Selective inhibition of long chain 3-ketoacyl-Coenzyme-A-thiolase by Trimetazidine MR in coronary heart disease induced reduction of inflammatory syndrome and oxidative stress in concordance with recovery of ECG and echocardiographic changes

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Abstract

The aim *of this clinical study was to evaluate the efficacy of treatment with trimetazidine modified release (MR) in addition to optimal standard medical therapy in patients with coronary heart disease - stable angina, unstable angina and non ST elevation myocardial infarction in inflammatory syndrome and oxidative stress reduction in concordance with recovery of ECG and echocardiographic changes.*

Design: *252 patients were included in a prospective study for a period of 3 years and separated in six groups in relation with type of coronary heart disease and addition of trimetazidine MR to optimal standard medical therapy. Clinic, electrocardiographic and echocardiographic evaluation were performed initial, at 1, 6 months, 1, 2 and 3 years and biologic, evaluation initial, at 1 and 6 months. Anti ox-LDL antibody titers and total antioxidant status serum level were measured for oxidative stress evaluation, C-reactive protein serum level and fibrinogen plasma level were evaluated as markers of inflammatory syndrome.*

Results: *A significant reduction in oxidative stress in terms of incidence of low total antioxidant status serum level at 1, 6 months, incidence of high anti ox-LDL antibody serum titers at 6 months and a significant reduction in inflammatory syndromes in terms of high C-reactive protein serum level and high fibrinogen plasma values at 6 months of follow up were observed in patients with unstable angina and non ST elevation myocardial*

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infarction treated with trimetazidine added to optimal standard medical therapy. This results were in concordance with significant reduction in incidence of ST depression on ECG at 1, 6 months, 1, 2 and 3 years and with significant improvement in echocardiographic measured left ventricular ejection fraction at 2 and 3 years in mentioned groups of patients. Global wall motion score index at 1, 2 and 3 years was significantly improved in all trimetazidine treated groups.

Conclusions: *Selective inhibition of long chain 3-ketoacyl-Coenzyme-A-thiolase by Trimetazidine MR was followed by a significant reduction in inflammatory syndromes and oxidative stress at 6 months of follow up in patients with unstable angina and non ST elevation myocardial infarction. These results were in concordance with significant reduction in incidence of ST depression on ECG and significant improvement in echocardiographic measured left ventricular function at 3 years of follow up.*

Keywords: *coronary heart disease; trimetazidine MR; oxidative stress; inflammatory syndrome; ST segment depression; left ventricular function*

Introduction

The superoxide anion, hydroxyl radical and hydrogen peroxide are the most important reactive oxygen species (ROS) involved and superoxide dismutase (SOD), glutathione peroxidase and catalase are the major endogenous antioxidant enzyme systems oxidized and decreased in ischemia-reperfusion injury. Energetic metabolism during myocardial ischemia and reperfusion is connected with cardiac function [1, 2,4,11]. Trial to manipulate energetic metabolism included stimulation of glucose oxidation and/or fatty acids metabolism inhibition. A lot of experimental studies observed that stimulation of glucose oxidation during myocardial ischemia and reperfusion is a benefit for ischemic heart. Trimetazidine (1-[2,3,4-trimethoxibenzyl] piperazine is a selective inhibitor of mitochondrial long chain fatty acids 3-ketoacyl-CoA-tiolase oxidation with induced inhibition of pyruvate dehydrogenase, indirect stimulation of glucose oxidation and production of membrane-protective glycolytic ATP. The switch of energetic substrate from fatty acids oxidation to glucose oxidation could explain antianginal effect of trimetazidine. With one molecule of oxygen by glucose oxidation are produced 6.4 ATP molecules in comparison with only 5.6 ATP molecules produced by fatty acids oxidation. Trimetazidine act as a specific partial inhibitor of fatty acid oxidation with indirect increase in glucose metabolism and many cardiac protective mechanisms which include diminished mitochondrial uncoupling, enhanced efficiency of mitochondrial ATP production with maintained contractile function, reduction of intracitoplasmic Ca^{2+} and cardiac function improvement, membranes protection by increasing phospholipids turnover, proton production and acidosis reduction, and reduced apoptosis[1,10,17,28].

