IMPROVING HEPATOCYTE BIOMARKERS VALUES WITH CONTINUOUS ENERGO-METABOLIC THERAPY IN POST MYOCARDIAL INFARCTION PATIENTS TREATED WITH STATINS

ELENA DINU[1], ADRIAN TASE[2]

[1,2]*University of Piteşti, County Emergency Hospital Piteşti*

Keywords: *hepatocyte biomarkers, energo-metabolic agent, post myocardial infarction*

Abstract: *Background. Current guidelines recommend statins post myocardial infarction (MI). The energo-metabolic agent trimetazidine is prescribed in this setting according to the physicians' decision related to co-morbidities, taking into consideration its proven beneficial effects in angina and heart failure. Goal. To test the hypothesis that continuous energo-metabolic therapy (CEMT) with trimetazidine could improve aminotransferase values in post-MI pts treated with high-dose statin. Method. We analysed retrospectively 01/01/08-31/12/12 a number of 1008 pts > 18 yrs old, newly diagnosed with ST elevation MI (relevant ECG + biomarkers) who underwent statin therapy in high dosages (atorvastatin 80 mg or rosuvastatin 40 mg). We selected 874 = 288 x 3 = 288 CEMT + 576 non-CEMT pts who remained on these dosages at least 12 months. The aminotransferase assessment was performed at 3, 6, 12 and 24 months. Results. After propensity matching (1:2), the 288 pts receiving CEMT were combined with 576 controls. The number of aminotransferase elevations was considerably lower in pts receiving CEMT than in controls. Conclusion. According to our results, CEMT could act quite similarly in hepatocyte as in myocardial cell, at mithochondrial level. However, a well organized study on this topic is warranted.*

Cuvinte cheie: *biomarkeri hepatocitari, agent energo-metabolic, post infarct miocardic*

Rezumat: *Introducere. Ghidurile curente recomandă statine post infarct miocardic (IM). Agentul energo-metabolic trimetazidină este prescris în această situaţie potrivit deciziei medicilor corelate cu comorbidităţile, luând în considerare efectele benefice dovedite în angină şi insuficienţă cardiacă. Scop. Testarea ipotezei potrivit căreia terapia continuă energo-metabolică (TCEM) cu trimetazidină poate ameliora valorile aminotransferazelor la pts post-MI trataţi cu doze mari de statină. Metodă. Am analizat retrospectiv 01/01/08-31/12/12 un număr de 1008 pts > 18 ani, nou diagnosticaţi cu IM acut cu supradenivelare de segment ST (ECG relevant + biomarkeri) care au primit terapie cu statină în doze mari (atorvastatină 80 mg sau rosuvastatină 40 mg). Am selecţionat 874 = 288 x 3 = 288 pts TCEM + 576 pts non-TCEM care au rămas pe aceste doze cel puţin 12 luni. Evaluarea aminotransferazelor s-a efectuat la 3, 6, 12 şi 24 luni. Rezultate. După echivalarea propensităţilor (1:2), cei 288 pts care primeau TCEM au fost combinaţi cu 576 martori. Numărul creşterilor nivelurilor aminotransferazelor a fost considerabil mai mic la pts care primeau TCEM versus martori. Concluzii. Potrivit rezultatelor noastre, TCEM poate acţiona oarecum similar în hepatocit cu celula miocardică, la nivel mitocondrial. Totuşi, un studiu bine organizat pe această temă este justificat.*

INTRODUCTION

The large statin trials show beyond doubt that total mortality is reduced in secondary prevention and that the number of patients (pts) needed to treat to prevent any given major endpoint make their use cost-effective (treating 1000 pts with a high dose statin would prevent 37 cardiovascular events).(1) The statins are the most effective and best tolerated agents for treating dyslipidemia. These drugs are competitive inhibitors of HMG-CoA reductase, which catalyzes an early, rate-limiting step in cholesterol biosynthesis. Higher doses of the most potent statins (atorvastatin and rosuvastatin) also can reduce triglyceride levels caused by elevated VLDL levels and, most importantly, stabilize vulnerable or ruptured plaque. The vulnerability of plaques to rupture and thrombosis is of greater clinical relevance than the degree of stenosis they cause. Statins affect stability of plaques in a variety of ways. They inhibit monocyte infiltration into the artery wall and inhibit macrophage secretion of matrix metalloproteinases in vitro. The metalloproteinases degrade extracellular matrix components and thus weaken the fibrous cap of atherosclerotic plaques.(2)

That is why they are administered on a large scale post-MI in adequate dosages. Current guidelines recommend HMG-CoA-reductase inhibitors (statins) in ST elevation MI therapy. On the other side of the coin, there are reported adverse events with statins focused on liver and expressed not necessarily by symptoms, but rather by higher aminotransferases values. The energo-metabolic agent trimetazidine is prescribed in this setting according to physicians' decision, taking into consideration its proven beneficial effects in angina and heart failure.

