REVIEW

Medical Therapy for Intermittent Claudication

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Medical therapy to improve symptoms, stabilise the underlying vascular disease and improve lower limb outcomes is an important and effective adjunct to lifestyle modification and surgical or endovascular interventions in patients with IC. Randomised placebo controlled trials have shown that the phosphodiesterase III inhibitor cilostazol 100 mg bid improves pain-free and maximum walking distance, as well as quality of life, in a range of patients with intermittent claudication in whom there is no evidence of tissue necrosis or rest pain. This review summarises the evidence from 8 pivotal trials of cilostazol involving over 2000 patients with intermittent claudication treated for up to 6 months. There is comparatively less evidence to support the use of other treatment modalities for relief of symptoms in intermittent claudication, but there is considerable interest in therapeutic angiogenesis to promote new vessel formation and enhance collateralisation of the lower limb using recombinant growth factor proteins or gene transfer strategies. The rationale for therapeutic angiogenesis is discussed, together with the most recent results from randomised trials in patients with peripheral arterial disease.

Introduction

The age-adjusted prevalence of atherosclerotic peripheral arterial disease (PAD) is approximately 12%, of which intermittent claudication (IC) is the most common symptom.1 IC is painful, disabling and infrequently requires surgical intervention, but patients complain of significant mobility and lifestyle restrictions which affect their quality of life (QOL). In the Edinburgh Artery Study, 4.5% of all men and women aged 55–74 years had IC.2 Thus, the clinical and prognostic significance of PAD, especially IC, should not be under-estimated. A diagnosis of PAD invariably means that significant occlusive arterial disease (silent or symptomatic) is present in other parts of the circulation.3 For example, up to two-thirds of patients with PAD have significant coronary artery disease (CAD) and 30–50% will have evidence of prior stroke on brain imaging.4 Not surprisingly, therefore, the severity of PAD, as reflected by the ankle-brachial pressure index (ABPI), correlates with reduced survival.5

Less than 10% of patients with IC require surgical or endovascular intervention, but they all require medical therapy (including pharmacological and non-pharmacological interventions) to improve symptoms, exercise tolerance and clinical outcomes (i.e reduced progression to critical limb ischaemia and improved patient survival). There are a number of drug therapies used to provide immediate relief of symptoms in IC,6 as well as treatments aimed at modifying the disease process in order to achieve atherosclerotic plaque stabilisation and regression (and indirectly improve lower limb blood flow and symptoms in the longer term).6,7

Pharmacological Therapies to Improve Symptoms in IC

Assessing the efficacy of drugs used for relief of IC (especially older drugs that were licensed prior to the international standardisation of clinical trial requirements for marketing approval) has been fraught...
Clinical trial design and regulatory requirements

The European Medicines Evaluation Agency has defined certain criteria for the design of (phase III) clinical trials to evaluate and register new treatments for IC. In particular, the primary endpoints must be based on standardised treadmill exercise tests to define pain-free and maximal walking distances; patients included in the trial must demonstrate repeatable symptoms and walking limitation on the treadmill at baseline, prior to randomisation; and the absolute claudication distance at baseline should be in the region of 100–300 m. Treadmill exercise tests are notoriously associated with wide intra- and inter-individual variability, there is a significant placebo effect and new guidelines exclude patients who might have other exercise-limiting symptoms as well as IC. Similar treadmill testing has been used to demonstrate the efficacy of antianginal drugs, but in ischaemic heart disease exercise-induced ECG changes (ST-segment depression) are more reproducible than symptoms. Unfortunately, in IC the evaluation of drug efficacy is based solely on symptoms and walking distance in the relatively artificial setting of a graded exercise device.

Cilostazol

Cilostazol (Pletal) is a phosphodiesterase III (PDE III) inhibitor which is licensed in the USA, Japan and parts of Europe (UK, Ireland, Germany) for the improvement of maximal and pain-free walking distances in patients with IC, in the absence of rest pain or evidence of peripheral tissue necrosis. The underlying mechanism of action is not entirely clear, but weak vasodilator activity, anti-platelet effects (improving collateral flow) and possibly a direct biochemical action on muscle oxygen consumption and pain threshold (via increased levels of cyclic AMP) might all contribute to the improved walking distances.

