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Vedolizumab efficacy exposure–response relationship for ulcerative colitis patients (GEMINI I) based on causal inference analysis

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Introduction

- Vedolizumab (ENTYVIO®) is a humanized monoclonal antibody targeting $\alpha_4\beta_7$ integrin that selectively blocks gut-specific lymphocyte trafficking[1]
  - Vedolizumab (300 mg via intravenous infusion at Weeks 0, 2, and 6, and every 8 weeks thereafter) is licensed to treat adults with moderately to severely active ulcerative colitis (UC) or Crohn's disease who have had an inadequate response with, lost response to, or were intolerant to a tumor necrosis factor (TNF) blocker or immunomodulator; or had an inadequate response with, were intolerant to, or demonstrated dependence on corticosteroids[2]
- Approval of vedolizumab for UC was based on the pivotal phase 3 study GEMINI I[3]
  - A significantly greater proportion of patients achieved clinical response at Week 6 (induction therapy) and clinical remission at Week 52 (maintenance therapy) with vedolizumab versus placebo
- It has been postulated that individuals with high drug clearance may be less likely to achieve positive efficacy outcomes from treatments for inflammatory bowel disease. For example, higher serum concentrations of anti-TNFα agents are reported to correlate with better clinical and endoscopic outcomes[4,5]
  - Given that the vedolizumab mechanism of action is distinct from that of anti-TNFα agents, with the potential for saturation of target receptors, a good understanding of the exposure–response relationship is essential[6]

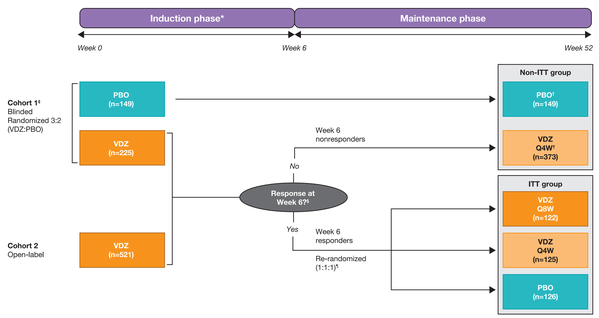
Aim

- To evaluate the relationships between vedolizumab induction exposure and efficacy outcomes in patients with UC

Methods

- GEMINI I was a phase 3, randomized, double-blind, placebo-controlled study investigating vedolizumab (300 mg) as induction and maintenance therapy in patients with UC (Figure 1)[3]
  - Patients with clinical response to vedolizumab at Week 6 were re-randomized (1:1:1) to receive vedolizumab every 8 weeks (Q8W), vedolizumab every 4 weeks (Q4W) or placebo up to Week 52 (maintenance phase)
  - Patients without response to vedolizumab in the induction phase received vedolizumab Q4W during the maintenance phase
  - Patients who received placebo during the induction phase continued to receive placebo in the maintenance phase

Figure 1. GEMINI I study design



Vedolizumab was administered at a dose of 300 mg

*Vedolizumab and placebo were administered on Days 1 and 15 of the induction phase

†Patients who discontinued vedolizumab or placebo during the induction phase were assigned to the respective non-ITT groups for the maintenance phase

‡Randomization was stratified by 1) concomitant use/non-use of glucocorticoids, and 2) concomitant use/non-use of immunosuppressants or prior use/non-use of TNFα inhibitors

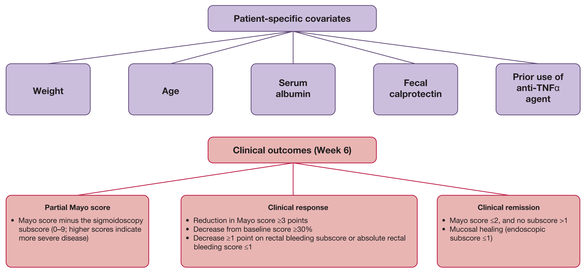
§Reduction in Mayo score ≥3 points and a decrease from baseline score ≥30% with a decrease of ≥1 point on the rectal bleeding subscale or an absolute rectal bleeding score ≤1

