Pharmacology of COR-003 (Levoketoconazole), an Investigational Treatment for Endogenous Cushing’s Syndrome

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ABSTRACT

In contrast to ketoconazole’s 2R,4S enantiomer, COR-003 (2S,4R-ketoconazole) is currently being investigated in a multinational phase 3 clinical trial for once-daily treatment of endogenous Cushing’s syndrome (eCS). COR-003 is an S-enantiomer of ketoconazole metabolized in the liver and eliminated predominately by the bile. COR-003 is a more potent inhibitor of human cytochrome P450 11B1 (CYP11B1) and a more effective inhibitor of cortisol synthesis compared with ketoconazole. The objective of this paper is to describe preclinical and clinical pharmacology findings for COR-003.

OBJECTIVE

To describe preclinical and clinical pharmacology findings for COR-003.

INTRODUCTION

Endogenous Cushing’s syndrome (eCS) is a rare endocrine disorder characterized by hypercortisolism with increased morbidity and mortality. Treatment options for Cushing’s syndrome include surgical resection, medical therapy, and bilateral adrenalectomy. Hydrocortisone (19 carbons) and aldosterone (19 carbons) are synthesized from cholesterol. The 11β-hydroxylase (CYP11B1) enzyme, present in the zona glomerulosa of the adrenal gland, catalyzes the conversion of 18-hydroxyprogesterone to cortisol. 

METHODS

Preclinical Pharmacology of COR-003: In vitro, COR-003 was shown to inhibit human CYP11B1 (IC50, 0.015 µM) and CYP21 (IC50, 0.002 µM) with greater potency compared with ketoconazole (IC50, 1.16 µM and 0.46 µM, respectively). 

Clinical Pharmacology of COR-003: In a 3-period, crossover, phase 1, drug-interaction study, healthy subjects received placebo, COR-003, or ketoconazole once daily on Days 1 to 4 and concomitantly with atorvastatin (40 mg QD). Atorvastatin AUC0-6h was higher with ketoconazole (641 ± 49 ng·h/mL) than COR-003 (481 ± 39 ng·h/mL) and placebo (263 ± 29 ng·h/mL) (P < 0.05). 

RESULTS

Preclinical Pharmacology of COR-003: In cell lines, COR-003 more potently and more effectively inhibited human CYP21 and CYP11B1 activity compared with ketoconazole. In rats, after a single oral application of increasing doses 2R,4S-ketoconazole, COR-003 more potently and more effectively inhibited human CYP21 and CYP11B1 activity compared with ketoconazole. 

Clinical Pharmacology of COR-003: In healthy subjects after 5 days of treatment, COR-003, compared with ketoconazole, more significantly decreased cortisol levels and serum corticosterone across groups. Mean (± standard error of the mean) AUC0-6h of cortisol was 56 ± 4% lower with COR-003 than with ketoconazole (600 ng/mL) (167 ± 6.8 ng/mL with COR-003 vs. 167 ± 6.8 ng/mL with placebo; P < 0.001).

SUMMARY

Corr-003 is a more potent inhibitor of human CYP11B1 and CYP21 than ketoconazole, resulting in decreased cortisol and corticosterone production, and COR-003 more significantly inhibited CYP21 and CYP11B1 activity in rats. COR-003 was more effective in inhibiting CYP21 and CYP11B1 activity in vitro and in vivo compared with ketoconazole. COR-003 showed 50% inhibition of corticosterone at the 100-mg/kg dose level, whereas ketoconazole showed 50% inhibition at 200 mg/kg. In clinical studies, COR-003 showed a greater reduction in serum cortisol by Day 4 in healthy volunteers than COR-003 and placebo. Mean (± standard error of the mean) AUC0-6h of cortisol was 56 ± 4% lower with COR-003 than with ketoconazole (600 ng/mL) (167 ± 6.8 ng/mL with COR-003 vs. 167 ± 6.8 ng/mL with placebo; P < 0.001). These findings suggest that COR-003 is a more potent inhibitor of cortisol synthesis compared with ketoconazole, and COR-003 was more effective in inhibiting CYP21 and CYP11B1 activity in vitro and in vivo compared with ketoconazole. COR-003 more significantly inhibited CYP21 and CYP11B1 activity in rats. In a 3-period, crossover, phase 1, drug-interaction study, healthy subjects received placebo, COR-003, or ketoconazole once daily on Days 1 to 4 and concomitantly with atorvastatin (40 mg QD). Atorvastatin AUC0-6h was higher with ketoconazole (641 ± 49 ng·h/mL) than COR-003 (481 ± 39 ng·h/mL) and placebo (263 ± 29 ng·h/mL) (P < 0.05).

REFERENCES


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