A total of 8 multicentre, randomised, placebo-controlled trials, ranging in duration from 12–24 weeks, evaluated the efficacy and safety of cilostazol in a total of 2702 patients with moderate-to-severe IC. Four of these trials, involving 1534 patients, have been published, and two of the trials also included an active comparator (pentoxifylline). The profile of effect of cilostazol develops over several weeks (Fig. 1), and a meta-analysis has provided an overview of the placebo-controlled trials and shown a 40% improvement in walking distance, relative to placebo, after 6 months treatment with cilostazol 100 mg twice daily (Fig. 2). Additional studies and clinical experience, especially in the USA where cilostazol has been used extensively for last 8 years, shows significant benefits in a range of patients with IC, including patients with diabetes. Table 1 summarises the major published (placebo-controlled) studies with cilostazol.

It is important to note that the patients enrolled in the cilostazol trials were typical of the IC population found in routine clinical practice. For example, they were mostly elderly (average age was 65 years), 60% had hypertension and 25% were diabetic. The baseline
cilostazol is not associated with ex-
base confirming that, unlike other PDEIII inhibitors
there is now an extensive post-marketing safety data-
maximum treadmill walking distance (and 95% confidence
et al
Strandness
et al
Money
Eur J Vasc Endovasc Surg Vol 34, September 2007
Study Duration of
Drug Dose No. of
Change in maximum
Change in pain-free
Change in ankle-
study subjects walking distance
walking distance
brachial pressure

Beebe et al.18 24 weeks Cilostazol 100 mg BD 175 +51% (p = 0.001) +59% (p < 0.001)
Placebo 170 +15% +20%
Dawson et al.19 12 weeks Cilostazol 100 mg BD 54 +30.5% (p < 0.01) +31.7% (p < 0.01)
Placebo 27 −9.3% −2.5%
Dawson et al.20 24 weeks Cilostazol 100 mg BD 227 +54% (p < 0.001) +76% (p = 0.0001) +6%
Pentoxifylline 400 mg TDS 232 +30% (p = 0.82) +60% (p = 0.07) +8%
Placebo 239 +34% +48% −1%
Money et al.21 16 weeks Cilostazol 100 mg BD 119 +40% (p = 0.0001) +9% (p = 0.0125)
Placebo 128 +15% +1%
Strandness et al.25 24 weeks Cilostazol 100 mg BD 124 +64% (p = 0.0003) +73% (p = 0.0015)
Pentoxifylline 128 +36% +44%
Placebo 125 +18% +29%
Elam et al.26 12 weeks Cilostazol 100 mg BD 95 +35% (p = 0.004) +9% (p < 0.001)
Placebo 94 +24.3% +1.2%

Table 1. Summary of changes in walking distance in each randomised controlled trial of cilostazol in patients with IC

No. of patients
698 cilostazol 100 mg bid
pentoxifylline 1200 mg per day
516 cilostazol 50 mg bid
cilostazol 100 mg bid
239 cilostazol 100 mg bid
cilostazol 100 mg bid
81 cilostazol 100 mg bid

Fig. 2. A summary of the efficacy data from the 4 published placebo-controlled trials of cilostazol18–21 for changes in maximum treadmill walking distance (and 95% confidence intervals). Adapted from reference 22.

ABPI was 0.64. These patients were also taking a range of other cardiovascular drugs, e.g. anti-hypertensive and lipid-lowering medications.

Cilostazol is generally well tolerated (Table 2), and there is now an extensive post-marketing safety database confirming that, unlike other PDEIII inhibitors (e.g. milrinone),28 cilostazol is not associated with excess cardiovascular deaths.29 Because of safety concerns with milrinone, cilostazol is contra-indicated in patients with heart failure and/or serious (ventricular) arrhythmias. Cilostazol does not prolong the QTc interval, and the contra-indication in arrhythmia does not include patients with lone atrial fibrillation.

