EXPOSURE-EFFICACY MODEL OF A MONOCLONAL ANTIBODY ADMINISTERED IN ACUTE GRAFT VERSUS HOST DISEASE

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Objective

To identify a population pharmacokinetic–pharmacodynamic (PK-PD) model of inolimomab, a monoclonal antibody directed against the alpha chain of the IL-2 receptor (CD25) administered in first-line treatment of patients with acute graft versus host disease (aGvHD) on ordinal efficacy categorical scores (IBMTR and Glucksberg's scale).

Methods

Patients

- A dose-escalating phase I-II study was conducted in patients with grade II to IV aGvHD after haematopoietic stem cell transplantation (HSCT).

Table I. Patient characteristics (n = 21)

Age	29 - 61 years	
Females (n = 9)	Solid tumors	(n = 5)
Males (n = 12)	Hematological disease	(n = 16)

- Patients were assigned to 1 of 4 cohorts (0.10, 0.20, 0.30 or 0.40 mg/kg) of inolimomab by i.v. infusion over a 30-minutes period, in combination with 2 mg/kg of methylprednisolone. Treatment was divided on 2 periods: an induction phase (daily adm during 1 or 2 weeks, depending on aGvHD status at day 9) and a maintenance phase (3 adm / week). Total duration of treatment was 4 weeks.

PK and PD assessments

- Blood samples were collected prior to and after administration and were quantified by a validated Enzyme-Linked ImmunoSorbent Assay (ELISA).

Table II. Assessments / pat

	n (range)
Serum	12 (7 – 23)
IBMTR	13 (3 – 23)
Glucksberg	12 (3 – 23)
Karnofsky	18 (7 – 25)
Skin	18 (7 – 25)
GUT	18 (7 – 25)
Liver	18 (7 – 25)

- aGvHD and performance status were evaluated from Day 1 to Day 28, as well as at follow-up using IBMTR, Glucksberg and Karnofsky scores (defined as composite scores). IBMTR determines aGvHD severity (grades 0 to 4) based on the scores of different organs (skin rash, diarrhoea volume, and total bilirubin concentrations). Glucksberg's score is a combination of the different organ scores and clinical performance. And finally , Karnofsky defines overall performance status of a patient (from 0 to 100 %). Independent organs as well as composite scores were considered for pharmacodynamics analysis.

PK and PKPD analysis

- **PK analysis** was carried out using mixed-effect modeling in NONMEM version V (FOCE) by testing 1 to 3 compartment models with linear or non linear elimination. Inter (IIV) and Intra individual variability were assumed to follow a log-normal distribution. Adequacy of the different developed models was evaluated with OF, GOF plots, and precision of parameter estimates. Potential covariates were tested and selected through plots, univariate tests in NONMEM and finally a backward approach using the LRT (Δ=10.83, p=0.001). After final model selection, correlation between all PK parameters were estimated, and parameter estimates used to simulate individual PK exposure.

- **Exposure** was defined as Cmax, Area Under the Curve (AUC), cumulated AUC, or AUC intensity (cumulated AUC/duration). PKPD relationship was explored through sophisticated graphics which plotted cumulative probabilities of the score grade versus PK exposure. Then we quantified potential **PKPD relationship** by a proportional odds model. For that, cumulative probabilities of observed score j were logit transformed and linked to PK exposure:

$$\text{logit}[P(Y \le j)] = f(\text{exposure})$$

- Nature of this link (f) was tested with different PD models, like Emax, log-linear or linear models. Inter individual variability on the logit followed a normal distribution and a log-normal distribution if it was on EA50. Estimation was performed using the LAPLACIAN estimation method. Adequacy of the different developed models and covariate testing was performed as for PK model.

- **Qualification** of our PK and PKPD analyses was based on visual predictive checks and predictive checks depending of the model purposes.

(1) Karlsson et al. 1998. A general model for time-dissociated PK-PD relationship exemplified by paclitaxel myelosuppression.

Results

- A 2-compartments model was the most appropriate to describe the data. Clearance was estimated at 0.077 l/hr (19 %), volume of compartment 1 at 2.76 l (26 %), volume of compartment 2 at 2.25 l (18 %) and inter-compartmental clearance at 2.22 l/hr (52 %). No covariate was found significant and a visual predictive check (n= 1000) on concentrations allowed us to qualify our model.

- PKPD exploratory analysis revealed that composite scores (IBMTR, Glucksberg and Karnofsky) were not linked to exposure whatever its calculation. On the opposite, organ scores showed apparent and increasing relationship between PK exposure and probabilities of lowest grade. Figure 1 show the most apparent relationship: with cumulated AUC.

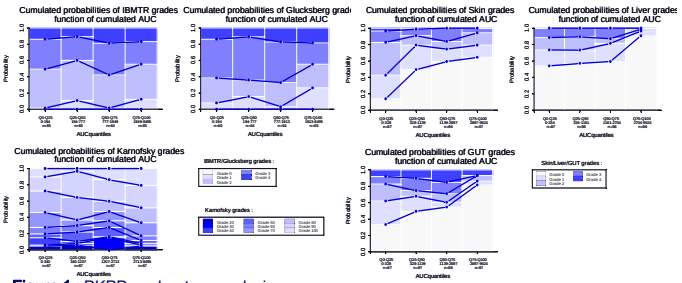

Figure 1 : PKPD exploratory analysis

- This relationship with organ scores was modelled for skin by an Emax model, and for gut and liver by a linear model, with IIV on the logit for all models. Moreover, we identified in the skin model 2 subpopulations of patients (sensitive / less sensitive) based on a mixture model for EA50 parameter. Most important parameters are presented in Table III.

Table III. Final parameter estimates of each organ

Skin model	Estimate	SE (%)	**Skin model**	Estimate	SE (%)
Emax	13.4	23	EA50 population 1	15900	35
Population 1 %	35	31	EA50 population 2	609	36
Gut model			**Liver model**		
slope	0.000339	60	slope	0.000429	87

- Qualification of our PKPD models was based on predictive checks (see Figure 2) and different statistical criteria. For instance, we choose time to the first transition to the safe grade.

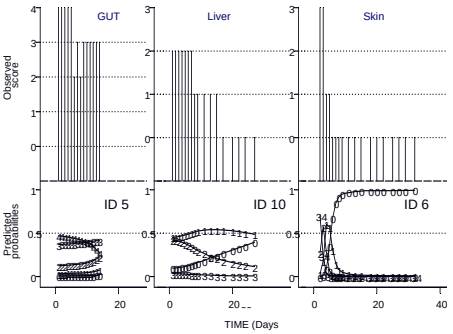

Figure 3 : PD profiles of patient ID5, ID10, and ID 6.

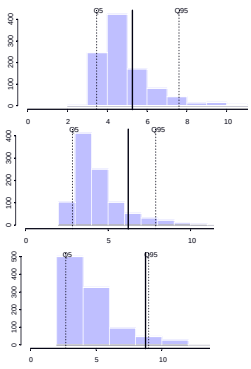

Figure 2 : PPC of the 3 models, skin, gut and Liver (top-down). Time to the first transition to the safe grade in 1000 simulated datasets.

Discussion - Conclusion

Inolimomab exposure–effect relationship has been identified and modelled for aGvHD targeted organ scores (skin, gut and liver). This model links cumulative AUC to grade score probabilities and correctly predicts majority of PD individual profiles (see Figure 3) and time necessary to response in a patient (see Figure 2). But conceptually, it can not predict appearance of aGvHD relapse or resistance to treatment (1). Nevertheless, this first modelling allowed to confirm effect of this first line treatment and more data should overcome this limitation.