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Entry-into-human study with the novel immunosuppressant SDZ RAD in stable renal transplant recipients

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Aims To evaluate the tolerability of single oral SDZ RAD doses in stable renal transplant recipients and the pharmacokinetics of ascending SDZ RAD doses when coadministered with steady-state cyclosporin A microemulsion (Neoral).

Methods This randomized, double-blind, placebo-controlled, sequential study involved 54 patients in six treatment groups; a different SDZ RAD dose (0.25, 0.75, 2.5, 7.5, 15, 25 mg) was assessed in each group. Patients received a single oral dose of SDZ RAD ($n=6$) or placebo ($n=3$) with their usual Neoral dose. SDZ RAD and cyclosporin A pharmacokinetic parameters were determined.

Results All SDZ RAD doses were well tolerated, with no discontinuations due to adverse events, serious adverse events, or deaths. Similar proportions of patients receiving SDZ RAD and placebo had at least one adverse event (44% and 50%, respectively). Mean changes in laboratory variables (baseline to endpoint) showed no clinically meaningful differences between SDZ RAD and placebo groups. SDZ RAD was absorbed rapidly and showed dose-proportional pharmacokinetics (dose: 2.5–25 mg), based on systemic exposure. Multiple postabsorptive phases in the pharmacokinetic profile indicate tissue distribution. The elimination half-life ranged from 24 to 35 h across the five highest dose groups. Pharmacokinetics were similar in men and women. Co-administration of escalating single oral SDZ RAD doses did not affect steady-state cyclosporin A pharmacokinetics.

Conclusions SDZ RAD was well tolerated; safety profiles of SDZ RAD and placebo were similar. SDZ RAD pharmacokinetics were dose-proportional across the range 2.5–25 mg in conjunction with cyclosporin A-based therapy, according to systemic exposure. Cyclosporin A pharmacokinetics were not affected by coadministration of single oral doses of 0.25–25 mg SDZ RAD.

Keywords: cyclosporin A, immunosuppressant, pharmacokinetics, safety, SDZ RAD, transplantation

Introduction

The immunosuppressive properties of rapamycin have been known for more than 15 years [1, 2], but the clinical development of the drug has been hampered by its limited oral bioavailability. A novel immunosuppressant, SDZ RAD, has recently been developed. SDZ RAD is a derivative of rapamycin but differs structurally by having a 2-hydroxyethyl chain at position 40. This modification allowed the development of a solid dosage formulation that is more convenient to administer than rapamycin, which must be prepared from a refrigerated stock solution just before use. SDZ RAD has a mechanism of action similar to that of rapamycin: inhibition of growth factor-driven proliferation of T cells and fibroblasts. SDZ RAD prevents graft rejection in rat models of allotransplantation (kidney, heart) [3]. SDZ RAD and cyclosporin A show synergism in immunosuppression both *in vitro* and *in vivo* [4].

The aim of the present study was to evaluate the safety and tolerability of single doses of SDZ RAD (0.25–25 mg) in stable renal transplant recipients and thereby to

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determine whether further large-scale clinical studies are justified. Other objectives were to determine the pharmacokinetics of ascending single oral doses of SDZ RAD during steady-state dosing with the microemulsion formulation of cyclosporin A (Neoral) and to assess the effect of single-dose SDZ RAD on the steady-state pharmacokinetic profile of cyclosporin A.

This study was presented in part at the American Society of Transplant Physicians' Sixteenth Annual Meeting, 10–14 May, 1997, Chicago, Illinois.

Methods

Study design

This was a phase-I, multicentre, randomized, double-blind, placebo-controlled, ascending-dose study of the tolerability and pharmacokinetics of SDZ RAD. The study was approved by the local Ethics Committee and patients gave written informed consent to participate in the study. Patients ($n = 54$) were allocated to six groups. In each group, six patients were randomized to the same single dose of SDZ RAD (0.25, 0.75, 2.5, 7.5, 15, or 25 mg), and three patients randomized to placebo. Patients received study medication under fasting conditions, together with their usual, individually selected Neoral dose. The SDZ RAD doses were evaluated in ascending order, starting with the 0.25 mg dose. Each subsequent dose was not assessed until the safety and tolerability of the previous dose had been evaluated for at least 11 days.

