

Quality of life with trimetazidine

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Abstract

Trimetazidine, a metabolic agent with anti-ischemic properties, has strong evidence of efficacy and tolerability in the treatment of patients with ischemic cardiomyopathy, including subjects with chronic angina and heart failure. There is now a growing evidence that trimetazidine has also a positive impact on quality of life of these patients. This seems to be a consequence of the clinical benefits provided by trimetazidine on one hand, and of its optimal tolerability profile on the other. Benefits of trimetazidine administration include symptom relief, particularly reduction of episodes of angina and dyspnea with a resulting improvement in exercise tolerance. The clinical effectiveness of trimetazidine can alone explain its impact on quality of life in a disease, such as ischemic cardiomyopathy, where poor quality of life is strongly related to the limitation of daily living activities imposed by symptoms.

Keywords: ischemic cardiomyopathy; trimetazidine; quality of life

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Introduction

Trimetazidine (TMZ) is a metabolic agent with anti-ischemic properties that acts by changing the patterns of myocardial energy substrate use during ischemia without any hemodynamic effect. TMZ has been shown to be an effective drug for the treatment of chronic angina both alone or in addition to conventional hemodynamic drugs [1]. Similarly some recent studies have demonstrated that TMZ improves symptoms and New York Heart Association (NYHA) functional class in patients with heart failure, mostly secondary to coronary artery disease (CAD) [2]. In most trials performed in patients with chronic angina and heart failure, assessment of TMZ effectiveness, as for other drugs, included objective measures of the amount of ischemia, exercise tolerance, such as duration during ergometric tests, and the threshold of symptom onset. In patients symptomatic for angina or dyspnea with reduced functional capacity, clinical improvement and the possibility of increasing daily living activities without symptoms seems to be closely linked to the improvement of quality of life (QOL) [3,4]. In fact, easy measures of disability in ischemic cardiomyopathy, such as the NYHA functional classification, are closely related to QOL scores [5,6]. Yet although these results can be translated into an improvement of QOL, in a broader sense, the latter remains an unresolved question. Currently, few data are available regarding the impact of TMZ on QOL in patients with both chronic angina and heart failure. Moreover, it should be emphasized that there is lack of data on the topic of QOL and TMZ treatment in the elderly.

Quality of life in chronic angina

Data concerning the effectiveness of TMZ as an anti-anginal drug are summarized in a meta-analysis of Ciapponi et al [1] that includes 23 studies, involving a total of 1,378 patients. According to this study, when compared both to placebo and to other anti-anginal drugs, TMZ reduces the rate of angina episodes by about 40% and nitroglycerin dosage by about 38%. Moreover TMZ, significantly improves work load—by about 13%—and extends the duration of physical exercise without anginal pain by about 10%. Very recently, a large network meta-analysis gathering the results of 218 clinical trials in over 19,000 stable angina patients completed these results. This meta-analysis assessing the anti-ischemic and anti-anginal efficacy of non-heart rate-lowering anti-anginal agents not only confirmed the significant clinical efficacy of trimetazidine compared with placebo, but it also confirmed that the benefits of trimetazidine are at least comparable if not superior (N.S.) to all of its direct therapeutic alternatives [7]. These results clearly indicate that TMZ administration in subjects with stable CAD is related to an improvement in exercise tolerance, with better performance regarding daily activities. Two studies more specifically addressed QOL using the Seattle Angina Questionnaire (SAQ), a 19-item self-administered questionnaire measuring five dimensions of coronary artery disease: physical limitations, anginal stability, anginal frequency, treatment satisfaction, and disease perception. The Trimetazidine MR in Patients with Stable Angina: Unique Metabolic Path (TRIUMPH) study [8] was an open-label, uncontrolled study that analyzed QOL in 846 patients with chronic stable angina. Patients were taking TMZ-MR for 8 weeks. At the end of the study, authors observed a significant improvement of QOL in all five dimensions of the SAQ: physical limitation scores increased from 50.7 +/- 0.7 to 61.0 +/- 0.6, angina stability improved from 57.6 +/- 0.9 to 92.5 +/- 0.7, angina frequency extended from 33.3 +/- 0.7 to 55.6 +/- 0.8, treatment satisfaction increased from 62.3 +/- 0.7 to 77.4 +/- 0.5, and disease perception improved from 36.7 +/- 0.6 to 55.5 +/- 0.7. The Trimetazidine in stable Angina twice Daily (TRIADA) study evaluated the efficacy and tolerability of 12-week treatment with modified-release TMZ in 74 patients with stable angina and positive exercise tests. The study confirmed the efficacy and safety of modified-release TMZ as a supplementary treatment

in CAD. A significant reduction in the angina attack rate ($p < 0.05$), improvement in exercise test results, reduction in the incidence of symptomatic and asymptomatic ischemia, and significant improvement in QOL ($p < 0.05$) based on the Seattle Angina Questionnaire were also observed [9].

