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Original Article

Effects of sustained-release trimetazidine on chronically dysfunctional myocardium of ischemic dilated cardiomyopathy – Six months follow-up result



A. Momen^{a,*}, M. Ali^b, P.K. Karmakar^c, M.Z. Ali^c, A. Haque^c, M.R. Khan^c, M.I. Khalil^c, M.S. Hossain^c, R.M. Huda^c, M.N. Goni^c

^a National Institute of Cardiovascular Diseases (NICVD), Dhaka, Bangladesh

^b Professor and Head, Department of Cardiology, National Institute of Cardiovascular Diseases (NICVD), Dhaka, Bangladesh

^c Assistant Professor, Cardiology, National Institute of Cardiovascular Diseases (NICVD), Dhaka, Bangladesh

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ABSTRACT

Background: Ischemic cardiomyopathy is a growing burden in third world countries. So far, benefits of trimetazidine in this group of patients have been suggested by clinical trials mainly conducted in Europe. We evaluated the effect of trimetazidine on ischemic dilated cardiomyopathy in our population.

Methods and results: 98 patients (aged 58.5 ± 9.2 years), admitted with decompensated heart failure with previous history of MI and/or documentation of significant CAD with previous CAG, were chosen for the study. Patients were randomized into two groups – one provided with trimetazidine 35 mg sustained released tablet, twice daily and the other with a placebo, along with other conventional medications. Patients were included if they had dilated LV (LVIDd > 57 mm) and left ventricular ejection fraction (LVEF) $\leq 40\%$. After 6 months, significantly higher number of patients in trimetazidine group were in NYHA class I (22% vs. 8%, $p = 0.03$) and class II (56% vs. 34%, $p = 0.01$); higher number of patients in placebo group were in NYHA class III class IV. Anginal episodes and use of sublingual nitrate per week were significantly lower in the trimetazidine group. Left ventricular diastolic dimension (59.7 ± 5.2 vs. 65.1 ± 6.1 , $p = 0.001$) was significantly different in the two groups as was the increase of LVEF (11% vs. 5.6%, $p = 0.001$). Hospitalization for worsening heart failure was significantly lower in trimetazidine group (13 vs. 22, $p = 0.047$).

Conclusion: Trimetazidine seems to be beneficial in patients with ischemic dilated cardiomyopathy in South Asian population and larger scale study with extended follow-up is needed.

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* Corresponding author.

E-mail address: abdulmomen71@yahoo.com (A. Momen).

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1. Introduction

Although there are considerable advances in therapeutics, heart failure remains a leading cause of mortality and morbidity in developed¹ and increasingly in developing countries.² It has a high fatality rate, with 5 years mortality in more than 50% cases, which exceeds that of many cancers.³ The prognosis worsens with advancement of heart failure and the mortality of patients with New York Heart Association (NYHA) class IV is as high as 50% per year.⁴

Trimetazidine (TMZ) (2,3,4-trimethoxybenzyl-piperazine dihydrochloride) has been reported to exert antiischemic properties without affecting myocardial oxygen consumption and blood supply.⁵ Additional studies have shown that TMZ may also be beneficial in patients with heart failure, in terms of LV function preservation and symptoms control.⁶⁻¹⁰ It is a metabolic modulator that is so far known to inhibit a key enzyme in fatty acid oxidation – the mitochondrial long-chain 3-ketoacyl coenzyme A thiolase – and shifts cellular energy substrate reference from fatty acids to glucose oxidation.¹¹ A shift toward glucose oxidation is likely to benefit hypoperfused myocardium, because the number of moles of ATP produced per mole of oxygen consumed is approximately 12% higher for glucose than of fatty acids. As a result, both left ventricular systolic function and diastolic filling are improved in patients with ischemic and diabetic cardiomyopathy and idiopathic dilated cardiomyopathy.^{6,8,12} The beneficial effect of this agent has also been attributed to preservation of the phosphocreatine (PCr) and adenosine triphosphate (ATP) intracellular levels¹³ and reduction of cell acidosis,^{14,15} calcium overload,¹⁵ and free-radical-induced injury caused by ischemia.¹⁶ It also improves endothelial dysfunction directly by decreasing nitric oxide inactivation through decreased production of lipid peroxidation,¹⁷⁻¹⁹ and indirectly through enhanced LV function.^{12,20,9} Recently TMZ was also shown to improve radial artery endothelium-dependent relaxation in chronic heart failure.¹⁸ This effect is correlated with decreased plasma levels of lipid-free radicals, suggesting an antioxidant action.

