Original Research

Effects of Hepatic Impairment on the Pharmacokinetics of Everolimus: A Single-Dose, Open-Label, Parallel-Group Study

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ABSTRACT

Background: Although the pharmacokinetics of everolimus, an oral mammalian target of rapamycin inhibitor, have been characterized in patients with moderate hepatic impairment, they have not been assessed in those with mild or severe hepatic impairment.

Objective: The goal of this study was to assess the pharmacokinetics and safety of everolimus in healthy volunteers with normal hepatic function and patients with mild (Child-Pugh class A), moderate (Child-Pugh class B), and severe (Child-Pugh class C) hepatic impairment in otherwise good health to inform dosing in the clinical setting.

Methods: A multicenter, open-label, Phase I study in which all enrollees received a single, 10-mg, oral everolimus dose was conducted. Blood samples for pharmacokinetic assessment were collected at predetermined time points up to 168 hours postdosing. Safety was also assessed. Proposed dose recommendations based on Child-Pugh status at baseline and day 8 were calculated based on $AUC_{0-\infty}$ geometric mean ratios and their associated 90% CIs. Post hoc analysis of the relationship between pharmacokinetic parameters and markers of hepatic function was also performed to identify thresholds for dose adjustment.

Results: Thirteen subjects with normal hepatic function and 7 patients with mild, 8 patients with moderate, and 6 patients with severe hepatic impairment were enrolled. Compared with normal subjects, everolimus $AUC_{0-\infty}$ for patients with mild, moderate, and severe hepatic impairment increased by 1.60-, 3.26-, and 3.64-fold, respectively. Based on Child-Pugh classification at day 8, the everolimus doses required to adjust the exposure of patients with mild, moderate, and severe hepatic impairment to that of normal subjects were 6.25, 3.07, and 2.75 mg, respectively. Thresholds for 2-fold everolimus dose reduction were 15.0 μmol/L for bilirubin, 43.1 g/L for albumin, and 1.1 for the international normalized ratio; using these thresholds could lead to underdosing or overdosing in some patients. Most adverse events were of grade 1 severity, ≤1 day in duration, and not everolimus related.

Conclusions: Everolimus exposure after a single 10-mg dose was influenced by the degree of hepatic impairment. Child-Pugh classification was found to be the most conservative means of guiding dose adjustment in patients with hepatic impairment. Based on these data, as well as previously reported data for patients with moderate hepatic impairment, everolimus once-daily dosing should be 7.5 mg and 5 mg in patients with mild and moderate impairment, respectively. Everolimus is not recommended in patients with severe hepatic impairment unless benefits outweigh risks; in that case, 2.5 mg once daily should not be exceeded. ClinicalTrials.gov identifier: NCT00968591. (*Clin Ther.* 2013;35:215–225)

Key words: healthy subjects, hepatic impairment, molecular therapeutics, pharmacokinetics.

INTRODUCTION

Mammalian target of rapamycin (mTOR) is a ubiquitously expressed intracellular serine/threonine protein

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kinase that plays a pivotal role in the regulation of cellular growth, proliferation, metabolism, and angiogenesis.[1] Dysregulation of signaling pathways upstream and downstream of mTOR is implicated in the pathogenesis of numerous cancers and tumor syndromes.[2–5] The dysregulation of mTOR signaling in such a large number of malignancies makes mTOR an attractive target for anticancer therapy. Data show that mTOR inhibition results in the abrogation of numerous cellular end points implicated in tumorigenesis, including cell cycle progression, cellular metabolism, cellular survival, and angiogenesis.[5]

