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Trimetazidine in Practice: Review of the Clinical and Experimental Evidence

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All of the following traditional agents for the management of stable angina pectoris include the symptomatic treatment with heart rate–lowering agents such as β-blockers or non-dihydropyridine Ca-channel blockers, or ivabradine—the first selective sinus node I_f channel inhibitor—vasodilatators and preventive use of angiotensin-converting enzyme inhibitors affect the parameters of circulation directly. Trimetazidine exerts its anti-ischemic action by modulating cardiac metabolism without altering the hemodynamic functions, therefore represents an excellent complementary potential to the conventional angina treatment. It has a beneficial effect on the inflammatory profile and endothelial function and shows diverse benefits by reducing the number and the intensity of angina attacks and improving the clinical signs and symptoms of myocardial ischemia given as monotherapy as well as combined with other antianginal agents. Patients undergoing coronary revascularization procedures or with comorbid left ventricular dysfunction and diabetes mellitus also benefit from the protective effects of trimetazidine.

Keywords: angina pectoris, cardiac metabolism, cardioprotective effect, diabetes mellitus

INTRODUCTION

Trimetazidine is an anti-ischemic agent widely used in the treatment of coronary artery disease. It inhibits the long-chain mitochondrial 3-ketoacyl coenzyme A thiolase enzyme in the mitochondria, resulting in the improvement of mitochondrial metabolism through inhibition of myocardial fatty acid uptake and oxidation and consequent stimulation of glucose oxidation. Unlike conventional drugs, trimetazidine exerts no effect on coronary flow, contractility, blood pressure, or heart rate. It has no significant negative inotropic or vasodilatory properties at rest or during exercise; therefore, it can be excellently combined with conventional pharmacotherapy of coronary artery disease, as add-on therapy, as well as substitution therapy when conventional drugs are not tolerated (class IIb; level B).[1–3] This article reviews the available literature evidence with the use of trimetazidine and future possibilities in the treatment of patients with coronary artery disease.

PHARMACOKINETIC PROPERTIES

The main trimetazidine formulations available on the market are the 20 mg immediate-release (IR) tablets administered 3 times a day and the 35 mg modified-release (MR) tablets, developed with an aim to maintain a sustained therapeutic plasma concentrations while increasing the patient compliance with a less frequent application of twice a day.

After oral administration, trimetazidine is rapidly absorbed from the intestinal tract, without significant effect of food on its bioavailability.[4] The mean peak plasma concentration (C_{max}) of the IR formulation

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was found to be 53.6 μg/L and was reached within 1.8 hours; the area under the plasma concentration–time curve ($AUC_{0-\infty}$) was 508.9 $\mu g \cdot L^{-1} \cdot h^{-1}$ after single and 831.4 $\mu g \cdot L^{-1} \cdot h^{-1}$ after multiple doses. Steady-state levels of trimetazidine are reached within 24 hours; it is biotransformed to a low extent into several metabolites only detectable in the urine. Trimetazidine is weakly bound to plasma proteins. Its elimination half-life is about 6 hours after single or repeated oral administration of IR tablets, with the majority of the drug excreted in the urine.[5,6] In patients with renal impairment and in elderly people, the elimination half-life of trimetazidine increases, whereas the renal clearance decreases when compared with healthy young subjects.[7]

Compared with the steady-state properties of the IR formulation, MR tablets have shown similar total exposure and interindividual variability, but a delayed time to peak and increased mean absorption times during a comparative pharmacokinetic study. There (MR vs. IR) was a decrease in peak plasma concentration (544 vs. 659 μg/L), a 31% increase in trough concentrations, a decrease in peak-trough fluctuation (86 vs. 121%), and an increase in plateau time (11 vs. 4 hours) with the use of the MR formulation.[8]

Trimetazidine does not seem to affect the pharmacokinetics of theophylline, digoxin, or cyclosporin.[9,10]

