ABSTRACT

Ischemic heart disease is the major cause of morbidity and mortality in the Western world. Patients often suffer a reduction in quality of life due to chronic stable angina, but therapeutic options can be limited due to concerns for heart rate and blood pressure, as well as side effect profiles. Even revascularization therapy has its limitations and newer agents are required to help in this battle for symptomatic relief. Ranolazine (Ranexa®, A. Menarini Pharma UK, High Wycombe, UK) is a drug with a novel mechanism of action that has been shown in several large trials to be an efficacious adjunctive agent in reducing symptoms of chronic stable angina. It is thought to work by inhibiting the late sodium current in cardiac myocytes, thereby reducing sodium and calcium overload that follows ischemia. This improves myocardial relaxation and reduces left ventricular diastolic stiffness, which in turn enhances myocardial contractility and perfusion. The drug is generally well tolerated and the evidence so far is encouraging, with a clear clinical benefit achieved in the target groups. Its main strength is that it does not appear to affect either heart rate or blood pressure. This review provides an insight into this treatment option, describes the clinical trials evidence, proposed mechanism of action, and pharmacokinetics, and outlines the indications for its use in chronic stable angina.

Keywords: adjunctive anginal treatment; chronic stable angina; ischemic heart disease; late sodium current; ranolazine

BACKGROUND

In the Western world, ischemic heart disease (IHD) is the most common cause of life-threatening illness, claiming more lives each year than any other single disease process. Chronic stable angina (CSA) is the most prevalent manifestation of coronary disease, affecting up to 5% of the over-40s population in most developed countries. It is estimated that, in every million people in the general population in most European countries, between 20,000 and 40,000 individuals suffer from CSA.1,2
Symptoms of angina impact adversely on quality of life, particularly physical functioning and role functioning, to such an extent that they may lead to premature retirement and lost earnings.3

**Therapeutic Options for Angina**

Pharmacological treatment and percutaneous or surgical revascularization provide symptom relief in the majority of patients, yet 10%-20% have chronic refractory angina, where symptoms persist despite optimum medical and revascularization therapy.4,5 Current pharmacological treatment aims to relieve symptoms of angina through nitric oxide donor drugs (short- and long-acting nitrates); limiting cardiac rate and contractility (phenylalkylamine and benzothiazepine calcium channel blockers [CCBs] or beta-blockers), with or without dihydropyridine vasodilating CCBs; and potassium channel openers.

While coronary artery bypass surgery (CABG) affords greater symptom relief, the majority of patients are managed using medical treatment.4,5 The benefit of percutaneous coronary intervention (PCI) over optimal medical therapy in improving angina symptoms has been shown by the Clinical Outcomes Utilization Revascularization and Aggressive Drug Evaluation (COURAGE) trial investigators;6 although this was not the study’s primary aim, it showed an improvement in patients’ Canadian Cardiovascular Society (CCS) status. This benefit has been proven more clearly by findings from the Randomized Intervention Treatment of Angina (RITA-2) trial7 and subsequent follow-up.8 At 3 months, 19.4% of patients in the PCI group were CCS class 2 or worse compared with 35.9% of patients in the medical treatment-only group. At 5 years’ follow-up, the prevalence of class 2 symptoms or worse was still slightly better in the PCI group (15% vs. 21.4%).

Angina can persist despite revascularization by either PCI or CABG.4,5 As with any invasive procedure, it is not without risk or complication. Pharmaceutical companies have continued to research new mechanisms of action to develop new antianginal therapies that can offer at least symptomatic relief, even if there is no impact on disease progression.

**Current Pharmacological Treatment**

To date, the conventional pharmacological treatments for CSA have been beta-blockers; oral and sublingual nitrates; CCBs; potassium channel openers; and sinus node blockers. For additional benefits, lipid-lowering agents, angiotensin-converting enzyme (ACE) inhibitors, angiotensin receptor blockers (ARB), and antiplatelet treatments are usually prescribed.2 Patients may also be taking medication for comorbid conditions or to control cardiovascular risk factors.

Unfortunately, despite these measures, a large body of patients still suffer from angina symptoms. This is often due to complicating factors in the management of the patients, such as comorbidities like asthma, chronic airways disease, bradycardia, or hypotension, which limit the number of agents that can be given.

Side effects can be troublesome and patients can suffer from a wide range of symptoms due to the various pharmacological agents used.9 For example, beta-blockers can cause bradycardia, exacerbation of asthma and peripheral vascular disease, and depression. CCBs can cause bradycardia, gastrointestinal complications, flushing, and dizziness. Nicorandil can cause headaches,