American Academy of Dermatology and American College of Cardiology

Walter Alexander

American Academy of Dermatology

The American Academy of Dermatology hosted approximately 16,874 attendees in Denver from March 21 to 25. There was heightened interest in agents for the treatment of psoriasis; four such sessions are described here.

Results After at Least 52 Weeks of Open Label Treatment with Ixekizumab, an Anti-IL-17A Monoclonal Antibody, in a Phase 2 Study in Chronic Plaque Psoriasis

- Kenneth B. Gordon, MD, Professor of Dermatology, Northwestern University, Feinberg School of Medicine, Chicago, Illinois

Clinical responses to ixekizumab treatment over 52 weeks in an open-label extension trial were maintained in a high proportion of patients with plaque psoriasis. The proportion, Dr. Gordon reported, was similar to that observed in the prior randomized treatment period.

Ixekizumab is a monoclonal antibody that neutralizes interleukin-17A (IL-17A), a pro-inflammatory cytokine that plays a critical role in the pathogenesis of psoriasis. In the prior randomized, placebo-controlled phase 2 study, IL-17A was shown to produce positive responses in patients with moderate-to-severe chronic plaque psoriasis.

The 20-week randomized, blinded portion of the trial was followed by a washout period extending to week 32. The 129 patients completing the 20 weeks of treatment could enter the open-label extension (OLE) period at week 32 and receive subcutaneous ixekizumab 120 mg given every four weeks. If their clinical response fell below PASI (Psoriasis Area and Severity Index) 75, they could enter the OLE before week 32. PASI scores are calculated based on psoriatic plaque redness, scaling, and thickness and the extent of involvement of various regions of the body. A PASI 75 response indicates a 75% improvement in PASI score from baseline.

Dr. Gordon presented data on four groups: all patients enrolled in the OLE; those initially assigned to placebo; week 20 responders (at PASI 75, 90, or 100 levels); and week 20 non-responders.

At week 20, 51 patients had less than a PASI 75 response, as did 24 additional patients between weeks 24 and 32. Forty-five patients maintained PASI 75 and entered the OLE at week 32.

Among patients assigned initially to placebo, about 80% (22) achieved and maintained PASI 75. "That's about equivalent to what was seen in the initial randomized part of the study for all patients," Dr. Gordon said. In addition, a slightly lower proportion of patients achieved and maintained PASI 90, and slightly more than 50% attained and maintained PASI 100. "To put that in context, if you remember the alefacept trials, there we were looking at PASI 75 rates of 21%. Now we have PASI 100s of twice that level," Dr. Gordon said.

Among week 20 responders, about 80% had PASI 90 responses through 52 weeks. "This is very distinct from the other medicines we've been using recently," Dr. Gordon said. PASI 100 responses in this group went from 25% at week 0 of the OLE to about 80% within 20 weeks and were sustained.

Among those who lost responses and then were treated again, PASI 75 was achieved in approximately 70% after about 20 weeks. "The great majority of these patients regain response. Likewise for PASI 90 and 100, the numbers remain high (approximately 50% and approximately 40%, respectively) and are consistent throughout," Dr. Gordon said.

No unexpected safety signals were observed. Discontinuations for adverse events were uncommon (2.4%). The most common treatment-emergent events were nasopharyngitis (10.0%), upper respiratory tract infections (7.5%), sinusitis (4.2%), and diarrhea (4.2%). Minor candidiasis was reported in 4.2%.

Dr. Gordon concluded, "Overall, a high proportion of patients responded to ixekizumab therapy and maintained the response over 52 weeks in this open-label extension."

Secukinumab Efficacy Stratified by Body Weight: A Subanalysis From the FIXTURE Phase 3 Study in Psoriasis

- Jacek C. Szepietowski, MD, University of Medicine, Wroclaw, Poland

A systematic review and meta-analysis of observational studies[1] conducted in 2012 showed higher rates of obesity among patients with psoriasis (odds ratio 1.66 overall, 2.23 with severe psoriasis), and other research[2] has suggested that obesity may reduce responses to biologic agents used to treat psoriasis. A subanalysis of FIXTURE (Full Year Investigative Examination of Secukinumab vs. Etanercept Using 2 Dosing Regimens to Determine Efficacy in Psoriasis) evaluated the effect of body weight on response to treatment with secukinumab in a pivotal phase 3 program in moderate-to-severe plaque psoriasis.