PHARMACODYNAMIC PROPERTIES COMPARED WITH CONVENTIONAL THERAPY

The cardioprotective effect of trimetazidine has not yet been fully understood; it has been attributed to direct cytoprotective actions, causing reduction of myocardial cell acidosis and calcium overload, preservation of intracellular ATP levels, increase of the antioxidant capacity, and protection against oxygen-free radical-induced toxicity.[1,11,12] Trimetazidine was shown to favorably alter the level of oxidative stress markers. In the study by Iskesen et al,[1] it increased the level of superoxide dismutase and glutathione peroxidase (major endogenous antioxidant enzyme systems responsible for limiting intracellular accumulation of oxygen radicals during normal aerobic metabolism) and decreased the level of malondialdehyde (the end product of lipid peroxidation). Trimetazidine also limits membrane damage induced by reactive oxygen species and protects tissue from free radicals with its antioxidant effects. It has been suggested that reactive oxygen species–mediated and nitric oxide (NO)-mediated damage enhances the release of proinflammatory mediators such as C-reactive protein (CRP), tumor necrosis factor alpha (TNF-α), interleukin 1 (IL-1), and IL-8 from macrophages both in inflammation and ischemia. Trimetazidine was shown to suppress the elevation of inflammatory markers such as CRP, TNF-α, and NO levels during coronary interventions, although in another study no significant difference between the levels of IL-8, TNF-α, C3 and C5, and highly sensitive CRP was observed. However, the IL-6 levels were significantly lower in both studies when the patients were treated with trimetazidine.[13,14]

The heart uses free fatty acids (FFAs) as a primary source of energy in the absence of ischemia because fatty acids produce more ATP than glucose oxidation. Myocardial FA oxidation (FAO) is a complex process that provides almost 70% of cardiac ATP in the fasting state, whereas the remaining portion yields mostly from the oxidation of the competing substrates lactate, glucose, and pyruvate. However, FFA metabolism leads to an increase in oxygen consumption and is a less efficient source of energy compared with glucose metabolism, theoretically requiring 11%–12% more oxygen for a given amount of ATP produced. The normal adaptive response during ischemia or in heart failure would be the switch in substrate metabolism away from fatty acid oxidation toward the more oxygen-efficient glucose metabolism to maximize efficiency, potentially balancing the mismatch between oxygen requirement and supply. Moreover, if myocardial fatty acid uptake overwhelms the oxidative capacity of the heart, FFAs can accumulate as intramyocardial lipids, which are associated with a so-called "lipotoxicity," leading to further impairment of the cardiac function, in addition to insulin resistance.[2,10,15]

Conventional pharmacologic therapy of ischemic heart disease focuses on a reduction in heart rate, preload, and postload with hemodynamically acting agents. In patients with coronary artery disease, anginal symptoms are usually precipitated by increased myocardial oxygen demand in a setting of coronary flow obstruction. Traditional antianginal agents can be classified into 2 major categories, heart rate–lowering agents or vasodilators.

Heart rate–lowering agents such as β-blockers, or non-dihydropyridine Ca-channel blockers (class I; level A) and ivabradine (class IIa; level B) reduce angina by reducing myocardial oxygen consumption. They also increase myocardial perfusion by increasing duration of diastole, the period where coronary flow occurs. β-blockers with NO-mediated vasodilator properties (such as nebivolol) also lessen the cardiac workload by decreasing the periferial arterial resistance and left ventricular filling pressure and improving the coronary flow reserve by dilating the coronary arteries. The risk of suffering cardiovascular death or myocardial infarction

was reduced by β-blockers by some 30% in postmyocardial infarction trials.[3,16–18]

The vasodilatator nitrates dilate venous capacitance vessels and coronary arteries and facilitate coronary collateral flow. It results in decreased venous return, thereby, reducing left ventricle (LV) wall stress and myocardial oxygen demand. Nitrates can also increase coronary flow and oxygen supply. However, tolerability is an important limitation to nitrate use. These drug classes can be well used in combination for the treatment of coronary artery disease.[17,18] In patients with coexisting ventricular dysfunction, hypertension, or diabetes, the use of angiotensin-converting enzyme inhibitors (class I; level A) is furthermore indicated and should be strongly considered in patients with other high-risk features, as angiotensin-converting enzyme inhibitors were shown to decrease the risk of myocardial infarction in patients with hypertension.[3,19,20] Besides conventional therapy, all patients with stable angina pectoris should be treated with aspirin and a lipid-lowering statin agent (class I; level A). Clopidogrel is indicated as an alternative in case of aspirin intolerance (class I; level B).[3]