So far, many short- and long-term studies revealed several benefits of TMZ in ischemic cardiomyopathy patients, including symptomatic relief, improvement of clinical status, reduction of ventricular volume and improvement of LV systolic and diastolic function, anti-inflammatory action producing low CRP level, and antioxidant action resulting in improvement of endothelial dysfunction. The purpose of our study was to evaluate the effects of TMZ in the Bangladeshi patients' population with ischemic dilated cardiomyopathy.

2. Methods and enrolment of patients

Patients admitted in the National Institute of Cardiovascular Diseases with decompensated heart failure were enrolled for the study. Among them, those who had previous history of acute myocardial infarction, revealed from history and previous documentation, were considered for the study. Patients having a history of previous coronary angiogram (CAG) with documented significant coronary artery disease

Table 1 – Inclusion and exclusion criteria.

Inclusion criteria

1. Patients admitted with decompensated heart failure later stabilized
2. With previous history of acute myocardial infarction and/or documented coronary artery disease on previous CAG
3. Not planned for revascularization
4. Dilated LV (LVIDd > 57 mm) and LVEF ≤ 40%

Exclusion criteria

1. Idiopathic dilated cardiomyopathy
2. Without documentation of myocardial infarction or coronary significant lesion in CAG
3. Valvular cardiomyopathy
4. Patients with renal impairment,
5. COPD
6. Severe comorbid condition

with or without coronary revascularization were also enrolled in this study. Patients planned for revascularization were excluded. Informed written consent was obtained before enrolment. A total 120 patients were screened and finally 102 patients fulfilled the inclusion and exclusion criteria. Of them, the ischemic nature of cardiomyopathy was demonstrated by CAG with significant stenosis of at least one major coronary artery in only 25 patients and the rest were diagnosed by history and previous documentation of acute myocardial infarction. After initial stabilization in the hospital, they were kept under observation at home for 1 month for further stabilization, and during that period at home, 4 patients developed worsening symptoms and were readmitted and were excluded from the study. Finally, 98 patients were enrolled in the study. Baseline examination and investigations were performed. Enrolled patients should have dilated LV (LVIDd > 57 mm) and LVEF ≤ 40%. Patients with dilated cardiomyopathy without documentation of myocardial infarction or coronary significant lesion in CAG were excluded. Patients with valvular cardiomyopathy, renal impairment, COPD, and other severe comorbid conditions were excluded from the study (Table 1).

2.1. Study design

The study design was double blinded, randomized, parallel, placebo-controlled. After a baseline evaluation of all inclusion and exclusion criteria, patients entered a run-in phase up to 4 weeks, at the end of which patients underwent a baseline echocardiogram and were then randomized to receive either TMZ (35 mg sustained-release preparation b.i.d.) or matching placebo (b.i.d.) for 6 months. The transthoracic echocardiogram was repeated at the end of the treatment period. Patients received a diary card to document the occurrence of episodes of chest pain and use of nitroglycerin spray.

2.2. Study of left ventricular function

All patients underwent transthoracic echocardiogram following the guidelines of the American Society of Echocardiography, using the parasternal and the apical views to calculate dimensions and evaluate global and regional left ventricular function.

2.3. Image analysis

All echocardiograms were performed using an Acuson Sequoia 512 echocardiograph (Acuson Corporation, Mountain View, CA, USA) and stored on videotape or onto electronic files. The echocardiograms were analyzed by two experienced investigators blinded on clinical data. Left ventricular end-diastolic and end-systolic diameters were obtained from the parasternal long-axis view. A biplane algorithm was used to calculate left ventricular volumes. Left ventricular end-diastolic volume and end-systolic volumes were obtained from the apical four- and two-chamber views using a modified Simpson's rule, from which ejection fraction was automatically calculated.

