REVIEW ARTICLE

Evidence-based symptom relief of intermittent claudication: efficacy and safety of cilostazol

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Intermittent claudication (IC) is a common, debilitating symptom of atherosclerotic peripheral arterial disease. There are two therapeutic objectives in patients with IC: relief of symptoms and secondary prevention of acute thrombotic complications. Among patients with Fontaine stage II disease, surgical revascularization for symptom relief is reserved for those in whom exercise/lifestyle modification and medical therapy has failed. To improve exercise tolerance in IC requires favourable alteration in the oxygen supply/demand relationship in the lower limb. Following the largest ever clinical trials programme in patients with IC, cilostazol, a phosophodiesterase III inhibitor, has been licensed for symptom relief in the UK. In double-blind, randomized, placebo-controlled trials involving over 2000 patients, cilostazol 100 mg b.d. produced significant and sustained improvements in pain-free and maximal walking distances as well as improved subjective assessments of quality of life. In particular, comparative studies with pentoxifylline (oxpentifylline) showed that cilostazol had significantly greater effects on functional outcome and exhibited good patient tolerance.

Keywords: cilostazol, intermittent claudication, symptomatic relief, phosphodiesterase III inhibitor, functional outcome

Introduction

Intermittent claudication (IC) is a symptom of peripheral arterial disease (PAD), occurring in around 40% of people with PAD. It results from atherosclerotic lesions restricting blood flow in the peripheral arteries [1]. Claudication is felt as discomfort, pain, fatigue, numbness or heaviness, and occurs during walking, resolving after a few minutes of rest. The location of the symptoms depends on the site of the stenosis. Buttock, hip or thigh claudication may develop in cases of proximal arterial occlusive disease involving the aorta or iliac arteries. Involvement of the femoral or popliteal arteries typically causes calf pain. Tibial and peroneal artery stenoses may cause foot pain.

The reported prevalence of PAD depends on the methods used to detect it. In the Edinburgh Artery Study [2] the overall prevalence of IC was 4.5% among men and women aged 55–74. In addition, 8% had asymptomatic impairment of blood flow and a further 16.6% had abnormal haemodynamic parameters indicative of PAD. Even when symptomatic, however, at least half of all individuals with IC never consult their doctor [3], perhaps mistakenly believing that their condition is a natural consequence of ageing. It has been estimated that for every 100 people who present to their doctor with IC, there will be an additional 100 with symptomatic IC who do not seek medical attention and at least a further 300 with asymptomatic PAD (Fig. 1) [3]. Of these 100 presenting patients, it has been calculated that five will require an intervention and two will require a major amputation. Thirty of these 100 patients will die – 16 from a cardiac event, four from a cerebrovascular event, three from other vascular events and seven from nonvascular events [3]. These data emphasize the importance of detecting and treating PAD.

Treatment approaches

Most patients diagnosed with IC are treated conservatively, with lifestyle measures and pharmacological treatment. Only a few are suitable for vascular

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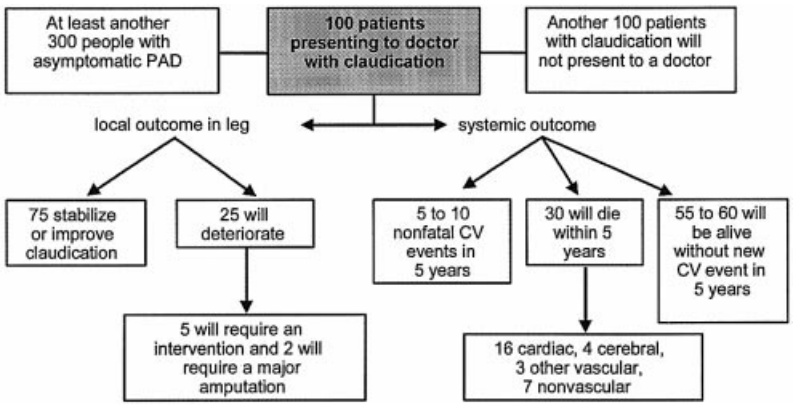

Fig. 1 Natural history of intermittent claudication. Reproduced with permission [3].

surgery or angioplasty [4]. Vascular surgery is generally considered to be appropriate only for patients with severe symptoms in whom the benefits outweigh the risks.

In view of the impact of IC on patients' quality of life, its significance as a marker for underlying atherosclerosis, and the potential for progression, two key goals can be identified (Table 1).