The aim of this clinical study was to evaluate the efficacy of treatment with trimetazidine modified release (TMZ MR) in addition to optimal standard medical therapy in patients with coronary heart disease - stable angina (SA), unstable angina (UA) and non ST elevation myocardial infarction (NSTEMI) in reduction of oxidative stress and inflammatory syndrome in correlation with ST segment depression on ECG and echocardiographic left ventricular function depression in coronary heart disease.

Methods

252 patients with high risk CHD were selected in a prospective study for a period of 3 years and separated in six groups in relation with type of CHD and addition of TMZ MR 35mg/tablet twice daily to optimal standard

Table 1. Baseline characteristics –number of patients (percentage)

Characteristics / groups	NSTEMI TMZ n=40	NSTEMI n=42	AI TMZ n=44	AI n=46	AS TMZ n=39	AS n=41
Age > 65	19(47.5%)	20(47.6%)	21(47.7%)	23(50%)	19(48.7%)	20(48.8%)
Male	23(57.5%)	24(57.1%)	26(59.1%)	28(60.9%)	24(61.5%)	25(61%)
Smokers	18(45%)	17(40.5%)	17(38.6%)	16(34.8%)	19(48.7%)	20(48.8%)
Hypertension[>140/90(130/80 in Diabetes Mellitus) mmHg]	27(67.5%)	28(66.7%)	29(65.9%)	30(65.2%)	27(69.2%)	28(68.3%)
Diabetes Mellitus	15(37.5%)	16(38.1%)	13(29.5%)	15(32.6%)	15(38.5%)	17(41.5%)
Body mass index >25 kg/m^2	32(80%)	33(78.6%)	34(77.3%)	36(78.3%)	31(79.5%)	32(78%)
Cholesterol>200mg/dl	30(75%)	30(71.4%)	30(68.1%)	31(67.4%)	31(79.5%)	30(73.2%)
LDL cholesterol>130mg/dl	29(72.5%)	30(71.4%)	29(65.9%)	32(69.6%)	30(76.9%)	29(70.7%)
HDL cholesterol<40mg/dl	31(77.5%)	34(81%)	36(81.8%)	34(73.9%)	30(76.9%)	31(75.6%)
Triglycerides>200mg/dl	16(40%)	17(40.5%)	16(38.1%)	19(39.1%)	17(43.6%)	18(43.9%)
Troponin T > 0,1ng/ml	36(90%)	39(92.9%)	0	0	0	0
CK-MB > 24U/l	31(77.5%)	32(76.2%)	0	0	0	0
Fibrinogen>400mg/dl	31(77.5%)	29(69%)	30(68.2%)	31(67.4%)	9(23.1%)	10(24.4%)
C-reactive protein > 0,5mg/dl	30(75%)	33(78.6%)	29(65.9%)	30(65.2%)	10(25.6%)	11(26.8%)
Anti ox-LDL antibody > 150 UI/l	37(92.5%)	38(90.4%)	33(75%)	37(80.4%)	8(20.5%)	9(22%)
Total antioxidant status <1.3mmol/l	38(95%)	39(92.9%)	37(84.1%)	38(82.6%)	9(23.1%)	10(24.4%)
ST depression > 0,05mV	40(100%)	42(100%)	30(68.2%)	33(71.7%)	6(15.4%)	7(17.1%)
Global wall motion score index (WMSI) > 1.4	34(85%)	36(85.7%)	30(68.2%)	34(73.9%)	30(68.2%)	34(73.9%)
Ejection fraction < 40%	9(22.5%)	10(23.8%)	9(20.5%)	9(19.6%)	6(15.4%)	7(17.1%)
Previous aspirin treatment	27(67.5%)	28(66.7%)	29(65.9%)	30(65.2%)	27(69.2%)	28(68.3%)
Optimal standard medical therapy						
Aspirin	40(100%)	42(100%)	44(100%)	46(100%)	39(100%)	41(100%)
Enoxaparinum	40(100%)	42(100%)	44(100%)	46(100%)	0	0
Clopidogrelum	40(100%)	42(100%)	30(68.2%)	33(71.7%)	0	0
Enalaprilum	36(90%)	38(90.4%)	38(86.4%)	42(91.3%)	38(86.4%)	42(91.3%)
Metoprololum	36(90%)	37(88.1%)	38(86.4%)	42(91.3%)	34(87.2%)	35(85.4%)
Simvastatinum / Atorvastatinum	28(70%)	29(69%)	28(63.6%)	30(65.2%)	26(66.7%)	27(65.9%)
Nitroglicerinum iv	46(100%)	44(100%)	46(100%)	44(100%)	0	0
Diltiazemum	2(5%)	3(7.1%)	4(9.1%)	3(6.5%)	2(5.1%)	2(4.9%)
Isosorbidi mononitras	16(40%)	17(40.5%)	10(25.6%)	11(26.8%)	10(25.6%)	11(26.8%)

