Optimisation of Intramuscular Sustained Release-Nano-Formulations Using In Silico Modelling

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Overview

- Antiretrovirals (ARVs) can find clinical application not only in the treatment of HIV infection but also in its prevention. Recently pre-exposure prophylaxis (PrEP) strategies have been developed for subjects who are at high risk of acquiring the infection [1].
- Currently available oral formulations necessitate lifelong, daily dosing and a suboptimal adherence, places the patient at risk of treatment failure and low rates of protection for PrEP [2].
- The introduction of injectable sustained-release nano-formulations (NFs) could represent a pharmacological option opening the possibility to simplify dosing regimens, increase adherence, reduce the amount of drug consumed and thus decrease the overall cost of the treatment and PrEP [3].
- Physiologically based pharmacokinetic (PBPK) modelling is the mathematical description of anatomical, physiological and molecular processes defining drug distribution (Figure 1b), through the integration of drug characteristics and patient-specific factors (Figure 1a) [18].

The aim of this study was to simulate the PK of intramuscular (IM) sustained release NFs using PBPK modelling. Existing ARVs available as oral formulations were assessed for compatibility. Theoretical target dose and release rate combinations for once weekly and once monthly formats were identified.

Results

- A summary of the predicted values for AUC, Cmax, and C0.4 for 8 ARVs along with dose and release rate combinations predicted to be optimal is shown in Table 1.
- Dolotegravir, efavirenz, en替rinatilb, ritampiravir, tenofovir and RPV were predicted to be the suitable candidates for monthly IM injection as shown in Figure 3.

Table 1: Summary of Dose, Infection Rate, Frequency of Administration and Pharmacochemistry of Solid Drug Nanoparticles Containing Antiretroviral Administered Intramuscularly

<table>
<thead>
<tr>
<th>Drug</th>
<th>IM Dose (mg)</th>
<th>Release Rate (h)</th>
<th>Frequency of Administration</th>
<th>AUC (ng/ml)</th>
<th>Cmax (ng/ml)</th>
<th>C0.4 (ng/ml)</th>
<th>Cut-off Level (ng/ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tenofovir</td>
<td>300</td>
<td>Weekly</td>
<td>15</td>
<td>10.2</td>
<td>2.3</td>
<td>1.2</td>
<td>20.0</td>
</tr>
<tr>
<td>Emtricitabine</td>
<td>200</td>
<td>Monthly</td>
<td>15</td>
<td>15.0</td>
<td>2.5</td>
<td>1.3</td>
<td>20.0</td>
</tr>
<tr>
<td>TDF/3TC</td>
<td>150</td>
<td>Weekly</td>
<td>15</td>
<td>10.0</td>
<td>2.0</td>
<td>1.1</td>
<td>20.0</td>
</tr>
<tr>
<td>Atazanavir</td>
<td>300</td>
<td>Weekly</td>
<td>15</td>
<td>10.0</td>
<td>2.0</td>
<td>1.1</td>
<td>20.0</td>
</tr>
<tr>
<td>Rilpivirine</td>
<td>300</td>
<td>Weekly</td>
<td>15</td>
<td>10.0</td>
<td>2.0</td>
<td>1.1</td>
<td>20.0</td>
</tr>
</tbody>
</table>

Concentration (ng/ml)

- These data are theoretical and currently there is no evidence to confirm or refute that these dose / release rate combinations can be achieved by active delivery systems.
- Candidate ARVs with potential for reformulation into IM depot were identified, providing the technological complexities associated with reformulation can be overcome for these agents.
- Based on known clearance of RPV, monthly exposure from 250 mg (2.5 mL volume) of latest existing formulation is theoretically achievable if release rate can be tuned to 0.002 h⁻¹.
- PBPK modelling may be a useful tool for defining product characteristics for sustained-release NF development.

References