Title: Assessment of tapering strategies for intravenous tocilizumab in rheumatoid arthritis patients. Clinical trial simulations.

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Introduction: Tocilizumab is an anti-interleukin 6 humanized monoclonal antibody approved for the treatment of rheumatoid arthritis (RA) [1]. In Europe, it is current practice to implement empirical dose tapering strategies [2] to avoid overtreatment, minimize side-effects and foster a reduction in costs. A new approach in autoimmune diseases is the Therapeutic Drug Monitoring (TDM)-guided dose tapering [4,5]. The aim was to compare different dose tapering strategies for iv tocilizumab and assess the performance of these strategies.

Methods: A previously developed PKPD model for iv tocilizumab [6] was used for simulations. A total of four scenarios were evaluated on a simulated population of 5000 individuals. In all scenarios, the 8 mg/kg/28 days was administered for six months. Then, different scenarios were considered:

- *Scenario 1: Label dosing*; Label-dosing was continued at 8 mg/kg/28 days [1].
- *Scenario 2: Mild Empirical dose tapering*; If disease remission/LDA, a 25% dose reduction of the initial label dose was applied, resulting in 6 mg/kg/28 days.
- *Scenario 3: Intense Empirical dose tapering*; If disease remission/LDA, a 50% dose reduction of the initial label dose was applied, leading to a final dosing of 4 mg/kg/28 days.
- *Scenario 4: TDM-guided dose tapering*; If C_{trough} at six months was ≥5 µg/mL, a dose reduction was applied. This dose reduction was conducted using a model-based algorithm [7] in which subsequent doses were chosen to approach the steady-state target C_{trough} of 5(±1) µg/mL. This PK target was chosen based on literature [6,8].

The different strategies were primarily evaluated on the proportion of patients who maintain remission/LDA one year after the intervention. Cost savings of direct drug costs were also estimated.
All PKPD simulations and dose optimizations were performed with R [9], using the differential equation-solving R-packaged deSolve.

Results: After six months of treatment at the initial dose, 77.5% of the simulated population was in DAS28 remission/LDA and 79.7% showed serum drug concentrations ≥5 µg/mL.

The overall proportion of simulated patients in DAS28 remission/LDA after one year of the intervention was comparable between the mild empirical dose-tapering strategy and the TDM-guided dose tapering strategy (80.3% and 78.2%, respectively). The intense empirical dose-tapering strategy showed a lower overall percentage of patients in DAS28 remission/LDA (69.0%). Likewise, one-year flare rates were lower for the mild empirical dose tapering and TDM-guided tapering strategies (6.5% and 10.6%, respectively) compared to a 24.8% flare rate for the intense empirical dose-tapering strategy. There was also a difference between the cost-savings among the three tapering strategies (relative dose intensity was of 80.4%, 61.2% and 71.0% for the mild and intense empirical dose-tapering and the TDM-guided dose tapering strategies, respectively).

Conclusions: From the *in silico* study, we demonstrated that the TDM-guided strategy using model-based algorithms approach performed similarly to mild empirical dose tapering strategies in overall remission/LDA rates but proved to be superior in target achievement and cost-savings. Further studies are needed to test new dose tapering strategies for iv tocilizumab based on TDM using the developed algorithms as a tool to optimize patients' treatment in clinical practice.

References:

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