¶Randomization was stratified by 1) cohort, 2) concomitant use/non-use of glucocorticoids, and 3) concomitant use or non-use of immunosuppressive agents or prior use or non-use of TNF antagonists

ITT, intent-to-treat; PBO, placebo; Q4W, every 4 weeks; Q8W, every 8 weeks; TNFα; tumor necrosis factor α; VDZ, vedolizumab

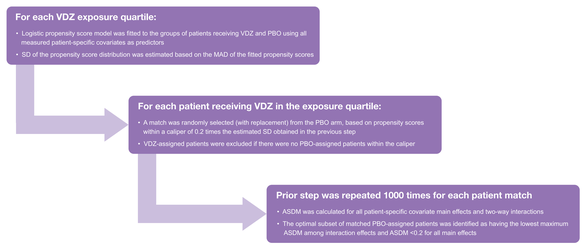
- This analysis included data from Week 6 of the GEMINI I induction phase
  - Clinical outcomes and patient-specific covariates are described in Figure 2
- Individual-predicted vedolizumab plasma concentrations and clearances were based on a prior population pharmacokinetic analysis[7]

Figure 2. Patient-specific covariates and clinical outcomes included in this analysis



- The limited dose-ranging information in GEMINI I yielded the potential for confounded causal interference regarding the exposure–response relationship. Consequently, a propensity score-based case-matching analysis was performed (Figure 3)

Figure 3. Methodology for case-matching based on propensity score



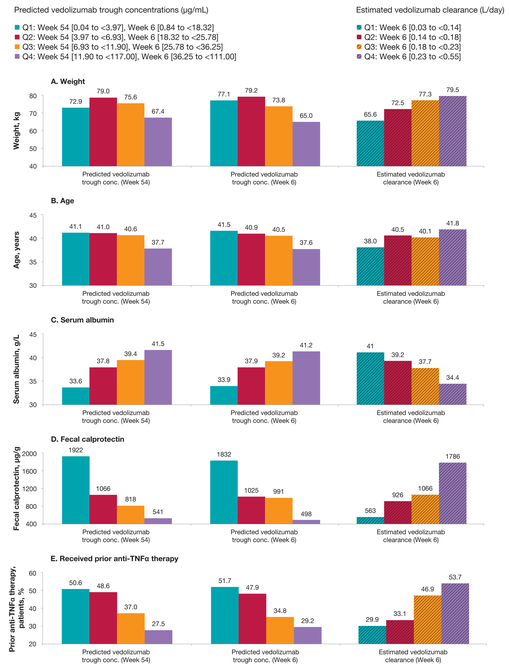
ASDM, absolute standardized difference in means; MAD, median absolute deviation; PBO, placebo; SD, standard deviation; VDZ, vedolizumab

- Quartiles of vedolizumab clearances and predicted Week 6 and steady state (arbitrary time point set to Week 54) trough vedolizumab concentrations were compared with outcomes for both unmatched and case-matched data
  - Steady-state was anticipated to commence from approximately Day 128, based on 5 times the linear elimination half-life of vedolizumab (25.5 days)[7]
  - Clearance cut-off points were estimated based on the population pharmacokinetic model, and plasma drug concentrations were predicted based on the model with the individual subject clearance estimates

