

HOW CAN MODELLING AND SIMULATION FUEL THE CLINICAL DEVELOPMENT OF BIOSIMILARS?

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Through the efficient use of modelling and simulation (M&S), decisions can be made increasing the probability of a successful outcome for biosimilar studies by integrating public domain information and in-house data.

The relatively low cost to enter the “generic” market and the size of the biologic drug market make entry attractive. However, the failure rate for biosimilars is deemed high, due to the complex manufacturing process and the high variability expected for biologics. Considering that the associated cost for developing a biosimilar is estimated at US\$100 million, there is a high risk-cost relationship in the establishment of clinical biosimilarity.¹

It is therefore of great interest to investigate the possibility to optimise the design of clinical trials of biosimilars in order to increase the studies’ efficiency (e.g., robust results, shorter duration, fewer patients, reduced cost). Because these studies have a great regulatory impact, they must be executed in accordance with regulatory guidelines for the evaluation of biosimilarity.^{2,3}

M&S has been used in the pharmaceutical industry for more than two decades, and can be of competitive advantage for drug sponsors seeking to improve their drug development process and decision making. The use of M&S for evaluating pharmacokinetic/pharmacodynamic (PK/PD) relationships can support a biosimilar programme, and offers high regulatory impact. In principle, regulators have accepted that PK/PD, dose-response and longitudinal analyses are more sensitive methods than clinical outcome analysis at a single fixed time-point to detect differences between the originator and biosimilar.⁴ Although traditional statistical methods are commonly used for the primary evaluation of pivotal clinical trial data,

model-based simulations are increasingly used to optimise the design of clinical PK, PK/PD and outcome studies for biosimilars, by leveraging quantitative knowledge of the new product against the originator.⁵ Additionally, the FDA acknowledges that M&S can be useful when designing studies, for example, when determining dose selection and defining the acceptable limits for PD similarity.

Through the efficient use of available public domain data and information on the new product, study design decisions can be made to increase the probability of a successful outcome. By integrating information across dose levels, using longitudinal PK/PD and disease-progression models, uncertainty can be reduced in the estimated PK, PD, efficacy and safety endpoints. The models allow variability within, and between, subjects to be estimated, and it is also possible to simultaneously account for multiple factors to explain variation in exposure and response across individuals, including the formation of anti-therapeutic antibodies.

Using the models for subsequent clinical trial simulation, various study designs can rapidly be explored in silico (doses, sample size, study duration, reduced sampling schedules, inclusion/exclusion criteria, and choice of statistical evaluation method). By simulating multiple virtual clinical studies and calculating the outcome for each study in accordance with regulatory guidelines, the probability of concluding PK/clinical similarity can be explored under various scenarios. The influence of an expected

difference between the originator and new product (e.g. 0, 1, 3, 5 or 10%) on the required sample size can easily be calculated, and the most cost-effective design with a sufficient probability of a successful outcome can then be chosen. These methods are also applicable for bridging results across study populations and therapeutic indications.

CASE STUDIES:

1. ADALIMUMAB BIOSIMILAR PK STUDY

When developing biosimilars, clinical trials demonstrating PK and PD similarity of the new product against the approved drug are required, and an insufficient sample size can jeopardise the study outcome. For adalimumab, an anti-TNF- α antibody used to treat a variety of autoimmune diseases, PK similarity trials often involve a higher-than-normal number of subjects, as high variability in the PK between patients is anticipated.

To explore whether the sample size of such studies can be reduced, a model-based approach was employed. The optimal number of subjects required for demonstrating PK similarity between a proposed biosimilar and the originator was studied using available literature information on the adalimumab originator, against and in-house data on the new biosimilar candidate.

