New drugs hold promise for psoriasis

IL-12 and IL-23: New therapeutic targets in psoriasis

Our understanding of the pathogenesis of psoriasis continues to evolve. Once thought to be a disease of the keratinocyte, our understanding of the immune system, including the T cell as a major contributor to psoriatic disease, has changed our approach to treatment. Treatments have been developed to target the IL-12/IL-23 p40 molecule, and multiple studies have shown relevance for this approach in psoriasis therapy. Here, we review the immunology and present clinical trial results for this new class of drugs.

T cells are one of multiple immune cells involved in psoriasis pathogenesis, and T-cell subsets are defined by their cytokine profile. IFN-γ and IL-2 are cytokine signatures of the Th1 population, and IL-4, IL-5 and IL-10 are signatures for the Th2 population.

Th17 cells have recently been shown to have relevance in treating psoriasis. Th17 cells are recognized by the cytokine profile of IL-17A, IL-17F, IL-6, TNF-α and IL-22. IL-22, the major Th17 cytokine, induces keratinocyte proliferation. There is evidence for IL-22 involvement in psoriasis, as it is increased in lesional skin compared to non-lesional skin, and after treatment, expression of IL-22 in psoriatic skin decreases. Increased IL-22 levels in the serum of psoriasis patients have been correlated to disease severity. This evidence suggests that Th17 cells are important for psoriatic disease. Notably, the cytokine responsible for proliferation and survival of Th17 cells is IL-23.

IL-23 is composed of two subunits, p19 and p40 (Figure 1). The p40 subunit is shared with the IL-12 cytokine, which also has a p35 subunit. IL-12 and IL-23, both produced by dendritic cells and macrophages, are functionally distinct. IL-12 promotes the differentiation of naïve T cells to Th1 cells, while IL-23 promotes proliferation and survival of Th17 cells. Polymorphisms in p40 and IL-23R have been linked to psoriasis susceptibility.

Drugs targeting the p40 subunit of IL-12 and IL-23 have been developed. Ustekinumab (previously known as CNTO 1275), manufactured by Centocor, Inc., and ABT-874, manufactured by Abbott Laboratories, have both been impressive in psoriasis clinical trials in the past year. The IL-12/IL-23 story is intriguing, as we now have a new pathway with evidence for functional significance and genetic susceptibility.

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Dear Colleagues,

On behalf of the International Psoriasis Council (IPC) and this issue’s co-editors Craig Leonardi, M.D., and Fernando Stengel, M.D., I am pleased to present the May 2008 edition of our clinical newsletter, *IPC Psoriasis Review*.

Published several times per year, *IPC Psoriasis Review* appraises important current clinical and research publications and provides commentary on those that we believe make the greatest contribution to our understanding of the disease and its treatment. In this issue, we include highlights of psoriasis data presented at the 21st World Congress of Dermatology 2007 and the 66th Annual Meeting of the American Academy of Dermatology (AAD) 2008. We also present select cases from our February 2008 IPC Meet the Experts Program, conducted at the AAD meeting and chaired by Dr. Kenneth Gordon—the first of several international case-based forums planned by IPC for this year.

The second IPC Meet the Experts program will occur during the 5th EADV Spring Symposium in Istanbul, Turkey, on May 23, 2008, and will be chaired by Professor Christopher Griffiths.

Already, 2008 has proven to be a productive year for IPC. In January, our Board of Directors met with the European Medicines Agency (EMEA) to discuss important issues facing psoriasis research and treatment and potential opportunities for IPC to provide input on the agency’s psoriasis-related activities. At our February meeting, we welcomed Robert Holland III to our Board of Directors. As former U.S. Executive Director to the World Bank and a prominent international businessman, Mr. Holland is certain to bring valuable insight and expertise to our organization, and will work with our Board Members on important fund-raising activities for our organization.

