Clinical efficacy in stable angina pectoris

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Abstract

Trimetazidine is indicated in the prophylactic treatment of angina pectoris attacks. Beyond 30 years of clinical experience, the use of the drug in clinical practice is also based on its presence in a large number of national and international guidelines. More particularly, the recommendations of the American College of Cardiology/American Heart Association (ACC/AHA) list Trimetazidine among the therapeutic options for the management of stable angina and mention its demonstrated efficacy in angina.1 In the 2006 recommendations of the European Society of Cardiology (ESC), Trimetazidine is the only antianginal treatment currently available in a large number of countries, and described as having shown its antianginal efficacy, which is recommended “to be used in combination therapy with haemodynamically acting agents for its absence of effect on arterial blood pressure or heart rate”.2 The level of evidence B defined for Trimetazidine in the ESC guidelines is the same as that defined for dihydropyridine calcium channel blockers and superior to that defined for long-acting nitrates or nicorandil (level C). The clinical data supporting the use of Trimetazidine in the management of stable angina is detailed hereafter.

Keywords : Angina pectoris, Trimetazidine MR

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Efficacy

The clinical efficacy of trimetazidine was initially assessed in comparison with a certain number of reference drugs used for the management of stable angina. These comparisons show similar anti-ischemic and antianginal benefits between trimetazidine and drugs such as a beta-blocker or a calcium antagonist. As long term monotherapy, trimetazidine presents comparable anti-ischemic and antianginal efficacy to that of a beta-blocker, as demonstrated in a multicenter, double blind, comparative trial in 149 stable angina patients (Detry/TEMS study, Figure 1) (1). A crossover comparison was also conducted with a calcium channel antagonist (Dalla-Volta study) (2). These results were confirmed in 2004 in a multicenter, double-blind, parallel-group study (TTS study) (3). These two trials show a similar efficacy between trimetazidine and its comparator in terms of decrease in angina attacks, increase in exercise tolerance as well as improvement in ergometric parameters.

Figure 1. Changes in time to onset of angina

Adapted from Detry JM et al (1994)
Efficacy in combination with other drugs

Due to its specific mode of action, trimetazidine offers an anti-ischemic and antianginal efficacy, which is always entirely additive to that of other antianginal agents, giving complementary and synergistic clinical benefits. In particular, the evaluation of the addition of trimetazidine to a calcium antagonist (4-6) or β-blocker (7-13) shows a reduction or elimination of residual angina attacks, and an increase in the exercise capacity of coronary patients. In a controlled, randomized, double-blind trial conducted versus placebo in 64 patients still showing ST-segment depression despite treatment with diltiazem 180 mg per day, the addition of trimetazidine enabled a gain of one increment (30 Watts) in the exercise test and delayed the onset of ischemic threshold by 2 min 41 sec (4). Similar results were obtained on clinical and ergometric parameters by Manchanda et al. in a double-blind, randomized, placebo controlled, 4-week follow-up (5,6). The Trimpol II study (7), a randomized, double-blind, placebo-controlled, trial in 347 coronary artery disease patients uncontrolled by metoprolol provides similar results. The results of this trial confirm the fully additional efficacy of trimetazidine to that of a β-blocker, regarding all exercise and clinical parameters (significant reduction in the number of angina attacks and in mean TNT consumption). Similar observations were made several years after TRIMPOL II in two other combination essays. The TACT trial assessed in a single-blind manner the additive benefits of trimetazidine versus placebo, in one 166 patients resistant to monotherapy with a β-blocker or nitrate derivative (8). The TRIUMPH study (9) assessed the clinical efficacy and tolerability profile of an eight-week trimetazidine treatment on top of conventional treatment (mainly nitrates, β-blockers, and calcium antagonists) in 846 stable angina patients followed-up according to an open-label design in daily practice. The results of the study show a significant improvement in angina symptoms and in quality of life assessed with the Seattle Angina Questionnaire in the stable angina patients after two months’ treatment with trimetazidine. The TRIMPOL I study (10) confirmed the efficacy and acceptability of trimetazidine MR in a group of 71 elderly patients (age > 65) with stable angina uncontrolled by their standard treatment. The results confirmed the additive efficacy of trimetazidine MR to a hemodynamic drug (beta-blocker, nitrate, or calcium antagonist). Another multicenter, observational study, TIGER (trimetazidine in GERiatric patients) (11), confirmed these results in 161 patients aged 65 to 86 years. Trimetazidine’s anti-ischemic and antianginal efficacies were assessed by exercise duration, time to 1-mm ST segment depression and relief of symptoms. After 12 weeks of treatment, the mean number or angina attacks per week decreased from 5.5 to 2.2 and the mean short acting nitrate consumption per week decreased from 4.3 to 1.4 (P<0.001 for both parameters), exercise duration significantly increased by 52 sec (p<0.001) and time to 1-mm ST segment depression increased from 358 to 399 sec (p<0.001) Therefore, while a majority of the available clinical evidence has clearly highlighted the limitations of combining two different drugs both aimed at restoring the balance between the myocardium’s oxygen supply and demand (14-21), the available data with trimetazidine confirm the benefits of the combination of a hemodynamic drug with a drug modulating cardiac energy metabolism like trimetazidine. As a matter of fact, two major trials have highlighted that adding trimetazidine to a hemodynamic drug like a beta-blocker is of greater benefit than combining two or more hemodynamic drugs.