Secukinumab has demonstrated rapid, robust, and durable efficacy with an acceptable safety profile in this population in phase 3 trials. Dr. Szepietowski and colleagues evaluated the impact of body weight on response to treatment in the 1,300-patient trial. Patients had received one of two doses of secukinumab (150 mg/300 mg, every four weeks), placebo, or etanercept (50 mg biweekly) for 52 weeks. For evaluation

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of the co-primary endpoints of PASI 75 and Investigators' Global Assessment (IGA) modified 2011 scores of 0/1 (clear or almost clear), patients were stratified by body weight: less than 90 kg or at least 90 kg.

Analysis showed secukinumab demonstrated rapid, high, sustained efficacy at both doses compared with etanercept, with higher responses at the higher dose of secukinumab. Body weight subgroups did not have differing responses. In the 300-mg secukinumab arm at week 12, PASI 75 responses were reported in about 78% of the 217 patients who weighed less than 90 kg and in about 72% of the 106 patients who weighed at least 90 kg. At week 52, PASI 75 responses were found for approximately 82%, 70%, and 58% of the under-90-kg patients (secukinumab 300 mg, secukinumab 150 mg, and etanercept 50 mg, respectively) compared with approximately 70%, 60%, and 52% in the 90-kg-or-more arm.

In addition, no major weight-based differences in the safety profile were reported. The exposure-adjusted incidence rates for treatment-emergent adverse events, however, were higher in subjects weighing 90 kg or more versus less than 90 kg in any secukinumab dose group (267.7 vs. 233.1 per 100 subject-years) and in the etanercept group (297.4 vs. 222.3 per 100 subject-years). Differences were driven, Dr. Szepietowski noted, largely by infections and infestations.

Dr. Szepietowski concluded that there was little influence of body weight on response rates.

Apremilast, an Oral Phosphodiesterase 4 Inhibitor, in Patients With Moderate-to-Severe Psoriasis: Results From the Randomized Treatment Withdrawal Phase of a Phase 3, Randomized, Controlled Trial (ESTEEM 1)

• Robert M. Day, PhD, Celgene Corporation, Warren, New Jersey; Jennifer Cather, MD, Modern Research Associates, Dallas, Texas

Apremilast is an oral small-molecule inhibitor of phosphodiesterase 4 (PDE4) specific for cyclic adenosine monophosphate (cAMP). PDE4 inhibition results in increased intracellular cAMP levels, modulating a wide array of inflammatory mediators.

ESTEEM 1 was a large, randomized, placebo-controlled, pivotal phase 3 study that evaluated apremilast in patients diagnosed with moderate-to-severe plaque psoriasis at least 12 months prior to screening. To be eligible, patients also had to be candidates for phototherapy and/or systemic therapy.

ESTEEM 1 investigators randomized about 1,250 patients by a 2:1 ratio to receive either apremilast 30 mg twice daily or placebo after an initial five-day titration period for the first 16 weeks. A maintenance period followed from weeks 16 to 32 during which placebo patients were switched to apremilast 30 mg twice daily and apremilast patients continued their dose. At week 32, apremilast patients with PASI 75 response were randomized to placebo (until loss of effect) or continued on apremilast. Topical agents were added to those not achieving PASI 75 response. Patients in the initial placebo arm continued with apremilast, but with topical agents added for those with less than a PASI 75 response.

The primary endpoint of PASI 75 response was reported as 33.1% in the apremilast arm and 5.3% in the placebo arm ($P < 0.0001$) at 16 weeks. For the major secondary endpoint of static Physician Global Assessment (sPGA) scores of 0–1 (indicating clear or almost clear), the rates were 21.7% versus 3.9%, respectively ($P < 0.0001$).

The mean percentage change from baseline in PASI score for the 77 patients receiving apremilast in weeks 0–52 and achieving PASI 75 at week 32 was approximately –80%. Among patients who had received placebo during weeks 0–16 and apremilast during weeks 16–52, the mean PASI score change from baseline was also approximately –80% for those achieving PASI 75 at week 32. Among patients who were not PASI 75 responders at week 32, the mean percentage change from baseline in PASI score was approximately –50% to –60%.

