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A network meta-analysis on the efficacy of 5-aminosalicylates, immunomodulators and biologics for the prevention of postoperative recurrence in Crohn's disease

Zhiping Yang [a,1], Xiaofei Ye [b,1], Qiong Wu [a,1], Kaichun Wu [a], Daiming Fan [a,*]

[a] Xijing Hospital of Digestive Diseases, Xijing Hospital, Fourth Military Medical University, 127 West Changle Road, Xi'an 710032, China
[b] Department of Health Statistics, Second Military Medical University, Shanghai 200433, China

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ABSTRACT

Background and aims: A number of agents have been evaluated in clinical trials to reduce the risk of postoperative recurrence in Crohn's disease (CD). The aim of this study was to compare the efficacy of 5-aminosalicylates, immunomodulators and biologics for postoperative prophylaxis of CD recurrence by using a network meta-analytical approach.

Methods: PubMed, Embase, and Cochrane Library were searched (update to November 2013) to identify randomized placebo-controlled, or head-to-head trials among the three drug classes for prevention of postoperative CD relapse. The primary endpoint for efficacy was endoscopic recurrence, and the secondary outcomes were clinical recurrence and adverse events. We conducted a Bayesian network meta-analysis with a mixed treatment comparisons to combine both direct and indirect evidences.

Results: Fifteen trials involving 1507 patients were included in this analysis. Biological agents were associated with a large and significant reduction of both endoscopic and clinical recurrence compared with placebo, 5-aminosalicylates, or immunomodulators. Immunomodulators showed greater efficacy in terms of endoscopic and clinical recurrence prophylaxis compared with 5-aminosalicylates or placebo, but with higher incidence of adverse events. 5-aminosalicylates were superior to placebo for prevention of clinical recurrence, without increasing the rate of side effect.

Conclusions: 5-aminosalicylates, immunomodulators, and biologics are more efficacious than placebo for postoperative CD prevention. Biologics are found to be the most effective medications to prevent CD recurrence.

1. Introduction

Despite evolving medical management of Crohn's disease (CD), approximately 70–80% of patients require intestinal surgery for medically refractory disease or complications during their disease course [1,2]. However, surgery does not cure the disease, and postoperative recurrence remains a significant concern in CD patients. Population-based studies reported the clinical recurrence rates ranging from 28% to 45% at five years and from 36% to 61% at ten years, respectively [3].

Efforts have been made in the preoperative, intraoperative and postoperative stages for prophylaxis of CD recurrence after surgery. First, doctors attempted to identify risk profile in a patient to predict the probability of relapse. To date, only tobacco smoking is a strong and modifiable risk factor [3,4]. Secondly, surgeons tried to improve surgical parameters to decrease the recurrence rate. Nevertheless, there is no single surgery-specific factor that has been conclusively associated with postoperative CD recurrence [3,5]. Finally, medical intervention following surgical resection has been considered as best option to prevent postoperative recurrence [6]. Various medications haven been evaluated in this setting, but no consensus on the optimal algorithm has been reached until now [7,8].

Agents that have been investigated include 5-aminosalicylates (5-ASA), thiopurines, antibiotics, probiotics, corticosteroids, interleukin-10, tumor necrosis factor (TNF) inhibitors, etc. [2,7] 5-ASA has modest benefit in preventing relapse of CD with

Abbreviations: CD, Crohn's disease; 5-ASA, 5-aminosalicylates; TNF, tumor necrosis factor; OR, odds ratio; CI, confidence interval; CrI, credible interval.

* Corresponding author.
E-mail address: daimingfan@fmmu.edu.cn (D. Fan).

[1] Contributed equally to this work.

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surgically-induced remission. However, this benefit is limited to mesalamine, not for sulfasalazine [9]. Thiopurines are more effective than placebo or mesalamine in preventing postoperative recurrence of CD, but at the expense of a high rate of adverse events leading to drug withdrawal [10]. Nitroimidazole antibiotics can reduce the risk of clinical and endoscopic recurrence in short-term compared with placebo, but the intolerable side-effects limit their use of high doses in clinical practice. [11] Available evidences have failed to show any efficacy for postoperative prophylaxis of CD by using probiotics [11,12], budesonide [13,14], and interleukin-10 [15]. Although the data are limited, the use of TNF inhibitors in the postoperative setting to prevent CD recurrence has shown great promise. [4,6] They seemed to dramatically reduce postoperative recurrence in selected CD patients [16]. However, the role of biologic therapy in the average-risk population and whether they are superior to other effective agents are still unclear.

