The Limits of Evidence in Drug Approval and Availability: A Case Study of Cilostazol and Naftidrofuryl for the Treatment of Intermittent Claudication

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ABSTRACT

Purpose: Despite numerous efforts to develop effective medications for the treatment of intermittent claudication (IC) over the past 4 decades, a gold standard medical management option has yet to be defined. Although not life-threatening, IC interferes with mobility and activities of daily living, significantly impairing quality of life and potentially causing depression. Cilostazol, the leading pharmacologic agent for IC in the United States, was approved by the US Food and Drug Administration (FDA) in 1999 based on controversial data. Meanwhile, naftidrofuryl, the first-line pharmacologic agent for IC in the United Kingdom and Europe, has never been approved by the FDA and therefore is not available in the United States. The clinical data for cilostazol and naftidrofuryl are plagued by flaws related to lack of protocol standardization, objective endpoints, and strict eligibility criteria in study subjects, making identification of a true treatment effect impossible. Furthermore, no prospective randomized trial comparing the efficacy of cilostazol and naftidrofuryl has been conducted, because the manufacturers of these agents have much to lose and little to gain from such a study.

Objective: This article provides an overview of the pharmacology of cilostazol and naftidrofuryl, and the clinical studies leading to their approval and clinical acceptance. It further explores the possible sources of bias in analyzing these clinical trials, some of which have been brought to light by the National Institute for Health and Clinical Excellence (NICE) of the United Kingdom in its technology appraisal guidance. It also speculates the ways in which economic incentives may affect drug-marketing decisions.

Methods: A literature review of pharmacology and clinical trials for cilostazol and naftidrofuryl was performed in PubMed. The majority of included clinical trials were initially identified through the most recent Cochrane review articles as well as the FDA's approval packet for cilostazol. The technology appraisal guidance of the National Institute for Health and Care Excellence of the United Kingdom and the manufacturer's response to this guidance document were located via an online search engine.

Findings: The clinical data for cilostazol and naftidrofuryl are plagued by flaws related to lack of protocol standardization, objective endpoints, and strict eligibility criteria in study subjects, making identification of a true treatment effect difficult. Furthermore, no prospective randomized trial comparing the efficacy of cilostazol and naftidrofuryl has been conducted.

Implications: The history of the evaluation, approval, and marketing of these drugs illustrates the limitations of data in the regulatory approval and marketing of agents whose benefit is subjective and difficult to quantify. Implementation of a standardized protocol with strict eligibility criteria, objective quantifiable measurement of drug effect, and validated endpoints will eventually allow development of an ideal pharmacotherapy for IC. (*Clin Ther.* 2014;36:1290–1301)

Key words: cilostazol, naftidrofuryl, pharmacotherapy for intermittent claudication, treatment for intermittent claudication, Pletal, Praxilene.

INTRODUCTION

Intermittent claudication (IC) is the most common manifestation of peripheral arterial disease (PAD)

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caused by atherosclerosis.[1] IC is defined by symptoms such as pain, cramping, numbness, or fatigue in the leg muscles brought on by walking and relieved by a few minutes of rest. Milder symptoms, such as claudication after one quarter mile of vigorous walking, may be associated with narrowing of only a single major leg vessel such as the superficial femoral artery, whereas severe symptoms (eg, claudication at 30 feet of walking at a modest pace) are often associated with narrowing or complete occlusion of several leg vessels.

According to the 2007 report of TASC (Trans-Atlantic Inter-Society Concensus) II, the prevalence of IC seems to increase from ~3% in patients aged 40 years to 6% in those aged 60 years.[1] Patients with claudication experience reduced quality of life and have a tendency to suffer from depressive symptoms associated with their restricted mobility.[2] Due to the presence of systemic atherosclerosis, patients with IC also are 3 times more likely to die of cardiovascular causes, primarily myocardial infarction and stroke, compared with patients without IC.[3] It has been estimated that the overall cost of PAD determined in >30,000 patients in the United States was ~$6000/patient per year, similar to the cost of caring for patients after myocardial infarction.[4]

The treatment goals for patients with IC include symptomatic relief and management of associated cardiovascular risk factors. Available treatments include exercise regimens and lifestyle modification (especially smoking cessation and weight loss), pharmacotherapy, and (in severe cases) catheter-based or surgical interventions to treat the arterial obstructions and improve blood flow.[1] Although exercise therapy with smoking cessation is the preferred initial treatment for all patients with IC, compliance with supervised exercise is poor, and most subjects remain symptomatic with compromised quality of life. Pharmacotherapy along with exercise and smoking cessation, therefore, plays an important role in selected patients with significant symptoms. Surgical and catheter-based interventions are reserved for patients with truly disabling symptoms, who fail to respond to smoking cessation, exercise, and pharmacotherapy.

Currently in the United States, only 2 drugs, pentoxifylline and cilostazol, are available with approval by the US Food and Drug Administration (FDA) for treating symptoms of IC. Although pentoxifylline (approved in 1984) has exhibited only modest effects versus placebo, cilostazol (approved in 1999) has exhibited greater efficacy in published trials compared with either placebo or pentoxifylline.[5,6] Despite numerous randomized, placebo-controlled trials, however, lack of protocol standardization and resulting inconsistencies in the demonstrated magnitude of therapeutic effect have created significant uncertainty as to the appropriate role of cilostazol.[7]

In the United Kingdom and Europe, naftidrofuryl oxalate has been available since 1972. Several meta-analyses have suggested a statistically significant and clinically meaningful effect of naftidrofuryl compared with placebo and/or pentoxifylline.[7–9] In the midst of uncertainties over the efficacy of these vasoactive drugs for IC, the National Institute for Health and Care Excellence (NICE) of the United Kingdom published a technology appraisal guidance in May 2011 based on systematic reviews, meta-analyses, and cost-effectiveness analyses.[10] This document concludes provocatively that naftidrofuryl oxalate is the only recommended option for the treatment of IC, whereas cilostazol is not recommended. Furthermore, the UK's Medicines and Healthcare Products Regulatory Agency suggested in its Drug Safety Update in April 2013 that cilostazol must be restricted to second-line treatment due to contraindicating risks in patients with congestive heart failure and interactions with other medicines.[11] Considering these advisory articles published by UK governmental regulatory agencies, it is not surprising to find that the proportional market share of naftidrofuryl oxalate, cilostazol, and pentoxifylline in England and Wales in 2009 were estimated to be 52%, 29%, and 4%, respectively.[12]

Despite the UK guidelines for IC treatment, naftidrofuryl is not FDA approved, and cilostazol is presently the mainstay pharmacologic agent for IC treatment in the United States. To date, no head-to-head clinical trials comparing the 2 drugs have been performed, and NICE's guidelines depend solely on meta-analyses of placebo-controlled trials. The heterogeneity of the clinical trials included in the meta-analyses performed over the past 20 years does not allow definitive conclusions on the relative merits of the 2 drugs.[13]

The lack of clarity in the roles of drugs for IC illustrates the regulatory and clinical problems that emerge when weak clinical data are used in the drug approval process. In the absence of compelling clinical data with precise objective endpoints, opportunities for bias are frequent and cost considerations assume