A loading dose of clofazimine to optimize treatment in patients with nontuberculous mycobacterial disease

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Abstract

Background: Clofazimine (CFZ) is a promising drug for the treatment of nontuberculous mycobacterial (NTM) disease. CFZ has a very long elimination half-life and accumulation of CFZ in plasma to reach steady-state ('stable') concentrations takes months. This implies that the drug is not contributing fully to the NTM treatment regimen for months. A loading dose may reduce the time to reach concentrations similar to those at steady-state (steady-state-like concentrations). We evaluated the pharmacokinetics (PK), safety and tolerability of a loading dose regimen in patients with NTM disease.

Methods. Adult participants received a four-week loading dose regimen of 300 mg CFZ once daily (QD), followed by a standard dose of 100 mg QD (combined with other antimycobacterial drugs). Blood samples for PK analysis were collected on three occasions; at four weeks (after the last loading dose), at one and four months. A population PK model for CFZ was developed based on PK data from this study and a comparator trial amongst patients with NTM disease that included a CFZ-based regimen (100 mg QD) without a loading dose (EUDRACT: 2015-003786-28). Model-based simulations were performed to assess the time to reach target concentrations (80% of the individual PK-model predicted steady-state trough (pre-dose) concentrations) for different dosing regimens.

Results. Twelve participants were included. The geometric mean peak and trough concentrations of CFZ after the last dose of the four-week loading regimen were 0.87 mg/L and 0.50 mg/L, respectively. Adverse events occurred frequently, but did not lead to discontinuation of CFZ. Our loading dose regimen reduced the predicted median time to target concentrations by 1.5 months compared to no loading dose (3.8 versus 5.3 months). Further time benefit was predicted with a six-week loading dose regimen (1.4 versus 5.3 months).

Conclusion. A four-week loading dose regimen of 300 mg QD significantly reduced the time to target concentrations of CFZ and was safe and well-tolerated. Extending the loading phase to six weeks may further decrease the time to target concentrations. A loading dose of CFZ is a feasible strategy to optimize the treatment of NTM disease.