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J. M. Kovarik
E. Rawlings
P. Sweny
O. Fernando
R. Moore
P. J. Griffin
P. Fauchald
D. Albrechtsen
G. Sodal
K. Nordal
P. L. Amlot

Pharmacokinetics and immunodynamics of chimeric IL-2 receptor monoclonal antibody SDZ CHI 621 in renal allograft recipients

J. M. Kovarik (✉)
Clinical Pharmacology,
Sandoz Pharma Ltd., CH-4002 Basel,
Switzerland

E. Rawlings · P. Sweny · O. Fernando · P. L. Amlot
Departments of Immunology and Nephrology, Royal Free Hospital School of Medicine, London NW3 14D, UK

R. Moore · P. J. Griffin
Cardiff Royal Infirmary, Cardiff, UK

P. Fauchald · D. Albrechtsen · G. Sodal · K. Nordal
Rikshospitalet, Oslo, Norway

Abstract SDZ CHI 621 is a murine-human chimeric monoclonal antibody (mAb) to the interleukin-2 (IL-2) receptor (CD25) intended for prophylactic immunosuppression against acute rejection in the first several weeks following kidney transplantation. A multicentre, prospective, dose-finding study was conducted in 37 primary, mismatched cadaver kidney transplant patients to assess its tolerability, pharmacokinetics and immunodynamics. Successive cohorts of patients were stratified to receive total doses of 20, 30, 40 or 60 mg (n = 4, 4, 14, 15, respectively) administered as 15- or 20-mg intravenous infusions with the first dose given preoperatively and subsequent doses within the first 10 days posttransplant. Daily mAb serum concentrations were analysed by a radioimmunoassay method and the percentage of peripheral T-lymphocytes expressing CD25 from serial blood samples was determined by FACScan. Intravenous administrations were well tolerated. mAb concentration profiles exhibited a biphasic decline with an initial $t_{1/2}$ of 14.4 ± 14.2 h, terminal $t_{1/2}$ of 13.4 ± 6.0 days, distribution volume (V_{ss}) of 6.9 ± 3.3 l and clearance of 17.4 ± 7.8 ml/h. The concentration-effect (mAb-CD25) relationship indicated that mAb concentrations exceeding a threshold of about 0.7 μg/ml corresponded to complete suppression of CD25 (≤ 3 % $CD25^+$ T-cells). The threshold mAb concentration was exceeded at all dose levels, whereas the duration above the threshold (and thus of CD25 suppression) rose with increasing dose: 20 mg, 20 ± 7 days; 30 mg, 32 ± 6 days; 40 mg, 37 ± 10 days; and 60 mg, 53 ± 17 days. As mAb concentrations declined below the threshold following the last dose, CD25 expression returned to baseline (18–44 % $CD25^+$ T-cells) within a few days.

Key words Immunosuppression · Monoclonal antibodies · Renal transplantation · Pharmacokinetics · Pharmacodynamics

Introduction

The development of antibody therapy in the prophylaxis against acute rejection in transplantation has progressed from aspecific polyclonal antisera to increasingly selective monoclonal antibodies, which have the potential to regulate specific immunological responses via functional receptors. In this context, rat and mouse monoclonal antibodies to the interleukin-2 receptor (IL-2R) have shown promise in preventing acute rejection in renal allograft recipients [1, 2]. However, their clinical use has been limited by the rapid development of neutralising antibodies. In an attempt to reduce immunogenicity, a chimeric mouse-human anti-IL-2R monoclonal antibody has been developed. SDZ CHI 621 contains a murine variable region (RFT5) and a human constant

region (IgG1$\varkappa$) and demonstrates high affinity for the CD25 activation antigen on the IL-2Rα chain. An investigation was designed to characterise the pharmacokinetics and immunodynamics of SDZ CHI 621 in renal allograft recipients.

Methods

A multicentre, open-label dose-finding study was undertaken in recipients of primary, mismatched cadaver kidneys. Successive cohorts of patients were stratified to receive total SDZ CHI 621 doses of 20, 30, 40 or 60 mg. Total doses were administered as 15- or 20-mg intravenous infusions delivered over 30 min. The first infusion was given prior to transplant surgery, with subsequent administrations within the first 10 postoperative days. Blood samples were collected daily for the determination of serum SDZ CHI 621 concentrations by a radioimmunoassay (RIA) method. For pharmacokinetic analysis, concentration-time data were fitted to a two-compartment, open model with first-order elimination from the central compartment. Blood samples were obtained twice weekly over the study duration for pharmacodynamic measurements. Specifically, lymphocyte subpopulations were analysed by FACScan flow cytometry (Becton-Dickinson) and the percentage of CD25A$^+$ T-cells was quantified.

Results and discussion

Patient population and clinical observations

Thirty-nine patients were enrolled in this investigation; data from the 37 who provided evaluable pharmacokinetic profiles are presented. There were 23 men and 14 women aged 48 ± 14 years (range 18–71 years) and weighing 74 ± 16 kg (range 46–103 kg). They were stratified as follows among the dose levels: 4 (20 mg), 4 (30 mg), 14 (40 mg), 15 (60 mg). The infusions of SDZ CHI 621 were safe and well-tolerated and no cytokine-release syndrome or hypersensitivity reactions were observed.

Pharmacokinetics

Peak serum SDZ CHI 621 concentrations at the end of the infusion ranged between 5 and 10 μg/ml; the distribution volume (V_{ss}) was 6.9 ± 3.3 l. Concentrations subsequently declined in a biphasic manner with a prolonged terminal disposition half-life of 13.4 ± 6.0 days. The total body clearance was 17.4 ± 7.8 ml/h; the between-subject variability in clearance was not influenced by body weight, supporting dosing on a milligram basis in adults.

Immunodynamics

The baseline percentage of CD25A$^+$ T-cells from pretreatment blood samples ranged from 18 % to 44 %. In the presence of SDZ CHI 621, CD25A was continuously suppressed, with the percentage of T-cells expressing this activation marker below 3 %. Clinically relevant suppression was maintained until SDZ CHI 621 concentrations declined to a threshold region around 0.7–1.0 μg/ml (as determined by RIA) following the last administration. At this point, CD25A counts returned to baseline within a few days. The concentration-effect relationship was also explored by plotting the paired determinations of SDZ CHI 621 concentration versus the percentage of CD25A$^+$ T-cells, pooling the data pairs from all study patients. Again, concentrations exceeding approximately 0.7–1.0 μg/ml were associated with CD25A suppression ($\leq$ 3 % CD25A expression), while concentrations below this threshold region were associated with the pre- and post-treatment baseline values (> 3 % CD25A expression). All cumulative dose levels assessed in this investigation yielded CD25A suppression; however, the duration of suppression increased with increasing total dose. Specifically, at total doses of 20, 30, 40 and 60 mg, the duration was 20 ± 7, 32 ± 6, 37 ± 10 and 53 ± 17 days, respectively. These data were used as a basis for dose selection in the indication of immunosuppressive prophylaxis following kidney transplantation.

References

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