Modeling of The Relationship Between Ustekinumab Exposure, Fecal Calprotectin and Endoscopic Outcomes in Patients with Crohn's Disease

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Background: Ustekinumab is approved for the treatment of patients with moderate-to-severe Crohn's disease (CD) and ulcerative colitis. In the UNITI endoscopy sub-study, only 17.4% of patients on ustekinumab achieved endoscopic response and 10.9% of patients achieved endoscopic remission at week 44 (w44).[1]

Aims: We aimed to investigate if improved endoscopic outcomes could be achieved through dose optimization based on a population pharmacokinetic-pharmacodynamic (popPK/PD) modeling and simulation analysis.

Methods: Data were obtained from 83 patients with moderate-to-severe CD (94% multi-refractory) enrolled in a prospective open-label cohort study.[2] All received ustekinumab 6 mg/kg IV induction, followed by 90 mg SC every eight weeks (q8w). Ustekinumab serum concentrations were measured during induction (w4) and at trough (w8, w16, w24). Fecal calprotectin (*f*Cal) was measured at baseline, and at w8, w16, w24. Endoscopic response (50% decrease in simple endoscopic score for CD [SES-CD]) and endoscopic remission (SES-CD ≤2) were assessed at w24. Modeling and simulation were performed using NONMEM 7.4.

Results: The PK of ustekinumab was well described by a 2-compartment model with first-order absorption and first-order elimination. Sequentially, an indirect response popPK/PD model was used to describe the inhibitory effect of ustekinumab exposure (Emax model) on the "generation rate" constant of *f*Cal. A logistic regression model was used to predict the probability of achieving endoscopic remission/response at w24 based on observed *f*Cal at w8 through an inhibitory Emax function. Volume of distribution (**1), and clearance (**0.75) were allometrically scaled. Ustekinumab clearance was found to increase with decreasing serum albumin. The terminal half-life of ustekinumab in a median patient (bodyweight 65 kg, serum albumin 42.7 g/L) was 21.8 days. *f*Cal decreased with increasing ustekinumab exposure. The probability of endoscopic remission at w24 increased from 2.1% to 10.0% with *f*Cal at w8 decreasing from 1,800 μg/g to 214 μg/g. The probability of endoscopic response at w24 increased from 10.0% to 17.9% with *f*Cal at w8 decreasing from 1,800 μg/g to 694 μg/g. Simulation-based comparison of q8w and q4w maintenance dosing predicted median trough concentrations at steady state of 1.2 mg/L and 4.8 mg/L ustekinumab, and of 833 μg/g and 437 μg/g *f*Cal, respectively. Associated endoscopic remission rates were estimated to be 4.1% on q8w dosing and 6.5% on q4w dosing (using *f*Cal at steady state instead of w8). Associated endoscopic response rates were estimated to be 16.3% on q8w dosing and 21.9% on q4w dosing. Study sample sizes of 1,368 and 774 patients would be required to identify statistically significant differences in the rates of endoscopic remission (NNT=42) and endoscopic response (NNT=18), respectively, between both study arms (1:1 randomization, α=5%, power=80%).

Conclusion: The developed models can be used to guide clinical trial design and to support model-informed dose optimization (stratified or individualized dosing) to improve endoscopic outcomes. Although our analyses showed that q4w dosing resulted in lower *f*Cal concentrations, the predicted increase in proportion of patients achieving endoscopic remission was limited.

References:

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