Model based support to biosimilarity assessment planning – A case study of pegfilgrastim

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Introduction

Pegfilgrastim (PG) is a recombinant pegylated granulocyte colony stimulating factor (GCSF) used in the treatment of chemotherapy induced febrile neutropenia (FN)[1]. PG induces the maturation, proliferation and survival of neutrophil precursors resulting in an increase in absolute neutrophil count (ANC). Administration of PG is associated with a high treatment cost which can be mitigated by the approval of biosimilar versions of the drug. However, the first approvals of biosimilar PG are very recent and reasons for the difficulties related to development of biosimilar PG were explored using model-based simulation in this work.

Objectives

i) To develop a population PK/PD model for PG and ANC using the data from three PG formulations tested in a clinical trial.

ii) To perform sensitivity simulations with the developed model to elucidate exposure sensitivity of PG and ANC to differences in delivered dose, EC50 and baseline ANC levels.

Methods

Model and data

- Data from a three-way cross-over clinical study (n = 174) comparing a potential biosimilar to two batches of the reference product (Neulasta®) was used in this work.
- A single dose (6 mg) was administered to the healthy volunteers. Washout between the administrations was considered to be complete.
- PG concentration and ANC were sampled simultaneously.
- An integrated bidirectional model was developed (Figure 1) where PG absorption was described by a sequential zero- and first-order absorption process and PG elimination was described by a parallel saturable non-specific and linear ANC dependent elimination.
- The model to describe ANC was based on previously developed neutrophil kinetic models[2]. PG induced neutrophil proliferation, maturation and margination through E_{MAX} models.
- Covariates were evaluated using full random effects modeling (FREM[3]).

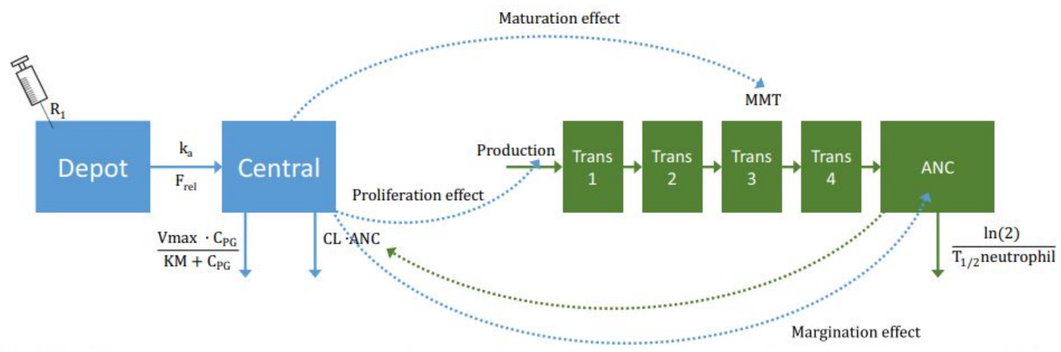

Figure 1: Final PKPD model for PG and ANC. PG influenced the proliferation, maturation and margination of ANC while ANC increased the elimination of PG through a linear effect.

Simulations

- Model performance was evaluated through model simulations of both PG and ANC and through posterior predictive checks of area under the curve (AUC) and maximum concentration (Cmax).
- A hypothetical two-way cross-over biosimilarity trial was simulated comparing a reference product to a test product with a perturbation.
- Dose differences (2,4,6,8,10%) and EC50 differences (5,50,500,1000,5000%) between the two administrations were simulated.
- The power to conclude biosimilarity given the differences in dose or potency were evaluated using Monte-Carlo mapped power (MCMP[4]).

References

[1] Roskos LK, Lum P, Lockbaum P, Schwab G, Yang B-B. Pharmacokinetic/pharmacodynamic modeling of pegfilgrastim in healthy subjects. J Clin Pharmacol. 2006;46:747–57

[2] Quartino AL, Friberg LE, Karlsson MO. A simultaneous analysis of the time-course of leukocytes and neutrophils following docetaxel administration using a semi-mechanistic myelosuppression model. Invest New Drugs. 2012;30:833–45.

[3] Yngman G, Nyberg J, Jonsson EN, Karlsson MO. Practical considerations for using the full random effects modeling (FREM) approach to covariate modeling [Internet]. Available from: https://www.page-meeting.org/default.asp?abstract=7365.

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Conclusions

- ✓ A population PKPD model was developed for pegfilgrastim.
- ✓ PK was sensitive to small changes in dose, PD less so. PK and PD were insensitive up to 50 fold differences in potency.
- ✓ With a 2% difference in dose, the 80% statistical power to conclude PK similarity required approximately 200 individuals.

Results

Model and data

The developed model performed well for both PG concentration and ANC as indicated by VPCs (Figure 2).

