Combined Torcetrapib-Atorvastatin Provides Many Lipoprotein Benefits

BY BRUCE JANCIN
Denver Bureau

ATLANTA — The novel HDL cholesterol–boosting drug torcetrapib, which is being developed solely as a combination pill with atorvastatin, results in favorable lipoprotein changes of unprecedented magnitude, Dr. Tom Thuren reported at the annual meeting of the American College of Cardiology.

He presented data from a multicenter, double-blind, phase II, dose-ranging study involving 493 patients with elevated LDL cholesterol in which torcetrapib 60 mg/day plus atorvastatin 10-80 mg/day—the doses in clinical development—resulted in dose-dependent 44%-66% increases in cardioprotective HDL cholesterol, along with LDL cholesterol reductions of 41%-60%.

The combination of torcetrapib 60 mg plus atorvastatin 80 mg also resulted in a 20% increase in apolipoprotein A-I compared with baseline in the 12-week study. The mean reduction in non-HDL cholesterol was 23% with torcetrapib 90 mg alone, 47% with atorvastatin 80 mg alone, and 61% with the two combined.

Moreover, the various torcetrapib/atorvastatin combinations resulted in salutary changes in lipoprotein particle size as assessed by nuclear magnetic resonance. There was a marked shift away from small, dense LDL particles—the subclass thought to be most highly atherogenic—in favor of large, buoyant LDL particles. Indeed, levels of small, dense LDL cholesterol dropped by 23-70 mg/dL in dose-dependent fashion, whereas large LDL particles increased by 32-68 mg/dL over baseline, noted Dr. Thuren, director of clinical development at Pfizer Global Research and Development, New London, Conn.

Simultaneously, the HDL_2 subfraction, which is believed to be particularly cardioprotective, jumped by 79%-198%, whereas HDL_3 rose by 22%-45%. HDL particle size increased in a dose-dependent fashion with torcetrapib, but was unaffected by atorvastatin.

Side effects were those associated with statin monotherapy, with one exception: There was a roughly 2-mm Hg increase in systolic blood pressure seen with torcetrapib alone or in combination with atorvastatin.

Torcetrapib is first in a new class of drugs that inhibit cholesterol ester transfer protein (CETP), which is responsible for transferring cholesterol from HDL to LDL.

Although the exuberant lipid changes seen with torcetrapib/atorvastatin in this phase II study are encouraging, what really matters, according to Dr. Thuren, is whether they translate into further reduction in cardiovascular events beyond that obtained with aggressive statin therapy alone. That question is the subject of large, ongoing, phase III, randomized clinical trials.

Pending outcome of these major trials, a new secondary analysis of the landmark Treating to New Targets (TNT) study may provide reason for optimism regarding the potential incremental clinical benefits of coupling HDL cholesterol–raising with LDL cholesterol–lowering.

Dr. Philip Barter presented an analysis of the relationship between cardiovascular events and on-treatment HDL cholesterol levels in TNT, a Pfizer-sponsored, randomized, double-blind study in which 10,001 patients with coronary disease were assigned to 10 mg or 80 mg/day of atorvastatin.

The 80-mg group showed a 22% relative risk reduction in major cardiovascular events compared with those on 10 mg during 5 years of follow-up (N. Engl. J. Med. 2005;352:1425-35).

A patient's HDL cholesterol level remained predictive of cardiovascular event risk both at high and low LDL cholesterol levels, suggesting that HDL cholesterol–raising may be a potential therapeutic target even in patients on aggressive LDL cholesterol–lowering therapy, noted Dr. Barter, professor of medicine at the University of Sydney and director of the Heart Research Institute, Camperdown, Australia. ■

Higher Statin Copays Cut Adherence by 37%

BY BRUCE JANCIN
Denver Bureau

ATLANTA — Higher prescription statin copayments have unintended negative consequences, Teresa B. Gibson, Ph.D., said at the annual meeting of the American College of Cardiology.

Her study of the health records of more than 93,000 statin users in employer-sponsored health plans demonstrated that higher copays were associated with significantly lower medication adherence, which in turn was linked to more emergency department visits and cardiovascular hospitalizations.

Health plan managers and policy makers use copays as a means of controlling prescription drug costs. It's a strategy designed to reduce consumption of prescription drugs and steer patients to preferred, less expensive medications. The use of copays is likely to continue to rise. But in patients with chronic medical conditions—such as known cardiovascular disease, or hyperlipidemia predisposing to heart disease—it's a strategy with troublesome side effects, according to Dr. Gibson of Thomson Medstat, a health care research services company in Ann Arbor, Mich.

