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Safety of biological therapies in ulcerative colitis: An umbrella review of meta-analyses

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ABSTRACT

Biological agents have proven clinical efficacy in the treatment of ulcerative colitis (UC). Their adverse effects have also been studied in a substantial number of primary studies and meta-analyses. Given the large volume of information that has been published, the aim of this umbrella review was to effectively summarize the accumulated evidence from randomized controlled trials (RCTs) on the safety of biological therapies for UC into one accessible and usable document.

Pubmed and Scopus databases were systematically searched through November 2017 to identify meta-analyses of RCTs that have investigated potential harms of biological agents (adalimumab, golimumab, infliximab, and vedolizumab) in patients with UC. Ten eligible meta-analyses were included. The body of available evidence supports the safety of biologic therapies in UC. Further research is needed to clarify the risk of any infection with biologics, for elderly and high-risk groups, for longer-term effects, and for head-to-head comparisons between the different biologics.

1. Introduction

Ulcerative colitis (UC) is a chronic, remitting and relapsing inflammatory bowel disease resulting in disability [1,2]. The standard treatment options consisted of 5-aminosalicylates, glucocorticoids and immunomodulators, for several decades. Biological therapies have been recently introduced, and significantly improved the management of patients with UC [3,4]. Infliximab (Remicade, Janssen and MSD/Merck) was the first biological agent regulatory approved for moderate-to-severe disease; then, two more tumor necrosis factor (TNF) antagonists, adalimumab (Humira, Abbvie) and golimumab (Simponi, MSD/Merck), and one anti-α4β7 antibody, vedolizumab (Entyvio, Takeda), received marketing authorization [5–8].

Biological therapies have shown their efficacy in UC [9]. However, their mechanism of action, including the regulation of activation and the maintenance of inflammation, may result in patient harm. There has been a debate on whether biologics are associated with important risk of adverse effects (such as serious infections, opportunistic infections, tuberculosis reactivation, and cancer), the magnitude of this risk, and whether the risk varies between different treatments or classes [10–12].

A large number of primary studies has already examined the safety of biological therapies in UC followed by several systematic reviews and meta-analyses. Given that meta-analysis of randomized controlled trials (RCTs) ranks high in the proposed hierarchy of evidence [13,14], an umbrella review of meta-analyses of RCTs on the safety of biologics in UC would be useful. An umbrella review is a comprehensive and systematic collection of the existing research syntheses, and an assessment of whether investigators addressing similar review questions, independently, have reached similar results and conclusions [15–17].

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2. Methods

PubMed and Scopus databases were systematically searched through 2017, to identify meta-analyses examining the potential harm of biological therapies in patients with UC. Search terms included: *adalimumab*, *golimumab*, *infliximab*, *vedolizumab*, *biologic(s)*, or *biologic(al) agent(s)*, combined with *ulcerative colitis* and *meta-analysis*. The search was limited to English language. Other restrictions were not imposed.

The titles and abstracts of identified published articles were scanned. The full text of the selected articles was retrieved and scrutinized further to verify eligibility. Meta-analyses of RCTs were the preferred source of evidence for this review, given that the RCT is considered the study design that is least likely to be biased [18]. Pooled analyses summarizing data across a non-systematically selected number of studies were excluded. Finally, the reference lists of included meta-analyses were examined to identify any eligible publications missed by the electronic database search.

The outcomes of interest for this umbrella review of meta-analyses were: (i) any infections; (ii) serious infections; (iii) opportunistic infections; (iv) tuberculosis; and (v) malignancies. Serious infections include infections associated with hospital admission, use of intravenous antibiotics, or death. Opportunistic infections are caused by pathogens that take advantage of an opportunity not normally available (such as a weakened immune system of the host). Examples of opportunistic infections include *Mycobacterium tuberculosis*, JC virus infection, *Nocardia* infection, cytomegalovirus or Epstein-Barr virus infection, oral or oesophageal candidiasis, varicella-zoster virus infection, herpes zoster infection, herpes simplex infection, *Pneumocystis jirovecii* infection, *Histoplasma capsulatum* infection, Legionella-induced pneumonia, and other unspecified opportunistic infections.

