Use of Biologics Cuts Stroke, Heart Attack Risk

BY BRUCE JANCIN
Denver Bureau

AMSTERDAM — Rheumatoid arthritis patients on tumor necrosis factor inhibitors appear to have a twofold reduction in stroke incidence, compared with similarly ill patients being treated with methotrexate or other traditional disease-modifying antirheumatic drugs, Dr. Will G. Dixon reported at the annual European Congress of Rheumatology.

There is evidence to suggest that rheumatoid arthritis (RA) patients on tumor necrosis factor (TNF) inhibitors may also have a reduced MI rate. This benefit appears to be confined to patients whose joint disease responds well to the medication, said Dr. Dixon of the University of Manchester (England).

He presented the first report from the British Society of Rheumatology Biologics Register, an ongoing observational database that in 2001 began prospectively enrolling all RA patients in the United Kingdom who were prescribed etanercept, infliximab, or adalimumab.

RA patients are known to have an overall mortality twice that of the general population, with most of the excess attributed to a steep increase in cardiovascular deaths, explained Dr. Dixon at the meeting, which was sponsored by the European League Against Rheumatism. Inflammation is known to play a central role both in RA and in atherosclerotic cardiovascular disease.

The study hypothesis was that inhibition of joint inflammation using powerful anti-TNF agents might produce a parallel reduction in the inflammation that triggers atherosclerotic plaque rupture and acute coronary and cerebrovascular events, he continued.

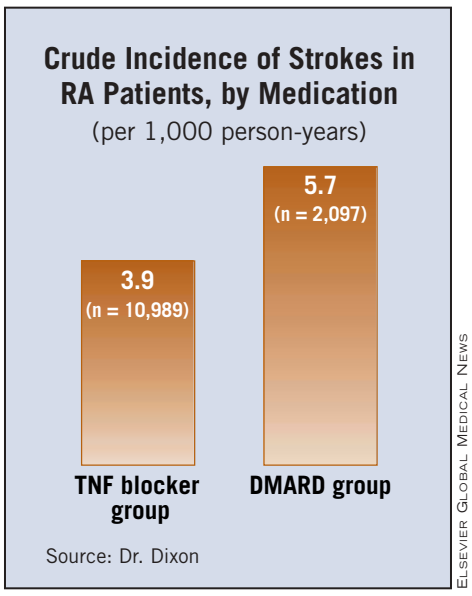
This first analysis of the British national registry data included 10,989 patients on a TNF antagonist for at least 6 months and a comparison arm that consisted of 2,097 RA patients treated with traditional disease-modifying antirheumatic drugs (DMARDs).

There were 42 strokes in the TNF blocker group and 12 in the DMARD group, translating into a crude incidence of 3.9 strokes per 1,000 person-years in RA patients on TNF inhibitors, compared with 5.7 strokes per 1,000 person-years in the DMARD group. After statistical adjustment for baseline differences between the two populations in terms of age, gender, RA severity, comorbidities, smoking status, and body mass index, being on a TNF inhibitor was independently associated with a 49% stroke risk reduction.

The MI analysis was done earlier, at a point when the TNF inhibitor group was smaller by roughly 2,000 patients. No difference in the MI rate between the two groups was found.

However, by restricting the analysis to patients whose RA responded well to anti-TNF therapy, a favorable trend was found. And upon further restricting the analysis to the first 6 months of follow-up—a prespecified secondary study end point on the grounds that marked inhibition of atherosclerotic inflammation might be expected to rapidly quell coronary plaque rupture—being on a TNF inhibitor was associated with a 72% reduction in MI. This difference didn't achieve statistical significance, however, because of small numbers, said Dr. Dixon.

"The clinical implication of these findings is that if we're able with the anti-TNF drugs to reduce rates of heart attacks and strokes in our patients, which are their leading cause of death, then it may be that in addition to improving their joint symptoms we may be reducing their mortality," he concluded. ■



ELSEVIER GLOBAL MEDICAL NEWS

Aliskiren Bests Ramipril for Hypertension in Diabetics

BY ERIK GOLDMAN
Contributing Writer

MADRID — Aliskiren, the novel renin-blocking drug, improved 24-hour blood pressure control and showed greater systolic pressure reductions, compared with ramipril, in diabetics with uncontrolled hypertension, according to data presented at the annual meeting of the European Society of Hypertension.

Aliskiren also can be safely combined with the ACE inhibitor in this population, the combination giving the greatest degree of pressure. Aliskiren works by blocking the renin-regulated conversion of circulating angiotensinogen to angiotensin-1. The new drug, also known by the brand name Rasilez, is the first of what may soon be a burgeoning class of renin blockers. It is being considered for approval by regulatory authorities in Europe and the United States.

