

Pharmacokinetic-Pharmacodynamic Modelling of Risankizumab in Plaque Psoriasis Real World Data

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Introduction

Psoriasis is a chronic immune-mediated inflammatory skin condition categorised by scaly plaques on the skin affecting over 125 million people worldwide worldwide (2 to 3 percent of the total population), according to the World Psoriasis Day consortium. Disease state can range from minor irritation to debilitating. Risankizumab has been shown to be more successful in terms of reduction in Psoriasis Area and Severity Index (PASI) than than placebo, ustekinumab, adalimumab and secukinumab (1, 2, 3, 4). Risankizumab is a humanised IgG1 monoclonal antibody that binds to and blocks the pro-inflammatory effects of IL-23 hence slowing, or preventing, lesion progression (5).

In part, drug exposure can explain variation in drug response. This study aimed to categorise the pharmacokinetics (PK) and pharmacodynamics (PD) of risankizumab through a joint PK/PD model using real-world data. A maximum effect (E_{max}) model inhibited progression of psoriatic skin lesions in the turnover PD mechanism describing PASI evolution while on treatment.

Methods

The study utilised a real-world dataset from the Biomarkers and Stratification To Optimise outcomes in Psoriasis (B-STOP) study, comprising 93 serum observations and 104 PASI scores from 50 patients (54% male; median weight 79.3 kg; median age 47 years). Patients received standard dosing of Risankizumab (150mg subcutaneously at weeks 0, 4, and every 12 thereafter). A sequential population pharmacokinetic-pharmacodynamic model was constructed using a non-linear mixed effect modelling approach in R (version 4.3.1) with the nlmixr2 package (version 2.0.9). Data below the limit of quantification (1 mg/L) were handled using the M3 method (6). Covariates including albumin, creatinine, creatinine clearance, and C-reactive protein were assessed in the development of the covariate model. Allometric scaling was incorporated into the model as a prior centred around 70 kg, and maximum inhibition (E_{max}) was fixed to 1. The objective function value (OFV) was used to compare the fits of nested models, where the difference in the OFV for models being compared served as a likelihood ratio test approximately following a chi-squared distribution, alongside goodness of fit plots and visual predictive checks.

Results

Pharmacokinetic data were best described by a one compartment model with a fixed absorption rate (Suleiman et. al $K_a = 0.299$) (7) and first-order subcutaneous absorption and elimination. The final model accounted for inter-individual variability (IIV) on clearance (CL) and volume parameters (V). Residual variability was best described using a proportional error model. A maximum effect (E_{max}) model inhibited progression of psoriatic skin lesions, utilising a turnover pharmacodynamic mechanism to describe PASI evolution while on treatment, where K_{in} represented lesion development and K_{out} represented the elimination rate constant of lesions. Inclusion of IIV on baseline PASI (BSL) and concentration at 50% of maximum inhibition (IC_{50}) with a combined proportional and additive error model best described the pharmacodynamic data. No covariates were retained in the model. CL/F was estimated at 0.3 L/day, V/F at 11.8 L, BSL at 12.7, IC_{50} at 0.1 mg/L and K_{out} at 0.03 day^{-1} .

$$\begin{aligned} \frac{d}{dt}(\text{skin}) &= -(K_a \cdot \text{skin}) \\ \frac{d}{dt}(\text{plasma}) &= (K_a \cdot \text{skin}) - \left(\frac{\text{CL}}{\text{V}} \cdot \text{plasma} \right) \\ \frac{d}{dt}(\text{PASI}) &= K_{in} \cdot \left(1 - \frac{E_{max} \cdot \left(\frac{\text{plasma}}{\text{V}} \right)}{IC_{50} + \left(\frac{\text{plasma}}{\text{V}} \right)} \right) - K_{out} \cdot \text{PASI} \end{aligned}$$

Differential equations: where PASI at time 0 was baseline PASI (BSL), K_a is the absorption rate constant, CL is clearance, V is volume of distribution, E_{max} is maximal inhibition, IC_{50} is 50% of maximum inhibition, K_{in} is lesion development and K_{out} is lesion turnover.

Parameter	Population Estimate (95%CI)	%RSE	BSV(CV%)
$K_a \text{ (day}^{-1}\text{)}$	0.229 (fix)		
CL/F (L/day)	0.323 (0.247, 0.423)	12.2	26.2
V (L)	11.8 (7.59, 18.5)	9.17	27.7
E_{max}	1.00 (fix)		
BSL (PASI)	12.7 (7.84, 20.5)	9.66	35.1
$IC_{50} \text{ (mg/L)}$	0.119 (0.0572, 0.249)	17.7	334
$K_{out} \text{ (day}^{-1}\text{)}$	0.0316 (0.0163, 0.0615)	9.83	0.0187
prop.err _{pk}	0.495		
prop.err _{pd}	0.728		
add.err _{pd}	0.0133		
coeff _{weight} on CL	0.750 (fix)		
coeff _{weight} on V	1.00 (fix)		