The commonest side effect is headache; the placebo-adjusted incidence was 20% in placebo-controlled trials. Transient diarrhoea, palpitation and dizziness (possibly because of cilostazol’s vasodilator effects) also have been recorded in more than 2% of patients in the 8 placebo-controlled trials (Table 2).22 These effects tend to subside after repeated dosing. An excess of bleeding episodes may occur with cilostazol, because of its antiplatelet effects, and this is more likely in patients also taking clopidogrel.29

Cilostazol undergoes extensive hepatic metabolism by the cytochrome P450 3A4 isoenzyme (CYP3A4) and therefore drugs which inhibit CYP3A4, e.g. cimetidine, erythromycin, and ketoconazole, will increase plasma cilostazol concentrations, but in clinical trials and in routine practice these interactions have not translated into an increase in cilostazol-related side effects.24

Cilostazol is perhaps the drug with the best evidence in support of its indication in IC. The clinical trial database involving over 2500 patients in double-blind, placebo-controlled studies far outweighs any other research in this field. As well as showing significant improvements in treadmill walking distance (which may underestimate the clinical benefit to individual patients in routine practice), cilostazol also improved various quality of life (QOL) scores in the context of double-blind trials. This conclusion is reflected in the SIGN guidelines, together with useful

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practical advice to stop cilostazol after 6 months if it is not clinically benefitting an individual patient and/or if their symptoms have changed and they no longer need drug therapy.\footnote{10}

Vascular disease-modifying therapies

As part of secondary prevention to reduce the risk of major life- or limb-threatening cardiovascular events, patients with PAD (especially those with IC) are routinely offered advice about lifestyle changes and treated with antiplatelet, antihypertensive and lipid-lowering drugs.\footnote{7} But to what extent do these interventions affect lower limb symptoms in PAD?

Smoking cessation among patients with IC does not significantly improve walking distance,\footnote{6} but it may reduce the severity of claudication and the risk of progression to rest pain.\footnote{30,31} Meta-analyses and randomised trials have shown that exercise significantly improves maximal walking time in patients with IC. The nature of the exercise should involve regular walking to near-maximum pain over a period of at least 6 months. The underlying mechanism by which exercise improves walking distance is unclear, but does not seem to work through improved ABPI or growth of collateral vessels.

Statins have powerful disease-modifying effects on the atherosclerotic plaque, and there is placebo-controlled trial evidence showing that simvastatin and atorvastatin improve treadmill walking distance in patients with PAD.\footnote{32,33} Furthermore, some of the effects of statins on lower limb function and exercise tolerance may be independent of their cholesterol-lowering effect.\footnote{34,35} In the Scandinavian Simvastatin Survival Study (4S study), only 4\% of (4000) patients had IC at baseline, but the incidence of ‘new or worsening’ IC was significantly lower in patients treated with simvastatin 40 mg compared with placebo.\footnote{36}

In terms of antihypertensive therapy, beta-adrenoceptor blockers do not worsen IC [6], but there is evidence that the combination of atenolol and nifedipine may reduce maximal treadmill walking distance.\footnote{37} Angiotensin converting enzyme (ACE) inhibitors, however, have been shown to improve walking distances.\footnote{38} Whether these effects are additive to those of cilostazol is not entirely clear, but in the randomised controlled trials cilostazol or placebo was added to ‘usual treatments’, which in a large proportion of participants included ACE inhibitor and/or statin therapy.

Therefore, the recommended medical therapy for patients with IC depends on whether cilostazol is licensed and available for local use. The case studies (1 and 2) show the recommended medical therapy for a patient with IC according to the availability of cilostazol.