The first goal is to reduce symptoms and improve quality of life. Key objectives include increasing walking distance, improving daily function and enhancing quality of life. Patients who are able to walk further without pain may find it easier to carry out everyday tasks and be more able to take part in family, social and leisure activities. Achieving these objectives may involve lifestyle measures, such as smoking cessation [5] and exercise training [6], and pharmacological management [7].

The second goal is to reduce overall cardiovascular risk. Secondary prevention measures are important in the management of IC. They may slow the progression of atherosclerosis and may help to prevent deaths from cardiovascular events [8]. Moreover, secondary preventive measures may help to avoid progression to acute or chronic lower limb ischaemia, and reduce the need for surgery or amputation [8]. Secondary prevention should be individualized to take account of the patient's particular risk profile. Key strategies include smoking cessation, antiplatelet therapy (with aspirin [9] or newer agents [10]), management of hyperlipidaemia [11], and management of diabetes and hypertension where appropriate [8]. There is increasing evidence that use of angiotensin-converting enzyme (ACE) inhibitors may be beneficial in patients with PAD, whether or not they have hypertension [12]. Unfortunately, there are few treatments that contribute to achieving both these goals.

Table 1 Goals of therapy for patients with intermittent claudication.

Reduce symptoms and improve quality of life	Reduce overall cardiovascular risk
Exercise	Antiplatelet therapy
Smoking cessation	Lipid reduction
Pharmacological management	BP and glycaemic control
	Smoking cessation
	ACE inhibitors

Guidelines for clinical trials into intermittent claudication

The European Agency for the Evaluation of Medicinal Products, which governs the regulation and licensing of therapies, has issued explicit guidelines about the requirements for clinical trials to evaluate the efficacy of treatments for IC. For Fontaine stage II PAD, the patients involved in the trials must demonstrate a reproducible exercise limitation at baseline (before randomization) and they must have an absolute claudication distance (ACD) of 100–300 m before randomization. The end-points used in clinical trials must include standardized exercise tests to evaluate exercise tolerance, pain-free and maximal walking distance and also tests for other clinical parameters, such as quality of life and ankle–brachial pressure index (ABPI).

These required end-points create some problems for investigators. Treadmill exercise testing is a difficult tool to use in clinical drug development. This has been shown in studies to evaluate antianginal agents. Treadmill testing tends to over-estimate the placebo effect and under-estimate the clinical benefit of treatments [13]. Treadmill performance may be limited by concomitant diseases distinct from the one being tested –

for example, the presence of chronic obstructive pulmonary disease. Lastly, treadmill performance does not necessarily reflect quality of life, outcomes or walking distance in practice.

To date, the only agent licensed for use in IC that has undergone clinical trials that conform to the guidelines is cilostazol. Older agents were not so rigorously tested. For example, when oxpentifylline (the first drug to be approved for IC) was studied in a trial conforming to the guidelines, it was found to be no more effective than placebo [14]. Further, when oxpentifylline was withdrawn and patients changed to placebo, the patients experienced no decrease in walking distance, whereas patients swapped from cilostazol to placebo found their walking distance was decreased [15]. Others have also found that oxpentifylline can be withdrawn without affecting walking distance [16,17]. The efficacy of oxpentifylline therefore remains debatable. In view of this, the recent evidence-based Scottish Intercollegiate Guidelines Network (SIGN) guidelines state that it is not possible to make any recommendation on the use of oxpentifylline in IC [18]. US recommendations also state that oxpentifylline 'should not be routinely used in patients with intermittent claudication' [19]. Similarly, a meta-analysis of randomized placebo-controlled trials with naftidrofuryl (a serotonin 5-HT_2 receptor antagonist, which is believed to have both vasoactive and metabolic effects in intermittent claudication) found only a small increase (average 59 m) in pain-free walking distance with naftidrofuryl, compared with placebo [20]. These data demonstrate the importance of rigorous testing in clinical trials.

Cilostazol

In terms of meeting current guidelines for clinical trials in IC, cilostazol has a database that is greater in terms of both quantity and quality than any other medical therapy that has previously been studied in IC. It has been available for 10 years in Japan and more recently in the USA and UK. Eight Phase III trials have assessed the efficacy and safety of cilostazol in reducing symptoms in patients with moderate-to-severe IC [21]. In total, 2702 patients were included in these trials. All were of a multicentre, randomized, double-blind, placebo-controlled, parallel-group design. Seven trials were conducted in the USA and one in the UK.

The trials ranged from 12 to 24 weeks in duration. The dosages of cilostazol used were 50 mg b.d., 100 mg b.d. and 150 mg b.d. (note that cilostazol is not licensed at a dose of 150 mg b.d.). All studies employed a placebo control. Two studies also used oxpentifylline 400 mg t.d. as an active control.

