American Heart Association Scientific Sessions 2012
American Association for the Study of Liver Disease
American College of Rheumatology/ Association of Rheumatology Health Professionals

Walter Alexander

In rapid succession, three meetings in November, offered the latest in basic and clinical research: the American Heart Association (AHA) Scientific Sessions 2012 in Los Angeles hosting almost 18,700 cardiologists, the American Association for the Study of Liver Disease (AASLD) in Boston with 8,400 liver specialists and the American College of Rheumatology (ACR/ARHP) in Washington, D.C., hosting 15,000 rheumatologists.

American Heart Association Scientific Sessions 2012

Similar Benefits for PA32540 and Aspirin In Preventing Cardiovascular Disease

- David J. Whellan, MD, Thomas Jefferson University/ Jefferson Medical College, Philadelphia, Pa.

PA32540, made by Pozen, is a coordinated-delivery tablet of enteric-coated aspirin 325 mg and an immediate-release formulation of the proton pump inhibitor omeprazole (Prilosec, AstraZeneca) 40 mg.

Dr. Whellan presented results for 1,049 patients enrolled in two identical randomized phase 3 studies. Patients received either a 6-month course of once-daily PA32540 or enteric-coated aspirin 325 mg. Study participants were at risk of aspirin-associated gastric ulcers because they were 55 years of age or older or were 18 to 54 years of age with a documented history of gastric or duodenal ulcer within 5 years prior to enrollment.

The American Heart Association recommends aspirin therapy for patients with established cardiovascular disease (CVD) or cerebrovascular disease in order to decrease the risk of future CVD events; however, gastrointestinal (GI) bleeding has been associated with chronic aspirin therapy, Dr. Whellan noted. Cessation of aspirin treatment that results from GI side effects might increase the risk of CVD events. Roughly 15% of the 24 million patients taking aspirin for secondary CVD prevention in the U.S. are at risk of upper GI adverse events, and about 12% stop aspirin altogether or reduce their intake because of these events.

The primary endpoint in the study was endoscopically confirmed gastric ulcer, defined as a mucosal break of 3 mm or greater in diameter in size with depth.

In study 301, the results showed that 3.8% of the PA32540 cohort and 8.7% of the aspirin 325-mg cohort had an endoscopically confirmed gastric ulcer ($P = 0.02$). In study 302, gastric ulcer rates were 2.7% and 8.5% for the two treatment groups, respectively ($P = 0.005$).

Overall, 92.8% of patients receiving PA32540 and 75.9% of patients receiving enteric-coated aspirin 325 mg experienced resolution of reflux at 6 months ($P < 0.001$). Only 1.5% of the PA32540 patients discontinued treatment because of prespecified upper GI adverse events compared with 8.2% of the aspirin 325-mg patients ($P < 0.001$).

Rates of treatment discontinuation caused by any adverse event were 6.7% with PA32540 and 11.2% with aspirin ($P < 0.05$).

The incidence and type of major adverse CVD events were similar in the two groups: 1.7% for PA32540 and 2.5% for enteric-coated aspirin 325 mg. Dr. Whellan commented:

> As physicians, we need to recognize that our patients who need aspirin for secondary cardiovascular disease prevention are often discontinuing conventional aspirin treatment because of aspirin-associated GI ulcers and GI symptoms. The significantly lower rate of treatment discontinuation with PA32540 is especially important, because patients at risk of an aspirin-associated gastric ulcer who stop aspirin therapy prematurely retain their risk of future cardiovascular events.

Finally, he noted that for CVD events, the findings were limited by the short duration of the study and study sample size.

Serelaxin and Acute Heart Failure: The RELAX–AHF Trial

- John R. Teerlink, MD, University of California–San Francisco
- John McMurray, University of Glasgow, Scotland

During pregnancy, cardiac output increases by 20%, vascular resistance decreases by 30%, arterial compliance goes up by 30%, renal blood flow increases by 50% to 85%, and creatinine clearance increases by 40% to 65%. The hormone relaxin mediates these adaptations beyond its known anti-ischemic, anti-inflammatory, and antifibrotic effects.

"These are the exact kinds of changes we'd like to see in acute heart failure," Dr. Teerlink said at a late-breaking clinical trial press briefing.

