Representation of Patients with CD-Related Complications in Randomized Clinical Trials

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Background: Biologic therapies have become mainstays of treatment of Crohn's Disease (CD) patients. However, exclusion of patients with complications of CD involved in randomized controlled trials (RCTs) may limit generalizability of their findings. Previous work has identified that patients with stricturing disease, fistulizing disease or use of TNF-a inhibitors were more likely to be excluded from RCTs[1]. Here, we characterize how biologic RCTs have excluded, omitted or presented data on participants with CD-related complications.

Methods: To characterize this, we conducted a systematic review of complication-related exclusion and inclusion criteria of primary manuscripts of RCTs. Manuscripts were included if they had a primary efficacy outcome and evaluated a biologic medication against at least one different medication (not including different doses of same biologic). Articles with less than 50 patients with CD or secondary studies re-appraising data from trials were excluded.

Results: 67 articles met inclusion criteria. Included studies were published between 1997 and 2021. Many RCTs excluded patients with fistula, abscess, stricture, ostomy, CD-related surgery, short bowel syndrome or those requiring enteral feeding (**Table 1**). While exclusion criteria often specified which CD-related related surgery (small bowel or colon) made participants ineligible, none of the reviewed RCTs detailed patient's prior surgery type. For the complications of fistula, abscess and CD-related surgery, many studies neither explicitly excluded patients with these complications nor included rates of these complications. Of all complications, patients with fistulas or CD-related surgery were best described, with data presented in 41.8% and 43.3% of studies, respectively. Three studies required fistulas for inclusion and two studies required CD-related surgery for inclusion. In the remaining studies presenting data on fistula and CD-related surgeries, average prevalence of these complications amongst participants was 20.1% and 40.0% respectively. A negative temporal trend was observed for the inclusion of patients that had undergone IBD surgery (β= -0.07, $p<0.0001$), but no trend was observed for inclusion of patients with fistulas. No studies presented data on patients with short bowel syndrome or requiring enteral feeding.

Table 1: Percentage of studies excluding, omitting, and presenting patients with IBD-related complications and average representation in those including patients with complications.

	Exclude	Omit	Data Present	Average (presented)[i]
Fistula	22.4	35.8	41.8	20.1
Abscess	46.2	52.2	3.0	20.0
Stricture	77.6	17.9	7.5	44.4
Ostomy	76.1	22.4	1.5	15.7
Small-Bowel Resections	28.3	NA	NA	NA
Colectomy	22.4	NA	NA	NA
CD-Related Surgery*	37.3	18.4	43.3	40.0
Short Bowel Syndrome	56.7	43.3	0	NA
Enteral Feeding	23.8	76.2	0	NA

Studies were considered to have excluded patients if they were explicitly excluded in the manuscript reviewed, its supplemental methods or the clinical trial registration and to have omitted patients if it neither presented any data on a complication's prevalence amongst participants nor excluded participants based on those complications. *IBD-Related Surgery included small-bowel resections or colectomy or both. [i]Averages exclude any study that including only patients with listed complication.

Conclusions: Our results suggest that there is limited representation of patients with complications of CD in RCTs, particularly for those with abscesses, strictures/stenosis, ostomies, small-bowel syndrome, and those requiring enteral feeding. While there is some representation of patients with fistula and CD-related surgeries, it is limited. Efforts should be made to accommodate participants with all these complications in clinical trials through methodologies such as stratification and propensity score matching. When necessary, RCTs should explicitly exclude patients with complications. If not excluded, RCTs should identify and present prevalence of participants with these complications in their text to enhance understanding of treatment for these subpopulations. Without adequately representing these patients in RCTs, retrospective real-world cohort studies are the best available sources of data on efficacy and safety of biologic medications in these subpopulations.

Works Cited:

1. Ha C, Ullman TA, Siegel CA, et al. Patients Enrolled in Randomized Controlled Trials Do Not Represent the Inflammatory Bowel Disease Patient Population. Clinical Gastroenterology and Hepatology 2012;10:1002-1007.

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