Results

- Trends between the patient-specific covariates and predicted trough concentrations and estimated clearance of vedolizumab were evident, for example (Figure 4):
  - Higher serum albumin levels were associated with higher quartiles of predicted vedolizumab trough concentration and lower quartiles of estimated vedolizumab clearance
  - Prior use of anti-TNFα therapy and higher levels of fecal calprotectin were associated with lower quartiles of predicted vedolizumab trough concentration and higher quartiles of estimated vedolizumab clearance
- For each quartile of vedolizumab trough concentrations at Week 54 and Week 6, the majority of absolute standardized difference in means (ASDM) for the patient-specific covariate main effects prior to case matching were >0.1. All ASDMs after case matching were <0.1, indicating good pairing between patients receiving vedolizumab and placebo[8]
- Exposure–response relationships for all exposure metrics and each outcome were evident in the quartile analyses of the unadjusted data (Figure 5). For example:
  - Greater proportions of patients achieved clinical remission and clinical response and lower partial Mayo scores (indicating less severe symptoms) with increasing predicted vedolizumab trough concentration at Week 54 and Week 6, and lower estimated vedolizumab clearance at Week 6
    - The exposure–response relationships were more robust for Week 6 partial Mayo score and clinical response than for clinical remission

Figure 4. Patient-specific covariates and predicted trough concentrations and estimated clearance of vedolizumab



Conc., concentration; Q, quartile

- After case-matching adjustment for potential confounding variables, these exposure–response relationships remained for partial Mayo score and clinical response endpoints (Figure 5)
- Vedolizumab clearance >0.14 L/day was associated with diminished efficacy outcomes (partial Mayo score decrease <2 units, clinical response odds ratio <4)
  - Based on this clearance cut-off and the approved dosing regimen for vedolizumab,[2] the following exposure targets were derived:

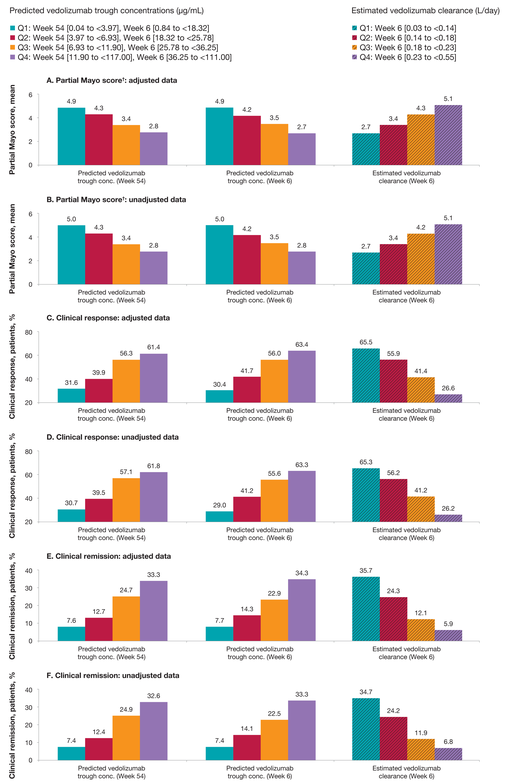
Vedolizumab exposure targets
(based on >0.14 L/day clearance cut-off)

Week 6 trough: >37.1 µg/mL | Week 14 trough: >18.4 µg/mL | Steady-state trough: >12.7 µg/mL

Conclusions

- Higher trough concentrations and lower clearance of vedolizumab were associated with better clinical outcomes, including greater rates of clinical response and improved partial Mayo score
- These exposure–response relationships will inform the design of future studies evaluating the impact of individualizing vedolizumab dose, starting as early as Week 6, on clinical outcomes in patients with high drug clearance (based on the identified clearance threshold of 0.14 L/day)

Figure 5. Exposure–response relationships (patients with available data [n=170 to n=179]*)



Criteria for partial Mayo score, clinical response, and clinical remission are described in Figure 2

*N ranged from 179 to 177 for unadjusted exposure response, and from 170 to 177 for adjusted exposure response

†Higher partial Mayo scores indicate worse disease

Conc., concentration; Q, quartile

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Acknowledgments

- This study was funded by Millennium Pharmaceuticals, Inc., a wholly-owned subsidiary of Takeda Pharmaceutical Company Limited. Medical writing assistance was provided by Chameleon Communications Ltd, UK (a Healthcare Consultancy Group Company), funded by Takeda Pharmaceuticals International
- This poster was presented at the American College of Gastroenterology Annual Scientific Meeting, October 14–19, 2016; Las Vegas, Nevada, USA