the challenge is that biologics tend to lose response over time. That's most problematic with some of the TNFs. There's some controversy about the degree to which IL-17s lose response; we're still trying to understand that, although some of the early studies seem to suggest there is an issue with secukinumab.[22] Then the IL-23 pathway, at least if we are talking about ustekinumab, from what we can tell, ustekinumab has the longest persistence, meaning that patients could go on it, have a good response, and stay on it for a couple of years before they may lose response.[20-22] We know our patients cycle from drug to drug to drug, so my goal is to minimize cycling as much as I can.

That said, I have a patient who was put on etanercept during a clinical trial when I was a resident, and he's still doing well on the drug at least 19 years later. Not a typical experience. So we have good data to guide our decisions, but there's still a bit of trial and error to see how a drug works for an individual patient.

DR. MENTER: Patients feel more comfortable with the safety of a drug that is FDA-approved for children. Currently, etanercept is approved for children four years and older, and ustekinumab is approved for adolescents. We'll have to wait awhile for these approvals in the IL-17s and IL-23s.

DR. GELFAND: I do agree with Dr. Menter that long-term safety data is very important, and I have some patients for whom that's a big priority. So if safety is a priority, TNF inhibitors tend to be the gold standard. They have been around since the early 2000s and we have a wealth of experience with these drugs across multiple disease applications.

CLOSING REMARKS

DR. COHEN: This has been an important endeavor to shed light on complicated MOAs and how dermatologists think of these medications in terms of an algorithm for treatment in these clinical scenarios. Dr. Friedman and I look forward to similar projects with other complicated dermatologic issues and diseases.

DR. FRIEDMAN: This was truly a fantastic review that provided an historical perspective on our current management approaches, evidence-based treatment guidance, and, even more important, anecdotal experience from two psoriasis champions: Drs. Alan Menter and Joel Gelfand. Despite our knowledge and the tools we have at our disposal to manage this chronic inflammatory condition, there is certainly more work to be done. As mentioned earlier, it's a marathon, not a sprint. ■

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MECHANISM OF ACTION MATTERS: A REVIEW OF NEW AND EMERGING BIOLOGICS

Release Date: December 2019
Expiration Date: December 2020

INSTRUCTIONS FOR CME CREDIT

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DEMOGRAPHIC INFORMATION

Profession
___ MD/DO
___ OD
___ NP
___ Nurse/APN
___ PA
___ Other

Years in Practice
___ >20
___ 11-20
___ 6-10
___ 1-5
___ <1

Patients Seen Per Week (with the disease targeted in this educational activity)
___ 0
___ 1-5
___ 6-15
___ 16 or more

Region
___ Northeast
___ Northwest
___ Midwest
___ Southeast
___ Southwest

Setting
___ Solo Practice
___ Community Hospital
___ Government or VA
___ Group Practice
___ Other
___ I do not actively practice

Models of Care
___ Fee for Service
___ ACO
___ Patient-Centered Medical Home
___ Capitation
___ Bundled Payments
___ Other

LEARNING OBJECTIVES

DID THE PROGRAM MEET THE FOLLOWING EDUCATIONAL OBJECTIVES?	AGREE	NEUTRAL	DISAGREE
Define biologic therapy.	_____	_____	_____
Review the mechanism of action (MOA) of approved and emerging biologics for the treatment of moderate to severe psoriasis.	_____	_____	_____
Review the MOA of approved and emerging biologics for the treatment of cutaneous diseases other than psoriasis.	_____	_____	_____
Discuss how the MOA of biologic therapeutics may affect clinical decision-making in dermatologic practice.	_____	_____	_____

POSTTEST QUESTIONS. PLEASE COMPLETE AT THE CONCLUSION OF THE PROGRAM.

1. Based on this activity, please rate your confidence in your ability to describe the mechanism of action (MOA) of approved and emerging biologics for the treatment of moderate to severe psoriasis (based on a scale of 1 to 5, with 1 being not at all confident and 5 being extremely confident).

a. 1
b. 2
c. 3
d. 4
e. 5

2. Based on this activity, please rate your confidence in your ability to understand how the MOA of biologic therapeutics may affect clinical decision-making in dermatologic practice (based on a scale of 1 to 5, with 1 being not at all confident and 5 being extremely confident).

a. 1
b. 2
c. 3
d. 4
e. 5

3. Which of the following agents is approved by the US Food and Drug Administration (FDA) for the treatment of moderate to severe psoriasis and psoriatic arthritis?

