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Population Pharmacokinetic and Pharmacodynamic Analysis of Pegloticase Administered by Intravenous Infusion in Two Dose Regimens to Subjects with Chronic Gout

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ABSTRACT

BACKGROUND/AIMS: Pegloticase is a PEGylated uricase that metabolizes uric acid (UA) into the more water soluble allantoin. Its mechanism of action and long half-life make it appealing as a treatment of chronic gout in patients refractory to conventional urate lowering therapy (ULT). This analysis aimed to describe the pharmacokinetics (PK) and pharmacodynamics (PD) of pegloticase in the target population.

METHODS: Two replicate, randomized, double-blind, placebo-controlled Phase 3 studies were conducted in persistently hyperuricemic subjects with chronic gout refractory to conventional ULT. The PK/PD analysis performed with the software NONMEM VI utilized data obtained from the 163 subjects that were intravenously infused 8 mg pegloticase over approximately 2 hours either every 2 or 4 weeks for 24 weeks. Samples for pegloticase, UA and antibody (Ab) assays were collected serially from baseline until 2 weeks after the last dose. Covariates tested were weight, height, body surface area (BSA), anti-pegloticase Ab titer, creatinine clearance, age, and sex. Model and covariate selection were based on standard criteria, e.g. decrease in objective function, residual variability, residual plots, and figures of goodness of fit.

RESULTS: Pegloticase PK was best described by a linear 1-compartment model with covariates BSA and Ab on both volume of distribution (Vc= 4.7 L) and clearance (CL= 0.014 L/h). Increased BSA and the presence of Ab were associated with an increase in both Vc and CL. An indirect model described the PD of pegloticase, where UA depletion rate was influenced by pegloticase and Ab titers. Pegloticase enhanced UA elimination. Ab titers diminished pegloticase's urate-lowering effect, with greater reduction at higher Ab titers.

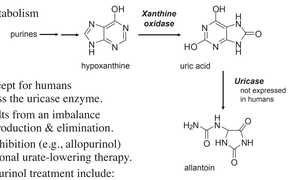
CONCLUSION: The PK of pegloticase was characterized by a 1-compartment model and its PD was described by an indirect model. Only BSA and anti-pegloticase Ab titer were retained as significant covariates in the final PK/PD model.

BACKGROUND

Gout

- Gout is the most common inflammatory arthritis in developed countries.
- Gout is characterized by hyperuricemia or elevated serum uric acid levels.
- The limit of uric acid solubility is 6.8 mg/dL, with a clinical target of < 6.0 mg/dL.
- Uric acid is a by-product of purine catabolism *(Figure 1)*.

Figure 1: Purine Metabolism



- Most mammals (except for humans & great apes) possess the uricase enzyme.
- Hyperuricemia results from an imbalance between uric acid production & elimination.
- Xanthine oxidase inhibition (e.g., allopurinol) is standard conventional urate-lowering therapy.
- Limitations of allopurinol treatment include:
  - Compliance issues
  - Dose adjustments, e.g., for renal impairment
  - Tolerability and safety profile, e.g., rash, GI toxicity, hypersensitivity syndrome
  - Ineffective in some, even with appropriate dosing

Pegloticase

- Pegloticase
  - Is a PEGylated uricase
  - Metabolizes uric acid into the more water soluble allantoin
- Pegloticase has been investigated for the treatment of chronic gout in patients refractory to conventional therapy.
- Phase I to III studies have been completed.
- Population pharmacokinetic (PK) and pharmacodynamic (PD) analyses were previously conducted using Phase 2 data.
- These analyses demonstrated that:
  - The PK of pegloticase is described by a 1-compartment model with linear elimination
  - The PD effect of pegloticase is described by a direct, inhibitory E_{max} model
  - Pegloticase has a long half-life (~17 days) and can be administered less frequently than non-PEGylated uricase
  - Pegloticase has a low EC_{50} (high potency) with a maximal inhibitory effect (E_{max}) of 83%.