2.4. Statistical analysis

Values are given as mean \pm 1 SD or as percentages where appropriate. Differences in mean values between groups were assessed using the two-tailed Student's *t*-test. Categorical variables were analyzed in chi-square test. Proportion was

analyzed by *z*-test. All calculated *p* value are 2-tailed and considered as significant when <0.05 .

3. Results

A total 98 patients with heart failure after stabilization were included in the study. The mean age of the study patients was 58.5 ± 9.2 years and 22% patients were female. Baseline characteristics were almost similar in two groups with no statistical significance (Table 2). 69% of the patients were smokers and 28% patients had history of schematic heart disease in first-degree relatives. 44% of the patients were diabetics. 97% of the patients had previous history of myocardial infarction and 26% patients had CAG done previously. 15% of the patients had history of previous PCI and 9% of the patients had a post-CABG status in two groups.

There was no statistically significant difference in CCS angina class and NYHA heart failure class in two groups. Most of the patients in both groups were in CCS anginal class II (60%

Table 2 – Baseline characteristics of the two groups.

Characteristics	Trimetazidine group (n = 55)		Placebo group (n = 53)		p value
Age, years (mean \pm SD)	58 \pm 9.5		59 \pm 8.9		0.955 ^{ns}
Male, no (%)	45	82	41	77	0.565 ^{ns}
Female, no (%)	10	18	12	23	
Smoking, no (%)	35	64	33	62	0.882 ^{ns}
Family history of IHD, no (%)	12	22	15	28	0.437 ^{ns}
Diabetes, no (%)	26	47	27	51	0.703 ^{ns}
SBP, mmHg (mean \pm SD)	110 \pm 5.6		112 \pm 6.0		0.072 ^{ns}
DBP, mmHg (mean \pm SD)	70 \pm 5.5		68 \pm 5.5		0.067 ^{ns}
Previous history of MI, no (%)	48	87	47	89	0.822 ^{ns}
Previous CAG, no (%)	15	27	10	19	0.301 ^{ns}
Prior PCI, no (%)	8	15	7	13	0.841 ^{ns}
Prior CABG, no (%)	5	9	4	8	0.524 ^{ns}
Angina: Canadian class, no (%)					
0	0	0	0	0	0.701 ^{ns}
I	11	20	10	19	
II	33	60	28	53	
III	12	22	15	28	
IV	0	0	0	0	
Heart failure: NYHA class, no (%)					
0	0	0	0	0.0	0.881 ^{ns}
I	3	6	2	4	
II	12	22	13	25	
III	40	73	38	72	
IV					
Medications					
Aspirin	55	100	53	100	–
Clopidogrel	45	82	43	81	0.926 ^{ns}
Beta blocker	42	76	43	81	0.545 ^{ns}
ACEI	45	82	44	83	0.869 ^{ns}
ARB	2	4	3	6	0.482 ^{ns}
Nitrates	34	62	35	66	0.304 ^{ns}
Frusemide	49	89	48	91	0.799 ^{ns}
Digoxin	49	89	48	91	0.799 ^{ns}
Spironolactone	28	51	28	53	0.842 ^{ns}
Serum creatinine, mg% (mean \pm SD)	1.1 \pm 0.9		1.2 \pm 0.4		0.853 ^{ns}
LVIDd, mm (mean \pm SD)	62.6 \pm 5.5		63.6 \pm 5.5		0.348 ^{ns}
LVEF, % (mean \pm SD)	32.9 \pm 6.6		33.1 \pm 6.2		0.687 ^{ns}

ns, non-significant.

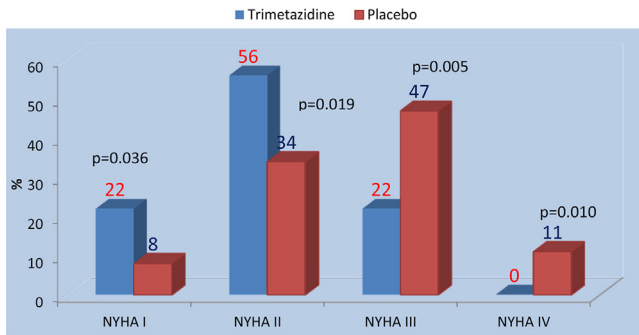


Fig. 1 – Heart failure NYHA class at 6 months in two groups.

vs. 53%, $p = 0.701$) and NYHA heart failure class III (73% vs. 72%, $p = 0.881$). None of the patients were in NYHA class IV. Baseline medications and renal function were comparable in two groups. LV dimension in diastole was enlarged (62.6 ± 5.5 vs. 63.6 ± 5.5 , $p = 0.348$) and LVEF was moderate to severely impaired in both groups (32.9 ± 6.6 vs. 33.1 ± 6.2 , $p = 0.687$) but was comparable in two groups.