Participants

Men and women, aged 18–65 years, were included in the study if they were recipients of a primary cadaveric renal transplant, had undergone transplantation at least 6 months before the start of the study, and were considered to be clinically stable at the start of the study. Their serum creatinine concentration had to be less than 207 μmol l^{-1}, with a creatinine clearance of at least 40 ml min^{-1} estimated on the basis of the Cockcroft-Gault formula [5]. Whole blood trough cyclosporin A concentrations had to be between 80 and 200 ng ml^{-1}. Patients had to be receiving twice-daily Neoral at a dose that had been stable for at least 3 weeks before screening, combined with prednisone at a dose of up to 15 mg day^{-1}, for at least 3 months.

Exclusion criteria included the following: graft rejection or continued tapering of corticosteroids from previous rejection therapy within 2 months before screening; use of other investigational immunosuppressants within 4 months or other investigational drugs within 4 weeks before screening; hypersensitivity to drugs of the same class as SDZ RAD or to components of the SDZ RAD formulation; liver, heart, or autonomic dysfunction; illness defined as significant by the investigator within 2 weeks before the study; and the use of any drug known to potentiate cyclosporin A nephrotoxicity or to interfere with cyclosporin A pharmacokinetics within 2 weeks before the study (with the exception of calcium antagonists if the dose regimen had been stable for at least 8 weeks before the start of the study). Azathioprine had to have been discontinued at least 4 weeks before the baseline assessment.

Tolerability

Adverse events were reported spontaneously by the patient or discovered from general questioning by the investigator, or after physical examination at any time, as required, up to 4 weeks after receiving SDZ RAD. The severity of the adverse events (mild, moderate, or severe), their relationship to study medication, and the occurrence of death, nonfatal serious adverse events, or adverse events resulting in the discontinuation of medication were recorded.

Patients underwent a general physical examination with ophthalmic assessment, echo- and electrocardiography, vital-signs assessment (blood pressure, pulse, body temperature), haematology, prothrombin time/partial thromboplastin time, blood biochemistry (including creatinine clearance), endocrinology, urinalysis, and markers of inflammation (fibrinogen, C-reactive protein, γ-globulin, and $\alpha 1$–, $\alpha 2$–, and β–proteins). The first laboratory assessment was made between 3 and 90 days before the start of the study (screening); patients returned for subsequent laboratory assessments up to 2 days before drug administration (baseline), on the day of drug administration (day 1), daily until day 7, and then on days 9 and 11.

Pharmacokinetic assessments

Whole blood samples (3.5 ml) were collected by means of a catheter inserted into a forearm vein. Samples for the determination of cyclosporin A concentrations were taken over one dosing interval (just before and up to 12 h after drug administration) one day before administration of SDZ RAD or placebo (day -1). After concomitant intake of Neoral with SDZ RAD or placebo, concentrations of cyclosporin A were again determined over one complete dosing interval (day 1) and, in addition, just before each morning dose of Neoral until 11 days after SDZ RAD or placebo intake. Samples for the determination of SDZ RAD concentrations were collected just before and up to 192 h after drug administration. Samples were immediately stored below -20° C pending analysis.

Cyclosporin A concentrations in whole blood were measured using a commercially available radioimmunoassay (Cyclo-Trac, INCSTAR Corp., Stillwater, Minnesota, USA). The limit of quantification (LOQ) was 15 ng ml^{-1}. Precision and accuracy were 5.7–17.7% and −1.7 to +3.5%, respectively, at concentrations of quality control samples between 15 and 2540 ng ml^{-1}. SDZ RAD concentrations in whole blood were quantified by means of a high-performance liquid chromatography/atmospheric pressure chemical ionization/mass spectrometry method [6]. The LOQ was 0.75 ng ml^{-1}. For the three quality control samples (0.75, 10, and 125 ng ml^{-1}) precision and accuracy ranged between 9 and 11% and −12 to −7%, respectively.