UA-unstable angina; NSTEMI- non ST elevation myocardial infarction; TMZ-trimetazidine

medical therapy (OSMT): Group 1-NSTEMI TMZ 40 patients with non ST elevation myocardial infarction treated with TMZ MR in addition to OSMT; Group 2-NSTEMI 42 patients with non ST elevation myocardial infarction with OSMT; Group 3-UA TMZ 44 patients with unstable angina treated with TMZ MR in addition to OSMT; Group 4-UA 46 patients with unstable angina with OSMT; Group 5-SA TMZ 39 patients with unstable angina treated with TMZ MR in addition to OSMT; Group 6-SA 41 patients with unstable angina with OSMT.

All patients planned to interventional and surgery evaluation and treatment in the future, patients with aspirin intolerance and previous trimetazidine treatment were excluded. CHD was documented by history, physical examination, ECG, CK-MB (Immunologic method), Troponin T (ECLIA technique). Clinical, biological, electrocardiographic, echocardiographic evaluation with role in cardiovascular risk assessment and additional markers were evaluated at baseline, 1, 6, months 1, 2 and 3 years. Markers of inflammatory syndrome: C-reactive protein serum level (by Immuno- tur-

Table 2. Oxidative stress results

	NSTEMI TMZ n=40	NSTEMI n=42	AI TMZ n=44	AI n=46	AS TMZ n=39	AS n=41
at 1 month						
Anti ox-LDL antibody > 150 UI/l	35%	35.7%	22.7%	23.9%	17.9%	19.5%
Total antioxidant status < 1.3mmol/l	25% p<0.025	50%	25% p<0.025	52.2%	17,9%	19,5%
at 6 months						
Anti ox-LDL antibody>150 UI/l	12.5% p<0.05	33.3%	9.1% p<0.05	26.1%	7.7% p<0.05	24.4%
Total antioxidant status<1.3mmol/l	22.5% p<0,05	47.6%	20.5% p<0,05	43.5%	23.1%	36.6%

Table 3. Inflammatory syndrome results

	NSTEMI TMZ n=40	NSTEMI n=42	AI TMZ n=44	AI n=46	AS TMZ n=39	AS n=41
at 1 month						
Fibrinogen>400mg/dl	57.5%	59,5%	50%	50%	15.4%	17.1%
C-reactive protein>0,5mg/dl	70%	71.4%	54.5%	54.3%	17.9%	19.5%
at 6 months						
Fibrinogen>400mg/dl	22.5% p<0.01	52.4%	22.7% p<0.025	47.8%	20.5%	39.3%
C-reactive protein>0,5mg/dl	25% p<0.025	47.6%	22.7% p<0.025	50%	23.1%	36.6%

Table 4. Left ventricular ejection fraction <40%

	NSTEMI TMZ	NSTEMI	UA TMZ	UA	SA TMZ	SA
Baseline	22.5%	23.8%	20.5%	19.6%	15.4%	17.1%
1 month	22.5%	23.8%	20.5%	19.6%	15.4%	17.1%
6 months	17.5%	28.6%	15.9%	21.7%	15.4%	22%
12 months	15%	33,3%	11.4%	26.1%	12.8%	24.4%
24 months	15% p<0.05	35.7%	9.1% p<0.005	28.3%	10.3%	24.4%
36 months	15% p<0.05	38.1%	11.4% p<0.05	30.4%	10.3%	26.8%

