Impact of Biologic Therapies on Risk of Major Adverse Cardiovascular Events in Crohn's Disease: Systematic Review and Meta-analysis of Randomized Controlled Trials

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Introduction

The efficacy of biologic therapies for the treatment of patients with inflammatory bowel disease (IBD) has been demonstrated in multiple randomized controlled trials (RCTs) and found to have superior therapeutic efficacy in patients with Crohn's Disease (CD)[1]. However, with numerous biologic therapies and small molecules currently in development, it is essential to fully explore the safety profile with the use of these novel agents.

The impact of biologic therapies on the risk of major adverse cardiovascular events (MACE), defined as a composite end point of myocardial infarction, cerebrovascular accident, or cardiovascular death, have been evaluated in several systematic review and meta-analyses in patients with other Immune-mediated diseases; such as psoriasis and rheumatic diseases [2,3,4].

Previous systematic reviews and meta-analyses have assessed the safety of these agents in IBD including CD; however, to our knowledge, the cardiovascular safety profile of these agents in this population is not well established[5]. These safety concerns surrounding the use of these agents has led recent studies to report MACE via an adjudication committee.

The aim of this systematic review and meta-analysis is to estimate the risk of MACE in adult patients with CD on biologic therapies in randomized controlled trials.

Methods and Materials

We systematically searched Medline, Cochrane Central Register of Controlled Trials, Scopus, and Embase databases from inception to March 2022 to identify eligible studies that assessed the risk of MACE in patients (age ≥ 18 years) with CD on biologic therapies. Only phase 3 active comparator or placebo controlled randomized trials were included in the analysis.

The systematic review and meta-analysis was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analysis statement (PRISMA) guidelines. The primary outcome was the rate of MACE observed in patients receiving biologic therapies during induction and maintenance phases of randomized controlled trials. Random effects model was used to calculate pooled odds ratios (ORs) and 95% CIs and I^2 statistics was used to assess heterogeneity.

Results

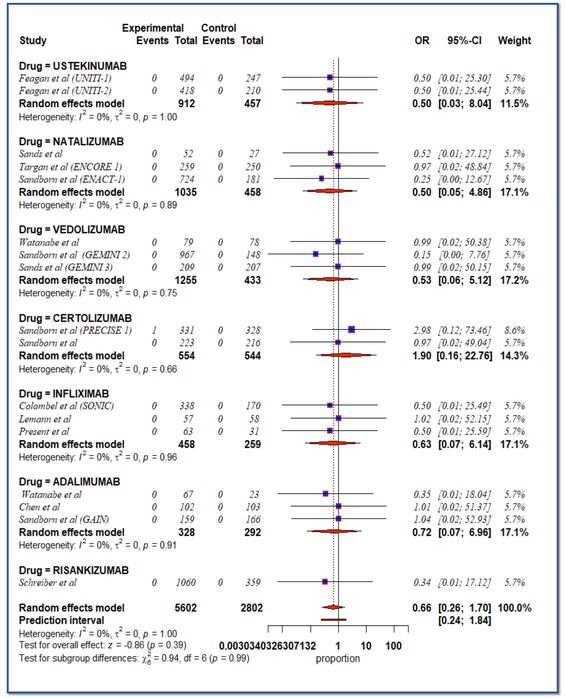

Figure 1. Frost Plot Evaluating Risk of MACE in induction RCTs.

Twenty-two studies involving 12196 patients with CD were included in our systematic review and meta-analysis. There was no evidence of statistical heterogeneity across the studies using I^2 statistics. Biologic therapies were not associated with increased risk of MACE during induction; infliximab (OR 0.63, 95% CI 0.07–6.14), adalimumab (OR 0.72, 95% CI 0.07–6.96), ustekinumab (OR 0.50, 95% CI 0.03–8.04), natalizumab (OR 0.50, 95% CI 0.05–4.86), vedolizumab (OR 0.53, 95% CI 0.06–5.12), certolizumab (OR 1.90, 95% CI 0.16–22.76) and risankizumab (OR 0.34, 95% CI 0.01–17.12). Biologic therapies were also not associated with increased risk of MACE during maintenance; infliximab (OR 0.72, 95% CI 0.01–5.10), adalimumab (OR 0.80, 95% CI 0.08–7.77), ustekinumab (OR 1.53, 95% CI 0.06–37.71), natalizumab (OR 1.02, 95% CI 0.02–51.59), vedolizumab (OR 0.70 95% CI 0.04–11.53), and certolizumab (OR 1.91, 95% CI 0.16–22.83).

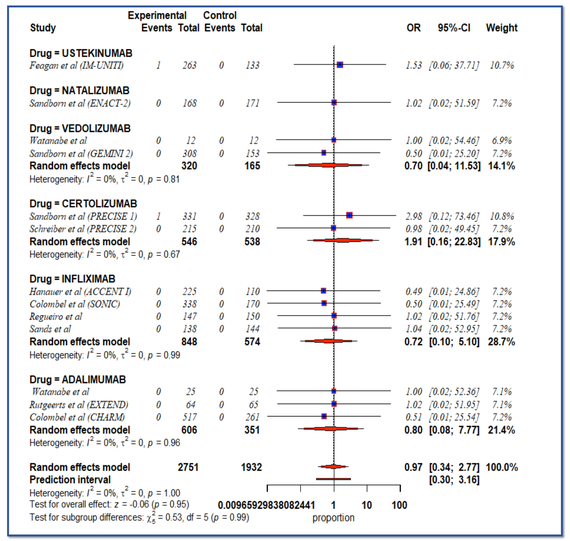

Figure 2. Frost Plot Evaluating Risk of MACE in Maintenance RCTs.

Discussion

This is the largest systematic review and meta-analysis of RCTs to examine the risk of MACE with the use of biologic therapies in patients with CD. Our analyses encompassed cardiovascular safety outcomes during both the induction and maintenance phases of treatment. The result of this analysis suggests that there is no significant difference in the risk of MACEs in CD patients treated with biologic therapies during the randomized controlled period (follow-up period ranged from 4-104 [median 26] weeks).

Several factors need to be considered when interpreting the findings. Few studies explicitly report assessment of cardiovascular/MACE events and very few established a committee for adjudicating suspected cases. The time frame of RCTs may not permit correct evaluation of MACE that may require time to develop, thus longer follow-up and in real-world settings will be needed to fully elucidate the risk in CD patients. Patients in RCTs are limited by exclusion criteria which generally exclude patients with a history or at risk of cardiovascular events.

As more therapeutic options are being approved for the treatment of CD, defining the safety profile of biologic therapy and novel small molecules is paramount as it will help clinicians to adequately weigh the risk/benefit ratio of these drug classes and will probably influence patterns of use.

Conclusions

In our study we found that the use of biologic therapies among adult patients with CD had no significant impact on the risk of MACE during the induction and maintenance period of randomized controlled trials. Patient level data were lacking, and meta-regression analysis were not performed to adjust for confounding factors.

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