Integrating Maintenance Efficacy and Safety of Vedolizumab and Other Advanced Therapies to Assess Net Clinical Benefit in the Treatment of Ulcerative Colitis: A Network Meta-analysis

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Background
- ULC (UC) has a substantial negative impact on patient quality of life, impairs patients’ ability to function, and places a substantial economic burden on healthcare systems.
- Advanced treatments are approved for moderate to severe UC include:
  - Vedolizumab (VDZ), an anti-integrin agent
  - Infliximab (IFX), adalimumab (ADA), and golimumab (GOL), tumor necrosis factor-α (TNF-α) antagonists
  - Tofacitinib (TOF), an oral Janus kinase (JAK) inhibitor

- The expansion of available therapies for moderate to severe UC means that up-to-date information on their comparative efficacy and safety is necessary to ensure optimal treatment decisions.
- VASARI was the first head-to-head randomized, controlled trial (RCT) comparing biologic therapies for UC, and showed that VDZ-referenced IO infusions (300 mg every 8 weeks) were superior to subcutaneous (SC) ADA injections (10 mg every 2 weeks) in achieving clinical remission and mucosal healing at week 52.

Results
- This study’s objective was to estimate comparative efficacy and safety of biologic therapies and tofacitinib for patients with moderate to severe UC by means of a network meta-analysis (NMA) of key efficacy and safety outcomes.

Methods
- A targeted review was conducted to identify key phase 2 and 3 RCTs of biologic therapies (VDZ, IFX, ADA, GOL, UST, and TOFA).
- Efficacy outcomes in the induction period were remission and response at 6/8 weeks.
- Efficacy outcomes in the maintenance period were remission and response at 52/54 weeks among responders at the start of maintenance.
- Differences in study design (treat-through vs re-randomized) across the relevant RCTs were accounted for by assessing efficacy outcomes conditional on response at start of maintenance.
- For treat-through studies, start of maintenance treatment was defined as week 6/8.
- All studies defined clinical response as a reduction in complete Mayo score of ≥3 points and ≥50% from baseline with an accompanying increase in partial Mayo score of ≥1 point or absolute rectal bleeding subscore of ≥1 point.
- Clinical response at 52 weeks was available on partial and complete Mayo score from VASARI, and as these numbers were similar (VDZ vs ADA relative risk based on complete and partial Mayo score was 1.28 and 1.22, respectively), it was deemed appropriate to proceed with the inclusion of VASARI within the efficacy analysis based on partial Mayo score.
- Capable Clinical remission was defined as a complete Mayo score ≤2 points and no individual subscore ≥1 point for all studies except VASARI, where partial Mayo score was used.
- Safety outcomes were overall adverse events (AEs), serious AEs, infections, and AEs leading to discontinuation as reported at 52/54 weeks.
- Odds ratios (ORs) with 95% credible intervals (CrIs) were estimated using probit and binomial NMA models, with results presented with VDZ IV 300 mg once every 8 weeks (Q8W) as the reference therapy.
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Figure 1. Network of Studies for the Induction and Maintenance Period for the Overall and TNF-α Antagonist Naïve and Experienced Populations

Figure 2. Network Meta-analysis Results for Induction Period Efficacy Outcomes for the Overall and TNF-α Antagonist Naive and Experienced Populations

Figure 3. Fixed Effect Network Meta-analysis Results for Maintenance Period Efficacy Outcomes in the Overall and TNF-α Antagonist Naïve and Experienced Populations

Figure 4. Fixed Effect Network Meta-analysis Results for Overall Population Efficacy Outcomes

Figure 5. Net Benefit Analysis: Maintenance Remission vs Safety Outcomes in Overall and TNF-α Antagonist Naïve Population

Conclusions
- Results from this NMA based on RCTs suggest that:
  - VDZ IV 300 mg was significantly more efficacious than ADA as assessed by clinical response and remission during induction in the overall population, but with a higher risk of infection.
  - VDZ IV 300 mg Q8W was more efficacious than ADA as assessed by clinical response and remission in the overall population.
  - TOFA 10 mg had the highest estimate of efficacy compared to all other therapies, but with a higher risk of infection.
  - The net benefit analysis of the overall population showed similar or better efficacy and lower overall AEs for VDZ IV 300 mg Q8W compared with other advanced therapies for UC.

Reference

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Net Benefit Analysis
- Plots of the benefits (remission rates) and risks (safety outcomes) of maintenance treatment for the overall and the TNF-α antagonist naïve subgroups.
- Overall, VDZ IV and SC therapies had similar rates of maintenance clinical remission and lower rates of AEs compared with other therapies.
- TOFA 10 mg had the highest rates of maintenance clinical remission, but with more infections than VDZ.
- The benefit-risk profile for VDZ IV 300 mg Q8W was favorable compared with the profiles of other treatments for UC.

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