MEETING HIGHLIGHTS

American Academy of Dermatology

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The American Academy of Dermatology held its 69th annual meeting from February 4 to 8, 2011, in New Orleans, drawing more than 16,500 people from over 90 countries. The meeting included nearly 400 scientific sessions in which more than 1,400 speakers presented the latest research and clinical information regarding the diagnosis and medical, surgical, and cosmetic treatment of skin, hair, and nail conditions. Summaries from a handful of these presentations are presented in this article.

High-Dose Isotretinoin (Accutane) Therapy: Positive Results in Nodulocystic Acne

- Amanda Cyrulnik, fourth-year medical student, Albert Einstein College of Medicine, New York, N.Y.
- Aron Gewirtzman, MD, Montefiore Medical Center, New York, N.Y.
- Kate Viola, MD, MHS, Yale–New Haven Hospital, Conn.
- Steven Cohen, MD, MPH, Montefiore Medical Center, New York, N.Y.

For patients with nodulocystic acne, high-dose oral isotretinoin (Accutane, Roche) may provide superior efficacy and quality of life when compared with conventional dosing, according to a retrospective study.

“This is the first study to re-evaluate high-dose isotretinoin therapy since [its] pivotal trials,” said Ms. Cyrulnik. Approved in 1982 by the FDA, isotretinoin is the only available therapy for cystic acne that is associated with permanent remission.

The FDA currently recommends isotretinoin specifically for patients with severe nodulocystic acne that has been unresponsive to conventional therapy. However, the 2007 American Academy of Dermatology guidelines recommended isotretinoin for patients with less severe acne that resists conventional treatment and for patients with psychological or physical scarring, Ms. Cyrulnik said. Acne vulgaris is associated with significant psychosocial effects, including low self-esteem, depression, and decreased quality of life, she added.

Most published studies recommend a single course of isotretinoin using 1 mg/kg daily, for a cumulative dose of 120 to 150 mg/kg over five to six months. Ms. Cyrulnik said:

However, at this recommended dose, more than 20% of patients will experience a relapse requiring an additional course of isotretinoin therapy within two years. This disappointing outcome led us to study a cohort of patients with cystic acne who received high-dose isotretinoin, which we defined as 1.3 mg/kg or more per day, to evaluate safety, efficacy, and tolerability, as well as the impact of this regimen on quality-of-life parameters.

The retrospective chart review included 80 patients with nodulocystic acne who were treated at Montefiore Medical Center between 2006 and 2009. Investigators also performed follow-up phone interviews with 59 patients using a validated acne quality-of-life questionnaire.

The average daily isotretinoin dose among the 80 patients was 1.6 mg/kg, for an average cumulative dose of 290 mg/kg. In addition, 12.5% of study patients experienced relapse during the period studied, although none of those who relapsed experienced the same acne severity that they had before treatment.

Ms. Cyrulnik said, “It’s interesting to note that four of the 10 patients who relapsed had some form of prior isotretinoin therapy.”

Nearly 90% of patients experienced no adverse drug events (AEs) other than the commonly experienced mucocutaneous effects, which are accepted as an inherent component of isotretinoin therapy.

She added, “The most common side effects were headache and musculoskeletal discomfort. Importantly, none of our patients experienced any psychiatric side effects, even though five of our patients had a pre-existing psychiatric history.”

Laboratory abnormalities, mostly mild, occurred in 39% of patients.

Regarding efficacy, 100% of patients were acne-free by their eighth physician visit. Moreover, high-dose isotretinoin therapy was significantly associated with improvements in self-perception, social functioning, and acne symptoms, while its association with emotional improvement trended toward significance. She said:

Our conclusion is that isotretinoin, prescribed at an average daily dose of 1.6 mg/kg for five to six months, is safe and remarkably effective compared to current standard dosing practices. For us, the most important finding was that patients’ quality of life improved significantly following this treatment regimen. We propose doses greater than 1.3 mg/kg per day as a possible treatment option for nodulocystic acne. Because the study was a single-provider, retrospective chart review, we encourage larger, prospective, multicenter studies using this therapeutic approach.

However, Jonette Keri, MD, Associate Professor of Dermatology at the University of Miami Miller School of Medicine, said, “I caution anyone who starts at a dose of 1.3 or 1.6 mg/kg per day.”

To prevent flares that these initial doses may cause, she initiates therapy at 0.1 to 0.5 mg/kg daily and increases the dose if needed and tolerated.

