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Review

Measuring Treatment Effects of Cilostazol on Clinical Trial Endpoints in Patients with Intermittent Claudication

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Summary: Intermittent claudication (IC) comprises the most common presenting symptoms of peripheral arterial disease (PAD), which itself is a manifestation of systemic atherosclerosis. Typical symptoms of IC are aching pain, numbness, and fatigue in the lower extremities. Symptoms are induced by walking or exercise and usually resolve with rest. The cornerstone of treating IC is risk-factor reduction and a supervised exercise regimen. Pharmacotherapy specifically indicated for the treatment of IC includes a new drug, cilostazol, and the traditional drug, pentoxifylline. Cilostazol also has antiplatelet, antithrombotic, and vasodilatory activity, as well as a positive effect on serum lipids. Eight multicenter clinical trials, seven in the U.S. and one in the U.K., used objective and subjective clinical endpoints to assess the treatment efficacy of cilostazol. Objective endpoints included maximal and pain-free walking distance (MWD and PFWD, respectively), the ankle–brachial index, peripheral hemodynamic measurements, and serum lipid levels. Subjective endpoints, assessed by patient questionnaires, included perceived functional status and health-related quality of life. Cilostazol treatment showed statistically significant increases in MWD and PFWD within 4 weeks, as well as improvements in physical functional status at 24 weeks, compared with placebo and pentoxifylline. Increases in high-density lipoprotein cholesterol and decreases in plasma triglycerides were also noted. Subjective assessments appeared to match objective parameters.

Key words: cilostazol, intermittent claudication, peripheral arterial disease, clinical trial endpoints

Introduction

Intermittent claudication (IC) is typified by aching pain, numbness, or fatigue, usually experienced in the calves but possibly also in the thighs or buttocks. Symptoms generally occur during walking or exercise and resolve with rest. Intermittent claudication is a debilitating condition that limits patients' ability to function normally and can severely affect health-related quality of life (HQL). It is a frequent manifestation of peripheral arterial disease (PAD), which itself is a manifestation of systemic atherosclerosis. The incidence of IC is approximately twofold higher in men than in women and increases sharply with age up to 75 years.[1] The overall prevalence of PAD is considerably higher than that of IC, indicating a high rate of asymptomatic disease. Rates for the latter have ranged from 1 to 3% in men aged 50–59 years, but abnormal pulse findings, which are diagnostic for PAD, have been reported in as many as 21% of men in this age group.[2]

Intermittent claudication is a serious disease, with estimated 5-, 10-, and 15-year all-cause mortality rates of 30, 50, and 70%, respectively.[3] Patients with PAD generally have widespread arterial disease and consequently are subject to the same risks as those with atherosclerosis, namely, significantly increased occurrence of stroke, myocardial infarction, angina, and cardiovascular death compared with the normal population. The mortality rate due to cardio- and cerebrovascular conditions in patients with IC is 2.5 times higher than in those with PAD without claudication.[3] Furthermore, compared with the normal population, men and women with IC have a two- and four-fold increased risk of death, respectively, due to coexistent cardiovascular disease.[1]

Primary goals in the treatment of IC are to alleviate symptoms, increase maximal and pain-free walking distance (MWD and PFWD, respectively), improve overall perceived functional status, and, ultimately, improve patients' HQL. Supervised exercise and aggressive risk-factor reduction, for example, modification in diet and smoking behavior, are the primary noninvasive strategies used to slow down or prevent progression of atherosclerosis and development of atherosclerotic complications.[4] Pharmacotherapy specifically indicated for IC, as well as the appropriate use of lipid-altering and antiplatelet agents, are also recommended to prevent or forestall the onset of limb-threatening events and improve overall survival.[5]

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Evaluating Clinical Trial Endpoints and Treatment Efficacy in Patients with Intermittent Claudication