Case 1: 69y male living in Derby, UK, with stable IC, type 2 diabetes and a maximum walking distance of 120 m which is causing significant life-restriction. His symptoms are bilateral and troublesome despite optimum BP and lipid control and use of aspirin 75 mg daily. HbA1c is 8.2\% (target HbA1c < 7\%). Investigations confirm diffuse, distal disease that is not amenable to percutaneous or surgical intervention. The patient does not have heart failure or trophic changes, and has been trying to exercise regularly for 6 months with only modest improvement.

This patient would be suitable for a therapeutic trial of cilostazol 100 mg bid, added to current therapy including exercise. This increases his maximum walking distance to 200 m, and the patient reports a significant improvement in symptom severity, exercise tolerance and quality of life. (If cilostazol is not effective after 6 months, the drug should be discontinued). The physician also increases his oral antidiabetic therapy (metformin and pioglitazone) to achieve better glycaemic control, which in turn is likely to benefit both micro- and macrovascular disease.

Case 2: A 78y female living in Milan, Italy, underwent a femoro-poplitel bypass 10 years ago. In the last 2 years, IC has gradually increased and her maximum walking distance is now 220 m. Her past medical history also includes a right carotid endarterectomy for amaurosis fugax 4 years ago. She takes very little exercise, and the clinical assessment shows BP 184/86 mmHg and fasting LDL-cholesterol 5.7 mmol/L. Serum creatinine and fasting glucose are normal. Her current therapies include aspirin 75 mg, dipyridamole 200 mg bid, simvastatin 40 mg, and bendroflumethiazide 2.5 mg.

In terms of her medical therapy to improve symptoms and cardiovascular outcomes, the focus of her management should be: (1) regular exercise to near-maximal pain threshold, ideally 3 or 4 times per week under supervision by an exercise...
Emerging Therapies: Molecular, Genetic and Cellular Approaches to Augment Growth of New and Collateral Vessels

The development of collateral vessels is an important physiological adaptation to chronic ischaemia due to occlusive arterial disease, and in patients with PAD the extent of collateralisation can have a major impact on symptoms, distal blood flow and lower limb outcomes.39 The regulation of new vessel formation is complex and incompletely understood, but in normal tissue turnover and repair there is a fine balance between pro- and anti-angiogenic pathways. In the context of vascular disease, the duration and severity of ischaemia, shear stress and activation of local inflammatory pathways strongly influence the angiogenic response.40

Formation of new (collateral) vessels involves at least 3 distinct biological processes. Angiogenesis is the sprouting of new capillaries from existing vascular structures, a process that is triggered by endothelial cell activation, migration and proliferation followed by remodelling and expansion of the extracellular matrix.40 Angiogenesis creates a fragile network of branching points and sprouts new vessels from arterioles that may lie upstream or downstream from occluded or tightly stenosed arteries. Vasculogenesis, however, is the in-situ formation of new blood vessels from circulating bone marrow-derived endothelial progenitor cells (EPCs).41 Vasculogenesis occurs in adults (as well as embryos), where EPCs differentiate into endothelial cells which fuse to form luminal structures. The process of arteriogenesis refers to an increase in wall thickness and luminal diameter of existing arteriolar collateral vessels via recruitment of perivascular and smooth muscle cells. Arteriogenesis develops a smooth muscle layer within the newly formed vessel in order to withstand arterial blood pressure. Inflammatory mediators and shear stress, rather than hypoxia, stimulate arteriogenesis.42

New vessel formation in the myocardium and lower limbs of patients with PAD is likely to involve a combination of angiogenesis, vasculogenesis and arteriogenesis (Fig. 3).40-43

Over the last 30 years a number of growth factors and cytokines have been identified which either stimulate or inhibit angiogenesis.44 In particular, three groups of growth factors have been targeted by the biotechnology industry for therapeutic angiogenesis: (1) the vascular endothelial growth factor (VEGF) family, which includes VEGF-A, VEGF-B, VEGF-C, and VEGF-D (post-transcriptional modification of VEGF-A results in 3 major isoforms: VEGF121, VEGF165 and VEGF189) (2) the fibroblast growth factor (FGF) family, e.g. FGF-2 (also known as basic FGF, bFGF) and FGF-4; and (3) granulocyte monocyte colony stimulating factor (GM-CSF, which activates circulating monocytes and stimulates release of bone marrow derived EPCs).

