Mechanism-Based Pharmacokinetic/Pharmacodynamic Model for Hepatoprotective Effect of Dexamethasone on Transient Transaminitis After Trabectedin (ET-743, Yondelis®) Treatment

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ABSTRACT

Background: Reversible transient elevations in transaminases have been observed after trabectedin (T) administration, despite no alteration in plasma PK. A PKPD model was developed to evaluate the time course of ALT elevation, tolerance development, and covariate effects following different dosing schedules in cancer subjects.

Methods: T was administered to 711 subjects as monotherapy (dose range: 0.024-1.8 mg/m^2) as 1-, 3-, or 24-hr infusions every 21 days; 1- or 3-hr infusions on days 1, 8, and 15 every 28 days; or 1-hr infusions daily for 5 consecutive days every 21 days. Population PKPD modeling was performed with covariate evaluation [dexamethasone use (469/711 pt), Eastern Cooperative Oncology Group PS scores (89.7% pts ≤ 1), and BW (36-122 kg)] on PD parameters, followed by model validation. Simulations assessed the influence of dosing regimen and selected covariates on the time course of ALT and the effectiveness of the dose reduction strategy.

Results: A precursor-dependent PKPD model described the temporal relationship between ALT elevation and T concentrations, where the transfer process of ALT from hepatocytes to plasma is stimulated by trabectedin plasma concentration. Overall, 66% of subjects had transaminitis. Mean predicted (%SEM) baseline ALT (ALT_0) and $T_{1/2}$ in plasma were 31.5 (5.1) U/L and 1.4 days, respectively. The magnitude of the T stimulation of the ALT transfer rate from hepatocytes to plasma was 11.4% per 100 pg/mL of trabectedin plasma concentration. Dexamethasone decreased the rate of T-induced ALT release from hepatocyte by 63% (P<0.001). Model validation results showed good concordance with the observed incidence of grade 3/4 toxicity. Simulations showed that severity of ALT elevation was dose- and schedule-dependent. The dose reduction strategy decreased the incidence of grade ≥3 toxicity by 13% and 39% following 2 and 4 cycles of therapy, respectively.

Conclusions: A PKPD model quantifying the hepatoprotective effect of dexamethasone on transient and reversible transaminitis after T treatment has been developed. The model predicts that coadministration of dexamethasone and the suggested dose reduction strategy will enhance the safe use of T in the clinic.

BACKGROUND

- Trabectedin (ET-743, Yondelis®) is a novel tetrahydroisoquinoline compound isolated originally from the marine ascidian *Ecteinascidia turbinate* and is now produced synthetically.[1]
- In Phase I/II studies of trabectedin monotherapy, reversible increases in serum concentrations of transaminases, bilirubin, and alkaline phosphatase were observed. These changes were noncumulative and transient at the studied doses and schedules. In general, increases in transaminases began 2 to 5 days after trabectedin administration, reached a maximum at day 5 through day 9, and resolved within 3 to 4 weeks.[2-11]
- The severity of alanine aminotransferase (ALT) or aspartate aminotransferase (AST) changes has also been related to exposure parameters such as maximum plasma concentration (C_{max}) or area under the concentration-time curve (AUC) of trabectedin.[12] Interestingly, several investigators observed that the severity of the increases in transaminases after trabectedin administration decreased with successive treatment cycles while plasma pharmacokinetics (PK) were unaltered.[13]
- In addition, dexamethasone administered prior to trabectedin also diminishes hepatotoxicity in humans and rats,[14-16] which might be related to the increase in clearance of trabectedin in humans.[17]

OBJECTIVES

- To develop a population pharmacokinetic/pharmacodynamic (PK/PD) model to characterize the time course of ALT concentrations following intravenous administration of trabectedin in cancer patients.
- To evaluate the effectiveness of concomitant administration of dexamethasone and the recommended dose reduction strategy to diminish ALT elevation following trabectedin administration.

METHODS

Data from 14 clinical studies (5 Phase I and 9 Phase II studies) including 711 patients receiving intravenous trabectedin as monotherapy (dose range: 0.024-1.8 mg/m^2) administered as 1-, 3-, or 24-hr infusions every 21 days; 1- or 3-hr infusions on days 1, 8, and 15 every 28 days; or 1-hr infusions daily for 5 consecutive days every 21 days were included in the analysis. Patient characteristics are summarized in **Table 1**.