At 6 months, statistically significant difference was found in NYHA heart failure class in two groups (Fig. 1). 22% of the patients in TMZ group vs. 8% of the patients in placebo group were in NYHA class I ($p = 0.036$) and there was 300% increase in number of patients in this class in TMZ group from baseline. 56% of the patients in TMZ group and 34% of the patients in placebo group were in NYHA class II ($p = 0.019$) and the increase in the percentage of patients in this class was 153% vs. 39%. Patients in NYHA class III were 22% vs. 47% ($p = 0.005$) and the reduction of patients in this class was 70% vs. 34%. 11% of the patients in placebo group were in NYHA class IV at 6 months (0% vs. 11%, $p = 0.010$).

Statistically significant improvement of angina class was observed in TMZ group (Fig. 2). 51% of the patients in TMZ group and 23% of placebo group were in the CCS class I at 6 months ($p = 0.002$). Patients in CCS class III were 16% vs. 33%, respectively ($p = 0.012$).

Anginal episode per week was significantly decreased in TMZ group (4.5 ± 1 vs. 8.0 ± 1 , $p = 0.001$) (Fig. 3). There was 38% decrease in angina episode in TMZ group and 7% increase in placebo group from baseline. Similarly, use of sublingual nitrate per week was significantly reduced in TMZ group (3.5 ± 1 vs. 7.2 ± 1 , $p = 0.001$) (Fig. 3). This corresponded to the

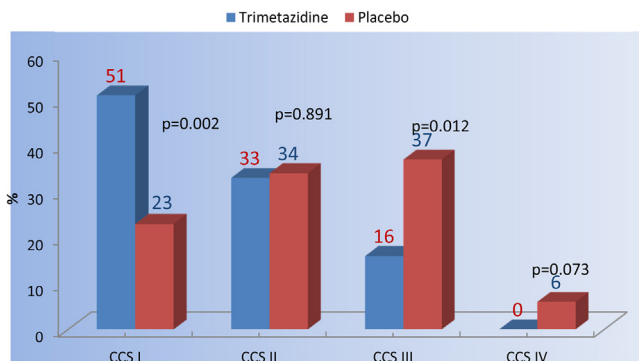


Fig. 2 – Anginal CCS class at 6 months in trimetazidine and placebo groups.

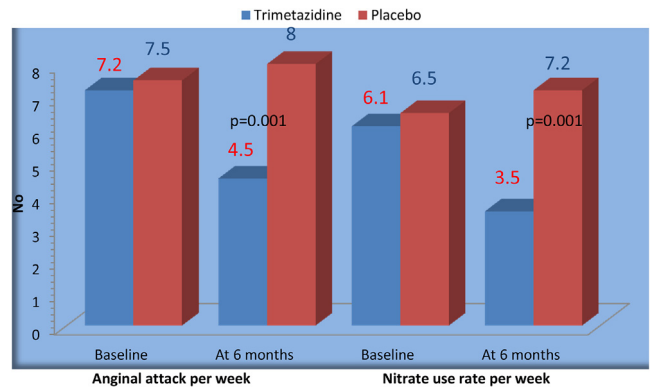


Fig. 3 – Anginal attack and nitrate use rate per week at baseline and at 6 months.