A. Bimekizumab
B. Risankizumab
C. Ustekinumab
D. Tildrakizumab

4. Which of the following biologic agents is a human monoclonal antibody that prevents binding of IL-17A, IL-17F, and IL-25 to the shared IL-17RA receptor?

A. Adalimumab
B. Etanercept
C. Brodalumab
D. Ixekizumab

5. Which of the following agents is a TNF-α inhibitor approved by the FDA for the treatment of hidradenitis suppurativa?

A. Omalizumab
B. Infliximab
C. Dupilumab
D. Adalimumab

6. You are treating a 26-year-old woman with moderate to severe psoriasis affecting 25% of her body surface area, including her scalp and nails. She has a family history of type 2 diabetes and cardiovascular disease. Her body mass index is 30 kg/m^2, and she has a history of optic neuritis. She was treated by her previous dermatologist with topical medications, to which she did not respond. She was then switched to methotrexate, but she could not tolerate the drug. You are considering initiating biologic therapy. Which of the following biologic classes would be a problematic choice given her history of demyelinating disease?

A. Interleukin (IL)-23 agents
B. Tumor necrosis factor-α agents
C. IL-17 agents
D. IL-12/23 agent

7. Which one of the following statements about biologic agents is true?

A. Biologics can be administered orally or subcutaneously.
B. Biologics are able to enter cells easily because they have a low molecular weight.
C. Biologics are proteins with highly specific targets.
D. As of November 2019, there were 8 biologic agents approved for the treatment of moderate to severe psoriasis.

ACTIVITY EVALUATION/SATISFACTION MEASURES

Rate your knowledge/skill level prior to participating in this course: 5 = High, 1 = Low _____

Rate your knowledge/skill level after participating in this course: 5 = High, 1 = Low _____

What percentage of information presented in this activity will be of use to you? ___0% ___20% ___40% ___60% ___80% ___100%

This activity improved my competence in managing patients with this disease/condition/symptom _____ Yes _____ No

Probability of changing practice due to this presentation: _____ High _____ Low _____ No change necessary

Please identify any barriers to change (check all that apply):

_____ Cost
_____ Lack of consensus or professional guidelines
_____ Lack of administrative support
_____ Lack of experience
_____ Lack of time to assess/counsel patients
_____ Lack of opportunity (patients)
_____ Reimbursement/insurance issues
_____ Lack of resources (equipment)
_____ Patient compliance issues
_____ No barriers
_____ Other. Please specify:
_____
_____

The design of the program was effective for the content conveyed ___ Yes ___ No

The content supported the identified learning objectives ___ Yes ___ No

The content was free of commercial bias ___ Yes ___ No

The content was relative to your practice ___ Yes ___ No

The content was evidence-based ___ Yes ___ No

The content was balanced ___ Yes ___ No

You were satisfied overall with the activity ___ Yes ___ No

Would you recommend this program to your colleagues ___ Yes ___ No

Quality of speaker presentations:

Joel L. Cohen, MD, FAAD: __Excellent ___ Good ___Fair ___Poor

Adam Friedman, MD, FAAD: __Excellent ___ Good ___Fair ___Poor

Joel M. Gelfand, MD, MSCE, FAAD: __Excellent ___ Good ___Fair ___Poor

Alan Menter, MD: __Excellent ___ Good ___Fair ___Poor

Please check the Core Competencies (as defined by the Accreditation Council for Graduate Medical Education) that were enhanced through your participation in this activity:

_____ Patient Care
_____ Practice-Based Learning and Improvement
_____ Professionalism
_____ Medical Knowledge
_____ Interpersonal and Communication Skills
_____ System-Based Practice

Additional comments:

_____

_____ I certify that I have participated in this entire activity.

This information will help evaluate this CME activity. May we contact you by email in 3 months to see if you have made this change? If so, please provide your email address below.

_____


practical
dermatology