"In this large cohort of continuing users of statins, we saw increasing drug copayments are a financial barrier to statin adherence. Reduced cost-sharing might be an effective intervention for these patients," she observed.

The average statin copay during the study period of 2000-2003 was $12 per month. Overall adherence to statin therapy during the first 18 months was 58%, meaning only 58% of the 93,296 patients had a filled statin prescription on at least 80% of days during follow-up. Higher copays were associated with a 37% reduction in adherence.

Total expenditures measured during the second 18 months of the study period didn't differ significantly between statin-adherent and nonadherent patients.

Adherent patients had lower medical expenditures, but this was counterbalanced by higher prescription drug expenditures and more physician office visits than for nonadherent patients.

Dr. Gibson's study was funded by Pfizer. ■

Pill Burden Influences Patient Adherence to Heart Drugs

BY BRUCE JANCIN
Denver Bureau

ATLANTA — Adherence to concomitant lipid-lowering and antihypertensive medications falls by an average of 9% with each additional background prescription drug a patient is on, Joshua S. Benner, Pharm.D., said at the annual meeting of the American College of Cardiology.

However, the relationship between the number of other drugs a patient is taking and adherence to antihypertensive and lipid-lowering drugs is curvilinear, not linear: The decline in adherence is steepest in patients already on up to three other medications at baseline, and it flattens out somewhat in those on four or more other drugs, according to Dr. Benner of ValueMedics Research, Falls Church, Va.

"Pill burden matters most for the patients who take the fewest additional number of medications," he said.

Dr. Benner presented a retrospective cohort study of patients enrolled in a large managed care plan. The study measured adherence to concomitant antihypertensive and lipid-lowering therapy and identifying predictors of treatment adherence. It involved 5,759 patients placed on both such medications within a 90-day period.

Adherence was poor overall, with 36% of patients remaining adherent to both therapies at 12 months' follow-up. Adherence was defined as having filled prescriptions for both medications on at least 80% of the days of follow-up.

Another predictor of adherence was initiating antihypertensive and lipid-lowering therapy together. After adjustment for comorbidities and demographic variables, patients who started the second therapy within 30 days of the first were 54% more likely to be adherent to both than were those who initiated the second therapy within 61-90 days. Sex and age were also closely linked to adherence. Women were 20% less likely than men to adhere to both drugs at 1 year. Patients aged 55-64 were 76% more likely and 65- to 74-year-olds were 37% more likely to be adherent than were those aged 18-44 years. ■

Could Health Benefits of Omega-3 Fatty Acids Be Just a Fish Story?

A systematic review of data on the risks and benefits of omega-3 fatty acids showed no clear benefit for mortality, cardiovascular disease, stroke, or cancer.

In a metaanalysis that included 48 randomized, controlled trials and 41 cohort studies, Lee Hooper, Ph.D., of the University of East Anglia, Norwich, England, and colleagues determined that the lack of effect was even more pronounced when studies with a high risk of bias were excluded (BMJ March 24, 2006;doi:10.1136/bmj.38755.366331.2F).

This result contradicts previous reviews of omega-3 trials that did show a beneficial effect on mortality, perhaps in part because the metaanalysis by Hooper et al includes the recently published results of a large trial. These results differed from the findings of the other large studies on this topic.

Altogether, the metaanalysis included nearly 37,000 participants in randomized, controlled trials as well as more than 560,000 participants in cohort trials. Some of the trials examined consumption of oily fish, while others studied subjects who took supplements.

In an editorial, Eric Brunner, Ph.D., of the Royal Free and University College London Medical School, emphasized that despite the results of this metaanalysis, there still remains good evidence that omega-3 fatty acids are beneficial for health. Extreme nutritional deficiency of these fats results in neuropathy, for example (BMJ March 24, 2006;doi:10.1136/bmj.38798.680185.47).

Furthermore, adequate intake of omega-3 fats is particularly important for women of childbearing age, since an estimated 25 g of maternal docosahexaenoic acid is needed during pregnancy and lactation to support the development of the child's brain.

But Dr. Brunner pointed to a paradox. Although nutrition experts advise increasing consumption of oily fish containing omega-3 fatty acids, industrial fishing has depleted the world's fish stocks by about 90% since 1950, and therefore the world probably doesn't have a sustainable supply of these fats.

—Robert Finn