The author is a freelance medical writer living in New York City.

RELAX–AHF, an international, multicenter, double-blind, placebo-controlled trial, tested whether these benefits would be produced by recombinant human relaxin-2 (serelaxin, Novartis) in 1,161 patients hospitalized for acute heart failure.

Patients were randomly assigned to receive standard care plus 48-hour intravenous (IV) infusions of placebo or serelaxin (30 mcg/kg/day) within 16 hours from presentation. All of the patients had dyspnea, radiographically confirmed congestion; elevated levels of brain natriuretic peptide (BNP) at 350 pg/mL or higher or amino-terminal pro-BNP (NT-pro-BNP) at 1,400 pg/mL or higher; mild-to-moderate renal insufficiency, as assessed by the Simplified Modification of Diet in Renal Disease equation; an estimated glomerular filtration rate of 30 to 75 mL/minute/1.73 m^2; and systolic blood pressure (BP) above 125 mm Hg. Mean age was 72 years.

For the primary endpoint of dyspnea relief over 5 days, there was a significant 19.4% increase in the area-under-the-curve (AUC) concentration with serelaxin (mean difference, 448 mm/hour [AUC 2,756 ± 2,588 vs. 2,308 ± 3,082]; $P = 0.0075$), and a nonsignificant trend in improved dyspnea relief on Likert time points at 6, 12, and 24 hours ($P = 0.702$).

For the secondary endpoint of CVD death or heart or renal failure, there was no benefit with serelaxin. The hazard ratio (HR) was 1.02 with a 95% confidence interval (CI) of 0.74 to 1.41 ($P = 0.89$]).

Cardiovascular death rates (not prespecified) were significantly lower with serelaxin (6.1%), compared with placebo (9.6%) ($P = 0.028$). The number of patients needed to treat (NNT) to prevent one death was 29.

Signs and symptoms of congestion were also significantly improved with the study drug. In addition, the need for IV medications, including cumulative diuretic doses and vasoactive drugs, was significantly reduced with serelaxin ($P = 0.0057$ for diuretics, $P = 0.01$ for vasoactive drugs).

Length of hospital stay (LOS) for those receiving serelaxin was reduced (3.9 vs. 3.5 days for placebo; $P = 0.029$), as was index hospitalization LOS (10.5 days vs. 9.6 days, respectively; $P = 0.039$).

Improvements in the biomarkers of NT-proBNP and creatinine ($P = 0.0002$ and $P < 0.0001$), in liver enzymes (alanine transaminase, ALT) ($P < 0.0010$), and in troponin T ($P < 0.0001$) were observed as well.

At 180 days, all-cause mortality rates (NNT = 25) were significantly reduced with serelaxin (7.3% of treated patients and 11.3% of placebo patients died) (HR = 0.63; 95% CI, 0.43–0.93; $P = 0.020$;).

Adverse events were generally similar between the groups, although renal impairment occurred less frequently with serelaxin (4.6% vs. 8.6% with placebo).

"I think serelaxin does improve dyspnea," said Dr. McMurray.

He cautioned, though, that benefits shown with small numbers of patients—as has been shown famously in the past with vesnarinone (Arkin-Z, Otsuka) and losartan (Cozaar, Merck)—may prove to be spurious when larger randomized trials are conducted.

Aspirin After Acute Myocardial Infarction

- Hurst M. Hall, MD, University of Texas Southwestern Medical Center, Dallas, Tex.

Is high-dose aspirin being prescribed indiscriminately to patients who have experienced an acute myocardial infarction (MI)?

In pursuit of this question, Dr. Hall examined the National Cardiovascular Data Registry (NCDR) ACTION Registry–GWTW (Get With The Guidelines) for 213,586 acute MI patients from 525 centers. Patients had been admitted between January 2, 2007, and March 31, 2011. Among these, 127,586 (59.8%) had non-ST-segment MI (NSTEMI).