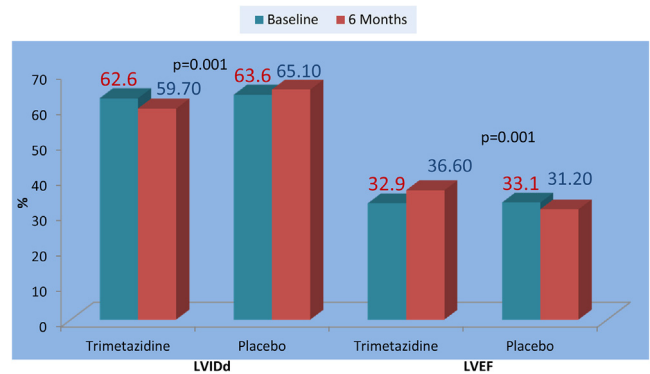


Fig. 4 – Left ventricular internal diameter in diastole and left ventricular ejection fraction in trimetazidine and placebo group at baseline and 6 months.

43% decrease in nitrate use per week in TMZ group and 11% increase in placebo group from baseline.

LV dimension was significantly decreased in TMZ group (59.7 ± 5.2 vs. 65.1 ± 6.1 , $p = 0.001$) (Fig. 4). There was 5% decrease in LVIDd in TMZ group and 2% increase in placebo group. Left ventricular ejection fraction (LVEF) was also significantly better in this group in contrast to placebo group (36.6 ± 5.5 vs. 31.2 ± 6.4 , $p = 0.001$) (Fig. 4). There was 11% increase of LVEF from baseline in TMZ group and in contrast there was 5.7% decrease in placebo group (Fig. 5). An

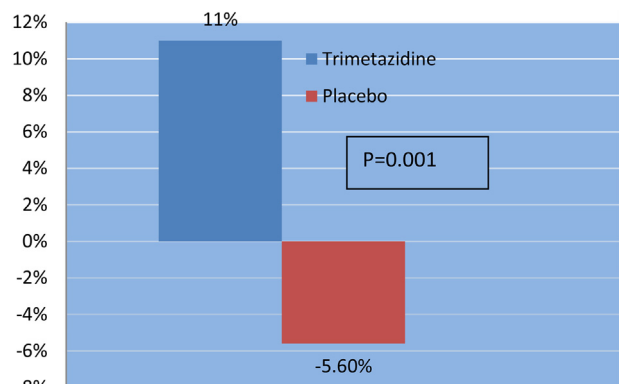


Fig. 5 – LVEF after 6 months in two groups.

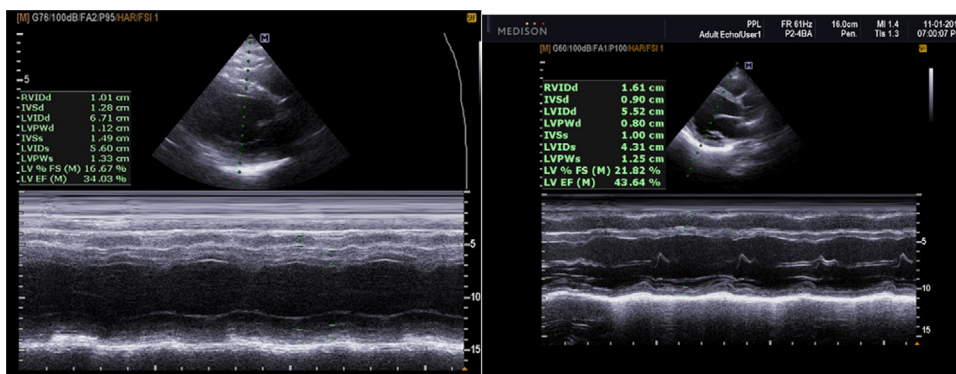


Fig. 6 – Echocardiographic changes of LV dimensions and functions of study patients at baseline and after 6 months of trimetazidine over standard therapy.

echocardiographic follow-up was shown in Fig. 6. Hospitalization rate for worsening heart failure was also significantly low in TMZ group in the 6-months period (13 vs. 22, $p = 0.047$).

4. Discussion

The present study shows that the addition of TMZ to standard therapy for heart failure improves patients' symptoms, including both NYHA class and CCS class, decreases anginal attacks per week, decreases sublingual nitrate use per week, and improves left ventricular dimension and systolic function in chronically dysfunctional myocardium in patients with ischemic cardiomyopathy with depressed left ventricular function.