UA-unstable angina; NSTEMI- non ST elevation myocardial infarction; TMZ-trimetazidine

bidimetry), fibrinogen plasma level (Turbidimetric method) and oxidative stress markers: anti ox-LDL antibody serum titers (ELISA technique) and total antioxidant status (ABTS ® Method-RANDOX) serum level were evaluated at baseline, 1 and 6 months.

Statistical Analysis: Comparison between groups was performed using Chi-squared test and multiple regression analysis. A value of $p < 0.05$ was considered statistically significant.

Results

Baseline characteristics of patients were represented by additional markers, old and new factors with role in cardiovascular risk evaluation and optimal standard medical therapy in accordance with ACC/AHA (2006, 2007) guideline update for the management of patients with stable angina, unstable angina /non ST-segment elevation myocardial infarction. It was no significant differences in baseline characteristics between study groups (*Table 1*).

Table 5. Wall motion score index (WMSI) ≥ 1.4

	NSTEMI TMZ	NSTEMI	UA TMZ	UA	SA TMZ	SA
Baseline	77,5%	76.2%	68.2%	69.6%	25.6%	26.8%
6 months	27.5% p<0,05	50%	22.7% p<0,005	50%	28.2%	29.3%
12 months	25% p<0,05	47.6%	15.9% p<0,005	45.7%	15.4% p<0.05	36.6%
24 months	20% p<0,025	45.2%	15.9% p<0,005	43.6%	12.8% p<0.05	39%
36 months	20% p<0,05	42.8%	15.9% p<0,025	39.1%	12.8% p< 0.05	39%

Table 6. Incidence of ST depression more than 0.05 mV on ECG

	NSTEMI TMZ	NSTEMI	UA TMZ	UA	SA TMZ	SA
Baseline	100%	100%	68.2%	71.7%	15.4%	17.1%
1 month	27.5% p<0,05	50%	25% p<0,025	50%	15.4%	17.1%
6 months	22.5% p<0,05	45.2%	18.2% p<0,005	45.7%	12.8%	14.6%
12 months	25% p<0,05	47.6%	15.9% p<0,005	45.7%	15.4%	36.6%
24 months	20% p<0,025	45.2%	15.9% p<0,005	43.5%	12.5%	19.5%
36 months	15% p<0,025	40.5%	11.4% p<0,01	34.8%	10.3%	24.4%

UA-unstable angina; NSTEMI- non ST elevation myocardial infarction; TMZ-trimetazidine

Oxidative stress results

Incidence of high anti ox-LDL antibody serum titers was significantly reduced at 6 months of follow up in NSTEMI and UA TMZ MR added to OSMT groups, only 12.5 % ($p<0.05$) of NSTEMI, 9.1% ($p<0.05$) of UA and 7.7% ($p<0.05$) of SA patients remained with an anti ox-LDL antibody serum titer >150 mU/ml, in comparison with 33.3% of NSTEMI, 26.1% of UA and 24.4% of SA OSMT patients.

Incidence of low total antioxidant status serum level was significantly reduced at 1 month of follow up in NSTEMI and UA TMZ MR added to OSMT groups, only 25% ($p<0.025$) of NSTEMI and 25% ($p<0.01$) of UA patients remained with a total antioxidant status serum level <1.30 mmol/l in comparison with 50% of NSTEMI and 52.2 % of UA OSMT patients. At 6 months of follow up in NSTEMI and UA TMZ MR added to OSMT groups, only 22.5 % ($p<0.025$) of NSTEMI and 20.5% ($p<0.01$) of UA patients remained with a total antioxidant status serum level <1.30 mmol/l significantly lower in comparison with 47.6% of NSTEMI and 43.5 % of UA OSMT patients (*Table 2*).