TRIMETAZIDINE IN STABLE ANGINA PECTORIS

Angina pectoris is a clinical syndrome of precordial discomfort, pressure, or pain due to transient myocardial ischemia. Symptoms are usually caused by atheromatous narrowing of 1 or more coronary arteries. Patients with stable angina not controlled by monotherapy with nitrates, β-blockers, or calcium-channel blockers are often treated with combinations of these drugs.[21] The effects of trimetazidine (60 mg/d) were compared with those of propranolol (40 mg/d) in a double-blind parallel group multicenter study in 149 men with stable angina. After 3 months, similar antianginal efficacy was observed between the both groups. However, the heart rate and the official blood pressure did not change in the trimetazidine group against the other group.[22] Several clinical trials and meta-analyses evaluated the role of trimetazidine in the treatment of stable angina pectoris in the past decades. Trimetazidine controls myocardial ischemia through intracellular metabolic changes and was found to be effective compared with placebo, alone, or combined with conventional antianginal agents. The most often evaluated parameters were the number of weekly angina attacks and mean weekly nitroglycerin consumption and time to 1-mm ST-segment depression during exercise capacity tests.[21]

The meta-analyses of trimetazidine in angina pectoris by Ciapponi et al included 23 studies with 1378 patients involved. Trimetazidine was shown to reduce by about 40% the mean number of weekly angina attacks compared with placebo [−1.44 (95% CI: −2.10 to −0.79)]. This finding was supported by the complementary findings that trimetazidine reduced the weekly consumption of nitroglycerin tablets [−1.47 (95% CI: −2.20 to −0.73)] and increased the exercise time to 1-mm ST-segment depression [0.32 (95% CI: 0.15–0.48)]. These modest benefits were apparent independently of whether trimetazidine was given as monotherapy or combined with another antianginal agent.[21] Trimetazidine can significantly improve left ventricular ejection fraction (LVEF) [6.88% (95% CI: 5.50 to 8.25)], reduce left ventricular end-systolic volume [11.58 mL (95% CI: 5.79 to 17.37)], and wall motion score index [0.23 (95% CI: 0.07 to 0.38)], as shown in the meta-analysis of 11 randomized controlled trials evaluated by Hu et al.[23] The findings were consistent in both the long term and the short term; the efficacy was also unchanged in patients with diabetes mellitus. The network meta-analysis of Danchin et al showed a comparable efficacy of trimetazidine in patients with stable angina pectoris to that of other non–heart rate-lowering antianginal treatments. Based on 218 trials in 19,028 patients, the analysis showed a mean improvement of +46 seconds for total exercise duration, +55 seconds for time to 1-mm ST-segment depression, and +54 seconds for time to onset of angina with trimetazidine. The results confirmed the benefits of trimetazidine on exercise tolerance and the most often evaluated clinical parameters. They also confirmed the prophylactic effect of trimetazidine on angina attacks in stable angina.[24]

Combined treatment of stable angina

Trimetazidine can be easily combined with any conventional antianginal drug due to its pharmacodynamic properties. Being a metabolic drug, trimetazidine is free of any hemodynamic action and has no negative inotropic or vasodilatory properties. It has been proven to be beneficial as complementary therapy in patients with stable angina. The combination of trimetazidine with β-blockers or long-acting nitrates significantly improves exercise stress test parameters and angina symptoms compared with placebo.[1–3,18] The TRIMPOL I study assessed the antianginal and anti-ischemic effect of trimetazidine in 700 patients with stable exercise-induced angina insufficiently controlled with conventional antianginal drugs. The study showed a significant improvement in the total duration of exercise (486.6 vs. 443.7 seconds), increase in total work, measured in the metabolic equivalent system (10.6 vs. 9.4), significant lengthening of time to 1-mm ST depression (389.9 vs. 337.8 seconds), and of the

time to onset of angina (450.3 seconds vs. 251.7 seconds) after 4 weeks of therapy. There was also a significant reduction in the number of daily episodes of angina (2.47 vs. 3.66) and a reduction in mean use of complementary trinitrine (1.8 vs. 2.94).[25] The TRIMPOL II study evaluated the antiischemic efficacy and tolerability of trimetazidine in combination with metoprolol compared with metoprolol only in 426 patients with stable angina pectoris for 12 weeks. There were significantly greater improvements in the metoprolol plus trimetazidine group than in the metoprolol-only group in time to 1-mm ST-segment depression, total workload, time to onset of angina, maximum ST-segment depression, mean weekly number of angina attacks, mean weekly nitrate consumption, and grade of anginal pain. There was no evidence of any development of tolerance to trimetazidine.[26] A substudy of TRMPOL II confirmed all these beneficial effects also in patients with a history of revascularization for coronary artery disease.[27]