Therapeutic angiogenesis: proteins or gene transfer?

Therapeutic angiogenesis aims to artificially boost the natural angiogenic response by increasing substantially the local concentrations of angiogenic growth factors in the lower limb, either by administering recombinant protein or the gene that codes for an angiogenic growth factor, or by administering EPCs that will synthesize multiple growth factors near to sites of new vessel formation.45,46 The strategy for clinical rehabilitation program; (2) As with many patients, simvastatin 40 mg is not achieving the recommended LDL-cholesterol target (<3 mmol/L, ideally <2 mmol/L). Switching to atorvastatin or rosuvastatin, and/or adding ezetimibe, would be reasonable options; (3) She has systolic hypertension and is likely to require at least 2 (probably 3) drugs to reach the goal of SBP<140 mmHg. Addition of an ACE inhibitor or angiotensin receptor blocker would be the preferred option. Surgical management would include assessment of the patency of her fem-pop graft.
development has focused mainly on local delivery of growth factors using gene transfer (delivered by intramuscular or arterial catheter).

The principal methods of gene transfer are based on using either a plasmid (naked DNA) or a viral vector (e.g. adenoviral or retroviral). Plasmid transfer is much less efficient (<10% enters the cell nucleus), but perceived to be safer and can produce increased local gene expression for up to 4 weeks. Viral-based vectors provide high rates of gene transfer, but can sometimes trigger immunological or inflammatory reactions. Retroviral vectors transfer RNA into the target cells, which is then converted to DNA and incorporated into the host genome. Theoretically, this should result in indefinite overexpression of the transgene.

**Randomised controlled trials of recombinant protein or gene transfer in IC**

Following the first case report of VEGF gene transfer in a patient with critical limb ischaemia, there have been 2 randomised controlled trials in patients with PAD to evaluate functional endpoints following administration of recombinant protein or gene transfer (Table 3).

The TRAFFIC study was a double-blind, placebo-controlled trial of single or repeat-dose intra-arterial recombinant FGF-2 (rFGF-2). The dose (30 mg/kg) was the maximum-tolerated dose of rFGF-2 shown in dose-response tests to avoid inducing systemic hypotension. Patients with IC received half the dose of FGF-2 down each femoral artery via a single arterial puncture and crossover catheter. Strict inclusion criteria required patients to have two reproducible treadmill tests during a 30-day screening period, evidence of infra-inguinal obstructive arterial disease and a resting ABI < 0.8 on the most affected limb. A total of 377 patients were screened to identify 190 who were eligible for randomisation. Patients were randomised to placebo, single-dose FGF-2 or two doses of FGF-2 (the second dose given 30 days later). Peak walking time at 90 days (the primary endpoint) was increased by 0.6 min with placebo, 1.77 min with single-dose rFGF-2 and by 1.54 min with double-dose rFGF-2. By analysis of variance, the difference between groups was \( p = 0.075 \), but in a secondary intention-to-treat analysis (involving all 190 randomised patients) the difference between groups was \( p = 0.034 \).

The Regional Angiogenesis with VEGF (RAVE) trial used an adenoviral vector to transfer the gene for VEGF121 (AdVEGF121) in patients with critical limb ischaemia and reproducible unilateral claudication. This was a multicentre, double-blind, placebo-controlled dose-finding study to assess the safety and efficacy of intramuscular AdVEGF121 in patients with unilateral PAD. A total of 105 patients with exercise-limiting IC on two baseline treadmill tests (peak walking time between 1 and 10 min) were stratified by diabetes status and randomised to low-dose (4 \( \times 10^7 \) PU) AdVEGF121, high-dose (4 \( \times 10^{10} \) PU) AdVEGF121 or placebo, administered as 20 intramuscular injections to the index leg in a single session. The primary efficacy endpoint (change in peak walking time) at 12 weeks was not different between the 3 groups: 1.8 ± 3.2 min (placebo) vs 1.6 ± 1.9 min (low dose) vs 1.5 ± 3.1 min (high dose). Secondary analyses, including change in peak walking time, ABI, claudication onset time and QOL measures (walking impairment questionnaire) were also similar among the 3 groups at 12 and 26 weeks.