For the remainder of 2008 and beyond, we will continue our efforts to foster collaboration among psoriasis professionals internationally and to expand our programs and activities to reach new audiences. We have a number of interesting and exciting programs planned, and we look forward to updating you on our progress in the September issue of *IPC Psoriasis Review*. Founded in 2004 by key thought leaders in the field of psoriasis, IPC is the only dermatologist-driven, global organization that actively pursues publications and creates psoriasis-specific programs, events and materials to share with our dermatology colleagues toward optimizing our understanding and treatment of psoriasis.

We hope this newsletter is informative and that the knowledge, experience and insights of our faculty are useful to you in treating your psoriasis patients. For additional copies of *IPC Psoriasis Review*, or to learn more about IPC, please visit www.psoriasiscouncil.org.

Sincerely,

Alan Menter, M.D., President
International Psoriasis Council
Meet the Experts
Treating difficult psoriasis cases

IPC’s first Meet the Experts program was held Feb. 1, 2008, in San Antonio, Texas. Nearly 100 participants attended the lively discussion, moderated by Kenneth Gordon, M.D. Dr. Gordon presented four cases of difficult-to-treat psoriasis patients to our panel of experts, Craig Leonardi, M.D., Alan Menter, M.D., and Bruce Strober, M.D., Ph.D. Here, we highlight two of the cases presented at this symposium. The clinical course of each case unfolds with the moderator’s questions in italics followed by the panelists’ responses.

Case 1: 53-year-old woman with psoriasis and a history of breast cancer

History and presentation
The patient has a 25-year history of psoriasis with 12% body surface area (BSA) involvement (Figure 1) of the trunk, scalp and limbs. In addition, she has a 15-year history of psoriatic arthritis with isolated interphalangeal joint (DIP, PIP) tenderness and swelling (Figure 2), and morning stiffness of the lower back and distal extremities for 90 minutes. There are no visible joint deformities.

X-rays show multiple erosions in DIP joints and early joint space narrowing of the sacroiliac joints. She was diagnosed with breast carcinoma six years ago. Treatment included a lumpectomy with negative nodal involvement, followed by tamoxifen therapy. There has been no recurrence of malignancy. Otherwise, she is healthy and does not drink alcohol.

Do you think the patient has permanent joint damage? How do the X-ray findings change or impact your therapeutic decisions?

PANELIST 1: Anyone who has a fixed, swollen joint for more than several months is likely to have radiological changes. There are few processes other than inflammatory arthropathy that would produce these clinical and radiological changes.

PANELIST 2: I would like to add that when you ask a patient about how long the joint stiffness and pain last, some will say that it lasts all day. I like to ask my patients, “In the morning, how long will it take for you to feel the best that you are going to feel that day?”

Given the sacroiliac changes, are there any special considerations for axial psoriatic arthritis? Many believe that TNF-inhibitors are better for axial disease. Given this patient’s psoriatic disease and her history of breast cancer, does this influence your treatment decision?

PANELIST 1: It is important to remember that this patient would be excluded from a clinical research study on any of the biologic drugs because of her prior history of breast cancer. We don’t have clinical trial experience in patients with breast cancer, so I would review the literature, discuss it with our rheumatology colleagues who have used these drugs longer than we have, and then I would discuss it with the oncologist. I would consider using a TNF-antagonist on this patient. She has progressive disease and is relatively young, 53, and I don’t want her disease to progress further. Some might begin with methotrexate because it’s “safer,” which is reasonable.

What would be your first treatment option if she did not have psoriatic arthritis?

PANELIST 2: A five-year cancer-free interval is a significant milestone but this does not mean “risk-free.” If you speak with oncologists and rheumatologists, there is growing ease with using TNF inhibitors in this kind of patient. While methotrexate is a good first choice, it may not be the best drug for her due to side effects. So, I would still consider using a biologic in this patient. You’ll have many discussions with specialists who manage the patient, yet the specialists may not know these drugs as well as you do.
PANELIST 3: I agree. Many times when I consult with other physicians, they are not as familiar with the biologics, and they assume you are using a new topical agent.