Another double-blind placebo-controlled study evaluated the combination of trimetazidine with the β-blocker atenolol compared with atenolol plus placebo in a 6-month treatment of 223 stable angina pectoris patients. Time to 1-mm ST-segment depression was increased by 44 seconds more in the trimetazidine group than in the atenolol-only group ($P = 0.005$). A significant difference was also found for the time to onset of angina pectoris ($P = 0.049$) and for the reason for stopping the exercise ($P = 0.02$).[28] The Trimetazidine in Angina Combination Therapy (TACT) investigators evaluated the effect of trimetazidine in stable angina patients who were resistant to nitrates or β-blockers. At inclusion and during the study, 52% of patients received long-acting nitrates, and 48% were treated with a β-blocker as monotherapy. Patients who received trimetazidine in addition to their conventional treatment had a significantly higher increase in their exercise test duration and time to 1-mm ST depression after 12 weeks of treatment and a greater decrease in the mean number of angina attacks per week ($P < 0.05$). There was also a significant improvement in time to angina onset ($P < 0.005$) compared with placebo. The mean consumption of short-acting or long-acting nitrates per week decreased in both groups, with a trend in favor of trimetazidine.[29]

Trimetazidine has been shown among others to increase time to 1-mm ST-segment depression and time to onset of angina and decrease the mean number of angina attacks and nitrate consumption in monotherapy as well as in addition to long-acting nitrate and β-blocker use.

TRIMETAZIDINE IN CORONARY INTERVENTIONS

Patients with symptomatic coronary artery disease with a significant stenosis are potential subjects to revascularization procedures to improve survival.[30,31] The reperfusion injury is a pathophysiological phenomenon that can occur as a result of damage to the myocardium after blood restoration after a certain period of coronary occlusion. Reperfusion of the ischemic heart causes the generation of oxygen-free radicals, which can damage cardiac cells. It may happen in general coronary syndromes, such as unstable angina, vasospastic angina, myocardial infarction with or without ST-segment elevation, whether or not followed by thrombolysis or angioplasty procedures, as well as in cardiovascular surgeries and in elective angioplasties.[1,32] Revascularization procedures, such as percutaneous coronary intervention (PCI) or coronary artery bypass grafting (CABG) can cause a transient ischemia of the myocardium, leading to metabolic changes inducing disturbances of the electrical activity and contractility of myocardial cells associated with hemodynamic disturbances. At that time, characteristic angina and electrocardiography abnormalities can also occur. Trimetazidine was shown to be beneficial in the improvement of myocardial protection during procedures involving reperfusion injury in several smaller studies.[13,33]

Percutaneous coronary intervention

Preprocedural acute oral administration of trimetazidine was evaluated in 266 patients by Bonello et al.[34] Postprocedural cardiac troponin I levels were significantly reduced in the trimetazidine group at 6, 12, 18, and 24 hours after PCI ($P < 0.001$), showing a reduced PCI-induced myocardial injury with trimetazidine use. One hundred one patients with stable or unstable angina pectoris were randomized to receive or not oral trimetazidine 20 mg 3 times a day for (5 ± 2) days before PCI and a loading dose of 60 mg 30 minutes before the intervention. Angina did not occur in trimetazidine group, compared with 25.5% in the control group ($P < 0.001$). The changes of ST-segment and T-wave during balloon dilatation in PCI procedure were less pronounced in the trimetazidine group (60.8% vs. 78.3%, $P < 0.05$). Ejection fraction in the trimetazidine group was higher than that in the control group 66.6% versus 63.0% ($P = 0.03$) 4 weeks after PCI.[35] Use of trimetazidine was evaluated in a randomized controlled trial of 138 patients with acute STEMI without ST-segment resolution after primary PCI. Trimetazidine was shown to

