POPULATION PHARMACOKINETICS OF RITUXIMAB IN RA PATIENTS: COMBINING TWO PHASE II STUDIES

INTRODUCTION

Rituximab, a B cell-specific, CD20-targeted therapeutic monoclonal antibody, is approved for the treatment of relapsed refractory, low-grade and follicular CD20+ B cell non-Hodgkin’s lymphoma (NHL) using a body surface area (BSA)-adjusted dosing regimen. However, a final dose of rituximab in RA, in combination with a short course of glucocorticoids (GC), is being explored as a novel approach to treating rheumatoid arthritis (RA).

In patients with active RA despite methotrexate (MTX) treatment, a single course of two infusions of rituximab (either alone or in combination with cyclophosphamide (CTX)) or continued MTX has been shown to improve disease symptoms significantly at 26 and 44 weeks post-treatment.

The population pharmacokinetics (POP PK) of rituximab in RA have been explored in two Phase II studies (A and B). The Phase IIa study included a smaller sample of patients than the Phase IIb study but this group was assessed more frequently. One dose level was explored in the Phase IIa study whereas two dose levels were explored in the Phase IIb study.

OBJECTIVES

To explore the POP PK of rituximab using data from two Phase II studies in patients with RA.

To investigate if a number of variables had an effect on the pharmacokinetics of rituximab; in particular, the potential effect of rituximab dose, and concomitant use of GC on rituximab pharmacokinetics.

METHODS

Study population

A total of 423 patients with RA from two Phase II studies were included in the analysis. Patients were randomised to receive one of the following three treatment regimens:

- Rituximab monotherapy (1000 mg intravenous (IV) on Days 1 and 15)
- Rituximab (1000 mg IV on Day 1) plus oral MTX (>10 mg/week)
- Rituximab (1000 mg IV on Day 1) plus oral MTX (10 mg/week)

All the patients in the Phase IIa study received methylprednisolone: 40 mg (Days 1, 3, 15, and 17) and prednisone 60 mg (Days 2 and 4–7) and on prednisone 30 mg (Days 8–14).

Phase IIb study: A total of 1214 serum rituximab concentrations from 315 patients with RA were included in the analysis. Patients were randomised to receive treatment as described in Table 1.

RESULTS

Model validation

A bootstrap re-sampling procedure was used to validate the model's stability and to estimate the 95% confidence intervals (CI). The model was repeatedly fitted to bootstrap replications of the data set. The 95% CI of the bootstrap estimates for each parameter were calculated.

A two-compartment model could not be fitted to the data from the Phase IIb study alone.

The fit of a two-compartment model was markedly better than that of a one-compartment model for the combined data from the two studies.

A three-compartment model did not improve the model fit compared with a two-compartment model.

CL and Vc estimated using the combined data set were similar to the estimates from the Phase IIa data alone (291 ml/day and 2000 mL for CL, and 174 L for Vc, respectively).

Final model: influence of covariates on rituximab PK

The covariates were partitioned into different categories and one compartment model was fitted for each category. The covariates were as follows:

- Sex
- Race
- Oral GC
- Rituximab dose
- BSA
- Duration of RA disease
- Area (BSA)
- Prior use of anti-tumour necrosis factor (TNF)-α inhibitors

Potential influence of the covariates on CL and Vc were all statistically significant. The potential influence of the covariates on CL and Vc were all statistically significant.

CONCLUSIONS

PK parameters for rituximab from the POP PK analysis of the combined data set did not differ from those published for the Phase IIa study alone.

The effects of BSA and gender on the CL and Vc of rituximab were confirmed.

Concomitant administration of high-dose GC decreased rituximab clearance by 12%; this effect will be confirmed in future analyses.

Rituximab dose was considered not to have any significant effect on Vc or CL.

REFERENCES