Inflammatory syndrome results

High plasma values of fibrinogen had significantly reduced incidence at 6 months: 22.5 % ($p<0.001$) in NSTEMI and 22.7% ($p<0.01$) in UA TMZ MR added to OSMT groups, in comparison with 52.4% in NSTEMI and 47.8 % in UA OSMT groups. Incidence of high serum level C-reactive protein (CRP>5 mg/l) was significantly lower at 6 months: 25% ($p<0.05$) in NSTEMI and 22.7% ($p<0.005$) in UA TMZ MR added to OSMT groups, in comparison with 47.6% in NSTEMI and 50 % in UA OSMT groups (*Table 3*).

Echocardiographic results

Left ventricular ejection fraction (2-D Echocardiography, volume/dimension Simp-

son's method) as a measure of global function was significantly improved at 24 and 36 months of follow up in NSTEMI and UA TMZ MR added to OSMT patients, only 15 % ($p<0.05$) of NSTEMI, 9.1 and 11.4% ($p<0.05$) of UA patients remained with an ejection fraction < 40% in comparison with 35.7 and 38.1% of NSTEMI, 28.3 and 30.4 % of UA OSMT patients. In comparison with baseline values, ejection fraction was improved in NSTEMI and UA TMZ MR added to OSMT patients and reduced in NSTEMI and UA OSMT (*Table 4*).

Global wall motion score index (WMSI, by 2-D Echocardiography, semi-quantitative evaluation of regional function assessment) was significantly improved at 6 months in NSTEMI and UA TMZ MR added to OSMT patients, only 25% ($p<0.05$) of NSTEMI and 15.9% ($p<0.005$) of UA patients remained with a global wall motion score index ≥ 1.4 in comparison with 47.6% of NSTEMI and 45.7 % of UA OSMT patients. At 12, 24 and 36 months in all TMZ MR groups regional left ventricular function was significantly improved in comparison with similar OSMT groups: at 12 months only 25% ($p<0.05$) of NSTEMI, 15.9% ($p<0.005$) of UA and 15.4% ($p<0.05$) of SA patients remained with a global wall motion score index (WMSI) ≥ 1.4 in comparison with 47.6% of NSTEMI, 45.7 % of UA and 36.6% of SA OSMT groups; at 24 months only 20% ($p<0.025$) of NSTEMI, 15.9% ($p<0.005$) of UA and 12.8% ($p<0.05$) of SA patients remained with a wall motion score index (WMSI) ≥ 1.4 in comparison with 45.2% of NSTEMI, 43.6 % of UA and 39% of SA OSMT groups; at 36 months only 20% ($p<0.05$) of NSTEMI, 15.9% ($p<0.025$) of UA and 12.8% ($p<0.05$) of SA patients remained with a global wall motion score index (WMSI) ≥ 1.4 in comparison with 45.2% of NSTEMI, 43.6 % of UA and 39% of SA OSMT groups (*Table 5*).

Electrocardiographic results

In NSTEMI and UA TMZ MR added to OSMT groups, incidence of ST depression more than 0.05 mV on ECG were significantly lower at 1, 6, months 1, 2 and 3 years in comparison with similar OSMT groups (*Table 6*).

Discussions

The burden of coronary heart disease demonstrates a great need for fundamental research in cellular myocardial metabolism and molecular mechanisms to evaluate the link between reduction of lipid peroxidation, membrane proteins degradation, inactivation of sodium/potassium ion channels and decrease in reactive oxygen species generation. Ion balance maintenance at cellular level is responsible for normal electric and mechanic cardiac activity. Alterations in potassium ion channel with essential role in electric activity generation, secondary to lipid peroxidation and membrane proteins degradation, are followed by free radicals mediated ion influx, increasing in myocardial cells excitability and arrhythmias. Major clinic expression of cardiac arrhythmias is sudden cardiac death responsible for more than a half of cardiovascular death. It was evaluated the efficacy of therapy on cellular myocardial metabolism, molecular mechanisms, ion channels activity, oxidative stress reduction, inflammatory syndrome reduction, ECG and echocardiography changes recovery [1, 2, 6, 7, 18, 19, 27, 30, 31, 34].