In this case, I would be having a long conversation—documenting in the chart how her psoriasis affects her quality of life, the arthritis, the fact that the oncologist has discussed the case with me, and that all of us will be involved in managing the patient going forward.

PANELIST 1: If this patient did not have psoriatic arthritis, I think phototherapy would be my first option, and since she is 53, I would add acitretin. Retinoids are not an issue here given her post-menopausal status.

Do you believe there is a difference between TNF-antagonists and anti-T cell agents with the potential reactivation of malignancy?

PANELIST 2: I believe the answer is no. However, I do know our experience is far less with the T-cell agents than with the TNF inhibitors. At this point, we just don’t know whether there are increased risks when using the T-cell agents.

I think we overstate malignancy issues in these scenarios. We have very little data to tell us how to approach treatment in these patients. Are we doing more harm by hiding behind theoretical malignancy issues?

Of the traditional systemic agents, the only drug that I fear in this scenario is cyclosporine, given its potent immunosuppression.

CLINICAL COURSE
A proposed treatment regimen was vetted with the oncologist, and methotrexate was initiated at 7.5 mg per week with folic acid supplementation and then increased to 20 mg per week after 12 weeks. There was some improvement in skin but little improvement in joints.

Acitretin 25 mg daily was added, and the methotrexate reduced to 15 mg per week. After 8 weeks, her skin improved significantly but there was no improvement in her joints. No laboratory abnormalities or tolerability problems were observed.

Can you comment about the combination of methotrexate and acitretin?

PANELIST 1: Since both drugs can be hepatotoxic, it is important to monitor liver function tests.

The skin has improved but the joints have not. What intervention would you do now?

PANELIST 3: I would start a TNF antagonist, with or without methotrexate, depending on the patient’s course. We would have the oncologist involved.

CLINICAL COURSE
Etanercept 50 mg once weekly was added. After 4 weeks, the arthritis symptoms had greatly improved. After 8 weeks, the skin was completely clear and arthritis symptoms were negligible. However, the patient began experiencing mild alopecia. Methotrexate was reduced to 10 mg per week, and acitretin was reduced to 10 mg per day. After 16 weeks, her skin and joints remained well-controlled, and the alopecia resolved. There was no recurrence of her malignancy.

What would you do if patient has a recurrence of breast cancer?

PANELIST 1: We’ve all had one or two patients on biologic drugs who have developed an internal malignancy, and we have to take it on a case-by-case basis, discuss it with the patient, and consider how severe the skin and joint symptoms are.

PANELIST 3: I would stop biologic therapy immediately. I may continue methotrexate while waiting to hear from the oncologist, but it is a difficult decision to continue biologic therapy in the setting of recurrence. I have had patients who are terminally ill, where it’s completely understood what’s going to happen, who are absolutely miserable with their psoriasis, but that’s a different kind of situation than what we’re talking about here.

PANELIST 2: Another point is that patients on chemotherapy for malignancies often clear their skin because of the chemotherapeutic regimen that is utilized. Oncologists know this because they’ve seen enough psoriasis in their patients clear during chemotherapy.
Case 2: 39-year-old obese man with psoriasis

History and presentation
The patient has a 15-year history of psoriasis without evidence of psoriatic arthritis. He has 15% BSA with active palmar psoriasis (Figure 3) and a body mass index (BMI) of 35 (220 lbs., 5’6”). He is taking statins for hypertension and insulin for diabetes mellitus. He has metabolic syndrome with fatty liver, and a positive PPD with a negative chest X-ray. He is not on isoniazid (INH) therapy.

What is metabolic syndrome and how does it impact treatment decisions?

PANELIST 1: The metabolic syndrome primarily involves obesity as its cardinal feature with a BMI over 30. It also involves issues believed to occur secondarily, such as issues involving the vasculature (e.g., hypertension), issues involving glucose metabolism, (e.g., insulin resistance) and then dyslipidemia (e.g., low HDLs and other abnormalities of lipid metabolism).