The aim of this study was to investigate the comparative efficacy of 5-ASA (only mesalamine), immunomodulators (azathioprine and 6-mercaptopurine) and biologics (infliximab and adalimumab) for the prevention of postoperative recurrence in CD. Because the number of randomized trials directly comparing these drug classes is limited, we performed a network meta-analysis to integrate both direct and indirect evidences across multiple trials. Network meta-analysis allows a unified, coherent analysis of all randomized controlled trials that compare these agents head to head or with placebo [17].

2. Materials and methods

2.1. Search strategy and trial identification

We did a bibliographic search in the databases of PubMed, Embase, and Cochrane Central Register of Controlled Trials to identify randomized, placebo-controlled, and head-to-head studies reporting the effect of mesalamine, azathioprine, 6-mercaptopurine, infliximab, and adalimumab on postoperative prophylaxis of CD recurrence. The PubMed search strategy is detailed in Appendix 1. Reference lists from systematic reviews and primary studies were hand-searched for additional relevant publications. The search was last updated on 15 November, 2013.

Studies were included if they met all of the following criteria: (1) randomized controlled design; (2) either placebo-controlled or positive-controlled among the three drug classes; (3) examined prophylactic treatment for postoperative CD; (4) had similar baseline characteristics in each arm to ensure effective random assignment; and (5) were published in English. If trial data sources overlapped in multiple reports, the study published as full-text with more sufficient information was included.

2.2. Data extraction, outcome measures and quality evaluation

Study selection and data extraction were analyzed by two independent investigators (Z.Y. and Q.W.); disagreements were resolved by consulting a third investigator (D.F.). We extracted data on the first author's name, year of trial publication, publication type, country of origin, number of centers involving in the trial, drug regimen in each intervention group, number of participants, and follow-up duration. Additional data about patient characteristics extracted when available included age, gender, proportion of current smokers, proportion of patients previously receiving intestinal surgery, disease duration, proportion of patients with penetrating behavior and perianal disease, and location of disease.

The prespecified primary outcome of interest was endoscopic recurrence according to the criteria of Rutgeerts. The Rutgeerts score not only serves as real-time assessment for endoscopic recurrence, but also provides prognostic information for further clinical recurrence [5]. We defined the score i2 or greater as endoscopic recurrence, i3 or greater as severe endoscopic recurrence. Secondary outcomes were clinical recurrence and adverse events. The definition of clinical recurrence in each study was summarized in Supplemental Table 1. From each study, we extracted incident number and rate of relapse for each intervention group.

Two independent reviewers (Z.Y. and X.Y.) evaluated the quality of individual studies on the basis of Jadad scale, which is a five-point score system in three aspects of randomization, blinding, and withdrawals and dropouts [18].

2.3. Statistical analysis

To best summarize the totality of available evidence, we conducted direct and network meta-analyses comparing 5-ASA, immunomodulators, biologics, and placebo. Whenever possible we used results from intention-to-treat analysis.

In conventional direct meta-analysis, two or more studies that compared two interventions of interest were statistically combined. We calculated the pooled odds ratio (OR) with 95% confidence interval (CI) by using a random-effects model. We used the Cochrane's Q test to assess heterogeneity of the treatment effect and considered a threshold P value less than 0.1 as statistically significant. We also used I^2 statistic to evaluate the magnitude of the heterogeneity among studies. A value greater than 50% indicates substantial heterogeneity. We used the Egger regression test to examine potential publication bias and defined its significance as a P value less than 0.05. The direct meta-analysis was done by using the software STATA (Version 12.0; Stata Corporation, College Station, Texas, USA).

Given the limited number of studies for direct comparisons, we used a network meta-analytical approach to simultaneously combine both direct and indirect comparisons between studies [19]. Network meta-analysis was conducted by using a Bayesian Markov-chain Monte Carlo method and fitted in the software ADDIS (Version 1.16.3; Drug Information Systems). Analytical results are presented as ORs with 95% credible intervals (CrIs). In the presence of minimally informative priors, CrI can be interpreted like conventional CI [17]. Rankings regarding treatment efficacy of the three drug classes and placebo were originally derived from Monte Carlo simulations and presented as the probability of possessing a specific ranking, in which the probabilities of different rankings of the same treatment were summed to 100% [20]. Pooled results were considered statistically significant for $P < 0.05$ or if the 95% CI (CrI) did not contain the value 1.

3. Results

3.1. Search results

A total of 292 citations were identified through electronic searches. Of these, 273 were excluded after title and/or abstract screening, leaving 19 studies for further evaluation. One study published as meeting abstract was duplicate with a full-length publication thereafter [21]. Two abstracts reported long follow-up survey of the previous trials [22,23]; but we could not access sufficient data on the primary or secondary outcome of interest. Another two studies were excluded due to the absence of an adequate control [24,25]. So the remaining 14 studies fulfilled our inclusion criteria [21–23,26–36]. One additional relevant study was identified through a manual search of the reference section of identified articles and former meta-analyses [37]. Finally, 15