The role of oxidative stress in cardiovascular disease was evaluated by both experimental and clinical studies. In this context the most accepted in atherosclerosis is hypothesis of endothelial dysfunction because of multiple aggression factors. Endothelial dysfunction could be produced by mechanic, viral or bacterial factors (Herpes virus, Cytomegalovirus, *Chlamydia pneumoniae*, *Helicobacter pylori*), toxic exposure (smokers), high level of metabolites (glucose, homocisteine), and turbulent blood flow, all this aggression are followed by atherosclerosis. These atherosclerotic lesions could be aggravated by metabolic stress – hyperglycemia and hypercholesterolemia. Clinic

expression of atherosclerosis at coronary level is ischemic heart disease: stable angina, unstable angina, acute myocardial infarction with or without ST segment elevation. The mediators produced in response to major cardiovascular risk factors including advances glycates end-products (AGEs), LDL and ox-LDL, angiotensin II and cytokines stimulate generation of reactive oxygen species (ROS) at endothelial level by a variety of enzymatic and non-enzymatic sources: ciclo-oxygenase, lipo-oxygenaze, Cyt P450, NAD(P)H oxidase, xantin-oxidase, mitochondrial respiration, uncoupled NO-sintetase and decreased endogenous antioxidant defense superoxid dismutase, catalase, glutation-peroxidase and non-enzymatic - glutathione, α tocopherol, ascorbat. ROS became the second messenger that transmits the signals which modulated gene expression in cardiovascular disease such as adhesion molecules, proliferate genes, cytokines, metalloproteinase. The generation of ROS is a consequence of life in aerobic environment. First target of ROS aggression isn't known, ADN alterations appears before detectable changes in lipid peroxidation and protein oxidative degradation [1-3, 6, 7, 11, 18-22, 27, 30, 31, 36, 37, 39].

Trimetazidine (1-[2,3,4-trimethoxibenzyl] piperazine is a selective inhibitor of mitochondrial long chain 3-ketoacyl-CoA-tiolase oxidation for long chain fatty acids with induced inhibition of pyruvate dehydrogenase, indirect stimulation of glucose oxidation and production of membrane-protective glycolytic ATP. The switch of energetic substrate from fatty acids oxidation to glucose oxidation could explain antianginal effect of trimetazidine. With one molecule of oxygen in glucose oxidation are produced 6.4 ATP molecules in comparison with only 5.6 ATP molecules produced by fatty acids oxidation. Trimetazidine act as a specific partial inhibitor of fatty acid oxidation with indirect increase in glucose metabolism and many cardiac protective mechanisms which include diminished mitochondrial uncoupling, enhanced efficiency of mitochondrial ATP production with maintained contractile function, reduction of intracitoplasmic Ca^{2+} and cardiac function improvement, membranes protection by increasing phospholipids turnover, reduction of proton production, acidosis and apoptosis [1, 10, 16, 17, 24, 28, 40].

In this prospective study on 252 patients with high risk coronary heart disease Trimetazidine modified release added to optimal standard medical therapy demonstrated in unstable angina and non ST elevation myocardial infarction patients an important antioxidant effect by a significantly reduced of high anti ox-LDL antibody serum titers incidence at 6 months and by a significantly increased of total antioxidant status serum level at 1 and 6 months in comparison with optimal standard medical therapy patients.

These results are in concordance with already published data about trimetazidine important role in protecting against ischemia and reperfusion injury: increases antioxidants, limits acidosis, sodium and calcium accumulation, maintains intracellular ATP levels, reduces CK release, preserves mitochondrial functions and inhibits neutrophil infiltration and neutrophil-mediated ROS production [17, 24, 26, 28, 40].

A recent study demonstrated efficiency of trimetazidine in reducing of oxidative stress in cardiac surgery - elective coronary artery bypass grafting (CABG)- using other markers: 2 weeks of pre-surgery TMZ treatment were followed by significant increased superoxide dismutase and glutathione peroxidase serum level, and significant reduced malondialdehyde in comparison with control group, without TMZ treatment [23].