Symptoms of IC cover a wide spectrum of severity. Accordingly, evaluation of clinical trial endpoints indicative of treatment efficacy have required a comprehensive approach encompassing both objective and subjective measurement tools. Hiatt *et al.*[6] have recommended specific guidelines for evaluating the clinical trial endpoints used in claudication studies. Based on these guidelines, exercise performance is best evaluated with objective graded treadmill testing and measurements of oxygen consumption. Measuring walking distance on a graded treadmill at 3 mph is recommended as an excellent indicator of the severity of claudication, and the pain that occurs following exercise has been shown to correlate with peripheral vascular blood pressure measurements.[7] Maximal oxygen intake following a standardized exercise protocol is impaired in patients with cardiovascular disease,[8] and improvement is a good indicator of treatment efficacy.

Objective assessments of treatment effects also include assessing the ankle–brachial index (ABI), measuring pulse volumes, determining lower extremity blood-flow velocity, and laboratory tests to determine potential changes in blood lipid levels.

Questionnaires recommended to assess patients' perceived functional status and HQL include the Medical Outcomes Scale Short Form-36 (SF-36) (Table I), which is a generalized quality-of-life questionnaire, and two disease-specific questionnaires: the Walking Impairment Questionnaire (WIQ) and the Claudication Outcome Measures (COM). The SF-36 measures patients' perception of their health status with respect to both physical health and mental well-being.[9] The WIQ characterizes walking speed, walking distance, and symptoms associated with walking difficulty, as wells as degree of walking impairment and efficacy of an intervention intended to improve walking ability.[10] The COM assesses severity of walking pain and discomfort over long and short distances.[11]

TABLE I Quality of Life Medical Outcomes Survey Short Form 36 (SF-36)

• Widely used general health questionnaire
• Used in six cilostazol trials conducted in the U.S.
• Consists of eight subscales and two summary scales
Physical component subscales
Physical function
Physical role
Bodily pain
General health perception
Mental component subscales
Social function
Emotional role
Mental health
Vitality
Summary scales
Physical component subscales
Mental component subscales

Cilostazol and pentoxifylline have demonstrated benefit for direct treatment of IC and are the only drugs approved in the U.S. for the treatment of this condition. Effects with pentoxifylline, however, have been inconsistent, and the American College of Chest Physicians Consensus Panel on Antithrombotic Therapy now recommends that pentoxifylline not be used routinely in patients with claudication.[12]

Cilostazol

Cilostazol, which was FDA-approved for use in the U.S. in 1999,[13] is an antiplatelet, antithrombotic agent and the newest available treatment option for IC. Cilostazol was first approved in Japan in 1988 for the treatment of ischemic leg ulcers and was found to improve dermal blood flow.[14] It was subsequently marketed in several countries for the treatment of chronic arterial occlusion. In recent Japanese studies, cilostazol was shown to be effective in preventing recurrence of cerebral infarction[15] and in maintaining the heart-rate circadian variation and decreasing the number of pauses between heart beats in patients with chronic atrial fibrillation associated with episodes of bradycardia.[16]

Cilostazol and its metabolites have a long half life of ~11–13 h, as well as good serum concentration (Cmax ~1300 ng/ml at 3 h) detectable for at least 36 h postdose, with steady state reached in 4 days.[17]

Cilostazol is a phosphodiesterase III inhibitor that suppresses cyclic adenosine monophosphate (cAMP) degradation.[18] The consequent increase in cAMP in platelets and blood vessels leads to inhibition of platelet aggregation and to vasodilation, respectively.[14, 19] Cilostazol shows potent antiplatelet effects both in vitro and in vivo and has also exhibited antithrombotic effects in experimental thrombus models.[15] It has been shown to inhibit the formation of small platelet aggregates, such as those induced by heparin treatment in chronic hemodialysis patients.[20] Cilostazol also directly inhibits smooth muscle proliferation and may enhance re-endothelialization, thus showing potential for reducing restenosis following percutaneous transluminal coronary angioplasty.[21]

