

Qualification of an exposure-categorical ordered multi-response population model of inolimomab in graft-versus-host disease

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Objectives: Inolimomab, a monoclonal murine antibody directed against IL-2R α (CD25) has shown promising results in the treatment of steroid-resistant acute graft-versus-host disease (aGvHD). Clinical effect is measured by categorical ordered scores quoted on different organs. The final clinical endpoint is obtained by combining those scores into a single score as IBMTR or Glucksberg scores which are non-ordered scores. Our purpose was to characterize the exposure-clinical endpoint of inolimomab.

Methods: Data arose from 21 patients with aGvHD (8 with IBMTR at score B, 11 at score C and 2 at score D) following Hematopoietic Stem Cell Transplantation after a median delay of 26 days (10 – 127 days). Inolimomab was administrated at 0.1, 0.2, 0.3 or 0.4 mg/kg daily associated with methylprednisolone (2 mg/kg) for 8 or 16 days depending of status at day 9. Then, for responder patients, administrations were continued three times a week until day 28. Inolimomab concentrations and PD data (aGvHD scores) were collected along the study. PD data were assessed in 4 grades according to IBMTR and Glucksberg classification in parallel with Karnofsky scores. Population analysis was developed using NONMEM to define the pharmacokinetic model, to test covariates, and when apparent, to model the exposure-effect relationship by a proportional odds model [1]. Modeling was finally qualified by predictive check [2].

Results: The best pharmacokinetic model was bi-compartmental. For each score, the most demonstrative exposure-effect graphics linked cumulative AUC to cumulated probabilities to observe a specific score. A categorical ordered score was fitted to each organ score. On the logit scale, the relationship was identified as an E_{max} model for skin (with 2 patient subpopulations: sensitive/less sensitive) and a linear model for intestinal tract and liver. No covariate was identified as influent on any of these parameters.

Then the model was correctly qualified by predictive check for each separate score. The final qualification consisted in combining the separate scores into the IBMTR score, just as what is performed by the clinicians. Once again predictive check confirmed the model.

Conclusions: Inolimomab exposure–effect relationships in first-line treatment of aGvHD have been identified and modeled. The discovered dose effect relationship allows to confirm the treatment response, then to establish the first step towards optimizing the doses of future trials.

References:

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