Trends-in-Medicine

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SUMMARY

The first new angina treatment in more than a decade is on the horizon. Results from two Phase III trials of sustained release ranolazine have been positive, and CV Therapeutics is expected to file an NDA sometime in 2002. Cardiologists are cautiously optimistic but not enthusiastic about ranolazine, and there may be FDA questions about trial design and QT prolongation.

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Angina Update: CV Therapeutics' Ranolazine

Ranolazine is a pFOX (partial Fatty Acid Oxidation) inhibitor that works by shifting ATP production away from fatty acid oxidation in favor of glucose oxidation. More oxygen is needed to phosphorylate a given amount of ATP during fatty acid oxidation than during carbohydrate oxidation. Ranolazine-induced shift in substrate utilization reduces oxygen demand without decreasing the ability of the tissue to do work

In March 2000, the Phase III **MARISA** (Monotherapy Assessment of Ranolazine In Stable Angina) trial showed that ranolazine, used as monotherapy, increased exercise time in NYHA Class I and II patients. Results from a second Phase III trial -- **CARISA** (Combination Assessment of Ranolazine in Stable Angina) trial, a 12-week, Phase III, 823-patient randomized, double-blind, placebo-controlled, parallel group study -- were presented in November 2001 at the American Heart Association meeting. CARISA compared adjunctive therapy with sustained release ranolazine 750 mg b.i.d. and 1000 mg b.i.d. to placebo.

- The primary efficacy endpoint was symptom-limited exercise duration at trough, and in a combined analysis, both ranolazine groups increased an average of 116 seconds, compared to an average increase of 92 seconds in the placebo group. The 750 mg group increased an average of 115 seconds, and the 750 mg increased an average of 116 seconds (both statistically significant). However, increases in exercise times on ranolazine were not significantly different among the three background therapies (atenolol 50 mg, diltiazem CD 180 mg, or amlodipine 5 mg).

- In terms of the secondary endpoint of frequency of angina attacks, ranolazine reduced attacks per week from an average of 1.7 to 1.3, compared to 0.6 on placebo.

- Small (<10 milliseconds) but statistically significant (p<=0.002) increases in QTc were observed compared to placebo. Serious adverse events were observed in 6%, 7%, and 7% of patients on placebo, ranolazine 750 mg, and ranolazine 1000 mg respectively.

An earlier, immediate-release (IR) formulation of ranolazine was abandoned after it was associated with lack of efficacy and QT prolongation. A paper published in 1999 by Dr. R.J. Gibbons et al reported on a 319-patient study comparing immediate-release ranolazine to placebo, concluding "Therapy with ranolazine 30, 60, and 120 mg t.i.d. was not superior to placebo. Our study does not support the published beneficial effects of similar doses of ranolazine on either myocardial ischemia or exercise performance or on anginal attacks during daily life in patients with angina pectoris." Other trials found that immediate-release ranolazine significantly increased exercise times but only at doses >240 mg and only for 8 to 12 hours post-administration, suggesting that the IR formulation was impractical because of the short duration of its effect.

CV Therapeutics' sustained release formulation of ranolazine has reduced the QT prolongation problem but not totally eliminated it. Sources are not worried about the QT issue, though the FDA is likely to pay careful attention to this potential problem. An expert said, "There is some QT prolongation with this drug, but it is minor, and I doubt anyone would be too concerned." Another expert said, "QT prolongation does not appear to be severe (but) all the potential downsides will not be known until it is given to lots of people for a longer period of time." A third said, "It looks like that is not really a problem, but the FDA is very sensitive to the QT prolongation issue."

Pooling of the arms of CARISA also has been a topic of interest. FDA officials explained that pooling data from different arms of a trial in order to achieve statistical significance is something on which the agency frowns. One official said, "Combining arms after the trial is over on the basis of what the data looked like is generally not acceptable…The analysis plan needs to be established before the data are unblinded. For example, suppose you had a dose response trial with 4 doses plus a placebo arm (a 5-arm trial). Suppose the plan was to test each dose separately for efficacy, but at the end of the trial none of the doses was statistically better than placebo. But if the two highest doses were put together, those combined arms would beat placebo. You would have to realize that there would be a number of things that could have been done -- all the active arms could have been combined, the highest 3, the lowest 2 or 3 (sometimes more is worse). You end up having an analysis driven by the data, and then the hypothesis tests can't be interpreted in the usual way because by searching for a significant result you have raised the likelihood that you're going to find one -- the probability of 0.05 no longer applies."