Table 1. Patient Characteristics Before Trabectedin Administration

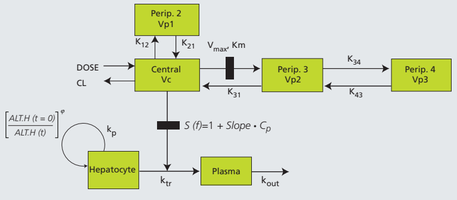
Patient Characteristics*	Index Dataset (N=498)	Test Dataset (N=213)	Combined Dataset (N=711)
Age, y (range)	56 (19-83)	53 (20-80)	55 (19-83)
Body weight, kg (range)	70 (36-122)	76.2 (41-148)	71 (36-148)
Sex, N (%)			
Male	157 (31)	83 (39)	240 (34)
Female	341 (69)	130 (61)	471 (66)
ALT (IU/L)	42 (1-3820)	43 (3-1386)	43 (1-3820)
Liver Metastasis, N (%)	105 (21)	4 (2.0)	109 (15)
Soft Tissue Sarcoma, N (%)	98 (20)	213 (100)	311 (44)
Performance Status, N (%)			
0	289 (43)	104 (49)	393 (44)
1	313 (46)	108 (51)	421 (48)
2	55 (8)	1 (<1)	56 (6)
3	15 (2)	-	15 (2)
4	2 (<1)	-	2 (<1)
Dexamethasone Use†			
No	50 (10)	NA	50 (7)
Yes	256 (49)	213 (100)	469 (64)
Unknown	213 (41)	NA	213 (29)

*Continuous variables are expressed as median (range), whereas categorical variables are expressed as counts (%).
†Study 10 included a crossover design to evaluate the effect of concomitant administration of dexamethasone on trabectedin pharmacokinetics and pharmacodynamics, resulting in the number of patients analyzed before and after the crossover. As a consequence, they are being counted twice for the purpose of this analysis.

An adaptive precursor-dependent model of indirect pharmacodynamic (PD) ALT effects was used to describe the 8919 ALT measurements from 498 patients included in the index dataset (**Figure 1**). This model consisted of two compartments: one represents the ALT in the hepatocyte [*ALT.H*] and the other represents the circulating plasma ALT [*ALT.P*]. The basic premise of this model is that the ALT elevation after trabectedin administration is produced by an indirect mechanism, and the development of tolerance and rebound is due to alteration in amounts of ALT in the hepatocytes (or the amount of hepatocytes). The model assumes a continuous production of ALT in the hepatocytes and the release of ALT from the hepatocytes into the blood is stimulated by trabectedin. The constant ALT production in the hepatocytes is characterized by a zero-order rate constant, k_{in}, which can be affected by a stimulatory feedback mechanism that modulates the rebound effect implicit in the system. The feedback mechanism is modeled as a power function of the ratio of baseline ALT in the hepatocyte [$ALT.H_0$] to *ALT.H* at any given time, thus, [$(ALT.H_0/ALT.H)^{\varphi}$], where φ is the estimated parameter that determines the magnitude of the influence of the feedback system. This function facilitates a decrease in the production rate of ALT in hepatocytes at high concentrations of ALT in hepatocytes.

ALT produced in the hepatocytes is then released to the plasma according to a linear process characterized by the first-order rate, k_{tr}. In addition, ALT is removed from the plasma following a linear process characterized by the first-order rate, k_{out}. The release of ALT from hepatocytes to plasma is stimulated by a linear function of trabectedin plasma concentrations [*Cp*], equivalent to *1 + Slope·Cp*. Although the mechanism of the apparent tolerance is not known, the model assumes that the stimulatory effect of trabectedin on the release of ALT from hepatocytes to plasma depletes the amount of ALT in the hepatocyte (or the number of hepatocytes) and produces the development of the tolerance phenomena. This assumption is conceptual in essence and likely an oversimplistic representation of the actual mechanism. In addition, a majority of patients appeared to have some elevation in ALT following trabectedin administration, but not all patients had a clearly observable increase.

Figure 1. Indirect Response Adaptive Pool Pharmacokinetic/Pharmacodynamic Model for ALT

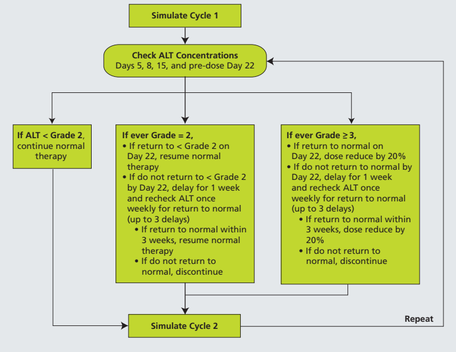


Therefore, a mixture model was implemented to allow the separate characterization of patients with or without ALT elevation following trabectedin administration. The population with no ALT elevation had no drug effect on k_{tr}, thus the administration of trabectedin had no influence on predicted ALT values.

