Population Pharmacokinetic Analysis of Emapalumab, a Fully Human, Anti-Interferon Gamma Monoclonal Antibody, in Children with Primary Hemophagocytic Lymphohistiocytosis

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Disclosures

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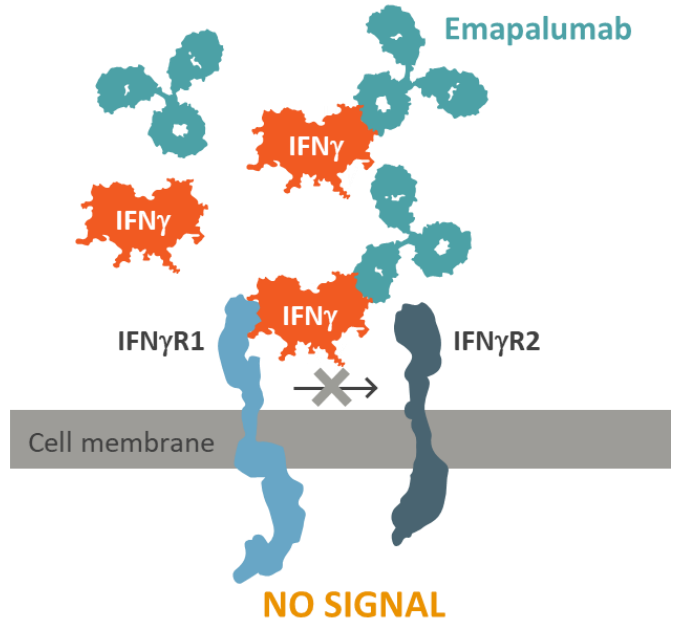
Introduction

- Primary hemophagocytic lymphohistiocytosis (HLH) is a rare syndrome characterized by pathologic immune activation and hyperinflammation[1,2]
- It typically manifests during infancy and is invariably fatal if untreated[1]
- Interferon gamma (IFNy) is considered a key contributor to the hyperinflammation of HLH[3–5]
- Thus, neutralization of IFNy could help control the disease until haematopoietic stem cell transplantation, the only curative treatment
- Emapalumab is a fully human, anti-IFNy monoclonal antibody that binds to and neutralizes IFNy[6]
- Emapalumab is the first and only approved (FDA) treatment for adult and pediatric patients with primary HLH with refractory, recurrent, or progressive disease, or intolerance to conventional HLH therapy[7]



1. Henter et al. Acta Paediatr Scand 1991;80:428–35; 2. Jordan et al. Blood 2011;118:4041–52; 3. Buatois et al. Transl Res 2017;180:37–52.e2; 4. Jordan et al. Blood 2004;104:735–43; 5. Pachlopnik Schmid et al. EMBO Mol Med 2009;1:112–24; 6. Hatterer et al. Cytokine 2012;59:570; 7. Gamifant Product Information, 2018;

Objectives

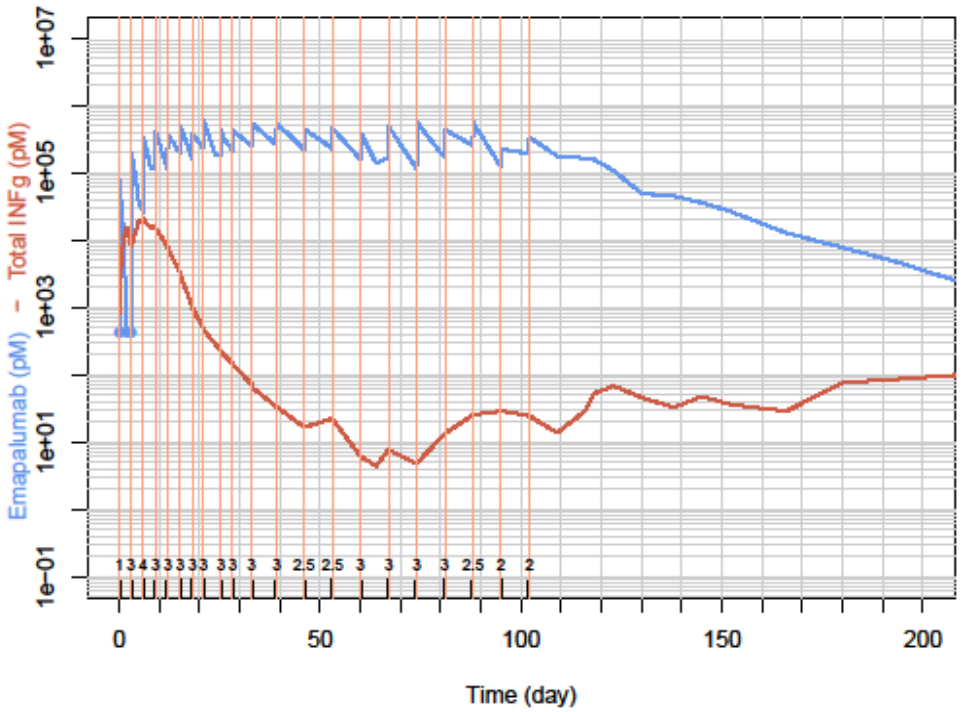
- To develop a population pharmacokinetic (PK) model to describe the PK profile of emapalumab in HLH patients
- To identify longitudinal relationships between emapalumab and total IFNy concentrations
- To perform a covariate analysis to identify which of the available covariates may contribute explaining variability in emapalumab pharmacokinetics

Methods

- PK data (trough and peak samples as shown in graph) were obtained from patients with primary HLH administered emapalumab intravenously as part of:
  - An open-label, single-group, phase 2/3 clinical trial (NCT01818492)[1]
  - Compassionate use program
- A population PK analysis was performed using nonlinear mixed effects modeling (NONMEM® version 7.3.0)
  - Predictive performance of the model was assessed using a visual predictive check

Concentration-time profiles of free emapalumab (blue, left log axis) and total IFNγ (red, left log axis)*

Patient: Boy aged 21.5 months, BW=9.1–11.62 kg



*Vertical orange lines: emapalumab administrations (doses indicated in mg/kg above the X-axis); Dots indicate BLQ (below the limit for quantification) values. BW, body weight.

1. ClinicalTrials.gov NCT01818492.

Patient Demographics

- At study start:
  - 39 infants (<1 year)
  - 4 children (9–14 years)
  - 3 adults (>20 years)
- Majority female (53% vs 47%)
- Body weight distribution reflects age range
- Levels of IFNy at Day 3 after start of emapalumab treatment indicator of disease severity
  - Large heterogeneity between and within patients (100–1,000,000 pg/mL)

HLH patients (N=49)	Mean (SD)	Median (range)
Age, years	4.5 (9.3)	1.2 (0.019–56)
Body weight at baseline, kg	16 (18)	9.2 (2.0–82)
IFNy at Day 3, pg/mL	20,450 (47,574)	1,963 (50–270,842)

SD, standard deviation.

Population PK model

- PK of emapalumab was adequately described by a two-compartment model
  - With linear clearance and a target-mediated, non-linear clearance
  - All model parameters were estimated with good precision
- Of the parameters examined, only **body weight** and **total IFNγ** (free and bound) levels **significantly influenced emapalumab PK**
- Tested covariates included:
  - Age, Race, Sex
  - Alanine aminotransferase
  - Creatinine clearance
  - Total bilirubin
  - Total IFNγ and body weight already included in the base model

PK parameter estimates from final model

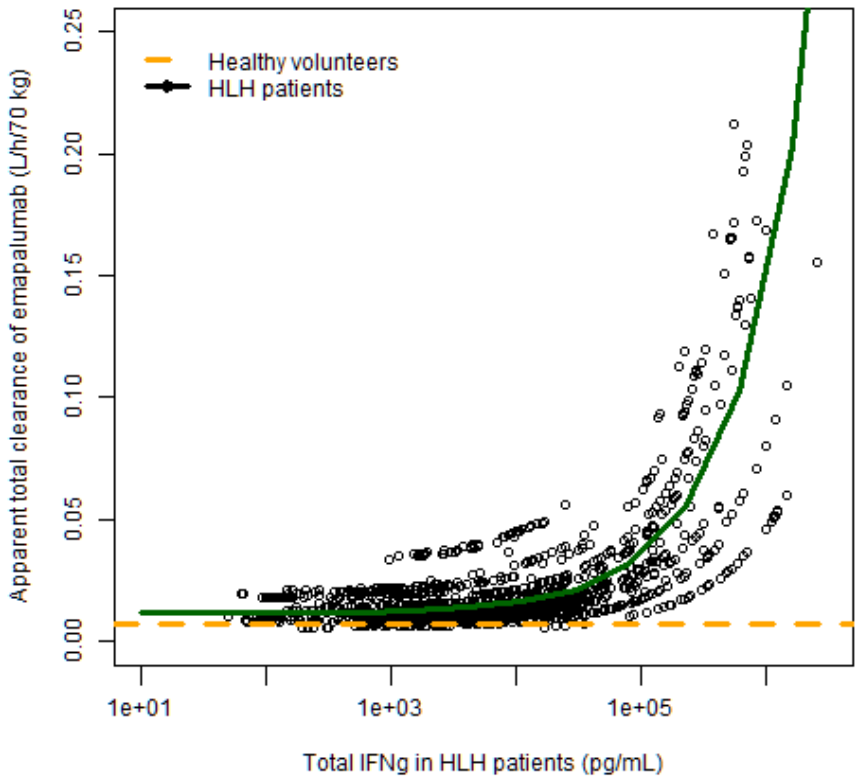
Parameters		Description	Estimate	RSE (%)
CLL	L/h/70 kg	Linear clearance	0.0116	29.7
CLNL	L/h/70 kg	Non-linear clearance (IFNγ dependent)	0.133	33.5
V1	L/70 kg	Central volume of distribution	4.16	4.4
Q	L/h/70 kg	Intercompartmental clearance	0.102	26.3
V2	L/70 kg	Peripheral volume of distribution	5.55	20.7
CLNL_IFNγ		Influence IFNγ on CLNL (power function)	+0.746	12.3
CL_BW		Allometric exponent on CLs	+0.886	11.9
V_BW		Allometric exponent on Vs	1 fixed	-
Residual variability			Estimate	RSV (%)
SIGMA		Standard deviation of residual variability (Additive in log domain)	0.306	30.6

Total clearance: $CL_{total} = (CLL + CLNL*(IFN\gamma_t/1{,}000{,}000)^{+0.746})*(BW/70)^{+0.886}$

Emapalumab clearance based on total IFNy

- For total IFNy levels from 10^3 to 10^6 pg/mL:
  - Total clearance (linear + target mediated) of emapalumab ranged from 0.0012 to 0.0140 L/h for a bodyweight of 5 kg
  - With corresponding terminal half-lives from 2.3 to 17.5 days
- This wide variance in clearances and half-lives partly explains the emapalumab dose adaptations that are required for treating primary HLH patients

Estimated apparent total clearance versus total IFNy concentrations in HLH patients*



*Semi-log graph on left. Log-log graph on right. Dots are individual predicted clearances in patients. Green line is the population predicted clearance. Orange dotted line is clearance in healthy volunteers.

Conclusions

- Total IFNγ concentration/production in HLH patients shows high inter- and intra-individual variability
- A two-compartment model well describes emapalumab PK
- Total clearance of emapalumab is significantly influenced by the production of IFNγ, leading to target-mediated drug disposition:
  - At moderate total IFNγ concentrations, emapalumab clearance is rather linear
  - At high total IFNγ concentrations, emapalumab clearance increases to become closely proportional to the total IFNγ concentration/production
- This modelling approach supported the proposed body-weight–based dosing scheme (i.e. mg/kg) of emapalumab in patients with primary HLH as well as dosing adaptations accounting for the variability in IFNγ production and guided by the evolution of laboratory and clinical parameters in response to emapalumab