Executive summary

Background

Peripheral arterial disease (PAD) is a debilitating condition caused by fatty deposits in the arteries of the legs and arms, leading to insufficient blood flow to the muscles. Diabetes, smoking, hypertension and elevated blood lipid levels are all important risk factors for progression of PAD. Intermittent claudication (IC) is the most common symptom of PAD, occurring in around 40% of patients. It is characterised by pain in the legs or buttocks during exercise, which subsides with rest. Disease progression can lead to pain at rest and in severe cases, necrosis and gangrene (< 1% per year). Furthermore, PAD is associated with an increased risk of cardiovascular events including myocardial infarction (MI) and stroke, and a mortality risk of around 2.5 times that of age- and sex-matched groups without PAD. The prevalence of IC has been estimated at 4.5%, based on a Scottish population aged 55 to 74 years. However, prevalence increases dramatically with age and with lower social class. The impact on patients' quality of life (QoL) is severe and comparable to that in patients with other cardiovascular conditions such as MI or stroke.

Cilostazol

Launched for use in the UK in 2002, Cilostazol (Pletal®) is an orally administered, selective phosphodiesterase III inhibitor, which, by increasing levels of cyclic adenosine monophosphate, exhibits a multifunctional mode of action. Cilostazol induces vasodilation, facilitating blood flow. The drug also inhibits platelet aggregation, and thus thrombus formation. This action favourably modifies plasma lipid levels, increasing high density lipoprotein-cholesterol and decreasing triglyceride levels, which may help to reduce the formation of fatty deposits in arteries (the cause of IC). Furthermore, cilostazol has anti-proliferative effects on smooth muscle cells.

Cilostazol is indicated for the symptomatic treatment of intermittent claudication, that is, the improvement of the maximal and pain free walking distances in patients with IC who do not have rest pain and who do not have evidence of peripheral tissue necrosis (PAD Fontaine Stage II) (1). Other pharmacological symptomatic treatments for IC include naftidrofuryl, pentoxifylline, and inositol nicotinate. Major UK and international treatment guidelines recommend cilostazol as the first-line treatment choice amongst other pharmacological treatments.

Clinical efficacy

Cilostazol (compared with placebo) increases the maximal and pain-free distances patients with IC can walk, as measured by treadmill tests. Compared with placebo, treatment with cilostazol 100 mg twice daily (bid) improved maximal walking distance, and statistical significance was achieved in seven out of ten studies. Results for pain free walking distance also demonstrated an improvement with cilostazol. Statistical significance was achieved in five of these studies. Treatment with cilostazol also improves physical aspects of QoL and various aspects of walking ability (measured via the SF-36 and WIQ questionnaires) over placebo. Another positive effect on IC that has been observed in cilostazol-treated patients is an increase in blood pressure in the limbs, which is typically low in IC patients. Evidence from RCTs also indicates that cilostazol improves patient's lipid profiles (e.g. cholesterol and triglycerides).

A pooled meta-analysis of nine cilostazol studies showed a statistically significant mean increase in ACD in favour of cilostazol compared with placebo (50.7% vs. 24.3%, $P = 0.0001$) and a statistically significant mean increase in ICD in favour of cilostazol compared with placebo (67.8% vs. 42.6%, $P = 0.0001$). Pentoxifylline showed no significant improvement over placebo for ACD. In this pooled analysis, cilostazol also showed

statistically significant improvements in physical aspects of QoL (SF-36) and various aspects of walking ability (WIQ), compared with placebo.

Safety

Cilostazol is generally well tolerated. The most common adverse events (AEs) across all studies included headache, diarrhoea, abnormal stools, peripheral oedema, and nausea. These events were generally of mild to moderate severity, transient or resolved after symptomatic treatment, and rarely required treatment discontinuation. Long-term treatment with cilostazol did not increase the incidence or severity of AEs. No relevant changes in liver or renal function were observed during cilostazol treatment.