The analysis showed that at hospital discharge, high-dose aspirin (325 mg) was prescribed for 61%, 162 mg was prescribed for 3%, and 81 mg was prescribed for 36%; 51% of the patients were discharged with high-dose aspirin alone. Among patients discharged with a prescription for clopidogrel (Plavix, Bristol-Myers Squibb/Sanofi), 69% also received high-dose aspirin, probably reflecting guidelines at the time of the study, Dr. Hall commented. Surprisingly, 44% of patients receiving triple therapy, which consisted of aspirin, clopidogrel, and warfarin (Coumadin, Bristol-Myers Squibb), were discharged with high-dose aspirin.

Although fewer than half of the patients who had undergone coronary artery bypass graft were discharged with high-dose aspirin, almost half of the patients managed with medications received high-dose aspirin. Both patterns are contrary to current recommendations.

The occurrence of a major bleeding event (i.e., a 4-mg/dL drop in hemoglobin, intracranial hemorrhage, or red blood cell transfusions) apparently had little effect on prescribing; 57% of patients with a major bleeding event in the hospital were discharged with high-dose aspirin, similar to the percentage (64%) of patients *without* a major bleeding event who received high-dose aspirin at discharge.

Looking at high-dose aspirin use across the spectrum of hospitals, Dr. Hall found a 25-fold variance with no apparent connection to other quality metrics. Based on high rates of high-dose aspirin use in high-risk subgroups for whom a guideline-based indication was lacking, he concluded that high-dose aspirin is overused in the U.S.

Combination Therapy After Myocardial Infarction: The UMPIRE Trial

- Simon Thom, MD, Imperial College, London, United Kingdom
- Discussant: Andrew M. Tonking, Monash University, Melbourne, Australia

Data from the Prospective Urban Rural Epidemiology (PURE) trial in 2011 showed that the use of drugs for the secondary prevention of cardiovascular disease (CVD) in high-income, middle-income, and low-income countries is disappointingly low worldwide, Dr. Thom said in a late-breaking clinical trial press conference.[1] In high-income countries, the chances of a post-MI patient being prescribed aspirin, a statin, and blood pressure (BP)–lowering therapy are about 40% to 50%, whereas

in low-income countries, post-MI patients are often prescribed no medications at all.

The primary hypothesis of UMPIRE (Use of a Multidrug Pill In Reducing Cardiovascular Events) was that a fixed-dose, combination-based strategy (a "polypill") intended to deliver preventive medications (aspirin, a statin, and two BP-lowering agents), compared with usual care, might improve adherence, systolic BP, and low-density lipoprotein-cholesterol (LDL-C) at the end of the study in patients at a high risk for CVD.

UMPIRE enrolled 2,004 participants in India and Europe with established CVD or an estimated 5-year CVD risk of at least 15%. Patients had been comparatively well treated at baseline. They were randomly assigned to receive either usual care or one of two fixed-dose combination pills:

- Version 1: aspirin 75 mg, simvastatin (Zocor, Merck) 40 mg, lisinopril (e.g., Zestril AstraZeneca) 10 mg, and atenolol (Tenormin, AstraZeneca) 50 mg
- Version 2: aspirin 75 mg, simvastatin 40 mg, lisinopril 10 mg, and hydrochlorothiazide (HCTZ) 12.5 mg

Primary outcomes were 24-month self-reported adherence to the indicated medication and changes from baseline in systolic BP and LDL-C levels. Participants receiving the fixed-dose combination regimen received their medication free of charge, but the usual-care patients received no study-based assistance.

Mean age was approximately 62 years, and 81.5% of the patients were men. In both groups, 88% of the patients had established CVD, and 28% had diabetes mellitus. Background medications were similar for both.

At the end of the study, adherence was 86% in the fixed-dose-combination group and 65% in the usual-care group (relative risk [RR] = 1.33; 95% CI, 1.26–1.41; $P < 0.001$).

Systolic BP values were 129.2 mm Hg with the combination and 131.7 mm Hg with usual care, for a difference of 2.6 mm Hg (95% CI, –4.0 to –1.1; $P = 0.0005$). LDL-C levels were 2.18 mmol/L with the fixed-dose combination and 2.29 mmol/L with usual care (RR = –0.11; 95% CI, –0.17 to –0.05; $P = 0.0005$). (*Note:* 1 mmol/L is equal to 38.67 mg/dL of cholesterol.)

Increased adherence was greater among patients with a high 5-year CVD risk and among those with low adherence at baseline.

