6 *Recent Advances in Management of Chronic Stable Angina: Newer Drugs*

Amal Kumar Banerjee

Abstract: Cardiovascular medicine has seen many advances in the treatment of coronary artery disease during the past 3 decades. As a consequence of this success is the increasing number of patients with severe coronary artery disease who now survive. In recent years less attention has been paid to chronic ischemic syndrome; a possible explanation is that most patients with angina refractory to medical treatment are referred for myocardial revascularization in order to improve symptoms and to prevent death and myocardial infarction. Unfortunately, available data do not support this common belief. Currently available antianginal agents include beta-blockers, calcium-channel blockers, and long-acting nitrates (LANs). Despite treatment with conventional agents and/or revascularization, many patients remain symptomatic. Availability of new agents, after more than two decades, like ranolazine, ivabradine and fasudil, that could be used in concert with other antianginal therapies without causing excessive reductions in myocardial O_2 demand determinants would be of enormous value. In contrast to classic hemodynamic agents, metabolic agent like trimetazidine, improves cardiac metabolism and cardiac energy availability in chronic stable angina.

INTRODUCTION

Various coronary artery disease (CAD) risk factors continue to increase in populations and as a result, the prevalence of CAD continues to increase. Therapeutic options include pharmacologic therapy, percutaneous coronary interventions (PCI), coronary artery bypass surgery (CABG) and newer therapies including enhanced external counterpulsation and investigational gene therapy. As the number of patients living with CAD is increasing, however, the number of patients with CAD that is refractory to these therapies also continues to increase. So, it remains important to develop new medical treatments for ischemic heart disease (IHD).

Current management paradigms focus on medications directed toward optimizing cardiac hemodynamic effects. In addition to hemodynamic treatments, a novel group of agents that work via other mechanisms are available for the treatment of myocardial ischemia. These agents improve cardiac metabolism and cardiac energy availability and are termed metabolic modulators.

Currently available antianginal agents include beta-blockers, calcium-channel blockers, and long-acting nitrates (LANs). Despite treatment with conventional agents and/or revascularization, many patients remain symptomatic. One year after coronary artery bypass grafting or percutaneous coronary intervention, 25 to 60% of patients continue to have angina and require antianginal medication. Conventional pharmacologic therapies exert an anti-ischemic effect by lowering determinants of myocardial O_2 demand (heart rate, myocardial contractility, or

wall stress). Although combination regimens of conventional antianginal therapies may provide incremental efficacy, such combination regimens may lead to excessive side effects or to a decrease in anti-ischemic efficacy.

It is generally recommended, based on reasonable evidence, that combinations of hemodynamic agents from 2 or even all 3 of these drug classes be used in persistently symptomatic patients. Nevertheless, as many as 5 to 15% of the patients with stable angina may be refractory to even triple therapy and yet not considered suitable for revascularization.[1,2] It is likely that large numbers have undesirable side effects on currently available therapies, particularly in combination, and might benefit from an alternative agent. Accordingly, great interest attends the evaluations of novel antianginal agents.

RANOLAZINE

Ranolazine is a new antianginal agent. Ranolazine is an orally active piperazine derivative with a novel mechanism of action that involves selective inhibition of the late sodium current. This action reduces the magnitude of ischemia-induced sodium and calcium overload and thereby improves myocardial function as well as myocardial perfusion.[3,4]

The antianginal effects of ranolazine are not dependent on reduction of heart rate or blood pressure or on increases of coronary blood flow. During exercise testing, patients are able to achieve an increased rate-pressure product at maximal exercise compared with placebo or beta-blocker.[5] The agent is a known inhibitor of myocardial fatty acid oxidation, resulting in preferential glucose oxidation.[6] The glucose pathway requires less oxygen for a given level of myocardial work, and this increased "oxygen efficiency" may be an important component of the anti-ischemic action.

Ranolazine is well tolerated; the principal side effects include dizziness, nausea, asthenia, constipation, and headache. Of concern is its propensity to dose-related prolongation of the QTc, the net effect of its inhibition of I_{Kr}, late I_{Na}, and late I_{Ca}. However, there has been no evidence of increased dispersion of repolarization nor any documented cases of *torsades de pointes*. Ranolazine is metabolized in the liver and excreted in the urine and is contraindicated with hepatic impairment. It is metabolized primarily by CYP3A, which is potently inhibited by diltiazem and verapamil, neither of which should be used concurrently. Ranolazine inhibits metabolic pathways for simvastatin and digoxin, and dose reductions of these agents may be required.