Pharmacokinetic parameters were determined for both SDZ RAD and cyclosporin A using noncompartmental methods [7].

For cyclosporin A ratios of t_{max}ss, C_{max}ss, C_{min}ss, and AUC_{τ}ss with and without coadministration of SDZ RAD or placebo were also calculated.

Statistical analysis

Because of the small number of patients in the study and within each group, data from the 18 patients receiving placebo were pooled for analysis. Data from the 36 patients receiving SDZ RAD ($n=6$ per group) were analysed by dose level and also as a pooled SDZ RAD group ($n=36$). Patients failing to provide data at any visit were excluded from the analysis for that visit and data were not carried forward to subsequent time points. For each patient, the endpoint was taken as the last observation after baseline.

For the tolerability analysis, the number of patients experiencing an adverse event was recorded and summarized by treatment group. The incidence rates of all adverse events were summarized by body system, severity, and treatment group. Changes in vital signs, laboratory data, electrocardiography, and physical examination data were summarized by treatment group, and any clinically significant abnormalities were recorded.

For pharmacokinetic analyses, the dose proportionality of C_{max} and AUC for SDZ RAD was assessed using linear regression on non-normalized data and one-factor analysis of variance (ANOVA) on logarithmically transformed dose-normalized data with least-squares comparisons between pairs of cohorts. The Kruskal–Wallis test (the nonparametric equivalent of ANOVA) was performed on dose-normalized data. The relationships of the dose-normalized C_{max} and AUC with body weight were also explored. For cyclosporin A, a two-factor ANOVA with dose, time, and the interaction term (time · dose) as sources of variation including estimate statements was determined to assess the dose level of SDZ RAD at which a pharmacokinetic interaction with cyclosporin A occurred. Potential changes in morning predose cyclosporin A concentrations (C_{min}ss) were investigated over time (11 days) after coadministration of single oral doses of SDZ RAD (0.25–25 mg) or placebo, using Hotelling's T^2 test (SAS 6.08, SAS Institute Inc., Cary, North Carolina, USA).

Results

All 54 patients completed the study, although 16 patients in the SDZ RAD groups (44%) and 10 patients in the placebo group (56%) violated an entry criterion (mainly serum creatinine level ≥207 μmol l^{-1}, use of azathioprine within 4 weeks of baseline, use of Neoral for <3 months before study, or <150 000 platelets/mm^3). However, these were judged, on a case-by-case basis, to be minor deviations that did not necessitate exclusion from the trial.

Baseline patient characteristics and concomitant medications are shown in Table 1. Age, weight, and height in the SDZ RAD and placebo groups were similar; the absolute number/proportion of women in the SDZ RAD group was higher than in the placebo group (8/22% *vs* 2/11%, respectively). Differences at baseline between the SDZ RAD and placebo groups were noted for the incidences of hyperparathyroidism (4/11% *vs* 5/28%), gastrointestinal disorders (7/19% *vs* 10/56%), hyperlipidaemia (10/28% *vs* 2/11%), hyperuricaemia (9/25% *vs* 8/44%), polycythaemia (7/19% *vs* 2/11%), cataract (5/14% *vs* 1/6%). Most of the patients in the SDZ RAD and placebo groups (32/89% and 17/94%, respectively) had hypertension at baseline. This was reflected by the relatively high proportions of patients receiving antihypertensive medication concomitantly with study medication.

Tolerability

The overall incidence of adverse events is shown in Table 2. No deaths, serious adverse events, or events that led to discontinuation of study medication were reported. No adverse event was considered to be definitely related to the study medication. The most frequently reported adverse events were headache in the SDZ RAD group (11% of patients) and dizziness in the placebo group (22%). Most adverse events (26/43 in the SDZ RAD group and 8/13 in the placebo group) were classified as mild; the remainder were classified as moderate. Adverse events in the SDZ RAD group were more diverse than those in the placebo group; a total of 36 adverse events occurred in the 36 patients in the SDZ RAD group (i.e. mean: 1 event per patient), with at least one adverse event in each of the 16 body systems considered. This compared with a total of 13 adverse events occurring in the 18

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