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Alimentary Tract

Efficacy of tumour necrosis factor antagonists on remission, colectomy and hospitalisations in ulcerative colitis: Meta-analysis of placebo-controlled trials

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ABSTRACT

Background: The potential for disease modification of tumour necrosis factor antagonists in ulcerative colitis remains debated.
Methods: We searched MEDLINE, the Cochrane Library and EMBASE. Clinical response/remission, mucosal healing, colectomy, disease-related hospitalisations, and adverse events were analysed by the methods of Peto and Der Simonian and Laird.
Results: Five trials enrolled 3654 patients (anti-tumour necrosis factor = 2338). Anti-tumour necrosis factor therapy was more effective than placebo to induce and maintain clinical remission, with a number needed to treat of 12 (95% confidence interval [CI], 7–35) and 6 (95% CI, 4–12) for adalimumab and infliximab, respectively. Anti-tumour necrosis factor therapy was more effective than placebo to induce and maintain mucosal healing, with number needed to treat of 9 (95% CI, 5–48), 7 (95% CI, 5–17), 4 (95% CI, 3–6) for adalimumab, golimumab and infliximab, respectively. Only infliximab was associated with a reduced need for colectomy. Both infliximab and adalimumab were associated with less hospitalisations. Anti-tumour necrosis factor therapy did not increase the risk of adverse events.
Conclusions: Anti-tumour necrosis factor therapy is more effective than placebo to induce and maintain clinical remission and mucosal healing. Both infliximab and adalimumab are associated with less hospitalisations. Infliximab reduces the need for colectomy. Anti-tumour necrosis factor therapy does not increase the risk of adverse events.

1. Introduction

Ulcerative colitis (UC) is a chronic and disabling condition with an annual incidence of 24.3 per 100,000 person-years in Europe and 19.2 per 100,000 person-years in North America [1]. Anti-tumour necrosis factor (TNF) therapy is increasingly used in UC patients [2,3]. In a French referral-centre-based cohort, the probability of receiving infliximab at 5 years was 29% in UC [3].

Infliximab was approved for UC refractory to standard medications in 2006 [4]. Two randomised controlled trials demonstrated that adalimumab is more effective than placebo in UC [5,6]. In 2012, adalimumab was approved for the treatment of moderate-to-severe UC in adults. More recently, a third anti-TNF agent, golimumab, demonstrated promising results for induction and maintenance of clinical remission, and achievement of mucosal healing in UC [7,8], and recently received approval in the United States and in Europe. The potential for disease modification of anti-TNF therapy in terms of colectomy and hospitalisations in patients with UC is still debated [2,9]. Recently, a meta-analysis evaluated the efficacy of TNF antagonists in inducing and maintaining remission in UC, but mucosal healing, colectomy and UC-related hospitalisations were not assessed [10]. Another meta-analysis

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evaluated clinical remission and mucosal healing, but not colectomy and UC-related hospitalisations [11].

The aim of this meta-analysis was to evaluate the clinical efficacy (clinical response, clinical remission, and mucosal healing rates), and for the first time the need for colectomy and UC-related hospitalisations of all TNF antagonists (infliximab, adalimumab and golimumab) that have been evaluated in randomised, placebo-controlled phase III trials in adults with moderately to severely active UC. Safety was also evaluated.

2. Methods

2.1. Search strategy and study selection

A literature search was conducted to identify placebo-controlled trials that evaluated efficacy and safety of TNF antagonists in UC. We conducted a computerised search of English language publications listed in the electronic databases of MEDLINE (source, PUBMED January 1990 to February 2013), the Cochrane Central Register of Controlled Trials (CENTRAL, The Cochrane Library 2013, Issue 2) and EMBASE (January 1990 to February 2013). Studies were identified using the following search terms: "*Tumor Necrosis Factor-alpha/antagonists and inhibitors*" as medical subject headings (MeSH) as well as *anti-TNF*, *infliximab*, *adalimumab* and *golimumab* as free text terms. These were combined with the set operator AND with studies identified with the search term "*ulcerative colitis*" as MeSH. Manual searches of reference lists from potentially relevant papers were used to identify any additional studies that may have been missed using the electronic search. We also hand-searched abstracts from the annual meetings of Digestive Disease Week, the American College of Gastroenterology, the European Crohn's and Colitis Organisation and the United European Gastroenterology Week between 2008 and 2012.