Table 1: Parameter Estimates

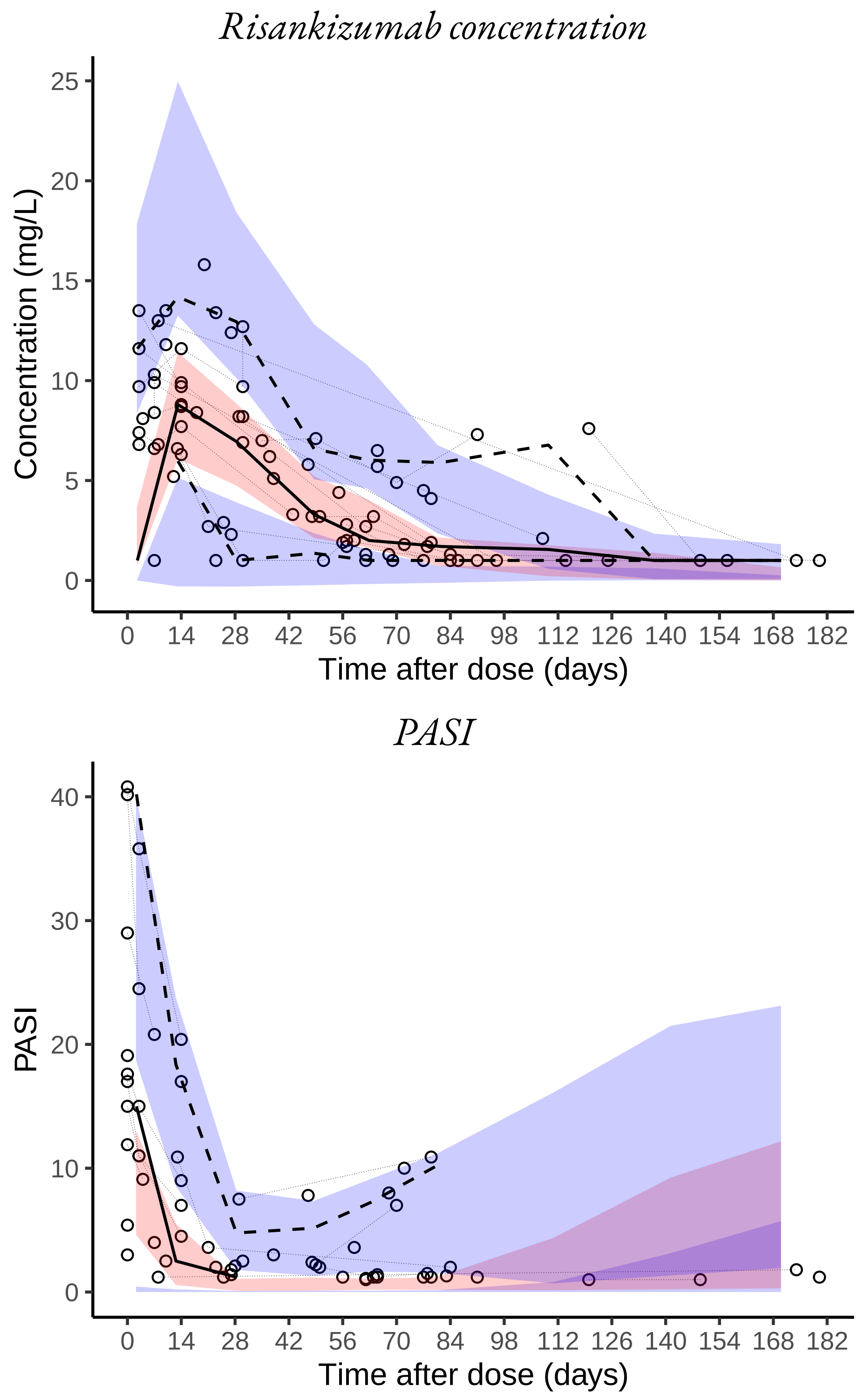


Figure 1: Visual Predictive Check, where black line is the median, dots are observed data. Dashed line is 25th and 75th interval. Red shading is prediction interval for median. Purple shading is prediction interval for 25th and 75th interval.

Conclusions

Pharmacokinetic and pharmacodynamic data from 50 patients was successfully evaluated to model the PK/PD of risankizumab in plaque psoriasis. Risankizumab pharmacokinetics were described with a one compartment pharmacokinetic model. Psoriasis Area and Severity Index was used to describe psoriatic lesion turnover.

Pharmacokinetic parameters were similar to those of previously published risankizumab models (7, 8). The pharmacodynamic model showcased lesion turnover consistent with other turnover models for psoriatic skin lesions, highlighting uniform turnover dynamics across different drugs, e.g., $k_{out} = 0.02 \text{ day}^{-1}$ (9).

The model was built on real-world data and updated as new data became available. Use of clinical trial data would be beneficial to confirm model development. Further improvement could be found through the incorporation of Z scores for estimating PASI, as seen in the work of Ooi et al via a bounded integer model (10).

A Bayesian therapeutic drug monitoring dashboard is under development to inform personalised dose minimisation strategies for risankizumab in psoriasis patients with clear or nearly clear skin.

Key points

Real world pharmacokinetic parameters were similar to those of risankizumab trials.

The pharmacodynamic lesion turnover parameter estimates were consistent with other turnover models for psoriatic skin lesions, highlighting the capture of disease dynamics that can be applied across different drugs.

Future work includes use of risankizumab pharmacokinetics to inform dose minimisation via a therapeutic drug monitoring dashboard with potential to expand to include multiple biologics.

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