1. The Michaelides et al. (12) study (Figure 2) is a randomized, double-blind, controlled trial comparing trimetazidine with isosorbide dinitrate (ISDN) in combination with a β-blocker. This study was the first to...
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confirm the superiority of the combination of a β-blocker plus trimetazidine over the combination of a β-blocker + ISDN. It shows that trimetazidine improves the clinical and exercise parameters to a significantly greater extent than isosorbide dinitrate. Results of the trial actually show that trimetazidine provides twice the reduction in angina symptoms as observed with ISDN. The time to ST-segment depression was improved by 81 seconds with the combination of β-blocker with trimetazidine (P<0.001) while it only increased by 15 seconds (NS) in the β-blocker + ISDN patients

2. More recently, the PARALLEL study (Figure 3), presented during the 2007 edition of the European society of Cardiology (ESC) was conducted in 903 patients with stable angina uncontrolled by β-blockers administered at optimal dose (13). This multicenter, randomized, parallel-group study compared the clinical efficacy and safety of the combination of the modified-release formulation of trimetazidine or isosorbide dinitrate (ISDN) with a beta-blocker during 12 weeks. In this trial, trimetazidine significantly decreased the number of weekly angina attacks and the mean weekly consumption of nitroglycerin more than ISDN. Trimetazidine MR also significantly improved the quality of life of patients as assessed by means of the Seattle Angina Questionnaire, and with better safety than ISDN.

In the process of developing the new modified-release formulation of trimetazidine MR, a clinical trial was conducted to specifically assess the drug’s efficacy and safety at minimum plasma concentrations (22). This study is an international, randomized, double-blind, placebo controlled multicenter trial involving 55 cardiology centers in nine countries (France, Belgium, Finland, Ireland, Israel, Latvia, Netherland, United Kingdom, Russia) and recruiting 223 stable angina patients. It assesses the efficacy of trimetazidine MR at the dose of one tablet twice daily after two months of treatment in stable angina patients who still had a positive exercise test (2-mm ST-segment depression and pain) despite β-blocker treatment (one tablet daily of atenolol 50 mg). The safety of trimetazidine MR was also evaluated for a period of six months. As required when dealing with a modified-release formulation, the efficacy of trimetazidine MR was evaluated at trough or minimum plasma concentration twelve hours after the last dose, i.e., just before the following dose in order to evaluate the quality of therapeutic coverage of the drug: after the last dose and just before the next dose. The trial shows that at minimum plasma concentrations, trimetazidine MR produces a significantly greater change in time to 1-mm of ST-segment depression in comparison with placebo (P=0.005): +47.9 seconds with trimetazidine MR vs. + 6.5 seconds with placebo. Trimetazidine MR also prolonged the time to onset of angina by 48.4 seconds, while it was increased only by 23.8 seconds in placebo control. The improvement with trimetazidine MR was essentially the same whether or not patients were well or poorly controlled with beta-blockers. In this trial, trimetazidine MR did not cause more adverse events than the placebo. This applied to all adverse events, whether serious or not. The general safety/acceptability of trimetazidine MR was reported as excellent, regarding not only vital and clinical signs but also laboratory parameters. Cardiovascular safety was well documented in this trial. Results show the absence of significant lengthening of QT interval on trimetazidine, i.e., the absence of any arrhythmogenic risk, as well as the absence of serious adverse events during the two weeks following the end of the trial (systematically documented) providing evidence of the absence of any rebound withdrawal syndrome after the treatment was discontinued.
Table 1. Summary of the main clinical trials evaluating the efficacy of trimetazidine in stable angina