The functional and echocardiographic data obtained in this study confirm previous short-term or middle-term studies. In a different randomized trial, TMZ was reported to demonstrate a significant benefit of improvement of heart failure functional class,¹⁰ left ventricular end-diastolic volume,²¹ wall thickness score index,¹² wall motion score index at rest,⁷ peak oxygen volume,¹² and the inflammatory process assessed by plasma level of C-reactive protein.^{10,22}

In a long-term (24 months) study²³ of evaluation of effect of TMZ on similar 200 patients of ischemic cardiomyopathy, there was a significant decrease in the frequency of anginal episodes per week (3.9 vs. 5.7, $p < 0.01$), lower weekly sublingual nitroglycerin (glyceryl trinitrate) tablet consumption (2.3 ± 0.8 vs. 6.1 ± 1.6 , $p < 0.01$) in TMZ than with placebo. This was supported by perfusion SPECT data. Compared with baseline values, summed stress score and rest score were significantly reduced with TMZ (from 19.8 ± 7.7 to 11.2 ± 6.1 , $p < 0.00001$ and from 12.4 ± 8.7 to 5.8 ± 3.3 , $p < 0.00001$, respectively) with a nonsignificant decrease from baseline values in placebo group. The gated SPECT showed an increase in systolic wall thickness score of 89.5% ($p < 0.00001$) and in ejection fraction of 23% with TMZ ($p < 0.001$) without significant changes in hemodynamic parameters. The most interesting finding of this study was a reduction of 30% mortality in the TMZ group (92% vs. 62%, $p < 0.0001$). This study was not powered to evaluate the mortality benefit and further large,

randomized, placebo-controlled studies are required to establish the effect.

In a single-center, open-label, randomized trial²² post hoc analysis with TMZ in chronic heart failure, 61 patients were randomized to either receive TMZ (20 mg t.i.d.) in addition to their conventional treatment or to continue their usual drug therapy for 4 years. Patients were evaluated at baseline and at 6, 12, 18, 24, 32, 36, 42, and 48 months with clinical examination, echocardiography, and 6-min walking test. TMZ added to usual treatment significantly reduced all-cause mortality (–56%; hazard ratio, 0.258; 95% CI, 0.097–0.687; log-rank test, $p = 0.0047$), heart failure hospitalization (–47%; log-rank test, $p = 0.002$), and improved patient functional status (NYHA class and 6-min walking test). In TMZ-treated patients, a significant increase of the left ventricle ejection fraction was also detected (LVEF, $p < 0.001$ at 48 months). The results were obtained from a post hoc extension and analysis in an open-label, nonplacebo-controlled study. The low number of deaths does not allow firm statements on the impact on mortality but generates a hypotheses to be confirmed in a multicenter, randomized, placebo-controlled trial. Hospitalization rate was also significantly decreased in the TMZ group in the current study (13 vs. 20, $p = 0.047$). Survival benefit was also observed in a different group of population of chronic stable angina in METRO trial²⁴ where inclusion of TMZ in the antianginal treatment of stable angina was independently associated with a significant reduction of mortality after surviving a myocardial infarction; odds ratio 0.36 (0.15–0.86; $p = 0.022$).

The functional and echocardiographic data obtained in this study confirm previous short-term or middle-term studies: improvement of LVEF was found in other studies: 5.4%,²⁵ 9%,¹⁰ 15%,²⁶ and 19.7%.¹² Brottier et al.²⁷ evidenced an improvement of LVEF and cardiac volumes in patients with severe ischemic cardiomyopathy after a 6-month treatment with TMZ; Fragasso et al.²⁸ and Rosano et al.²⁰ reported a relevant improvement of clinical status and EF after 6-month TMZ treatment in diabetic subjects with ischemic cardiomyopathy.

Almost similar benefit was also found in our study and the increase in LVEF was 11%. Follow-up for only 6 months and assessment of LVEF by transthoracic echocardiography, differences in patient characteristics, and particularly the

high prevalence of diabetic patients (about 54%) in our study may be responsible for a lower but significant increase of LVEF. Rosano et al.²⁵ reported in diabetic ischemic cardiomyopathy patients an increase of LVEF by $5.4 \pm 0.5\%$ ($p < 0.05$) in the TMZ group, while it remained unchanged in the placebo group $-2.4 \pm 1.1\%$ (ns), $p < 0.01$ between groups and improvement in LV diastolic function was also found.

