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CLINICAL AT

Comparative Effectiveness of Immunosuppressants and Biologics for Inducing and Maintaining Remission in Crohn's Disease: A Network Meta-analysis

Glen S. Hazlewood,[1,*] **Ali Rezaie,**[3,*] Meredith Borman,[1] Remo Panaccione,[1] Subrata Ghosh,[1] Cynthia H. Seow,[1,2] Ellen Kuenzig,[2] George Tomlinson,[4] Corey A. Siegel,[5] Gil Y. Melmed,[3] and Gilaad G. Kaplan[1,2]

[1]Department of Medicine, [2]Departmet of Community Health Sciences, University of Calgary, Calgary, Alberta, Canada; [3]Department of Medicine, Cedars-Sinai Medical Center, Los Angeles, California; [4]University Health Network, University of Toronto, Toronto, Ontario, Canada; [5]Department of Medicine, Dartmouth-Hitchcock Medical Center, Lebanon, New Hampshire

This article has an accompanying continuing medical education activity on page e14. Learning Objective: Upon completion of the CME activity, successful learners will be able to compare different treatment strategies in managing Crohn's disease and understand the purpose of conducting a network meta-analysis.

See Covering the Cover synopsis on page 266.

BACKGROUND & AIMS: There is controversy regarding the best treatment for patients with Crohn's disease because of the lack of direct comparative trials. We compared therapies for induction and maintenance of remission in patients with Crohn's disease, based on direct and indirect evidence. **METHODS:** We performed systematic reviews of MEDLINE, EMBASE, and Cochrane Central databases, through June 2014. We identified randomized controlled trials (N = 39) comparing methotrexate, azathioprine/6-mercaptopurine, infliximab, adalimumab, certolizumab, vedolizumab, or combined therapies with placebo or an active agent for induction and maintenance of remission in adult patients with Crohn's disease. Pairwise treatment effects were estimated through a Bayesian random-effects network meta-analysis and reported as odds ratios (OR) with a 95% credible interval (CrI). **RESULTS:** Infliximab, the combination of infliximab and azathioprine (infliximab + azathioprine), adalimumab, and vedolizumab were superior to placebo for induction of remission. In pairwise comparisons of anti–tumor necrosis factor agents, infliximab + azathioprine (OR, 3.1; 95% CrI, 1.4–7.7) and adalimumab (OR, 2.1; 95% CrI, 1.0–4.6) were superior to certolizumab for induction of remission. All treatments were superior to placebo for maintaining remission, except for the combination of infliximab and methotrexate. Adalimumab, infliximab, and infliximab + azathioprine were superior to azathioprine/6-mercaptopurine: adalimumab (OR, 2.9; 95% CrI, 1.6–5.1), infliximab (OR, 1.6; 95% CrI, 1.0–2.5), infliximab + azathioprine (OR, 3.0; 95% CrI, 1.7–5.5) for maintenance of remission. Adalimumab and infliximab + azathioprine were superior to certolizumab: adalimumab (OR, 2.5; 95% CrI, 1.4–4.6) and infliximab + azathioprine (OR, 2.6; 95% CrI, 1.3–6.0). Adalimumab was superior to vedolizumab (OR, 2.4; 95% CrI, 1.2–4.6). **CONCLUSIONS:** Based on a network meta-analysis, adalimumab and infliximab + azathioprine are the most effective therapies for induction and maintenance of remission of Crohn's disease.

Keywords: Network Meta-analysis; IBD; Anti-TNF Therapy; Immunosuppressive Agents.

Crohn's disease is a chronic inflammatory condition of the intestinal tract that affects individuals in the prime of their lives, subjecting them to social stigma, impinging on their ability to attend work or school, and reducing their quality of life.[1] The United States spends approximately $6.1 billion annually on direct inflammatory bowel disease health care costs, with the major drivers of cost being hospitalizations, surgeries, and medications.[2] Over the past few decades the rate of intestinal resections for Crohn's disease has been reduced after the introduction of immunosuppressant drugs (ie, azathioprine/6-mercaptopurine and methotrexate) and then anti–tumor necrosis factor (TNF) therapy (infliximab, adalimumab, and certolizumab).[3]

However, the choice of induction and maintenance strategy remains challenging. Although multiple trials exist, most are placebo-controlled, with a lack of head-to-head trials between active treatments. The paucity of head-to-head clinical trials has raised controversial therapeutic decisions including the choice between immunosuppressants vs anti-TNF therapy, choosing within a class of medication, and deciding whether to prescribe anti-TNF monotherapy vs concomitant anti-TNF with immunosuppressants.[4,5] Moreover, gastroenterologists now must contend with the positioning of vedolizumab in the therapeutic paradigm of

*Authors share co-first authorship.

Abbreviations used in this paper: CDAI, Crohn's Disease Activity Index; CrI, credible interval; OR, odds ratio; TNF, tumor necrosis factor; WDAE, withdrawals due to adverse events.