Five studies employed a constant load treadmill (12.5% grade in four; 10% grade in one). Three studies used a variable load treadmill (starting at 0%, with the grade increased 3.5% every 3 min). The speed was held constant at 3.2 km/h (2 miles/h).

Patients' baseline characteristics and medical histories were similar across trials. Within each trial, there were no significant baseline differences between the treatment groups. The mean age of the study population was about 65 years and 76% of patients were men (reflecting the age and sex distribution of the disorder). The average ABPI was 0.64. Ninety per cent of the patients were Caucasian. About 41% were current smokers, and 51% had a history of smoking; only 8% had never smoked. The medical histories of the patients were characteristic of the population seen in the published literature for studies in patients with IC:

- 60% had hypertension;
- 25% had diabetes;
- 22% had at least one previous myocardial infarction.

Many patients had additional comorbid conditions that are typical in the intermittent claudication population, including nonexercise limiting angina (18%), a history of an arrhythmia (12%), a history of a transient ischaemic attack (7%), nonexercise limiting congestive heart failure (5%) and a history of stroke (4%). Therefore, the population used for the clinical trials is clearly representative of the 'real world' population of patients seen in practice.

Efficacy

Efficacy analyses were performed on the intention to treat population. Because three different treadmill protocols were used, the percentage change from baseline rather than change in metres was used to compare studies. An overview (Fig. 2) shows that cilostazol increased the maximal walking distance in a dose-dependent manner compared with placebo [21]. One study of particular note is a large 24-week study comparing 50 mg b.d. and 100 mg b.d. doses of cilostazol with placebo in 516 patients [22]. This study was performed on a constant load treadmill. The clinical and statistical superiority of both cilostazol doses over placebo was noticeable as early as week 4, with continued improvement at all subsequent time points. After 24 weeks, the geometric mean improvement in maximal walking distance was 51% ($P < 0.001$ vs. placebo) in the cilostazol 100 mg b.d. group and 38% ($P < 0.001$ vs. placebo) in the cilostazol 50 mg b.d.

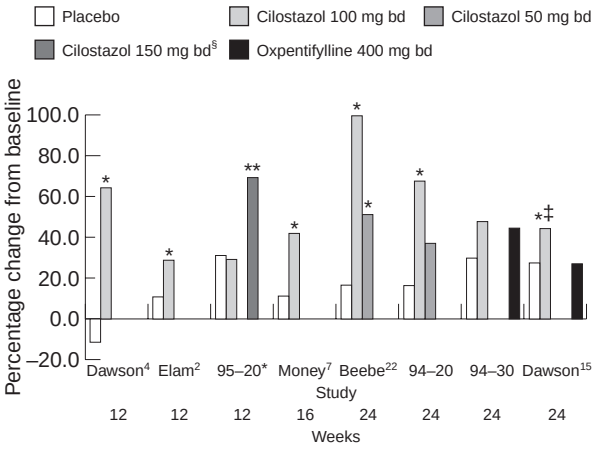

Fig. 2 Efficacy results from eight clinical trials with cilostazol. Reproduced with permission [21]. *Cilostazol 50 mg or 100 mg b.d. significantly better than placebo; ‡Cilostazol 100 mg b.d. significantly better than oxpentifyline; **Cilostazol 150 mg b.d. significantly better than cilostazol 100 mg b.d. or placebo; §unlicensed dose.

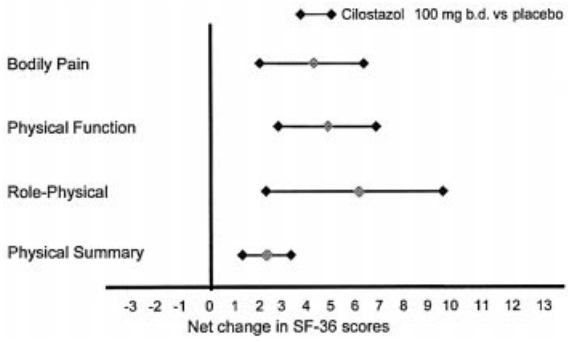

Fig. 3 Effect of cilostazol on quality of life using the SF-36: data from six pooled US trials.

group. This equates to a mean increase in distance walked, from 130 m at baseline to 259 m at week 24 for the cilostazol 100 mg b.d. group, and from 132 m to 199 m for the cilostazol 50 mg b.d. group.

