INDIRECT TREATMENT COMPARISON OF USTEKINUMAB VERSUS OTHER BIOLOGICS IN MODERATE TO SeVERE CROHN’S DISEASE: A 1-YEAR TREATMENT SEQUENCE ANALYSIS

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Introduction

• Crohn’s disease (CD) is a chronic, progressive, non-inflammatory intestinal disease affecting different parts of the gastrointestinal tract and is characterised by periods of remission and relapse [1].
• The use of biologics (infliximab, adalimumab, vedolizumab) in CD has been reserved for patients who have failed, have contraindications, or are intolerant to conventional therapy. Phase III trials indicate these therapies are significantly more effective than standard of care in inducing and maintaining response and remission [2].
• Ustekinumab is fully human IgG1 monoclonal antibody directed against IL-12/23 for which phase III results in Crohn’s disease recently came available [3].
• Trials in CD are similarly designed placebo-controlled induction and maintenance studies in which patients responding to induction with the specific biologic are randomised to active treatment or withdrawn to placebo and compared to placebo [4].
• A lack of comparability between placebo arms in different biologic trials has previously been identified in the literature [7]. The lack of comparability between “placebo” arms suggests that traditional evidence synthesis methods may not be appropriate to capture the true relative treatment effects of ustekinumab.

Objective

• Indirect evidence is needed to better inform decision-makers on the clinical efficacy of ustekinumab in CD. In order to overcome important methodological challenges linked to the feasibility of a standard indirect treatment comparison (ITC) due to conceptual heterogeneity and low placebo armistransitivity potential, an ITC of one-year efficacy data was conducted, taking into account the entire treatment pathway of response to induction and maintenance of therapy.

Methods

• A systematic literature review identified randomised controlled trials for induction and maintenance of clinical efficacy evaluating ustekinumab, infliximab, adalimumab, or vedolizumab.
• A treatment sequence analysis was conducted: the relative probability of achieving response (Crohn’s Disease Activity Index (CDAI) reduction of 70 points) at the end of induction was multiplied by the conditional probability of maintaining response or remission after one year (Figure 1).

Results

• Placebo-to-placebo maintenance response and remission rates had to be imputed from the ustekinumab maintenance trial IM-UNITI across all biologics’ maintenance phases as they were only available for IM-UNITI (Placebo-to-placebo: patients received placebo in both induction & maintenance phases).
• Separate analyses were conducted for CDAI-100 clinical response reduction of 100 points and clinical remission (CDAI under 150) in patients having either failed conventional or anti-TNF therapy.
• Analyses were performed in WinBUGS, using a Bayesian framework.
• Outputs were Bayesian posterior distribution probabilities for ustekinumab to perform better than each comparator over the entire treatment pathway.
• The number needed to treat (NNT) was calculated, applying the ORs obtained through the treatment sequence analysis on the IM-UNITI placebo rates to generate absolute treatment response and remission rates for each comparator.

Results

• Significant levels of heterogeneity were detected by a chi square test, suggesting that placebo maintenance arms are not appropriate common comparators across biologic trials and challenging the feasibility of a traditional network meta-analysis (NMA) in the maintenance phase.
• In total, 12 trials were included in the treatment sequence analysis. In patients having failed conventional therapy, six trials reported induction results, and four reported maintenance results. In patients having failed anti-TNF therapy, six trials reported induction results and three reported maintenance data.

Discussion

• The treatment sequence analysis is based on previous publications addressing the unfeasibility of standard ITCs due to a lack of true common comparator during maintenance [8,9]. Randomization of each trial is preserved up to the end of induction but not after entry into maintenance.
• Placebo-to-placebo rates used were only available for ustekinumab in IM-UNITI and were used across maintenance phases for different comparators. These rates were adjusted for remission rates at the end of induction in order to account for variation in response criteria across the included trials.
• Comparisons with infliximab are limited due to the fact that the trial by Targan et al. was fairly old and the induction phase in ACCENT I fairly small, with a high number of missing data in its placebo arm and inverse dose-specific response rates observed in the active treatment arms.
• Comparisons to adalimumab patients who failed anti-TNF therapy are limited due to differences in the inclusion of prior treatment failures across trials.
• Sensitivity analyses conducted to account for the additional uncertainty associated with the imputed placebo-to-placebo rates for the vedolizumab, adalimumab and infliximab trials revealed no changes in conclusions. The two other sensitivity analyses conducted (using data for the truly naïve subgroup of IM-UNITI patients, conducting all analyses within a frequentist framework) did not impact the conclusions of the base case analysis either.

Conclusions

• As a standard ITC was unfeasible, this novel approach addresses issues of similarity and transitivity and seems most appropriate to compare one year efficacy of biologics in CD.
• The entire treatment sequence of induction followed by maintenance suggests a higher likelihood of response or remission at year 1 with ustekinumab compared to vedolizumab or adalimumab.

Acknowledgment & References

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