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Comparative Efficacy of Biologic Therapy in Biologic-Naïve Patients With Crohn Disease: A Systematic Review and Network Meta-analysis

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Abstract

Objective: To study the comparative efficacy of biologic therapy in the management of biologic-naïve patients with Crohn disease (CD).

Patients and Methods: We conducted a systematic review of randomized controlled trials published from January 1, 1985, through September 30, 2013, comparing biologic agents (infliximab [IFX], adalimumab [ADA], certolizumab pegol, natalizumab, vedolizumab, and ustekinumab) with each other or placebo for inducing and maintaining clinical remission in adults with moderate to severe CD. To increase comparability across trials, we focused on a subset of biologic-naïve patients for the induction end point and on responders to induction therapy for the maintenance end point. We followed a Bayesian network meta-analysis approach.

Results: We identified 17 randomized controlled trials of good methodological quality comparing 6 biologic agents with placebo, with no direct comparison of biologic agents. In network meta-analysis, we observed that IFX (relative risk [RR], 6.11; 95% credible interval [CrI], 2.49-18.29) and ADA (RR, 2.98; 95% CrI, 1.12-8.18), but not certolizumab pegol (RR, 1.48; 95% CrI, 0.76-2.93), natalizumab (RR, 1.36; 95% CrI, 0.69-2.86), vedolizumab (RR, 1.40; 95% CrI, 0.63-3.28), and ustekinumab (RR, 0.61; 95% CrI, 0.15-2.49), were more likely to induce remission than placebo. Similar results were observed for maintenance of remission. Infliximab had the highest probability of being ranked as the most efficacious agent for induction (86%) and ADA for maintenance of remission (48%).

Conclusion: On the basis of network meta-analysis, IFX may be most efficacious agent for inducing remission in CD in biologic-naïve patients. In the absence of head-to-head treatment comparison, the confidence in these estimates is low. Future comparative efficacy studies are warranted.

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Inflammatory bowel diseases (IBDs) affect more than 4 million people worldwide, with an increasing global incidence.[1] Both ulcerative colitis and Crohn disease (CD) are associated with substantial morbidity, with frequent hospitalizations, operation, and need for corticosteroids and immunosuppressive medications. These conditions often result in poor quality of life and loss of workplace productivity. The total economic burden of CD exceeds $18,000 per patient per year in the United States.[2] Biologic therapy with anti–tumor necrosis factor-α (anti–TNF-α) medications, alone or in combination with immunomodulators, is currently the most effective treatment for induction and maintenance of clinical remission, with multiple randomized controlled trials (RCTs) exhibiting superiority of anti–TNF-α agents over placebo.[3-8] Antibodies to α_4-integrins that inhibit lymphocyte migration, such as natalizumab (NAT), are currently reserved for patients who fail to respond to anti–TNF-α agents,[9] primarily owing to the risk of serious adverse effects such as progressive multifocal leukoencephalopathy[10]; however, the gut-specific lymphocyte migration inhibitor vedolizumab (VEDO) does not appear to have this serious adverse effect.[11] Ustekinumab (UST), an interleukin 12/23 (IL-12/23) antagonist, has also been found to be effective in inducing and maintaining clinical response in patients with CD.[12]

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It is unclear whether one biologic agent is more effective than others; there are no head-to-head clinical trials comparing different biologic agents with each other, and it is unlikely that such a clinical trial will be performed in the near future owing to sample size and cost considerations. Current decisions on the choice of biologic agents are primarily driven by patient preference, relative cost based on insurance coverage, and anecdotal experience of the treating physician. In the absence of direct evidence from comparative efficacy clinical trials, network meta-analysis, also known as multiple-treatment meta-analysis or mixed-treatment comparisons, can help assess comparative efficacy of several interventions and synthesize evidence across a network of RCTs, especially if there is weak (or no) direct evidence.[13-15] Such indirect comparisons of competing interventions, adjusted by a common control such as placebo, can partially take account of prognostic characteristics of patients in different trials. In a recent network meta-analysis, Stidham et al[16] observed that all anti−TNF-α agents are effective for induction and maintenance of clinical remission and response in patients with CD, although adalimumab (ADA) appeared superior to certolizumab pegol (CZP) for induction of remission. However, they included all patients, regardless of previous anti−TNF-α exposure status; it is well known that patients with primary nonresponse or loss of response to one anti−TNF-α agent have suboptimal response to a second agent. Moreover, they limited analysis only to anti−TNF-α agents and did not compare the relative efficacy of anti-integrins and anti−IL-12/23 agents.

Hence, in this systematic review, we sought to compare the relative efficacy of all available biologic agents (infliximab [IFX], ADA, CZP, NAT, VEDO, and UST) for induction and maintenance of medically induced clinical remission in patients with moderate to severe CD by using a standard pairwise meta-analysis of direct treatment comparisons and by using a Bayesian network meta-analysis combining direct and indirect treatment comparisons. To improve comparability of patients across trials, we included data only from biologic-naïve patients in trials of induction therapy; likewise, for comparing the efficacy for maintenance of remission, we included data only from the subset of patients who initially responded to induction therapy with the index biologic agent in these trials.

PATIENTS AND METHODS

This systematic review was reported according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines,[17] and the process followed an a priori established protocol. The search strategy, data extraction methodology, and quality assessment were adapted from the American College of Gastroenterology systematic review on the efficacy of biologic therapy in patients with IBD.[18]

Selection Criteria

Studies included in this meta-analysis were RCTs that met the following inclusion criteria: (1) *Patients:* adults with moderate to severe CD (based on Crohn's Disease Activity Index [CDAI] >220 but <450) who had never previously been treated with a biologic agent (first-time users or biologic-naïve patients); (2) *Intervention:* biologic therapy with anti−TNF-α agents (IFX, ADA, and CZP), anti-integrin agents (NAT and VEDO), or anti−IL-12/23 agent (UST) for induction and/or maintenance of remission, with a minimum duration of therapy of 14 days in trials reporting induction of remission in active disease and a minimum duration of therapy of 22 weeks in trials reporting maintenance of remission. (3) *Comparator:* another biologic agent or placebo or an alternative intervention with at least 2 biologic agents having been compared with common intervention (to form a network for indirect comparison). (4) *Outcome:* induction of clinical remission (CDAI <150; if unavailable, then clinical response with a decrease in CDAI by more than 100 or 70 points from baseline) and maintenance of medically induced remission (in patients with clinical response to induction therapy).

We excluded (1) observational studies, (2) trials of combination therapy (biologic agents with immunomodulators) without a placebo arm (unable to form a network for indirect comparisons) or trials of biologic agents not used in clinical practice (eg, CDP571), and (3) pediatric studies. For RCTs of induction therapy, trials assessing the efficacy of a biologic agent in biologic-exposed patients and trials that did not separately report outcomes

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