A population PK model for adalimumab in rheumatoid arthritis patients following a 40 mg subcutaneous injection of the EU and US approved formulations was implemented in the clinical trial simulation software Simulo.⁶The

effect of patient body weight was also incorporated into the model, along with the influence of anti-adalimumab antibodies. Various study designs, with varying sample sizes, were simulated 1000 times. For each simulated clinical trial, the differences in the maximal drug concentration (C_{max}) and the area under the drug concentration-time curve (AUC) between the new product and the reference, were evaluated using traditional statistical bioequivalence testing methods. The overall likelihood of having a successful study outcome was eventually predicted for the various simulated study design scenarios.

The analysis indicated that studies including more than 150 subjects did not give any significant improvement in the probability of showing bioequivalence when compared with studies in smaller cohorts. It also showed that a difference in anti-adalimumab antibodies of 15% is likely to decrease the likelihood of successful results being achieved for all pairwise comparisons.

By using this model-based simulation approach, accounting for already available adalimumab data, the number of subjects required to demonstrate PK similarity could be reduced by 40–60%, compared to the originally proposed design. This demonstrated the advantages of using such methods to assist in the design of pivotal PK studies to cut cost and save time. The methodology can also easily be applied for PD markers and clinical outcome endpoints.

2. DISEASE PROGRESSION MODEL FOR RITUXIMAB

The purpose of this example was to justify extrapolation of efficacy for a rituximab biosimilar candidate across patient populations not directly studied in the clinical development programme.

Model-based simulations were undertaken to predict the efficacy when rituximab is administered in monotherapy in asymptomatic, relapsed or resistant follicular lymphoma patients. A parametric time-to-event model describing the relationship between rituximab exposure and clinical outcome measured as progression free survival (PFS) in the different patient was used.

The simulated PFS for a hypothetical biosimilar candidate and rituximab together with a comparison of reported values in the literature for a pivotal study in follicular lymphoma patients are presented in Figure 1 and Table 1.

FIGURE 1
SIMULATED PFS FOR PIVOTAL STUDY THE LINES SYMBOLISE 5TH, 50TH AND 95TH QUANTILES FOR EACH TREATMENT ARM (RITUXIMAB IN GREEN AND RED LINES FOR BIOSIMILAR)

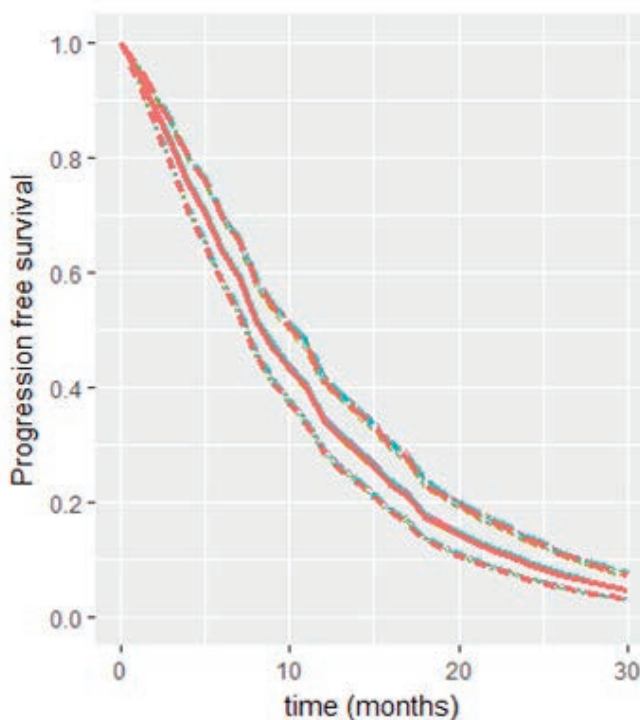


TABLE 1
COMPARISON OF OBSERVED AND PREDICTED OUTCOMES FOR PIVOTAL STUDY

	OBSERVED MEDIAN TIME TO PROGRESSION (MONTHS)	PREDICTED PFS (MONTHS) (90% CI)	
Condition	Pivotal study	Rituximab	Biosimilar candidate
All patients	9.0	8.4 (7.4, 10.5)	8.3 (7.1, 10.2)

Model based prediction for PFS were similar to the reported PFS value (9.0 months) in the pivotal study. No differences between biosimilar and originator were predicted (8.3 vs 8.4 months), evidencing that the clinical response is expected to be similar in the simulated population.