Meta-analysis articles reporting effect estimates for at least one of the above outcomes were eligible for inclusion. The following data were extracted: first author's last name, journal, year of publication, patient characteristics, medication types, outcomes examined, numbers of included studies and subjects, and estimated effect sizes along with the corresponding 95% confidence intervals (CI).

As this is a descriptive review of meta-analyses, no statistical analysis was performed.

3. Results

3.1. Search results

Overall, 466 records were identified through database searches (PubMed: 164, Scopus: 302). After screening the titles and abstracts, 31 publications were retrieved for further review. Their full text was read and the reference lists were checked. Finally, 10 meta-analyses synthesizing evidence from RCTs, and reporting one or more of the outcomes of interest, were included in this review [19–28]. The publication dates ranged between 2013 and 2017. Of note, these meta-analyses are chronologically built on an ever-expanding array of studies, and so there are inherent correlations from an earlier meta-analysis to a later one.

3.2. Characteristics of meta-analyses included in the umbrella review

All meta-analyses compared biological therapies with placebo in adults except for one [22] that involved a RCT in children. Techniques of network meta-analysis were also used [20,21]. The number of studies included in each meta-analysis varied between 2 [25] and 16 [20]. The patients on biological therapies were between 362 [26] and 3292 [20], while those on placebo ranged from 198 [23] to 1858 [20]. The safety of anti-TNF treatments (adalimumab, golimumab, and infliximab) was examined in 8 meta-analyses [19–22,24,25,27,28], while the safety of the anti-integrin agent vedolizumab was assessed in 5 meta-analyses [19–21,23,26]. All four biological agents were examined in the recently published meta-analyses [19–21]. Induction and maintenance phases were considered in 9 meta-analyses, either individually [21,22] or combined in one group [19,20,23,24,26–28] (Table 1).

3.3. Outcomes

3.3.1. Any infection

Three meta-analyses [19–21] have reported effect estimates for developing any infection in the treatment of UC using adalimumab, golimumab, infliximab, and vedolizumab (Table 1). In most analyses, the summary estimates for any infection were not statistically significant, either when all biological agents (together) were compared to placebo, or when each agent was individually evaluated against placebo. The meta-analytic estimates became significant: (i) when golimumab was assessed against placebo in the maintenance phase (Relative Risk based on one study, 1.38; 95% CI, 1.04–1.84) [19]; (ii) when adalimumab and infliximab together were compared with placebo (Relative Risk based on four studies, 1.16; 95% CI, 1.00–1.34) [19]; and (iii) when all four biological drugs were examined against placebo grouping together the induction and maintenance phases (Odds Ratio based on 16 studies, 1.18; 95% CI, 1.02–1.36) [20].

3.3.2. Serious infections

In total, seven meta-analyses studied the incidence of serious infections in biologics-based treatment of UC [19–22,24–26]. Adalimumab [21,22,25] and vedolizumab [19,21,26] were individually examined against placebo in three meta-analyses, while golimumab and infliximab in two meta-analyses [21,22]. Combined effects of adalimumab, golimumab, and infliximab, and of all four biologics, versus the placebo arms, were examined in two [19,24] and one meta-analysis [20], respectively. Two meta-analyses gave estimates for patient populations in the induction [22,25] or the maintenance [21,22] phase, while in three meta-analyses, induction and maintenance phases were combined [20,24,26]. All summary effect estimates for serious infections were statistically non-significant. The trial that involved children did not report any cases of serious infections [22].

3.3.3. Opportunistic infections

Opportunistic infections were studied in five meta-analyses [19,20,23,25,28]. Summary effect estimates were given either for individual comparisons, e.g. adalimumab [25] or vedolizumab [23] against placebo, or for combinations of three (adalimumab, golimumab and infliximab) [28] or of all four biological agents [19,20], relative to placebo. Both the induction and the maintenance phases were considered. All meta-analyses produced statistically non-significant results.

3.3.4. Tuberculosis

Tuberculosis, as an outcome in biologics-based treatment of inflammatory bowel disease, was evaluated in one large meta-analysis [20]; however, summary effect estimates for UC were not reported, because the total number of tuberculosis cases was very limited.

3.3.5. Malignancies

Five meta-analyses [20,23–25,27] examined the risk of malignancies, but three [24,25,27] gave estimates of relative risk. All the

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