Pharmacokinetic, Pharmacodynamic, and Safety/Tolerability Profiles of CG100649, a Novel COX-2 Inhibitor: Results of a Phase I, Randomized, Multiple-dose Study in Healthy Korean Men and Women

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ABSTRACT

Background: CG100649 is a novel anti-inflammatory drug that is currently under development. CG100649 demonstrates a dual mechanism of action on cyclooxygenase-2 and carbonic anhydrase that may result in favorable treatment effects and few adverse gastrointestinal and cardiovascular events.

Objective: The objective of this study was to evaluate the safety, pharmacokinetic, and pharmacodynamic profiles of administering multiple oral doses of CG100649 to healthy Korean volunteers.

Methods: This was a randomized, double-blind, placebo-controlled, multiple ascending oral dose study that was performed on 8 male and 8 female subjects per dose cohort. Each subject was randomly selected to receive either a single loading dose followed by 6 days of once-daily placebo (n = 4; 2 male and 2 female subjects) or CG100649 (n = 12; 6 male and 6 female subjects). Each subject was administered 1 of 3 sequential dose levels (8-mg loading dose + 2 mg/d, 10-mg loading dose + 4 mg/d, or 12-mg loading dose + 8 mg/d). Blood samples for pharmacokinetic analysis were obtained ≤480 hours after the last dose. Blood samples for measuring serum thromboxane B_2 (TXB_2) and ex vivo lipopolysaccharide-stimulated prostaglandin E_2 (PGE_2) (markers of cyclooxygenase-1 and cyclooxygenase-2 activity, respectively) and urine samples for measuring prostanoid metabolites were collected ≤21 days after the last dose.

Results: During steady state, the median T_{max} in blood and plasma after the last dose ranged from 3 to 10 hours and 3.5 to 7.3 hours, respectively. Mean terminal $t_{½}$ values in blood and plasma ranged from 121 to 203 hours and 100 to 167 hours, respectively. Whole blood concentrations were 50 to 70 times higher than plasma concentrations in all 3 dose cohorts in both male and female subjects. Compared with baseline, serum TXB_2 diminished by 68% to 91% at 8 hours after the administration of the last dose in all 3 cohorts ($P < 0.001$). Ex vivo lipopolysaccharide-stimulated PGE_2 was maximally inhibited (89%–96%; $P < 0.001$) by all 3 dose levels on day 7. Urinary prostacyclin metabolite was inhibited by 64% ($P < 0.001$) on day 7 (12–24 hours) but only by the highest CG100649 dose. There were no clinically significant drug-related changes in blood pressure between treatment groups. The most frequently encountered adverse events were aphthous stomatitis and dyspepsia.

Conclusions: CG100649 was well tolerated and demonstrated a whole blood concentration that is ~50 to 70 times higher than in plasma in these healthy subjects. CG100649 suppressed TXB_2 and PGE_2 at all 3 doses, and only the highest dose suppressed the urinary excretion of the urinary prostacyclin metabolite. (*Clin Ther*. 2015;37:197–210)

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INTRODUCTION

Hypertension and arthritis are among the most common chronic conditions in the United States. People with osteoarthritis (OA) and rheumatoid arthritis are at higher risk than the general population for developing several comorbid conditions, particularly cardiovascular disease.[1,2] Approximately 24.3 million US adults ≥35 years of age have OA, and ~40% of people with OA also have stage I to III hypertension as defined by the Joint National Committee VI guidelines.[3] Concomitant use of traditional NSAIDs or selective cyclooxygenase (COX)-2 inhibitors with antihypertensive drugs is therefore common among subjects with arthritis. The previously developed first-generation NSAIDs were nonselective and inhibited both COX-1 and COX-2, allowing gastrointestinal erosions to develop in many subjects, along with reduced inflammation and pain relief. Selective COX-2 inhibitors (coxibs) were developed with the aim of reducing the incidence of the serious adverse events in the upper gastrointestinal tract that are associated with the administration of traditional NSAIDs, which result as a consequence of the inhibition of COX-1–derived prostanoids.[4,5] Compounds that exhibit greater COX-2 selectivity are thought to demonstrate a lower potential for gastrointestinal injury while also maintaining anti-inflammatory effects by inhibiting COX-2.

However, recent studies have reported the increased risk of adverse cardiovascular events, including blood pressure elevation and coxib-induced myocardial infarction.[6–10] In the literature, the most frequently reported mechanism that accounts for the cardiovascular toxicity of coxibs is the eicosanoid imbalance theory.[11,12] Although NSAIDs inhibit both COX isoforms, the inhibition of COX-2 decreases prostacyclin (PGI_2), a vasodilator and modulator of platelet activation, without reducing COX-1–dependent thromboxane A_2 (TXA_2), thereby contributing to platelet aggregation and vasoconstriction.[13,14] Moreover, COX-2 plays an important role in the pathogenesis of atherosclerosis as a source of PGI_2, thereby producing more TXA_2 and thus inhibiting COX-2. This action has a profound effect on prostanoid balance, and in so doing, favors TXA_2 production and promotes platelet-dependent thrombosis. Of the available COX-2 inhibitors, most studies directly compared celecoxib and rofecoxib at equal antirheumatic dosages. All such comparative studies reported that rofecoxib demonstrates statistically more cardiovascular toxicity than celecoxib, indicating that cardiovascular toxicity is compound specific rather than a class effect that is characteristic of all COX-2 inhibitors.[9] The cardiorenal and blood pressure–elevating actions of COX-2 inhibitors are also important determinants of cardiovascular risk, and differences between coxibs have been reported. The nanomolecular affinity of sulfonamide COX-2 inhibitors, such as celecoxib and valdecoxib, for carbonic anhydrase (CA) II suggest a possible additive diuretic effect that could counteract COX-2–induced inhibition of renal hypertension, although this has not been confirmed in short-term clinical trials.[15,16]

CG100649 is a synthetic NSAID currently being developed for the relief of chronic pain and the treatment of the painful signs and symptoms associated with OA and rheumatoid arthritis. CG100649 is a novel NSAID that, due its postulated dual inhibition of COX enzymes and CA-I/II, might limit the propensity for NSAID-induced hypertension and thereby attenuate associated cardiovascular risks.[17] CG100649 did not elevate blood pressure in healthy volunteers or OA subjects in any of the previous clinical studies, including 4 Phase I and 1 Phase II trials.[18] The objective of the present trial was to evaluate the safety, tolerability, pharmacokinetics, and pharmacodynamics of supratherapeutic multiple oral doses of CG100649 compared with placebo in healthy Korean volunteers. The previous Phase II study reported that a single loading dose of 8 mg followed by once-daily 1.2-mg maintenance doses of CG100649 for 3 weeks to patients with OA was well tolerated and highly efficacious.[18] The highest daily dose used in this study (cohort 3, initial 12-mg loading dose on day 1 followed by 8 mg/d) is 6.67-fold higher than the daily efficacy dose established for the treatment of OA.

SUBJECTS AND METHODS

Subjects

All subjects were healthy adults (inclusive range, 19–55 years) with a weight >50 kg for men and >45 kg for women. All subjects were within 20% of their