7/15/2020 #1259: Sustained and rapid B-cell depletion with ofatumumab: Population pharmacokinetic B-cell modeling...

Abstract 1259

Sustained and rapid B-cell depletion with ofatumumab: Population pharmacokinetic B-cell modeling in relapsing MS patients

Type: Poster Presentation
Keyword: Disease Modifying Therapies – Mechanism of Action

Authors: G. Graham[1], J. Kahn[2], M. Savelieva[1], H. Yu[1], R. Pingili[2], R. Willi[1], K. Ramanathan[1], O. David[1], D.A. Haering[1], M. Bagger[1]; [1]Novartis Pharma AG/Basel/Switzerland, [2]Novartis Pharmaceuticals Corporation/East Hanover, NJ/United States of America

Background

In the Phase 3 ASCLEPIOS trials, ofatumumab 20 mg subcutaneous (s.c.; initial doses: Days 1, 7, 14; subsequent doses: every 4 weeks from Week 4 onwards) showed superior efficacy versus teriflunomide in relapsing MS patients.

Objectives

To characterize the pharmacokinetic (PK) relationship of ofatumumab for B-cell counts in RMS patients, assess the PK and B-cell dynamics given the Phase 3 dose regimen through PK-B cell simulations and explore the effect of covariates on PK and B cells.

Methods

The PK-B cell model was developed using data from Phase 2 (OMS115102, MIRROR, APLIOS) and Phase 3 (ASCLEPIOS I and II) trials. Nonlinear mixed effects modeling was performed using Monolix (v.2019R2) and R (v.3.6.1) programs. Simultaneous fitting was performed to assess the interaction between PK and B cells. A priori selected covariates were included in the covariate analysis and only those with significant effects based on a Wald test were included in the final model. The effect of body weight, age, administration route, s.c. injection device, and baseline B-cell count on PK and B-cell parameters were evaluated.

Results

In total, 9,168 plasma concentrations from 1,440 patients were included in the PK analysis and 17,158 B-cell counts from 1,486 patients in the B-cell analysis. A quasi-steady state binding model with two compartments and a first order absorption for s.c. administration with a time effect on the target synthesis rate adequately described ofatumumab PK. An indirect response model was used to describe the stimulation of B-cell lysis by free ofatumumab concentrations. Simulations demonstrated a rapid, median B-cell depletion to <10 cells/μL in 8.75 days; no signs of B-cell repletion occurred between doses, and that over 94% of patients had <10 cells/μL at B-cell steady state and pre-dose. Effect of weight on the steady state area under the curve was 71.8% higher and 52.0% lower for a 50 kg (5^{th} percentile) and 110 kg (95^{th} percentile) patient relative to a 70 kg patient (median), respectively. Steady state maximum concentrations were similar. Regardless of weight, all patients achieved low B-cell counts, similar to results observed in the Phase 3 ASCLEPIOS trials. Baseline age, B-cell counts and injection device had negligible effect on PK parameters.

Conclusions

The PK-B cell model showed early, rapid, and sustained B-cell depletion with ofatumumab, confirming the rationale for the chosen Phase 3 dosing regimen. No change in dosing schedule is warranted based on body weight effect on ofatumumab PK.

Print

https://cpaper.ctimeetingtech.com/msdc2020/submission/preview/print?publication_id=1259 1/1