As demonstrated in a recent animal model,[22] cilostazol decreases serum triglycerides and increases high-density lipoprotein cholesterol (HDL-C). The drug has also been shown to improve insulin sensitivity in a rat model of noninsulin-dependent diabetes mellitus.[23]

Effect of Cilostazol on Clinical Trial Endpoints

Eight Phase III, multicenter, randomized, double-blind, placebo-controlled trials (one in the U.K. and seven in the U.S.) have demonstrated the efficacy of cilostazol.[11, 24–30] A total of 2,702 patients with a mean age of 65 years participated in these studies; 76% were men, 89% were Caucasian.[28] Risk factors were typical of IC patients: 60% had a history of hypertension, 26% had diabetes, and 40% were active smokers. Trials ranged from 12–24 weeks in duration and compared cilostazol with placebo or 400 mg pentoxifylline t.i.d. Patients typically received the recommended dosage of 100 mg oral

cilostazol b.i.d., although the 50 mg b.i.d. dosage was evaluated in two studies and the 150 mg b.i.d. dosage in one.

In six clinical trials, graded treadmill testing demonstrated that patients who received cilostazol (100 mg b.i.d.) increased their MWD by 41–54% compared with placebo.[11, 24–26, 28, 29] In a trial comparing cilostazol 100 mg b.i.d. with pentoxifylline 400 mg t.i.d. and placebo, the MWD in cilostazol-treated patients increased 54% from baseline compared with a 30% increase in those treated with pentoxifylline ($p < 0.001$) and a 34% improvement in the placebo group (Fig. 1).[26] In another trial, cilostazol 100 mg b.i.d. treatment also resulted in a significant ($p < 0.001$) improvement in MWD of up to 51% compared with placebo (Fig. 2).[11] The superiority of active treatment with cilostazol over placebo or pentoxifylline was noted as early as in the fourth week in these trials.[11, 26]

In one study, the benefit of treatment with cilostazol was demonstrated by examining its withdrawal.[30] A significant loss of walking ability ($p = 0.001$) was observed in cilostazol-treated patients with IC following withdrawal of the agent after 24 weeks of therapy. In contrast, the pentoxifylline-treated patients demonstrated no decrease in walking ability following drug withdrawal. In studies in which the ABI was evaluated, improvement was also noted in this parameter compared with placebo.[25, 27]

The beneficial effects of cilostazol on serum lipids have also been demonstrated in patients with IC. After 12 weeks of cilostazol therapy (100 mg b.i.d.) in 189 patients with IC, HDL-C increased 10% ($p < 0.001$), apolipoprotein A1 increased 6% ($p < 0.01$), and plasma triglycerides decreased 15% ($p < 0.001$).[27] Individuals with baseline hypertriglyceridemia (> 140 mg/l) experienced the greatest changes in HDL-C and triglyceride concentrations, whereas low-density lipoprotein cholesterol and lipoprotein(a) levels were unaffected. Cilostazol treatment in these patients resulted in statistically significant increases in treadmill walking time (35%) and in the ABI (9%), thus indicating that the drug simultaneously improves physical capacity and plasma lipid profiles.[27]

In studies that have looked at HQL measures in patients with IC,[11, 25] the physical health concepts of the SF-36 showed improvement at 16–24 weeks in patients on cilostazol. Similarly, there were improvements in patients' perceptions of walking speed and distance on the WIQ, as well as walking pain/discomfort on the COM.

Cilostazol Safety

Overall, the data so far indicate that the gains of cilostazol treatment greatly outweigh the risks. During the approximately 2 years that cilostazol has been in use in the U.S., it has been found to be safe and generally well tolerated, even in patients with renal or mild hepatic impairment. The main side effects have been headache, diarrhea, and palpitation.[11, 31, 32] Premarketing clinical trials have shown no serious adverse effects.