Dr. Thom concluded, "A fixed-dose-combination strategy, including aspirin, statin and two blood pressure–lowering drugs improves adherence, blood pressure, and cholesterol in patients with established cardiovascular disease and in those at high risk."

The 33% increase in adherence over a median interval of 15 months, he noted, was evident even though the included population had an unusually high reported use of indicated medications at the outset.

Dr. Tonkin noted that although providing the free polypill might have favored adherence in the fixed-dose-combination group, the high persistence of medication use in the usual-care group (82% receiving statin, antiplatelet, and antihypertensive drugs, compared with 5% to 50% in the PURE trial) mitigated against the demonstration of a benefit. UMPIRE findings, therefore, probably underestimate the likely benefit of polypill adherence.

Dr. Tonkin also commented that the small systolic BP decrease conferred major public health benefits.

"UMPIRE findings," he said, "should inform government policies and strategies."

REFERENCE

1. 1. Yusuf S, Islam S, Chow CK, et al. Use of secondary prevention drugs for cardiovascular disease in the community in high-income, middle-income, and low-income countries (the PURE Study): A prospective epidemiological survey. *Lancet* 2011;378:1231–1243).

American Association for the Study Of Liver Disease

MK-5172 With Peg-Interferon-alfa/Ribavirin For Hepatitis C Virus Genotype 1

- Patrick Marcellin, MD, PhD, University of Paris-Diderot, Clichy, France

Patients with hepatitis virus C infection (HCV) who were treated with the investigative agent MK-5172 (Merck) plus peg-interferon alfa-2b and ribavirin (PegIntron/Rebetol, Schering/Merck) have achieved high rates of undetectable virus. The findings consisted of complete early viral response and sustained virological response at week 12 (SVR12), researchers reported. These interim findings are from a phase 2 trial.

MK-5172 is a potent, next-generation nonstructural protein (NS3/4A) inhibitor. Genotype 1 affects about 70% of patients.

"Among treatment-naive, noncirrhotic, hepatitis C genotype 1-infected patients, a 12-week regimen of MK-5172 100 mg, once-daily dosing orally, in combination with 24 to 48 weeks of pegylated interferon plus ribavirin, is highly efficacious and is equally as efficacious as the higher doses in achieving SVR12," said Dr. Marcellin in his poster presentation.

The primary endpoint of this phase 2 study was complete early viral response in four regimens of MK-5172, combined with peg-interferon alfa-2b/ribavirin, compared with a control arm of a 4-week lead-in of peg-interferon alfa-2b/ribavirin, followed by daily boceprevir (Victrelis, Merck) 200 mg.

Subjects receiving MK-5172 in all of the groups (100 mg, 200 mg, 400 mg, and 800 mg) achieved complete early viral response at 12 weeks, ranging by group from 82.8% to 93% and compared with the control arm at 74.2%

The investigators enrolled two cohorts of treatment-naive subjects—a "vanguard" cohort of 136 subjects and a second cohort of 196 subjects. They reported SVR12 results on the vanguard group in this interim analysis.

After 12 weeks of treatment, 25 of 26 patients (96.2%) in the vanguard cohort who received MK-5172 100 mg once daily plus peg-interferon alfa-2b/ribavirin achieved SVR12, compared with 13 of 24 controls (54%). For the other arms of the vanguard cohort, SVR12 results ranged from 81.5% to 86.7%.

One patient in the MK-5172 800-mg arm experienced a serious adverse event caused by elevated levels of alanine aminotransferase (ALT) and total bilirubin, which returned to normal after therapy was stopped.

Studies of interferon-free regimens using MK-5172 once-daily

100 mg are planned.

Dr. Marcellin's study was supported by Merck Sharp & Dohme, a subsidiary of Merck & Co.

Telaprevir or Boceprevir With Peg-Interferon alfa/Ribavirin for Hepatitis C: The French Early Access Program (ANRS CP20–CUPIC Trial)

- Christophe Hezode, MD, Hôpital Henri Mondor, Creteil, France

In a large cohort of patients with compensated (Child–Pugh class A) cirrhosis who were receiving telaprevir (Incivek, Vertex) or boceprevir (Victrelis, Merck) for hepatitis C virus (HCV) infection in triple combination in the Compassionate Use of Protease Inhibitors in viral C Cirrhosis (CUPIC) trial, high rates of on-treatment virological response were accompanied by poor safety, compared with phase 3 trials.

