

Beneficial long-term effects of Vastarel MR in patients with stable coronary artery disease developing left ventricular dysfunction

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Abstract

During the past two decades, the management of chronic coronary artery diseases has improved considerably, as a result of both pharmacotherapy and revascularization procedures. However, the course of chronic coronary artery disease, with an increase in the number of patients surviving after acute coronary syndrome, has led to an increase in the number of patients with ischemic left ventricular dysfunction. Despite treatment with conventional drugs, a high proportion of patients remain symptomatic. Both experimental and clinical studies in patients with heart failure have demonstrated that agents that inhibit fatty acid oxidation, with a consequent stimulation of glucose oxidation, may increase contractile function and have cytoprotective effect on cardiomyocytes in the failing heart. Trimetazidine (Vastarel MR) is the first cytoprotective agent to exert an anti-ischemic effect. Its lack of effects on hemodynamic parameters gives this drug a potential advantage. This article aims to review the current data on effects of Vastarel MR in patients with chronic coronary artery disease and left ventricular dysfunction.

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Introduction

Myocardial ischemia most commonly develops as an imbalance between coronary artery blood flow and increased demands for myocardial power and oxygen consumption. As a result of myocardial ischemia, there is a reduction in aerobic formation of ATP, and consequently anaerobic glycolysis, lactate formation, and a decrease in cell pH may develop [1].

The increase in myocardial oxygen demand is compensated by an increased blood flow and coronary oxygen supply in normal individuals. In most patients with chronic CAD, angina is caused by increased myocardial oxygen demands of exercise or emotional stress that cannot be met by an increase in coronary blood flow.

Three classes of drugs traditionally have been used for treatment of chronic coronary artery disease

(CAD): β -blockers, calcium channel blockers, and nitrates. Despite optimal treatment with these agents, more than 50% of patients with CAD optimally treated for exercise-induced angina have clinical manifestations of disease [2,3].

Trimetazidine (Vastarel MR) in the treatment of stable angina

On the basis of the pathogenetic mechanism described above, the treatment of stable angina has been directed primarily towards increasing myocardial blood flow and decreasing oxygen demand in the myocardium. In myocardial ischemia, fatty acid oxidation and glucose oxidation are decreased, whereas glycolysis becomes a more prominent source of ATP [4]. High levels of fatty acid oxidation are associated with a decrease in glucose oxidation; thus the inhibition of fatty acid oxidation may have a beneficial metabolic action because, in the ischemic heart, fatty acids are a less efficient source of myocardial energy than glucose with respect to oxygen consumption [5–7]. Many experimental and clinical data have shown that shifting the energy substrate preference from fatty acid metabolism to glucose oxidation may be a metabolically economic way of producing ATP with decreased consumption of oxygen [8,9]. Trimetazidine (Vastarel MR) is the first agent to be developed that selectively and partially inhibits long-chain 3-ketoacyl coenzyme A thiolase (3-KAT), an enzyme involved in fatty acid β -oxidation.

There are several mechanisms of action by which trimetazidine promotes the preservation of the membrane structure and cellular composition of cardiomyocytes: limitation of intracellular acidosis, prevention of the excessive production of free radicals and calcium overload, and correction of disturbances in transmembrane ion exchange [10,11].

A meta-analysis of 12 double-blind, randomized, controlled clinical trials of trimetazidine in the treatment of stable angina [12] showed that trimetazidine caused significant reductions in the number of angina attacks and improved the time to 1 mm ST-segment depression and the total work at peak exercise. Meta-analysis confirmed that trimetazidine is effective as an antianginal agent when used alone or in combination with traditional hemodynamic agents, without compromising hemodynamics and without side effects. In a multinational, randomized, double-blind, placebo-controlled study [13], the modified-release formulation of trimetazidine, Vastarel MR, has been shown to improve both symptoms and myocardial ischemia significantly. Patients with stable angina received atenolol 50 mg per day and Vastarel MR 35 mg or placebo. The primary endpoint, time to 1 mm