As rituximab variability in the therapeutic response is partly explained by rituximab PK, the addition to the PK/PD model of factors suggested to influence rituximab efficacy, could help to determine the efficacy response in unobserved populations such as FCGR3A polymorphism carriers, whereby patients with valine allotype have higher probability of response to rituximab than phenylalanine carriers.

In summary, disease progression model simulations supported that extrapolation across asymptomatic, relapsed or resistant follicular lymphoma patient

populations receiving rituximab in monotherapy. As efficacy is expected to be similar between the biosimilar and the originator in all populations, clinical extrapolation is supported across all oncological indications.

3. EXPECTED CLINICAL OUTCOME OF RITUXIMAB BIOSIMILAR CANDIDATE IN RHEUMATOID ARTHRITIS

A model characterising the PK and PD relationship of rituximab was used to inform about the expected differences in the clinical response given differences in rituximab exposure. A population PK/PD model was developed from the literature to compare the clinical response in rheumatoid arthritis (RA) patients between rituximab and a proposed rituximab biosimilar. The model adequately characterised the time course of DAS28 (Disease Activity Score in 28

Joints) as a function of the rituximab concentrations.

The efficacy results after 1000 simulations of 100 RA patients following 2x1000 mg every 2 weeks of either biosimilar or rituximab is depicted in the Table 2.

Reference values for DAS28 change from baseline in rituximab biosimilar studies were similar to the predicted mean for rituximab, and completely within the 90% CI, evidencing the capability of the implemented disease model to reproduce the clinical outcome. The time course of DAS28 were comparable between treatment groups. At week 24, mean changes from baseline in DAS28 were not significantly different between groups (-1.956 vs. -1.963, respectively).

In conclusion, model-based simulations were undertaken to evaluate the differences on clinical outcome in RA patients based on the established rituximab PK/PD relationship. The time course of mean DAS28 changes from baseline is expected to be similar between biosimilar and originator, supporting study design and evaluation of biosimilar rituximab studies in the RA population.

4. PK/PD MODEL OF PEGFILGRASTIM

Pegfilgrastim, the long-acting version of filgrastim, is acting on hematopoietic cells to stimulate production, maturation and activation of neutrophils. The

TABLE 2
PREDICTED DAS28 CHANGE FROM BASELINE

	PREDICTED DAS28 CHANGE FROM BASELINE			
	WEEK 8	WEEK 12	WEEK 16	WEEK 24
rituximab	-1.814 (-4.939, 0.3367)	-1.923 (-5.19, 0.2878)	1.938 (-5.25, 0.2824)	-1.956 (-4.708, 0.1216)
biosimilar	-1.815 (-4.954, 0.3456)	-1.92 (-5.198, 0.3098)	-1.932 (-5.288, 0.2981)	-1.963 (-4.683, 0.1232)

PK of pegfilgrastim is nonlinear, and clearance decreases with increases in dose. Neutrophil receptor binding is an important component of the clearance of pegfilgrastim, serum clearance being directly related to the number of neutrophils. Therefore, a large variability in the PK of pegfilgrastim is expected. No biosimilar of pegfilgrastim has been approved in the US or Europe to date.

In this context, a model-based approach was used to support the comparative effectiveness of a new biosimilar and reference pegfilgrastim, using receptor-mediated models.