All and all, this adds up to high cardiovascular risk and therefore higher rates of cardiovascular disease such as myocardial infarction. But it has to be emphasized that the obesity is the essential problem, and all that follows is probably related to the cytokines and the adipocytokines that the obese tissue releases, including TNF-α and IL-6. Then everything tumbles downhill, and that’s why obesity is probably the No. 1 health issue in the developed world.

Do you think this patient is at greater risk of heart disease because of his psoriasis?

PANELIST 3: Well, I think it’s premature at this point. We don’t completely understand the linkage between metabolic syndrome and psoriasis. We know that its incidence is increased in psoriatic diseases, but we don’t know if treating psoriasis will affect this condition. The coronary artery disease story is absolutely fascinating, but this is one of those areas where we have snippets of information; we can generate a hypothesis, but proof of concept is yet to be demonstrated.

PANELIST 1: I would say there’s enough in the literature to suggest a true cardiovascular risk in people with this kind of psoriasis. Dr. Joel Gelfand’s study showed that myocardial infarction (MI) risk is higher in patients with more severe psoriasis when they’re younger, and another study showed that severe psoriasis patients live three to four years less, independent of treatment. Why? Probably because of cardiovascular sequelae. There is also an abundance of rheumatologic data showing that a very similar inflammatory disease, rheumatoid arthritis (RA), does the same things in regard to cardiac risk, and using good anti-inflammatory medications reduces those risks in RA studies.

Are there other interventions you would consider because of these other health problems?

PANELIST 2: This patient is a diabetic, and lifestyle modification of diet and exercise is always appropriate.

What steps do you take prior to treating this patient with immunosuppressive therapy? How does tuberculosis (TB ) impact your decision making process?

PANELIST 3: It is important to place a PPD for every patient about to start long-term immunosuppressive therapy. This is recommended by the U.S. Centers for Disease Control. This includes biologics, cyclosporine, prednisone and methotrexate, although the risk is probably less with this drug.

In the United States, 5 mm of induration or more is considered positive. A positive PPD should be followed by a chest X-ray. If the chest X-ray is negative, the patient has a diagnosis of latent TB; i.e., he or she has been TB-exposed.

The current U.S. guidelines call for nine months of INH therapy. Other countries may have different requirements. I believe that at least one month of INH is necessary to make sure the patient tolerates the medication. At that point, you can consider starting immunosuppressive therapy.
If the chest X-ray is positive, the patient has active TB, which absolutely must be addressed. The patient must be treated for active TB before starting immunosuppressive therapy (Figure 4).

What is the most appropriate treatment option?

PANELIST 2: When it comes to palmar plantar disease, I will start retinoids if the patient is not a female of child-bearing potential, but then rapidly move to efalizumab if unsuccessful.

PANELIST 3: I’ll use efalizumab first for patients with severe hand and foot psoriasis, because we have data generated from a placebo-controlled study that shows efalizumab was effective in treating hand and foot psoriasis. Is it the only biologic effective in treating hand and foot psoriasis? Probably not. Currently, it’s the only one that has data, and it’s a great place to start.

Does weight-based dosing make a difference?

PANELIST 1: Both infliximab and efalizumab are weight-based drugs. They seem to perform consistently across all weight ranges. Like infliximab, adalimumab is a potent TNF-antagonist and does well in heavy patients. As would be expected, adalimumab has a weight-based effect, but not nearly to the same degree as etanercept.

CLINICAL COURSE
Methotrexate was discontinued due to abnormal liver function tests (LFTs). Acitretin was also discontinued because of abnormal LFTs. Three courses of alefacept were given, each with some clearing. After discovery of a positive PPD test, the patient was given a nine-month course of INH therapy. One month after beginning INH, efalizumab was started at 1 mg/kg weekly. After three months, the skin had greatly improved, and the LFTs returned to normal levels. After six months, the skin had almost completely cleared.