OBJECTIVE

- The study was designed to characterize the PK and PD of pegloticase when administered to the target population in Phase III studies.
  - The target population consisted of patients with chronic gout refractory to conventional therapy

METHODS

Population

- Persistently hyperuricemic subjects with chronic gout refractory to conventional therapy were enrolled in this study.
- Inclusion criteria included:
  - Men and women ≥ 18 years of age
  - Hyperuricemic with a screening serum uric acid (SUA) ≥ 8 mg/dL
  - Symptomatic gout
  - Subjects in whom conventional therapy (allopurinol) was contraindicated or had been ineffective
  - Subjects without solid organ transplantation

Study Design

- Data were obtained from two replicate, randomized, double-blind, placebo-controlled Phase 3 studies.
- Treatments administered in these studies were:
  - Pegloticase 8 mg infused IV over 2 hours, every 2 weeks
  - Pegloticase 8 mg infused IV over 2 hours, every 4 weeks
  - Placebo
- The treatment duration was 24 weeks.
- Blood samples were collected periodically to assay:
  - Serum pegloticase
  - Plasma and serum uric acid
  - Antibodies against pegloticase or PEG
- *Table 1* presents a summary of the sampling schedule.

Table 1: Sampling Schedule

Week	Dose	PK/PD Sample	Antibody Sample
1	1	X[a,b]	X
3	2	X	X
5	3	X[b]	X
7	4	X	
9	5	X[a,b]	X
10	.	X	
11	6	X[a]	
12	.	X	
13	7	X	X
15	8	X	
17	9	X	X
19	10	X	
21	11	X[a,b]	X
22	.	X	
23	12	X[a]	
24	.	X	
25	.	X	X

[a]Including 2-hour post-dose sample; [b]Including 24-hour post-dose sample

Analytical Methods

- Serum pegloticase and plasma uric acid were measured as enzymatic activity using a coupled enzymatic reaction.
- The lower limits of detection for each assay were:
  - 0.600 mcg/mL for pegloticase
  - 0.5 mg/dL for plasma uric acid
- Antibody levels were assayed by ELISA.

Population PK/PD Analysis

- Dataset construction
  - Subjects who received active treatment were included in the dataset.
  - Actual doses, infusion rates, dosing times and sampling times were used.
  - Concentration values below the lower limit of detection were set to missing (pegloticase) or ½ LLOQ (uric acid).
- NONMEM version VI, level 2.0 was the modeling software utilized.
- Various PK structural models were tested, including
  - 1 and 2 compartment models
  - Linear & non-linear elimination processes
- After the base (structural) PK model was chosen, covariates were evaluated for potential inclusion in the model.

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Population PK/PD Analysis (continued)

- Covariates tested by forward stepwise analysis were:
  - Demographic traits (weight, height, body mass index, body surface area [BSA], ideal body weight, age, sex, creatinine clearance)
  - Disease-related variables (presence of tophi, screening serum uric acid values, number of gout flares)
  - Other comorbidities (presence of diabetes, hypertension, allergy or GI intolerance to allopurinol)
  - Antibody titers
    - The highest anti-pegloticase antibody titer measured for each individual was used to characterize this covariate.
- Following determination of the PK model (with covariates), different PD models were tested, such as:
  - Effect compartment model
  - Direct model
  - Indirect model
- Standard model discrimination criteria were used to select both PK and PD models:
  - Objective function
  - Akaike information criterion (AIC)
  - Residual variability
  - Residual plots
  - Goodness-of-fit figures

RESULTS

Population Characteristics

- 163 subjects (131 men and 32 women) were included in the PK/PD analysis *(Table 2)*.
- 83 subjects received pegloticase every 2 weeks, while 80 subjects received pegloticase every 4 weeks.

Table 2A and B: Patient Characteristics

Subject Demographics (n=163)	Mean (CV%)	Median (Range)
Age (years)	56 (26%)	57 (23-89)
Body Weight (kg)	99.1 (25.1%)	96.2 (48.2-191)
Height (cm)	174 (6.28%)	175 (145-193)
Body mass index (kg/m^2)	32.8 (22.5%)	31.5 (15.0-65.9)
Body surface area (m^2)	2.12 (13.3%)	2.12 (1.44-2.88)
Ideal body weight (kg)	68.2 (16.3%)	70.5 (38.6-86.8)
Screening creatinine clearance (mL/min)* (n=162)	92.4 (55.4%)	84.5 (17-264)
Screening serum uric acid (mg/dL) (n=161)	9.80 (17.7%)	9.80 (5.40-14.9)
Number of acute gout flare ups in the past 18 months (n=161)	9.70 (113%)	6 (0-90)