Pain-free walking distance also increased by 59% ($P < 0.001$ vs. placebo) in the cilostazol 100 mg b.d. group and 48% ($P < 0.001$ vs. placebo) in the cilostazol 50 mg b.d. group. However, it is important to note that the treadmill test for this study required patients to walk at 3.2 km/h (2 miles/h) on a constant slope of 12.5%, walking at an intensity equal to 6 metabolic equivalents (METs) or an intensity two to three times greater than their normal walking. Any improvement measured under these conditions would be likely to underestimate the true improvement in distance that would occur under normal walking conditions.

As noted above, a comparative trial with oxpentifylline showed a clear superiority of cilostazol over both oxpentifylline and placebo [14]. This 24-week study in 698 patients compared cilostazol 100 mg b.d. with oxpentifylline 400 mg t.d. and placebo, using a variable load treadmill. From week 4 onwards, patients treated with cilostazol showed a significantly greater improvement in maximal walking distance than patients treated with oxpentifylline. The difference between treatments continued to increase over the course of the study. At week 24, patients treated with cilostazol 100 mg b.d. had increased their maximal walking distance by 107 m, compared with 64 m for patients treated with oxpentifylline and 65 m for patients receiving placebo.

Thus, at week 24, cilostazol 100 mg b.d. clinically and statistically ($P < 0.001$) increased walking distance. In contrast, the effect of oxpentifylline on walking distance in this study was not significantly different to placebo.

Quality of life

Cilostazol has been shown to improve not only walking distance but also quality of life, as assessed by the Medical Outcomes Scale Short Form-36 (SF-36) [23]. The SF-36 is widely used to evaluate patients' physical abilities, behaviours and emotions, as well as patients' own perceptions of their general health and well-being, and has been validated as a marker of functional change in clinical trials [24]. The quality of life data support the treadmill data and provide evidence that the physical activity and mobility aspects of quality of life are significantly improved in cilostazol-treated patients compared with placebo (Fig. 3). The physical summary score provides an overall assessment of physical functioning. This score improved significantly in patients receiving cilostazol 100 mg b.d., compared with placebo. As was expected, cilostazol had no effect on quality of life measurements associated with mental or emotional well-being, and the overall mental component score did not differ between the cilostazol and placebo groups. Vitality, however, which assesses how tired or worn-out a person feels, showed significantly better scores in cilostazol-treated patients than in those receiving placebo.

Tolerability

In the eight major Phase III trials in IC, which included some 2700 patients, cilostazol was generally well tolerated with most adverse events of mild-to-moderate

Table 2 Adverse events occurring in more than 2% of patients during Phase III clinical trials with cilostazol

	Cilostazol		
	50 mg b.d. (*n* = 303)	**100 mg b.d. (*n* = 998)**	**Placebo (*n* = 973)**
Headache	26	34	13
Palpitation	5	10	1
Tachycardia	4	4	1
Oedema	8	7	4

severity [21]. No consistent clinically relevant laboratory abnormalities occurred in patients treated with cilostazol. All-cause mortality and cardiovascular morbidity appeared comparable to placebo, with a mortality rate of 0.7% in the placebo group and 0.8% in the cilostazol group. In addition to the safety data from US and UK clinical trials described above, considerable safety data are available from the clinical use of cilostazol in other countries such as Japan, where it has been in use for various vascular disorders for more than a decade. About 1.5 million patients have received cilostazol worldwide. The safety profile of cilostazol in the wider population parallels that reported in the eight US/UK trials in IC. The most commonly reported adverse events are shown in Table 2.

In view of the adverse experiences that occurred with another phosphodiesterase III inhibitor that had been developed for use in congestive heart failure, milrinone, where patients developed fatal arrhythmias, cardiac safety was closely examined during clinical trials with cilostazol. There was no evidence of excess mortality or serious cardiovascular complications. According to data from 12-lead electrocardiograms, there were no excess arrhythmias in the cilostazol group compared with placebo, although there was a very slight increase in QT_c of 3 ms in the cilostazol group. Further, the considerable postmarketing data from Japan have revealed a similar adverse event profile to that seen in the clinical trials [21]. Lastly, it is important to note that cilostazol is contraindicated in heart failure unlike milrinone which had been specifically developed for that indication.

Conclusions

IC is a common and often disabling disorder, which has a major impact on patients' abilities to perform everyday activities. Cilostazol represents a novel treatment for this painful condition. It is the first treatment to show significant improvements in maximal and pain-free walking distances in large-scale clinical trials of patients with IC. Compared with placebo, cilostazol 100 mg b.d. significantly improves pain-free and maximal walking distances. The greatest benefits with cilostazol are observed following treatment for 16–24 weeks, although some benefit from treatment may be observed from weeks 4–12.

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