Mr. Sonnenreich, based in Washington, D.C., is the editor of the Maruho Derma Report.
Briakinumab (ABT-874) for Psoriasis: A Pooled Analysis of Phase 3 Clinical Trials

- Richard G. Langley, MD, Dalhousie University, Halifax, Nova Scotia, Canada
- Kenneth Gordon, MD, North Shore University Health System and University of Chicago Pritzker School of Medicine, Northbrook, Ill.
- Michele L. Olds, MD, Abbott Laboratories, Abbott Park, Ill.
- David A. Williams, Abbott Laboratories, Abbott Park, Ill.

Patients taking Abbott’s briakinumab, an investigational interleukin (IL)-12 and IL-23 blocker for psoriasis, require monitoring for infection, non-melanoma skin cancer, and major cardiovascular adverse events (AEs), according to the session leaders.

Briakinumab (ABT-874) is a fully human monoclonal antibody targeting the p40 subunit common to IL-12 and IL-23. To characterize its safety and efficacy beyond what any individual clinical trial has shown, the researchers pooled week 12 results of three randomized, double-blind, placebo-controlled phase 3 trials.

“Our main rationale for pooling the data is that in phase 3 studies, many times you’re powering for efficacy, not safety,” said Dr. Langley.

The investigators wanted to analyze both, he said. The trials included 1,258 patients with moderate-to-severe psoriasis who were treated with briakinumab; 624 patients received placebo. In all three studies, briakinumab-treated patients received subcutaneous doses of 200 mg at baseline and at week 4, then 100 mg at week 8 and monthly thereafter.

At week 12, briakinumab was found to be superior in efficacy to placebo, as measured by Physician Global Assessment (PGA) scores, the Psoriasis Area and Severity Index (PASI), and the Dermatology Life Quality Index (DLQI). In particular, 75.1% of briakinumab-treated patients achieved PGA scores of 0 to 1 (clear skin or minimal psoriasis) at week 12 (P < 0.001). Moreover, 80.8% of briakinumab-treated patients achieved a 75% reduction in PASI scores (PASI 75), and nearly one-third of briakinumab-treated patients achieved PASI 100 (P < 0.001 for all endpoints).

During the studies, 20.2% of briakinumab-treated patients withdrew, usually because of a lack of efficacy (15.1%) and AEs (1.4%). Perhaps most pertinent to the pooled safety analysis was the fact that 39.4% of the briakinumab-treated patients had some cardiovascular history at baseline, Dr. Langley said.

While under treatment, 1.8% of briakinumab patients experienced serious infections compared with 0.6% of the placebo group. The investigators also documented 10 malignancies in the treated group and one malignancy in the placebo group. Treatment-emergent non-melanoma skin cancer occurred in 1.8% of the briakinumab patients (including one basal cell carcinoma, four squamous cell carcinomas, and one lip neoplasm) versus none in placebo-treated patients.

Among briakinumab patients, said Dr. Langley, five major cardiovascular AEs, including one death, were also reported, compared with no cardiovascular AEs or deaths in the placebo group. Accordingly, said Dr. Langley, the investigators concluded:

The efficacy results are certainly robust. We’re seeing significant improvement compared to placebo. However, we had higher rates of infection, non-melanoma skin cancer, and major cardiovascular adverse events when we compared treated patients versus placebo. This highlights the need to monitor for these events in larger psoriasis populations.

Biologic Therapies for Psoriasis Comorbidities

- Craig L. Leonardi, MD, Saint Louis University, St. Louis, Mo.

When prescribing a biologic drug for psoriasis, dermatologists must consider the impact of comorbid conditions, according to American Academy of Dermatology psoriasis guidelines.

To illustrate proper application of the guidelines, Dr. Leonardi outlined the hypothetical case of an obese 31-year-old woman of childbearing age with widespread psoriasis who required systemic treatment. Previously, she also had 300 psoralen plus ultraviolet A (PUVA) treatments plus two years of narrowband ultraviolet B treatments. These modalities contributed to the development of photodamage, basal cell carcinoma, and squamous cell carcinoma in this patient.

Dr. Leonardi said, “When you start pushing ultraviolet therapy this hard, patients begin to develop comorbid issues.”

The patient also has the metabolic syndrome, which includes hypertension, elevated cholesterol and triglyceride levels, and non-insulin-dependent (type-2) diabetes.

“These issues guide treatment selections,” he added.

Prescribing oral acitretin (Soriatane, Stiefel) is ruled out if patients are of childbearing age, he said. The FDA recommends that women who have used this drug avoid pregnancy for three years after treatment ends. Similarly, he said that although oral cyclosporine (Sandimmune, Novartis) is highly effective for psoriasis, its nephrotoxicity and side effects (including rising triglyceride levels) make it an unattractive long-term choice. Furthermore, patients are at risk for elevated liver enzymes as a result of obesity and comorbid medications. These factors contraindicate the use of methotrexate, said Dr. Leonardi. He commented:

All of these factors make biologic therapy a much more attractive option. Biologics are not nephrotoxic or hepatotoxic and have no other interactions with internal organ systems that we’re aware of. And biologic therapies will not interact with other therapies that a patient may be taking.