Another use of TMZ with possible implications for QOL is in association with sildenafil in subjects with CAD and erectile dysfunction. Rosano et al [10] demonstrated that TMZ plus sildenafil was more effective in controlling episodes of myocardial ischemia during sexual activity than nitrates alone (-45 +/- 11% versus -18 +/- 7%, $p < 0.04$). In light of these results, authors suggested that long-term nitrate therapy could be safely switched to TMZ therapy when treatment for erectile dysfunction is required.

Quality of life in left ventricular dysfunction patients

Heart failure progressively decreases the functional capacity of patients, which impacts day-to-day activities at home, leisure-time interests and performance at work. From a patient's perspective, these limitations imposed by the disease, which adversely affect QOL, are of at least equal importance to the constellation of symptoms and signs that form the basis of the medically orientated approach to health assessment. An improvement of clinical conditions with TMZ in patients with heart failure has been observed in several studies [11–15]. This was underlined in the meta-analysis by Gao et al [2], which included 17 trials with data for 955 patients, where TMZ administration led to a significant improvement in NYHA class ($p < 0.01$) and exercise tolerance ($p < 0.01$) compared to placebo.

In recent years, randomized studies have focused more specifically on QOL. Vitale et al [11] evaluated QOL in a double-blind study of 62 elderly patients (mean age 78 years) with ischemic cardiomyopathy who were randomized to TMZ 20 mg three times a day or placebo. A visual analogue scale measuring the general wellbeing assessed QOL. A significantly greater number of patients allocated to trimetazidine improved their NYHA functional class compared with those allocated to placebo. QOL significantly improved in all patients treated with TMZ, while it remained unchanged in those allocated to placebo.

A study by Fragasso et al [12] enrolled 55 patients with heart failure, not only of ischemic origin, who were randomly allocated in an open-label fashion to either

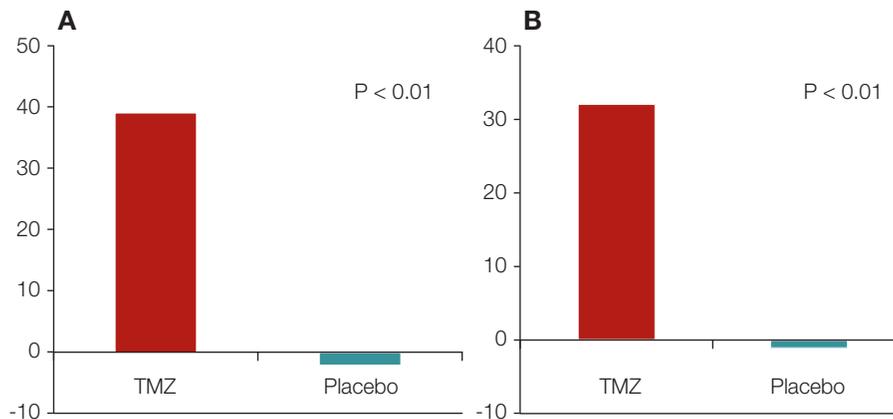


Fig. 1 Percentage change of physical (A) and social (B) McNew QOL questionnaire with trimetazidine and placebo [16].

conventional therapy plus TMZ (20 mg three times daily) or conventional therapy alone. At the end of the study, the TMZ group showed a substantial improvement of NYHA functional class compared to baseline, with 25% of patients in NYHA class I-II at baseline versus 89% at follow up. NYHA class worsened in the control group, with 48% of patients in NYHA class I-II at baseline versus 22% at follow up. The authors also observed an increase in exercise capacity in the TMZ group, from 7.37 ± 2 metabolic equivalents (METS) to 8.7 ± 2 METS. The authors assessed QOL with two tests: a visual analogue scale and a left ventricular (LV) dysfunction questionnaire (LVD-36) in order to measure the impact of LV dysfunction on daily life. The study demonstrated a significant decrease in LVD-36 score (from 18 to 15, $p=0.038$) and no significant increase of visual analogue scale, which went from 63% to 71% ($p=0.07$).

Improving QOL represents a challenge, especially for elderly subjects. There is lack of data in this group of patients regarding TMZ, as there is for other drugs. Our group specifically investigated the effects of TMZ on different areas of QOL in elderly patients with ischemic dilated cardiomyopathy (mean age 78 ± 3.4 years) using a self-administered questionnaire, the MacNew Quality of Life After Myocardial Infarction. We showed a significant improvement in physical and social areas in patients randomized to TMZ, but not in those randomized to placebo [12] (Fig. 1 [16]). Benefits of TMZ on QOL could be related to several factors. First, in patients with ischemic cardiomyopathy and recurrent angina, increased well-being could be a consequence of its anti-angina effects. Moreover, the improvement

in exercise tolerance and a direct action on skeletal muscle mass could play a role [17].

Conclusions

Available data suggest that TMZ has a positive impact on QOL in patients with ischemic cardiomyopathy. This benefit is at least in part related to the improvement of symptoms and to the increase of exercise tolerance observed in such patients. However, more recent studies suggest that TMZ impacts QOL in a broader way, probably with unknown mechanisms of action. Further randomized trials, possibly focusing on QOL as a primary endpoint, are needed to better clarify TMZ's effects on QOL. •

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