In stable CAD patients, ranolazine has demonstrated anti-ischemic efficacy alone and as part of a combination regimen with submaximal doses of other antianginal agents without significantly affecting heart rate or wall stress.

The Monotherapy Assessment of Ranolazine in Stable Angina (MARISA) trial investigated the anti-ischemic effects of ranolazine and long term survival of 191 patients with chronic severe angina.[7] Treatment with ranolazine resulted in a 24 to 56 second improvement in exercise tolerance in patients who took 500 to 1500 mg of ranolazine twice daily.

The Combination Assessment of Ranolazine in Stable Angina (CARISA) trial investigated the effect of ranolazine in combination with other antianginal agents.[8] In this phase 3 double-blind, placebo-controlled clinical trial, 823 patients with refractory angina, who were receiving standard therapy with atenolol, diltiazem or amlodipine, were randomized to placebo, ranolazine at 750 mg twice daily, ranolazine at 1000 mg twice daily. After 12 weeks, patients in both ranolazine arms had 26% increase in total exercise time and a decrease in the number of anginal episodes per week. The time to onset of 1mm ST-segment depression during exercise testing did not change.

The ERICA (Efficacy of Ranolazine In Chronic Angina) Trial[9] demonstrated that ranolazine was an effective antianginal agent in patients with stable CAD and persisting angina despite a maximum recommended dosage of 10 mg/day amlodipine. The addition of 1,000 mg ranolazine twice a day significantly reduced the frequency of angina episodes and rate of nitroglycerin consumption and had a consistent treatment effect across subgroups including gender, age, and LAN use. Ranolazine was well tolerated; most adverse effects were mild to moderate, and

antianginal efficacy was unrelated to changes in blood pressure or heart rate. Ranolazine is a promising anti-ischemic therapy that may be valuable in a wide variety of subsets of patients with CAD who remain symptomatic despite treatment with other anti-ischemic agents.

Because ranolazine prolongs the QTc, the FDA approval is limited to patients who have not responded to other antianginal drugs, and its use in combination with amlodipine, beta-blockers, or long-acting nitrates is recommended. The daily dose should be limited to 1,000 mg and precautions are advised regarding QTc prolongation.

TRIMETAZIDINE

It is fatty acid oxidation inhibitor and acts via selective inhibition of 3-ketoacyl CoA thiolase. Its efficacy in the treatment of angina has been evaluated in a number of studies as monotherapy or in combination, in acute and chronic administration, as initial treatment or in patients resistant to beta blockers or calcium channel blockers.[10-12] The Trimetazidine, European Multicenter Study (TEMS)[13] included patients with stable angina and documented CAD. Patients were randomly assigned to treatment with trimetazidine or propranolol orally for 3 months. The time to ST-segment depression on exercise testing and the time to onset of symptomatic angina were comparable in both groups. In another study,[14] trimetazidine was added to standard antianginal therapy (with long-acting nitrates, calcium channel blockers, and beta blockers). After 4 weeks of therapy, there were significant reductions in the number of symptomatic episodes of angina and significant improvements in the time to ischemia related ECG changes on exercise testing.

In a large recently published meta-analysis,[15] 12 clinical studies of trimetazidine performed between 1985 and 2001 were evaluated. Trimetazidine emerged as efficacious in the treatment of angina pectoris both as monotherapy and in combination with other antianginal agents. Trimetazidine significantly reduced the number of symptomatic anginal episodes and improved the time to objective, exercise-induced ECG changes.

The mechanism of action of trimetazidine, based on a switch from fatty acids to glucose utilization makes this drug an attractive treatment for angina pectoris in diabetic patients. The TRIMPOL-I, trial[16] had shown that, 4 weeks of treatment with trimetazidine resulted in a significant improvement in exercise capacity and in exercise duration in the entire patient population in the subgroup of diabetic patients.

Trimetazidine has got beneficial effect on patients with left ventricular dysfunction.[17]

TRIMPOL-II study has shown that trimetazidine provides anti-anginal efficacy in post-revascularized patients with recurrent angina despite a monotherapy with metoprolol.[18]

FASUDIL

Fasudil is a Rho-kinase inhibitor and therefore Rho kinase, an intracellular signaling molecule involved in the vascular smooth muscle contractile response to agonists such as acetylcholine, angiotensin II, endothelin, norepinephrine, platelet-derived growth factor, and serotonin, and therefore has been proposed as a therapeutic target for treating stable angina.