Considering the patient’s obesity, Dr. Leonardi said that adalimumab (Humira, Abbott), which achieves PASI 75 in 70% to 80% of patients, initially worked well, although it can lose efficacy over time.

“We see this sometimes with biologic drugs,” he said.

In choosing a second-line biologic, he said that the patient’s existing risk for cardiovascular events—coupled with the elevated risk of major cardiovascular AEs that surfaced in clinical trials of ustekinumab (Stelara, Centocor Ortho Biotech) and, to a higher degree, with briakinumab—steer him toward a tumor necrosis factor (TNF) antagonist. He explained:
I might choose infliximab [Remicade, Centocor Ortho Biotech] in my practice because it allows weight-based dosing. We also know that etanercept [Enbrel, Amgen/Pfizer], adalimumab, and infliximab reduce cardiovascular risk profiles in patients with rheumatoid arthritis. We suspect that they also do this in patients with psoriasis and psoriatic arthritis.

Registries that track patients’ experiences with psoriasis treatments over time will help physicians better understand the impact of biologic drugs that target IL-12 and IL-23 (such as ustekinumab and briakinumab) upon the risk of cardiovascular AEs.

Dr. Leonardi said, “I believe it’s a class effect. We have some small signals that raise concerns in the ustekinumab trials, and a pretty significant signal in the briakinumab study submitted to the FDA in late 2010.”

In January 2011, Abbott withdrew its Biologics License Application (BLA) for briakinumab following FDA feedback that additional studies might be required.

Evolving Topical Therapies for Onychomycosis

- Boni E. Elewski, MD, University of Alabama, Birmingham, Ala.

The low efficacy rates of topical preparations for onychomycosis have left many dermatologists wanting better solutions, said Dr. Elewski. Spurred by a need for new options, researchers have developed some new devices and a new topical drug, she added.

The most recently approved topical medication approved by the FDA for onychomycosis was ciclopirox lacquer 8% (Penlac, Sanofi-Aventis) in 1999.

“However, she said, “In its two FDA trials, it achieved unimpressive cure rates—5.5% and 8.5%.”

The objective of topical onychomycosis treatments is to provide efficacy particularly for mild-to-moderate cases, said Dr. Elewski.

“Topicals can be used as primary treatment, as adjuncts to systemic therapy to enhance cure rates or after systemic therapies to prevent re-infection or maintain remission,” she noted.

Although many studies have mainly used stronger concentrations of existing agents over the past decade, Dr. Elewski said, “No topical treatments for onychomycosis have made it through the FDA.”

She said this is partly because current FDA guidelines require enrollment of mild-to-severe cases in the same study, although topical antifungal agents may not be the best choice for severe disease. Research is under way to investigate devices that can introduce topical medications through the nail bed as well as topical modalities that don’t require antifungal medications. Dr. Elewski said that she plans to be an investigator in a multicenter phase 3 study of the first in a new class of topical antifungal agents in 2011. The study will be sponsored by Anacor/Schering-Plough.

“It is a boron-based compound that was specifically designed to penetrate the nail. That’s exciting because this is the first new drug that will be studied for onychomycosis. Preliminary data have looked quite good,” she said.

Other topical options include laser therapy. Dr. Elewski is currently evaluating the long-pulsed neodymium yttrium aluminum garnet (Nd:YAG) 1,064-nm laser for use in mild, moderate, and severe onychomycosis.

“We’re treating patients five or six times with approximately 300 pulses at 16 joules/cm².”

In another ongoing study, Dr. Elewski is evaluating iontophoretic application of topical terbinafine (Lamisil, Novartis), which involves formulating a molecule with an electrical charge in a carrier that promotes solubility. In this trial, investigators apply the drug to a pad, place the pad over the affected area, and send a small electric current through the pad. Basically, the current pushes the drug into the nail.

Photodynamic therapy appears to be a viable topical option for patients who do not respond to topical drug therapy, Dr. Elewski said. In an open-label trial enrolling 30 patients, investigators treated nails for 10 nights with 20% urea ointment under occlusion so that the nails could be easily removed. The patients then received three treatments with 20% aminolevulinic acid topical solution, followed by 360 to 570 nm (red) of light at 40 joules/cm². Twelve months after treatment was concluded, 43% of patients were cured.

Dr. Elewski is also considering conducting an investigator-initiated trial of photodynamic therapy for onychomycosis.

REFERENCES