ST-segment depression, was increased significantly in the group receiving the modified-release formulation of trimetazidine, compared with the group receiving placebo. Another open clinical trial included 906 patients with stable angina experiencing at least three angina attacks per week for more than 6 months despite traditional angina treatment with long-acting nitrates, β -blockers, or calcium antagonists. After 2 months of treatment with Vastarel MR 35 mg twice a day, there was a significant ($P < 0.0001$) decrease (67%) in the number of angina attacks per week and a significant ($P < 0.0001$) decrease (71%) in the number of short-acting nitrates taken per week in the group treated with the modified-release formulation of trimetazidine [14]. The findings of these studies suggest that the modified-release formulation of trimetazidine may be more effective than the immediate-release formulation with respect to relief of angina. In an Indian multicenter prospective study of 279 patients with stable angina, the immediate-release formulation of trimetazidine was substituted with the modified-release formulation, leading to a reduction in the mean frequency of angina by four attacks per week and the consumption of glyceryl trinitrate by 3.6 tablets per week [15].

Trimetazidine (Vastarel MR) in the treatment of left ventricular dysfunction

Treatment of angina in patients with heart failure represents a multicomponent pharmacologic approach. In patients with left ventricular dysfunction, treatment of angina with combinations of classic hemodynamic antianginal drugs may often have adverse effects on hemodynamics and ventricular function. Thus there is a need also to treat angina with hemodynamically “neutral” drugs without compromising hemodynamic parameters. The anti-ischemic effects of trimetazidine, by decreasing fatty acid oxidation and preserving ATP production at the cellular level and thereby reducing intracellular acidosis, influence these overlapping pathogenetic processes in ischemic heart failure. Several data show that myocardial contractile dysfunction in patients with heart failure is conditioned by the alteration of substrate metabolism [7,16]. Prevention of intracellular acidosis and calcium overload can be important “cardioprotective” effects in both ischemia and heart failure [17]. The beneficial effect of trimetazidine on energy metabolism may contribute to an improvement in myocardial systolic function in patients with left ventricular dysfunction caused by CAD.

Brottier et al [18] first showed that treatment with trimetazidine for 6 months increased radionuclide ejection fraction by 9.3% in patients with ischemic cardiomyopathy. The effects of trimetazidine in

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Vastarel MR in chronic CAD and LV dysfunction

patients with left ventricular dysfunction and diabetes were assessed in randomized studies by Fragasso et al [19] and Rosano et al [20]. In both studies, 6 months of treatment with trimetazidine resulted in a significant increase in left ventricular ejection fraction (LVEF) and a decrease in end-diastolic volumes. Vitale and colleagues [21] showed similar effects of trimetazidine on ventricular function and volumes in elderly patients: LVEF increased by $5.3 \pm 1.3\%$ ($P < 0.05$) after 6 months in the trimetazidine group and remained unchanged in the placebo group (1.8% before treatment; 1.9% after treatment; a difference of 0.1% which was NS).

In a recent study of 82 stable patients with ischemic cardiomyopathy [22], my colleagues and I found that a subgroup of patients treated with a daily dose of 70 mg trimetazidine in conjunction with standard therapy over a 3 month period exhibited an increase in LVEF by $3.5 \pm 6.72\%$ in the trimetazidine group (compared with $0.8 \pm 8.06\%$ in controls; $P = 0.05$; Figure 1) and an improvement in tolerance to physical activity of 30.0 ± 0.7 m in the trimetazidine group (compared with 2.0 ± 18.85 m in controls, $P < 0.001$; Figure 2). The increase in LVEF in the trimetazidine group was accompanied by a decrease in left ventricular volumes: left ventricular end-systolic volume decreased by 23 ± 28.4 ml (from 143 ± 22 ml to 120 ± 18 ml) in the trimetazidine group and by 9.0 ± 31.9 ml (from 148 ± 24 ml to 139 ± 21 ml) in the control group ($P < 0.05$). These findings showed that, in patients with moderate ischemic left ventricular dysfunction, modified-release trimetazidine is able to relieve the symptoms of heart failure and improve left ventricular function. The drug was well tolerated and did not cause any hemodynamic adverse effects. Our study was the first to test the effect of modified-release trimetazidine in a daily dose of 70 mg in patients with ischemic cardiomyopathy.