Further gene therapy trials in patients with IC are on-going based on different genes and more sophisticated vectors to achieve higher rates of transfection. For example, the Del-1 for therapeutic angiogenesis trial (DELTA-1) is assessing a plasmid-mediated approach to induce angiogenesis and arteriogenesis using the angiomatrix protein Del-1 (developmentally regulated endothelial locus 1). VLT5-589 is an investigational non-viral therapeutic comprising a plasmid expressing Del-1 formulated with poloxamer 188 (facilitating agent). Over 100 patients with IC will be randomised in the DELTA-1 trial.

**Bone marrow derived EPCs**

EPCs are involved in vasculogenesis, and experimental studies in animal models of PAD have shown that implantation of bone marrow mononuclear cells

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Table 3. Summary of randomised, controlled trials of single or multiple administrations of DNA or recombinant protein to stimulate angiogenesis in patients with PAD

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Patient group (No. of subjects)</th>
<th>Route of Administration</th>
<th>Efficacy Assessment</th>
<th>Endpoint (result)</th>
<th>Trial Name</th>
</tr>
</thead>
<tbody>
<tr>
<td>Recombinant protein</td>
<td>FGF-2 (n = 174)</td>
<td>i.a</td>
<td>90 days</td>
<td>Peak walking distance (positive)</td>
<td>TRAFFIC47</td>
</tr>
<tr>
<td>Gene therapy</td>
<td>VEGF121 (Adenoviral) (n = 105)</td>
<td>i.m</td>
<td>12 &amp; 26 weeks</td>
<td>Exercise tolerance (negative)</td>
<td>RAVE48</td>
</tr>
</tbody>
</table>
promotes collateral vessel formation with increased incorporation of EPCs into networks of new vessels. The TACT study was a randomised controlled trial of autologous bone marrow derived mononuclear cells, including EPCs, which were implanted into critically ischaemic limbs. Clinical improvements (decreased rest pain) were recorded in 39 out of 45 patients, and there were significant increases in ABPI from 0.35 at baseline to 0.47 after 1 month. The attraction of cellular-based therapy is that EPCs will secrete a range of angiogenic factors to promote a co-ordinated response leading to new vessel formation. This strategy, especially in critical ischaemia, may be more effective than single protein or gene transfer techniques.

Conclusions
IC is a common, painful and disabling symptom. Medical therapy has an important role as an adjunct to lifestyle modification and (in a small subgroup of patients) surgical or endovascular procedures. The focus of treatment is on symptom relief, and secondary prevention to reduce the risk of major life- or limb-threatening cardiovascular complications. There is good evidence from randomised controlled trials that cilostazol improves maximum and pain-free walking distance, as well as QOL, in patients with IC, although the underlying mechanisms are unclear. Statins and ACE inhibitors – used extensively for cardiovascular risk modification and to slow disease progression and prolong survival in patients with atherosclerotic disease – also improve exercise tolerance in patients with PAD, in part through changes in vascular structure and function.

In the future, management strategies for PAD will include treatment modalities that augment new vessel formation and preserve tissue viability. This will be especially appropriate for patients with critical limb ischaemia, rest pain and/or failed revascularisation. Considerable research is ongoing to refine the instruments for therapeutic angiogenesis based on recombinant proteins and/or gene transfer. In particular, selecting the right gene or protein, and refining the mode and route of administration will be key to improving the durability and magnitude of the angiogenic response.

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