*Calculated using Cockroft-Gault formula

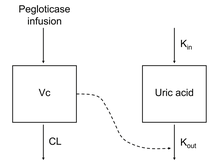
Subject Demographics	Number
Sex Male/Female	131/32
Presence of tophi Yes/No	122/41
Diabetes mellitus Yes/No	41/122
Hypertension Yes/No	119/44
Allergy or gastrointestinal intolerance to allopurinol Yes/No	96/67
Overall anti-pegloticase antibody level	
No increase	16
Low increase [0 < titer ≤ 810]	49
Moderate increase [810 < titer ≤ 7290]	33
High increase [7290 < titer]	50
Unknown change	15

RESULTS (continued)

PK/PD Model

- 1176 serum pegloticase concentrations and 3358 plasma uric acid concentrations were fitted simultaneously.
- The PK of pegloticase was best described by a 1-compartment model.
- The PD of pegloticase was characterized by an indirect inhibitory model.
- The final PK/PD structural model is depicted in *Figure 2*.

Figure 2. Final Model: 1-compartment PK model and Indirect PD model



- Differential equation for the PK model

$$\frac{dC}{dt} = dose - \frac{CL}{Vc} \cdot C$$

C = serum pegloticase concentration
t = time
$dose$ = pegloticase dose
CL = clearance
Vc = volume of distribution

- Differential equations for the PD model

$$\frac{dUA}{dt} = K_{in} - \left[K_{out} \cdot \left(1 \quad Stim\right)\right] UA$$

$$Stim = Slope \cdot C$$

$$IC = \frac{K_{in}}{K_{out}}$$

K_{in} = production rate of uric acid (UA)
K_{out} = rate of UA depletion from plasma
t = time
$Slope$ = proportionality factor
$Stim$ = stimulation factor
C = serum pegloticase concentration
IC = initial condition (baseline UA)

- Covariates included in the final PK model were:
  - BSA on CL and Vc
  - Anti-pegloticase antibody response (Ab) on CL and Vc
- BSA was centered around the mean value.
- Anti-pegloticase antibody response categories used in the PK model were:
  - No increase
  - Increase
- An increase in BSA or Ab was associated with an increase in both PK parameters.
- Example of coding of covariates in PK model:

$$\theta_{individual\_no\_Ab\_increase} = \left[\theta_{Vc\_population\_no\_Ab\_increase} \cdot \left(\frac{BSA}{2.12}\right)^{\theta_{BSA\_Vc}}\right] \cdot e^{\eta_{Vc}}$$

$$\theta_{individual\_Ab\_increase} = \left[\theta_{Vc\_population\_Ab\_increase} \cdot \left(\frac{BSA}{2.12}\right)^{\theta_{BSA\_Vc}}\right] \cdot e^{\eta_{Vc}}$$

- Covariate included in the final PD model:
  - Anti-pegloticase antibody response on Slope parameter of PD model
- Anti-pegloticase antibody response (Ab) categories for the PD model were:
  - No increase in Ab titers
  - Low increase in Ab titers (0 < titer ≤ 810)
  - Moderate increase in Ab titers (810 < titer ≤ 7290)
  - High increase in Ab titers (7290 < titer)
  - Unknown increase in Ab titers (due to analytical reasons or subject dropout)
- An increase in Ab titers was associated with a decrease in the Slope parameter of the PD model.

PK/PD Parameters

- PK/PD parameters are presented in *Table 3*.
- Goodness-of-fit plots are presented in *Figures 3a, 3b, 3c* and *3d*.
- An example of an individual fit for a typical patient is presented in *Figures 4a* and *4b*.
- Residual variability:
  - Pegloticase = 30.8%
  - Uric acid = 64.0%

Table 3. Population PK/PD Parameter Estimates

Parameter	Mean	Coefficient of variation (%)	
		Inter-Subject*	Inter-Occasion
Vc if no Ab increase (L)	4.73	24.7	18.2
Vc if Ab increase (L)	5.93		
BSA Exponent Vc	1.73	Not estimated	
CL if no Ab increase (L/h)	0.0145	39.6	17
CL if no Ab increase (L/h)	0.0191		
BSA Exponent CL	1.12	Not estimated	
K_{in} (mg/dL/h)	0.727	14.6	31.9
K_{out} (1/h)	0.079	9.34	31.3
Slope if no Ab increase (mL/mcg)	3.93	112	51.1
Slope if low Ab increase (mL/mcg)	1.60	236	24.6
Slope if moderate Ab increase (mL/mcg)	0.578	163	22.3
Slope if high Ab increase (mL/mcg)	0.0526	39.8	16.8
Slope if unknown Ab increase (mL/mcg)	0.380	Not estimated	26.8