<table>
<thead>
<tr>
<th>Author</th>
<th>Study design</th>
<th>Randomized patients TMZ/comparator</th>
<th>Follow-up interval</th>
<th>Endpoints</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 Detry JM et al (1994)</td>
<td>randomized, double-blind parallel group, vs propranolol</td>
<td>149 (71/78)</td>
<td>3 Months</td>
<td>Anginal attacks, NTG consumption, ETT parameters 24h ambulatory ECG</td>
</tr>
<tr>
<td>2 Dalla-Volta S et al (1990)</td>
<td>randomized, double-blind parallel groups crossover trial, vs nifedipine</td>
<td>39/39</td>
<td>6 weeks</td>
<td>Anginal attacks, NTG consumption, ETT parameters</td>
</tr>
<tr>
<td>5 Manchanda SC et al (1997)</td>
<td>randomized, double-blind, placebo controlled, in combination with diltiazem</td>
<td>64 (32/32)</td>
<td>4 weeks</td>
<td>Anginal attacks, NTG consumption, ETT parameters</td>
</tr>
<tr>
<td>7 Chazow EI et al (2005)</td>
<td>randomized, placebo controlled, in combination with beta-blockers</td>
<td>177 (90/87)</td>
<td>12 weeks</td>
<td>Anginal attacks, NTG consumption, ETT parameters</td>
</tr>
<tr>
<td>8 Szwed H et al (2001)</td>
<td>randomized, double-blind placebo-controlled, parallel group study, in combination with metoprolol</td>
<td>426 (179/168)</td>
<td>12 weeks</td>
<td>Anginal attacks, NTG consumption, ETT parameters</td>
</tr>
<tr>
<td>9 Michaelides AP et al (1997)</td>
<td>randomized, double-blind isosorbide dinitrate-controlled trial</td>
<td>53 (27/26)</td>
<td>2 Months</td>
<td>Anginal attacks, NTG consumption, ETT parameters</td>
</tr>
<tr>
<td>11 Makolkin et al (2004)</td>
<td>open-label, uncontrolled trial</td>
<td>906</td>
<td>8 weeks</td>
<td>Anginal attacks, NTG consumption, Quality of life</td>
</tr>
<tr>
<td>12 Giezer MG et al (2007)</td>
<td>open-label, randomized, isosorbide dinitrate parallel group study</td>
<td>903</td>
<td>12 weeks</td>
<td>Anginal attacks, NTG consumption, Quality of life</td>
</tr>
</tbody>
</table>
3. Overall clinical efficacy in stable angina

Trimetazidine has generated and is continuing to generate important scientific and medical interest as demonstrated by its bibliographical dossier. Over time, several meta-analyses were carried out, offering a global overview on the clinical efficacy and safety of the drug in the management of stable angina (23-26). After the first work from Klein et al (23), the Cochrane independent working group undertook an evaluation of trimetazidine’s efficacy through a meta-analysis gathering all the results of clinical studies meeting the strictest quality criteria: randomized, double-blind, versus reference product (placebo or another active treatment) (24). This meta-analysis includes the results of 23 randomized trials in more than 1378 stable angina patients. The results clearly confirm the overall anti-ischemic and antianginal efficacy of trimetazidine as they show both a significant improvement in exercise test parameters and significant reduction in the number of mean weekly angina attacks, and mean weekly nitrate consumption. The results actually led the Cochrane working group to conclude that “trimetazidine is effective in the treatment of stable angina compared with placebo, alone or combined with conventional agents.” This work was updated several years after by another meta-analysis strictly conducted according to the same methodology (25). It includes the results of 22 studies conducted with trimetazidine 20 mg and trimetazidine MR between 1967 and 2008 in more than 2700 angina patients. This work led to similar conclusion as it showed that trimetazidine significantly reduces the mean weekly number of angina attacks, increases exercise capacity by 23 seconds, and increases the time to 1-mm ST-segment depression versus placebo by 34 seconds. Furthermore, analysis of tolerance data shows that trimetazidine does not cause more adverse events than placebo.