Registration trials revealed rash, pruritus, and anemia among patients receiving telaprevir and anemia and dysgeusia in those receiving boceprevir. Few cirrhotic patients, however, were included in registration trials. CUPIC's primary aim was to determine the rates of sustained virological response (SVR) in this population. The interim analysis evaluated the safety and tolerability of antiviral therapy at week 16.

Among 497 patients evaluated, all had HCV genotype 1 with compensated cirrhosis and were nonresponders to prior therapy. Nonresponders included relapsers and partial responders (below the response criterion of greater than a 2 $\log_{10}$ HCV RNA decline at week 12) to prior therapy. Null responders were excluded.

Triple therapy included pegylated interferon alfa-2b/ribavirin (PegIntron Rebetol) and either telaprevir 750 mg every 8 hours (n = 292) or boceprevir 800 mg every 8 hours (n = 205).

Among patients receiving telaprevir, serious adverse events were reported in 45.2% of patients and led to discontinuation in 14.7%. Anemia at grade 2 or higher was reported in 30.4% of patients, with blood transfusions needed in 16.1% and ribavirin dose reductions needed in 13.0%.

For patients receiving boceprevir, serious adverse events were reported in 32.7% of patients, causing discontinuation in 7.3%. Grade 2 or higher anemia occurred in 27.8% of patients, with blood transfusions needed in 6.3% and ribavirin dose reductions needed in 10.7%.

The multivariate analysis showed the following:

- A baseline predictor of anemia (below 8 g/dL) or blood transfusions tended to be female sex (odds ratio [OR] = 2.19; 95% CI, 1.11–4.33; P = 0.023).
- There was no lead-in phase (OR = 2.25; 95% CI, 1.156–4.39; $P = 0.018$).
- Patients were 65 years of age or older (OR = 3.04; 95% CI, 1.54–6.02; $P = 0.0014$).
- Hemoglobin values were 12 g/dL or below for women and 13 g/dL or below for men (OR = 5.30; 95% CI, 2.49–11.25; $P < 0.0001$).

At 16 weeks, efficacy rates (defined as undetectable HCV RNA levels) for the intent-to-treat (ITT) population were 67% for telaprevir and 58% for boceprevir.

Dr. Hezode concluded that before these regimens are prescribed, risk–benefit ratios should be assessed in treatment-experienced patients with cirrhosis on a case-by-case basis because of the high risk of severe complications.

"However, those without predictors of severe complications should be treated cautiously and carefully monitored," he said.

Achillion Press Event: The Hepatitis C Virus Connection

- Fred Poordad, MD, University of Texas; Texas Liver Institute; and Alamo Medical Research, San Antonio, Tex.
- Andrew Muir, MD, Duke Clinical Research Institute, Durham, N.C.

The current standard of care for HCV genotype 1 infections is a first-generation protease inhibitor, namely telaprevir (Incivek) or boceprevir (Victrelis) in combination with pegylated interferon and ribavirin for 24 to 48 weeks. That standard of care, however, is limited by considerable treatment failures, significant side effects, a long duration of therapy, and inconvenient administration and dosing. The goal of developing safe and effective interferon-free regimens with convenient dosing is widely sought through combination therapies.

The optimal direct-acting antiviral treatment strategy for HCV infection combines "best-in-class," second-generation protease inhibitors (PIs) and nonstructural protein (NS5A) inhibitors. What differentiates best-in-class agents from the field is that they demonstrate potent activity against the resistant mutations that commonly plague first-generation agents while interfering with HCV replication and potentially suppressing and eradicating reservoirs of hidden virus outside the liver.

Achillion's sovaprevir (formerly ACH-1625), a second-generation PI, was tested in a phase 2 randomized, placebo-controlled trial among HCV genotype 1 treatment-naive patients in combination with pegylated interferon/ribavirin in what was termed "a challenging real-world patient population." In the trial segment evaluating 12 weeks of therapy, early virological responses were noted in 58 patients (100%), and sustained virological responses (SVRs) were noted in 77% to 85% of all sovaprevir groups receiving 200 mg, 400 mg, or 800 mg once daily.