When apremilast patients lost their PASI 75 response after being randomized to placebo in weeks 16–32, 70.3% of them regained PASI 75 responses with re-initiation of apremilast 30-mg twice-daily treatment.

Among the 46 patients who had nail psoriasis at baseline, a mean 60.2% decrease from baseline in the Nail Psoriasis Severity Index (NAPSI) was observed at week 52. Of the 49 patients who had scalp psoriasis defined as moderate or greater at baseline, 72.9% had reductions of their scalp symptoms to clear or almost clear (Scalp and Palmoplantar Psoriasis Global Assessment [ScPGA] 0 or 1) at week 52. Dr. Day emphasized that in plaque psoriasis in the nails and scalp—areas known to be difficult to treat—improvements were meaningful in the majority of patients.

The incidence of serious adverse events was low and comparable across treatment groups during the placebo-controlled period, with discontinuation for diarrhea and nausea of less than 2% in the apremilast 30-mg twice-daily group through week 52. Longer exposure to apremilast, Dr. Day said, did not increase adverse events.

ESTEEM 2 co-author Dr. Cather commented: "Together with the observed long-term consistent safety and tolerability profile, these findings are encouraging."

Apremilast, an Oral Phosphodiesterase 4 Inhibitor, in Patients With Moderate-to-Severe Psoriasis: 16-Week Results of a Phase 3, Randomized, Controlled Trial (ESTEEM 2)

• Carle Paul, MD, PhD, Toulouse University, Toulouse, France

Apremilast is an oral phosphodiesterase 4 inhibitor that regulates cellular inflammatory mediators. In the phase 3 ESTEEM 2 trial, investigators enrolled 274 patients in the apremilast arm and 137 in the placebo arm. Patients had a diagnosis of moderate-to-severe plaque psoriasis (PASI 12 or more; body surface area [BSA] of 10% or more; sPGA of 3 or more) for at least 12 months prior to screening. Included patients also had to be candidates for phototherapy and/or systemic therapy.

Patients were randomized 2:1 to receive either apremilast 30 mg twice daily or placebo for the first 16 weeks, followed by a maintenance phase during weeks 16–32. In that period, placebo patients were switched to apremilast 30 mg twice

daily through week 32. ESTEEM 2 also included a randomized withdrawal phase for responders from weeks 32 to 52 based on initial apremilast randomization and PASI 75 response.

The ESTEEM 2 primary endpoint was PASI 75 response at week 16.

A significantly higher percentage of patients receiving apremilast 30 mg twice daily achieved a PASI 75 response compared with patients who received placebo (28.8% vs. 5.8%; $P < 0.0001$) at 16 weeks. Statistical significance at week 16 was also demonstrated for the major secondary endpoint, sPGA scores of 0–1 (20.4% vs. 4.4%; $P < 0.0001$).

Dr. Paul noted that apremilast 30 mg twice daily compared with placebo also demonstrated beneficial effects in difficult-to-treat areas of scalp, nails, palms, and soles. Apremilast versus placebo resulted in improvements for the scalp (ScPGA 0–1: 40.9% vs. 17.2%; $P < 0.0001$), the nails (NAPSI 50: 44.6% vs. 18.7%; $P < 0.0001$), and palm and soles (Palmoplantar Physician Global Assessment [PPPGA] 0–1: 65.4% vs. 31.3%; $P = 0.0315$).

Most adverse events, Dr. Paul said, occurred in the first or second week of treatment, were mild or moderate in severity, and did not lead to discontinuation of therapy. Diarrhea was reported in 15.8% of apremilast patients and nausea in 18.4% (vs. 5.9% and 6.6% in the placebo arm, respectively).

"Patients need to be warned about these events. They can be managed," he said. Dr. Paul also commented that doses of apremilast were titrated over the first few days of treatment. "You need to titrate the dose to prevent rapid occurrence of events," he said.

"Apremilast may represent a novel oral therapy with a favorable benefit–risk profile for patients with moderate-to-severe plaque psoriasis," Dr. Paul concluded.

