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

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ABSTRACT

Background: Transient sammitisins in humans have been observed after trabectedin (ET-743, Yondelis)® administration, despite no elevation in peak plasma levels of the agent. A PKPD model was developed to evaluate the time course of ALT elevation, balance development, and possible effects following a delayed administration of a single agent.

Methods: Two administered 71 TD subjects as microdose (pre G1; 8.18 mg/m² Q3W, 3 hr, 1300 µg/m²); 4 in a infusion on day 1, 4, and 10 were evaluated using concomitant with statin therapy combination (ALT≥33 IU/L). Between Experimental Data and Predicted Data was validated simulating the administered dosage regimens and statistical concordance to the time course of ALT and effectiveness of the dose reduction strategy. Results: A precursor-dependent PKPD model described the temporal relationship between ALT elevation and the metabolic rate of trabectedin. ALT elevation is related to exposure parameters such as the maximum plasma concentration (Cp,max) of trabectedin and the area under the concentration-time curve (AUC) of trabectedin.

Objective: To develop a population pharmacokinetic/pharmacodynamic (PKPD) model to characterize the effect of dexamethasone on the time course of ALT elevation and the effectiveness of a delayed dose reduction strategy following trabectedin administration in human.

RESULTS

• Dexamethasone decreased the rate of trabectedin-induced ALT release from hepatocytes. ALT elevation was dose- and schedule-dependent. The dose reduction strategy decreased the incidence of Grade 2 or worse.

• Model validation results showed good concordance with the observed incidence of Grade 2 or worse.

• Dexamethasone use was closed site and schedule-dependent. The dose reduction strategy decreased the incidence of Grade 2 or worse.

• Between patients variances in the model parameters and residual variability in the ALT elevation are not dependent on the dose or the administration method of dexamethasone.

• The model developed using this dataset was not relevant in evaluating performance on the evaluation of the model, the variability of the model parameters were updated using the combined dataset (index and test data).

The validated model was used to make the relationship between trabectedin dose and time course, and the influence of walthelinesokinetics and the functional and the effectiveness of the dose reduction strategy implemented in a Phase 1 clinical trial, which is depicted in Figure 2.

CONCLUSIONS

• A semi-physiological model quantifying the hepatoprotective effect of dexamethasone in transient sammitisins after trabectedin administration.

• The model predicts that coadministration of dexamethasone and the effective dose reduction strategy will enhance the safety of UT in the clinic.

REFERENCES


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Table 1. Patient Characteristics Before Trabectedin Administration

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Index Dataset (n=206)</th>
<th>Test Dataset (n=8)</th>
<th>Combined Dataset (n=214)</th>
</tr>
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<tbody>
<tr>
<td>Age, y</td>
<td>66 (20)</td>
<td>72 (16)</td>
<td>69 (20)</td>
</tr>
<tr>
<td>Body weight, kg</td>
<td>82 (23)</td>
<td>86 (16)</td>
<td>85 (20)</td>
</tr>
<tr>
<td>Male</td>
<td>16 (80)</td>
<td>2 (100)</td>
<td>18 (84)</td>
</tr>
<tr>
<td>Female</td>
<td>4 (20)</td>
<td>0 (0)</td>
<td>4 (16)</td>
</tr>
</tbody>
</table>

Table 2. Pharmacodynamic Parameter Estimates for the Final PKPD Model

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Typical Value</th>
<th>Variability</th>
<th>Between-Patient Variability</th>
</tr>
</thead>
<tbody>
<tr>
<td>CL</td>
<td>200</td>
<td>0.015</td>
<td>0.015</td>
</tr>
<tr>
<td>Vmax</td>
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<td>0.015</td>
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</tr>
<tr>
<td>Km</td>
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<td>0.015</td>
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<tr>
<td>ktr</td>
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<td>0.015</td>
</tr>
<tr>
<td>kout</td>
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</tr>
<tr>
<td>S(f)</td>
<td>1.015</td>
<td>0.015</td>
<td>0.015</td>
</tr>
<tr>
<td>phi</td>
<td>1.015</td>
<td>0.015</td>
<td>0.015</td>
</tr>
</tbody>
</table>

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

Figure 2. Dose Reduction Simulation Process

Figure 3. Observed and Predicted ALT Values After Trabectedin Treatment

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

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

Model validation results showed good concordance with the observed incidence of Grade 2 or worse.

Of the 184 patients, 91% were male and 9% were female. The median age was 66 years (range, 40–80 years).

ALT incidence was dose-dependent, with a trend of increased incidence with each dose group.

Dexamethasone dose was not associated with a significant change in ALT.

Overall, 96% of patients had transfusions.

Simulated incidence of liver toxicity grade on Day 5 post infusion during Cycle 1 was 2%. Treatment was dose-decreased in 3 weeks, dose reduce by 20%.

Model prediction results showed good concordance with the observed incidence of grade 2 or worse.

The dose reduction strategy decreased the incidence of Grade 2 or worse.

Between patients variances in the model parameters and residual variability in the ALT elevation are not dependent on the dose.

The validated model was used to evaluate the effectiveness of concomitant administration of dexamethasone and the effectiveness of the dose reduction strategy implemented in a Phase 1 clinical trial, which is depicted in Figure 2.

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