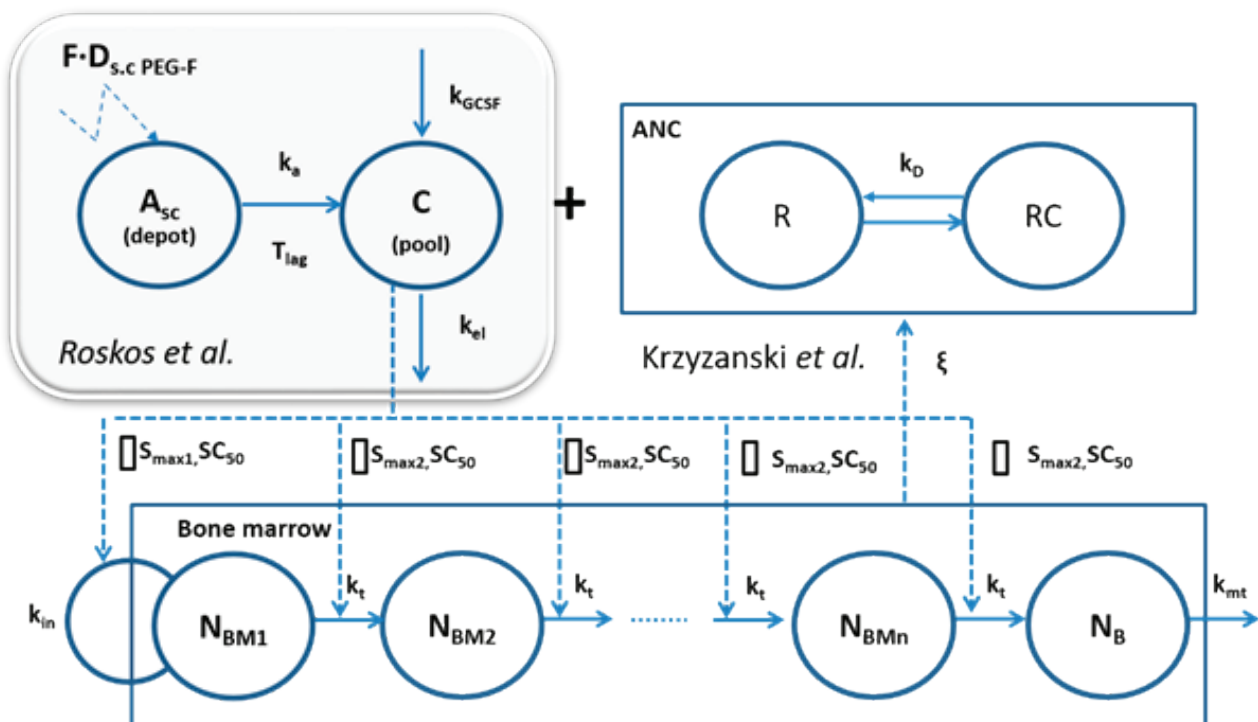
The published PK model parameters of pegfilgrastim in healthy subjects^{7,8} consisted of a one-compartmental PK model with first-order delayed absorption process (Figure 2). A non-linearity was introduced through the relationship between the receptor-mediated

clearance of G-CSF and the neutrophil count in the bone marrow and blood.

The neutrophil dynamics was based on a PD model where the maturation of the neutrophil precursor in the bone marrow is described by a sequence of transit (aging) compartments. The stimulatory effect of pegfilgrastim on neutrophil production and maturations is driven by the serum concentrations.

The PK/PD = model was implemented in Simulo.⁶ The effect of dose in the sensitivity of PK and PD equivalence testing was evaluated to explore Type I error rates under various study designs.

FIGURE 2
SCHEMATIC ILLUSTRATION OF THE POPULATION PK/PD MODEL FOR PEGFILGRASTIM^{7,8}



CONCLUSION

The benefit of adopting M&S when developing biosimilars has been shown from motivating examples in the application to the study design, clinical extrapolation and clinical interpretation of

the outcomes. This approach may yield more informative studies and analyses than would otherwise be feasible, given the constraints on time and resources that are usually allocated to a biosimilar development programme.

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