American College of Cardiology

The American College of Cardiology (ACC) 63rd Scientific Sessions took place in Washington, D.C., from March 29 to 31. About 19,000 people attended, including 4,000 cardiologists and 9,000 physicians, nurses, and other medical professionals. Among the many high-interest sessions this year, some surprising results were not without their controversies. The clear superiority of heparin over bivalirudin in HEAT PPCI, in contrast to findings in the EUROMAX and HORIZONS-AMI trials, and opposing findings in the two SYMPLICITY trials of renal denervation, are presented below and are fueling active discussion.

HEAT PPCI (How Effective Are Antithrombotic Therapies in PPCI [Primary Percutaneous Coronary Intervention])

- Rod Stables, MD, Liverpool Heart and Chest Hospital, Liverpool, United Kingdom

In primary percutaneous coronary interventions (PPCIs) for ST-elevation myocardial infarction (STEMI), bivalirudin and heparin appear to have similar anti-ischemic efficacy and similar rates of major adverse cardiac events (MACE). Guideline-recommended use of selective "bailout" glycoprotein IIb/IIIa inhibitors (GPIs) is increasingly the norm as part of antithrombotic therapy. Bivalirudin plus selective GPI use is an established treatment option (7% to 15% of cases).

It is known, Dr. Stables said in an ACC press briefing, that bleeding is associated with less favorable outcomes and that increased GPI use results in increased bleeding with both bivalirudin and heparin. However, determining the relative performance of bivalirudin and heparin with respect to bleeding with differential GPI use requires a direct comparison.

HEAT PPCI, a single-center, randomized, open-label trial of 1,829 patients (median age, approximately 63 years) with suspected myocardial infarction (MI), compared bivalirudin (bolus of 0.75 mg/kg, followed by an infusion of 1.75 mg/kg per hour) plus a selective GPI to heparin (bolus of unfractionated heparin 70 units/kg) plus a selective GPI. Patients were followed for 28 days and assessed for the primary endpoint of combined all-cause death, stroke, repeat MI, or unplanned repeat procedure.

The endpoint was reported in 8.7% of patients receiving bivalirudin and in 5.7% of patients receiving heparin ($P = 0.01$; relative risk [RR] = 1.52; 95% CI, 1.1–2.1). A larger difference between treatment arms was noted for stent thrombosis, with a rate of 3.4% for bivalirudin compared with 0.9% for heparin ($P = 0.001$; RR = 3.91; 95% CI, 1.6–9.5). Stent thrombosis differences between the two arms, Dr. Stables said, drove the MACE disparity.

Major bleeding, the primary safety outcome, was similar between groups (3.5% for bivalirudin, 3.1% for heparin).

Dr. Stables concluded that preferential use of heparin would reduce MACE, stent thrombosis, and reinfarction events without an increase in bleeding complications.

"In the UK," Dr. Stables said, "bivalirudin costs approximately 400 times as much as heparin." He noted that some critics of the trial suggested the bivalirudin dose was too low. "If we use additional vials of bivalirudin with prolonged infusions … we may approximate heparin, but the cost differential could then be 1,500 times."

A Phase 3 Double-Blind, Randomized Study to Assess the Safety and Efficacy of Evolocumab (AMG 145) in Hypercholesterolemic Subjects Unable to Tolerate an Effective Dose of Statin

- Erik S.G. Stroes, MD, Academic Medical Center, Amsterdam, Netherlands

Cardiovascular risk and mortality risk are reduced by about 22% and 10%, respectively, for every decrease in low-density lipoprotein-cholesterol (LDL-C) of 39 mg/dL.[3] Evolocumab, a fully human monoclonal antibody against proprotein convertase subtilisin/kexin 9 (PCSK9), yielded potent reductions in LDL-C among statin-intolerant patients in the GAUSS-2 (Goal Achievement after Utilizing an anti-PCSK9 antibody in Statin intolerant Subjects [NCT01763905]) study.

GAUSS-2, a 12-week, randomized, double-blind, placebo- and ezetimibe-controlled, multicenter phase 3 study, aimed to evaluate the efficacy and safety of evolocumab in statin-intolerant hypercholesterolemic patients.