In a randomized study¹² with 38 patients with postnecrotic left ventricular dysfunction (ejection fraction: $33 \pm 5\%$) and multivessel coronary artery disease, 2 months treatment with TMZ had significant improvements in the rest and peak systolic wall thickening score index (13% and 20.7%, $p < 0.001$) and ejection fraction (19.7% and 14.1%, $p < 0.001$) without concomitant changes in heart rate and blood pressure. Peak VO₂ was also significantly increased in patients taking TMZ (15%, $p = 0.001$ vs. controls).

In another study,¹⁰ 61 patients of ischemic cardiomyopathy were followed up for 18 months with a significant improvement of LVEF and there was limited inflammatory response in patients treated with TMZ, as C-reactive protein plasma concentrations remained stable throughout the study in contrast to placebo. Similar results were also found at 4 years follow-up where, CRP plasma levels remained stable while its level was significantly increased with time in patients receiving standard therapy.²²

In a recent trial,²⁹ in elderly patients with ischemic dilated cardiomyopathy, TMZ improved clinical condition and QOL on both social and physical scales.

Fragasso et al.³⁰ reported that TMZ effects were also evident in nonischemic patients; they evidenced a significant improvement of functional class and left ventricular function in patients with both ischemic and nonischemic heart failure. In another study³¹ in idiopathic dilated cardiomyopathy, TMZ increased cardiac function and had both cardiac metabolic effect by increasing oxidation of glucose and extracardiac metabolic effects by improving whole-body insulin sensitivity and glucose control in these insulin-resistant patients; and additionally, the TMZ-induced increase in ejection fraction was associated with greater β 1-adrenoceptor occupancy, suggesting a synergistic mechanism.

The beneficial effects of TMZ are related to the peculiar mechanism of action of the drug. TMZ exerts myocardial antiischemic effect independently from changes in oxygen supply-to-demand ratio.^{11,32,33} The antiischemic effect of TMZ are obtained at a cellular level, by shifting the energy substrate reference from fatty acid oxidation to glucose oxidation by rapidly restoring the phosphorylation processes, protecting cardiac cells against intracellular acidosis, preventing the intracellular accumulation of sodium and calcium ions, and finally by reducing oxidative damage.^{15,34} All these properties contribute to protect myocardial cell against necrotic and apoptotic cell death. These 2 steps are considered fundamental in regulating the LV remodeling and the progressive decline of the contractile function occurring during the normal evolution of ischemic cardiomyopathy.¹⁹ The beneficial effects of TMZ on left ventricular function and NYHA class are due to a preservation of cardiac phosphocreatine and adenosine triphosphate (PCr/ATP) ratio.²¹ The preservation of LVEF could be explained, at least partly, by the effects of the drug in maintaining the integrity of cell membranes as well as

mitochondrial structure and function.³⁵ In addition, the increase of glucose oxidation induced by TMZ may, in turn, enhance the resynthesis of glycolytic ATP and improve contractility and microvascular function. Finally, it is also possible that chronically hibernated cells increased their energy metabolism after TMZ treatment and became effective in producing a contractile activity, contributing to improve the contractile response and to limit further decline of the LV function. Recent data reported in patients with ischemic cardiomyopathy confirm that TMZ treatment improved the contractile response to a challenge of dobutamine without inducing any hemodynamic changes.¹² This amelioration of contractility is also evident during dobutamine-induced ischemic dysfunction in patients with coronary artery disease and a normal LVEF at rest.⁷ The anti-inflammatory and antioxidant benefit of the drug may contribute to the benefit.

5. Limitations of the study

We followed up patients only for 6 months and longer-term follow-up may strengthen the results. Assessment of other LV dimension and volume and LV diastolic function could have been done to enrich the results.

6. Conclusion

The addition of sustained-release TMZ on conventional drugs for treatment of ischemic cardiomyopathy improved symptoms, LV dimension, and function, and reduced hospitalization for worsening heart failure. Though many studies from European population already showed similar results, very few reports are found from the south Asian population. Further large-scale study with extended follow-up may strengthen the current evidences.

Conflicts of interest

The authors have none to declare.

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