We hope these case reviews were informative and helpful in your treatment of psoriasis patients.

Highlights from our Meet the Experts program in Istanbul, Turkey, will be presented in the September 2008 IPC Psoriasis Review.

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Meet the Experts Faculty: From left: Craig Leonardi, M.D., Alan Menter, M.D., Bruce Strober, M.D., Ph.D., and Kenneth Gordon, M.D.

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New Drugs, cont’d

Clinical trial results for ustekinumab
Phase III ustekinumab data were first presented by Craig Leonardi, M.D., at the 21st World Congress of Dermatology (WCD) in Buenos Aires, Sept. 30-Oct. 5, 2007. This expands the data discussed in the September 2007 issue of IPC Psoriasis Review. The Phoenix II trial had three experimental groups: 45 mg ustekinumab, 90 mg ustekinumab and placebo, with approximately 400 patients per group. Each group received an injection at week 0, 4, and every 12 weeks thereafter. The primary endpoint was PASI 75 at week 12. At week 12, after receiving 2 doses of ustekinumab, 67% of patients receiving the 45 mg dose and 76% of patients receiving the 90 mg dose achieved PASI 75, compared to 4% of the placebo group. At week 28, 70% and 79% of those receiving the 45 mg dose and 90 mg dose, respectively, achieved PASI 75. Ustekinumab provides sustained improvement with 12-week intervals between doses. These results were similar to those seen in the phase II program. The safety data presented through week 12 were very similar to placebo. While the initial safety profile is favorable, the long-term safety of this drug will be established in a four-year extension study.

Data from a second phase III ustekinumab trial were presented by Dr. Leonardi at the 66th Annual Meeting of the American Academy of Dermatology, Feb. 1-5, 2008, in San Antonio, Texas. The Phoenix I trial was similar in design to Phoenix II with approximately 250 patients per group, but at week 40, there was randomization to placebo to determine loss of response. During the randomized withdrawal period, there was a gradual recurrence of disease over time. In the 45 mg group, at week 40 the drug was withdrawn, and response was maintained in 64%, 29% and 20% at weeks 52, 64 and 76, respectively. Similar results were seen in the 90 mg group when randomized to placebo. The phase III results for ustekinumab have been accepted for publication in The Lancet.

Clinical trial results for ABT-874
Phase II ABT-874 data were also presented at the WCD by Kenneth Gordon, M.D., and have since been published. This phase II study was a dose-finding study, and six treatment groups with 30 patients each were evaluated. The following doses were used: 1 dose of 200 mg, 100 mg every other week (eow), 200 mg/week for 4 weeks, 200 mg eow, 200 mg/week and placebo. At week 12, PASI 75 was achieved by 63% (200 mg dose), 93% (100 mg eow), 90% (200 mg 4 doses), 93% (200 mg eow) and 90% (200 mg/week), compared to 3% of the placebo group. Escalating doses beyond 100 mg eow do not seem to improve efficacy. The treatment was well-tolerated. As with ustekinumab, further studies are needed to establish long-term safety of this new treatment.

CURRENT STATUS
Ustekinumab was submitted to the U.S. Food and Drug Administration (FDA) and European Medicines Agency for approval for psoriasis in December 2007, with the FDA Advisory Committee scheduled for June 17, 2008. Ustekinumab is currently in phase II trials for psoriatic arthritis, and ABT-874 has just completed enrollment of its phase III trials for psoriasis.

COMMENTARY
The anti-IL12/IL-24 p40 drugs, ustekinumab and ABT-874, have shown impressive results in psoriasis clinical trials. Although the early safety data is very favorable, long-term safety should be carefully considered, particularly in areas with endemic diseases caused by intracellular organisms. This new class of drugs enhances our understanding of the pathways involved in psoriasis pathogenesis and provides potential new and effective treatment options.

Additional reading: