Comparison of Tolerance Models for Neopterin Elevation Following Interferon beta-1a or PEGylated Interferon beta-1a treatment in Rhesus Monkeys

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ABSTRACT

Objective:

Seven tolerance models were compared to describe the neopterin response as a pharmacodynamic marker and to explore the mechanisms of tolerance development in Rhesus monkeys after administration of interferon beta-1a (IFN) or PEGylated interferon beta-1a (PEG-IFN).

Methods:

PEG-IFN, IFN, and neopterin concentration data were collected in two single-dose PK/PD studies and one multiple-dose toxicity study, from a total of 76 monkeys. A two-compartment PK model and an indirect stimulatory PD model were developed [1]. Seven tolerance models were compared, including an indirect moderator tolerance model, a direct moderator model, a tolerance pool model, a tolerance adaptive model, partial agonist model, competitive antagonist model, and a noncompetitive antagonist model [2], to select the best model to describe the data. The analysis was carried out using nonlinear mixed effect modeling tool, NONMEM 7.2.

Results:

All tolerance models fit the data better than the base model which did not include tolerance, with the indirect moderator tolerance model providing the best fit, and the tolerance pool model the least fit. Based on the indirect moderator tolerance model, BASE (neopterin baseline) was 2.88 ng/mL, the LOSS (first-order elimination rate) was 0.0095 h^{-1}, the MRT (mean resident time for the delayed neopterin response) was 8.24 h for IFN and 7.85 h for PEG-IFN, the KTOL (the rate constant for tolerance compartment) was 0.0593 h^{-1}, the TC50 (concentration in tolerant compartment to achieve 50% of tolerance) was 0.0261, the Emax (maximum stimulating effect) was 1710, the EC50 (concentration to achieve 50% of E_{max}) was 574 pg/mL for IFN and was 8220 pg/mL for PEG-IFN. The results suggest that the development of tolerance, which resulted in similar neopterin response between PEG-IFN and IFN, is more likely due to negative feedback of neopterin or down-regulation of IFN receptors than due to an exhausted neopterin precursor pool.

Conclusions/Relevance:

An indirect moderator tolerance model was selected as the best model from seven tolerance models to describe the development of tolerance in neopterin elevation following IFN or PEG-IFN treatment in Rhesus monkeys.

INTRODUCTION

- PEG-IFN is formed by covalently attaching a single, linear 20 kDa methoxypolyethyleneglycol-O-2-methylpropionaldehyde moiety to the N-terminal alpha-amino group of IFN beta-1a, the latter being a first-line treatment for Multiple Sclerosis (MS). PEG-IFN is being developed to offer patients with MS a more convenient alternative to current first-line disease modifying therapies, while maintaining the established efficacy, safety, and tolerability of IFN beta-1a therapy.
- Rhesus monkeys were pharmacologically responsive to IFN beta-1a treatment, as shown by serum neopterin elevation.
- Daily injection of IFN beta-1a resulted in development of tolerance, regarding neopterin response.
- Treatment with IFN beta-1a and PEG IFN beta-1a resulted in similar neopterin responses despite differences in PK profiles.
- The data was fitted with seven tolerance models [2]. The goodness of fit was compared [3, 4].

METHODS

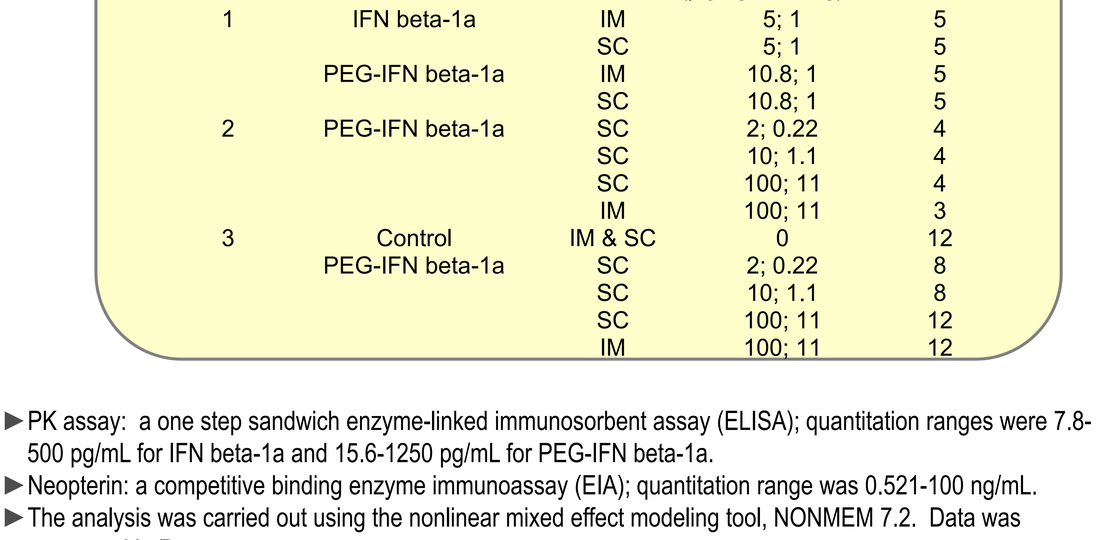
- Three studies using Rhesus monkeys were conducted to evaluate PK, PD, immunogenicity, and toxicity of PEG-IFN beta-1a. More details could be found in the reference. Study designs are summarized in Table 1.

Table 1 Summary of Study Designs

Study #	Test Article	Route	Dose (μg/kg; MIU/kg)	n
1	IFN beta-1a	IM	5; 1	5
		SC	5; 1	5
	PEG-IFN beta-1a	IM	10.8; 1	5
		SC	10.8; 1	5
2	PEG-IFN beta-1a	SC	2; 0.22	4
		SC	10; 1.1	4
		SC	100; 11	4
		IM	100; 11	3
3	Control	IM & SC	0	12
	PEG-IFN beta-1a	SC	2; 0.22	8
		SC	10; 1.1	8
		SC	100; 11	12
		IM	100; 11	12

- PK assay: a one step sandwich enzyme-linked immunosorbent assay (ELISA); quantitation ranges were 7.8-500 pg/mL for IFN beta-1a and 15.6-1250 pg/mL for PEG-IFN beta-1a.
- Neopterin: a competitive binding enzyme immunoassay (EIA); quantitation range was 0.521-100 ng/mL.
- The analysis was carried out using the nonlinear mixed effect modeling tool, NONMEM 7.2. Data was processed in R.
- Software: NONMEM, version VII, level 2.0; R version 2.12.2
- PK model: 2-compartment with 1st order-absorption; post-hoc PK parameters were entered in the data set for sequential PK/PD modeling
- Schematic view of the seven models are shown in Figure 1 [2].

FIGURE 1. Schematic View of PK, PD, and Tolerance Models



CL=clearance; Cp=serum drug concentration; EC_{50}=drug concentration to achieve 50% of maximum effect; E_{max}=maximum effect; Ka=absorption rate; Ke=elimination rate; KP=zero-order synthesis rate of pre-cursor pool; KTR=1st order transition rate leaving transit compartment; LOSS=first-order loss rate; NEOP=neopterin; POOL=precursor pool concentration; SYN=synthesis rate; SYN0=synthesis rate at baseline; V=volume of distribution; TOLERAN=tolerance compartment; TR_1=transit compartment 1; TR_5=transit compartment n.

RESULTS

- The differential equations, initial state, assumptions and objective function values are shown in Table 2.
- The final parameter estimates are listed in Table 3.
- The visual predictive check for the best model is shown in Figure 2.

Table 2 Model Functions and Objective Function Values

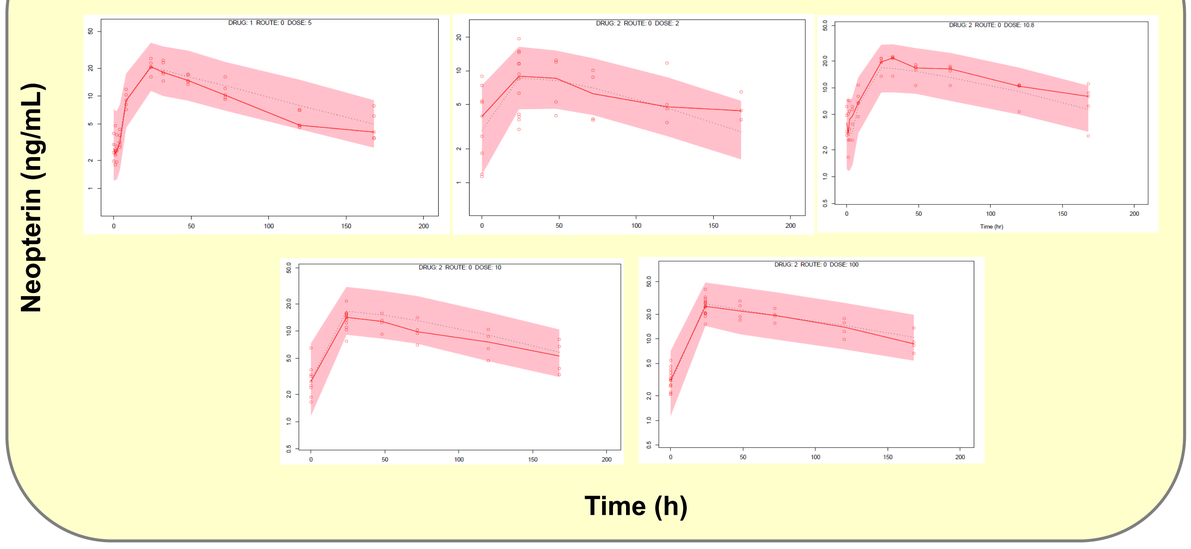
Model	Equations	Initial state assumptions	OFV
1	EFFECT=1+Emax*CP/(EC50+CP) dTR1/dt=SYN*EFFECT-KTR*TR1 dNEOP/dt=KTR*TR5-NEOP*LOSS	NEOP(0)=BSL SYNTH=BSL*LOSS TR1(0)=…=TR5(0)=SYNTH/KTR	-478
2	EFFECT=1+Emax*CP/(EC50+CP) TOLE=1-TOLERAN/(TC50+TOLERAN) dTR1/dt= SYNTH*EFF*TOLE-KTR*TR1 dNEOP/dt=KTR*TR5-NEOP*LOSS dTOLERAN/dt= KTOL*NEOP-KTOL*TOLERAN	NEOP(0)=BSL SYNTH=BSL*LOSS TR1(0)=…=TR5(0)=SYNTH/KTR	-687
3	EFFECT=1+Emax*CP/(EC50+CP) dPOOL/dt=KP-SYNTH*POOL*EFFECT dTR1/dt= SYNTH*EFFECT*POOL-KTR*TR1 dNEOP/dt=KTR*TR5-NEOP*LOSS	NEOP(0)=BSL POOL(0)=PBASE SYNTH=BSL*LOSS/PBASE KP=BSL*LOSS TR1(0)=…=TR5(0)=LOSS*BSL/KTR	-536
4	EFFECT=1+Emax*CP/(EC50+CP) ADAPT=(PBASE/POOL)**POW dPOOL/dt=KP*ADAPT-SYNTH*EFFECT*POOL dTR1/dt= SYNTH*EFFECT*POOL-KTR*TR1 dNEOP/dt=KTR*TR5-NEOP*LOSS	NEOP(0)=BSL POOL(0)=PBASE SYNTH=BSL*LOSS/PBASE KP=BSL*LOSS TR1(0)=…=TR5(0)=LOSS*BSL/KTR	-556
5	dCE=KE*CP-KE*CE dTR1/dt=KTR*CE-KTR*TR1 EOUT=ENOLL+EMAX*TR5/(EC50+TR5)-TOLERAN dTOLERAN=GR*KG*EOUT-KG*TOLERAN NEOP=EOUT	ENOLL=BSL*(1+GR)/GR NEOP(0)=BSL	-639
6	EFFECT=1+ (EMAX*CP*TC50+TMAX*TOLERAN*EC50)/ (EC50*TC50+EC50*A(10)+TC50*CP) dTOLERAN= KTOL*CP-KTOL*TOLERAN dTR1/dt=SYN*EFFECT-KTR*TR1 dNEOP/dt=KTR*TR5-NEOP*LOSS	NEOP(0)=BSL SYNTH=BSL*LOSS TR1(0)=…=TR5(0)=SYNTH/KTR	-645
7	EFFECT=1+ EMAX*CP/(CP+(EC50/TC50)*TOLERAN+EC50) dTOLERAN= KTOL*CP-KTOL*TOLERAN dTR1/dt=SYN*EFFECT-KTR*TR1 dNEOP/dt=KTR*TR5-NEOP*LOSS	NEOP(0)=BSL SYNTH=BSL*LOSS TR1(0)=…=TR5(0)=SYNTH/KTR	-645
8	EFFECT=1+ EMAX*CP*TC50/(CP*TC50+EC50*TC50+A(10)*EC50+CP*A(10)) dTOLERAN= KTOL*CP-KTOL*TOLERAN dTR1/dt=SYN*EFFECT-KTR*TR1 dNEOP/dt=KTR*TR5-NEOP*LOSS	NEOP(0)=BSL SYNTH=BSL*LOSS TR1(0)=…=TR5(0)=SYNTH/KTR	-632

Model 1=no tolerance; Model 2=indirect moderator model; Model 3=tolerance pool; Model 4=adaptive pool; Model 5 direct moderator; Model 6=partial agonist; Model 7=competitive antagonist; Model 8=noncompetitive antagonist

Table 3 Final population PD parameters for the Indirect Moderator Model

Parameter	Definition	Estimate	Standard Error
Baseline	Neopterin baseline	2.88	6
LOSS	First order loss rate of neopterin	0.0095	7
Emax	Maximum Stimulating Effect	1710	94
EC50 (IFN)	IFN beta-1a concentration to achieve 50% of maximum effect	574	27
MRT (IFN)	IFN beta-1a drug effect mean residence time in transit compartments	8.24	5
EC50 (PEG-IFN)	PEG-IFN beta-1a concentration to achieve 50% of maximum effect	8220	37
MRT(PEG-IFN)	PEG-IFN beta-1a drug effect mean residence time in transit compartments	7.85	7
KTOL	rate of tolerance development	0.0593	34
TC50	concentration in the tolerance compartment at half the maximal tolerance	0.0261	122
SD	Residual error coefficient	0.166	7
$w^2_{baseline}$	inter-subject variance for baseline	0.277	29
w^2_{Emax}	inter-subject variance for baseline	0.0711	26
$cov_{baseline\_Emax}$	Covariance between baseline and Emax	0.0724	46

Figure 2 Visual Predictive Check for the Indirect Moderator Model



DISCUSSIONS

- The indirect moderator model showed the best fit, which might suggest that the tolerance was more likely due to negative feedback of neopterin or down-regulation of IFN receptors than due to an exhausted neopterin precursor pool. However, the mechanism of tolerance needs additional experimental exploration.
- The tolerance in Rhesus monkeys are in contrast to those in humans, where neopterin elevation was of longer duration following PEG-IFN treatment than that following IFN treatment at comparable doses [5].

CONCLUSIONS

An indirect moderator tolerance model was selected as the best model from seven tolerance models to describe the development of tolerance in neopterin elevation following IFN or PEG-IFN treatment in Rhesus monkeys.

REFERENCES

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DISCLOSURES

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