The ONTARGET Study

By Luc Lanthier

The angiotensin II receptor blocker (ARB) telmisartan is not inferior to the angiotensin-converting enzyme (ACE) inhibitor ramipril in subjects with vascular disease or high-risk diabetes, but the combination of the two drugs is associated with a greater number of side effects without observed benefits.

This is the conclusion of the Ongoing Telmisartan Alone and in Combination with Ramipril Global Endpoint Trial (ONTARGET), presented at the American College of Cardiology congress in March 2008. This study, which aimed at evaluating the impact of telmisartan and the combination of telmisartan/ramipril compared to ramipril alone in a high-risk population such as the one studied in the Heart Outcomes Prevention Evaluation (HOPE) study, included 25,620 patients aged 55 years or older with cardiovascular disease (coronary, cerebrovascular or peripheral) or high-risk diabetes without any evidence of heart failure. Patients were followed for an average of 56 months.

The primary outcome studied was a composite of death from cardiovascular causes, myocardial infarction, stroke or hospitalization for heart failure. To be considered equivalent to ramipril, the confidence interval of the relative risk between the two treatments evaluated had to be > 1.13. Even with a slightly greater decrease in blood pressure (BP) with telmisartan (0.9 mmHg/0.6 mmHg) and in the combination treatment group (2.4 mmHg/1.4 mmHg), the primary outcome was practically identical in the three treated groups (16.5% of events in the ramipril group, 16.7% in the telmisartan group, 16.3% in the combination group, RR telmisartan vs. ramipril 1.01, 95% CI 0.94 to 1.09; RR combination vs. ramipril 0.99, 95% CI 0.92 to 1.07). Since the confidence interval was smaller than 1.13, the authors concluded that telmisartan was not inferior, but equivalent to ramipril.

Moreover, no predefined subgroup showed a greater benefit of using one medication over the other. Furthermore, there was no notable discrepancy for the different secondary endpoints evaluated. As for tolerance, telmisartan was slightly better tolerated than ramipril (treatment discontinued in 23% of patients vs. 24.5% for ramipril, \( p = 0.02 \)), but the combination of treatments was clearly less tolerated (treatment discontinued in 29.3%, \( p < 0.001 \)). Subjects taking telmisartan presented less coughing and angioedema than subjects taking ramipril, but showed more hypotension. The combination-therapy group also experienced more hypotension, syncope, renal dysfunction and hyperkalemia.

Thus, it seems that ARBs are equivalent to ACE inhibitors as vascular-protective agents, which may seem surprising at first. This probably has several explanations, and the sum of favorable effects for these classes individually equal each other in total. Therefore, the accumulation of bradykinin would favor ACE inhibitors, but the converting enzymes that escape ACE inhibitors could favor ARBs. The larger decrease in BP should have favored ARBs, but since these subjects had probably become normotensive with the ACE inhibitor, it seems that hypotension becomes deleterious at a certain point, as demonstrated in the combination group. In fact, it would be interesting to review the benefit of the HOPE study with respect to initial BP, considering the results from ONTARGET, to re-evaluate the proportion of benefit from these agents due to their hypotensive effect.

For the clinician, the ONTARGET study will add the possibility of using an ARB to treat subjects at high vascular risk. However, some questions remain: is it a class effect or should we use telmisartan for this indication? Of course, the study does not answer this question, but the results from other studies demonstrating an equivalence between ACE inhibitors and ARBs in heart failure are reassuring when used with the correct dosage. In regards to cost ratio, since ramipril is now in generic form in Canada, the cost of the drug will need to be considered in selecting an agent, an argument that Dr. John McMurray puts forth in the editorial accompanying the ONTARGET article in the New England Journal of Medicine.

It will also be interesting to see the results of the Telmisartan Randomized Assessment Study in ACE Intolerant Subjects with Cardiovascular Disease (TRANSCEND) in the upcoming months, which compares telmisartan to placebo in subjects at high vascular risk (like HOPE) but intolerant to ACE inhibitors. After ONTARGET, we can anticipate that a benefit of the ARB will be confirmed, but it remains to be seen. In the opposite case, we might have to revisit the whole concept of vascular protection. To be continued...

Further reading:

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