Dr. Poordad said that sovaprevir demonstrated a high pharmacological barrier to resistant mutations associated with telaprevir and boceprevir (V36M, T54A/S, V55A, A156S, and I/V170A) and suppressed the virus with the A80K polymorphism, found in 47% of genotype 1a HCV patients and known to reduce susceptibility to treatment.

Adverse events with sovaprevir were similar to those for placebo. The FDA has endorsed the 200-mg and 400-mg doses for future trials.

Further study of the all-oral combination of sovaprevir with the second-generation NS5A inhibitor ACH-3102 plus ribavirin is planned for 2013. Second-generation NS5A inhibitors, Dr. Muir said, have shown 10-fold to 100-fold improved activity against resistant mutations while remaining safe and well tolerated.

Enrollment is ongoing for a phase 2a study of ACH-3102 plus ribavirin in treatment-naive patients with HCV genotype 1b.

American College of Rheumatology/ Association of Rheumatology Health Professionals

Apremilast in Psoriatic Arthritis: PALACE-1, Phase 3

- Arthur Kavanaugh, MD, University of California San Diego, San Diego, Calif.

PALACE-1 is the first of three pivotal phase 3 randomized, placebo-controlled studies that are evaluating the novel, oral small-molecule inhibitor of phosphodiesterase-4 (PDE_4) in patients with psoriatic arthritis (PsA) who previously received oral disease-modifying antirheumatic drugs (DMARDs), biologic therapy, or both, or who had not responded to an anti-tumor necrosis factor (TNF) agent. PDE_4 inhibitors increase intracellular cyclic adenosine monophosphate (cAMP) levels and modulate the production of both pro-inflammatory and anti-inflammatory mediators.

In the study, oral apremilast (Celgene) was given alone—30 mg twice daily (n = 168); 20 mg twice daily (n = 168); or placebo (n = 168)—or in combination with oral DMARDs. The mean patient age was 50 years, and the mean PsA duration was 7.5 years. The mean Psoriasis Area and Severity Index (PASI) score was 8.5 on a scale of 0 (zero) to 72. About 75% of the patients had used DMARDs, and TNF blocker therapy had failed in 22%. A 24-week treatment period was completed by 150 placebo patients and 146 of 148 patients receiving apremilast 20 mg twice daily and 30 mg twice daily, respectively.

For the American College of Radiology primary endpoint of ACR20 (20% or better improvement) at week 16 (for the per-protocol population, N = 489), rates were 19% for placebo, 31% for apremilast 20 mg twice daily ($P < 0.02$), and 40% for apremilast 30 mg twice daily ($P < 0.0001$).

At week 16, an analysis of ACR20 responses, stratified by biologic experience, revealed the following respective rates: 24%, 31%, and 43% for biologic-naive patients; 5%, 31%, and 28% for biologic-experienced patients; and 6%, 21%, and 23% for patients not responding to biologic TNF inhibitors.

"Those are pretty striking differences in favor of the active treatment group—for both biologic-experienced and TNF failures at week 16. Both of these two groups of patients tend to be refractory. I think that's encouraging support for the potential efficacy of this compound," Dr. Kavanaugh commented.

A further 16-week analysis of DMARD use revealed lower ACR20 responses among patients receiving apremilast plus DMARDs than in patients receiving apremilast alone, both in the overall and biologic-naive populations. This counterintuitive attenuation of benefit for the combination, Dr. Kavanaugh said, remains unexplained.

At week 24, ACR responses for placebo, apremilast 20 mg twice daily, and apremilast 30 mg twice daily were as follows: ACR20, 13%, 36%, 45%; ACR50, 4%, 16%, and 22%; and ACR70, 1%, 6%, and 12%.

Among secondary endpoints at week 24, mean changes in the Health Assessment Questionnaire–Death Index (HAQ–DI), a measure of disability; mean changes in the Pain Visual Analogue Scale; and good or moderate responses, as assessed by European League Against Rheumatism criteria, all displayed significant dose-related improvements for apremilast.