improve the left ventricular function at days 30 and 180, as measured by the LVEF, which was 51% versus 45% and 56% versus 49%, respectively ($P < 0.05$).[36] Another open-label, randomized controlled study with trimetazidine pretreatment in 44 patients undergoing PCI found that the mean ST-segment elevation and the mean amplitude of the T-wave alterations during all balloon inflations were significantly lower in the trimetazidine group ($P = 0.001$). The maximal amplitude of the T-wave alterations was 4.50 mm with trimetazidine versus 9.25 mm in control patients, with an even higher significance level ($P = 0.0005$). Mean time from balloon inflation to onset of angina was 50 seconds with trimetazidine versus 32 seconds for the control group ($P = 0.03$) and the mean time to pain relief after deflation was 19.3 seconds with trimetazidine versus 28.2 seconds ($P = 0.001$). Maximal ST-segment elevations and mean ST-elevation values during sequential balloon inflations were also significantly lower with trimetazidine ($P = 0.018$). Angina episodes and rhythm disturbances were more frequent in the control group.[33]

The effect of trimetazidine as a postintervention drug (started 24 hours after the PCI) was evaluated in a controlled study in 51 patients with coronary artery disease undergoing PCI. The group receiving trimetazidine treatment showed a statistically significant improvement of left ventricular systolic performance ($P < 0.001$), augmentation of the parasympathetic band of heart rate variability ($P < 0.001$), and decline of P1/P2 ratio ($P < 0.01$) in the power spectral analysis of heart rate variability and 2-dimensional and Doppler echocardiographic examinations.[37]

Coronary artery bypass grafting

The effects of trimetazidine on ischemic injury and myocardial reperfusion were also studied in patients undergoing CABG. A randomized, double-blind, prospective study in 60 patients identified the change in plasma markers of a myocardial aggression (troponin T and CK-Mb) in patients receiving placebo or medication at a dose of 60 mg/d, starting from 12 days during preoperative period up to 5 days during postoperative period. Both troponin T and CK-Mb reached highly significant values ($P = 0.0001$) in the control group compared with the treated group at the 4 moments analyzed: 5 minutes after aortic declamping, and at subsequent 12, 24, and 48 hours.[32]

Summarily, trimetazidine showed an improvement in several ischemic parameters, such as reduction in the frequency of angina pectoris attacks and myocardial damage during PCI and CABG. It also improved left ventricular function during follow-up after percutaneous angioplasty.

TRIMETAZIDINE IN LEFT VENTRICULAR DYSFUNCTION AND DIABETES MELLITUS

In one of the newest placebo-controlled studies published this year, Xu et al examined the effect of trimetazidine on recurrent angina pectoris and left ventricular structure in elderly multivessel coronary heart disease patients with diabetes mellitus after drug-eluting stent implantation. At 2-year follow-up, patients in the trimetazidine group (n = 255) showed significant improvements in the incidence ($P = 0.024$) and severity of angina pectoris, compared with the control group, as well as silent myocardial ischemia ($P = 0.009$) and angina pectoris free survival ($P = 0.011$). LV function and structure in trimetazidine-treated patients were relatively stable at 2-year follow-up, whereas they deteriorated in the control group (n = 255) with a significant difference between groups (all $P < 0.01$).[38]

Left ventricular failure can characteristically develop in ischemic heart disease. Because of the diffuse distribution of coronary atherosclerosis and the diffuse reduction of coronary blood flow and reserve, elderly patients often show a decrease in left ventricular function or an inability to adjust left ventricular performance to meet the peripheral metabolic needs. In conditions of high oxidative stress, such as diabetes mellitus and chronic heart failure, free radical production is increased and contributes to endothelial dysfunction. The metabolic action of trimetazidine may prevent the consequences of the oxidative stress and improve myocardial function in situations where left ventricular function is impaired; it can even improve the reverse remodeling of chronically dysfunctional myocardium. In heart failure, trimetazidine can improve the contractility, the ventricular function, and the functional capacity.[39]

In patients with diabetes mellitus, the myocardial glucose utilization is impaired. Altered insulin signaling leads to decreased myocyte glucose uptake and utilization, associated with an increased concentration of FFAs. Additionally, they have an accelerated atherogenesis with involvement of peripheral segments of major coronary arteries and peripheral branches, reducing regional coronary perfusion and causing diffuse hibernation of the myocardium. Diabetes thus may lead to ventricular dysfunction independent of and additive to coronary artery disease and hypertension.[40–43]