PURPOSE

The aim of this study was to test the hypothesis that continuous energo-metabolic therapy (CEMT) with trimetazidine would improve hepatocyte energetic metabolism, as it does in myocardial cell and, subsequently normalize

[1]Corresponding author: Elena Dinu, Str. Băilor, Nr. 4, Bl. D13, Sc. A, Et. 1, Ap. 7, Piteşti, Judeţul Argeş, România, E-mail: elen_dinu@yahoo.com
Article received on 07.01.2014 and accepted for publication on 10.04.2014
ACTA MEDICA TRANSILVANICA June 2014;2(2):245-246

aminotransferase values in this type of pts. Trimetazidine is a metabolic agent that has no haemodynamic effects. It has been shown to preserve energy balance and prevent disturbance of ion haemostasis during ischaemia. Its specific mechanism of action is unknown, but its anti-anginal effects are attributed to modulatory effects on intracellular calcium. Trimetazidine also stimulates glucose oxydation and acts as a partial fatty acid oxydation inhibitor.(3)

METHODS

We analyzed retrospectively 01/01/08-31/12/12 a number of 1008 pts admitted in our clinic, > 18 yrs. old, both genders, newly diagnosed with ST elevation MI by pain, relevant changes on the ECG, biomarkers. These pts underwent statin therapy in high dosages (atorvastatin 80 mg or rosuvastatin 40 mg, both originals) from the onset of MI symptoms, at least 12 months. Within this larger group, we selected 874 pts: 288 with CEMT considered as study group, and 576 without CEMT, taken as controls. Liver damage is revealed by liver enzyme elevation. The aminotransferases (transaminases) are sensitive indicators of liver cell injury. Aspartate aminotransferase (AST) is found in the liver, cardiac muscle, skeletal muscle, kidneys, brain, pancreas, lungs, leukocytes, and erythrocytes in decreasing order of concentration. Alanine aminotransferase (ALT) is found primarily in the liver.

These tests can be used for several reasons, as follow the response to potential adverse treatment. A typical battery of blood tests used for initial assessment of liver disease includes measuring levels of serum ALT and, respectively, AST, especially the first one, alkaline phosphatase, direct and total serum bilirubin, and albumin and assessing prothrombin time.

The pattern of abnormalities generally points to hepatocellular versus cholestatic liver disease.(4)

The liver carries out thousands of biochemical functions, and laboratory tests measure only a limited number of these functions. In fact, aminotransferases do not measure liver function at all, but they detect liver cell damage. To increase both the sensitivity and the specificity of laboratory tests in the detection of liver dysfunction, it is better to use both aminotransferases. The gauge of hepatocellular function by aminotransferases was performed initially, at 3, 6, 12 and 24 months with a Konelab Prihe 60 device and Clinilab reactives. The reference ranges for hepatocyte biomarkers are as follows: ALT = 0-40 UI/L, AST = 0-37 UI/L. Significant values were considered > three times superior range limit (ALT x3 > 120; AST x3 > 111) and > five times superior range limit (ALT x5 > 200; AST x5 > 185).

Concerning the hepatotoxicity, initial post-marketing surveillance studies of the statins revealed an elevation in hepatic transaminase to values greater than three times the upper limit of normal, with a dose related incidence. However, in the placebo-controlled outcome trials in which 10 to 40 mg doses of six various statins were used, the incidence of 3-fold elevations in hepatic transaminases was 1-3% in the active drug treatment group and 1,1% in placebo. No causes of liver failure occurred in these trials. It is therefore reasonable to measure aminotransferases, especially ALT at baseline and thereafter when clinically indicated. Echocardiography and abdominal echography were performed initially, at 6, 12 and 24 months by experienced professionals.

RESULTS

After propensity matching (1:2), the 288 pts receiving CEMT were combined with 576 controls. The main results are displayed in the following table. We mention that initially, in all these pts, aminotransferases values were in normal range.

Table no. 1. Results of control and study groups at 3, 6, 12, 24 months

	3 months		6 months		12 months		24 months	
	study	**control**	**study**	**control**	**study**	**control**	**study**	**control**
ALT pts > x3	4,17 %	4,84 %	2,43 %	5,21 %	1,74 %	4,17 %	0,70 %	1,74 %
ALT pts > x5	0,35 %	1,74 %	0,00 %	1,74 %	0,00 %	0,35 %	0,00 %	0,00 %
AST pts > x3	3,82 %	4,17 %	2,43 %	4,51 %	1,74 %	4,84 %	0,70 %	1,39 %
AST pts > x5	0,00 %	1,39 %	0,00 %	0,70 %	0,00 %	0,35 %	0,00 %	0,35 %

Our outcomes are a bit higher than those in the literature. This is partly due to particular reactivity of our study population. On the other side, in a large number of clinical trials, the statin dosages are lower than atorvastatin 80 mg or rosuvastatin 40 mg. We have to mention that all our pts received original products. The duration of biomarkers abnormalities was in all cases < 6 months, so there is no chronic hepatic dysfunction in our pts. Another mention is that, after 12 months, in a number of pts with normal aminotransferases values, the statin dosage was reduced by other physicians. The left ventricular ejection fraction improved in CEMT group, but this result is beyond our present scope and will be developed in other paper. The first abdominal echocardiography revealed 0,70% non-alcohol hepatic steatosis in both groups. The next echo examinations did not find either any evolution of these cases, or new cases. There are two limits: the relative small number of pts. and the retrospective approach.

CONCLUSIONS

Metabolic and hepatic dysfunctions are quite frequently associated in clinical practice. In pts with suspected liver dysfunction, an appropriate approach to evaluation is initial testing for routine liver tests focused on ALT and AST. In our study, CEMT was associated with lower risk for hepatocyte adverse events after high dose statins. The beneficial outcome of trimetazidine could be interpreted by a hepato-cellular energo-metabolic effect similar with myocardial setting, at mitochondrial level. We consider that there is a necessity of well organized clinical studies with respect to statin associated adverse events.

REFERENCES

1. Opie LH, Gersh BJ. Drugs for the heart, 7th edition, Saunders Elsevier; 2009. p. 341-372.
2. Brunton L et al. Goodman &Gilman's The Pharmacological Basis of Therapeutics, 12th edition, McGraw Hill; 2011. p. 892-896.
3. Camm J et al. The ESC Textbook of Cardiovascular Medicine, second edition, Oxford University Press; 2009. p. 643.
4. Tase A. Farmacologie esenţială, Editura Universităţii din Piteşti, 2011, ISBN: 978-606-560-205-2, www.upit.ro.