More than 95% of adverse events were mild or moderate in severity, with low withdrawal rates: 4.8% for placebo, 6.0% for apremilast 20 mg twice daily, and 7.1% for apremilast 30 mg twice daily. The most common adverse events were diarrhea (2.4% for placebo, 11.3% for 20 mg twice daily, and 19.0% for 30 mg twice daily) and nausea (6.5%, 9.5%, and 18.5%, respectively). No opportunistic infections or reactivations of tuberculosis or lymphoma were observed.

Dr. Kavanaugh concluded, "Oral apremilast demonstrated efficacy across all psoriatic arthritis outcome measures, including pain, disability, and physical function."

A New Drug Application submission to the FDA, based on the combined PALACE program for PsA, is expected in the first half of 2013.

Tofacitinib for Rheumatoid Arthritis: Phase 2, Phase 3, and Extension Studies

- Gerd-Rüdiger Burmester, MD, Charité–University Hospital, Berlin, Germany

Tofacitinib (Xeljanz, Pfizer) was approved by the FDA on November 6, 2012, for adults with moderately to severely active rheumatoid arthritis (RA) who have had an inadequate response to, or who are intolerant of, methotrexate. This novel oral Janus kinase (JAK) inhibitor is a targeted immunomodulator and a DMARD.

Although tofacitinib has shown consistent efficacy in a broad range of clinical measures and patient types, data are limited regarding patients with inadequate responses to DMARDs, including TNF inhibitors. Dr. Burmester's analysis explored the benefits of tofacitinib 5 mg or 10 mg twice daily versus placebo in these difficult-to-treat patients in data pooled from nine randomized phase 2 and phase 3 studies (N = 614) and from two open-label, long-term extension studies (N = 510).

In the overall pooled population, based on 3-month American College of Radiology ACR20 data, 33% of patients had not responded to one TNF inhibitor, 13% had not responded to two TNF inhibitors, and 3% had not responded to one TNF inhibitor. The reason for treatment failure was a lack of efficacy for 82% of the patients and adverse events in 13%.

Among the individual trials, some phase 2 studies included inadequate DMARD responses from methotrexate patients also receiving tofacitinib alone and other studies included inadequately responding methotrexate patients receiving tofacitinib. Phase 3 studies re-enrolled the same groups, adding patients with inadequate responses to DMARDs who were receiving tofacitinib and nonbiologic DMARDS or tofacitinib monotherapy. A further trial was conducted to evaluate inadequate responses to TNF inhibitors in patients receiving tofacitinib and methotrexate.

Three-month ACR20, ACR50, and ACR70 results versus placebo among inadequate responders to TNF inhibitors showed highly significant improvements ($P < 0.0001$) at both tofacitinib doses for ACR20 and ACR50 and significant improvements ($P < 0.05$) at both doses for ACR70.

For patients who did not respond to one TNF inhibitor, ACR20 responses were reported in 43.7% of patients receiving tofacitinib 5 mg twice daily and in 50% of those receiving tofacitinib 10 mg twice daily, compared with 24% of patients receiving placebo ($P < 0.0001$).

The pattern of highly significant ($P < 0.0001$) dose-related improvements over placebo for tofacitinib 5 mg and 10 mg twice daily persisted among patients who had not responded earlier to a TNF inhibitor because of a lack of efficacy.

Benefits of tofacitinib, when compared with placebo in the HAQ–DI (which measures physical function) at 3 months, were highly significant for all nonresponders to TNF inhibitors and were at least significant for nonresponders to one or two TNF inhibitors. For the Short-Form 36-item Health Survey (SF-36) (bodily pain) and for the Functional Assessment of Chronic Illness Therapy–Fatigue (FACIT–F), the benefits from baseline with both tofacitinib doses were highly significant ($P < 0.0001$).

The long-term extension trial analysis also demonstrated 24-month persistent ACR20, ACR50, and ACR70 benefits and Disease Activity Scale at 28 joints/C-reactive protein/erythrocyte sedimentation rate (DAS28–CRP–ESR) benefits for pooled inadequate TNF inhibitor responders, reflecting low disease activity in 32.8% of patients (i.e., scores of 3.2 or lower). Clinical remission (a DAS28 score of below 2.6) was reported in 17.9% of patients. No new safety signals appeared in the population with inadequate responses to TNF inhibitors.