Because it is classified as a phosphodiesterase III inhibitor, cilostazol is contraindicated in patients with congestive heart failure (CHF). Other phosphodiesterase III inhibitors have been observed to increase morbidity and mortality in patients with New York Heart Association (NYHA) class III or IV CHF, which these drugs were intended to treat. However, cilostazol has not been found to precipitate or worsen CHF in any clinical trial to date. Furthermore, no clinically significant drug interactions between cilostazol and acetylsalicylic acid, warfarin, or lovastatin have been reported.[33–35]

The most common cardiovascular adverse events that have occurred since the drug was launched in 1999 are tachycardia, palpitations, and hypertension. However, the incidence of these events has been minimal: 0.3/1000 patient exposure years for tachycardia and palpitations and 0.1/1000 patient exposure years for hypertension.[28] In clinical trials involving 1,351 patients with IC who received cilostazol compared with 1,038 who received placebo, 0.7 and 0.5% of cardiovascular-related adverse events, respectively, resulted in death.

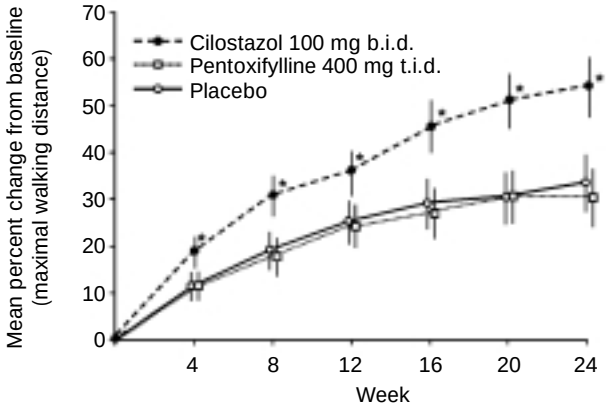

FIG. 1 Mean (± 95% confidence interval) percent change from baseline in maximal walking distance for patients with intermittent claudication who received cilostazol, placebo, or pentoxifylline. *$p < 0.05$ at each 4-week time point for cilostazol versus placebo and pentoxifylline. Reprinted from *Am J Med*, Vol. 109, Dawson *et al.*, A comparison of cilostazol and pentoxifylline for treating intermittent claudication, pp. 523–530 (2000) (Ref. No. 26) with permission from Excerpta Medica, Inc.

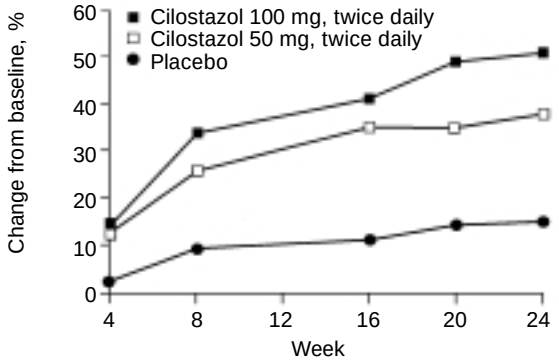

FIG. 2 Geometric mean percent change from baseline in maximal walking distance for cilostazol 100 mg and 50 mg b.i.d. compared with placebo. Reprinted from Ref. No. 11 with permission.

Conclusions

Evidence from the cilostazol clinical trials indicates that adequate assessment of treatment effect in patients with IC requires a comprehensive approach with a variety of objective and subjective measurement tools. No single tool has the capacity to measure both objective clinical endpoints—MWD and PFWD, for example—and subjective clinical outcomes, such as functional status and HQL. Treadmill testing used in the cilostazol studies demonstrated a significant advantage of cilostazol over placebo and pentoxifylline in improving MWD and PFWD. Furthermore, a correlation between these objective clinical trial endpoints and subjective clinical outcomes, as measured by functional status questionnaires, was suggested: patients experienced improved physical functioning with cilostazol and consequently, a better HQL.

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