Trimetazidine therapy have many cardioprotective effects on energy metabolism, anti-ischemic effect at cellular level, hydroionic balance, coronary microcirculation, potential anti-inflammatory process, oxidative stress and reduced apoptosis, increase in glucose metabolism witch may explain the results of

this clinical study. Results on direct effect of trimetazidine on decrease activation of myocardial uncoupling protein by depressed fatty acid oxidation are still expected [12, 14, 24, 26].

In already published data and in actual study trimetazidine demonstrated anti-inflammatory effects in terms of C reactive protein serum level reduction: in patients treated with trimetazidine modified release added to optimal standard medical therapy in comparison with optimal standard medical therapy patients the incidence of high serum level C-reactive protein and high plasma values of fibrinogen was significantly reduced at 6 months in unstable angina and non ST elevation myocardial infarction [12, 25, 33, 35, 38].

Comparable results were obtained with a significant increase in C-reactive protein serum level in patients with ischemic dilated cardiomyopathy receiving usual medication compared with trimetazidine added to their usual treatment patients at 12 and 18 months [12].

Other recent study demonstrates a significant reduction of plasma C-reactive protein level in the course of acute myocardial infarction treated with streptokinase and intravenous trimetazidine infusion compared with the group of patients without trimetazidine treatment [33].

In an interventional study published in 2006, treatment with oral TMZ for three days before coronary angioplasty significantly suppressed the elevation of inflammatory markers after PTCA, TMZ preventing inflammatory cardiovascular events after PTCA: in the TMZ group, CRP and nitrite levels were significantly lower than in the control group at each time point of the pre- and post-angioplasty periods [25].

In actual study, left ventricular ejection fraction was significantly improved at 24 months and wall motion score index at 6, 12 and 24 months in unstable angina and non ST elevation myocardial infarction patients treated with trimetazidine modified release added to optimal standard medical therapy in comparison with optimal standard medical therapy patients.

At 12 and 24 months wall motion score index was significantly improved also in stable angina patients treated with trimetazidine modified release added to optimal standard medical therapy in comparison with optimal standard medical therapy stable angina patients.

Comparable results were published regarding significantly improved of left ventricular function and wall motion score index at 6 months of trimetazidine treatment in addition to optimal medical therapy in 47 elderly patients with chronic stable angina [38].

In recent studies treatment with trimetazidine added to the usual treatment for up to 18 months was well tolerated and induced functional improvement in patients with ischemic dilated cardiomyopathy. Trimetazidine treatment was associated with a significant improvement of LV function and the remodeling process at 12 and 18 months. The effects of trimetazidine on energy metabolism, hydroionic balance, coronary microcirculation, and oxidative stress contribute positively to its beneficial effects on LV remodeling and long term cardioprotection observed in these studies [8, 9, 12, 29].

In patients with ischemic cardiomyopathy trimetazidine ameliorated myocardial function without hemodynamic changes with significant improvement in left ventricular ejection fraction and wall motion score index [8,13].

Incidence of ST depression were significantly lower at 1, 6, 12 and 24 months in unstable angina and non ST elevation myocardial infarction patients treated with trimetazidine modified release added to optimal standard medical therapy in comparison with optimal standard medical therapy patients.

Similar trimetazidine benefits on ECG evolution were documented in the acute phase of myocardial ischemia induced by balloon inflation during angioplasty, in terms of decreased ECG changes during and after the procedure [32].

In concordance with our ECG results were results in Trimetazidine in Angina Combi-

nation Therapy (TACT) study: time to 1 mm ST depression during exercise test in patients with stable angina at 3 months of follow up was significantly increased in trimetazidine group versus placebo group [9].

Conclusions

Selective inhibition of long chain 3-ketoacyl-Coenzyme-A-thiolase by Trimetazidine MR was followed by a significant reduction in inflammatory syndromes and oxidative stress at 6 months in patients with unstable angina and non ST elevation myocardial infarction. These results were in concordance with significant reduction in incidence of ST depression and significant improvement of echocardiographic measured left ventricular function at 3 years of follow up in mentioned groups of patients. Global wall motion score index at 1, 2 and 3 years was significantly improved in all trimetazidine treated groups.

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