The pooled data, Dr. Burmester concluded, revealed consistent improvements in signs and symptoms, physical function, and patient-reported outcomes in SF-36 for bodily pain and FACIT–F while also showing that responses were maintained over a period of 24 months.

Tofacitinib is also discussed in this month's Pharmaceutical Approval Update column on page 13.

Ustekinumab in Active Psoriatic Arthritis: PSUMMIT, Phase 3

• Alan Mendelsohn, MD, Janssen Research & Development, LLC, Springhouse, Pa.

In earlier reporting PSUMMIT-1 results, Janssen's ustekinumab (Stelara), a fully human anti-interleukin-12/23p40 monoclonal antibody approved for adults with moderate-to-severe psoriasis, demonstrated efficacy in reducing signs and symptoms of active psoriatic arthritis (PsA) through 24 weeks.

PSUMMIT-1 *P*hase 3 Multicenter, Randomised, Double-blind, Placebo-controlled trials of *U*stekinumab, a Fully Human anti-IL-12/23p40 *M*onoclonal Antibody, Ad*m*inistered Subutaneously, *i*n Subjects with Active Psoriatic Ar*t*hritis) enrolled 615 patients with active disease despite having taken DMARDs, nonsteroidal anti-inflammatory agents (NSAIDs), or both. Patients were randomly assigned to receive ustekinumab at either 45 mg (n = 205) or 90 mg (n = 204), or placebo (n = 206) at weeks 0, 4, and every 12 weeks thereafter. Stable doses of concomitant methotrexate were permitted but not mandated; about 50% received concomitant methotrexate. Patients who had been treated earlier with anti-TNF agents were excluded from the study.

At week 24 in PSUMMIT I, 42% and 50% of patients receiving ustekinumab 45 mg and 90 mg, respectively, achieved at least a 20% improvement (ACR20) in signs and symptoms, the primary endpoint, compared with 23% of patients receiving placebo ($P < 0.001$). Regardless of methotrexate use, ACR responses were greater with ustekinumab than with placebo.

Reporting longer-term safety and efficacy results, Dr. Mendelsohn said that the primary endpoint of ACR20 went from 22.8%, 42.4%, and 49.5% for placebo, ustekinumab 45 mg, and ustekinumab 90 mg, respectively, at week 24 to 65.2% (for placebo patients crossing over to ustekinumab 45 mg), 56.7%, and 60.3% at week 52.

Secondary endpoint ACR50 responses increased from 8.7%, 24%, and 27.9% for placebo, ustekinumab 45 mg, and ustekinumab 90 mg, respectively, at week 24 to 38.0% (for placebo patients crossing over to ustekinumab 45 mg), 31.4%, and 37.0%, respectively, at week 52.

ACR70 responses, which had increased significantly ($P < 0.001$) for the two ustekinumab doses at 24 weeks, increased nonsignificantly at week 52 (from 2.4%, 12.2%, and 14.2% to 16.3%, 18.0%, and 21.2%).

Improvements in swollen and tender joint counts noted at 24 weeks increased somewhat at 52 weeks. The Psoriasis Area and Severity Index (PASI 75) and HAQ–DI responder rates (achieving an improvement of 0.3 or more from baseline) improved similarly, as did moderate or good responder rates in DAS28–CRP.

Among patients with enthesitis (n = 425) or dactylitis (n = 286) at baseline, improvements initially observed at week 24 continued at week 52, increasing to 100% for the placebo-to-ustekinumab 45-mg group, the ustekinumab 45-mg group, and the ustekinumab 90-mg group.

One or more serious adverse events were reported in 0.5% of patients switching from placebo to ustekinumab 45 mg, in 1.0% of patients in the ustekinumab 45-mg group, and in 1.0% of those in the ustekinumab 90-mg group. Safety profiles were consistent with those observed through week 24, Dr. Mendelsohn said.

He concluded, "In patients with active psoriatic arthritis, ustekinumab continued to reduce the signs and symptoms of arthritis; improve physical function, enthesitis, and dactylitis; and improve plaque psoriasis through week 52, at a rate similar to that reported for other biologic treatments." ■