Fasudil is bioavailable after oral administration and has a half-life of 5.5 ± 0.87 hours in tablet form. In phase 2 dose-finding trials conducted in Japanese patients with stable effort angina, fasudil monotherapy at doses ranging from 5 mg three times daily to 40 mg three times daily increased maximum exercise time and time to the onset of $\geq$ 1 mm ST-segment depression compared with baseline. Fasudil was well tolerated, with minimal effects on blood pressure or heart rate at rest or during exercise.[19]

One phase 2 dose-finding trial[20] in patients with stable angina showed that titrating fasudil to 80 mg three times daily over eight weeks improved exercise time compared with baseline, with a statistical trend toward improvement compared with placebo. A significant, nearly four-fold increase in mean time to $\geq$ 1 mm ST-segment depression (myocardial ischemia) compared with placebo was observed at peak (1 hr after dosing) with a fasudil dose of 80 mg three times daily.

IVABRADINE

It is established that tachycardia is a risk factor for ischemic cardiac events; accordingly heart rate reduction may improve outcomes. Beta blockers and some calcium channel blockers reduce heart rate but their use may be limited by negative inotropic effects and several contraindications. Ivabradine, a selective sinus node I_f channel inhibitor, represents a therapeutic innovation in the treatment of ischemia. Preclinical and early clinical studies show that ivabradine can reduce heart rate without affecting cardiac systolic function, suggesting that I_f inhibition may be an effective approach to minimise both angina and the underlying ischemia. *In clinical studies ivabradine has anti-anginal and anti-ischemic effects in patients with stable angina and has comparable efficacy to atenolol and amlodipine. This anti-ischemic effect is also observed in elderly patients in whom there is a greater incidence of stable angina. Furthermore, the absence of additional cardiac effects associated with I_f inhibition suggest that this approach may be effective in other patient groups, such as those at risk of acute coronary events or compromised left ventricular function.* Further clinical trials with ivabradine to evaluate fully the therapeutic potential of I_f inhibition are ongoing.

The INITIATIVE trial (INternatIonal TrIAL on the Treatment of angina with IVabradinE versus atenolol) assessed the anti-anginal and anti-ischemic effects of ivabradine compared with the beta blocker, atenolol. Selective I_f inhibition with ivabradine treatment produced similar anti-anginal and anti-ischemic effects to atenolol both after one month and four months of treatment. At four months, total exercise duration at trough drug activity increased by 86.8 seconds with ivabradine (7.5 mg), compared to 78.8 seconds with atenolol (100 mg). Ivabradine was at least as effective as atenolol in time to limiting angina and time to 1 mm ST segment depression.[21]

Inhibition of this ionic current should allow control of heart rate without the deleterious consequences on force of contraction, peripheral circulation, bronchial tone, bowel transit, and glucose and triglyceride metabolism associated with calcium channel or beta-blockers.

Hence, ivabradine has been indicated for the symptomatic treatment of chronic stable angina.

The most frequent adverse drug reaction associated with ivabradine is visual symptoms, consisting mainly of increases in brightness in limited areas of the visual field, which are transient and do not disturb patients' activities.[21]

CONCLUSION

The management of CAD and resultant myocardial ischemia continues to be an ongoing challenge. Along with traditional hemodynamic methods, ranolazine, trimetazidine, ivabradine and fasudil represent a promising new therapeutic approach in stable angina.

Ranolazine is the first agent from a new class of antianginal agents to be approved by FDA in almost 25 years, and its potential widespread use warrants careful review of the evidence for benefit and harm.

Fasudil may be a useful adjunctive therapy to standard therapies for stable angina.

The potential benefits of ivabradine are clear. After a gap of decades, there is at last a new class of anti-anginal therapy, for those patients who are unable to tolerate beta-blockers, or in whom beta-blockers are contraindicated, there is another way we can try to succeed.

Trimetazidine decreases fatty acid oxidation and acts as metabolic modulators that improve biochemical efficiency of cardiac myocyte during ischemia, and represents a promising new therapeutic approach in stable angina.

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