Trimetazidine improved the endothelium-dependent relaxation (determined by intra-arterial infusion of acetylcholine) and decreased systemic oxidative marker levels in patients with chronic heart failure secondary

to ischemic cardiomyopathy in the study of Belardinelli et al. Patients receiving trimetazidine had a significant improvement in radial artery diameter in response to each dose of acetylcholine infusion and a greater peak oxygen uptake compared with placebo ($P < 0.01$). Furthermore, plasma levels of the oxidative markers malondialdehyde and lipid hydroperoxide were significantly reduced at 4 weeks in patients receiving trimetazidine ($P < 0.001$). The antioxidant properties of trimetazidine may contribute to the improvement of the endothelial dysfunction.[40]

In the study by Vitale et al, 47 elderly patients with chronic stable angina on optimal medical therapy were randomized to receive, in addition to their standard therapy, either trimetazidine or placebo for 6 months. At the end of the study, patients receiving trimetazidine showed a greater left ventricular function and an improved diastolic function shown by smaller left ventricular diastolic and systolic diameters and volume indices on echocardiography compared with patients receiving placebo with high levels of significance ($P < 0.0001$). Symptomatic patients for angina treated with trimetazidine showed a significant improvement in the number of anginal episodes and a significant decrease in the number of nitroglycerin tablets used after 6 months, whereas no significant changes were observed in patients receiving placebo ($P < 0.01$).[43] Nineteen nondiabetic patients with idiopathic dilated cardiomyopathy were studied and randomized to single-blind trimetazidine or placebo. Myocardial perfusion, FFA, and total oxidative metabolism were measured using positron emission tomography. In idiopathic dilated cardiomyopathy with heart failure, trimetazidine increased cardiac function. Cardiac FFA oxidation modestly decreased and myocardial oxidative rate was unchanged, implying increased oxidation of glucose. Trimetazidine improved whole-body insulin sensitivity and glucose control in these insulin-resistant idiopathic dilated cardiomyopathy patients, thus hypothetically countering the myocardial damage of insulin resistance. Additionally, the trimetazidine-induced increase in ejection fraction was associated with greater β1-adrenoceptor occupancy, suggesting a synergistic mechanism.[44]

Further 17 trials with data for 955 patients showed that trimetazidine therapy was associated with a significant improvement in LVEF in patients with both ischemic and nonischemic heart failure. Exercise duration and NYHA classification were improved with trimetazidine therapy; more importantly, trimetazidine had a significant protective effect for all-cause mortality (relative risk: 0.29; 95% confidence interval: 0.17 to 0.49; $P < 0.00001$) and cardiovascular events and hospitalization (relative risk: 0.42; 95% confidence interval: 0.30 to 0.58; $P < 0.00001$).[45] The use of trimetazidine also decreased hospitalization for cardiac causes, improved clinical symptoms and cardiac function, and simultaneously ameliorated left ventricular remodeling in patients with chronic heart failure.[46] Thirty-two patients with type 2 diabetes and ischemic cardiomyopathy were randomized to receive either trimetazidine or placebo for 6 months. At the end of the study, baseline left ventricular end-diastolic diameters increased in the placebo group, whereas they decreased in the trimetazidine group from 63.2 to 58 mm ($P < 0.01$ compared with baseline). Compared with baseline, LVEF increased by 5.4% ($P < 0.05$) in the trimetazidine group, whereas it remained unchanged in the placebo group ($P < 0.01$ between groups). A significant improvement in wall motion score index and in the E/A wave ratio was also detected in patients treated with trimetazidine, but not with placebo.[42]

The diabetic substudy of TRIMPOL I study assessed the anti-ischemic efficacy and tolerability of trimetazidine in 50 patients with diabetes with stable effort angina. After 4 weeks, a significant improvement in exercise tolerance (440.2 vs. 383.2 seconds; $P < 0.01$), time to 1-mm ST-segment depression (358.3 vs. 301.6 seconds; $P < 0.01$), time to onset of anginal pain (400.0 vs. 238.3 seconds; $P < 0.01$), and total work (9.39 vs. 8.67 metabolic equivalents, $P < 0.01$) was shown with the use of trimetazidine. Other findings included a significant decrease in the mean frequency of anginal episodes (3.06 vs. 4.79 per week; $P < 0.01$) and in mean nitrate consumption (2.29 vs. 4.2 doses/wk).[47]