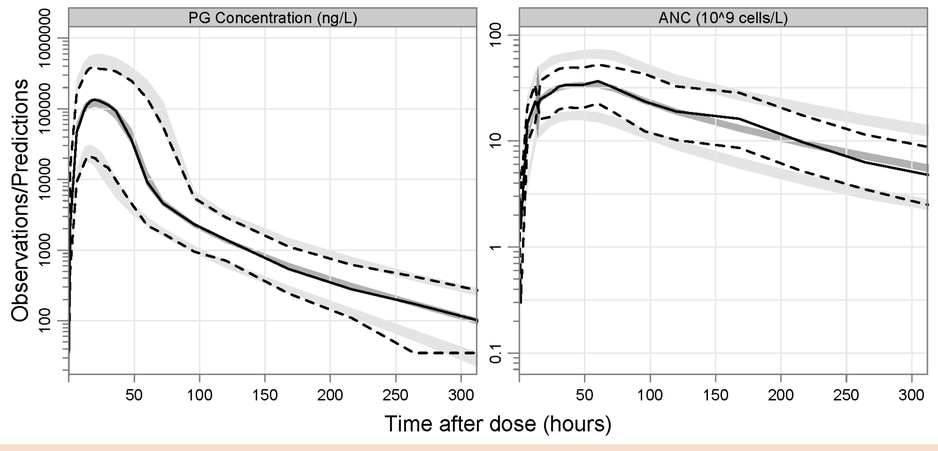

Figure 2: VPC of the final model PKPD model stratified by observation type (PG or ANC).

FREM revealed that little (~2%) of the observed variability in either AUC or Cmax could be explained by any of the tested covariates (race, sex, age lean body weight, BMI, weight, formulation and period).

Simulations

Simulations of a hypothetical two-way cross-over biosimilarity trial with dose differences between administrations is presented in Figure 3. The power to conclude PK and PD similarity given dose or potency differences between the administrations is presented in Figure 4.

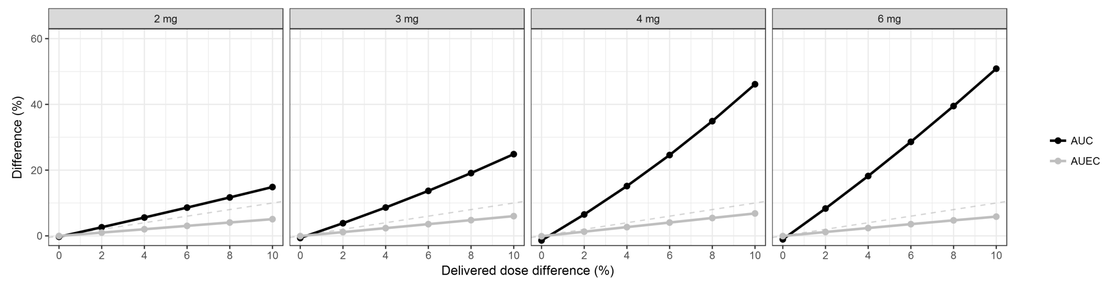

Figure 3: Geometric mean area under the pegfilgrastim concentration-time curve (AUC, black) and geometric mean area under the ANC-time curve (AUEC, grey) differences versus difference in delivered dose, stratified by nominal dose. The grey dashed line is an identity line.

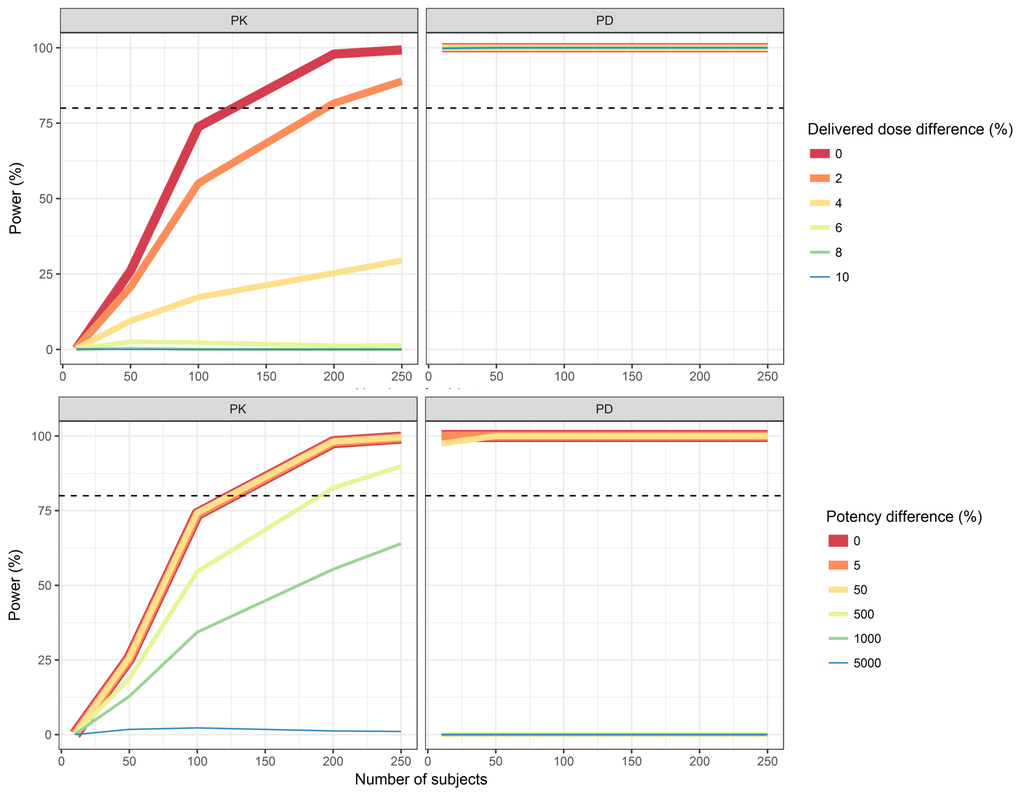

Figure 4: Statistical power to conclude PK and PD similarity in a study with a two-way cross-over design with delivered dose differences (top panels) or potency differences (bottom panels) between a reference and test products. The nominal dose administered was 6 mg. The horizontal dashed line indicates 80% power.