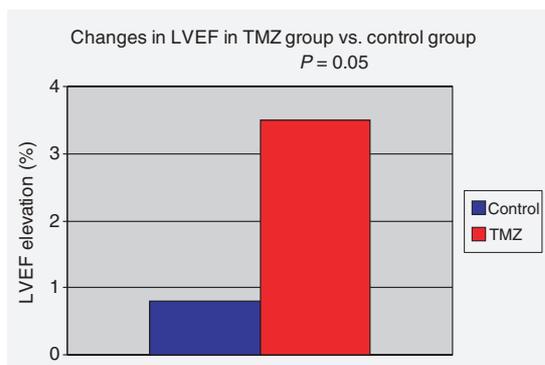


Figure 1. Changes in left ventricular ejection fraction (LVEF) in patients with stable ischemic cardiomyopathy treated with a daily dose of 70 mg trimetazidine (TMZ; Vastarel MR) in conjunction with standard therapy for 3 months (red column), compared with that in controls (blue column). The difference between groups was significant ($P = 0.05$).

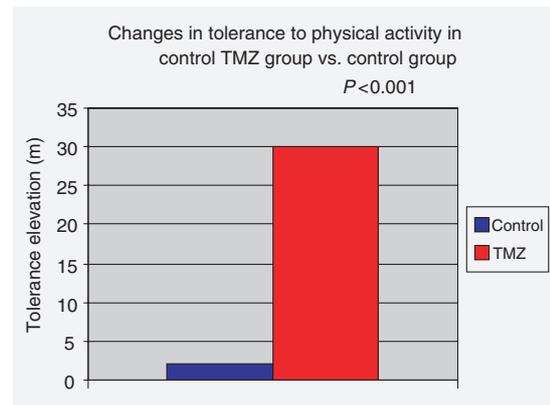


Figure 2. Changes in tolerance to physical activity in patients with stable ischemic cardiomyopathy treated with a daily dose of 70 mg trimetazidine (TMZ; Vastarel MR) in conjunction with standard therapy for 3 months (red column), compared with that in controls (blue column). The difference between groups was significant ($P < 0.001$).

El-Kady and associates studied 200 patients aged 55 ± 12 years with ischemic left ventricular dysfunction resulting from multivessel CAD, who were allocated randomly to either a study group receiving trimetazidine or a placebo group for 2 years. After the 2 years, there was an increase in left ventricular function of 23% in the trimetazidine group, compared with one of only 0.5% in the placebo group; left ventricular volumes, assessed by single photon emission computed tomography, showed decreases [23]. A significant survival benefit was observed in the trimetazidine group, with a mortality rate of 8% compared with one of 38% in the placebo group. In the recent post-hoc analysis of the Villa Pini D'Abruzzo Trimetazidine Trial involving 61 patients with ischemic cardiomyopathy in a 48 month follow-up period, trimetazidine significantly reduced all-cause mortality (by 56%: hazard ratio 0.258, 95% confidence interval 0.097 to 0.687; log-rank test, $P = 0.0047$) and number of admissions to hospital because of heart failure (47% decrease; log-rank test, $P = 0.002$). In trimetazidine-treated patients, a significant increase in LVEF and improvement in 6 min walk test was observed [24].

The findings of these last two studies showing significant effects of long-term treatment with trimetazidine on mortality in patients with CAD and left ventricular dysfunction emphasize the importance of confirming the effects of trimetazidine in a multicenter, randomized, placebo-controlled trial, to demonstrate its impact on mortality.

Conclusions

Analysis of clinical trials suggests that metabolic intervention in the management of patients with CAD and

left ventricular dysfunction represents a promising therapeutic approach. Its anti-ischemic properties and absence of hemodynamic effects make the modified-release formulation of trimetazidine, Vastarel MR, a good treatment option in patients with left ventricular dysfunction. This modified-release formulation has no any adverse effects in patients with ischemic cardiomyopathy and may afford better patient compliance with treatment, because of its reduced frequency of administration compared with the conventional formulation. Improvements in left ventricular contractility and functional class demonstrated in clinical trials with Vastarel MR are further indications that addition of this agent to conventional treatment may have beneficial effects for patients with ischemic left ventricular dysfunction. Recent studies demonstrating beneficial effects on mortality derived from long-term administration of trimetazidine in patients with ischemic left ventricular dysfunction suggest the necessity for a large multicenter trial to prove this influence. ■

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