Between patients variabilities in the model parameters and residual variability in the ALT measurements were assumed to follow a lognormal distribution. Covariate analysis was performed using a stepwise approach and the likelihood ratio test. Covariates explored in the analysis included age, body weight, BSA, sex, ECOG performance status, liver metastases, concomitant administration of dexamethasone, and tumor type. The model developed using the index dataset was externally evaluated based on its predictive performance on the test dataset (4068 ALT measurements from 213 cancer patients with soft tissue sarcoma) and the estimates of the model parameters were updated using the combined dataset (index and test dataset).

The validated model was used to evaluate the relationship between trabectedin dosing regimen and ALT time course, and the influence of selected covariates on the ALT profile and the effectiveness of the dose reduction strategy implemented in a Phase II clinical trial, which is displayed in **Figure 2**.

Figure 2. Dose Reduction Simulation Process



RESULTS

Figure 3. Observed and Model-Predicted ALT Values After Trabectedin Treatment

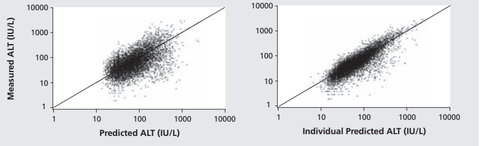


Table 2. Pharmacodynamic Parameter Estimates for the Final PK/PD Model

	Typical Value		Between-Patient Variability (%)	
Parameter	Final Estimate	RSE (%)	Final Estimate	RSE (%)
k_{out} (hr^{-1})	0.0193	11.2	67.68	42.6
Slope (mL/pg)	0.114	20.1	143.87	18.9
Shift in slope due to known and unknown concomitant dexamethasone use (mL/pg)	-0.0744	28.9	-	-
Patients with elevated ALT (%)	65.7	4.4	-	-
$ALT.H_0$ (IU/L)	5860	15.6	171.76	40.0
$ALT.P_0$ (IU/L)	31.5	5.1	52.54	12.0
φ	0.865	25.7	-	-
Residual variability (%)	52.73	12.8	-	-

RSE (%): relative standard error of the mean (%).
The estimate of the covariance (%SEM) between the random effects of *Slope* and $ALT.P_0$ was –0.398 (16.2), equivalent to a correlation coefficient (r^2) of 0.277.

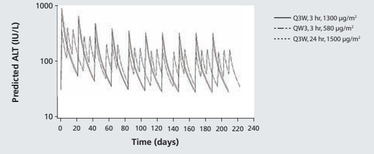
Table 3. Comparison of Simulated and Observed Grade ≥3, Grade 3, and Grade 4 Transaminitis Following Trabectedin 1.5 mg/m^2 Administered as 24h Intravenous Infusion Every 3 Weeks

ALT/SGPT	Simulated Incidence*	Observed Incidence (95%CI), %†
Grade ≥3	53.2	50.2 (45.6 – 54.9)
Grade 3	38.5	41.9 (37.3 – 46.5)
Grade 4	14.7	8.3 (5.7 – 10.9)

*Simulated incidence of liver toxicity grade on Day 5 post infusion during Cycle 1 of trabectedin treatment.
†Incidence of transaminitis in Phase II studies conducted with trabectedin 1.5 mg/m^2 administered as 24h intravenous infusion every 3 weeks (N=444).

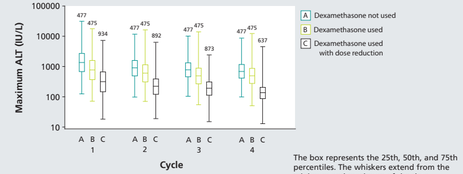
- Overall, 66% of patients had transaminitis.
- Magnitude of the stimulation of the ALT transfer rate from hepatocytes to plasma was 11.4% per 100 pg/mL of trabectedin plasma concentration.
- Dexamethasone decreased the rate of trabectedin-induced ALT release from hepatocyte by 63% (P<0.001).

Figure 4. Effect of Dose and Inter-Dose Interval on the Simulated Time Course of ALT



- Model validation results showed good concordance with the observed incidence of grade 3/4 toxicity.

Figure 5. Effect of Dexamethasone and Dose-Reduction Strategy on Maximum ALT Elevation



- Simulations showed that severity of ALT elevation was dose- and schedule-dependent.
- Effect of dexamethasone and the dose reduction strategy on ALT values revealed a reduction of the grade ≥3 toxicity incidence by 13% and 39% following 2 and 4 cycles of therapy, respectively.

CONCLUSIONS

- **A semi-physiological model quantifying the hepatoprotective effect of dexamethasone on transient and reversible transaminitis after trabectedin treatment has been developed.**
- **The model predicts that coadministration of dexamethasone and the suggested dose reduction strategy will enhance the safe use of trabectedin in the clinic.**

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