Even more recently, in order to update and extend the results from the Cochrane meta-analysis, which focused on head-to-head comparisons, a network meta-analysis (mixed treatment comparison) was conducted using data from comparator-and placebo-controlled trials that evaluated the efficacy of antianginal agents that do not affect heart rate, (meaning likely to be prescribed in the same conditions as trimetazidine) (26). Antianginal agent subgroups included in the analyses were dihydropyridines calcium antagonist (amlodipine, felodipine IR, and sustained release [SR], isradipine, nicardipine, nifedipine IR and SR, nisoldipine IR and SR), long-acting nitrates (isosorbide mononitrate IR and SR, isosorbide dinitrate IR and SR, nitroglycerin SR, nitroglycerin patches), nicorandil, and ranolazine SR. All of the molsidomine trials had to be excluded due to inappropriate designs. In order to be included, trials had to be randomized, controlled, single- or double-blind, parallel-group or cross-over clinical trials assessing the treatment of stable angina pectoris or stable ischemic disease in adult patients. At least one treatment arm had to include a treatment of interest. 218 trials obtained from 213 references covering a period from 1996 to 2010 were included. The data set included a total of 19 028 patients.

In the overall set, trimetazidine significantly improved ergometric parameters and clinical criteria compared with placebo. Effect sizes of +0.38 (95% CI [0.23; 0.55]) corresponding to a 46-second increase in the total exercise duration, of +0.46 (95% CI [0.29; 0.64]) corresponding to a 55-second increase in time to 1-mm ST-segment depression, and of +0.45 (95% CI [0.20; 0.70]) corresponding to a 54-second increase in the time to onset of angina were noted. In the overall set, the meta-analysis also shows comparable efficacy between trimetazidine and other antianginal agents in terms of total exercise duration, Time to 1-mm ST-segment depression, and time to onset of angina observed (pooled and by subgroup) as well as on clinical parameters (mean weekly number of angina attacks and mean weekly nitrate consumption). When antianginal agents were pooled, effect sizes of +0.06 (95% CI [-0.10; 0.23]) corresponding to a 7 second increase in the total exercise duration, of -0.01 (95% CI [-0.19; 0.18]) corresponding to a -1 second decrease in the T1, and of +0.07 (95% CI [-0.18; 0.33]) corresponding to a 8 second increase in the time to onset of angina were noted in favor of trimetazidine; however, these differences compared with other classes of drugs were not statistically significant.

In conclusion, the trimetazidine’s extensive clinical program undertaken over the past twenty years has confirmed a consistent and indisputable clinical efficacy and acceptability of trimetazidine for the management of patients with chronic stable angina.
References
บทคัดย่อ

ไตรเมตาซิดีน เอ็มอาร์ มีข้อบ่งใช้ในการป้องกันอาการเจ็บหน้าอกจากภาวะหลอดเลือดหัวใจตีบ จากประสบการณ์ทางคลินิกกว่า 30 ปีแสดงให้เห็นถึงประสิทธิภาพในการลดอาการเจ็บหน้าอก ทำให้การใช้ยาในทางวิชาการมีถูกต้องและเหมาะสม ให้ใช้ในการรักษาจำเป็นต้องใช้ยาในแนวทางการรักษาของ American College of Cardiology และ American Heart Association (ACC/AHA) และในแนวทางการรักษาปี 2006 ของ European Society of Cardiology (ESC) ได้กำหนดให้ไตรเมตาซิดีน เอ็มอาร์ เป็นทางเลือกในการรักษา stable angina โดยแนะนำว่า “ให้ใช้ร่วมกับยาเป็นยามาตรฐาน เพราะยาไม่มีผลต่อความดันโลหิตหรืออัตราการเต้นของหัวใจ” ไตรเมตาซิดีน เอ็มอาร์ ถูกจัดให้อยู่ในหมวดหลักฐานระดับ B ในแนวทางการรักษาของ ESC ซึ่งเป็นระดับเดียวกันกับ dihydropyridine calcium channel blocker และอยู่เหนือกว่า long-acting nitrates หรือ nicorandil (ระดับ C)

คำสำคัญ: อาการเจ็บหน้าอกจากภาวะหลอดเลือดหัวใจตีบ, ไตรเมตาซิดีน เอ็มอาร์