*Percent relative standard error for PD parameters, derived from h for PK parameters

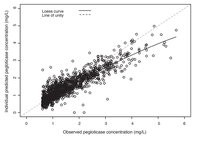


Figure 3a: Individual Predicted vs. Observed Concentrations for Pegloticase (n=163)

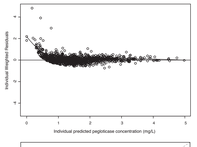


Figure 3b: Individual Weighted Residuals vs. Predicted Pegloticase Concentrations

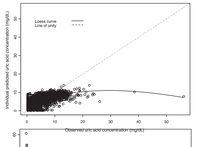


Figure 3c: Individual Predicted vs. Observed Concentrations for Uric Acid (n=163)

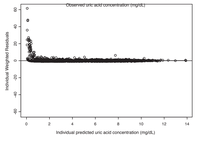


Figure 3d: Individual Weighted Residuals vs. Predicted Uric Acid Concentrations

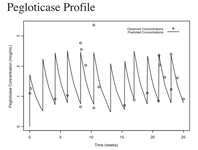


Figure 4a: Example of Individual Pegloticase Profile

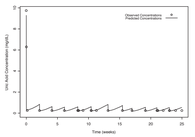


Figure 4b: Example of Individual Uric Acid Profile

DISCUSSION

PK

- The statistical and graphical criteria indicated that the PK of pegloticase was best described by a 1-compartment model, suggesting that pegloticase is confined to the intravascular space.
- Findings are consistent with large pegloticase size:
  - Approximately 496 kDa
  - With hydration of the PEG moieties, the apparent molecular weight is even larger.
  - Other therapeutic biologics tend to cross blood capillaries slowly.
- The inclusion of Ab as a significant covariate on CL can be explained by Ab facilitating the CL of pegloticase.
- Since antibodies were non-neutralizing, the inclusion of Ab as a significant covariate on Vc may be explained by the formation of antibody/pegloticase complexes, with possible cellular uptake by the RES.
  - An increase in the fraction of intracellularly-bound pegloticase is associated with a decrease in the free intracellular pegloticase fraction, translating into an increase in Vc.

PD

- Uric acid value is an appropriate biomarker, as it is the direct target of pegloticase and correlates well with clinical outcomes.
- An indirect model chosen to describe the PD of pegloticase reflects its mechanism of action.
  - Pegloticase affects the elimination of UA rather than its formation.
  - It affects the rate of UA depletion from the plasma to produce the observed decreases in UA levels.
  - Baseline creatinine clearance was not a significant covariate of the effect of pegloticase on plasma uric acid (PUA) levels.
- In persistent responders, the rate of UA elimination was increased to varying degrees by pegloticase (quantified by different Slope PD parameters), while post-dose UA levels remained well below the solubility limit.
- In addition, despite the target audience in the Phase 3 trials being those with chronic gout refractory to conventional therapy, 42.4% of subjects receiving the proposed clinical dose of 8 mg every 2 weeks had a persistent response to pegloticase (PUA <6 mg/dL 80% of the time in Months 3 and 6).

Antibodies

- While the inclusion of anti-pegloticase antibody titer helped explain the variability in the PK/PD model, the titer itself has limited utility in the clinical setting.
  - The highest anti-pegloticase antibody observed for each individual was incorporated into the model, irrespective of any temporal relationship between rise in titer and loss of pegloticase activity.
  - The majority of individuals with transient response to pegloticase tended to have a maximum anti-pegloticase antibody titer of 2430 and above.
  - The time at which PUA response was lost was associated with highly variable anti-pegloticase antibody titer, ranging from 30 to 196830.
  - A specific antibody titer value cannot be used to predict loss of pegloticase activity.
- Therefore, assessment of antibody titer is not useful for monitoring loss of effect in a clinical setting.

CONCLUSIONS

- Pegloticase PK was best described by a linear 1-compartment model:
  - Covariates included BSA and Ab on both Vc and CL
  - Increased BSA and the presence of Ab were associated with an increase in both Vc and CL
- An indirect model described the PD of pegloticase, where uric acid depletion rate was influenced by pegloticase and Ab titers:
  - Pegloticase enhanced UA elimination in a concentration-dependent manner
  - Ab titers diminished the pegloticase urate-lowering effect, with greater reduction at higher Ab titers