Investigators enrolled 307 patients (mean age approximately 62 years, 46% women), assigning them to one of two subcutaneous evolocumab doses (140 mg every two weeks or 420 mg per month, plus daily placebo) or one of two oral ezetimibe groups (a placebo injection every two weeks or monthly, plus 10 mg oral ezetimibe daily).

More than 94% of all enrolled patients completed the study. Dr. Stroes reported that the primary efficacy endpoint of percentage change from baseline in LDL-C at mean of weeks 10 and 12 and at week 12 was –18% and –56% for the biweekly ezetimibe and evolocumab patients, respectively. For monthly ezetimibe and evolocumab, it was –15% and –53%. The treatment differences for evolocumab versus ezetmibe, for both the 10/12 week averages and at week 12 (–37% and –38%) were highly significant ($P < 0.001$). Differences were similar for monthly administration of evolocumab (–39% and –38%, $P < 0.001$).

Musculoskeletal side effects were reported in 12% of patients on evolocumab compared to 23% on ezetimibe. Discontinuations for treatment-related side effects occurred in 8% of evolocumab patients and 13% of ezetimibe patients. The most commonly reported adverse events for evolocumab versus ezetimibe included headache (8% vs. 9%), muscle pain (8% vs. 18%), pain in extremities (7% vs. 1%), and muscle spasms (6% vs. 4%).

Dr. Stroes concluded, "The LDL-C–lowering efficacy combined with good tolerability make evolocumab a promising option to address the unmet clinical need in high-risk hypercholesterolemic patients with statin intolerance."

Renal Denervation in Patients With Uncontrolled Hypertension: Results of the SYMPLICITY HYPERTENSION 3 Trial

• Deepak L. Bhatt, MD, MPH, Brigham and Women's Hospital Heart and Vascular Center, Boston, Massachusetts

Among the 250 patients with severe resistant hypertension enrolled in the SYMPLICITY HTN-3 trial, renal denervation failed to meet its primary and secondary efficacy endpoints. The trial, the largest and most rigorously designed evaluation of renal denervation, was blinded and included a sham procedure, said Dr. Bhatt. While renal denervation for the treatment of uncontrolled hypertension is approved in more than 80 countries, it is still investigational in the U.S.

Trial investigators randomly assigned 535 patients at 88 U.S. centers with resistant hypertension and systolic blood pressure of 160 mm Hg or higher (135 mm Hg or higher ambulatory blood pressure) to renal denervation or angiography alone. Patients in both groups continued their regimens of three or more antihypertensive drugs, including a diuretic at the highest tolerated doses. The primary efficacy endpoint was the decrease in office systolic blood pressure from baseline to six months. Mean age was about 57 years (approximately 62% male).

With systolic blood pressure reductions at –14.1 mm Hg in the renal denervation arm versus –11.7 mm Hg in the sham procedure arm, the absolute reduction between groups of 2.39 mm Hg was not significant ($P = 0.26$). The secondary endpoint, change from baseline to six-month follow-up in mean systolic 24-hour ambulatory blood pressure, was also statistically nonsignificant at 1.96 mm Hg ($P = 0.98$), with a systolic blood pressure reduction of 6.8 mm Hg in the renal denervation arm versus 4.8 mm Hg reduction in the control arm.

Reductions in systolic blood pressure as compared with baseline were significant in both groups.

Analysis of blood pressure changes by tertile revealed no significant differences among groups. There was a strong trend (interaction P value, 0.09) toward differences in response between African-Americans and non-African-Americans. Among African-Americans there was a 2.25 mm Hg increase in systolic blood pressure ($P = 0.53$) as compared with –6.63 mm Hg for non-African-Americans ($P = 0.01$).

The safety goal of a 9.8% or lower adverse event rate was easily met, with an event rate of 1.4% for renal denervation and 0.3% for the sham control arm. Only one case of renal stenosis, in the renal denervation arm, was reported. Major adverse event rates were 1.4% for the renal denervation arm and 0.6% for the sham procedure ($P = 0.67$).