Everolimus, an oral mTOR inhibitor in clinical development since 1996, was initially approved for use as an immunosuppressant in solid organ transplant recipients. More recently, everolimus has demonstrated efficacy and manageable toxicity in several large Phase III clinical trials of advanced cancers and tuberous sclerosis complex (TSC).[6–10] Currently, everolimus is approved in various countries for the prophylaxis of organ rejection in adult allogeneic renal or cardiac transplant recipients at mild to moderate immunologic risk; adults with sunitinib- or sorafenib-refractory advanced renal cell carcinoma; adults with progressive pancreatic neuroendocrine tumors that are unresectable, locally advanced, or metastatic; women with hormone receptor–positive, human epidermal growth factor receptor 2–negative breast cancer in combination with exemestane after failure to improve with letrozole or anastrozole; adults with renal angiomyolipoma and TSC not requiring immediate surgery; and adults and children with subependymal giant cell astrocytoma associated with TSC that require intervention but are not suitable for resection. Everolimus dosing is 2 mg once daily in the transplant setting and 10 mg once daily in the oncology setting.

Everolimus pharmacokinetics have been well characterized in healthy subjects, solid organ transplant recipients, patients with advanced solid tumors, and patients with moderate hepatic impairment (Child-Pugh class B)[11–15] and have been shown to be unaffected by age, sex, or weight in adults.[11] Everolimus is rapidly absorbed after oral administration, with a median T_{max} in blood of 1 to 2 hours postdose.[11–13] As a daily regimen, everolimus AUC and C_{max} are dose proportional up to 10 mg/d.[11,13] For example, in a study of patients with advanced solid tumors, everolimus C_{max} and AUC (mean [SD]) at steady state were 5.4 (1.8) ng/mL and 238 (77) ng·h/mL, respectively, with everolimus 5 mg/d and 13.2 (7.9) ng/mL and 514 (231) ng·h/mL with everolimus 10 mg/d.[13] The main pathway of everolimus metabolism occurs in the liver and gut via the cytochrome P450 3A4 isozyme (CYP3A4).[11,16] The vast majority of everolimus is excreted in bile, with only 2% excreted in urine.[11] In both healthy subjects and patients with advanced solid tumors, the everolimus terminal $t_{½}$ is ~30 to 35 hours.[11–13] After 2-mg and 4-mg everolimus doses, mean CL/F was 19.7 (5.4) L/h and 19.4 (5.8) L/h, respectively, in healthy volunteers.[11,12]

Given that everolimus is metabolized mainly in the liver through CYP3A4, hepatic impairment could affect everolimus disposition. A previous study conducted by Kovarik et al[12] found that compared with healthy controls (n = 8), age- and sex-matched patients with moderate hepatic impairment (Child-Pugh class B; n = 8) treated with a single 2-mg everolimus dose (the dose used for immunosuppression) had a significantly reduced CL/F (9.1 [3.1] vs 19.4 [5.8] L/h; P = 0.01), a significantly higher AUC (245 [91] vs 114 [45] ng·h/L; P = 0.01), and a significantly longer $t_{½}$ (79 [42] vs 43 [18] hours; P = 0.04). Everolimus C_{max} was comparable between groups (11.7 [4.3] ng/mL for hepatically impaired patients vs 15.4 [8.6] ng/mL for healthy controls; P = 0.32), as was T_{max} (0.7 [0.3] hours vs 0.8 [0.5] hours) and the percentage of everolimus bound to protein (73.8% [3.6%] vs 73.5% [2.4%]; P = 0.88). To more fully characterize everolimus pharmacokinetics in patients with hepatic impairment to inform dosing in the clinical setting, we investigated the pharmacokinetics and safety of everolimus in patients with mild, moderate, and severe hepatic impairment in otherwise good health.

PATIENTS AND METHODS

Study Design and Patients

In this multicenter, open-label, parallel-group, single-dose, Phase I study, all subjects received a single 10-mg everolimus dose administered on day 1 as two 5-mg tablets after consumption of a light, low-fat breakfast of ~350 calories and 1 to 2 g of fat. The specific foods varied by country, but all breakfasts included a carbohydrate (biscuit, bread, or semolina), protein (egg whites or banana), and a fruit/sugar (strawberry jam, raisins, or baked apple with sugar).

All subjects, including patients with hepatic impairment, volunteered to participate in the study. Healthy subjects and patients with hepatic impairment were eligible to participate if they were 18 to 75 years of age; weighed ≥50 kg; and had good health determined by