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Crohn's disease.[6] Numerous treatment algorithms have been proposed by clinical experts in an attempt to synthesize the literature because direct comparative efficacy trials are lacking.[4] In keeping with this, comparisons of biologic treatment strategies for Crohn's disease were listed by the Institute of Medicine as one of the top priorities for comparative effectiveness research.[7,8]

Where direct head-to-head evidence is lacking, indirect evidence may help inform decision making that aims to maximize efficacy, minimize toxicity, and optimize costs. An indirect treatment comparison can be made between 2 treatments if each treatment has been compared with a common comparator. Comparisons are made between treatment effects, not individual treatment arms, thereby preserving randomization.[9] For example, if one trial compares treatments A and B and another trial compares treatments B and C, an indirect comparison between treatments A and C can be determined by comparing the relative effects (eg, odds ratios) of the 2 trials. A Bayesian network meta-analysis (or mixed treatment comparison) considers all indirect and direct evidence, to determine the relative treatment effects between all interventions that can be linked through shared comparators.[9] Considering indirect evidence adds strength to the estimation of treatment effects, even where head-to-head trials are available.[9]

The primary objective of this study was to compare the efficacy of therapies for induction and maintenance of remission including azathioprine/6-mercaptopurine, methotrexate, approved anti-TNF therapies (infliximab, adalimumab, and certolizumab), vedolizumab, or their combination in adult patients with Crohn's disease, based on direct and indirect evidence from randomized controlled trials.

Methods

Eligibility Criteria

We included all randomized controlled trials that assessed treatments (azathioprine/6-mercaptopurine, methotrexate, infliximab, adalimumab, certolizumab, and vedolizumab) alone or in combination in adult patients with Crohn's disease. We included trials assessing induction of remission of immunosuppressants between 12 and 17 weeks. We included trials assessing the induction of remission of biologic therapy between 4 and 17 weeks because the onset of action of biologic therapies is more rapid. Trials assessing maintenance of remission had to be at least 24 weeks in duration.[10]

Studies assessing natalizumab were excluded because prescription of natalizumab is restricted to individuals failing immunosuppressive and anti-TNF therapy.[11] We also excluded trials studying only pediatric (age, <18 y) or postoperative patients, studies in which the treatment was not fixed (eg, standard of care), studies with a randomized withdrawal design, trials with a cross-over design, studies exclusively assessing fistulizing Crohn's disease, and studies that did not report remission as an outcome. After identification of eligible studies, trials that could not be linked within the network through a shared comparator were excluded.

The primary outcome was remission, which was defined as a Crohn's Disease Activity Index (CDAI) less than 150. When the CDAI was not reported, we used the remission criteria defined in the study. Secondary end points included total withdrawals and withdrawals due to adverse events (WDAEs). Total withdrawals were defined as the total number of patients who were withdrawn from the study for any reason after randomization. WDAEs were collected as defined by the study.

Literature Search and Study Selection

Trials were identified through existing Cochrane systematic reviews and a technical report from the American Gastroenterology Association.[10,12–16] We updated the database search from January 2007 (ie, the earliest search date of the Cochrane reviews) to June 2014 in MEDLINE, Embase, and the Cochrane Central register of controlled trials. The database search strategy was adapted from the systematic reviews (the full search strategy is available in the Supplementary Materials and Methods). We supplemented this with a search of trial registries (www.clinicaltrials.gov) and by screening all American College of Gastroenterology, Digestive Disease Week, United European Gastroenterology Week, and European Crohn's and Colitis Organization conference proceedings published from January 2007 through June 2014. For vedolizumab, a separate literature search was performed from 1966 through June 2014 on the earlier-noted research databases. Search results were screened by 2 independent reviewers (A.R., M.B.) first by title and abstract and then by full text. Disagreements were resolved through consensus and discussion with a third reviewer (G.G.K.). Selected studies were reviewed independently by 5 experts in the inflammatory bowel disease literature (R.P., S.G., C.H.S., G.Y.M., and C.A.S.) to confirm the inclusion and exclusion of trials.

Data Collection and Quality Appraisal

Data were abstracted for relevant study characteristics (Supplementary Table 1) and for all primary and secondary outcomes. For induction, remission was extracted at the time of the primary outcome specified in the trial, with the following exception: we used data at or closest to 12 weeks when the time point of the primary outcome was not specified or induction was not the primary goal of the study. For maintenance, remission was extracted at the end of the trial. Total withdrawals and WDAEs were extracted at trial end for both induction and maintenance trials. Data were extracted on a basis of intention-to-treat analysis.

In each trial arm, we abstracted the total number of patients randomized and the total number of patients who experienced the outcome. If only percentages were reported, the number of patients with the outcome was calculated and rounded to the nearest whole number. For data available only in graphic format, images in the highest resolution available were digitized and extracted using the software program Graphclick (version 3.0.2; Arizona Software; www.arizona-software.ch/graphclick/). Any disagreements were resolved through discussion and repeat extraction. The quality of trials was rated through the Cochrane Risk of Bias tool.

Synthesis of Results

For the main analysis we excluded trials with a high risk of bias. Treatment effects for remission and total withdrawals were determined using a random-effects Bayesian network meta-analysis (mixed treatment comparison). A random-effects