In this population of patients with severe resistant hypertension who were receiving optimal pharmacological therapy and who were closely monitored, SYMPLICITY HTN-3 revealed no added treatment benefit for renal denvervation, Dr. Bhatt said.

With respect to prior trials without sham controls showing renal denervation benefits, Dr. Bhatt added, "These results underscore the importance of blinding and sham controls in evaluations of new devices." He also noted the need for further rigorously designed clinical trials.

The Global SYMPLICITY Registry: Safety and Effectiveness of Renal Artery Denervation In Real-World Patients With Uncontrolled Hypertension

• Michael Böhm, MD, University of Homburg/Saar, Germany

Analysis of the first 1,000 patients in the largest-to-date real-world registry of uncontrolled hypertension patients treated with renal denervation revealed significant blood pressure lowering and low adverse events at six months, Dr. Böhm said in a late-breaking trial presentation of Global SYMPLICITY Registry results. The trial was conducted at 231 international sites in 37 countries. Included patients were on three or more antihypertensive medications at baseline. Patients had baseline systolic office pressures of at least 160 mm Hg and baseline ambulatory systolic blood pressures of at least 135 mm Hg.

Mean office systolic blood pressure dropped 11.9 mm Hg at six months for the overall population of 751 patients. It increased by 14.2 mm Hg in patients whose baseline systolic blood pressures were below 140 mm Hg at baseline, decreased by 4.6 mm Hg in those with baseline systolic blood pressures of 140–159 mm Hg, and decreased by 21.4 mm Hg in those with baseline systolic blood pressures of 160 mm Hg or more. Decreases of more than 10 mm Hg were reported in 68% of patients.

Only five adverse events were attributed to the procedure; four (0.34%) were access site complications and the other was a successfully treated renal artery dissection.

When Dr. Böhm presented the Global SYMPLICITY results, findings from another renal denervation trial, SYMPLICITY HTN-3, had already taken center stage at the ACC meeting. That randomized trial among 250 patients found no benefit for

renal denervation versus a sham procedure. The finding led some experts to suggest that the invasive SYMPLICITY renal denervation technique—which uses radiofrequency radiation to ablate the sympathetic nerves in the renal artery—may be producing no more than a placebo effect.

Responding in an interview, Dr. Böhm listed factors in SYMPLICITY HTN-3 that make a placebo response unlikely as the sole effect: Patients had been pushed to their highest tolerated doses of antihypertensive medications before the renal denervation treatment (raising the bar to show responses), African-Americans did not respond at all to the procedure (lowering the overall response rate), and most of the procedures were performed by operators completely new to the technique, increasing chances of less than optimal results. Dr. Böhm emphasized that the registry procedures were performed by operators who had conducted at least 30 procedures. (In an e-mail response, Deepak Bhatt, MD, the lead investigator of SYMPLICITY HTN-3, replied that the experience of the operators did not affect the magnitude of the responses.)

While acknowledging the limitations of comparing a registry with a randomized, blinded, controlled study, Dr. Böhm stated: "The reduction in blood pressure is numerically larger in the global registry at six months after treatment."

The stark differences between the findings of SYMPLICITY HTN-3 and the Global SYMPLICITY Registry reflect the investigational status of renal denervation in the United States and its widespread approval and use in Europe (with some application in patients with less severely resistant hypertension).

The impact of the failure to show benefit in SYMPLICITY HTN-3 was clear in an interview with Dr. Böhm. "I think the hype is over. Of course, we had a little bit of hype in Europe, not only in Germany."

REFERENCES

1. Armstrong AW, Harskamp CT, Armstrong EJ. The association between psoriasis and obesity: a systematic review and meta-analysis of observational studies. *Nutr Diabetes* 2012;Dec 3;2:e54. doi: 10.1038/nutd.2012.26.
2. Clark L, Lebwohl M. The effect of weight on the efficacy of biologic therapy in patients with psoriasis. *J Am Acad Dermatol* 2008;58(3):443–446.
3. Cholesterol Treatment Trialists' Collaboration, Baigent C, Blackwell L, et al. Efficacy and safety of more intensive lowering of LDL cholesterol: a meta-analysis of data from 170,000 participants in 26 randomised trials. *Lancet* 2010;376(9753):1670–1681. ■