SIDE EFFECTS AND TOLERABILITY

In clinical studies, trimetazidine was well tolerated in general; the experienced side effects were usually mild and resolved after the discontinuation of the drug. According to a systematic review and meta-analysis evaluating trimetazidine use, the number of the total observed adverse events and the dropout rates were very low. In controlled studies, the side effects more frequently present in the trimetazidine group were gastric or esophageal burning, muscular cramps, dizziness, effort induced discomfort, depression, sedation and/or drowsiness, palpitations, visual disturbances, anorexia, and hyperorexia. In placebo-controlled trials, there was no significant difference between the arms regarding dropouts or adverse events. In studies with active comparator, the dropout number was lower compared with that of with other antianginal drugs.[21] Lately, concern arose regarding the safety of trimetazidine-containing medicines following reports of Parkinson syndrome and other motor disorders such as tremor, muscle rigidity, and walking

disorders and restless legs syndrome.[48] These symptoms were seen in some patients with no history of Parkinson syndrome, and in many cases, their symptoms resolved when they stopped taking trimetazidine. As a result of a thorough investigation of available data in connection with this concern, the Committee for Medicinal Products for Human Use decided that trimetazidine should not be prescribed for patients with Parkinson disease, Parkinsonian symptoms, or related movement disorders and for patients with severely reduced kidney function. For patients with moderately reduced kidney failure and elderly patients, the dose should be reduced to adapt to the prolonged renal elimination of the drug. Nevertheless, the Committee for Medicinal Products for Human Use concluded that the benefits of trimetazidine therapy continue to outweigh the risks in patients with angina pectoris. To confirm this opinion, the newest European Society of Cardiology (ESC) guideline recommends trimetazidine as a second-line therapy in combination with other drugs for the successful treatment of angina pectoris syndrome.[3,49]

DISCUSSION

Trimetazidine is a metabolic agent, protecting the heart from ischemic damage and oxidative stress.[1,11,12] It has a confirmed clinical benefit in patients with a coronary artery disease, with a prophylactic effect on angina attacks and can be excellently used in combination with other antianginal agents due to its lack of hemodynamic action. It leads to an improvement in the total exercise test duration and time to 1-mm ST-segment depression; it also delays the time to onset of angina, reduces the number of angina attacks, the need for nitrate consumption, and the grade of anginal pain.[21,23–26,28–30]

Patients with frequent comorbidities such as left ventricular dysfunction or diabetes mellitus show similar results in ameliorating the clinical symptoms of angina pectoris. The use of trimetazidine in patients with impaired myocardial function may lead to improved left ventricular ejection fraction and endothelium-dependent relaxation as well as reduced left ventricular end-systolic volume and wall motion score index, implicating improvement in the work of the myocardium and ventricular remodeling. Trimetazidine also decreases hospitalization for cardiac causes and showed a protective effect for all-cause mortality and cardiovascular events in patients with heart failure.[23,36,40,43,45,46]

In patients with stable angina undergoing revascularization procedures, the use of trimetazidine may prevent the myocardium from the potential reperfusion injury; given after PCI, it improves left ventricular systolic performance and causes augmentation of the parasympathetic band of heart rate variability. Its use leads to reduced changes of ST-segment and T-wave during balloon dilatation in PCI procedure, longer time from balloon inflation to onset of angina, and shorter time to pain relief after deflation. In patients undergoing CABG, trimetazidine therapy resulted in a reduced injury of the cardiac cells, demonstrated by the significant reduction in troponin T and CK-Mb marker levels in the treated group.[32–35,37]

Coronary artery disease with coexistent diabetes mellitus tends to affect distal arteries and is more likely to display diffuse lesions due to impaired myocardial glucose utilization. Patients with diabetes often undergo revascularization treatments, because heart disease due to diabetes often results in complications of the large vessels. However, revascularization—as long as the microvasculature suffers lesion—cannot be effective by itself. In such cases, pharmacological treatment (often as supplement) is the most effective for relieving the patient's symptoms.[47] Furthermore diabetes mellitus induces microvascular damage within the myocardium, without coexistent changes in the extramural coronary arteries.[50] There is a good clinical response in patients with angina with coexistent diabetes mellitus to trimetazidine treatment. It may compensate the deteriorated glucose uptake utilization of myocardial cells resultant to the altered insulin levels and even might have a cardioprotective effect in patients at risk of diabetic cardiomyopathy.[41,42,51]

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