We performed a manual selection of studies which satisfied the following inclusion criteria: (i) placebo-controlled trials, (ii) enrolment of adult UC patients treated with any biologic. Potentially eligible articles were reviewed in a blind manner by two different investigators (A.L. and L.P.B.), with any discrepancies resolved by discussion.

2.2. Outcome measures

The outcome measures were defined *a priori*. The efficacy endpoints were clinical response, clinical remission, and mucosal healing at weeks 6–8 and weeks 52–54, as well as colectomy rates and UC-related hospitalisations during follow-up.

For efficacy analysis, adalimumab and golimumab induction trials and the induction part of two infliximab maintenance trials were combined [4,5,7], while golimumab data were analysed separately from adalimumab/infliximab data for maintenance trials [4,6,8]. For the adalimumab and infliximab maintenance trials, the goal was to induce a sustained clinical remission whereas the golimumab maintenance trial was a withdrawal trial, where the goal was to maintain remission or response among patients who had previously been treated with golimumab, and responded. Importantly, in both the infliximab and golimumab trials, patients were naïve to anti-TNF therapy, whereas in one of the two adalimumab trials, 39% of patients had previous exposure to anti-TNF therapy. Hence, the impact of previous exposure to anti-TNF therapy on adalimumab results was analysed by a sensitivity analysis which excluded patients with previous exposure to infliximab.

For safety, we analyzed overall adverse events, serious adverse events, deaths, malignancies, and serious infections. Serious infections were defined as infections requiring antimicrobial therapy or hospitalisation.

2.3. Data collection

The individual results of the primary research studies were abstracted on to a Microsoft Excel spreadsheet (XP professional edition; Microsoft Corp, Redmond, WA, USA) as dichotomous outcomes. Agreement between investigators was >95% and disagreements in data extraction were resolved by consensus between the two investigators (AL, LPB). The review protocol was not registered.

2.4. Assessment of risk of bias

This was performed independently by two investigators (AL, LPB), with disagreements resolved by discussion with a third investigator. Risk of bias was assessed as described in the Cochrane handbook [12], by recording the method used to generate the randomisation schedule, the method used to conceal allocation of treatment, whether blinding was implemented, what proportion of patients completed follow-up, whether an intention-to-treat analysis was extractable, and whether there was evidence of selective reporting of outcomes. Quality of clinical trials was assessed with the Jadad score [13], obtained by adding results to three questions concerning randomisation, blinding and handling of withdrawals/dropouts. This score varies from 0 to 3, and higher quality clinical trials have higher scores.

2.5. Statistical analysis

Data analysis was performed according to the methods of Peto [14] and Der Simonian and Laird [15]. The statistical heterogeneity was tested for each analysis [16]. A random effect model was used to combine the data. All analyses were performed according to random effect model even when heterogeneity (I^2) was <25%. The overall treatment effect was estimated by a weighted average of individual effects, with weights inversely proportional to variance in observed effects. The effects measures estimated were the relative risk (RR) between the anti-TNF and the placebo groups, with 95% confidence intervals (CIs) [17]. The number needed to treat (NNT) for each outcome of interest was calculated from the reciprocal of the risk difference.

Review Manager version 5.0.23 (RevMan for Windows 2008, the Nordic Cochrane Centre, Copenhagen, Denmark) was used to generate Forest plots of pooled RRs for primary and secondary outcomes with 95% CIs.

3. Results

3.1. Literature search results

The initial search of online databases yielded 922 papers and was supplemented with 4206 conference abstracts. A total of 5128 studies were identified. The main reasons for excluding the studies were: inclusion criteria not met ($n = 5097$), sub-group analysis of randomised controlled trials ($n = 11$), no placebo arm ($n = 3$) [18–20], abstract of full-length papers ($n = 4$), studies on acute severe UC ($n = 5$) [21–25], or duplicate publication ($n = 1$) (Supplementary Figure S1).

A total of seven articles reporting five clinical trials were included in this meta-analysis, all available as full-length papers [2,4–8,26]. The Cochrane Collaboration's tool for assessing risk of bias did not reveal any bias [12].

Two articles evaluated adalimumab [5,6], two golimumab [7,8], and one reported two separate trials of infliximab [4]. Two articles were *post hoc* analyses of randomised controlled trials, reporting