Dr. Yagiz Uresin, professor of clinical pharmacology at Istanbul (Turkey) University, presented a multicenter international study of 837 patients with diabetes and hypertension. At baseline, the patients had blood pressures of over 155 mm Hg systolic and 98 mm Hg diastolic.

After a washout period and a placebo run-in of 2-4 weeks, the patients were randomized to aliskiren monotherapy, 150 mg/day; ramipril monotherapy, 5 mg/day; or a combination of 150 mg aliskiren plus 5 mg ramipril per day. After 4 weeks, the investigators doubled the doses in all study groups.

After 8 weeks, aliskiren gave mean pressure reductions of 14.7 mm Hg systolic and 11.3 mm Hg diastolic. This was significantly better than the 12.0- and 10.7-mm Hg reductions with ramipril alone. In combination, the two drugs gave mean pressure reductions of 16.6 mm Hg systolic and 12.8 mm Hg diastolic.

With a target pressure of 130/80 mm Hg, slightly over 8% of the patients in the monotherapy arms could be considered well controlled by the end of the study. Combination therapy bumped this up to 13%. The low number of patients who were able to reach target pressures reflects the difficulty of treating long-standing hypertension in diabetic patients, said Dr. Uresin.

A separate subgroup analysis drawn from the same international cohort showed that aliskiren alone and in combination with ramipril gave significantly better round-the-clock diastolic pressure control than did ramipril alone.

A total of 173 patients, 55 on ramipril alone, 57 on aliskiren alone, and 61 on the combination, underwent 24-hour ambulatory monitoring. Using the smoothness index, a scale that measures the consistency of pressure control over a 24-hour period, the investigators found that aliskiren alone and in combination with ramipril provides significantly greater consistency over the course of a day. Smoothness index scores correlate with reversal of left ventricular hypertrophy and carotid artery wall thickening.

The difference between renin-blockade and ACE inhibition was greatest in the early morning hours. At 21-24 hours post dose, the renin blocker alone and in combination with ramipril gave significantly better pressure control than did ramipril alone. Systolic pressures remained between 4 and 12 mm Hg below baseline in patients on aliskiren or aliskiren plus ramipril. In the ramipril group, systolic pressure rose to near baseline levels at the end of the 24-hour dosing cycle.

Adverse effects in the new study were similar to those in earlier trials showing aliskiren as having a low side-effect profile. About one-third of the patients in each monotherapy group had some untoward effects, the most common being headache, cough, nasopharyngitis, and diarrhea. These were mild and self-limiting in the vast majority. Just over 2% of the ramipril monotherapy group and just under 3% of the aliskiren group had serious side effects; the incidence was reduced to 1.4% for the combination.

Adding aliskiren to ramipril can cut the incidence of coughing, the most common reason patients quit ACE inhibitor therapy. Dr. Uresin noted the incidence of cough was just under 5% in the ramipril-alone group, just over 2% for aliskiren, and 1.8% in those taking the combination. The difference was statistically significant. The mechanism underlying the cough attenuation may have to do with reduced bradykinin levels following renin blockade, he said. ■

Post–Heart Attack Mortality Soars in Diabetes Untreated at Discharge

WASHINGTON — Diabetic patients who had myocardial infarctions and had not resumed their antihyperglycemia medications by discharge were 24% more likely to die within 1 year than were similar patients who had resumed their medications at discharge, according to a report during a poster presentation at the annual scientific sessions of the American Diabetes Association.

The increased risk of death was especially telling in the first 30 days after discharge, said Dr. Silvio Inzucchi, principal investigator and professor of medicine at Yale University, New Haven, Conn. He and his associates reviewed the charts of Medicare patients aged 65 years and older in the National Heart Care Project. All of the patients had a confirmed acute MI and previously documented diabetes treated with antihyperglycemic agents. The study excluded those who died before discharge, were transferred to another facility, or needed long-term hemodialysis.

Of the 8,751 patient charts, 1,170 (13%) indicated patients had not resumed their diabetes medications by discharge. Within 1 year of discharge, 38% of these patients had died. The 1-year mortality rate was 28% in the 7,581 who were taking their diabetes medications at discharge.

Notably, 36% of the deaths occurred within the first 30 days after hospital discharge in patients who had not resumed diabetes medications at discharge, compared with 23% of the deaths in those discharged on diabetes medications. The difference was statistically significant after multivariate Cox analysis for 78 clinical variables, including admission glucose, complications, and ventricular function, was used to evaluate the association between discharge on diabetes therapy and outcome. Patients who had not resumed their antihyperglycemic agents at discharge also were more likely to be discharged without receiving statins, β-blockers, ACE inhibitors, and aspirin.

The study is limited by the lack of data about changes in patients' prescriptions after discharge. It is unclear whether patients immediately visited their primary care doctors and resumed their antihyperglycemic medications.

Dr. Inzucchi said cardiologists need to address diabetes during discharge planning, if only to have patients follow up with their primary doctors.

—Marianne Reid Gildea