Despite the positive findings in CARISA, cardiologists appear to be cautious about the outlook for sustained-release ranolazine. A California cardiologist said, "I've heard about the drug and the study. It seems like a useful tool in the treatment of resistant angina. I think the study showed that it helps reduce symptoms in patients, allowing for more exercise and less chest pain. There was no dramatic improvement, and the study was not designed to see if this will prolong life or not. I don't think ranolazine will be very widely used until more data (both on preventing death and heart attacks, as well as safety data) is available." A Utah cardiologist said, "It likely will add significantly to our ability to treat chronic angina patients." A New England cardiologist said, "Ranolzaine is the first new anti-anginal agent in a long time. The trials seems to show some beneficial effects. Ranolazine looks promising, and the two trials are persuasive."

The ease with which patients were enrolled in the CARISA trial may indicate that there are more angina patients in the country than previously thought. A doctor said, "I think there are a lot of people with angina who are inadequately treated. We think because of PTCA and CABG that we have cured angina, but there are still a lot of people who are limited by angina. Some of that may be because they are still symptomatic despite maximum medical therapy, and some we, as physicians, may be missing because we may not be thorough enough in discovering how limited patients are. Maybe we think the ones who are revascularized don't have angina, so we don't ask, expecting the patients to volunteer the information and they don't. The conventional wisdom is that we've rid ourselves of angina, but maybe we can do better."

On average, sources predicted that they expect to prescribe it for an average of 32% of their angina patients, particularly those with continued pain despite treatment with other known medications. Dr. Harlan Krumholz of Yale commented, "If we just approve the medication without getting people to think a little more about what angina is and the burden of it, ranolazine will get some market share, but the real opportunity will come if we are more aggressive in identifying angina patients. If the real goal is to eliminate angina – either with medications or intervention -- then this drug may play an important role. Ranolazine can help bring attention to this problem."

When ranolazine is approved by the FDA, cardiologists are likely to experiment with it to find how it performs in a clinical setting. A source said, "The data is persuasive enough, but what will drive usage is the clinical experiences. In the trial, the endpoint was how many more seconds a patient could exercise. The question is whether, in clinical usage, people will really feel better and be able to do more. Are seconds important?… I think toleration (side effects) and how patients feel will determine usage."

Most sources predicted that clinical cardiologists will not be slower to refer patients for either PTCA or CABG once ranolazine is available. A West Coast cardiologist said, "The use will vary widely by different doctors. Some are quick to do angioplasty and won't try this drug. Others want to avoid interventions and will try this before angioplasty and surgery." Another cardiologist said, "Doctors will use it in patients not totally treatable by revascularization." A third source said, "Ranolazine won't slow down interventionalists, but it will be a patient preference issue. Patients who don't want a procedure should get this medication, and not all patients want an intervention. The risk in a catheterization is small, but there is a risk."

Angina will be the topic of a survey by the European Society of Cardiology beginning in March 2002. Angina pectoris is the most prevalent manifestation of coronary artery disease. It occurs as the initial presentation of coronary heart disease in almost half of patients. Some patients have a prognosis similar to the general population, but others have a substantially higher risk of death, MI and other cardiovascular events. The Euro Heart survey is designed to collect information that will aid in prognostic assessment and risk stratification by identifying those patients most likely to benefit from revascularization and/or medical therapy. The multi-center survey will involve 300-500 sites in about 24 countries, with the goal of taking a " snapshot " of the angina diagnosis and management practices current in use across Europe. A follow-up survey will be conducted in 2003 to compare outcomes with practice patterns.

Few other new therapies for angina are on the horizon. An expert said, "There aren't many (other new therapies) out there. That's is why these drugs get more press from small studies." Another source said, "Angiogenesis therapy is being investigated, but that's not coming in the near term." A third doctor commented, "There is not another good medication coming soon." ♦