Patients Enrolled in Randomized Controlled Trials Do Not Represent the Inflammatory Bowel Disease Patient Population

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This article has an accompanying continuing medical education activity on page e78. Learning Objectives—At the end of this activity, the successful learner will be able to identify the potential limitations of clinical trial data when translated to a real-world clinical practice.

See editorial on page 1008.

BACKGROUND & AIMS: Multiple randomized controlled trials (RCTs) have been conducted to determine therapeutic efficacy of the biological agents for the inflammatory bowel diseases (IBD). However, the external validity of findings from RCTs might be compromised by their stringent selection criteria. We investigated the proportion of patients encountered during routine clinical practice who would qualify for enrollment into a pivotal RCT of biological agents for IBD. **METHODS:** We performed a retrospective cohort study of adult patients with moderate–severe IBD who presented to a tertiary referral center. Inclusion and exclusion criteria were extracted from published RCTs of biologics approved by the Food and Drug Administration and applied to the study population. **RESULTS:** Only 31.1% of 206 patients with IBD (34% with Crohn's disease [CD], 26% with ulcerative colitis) would have been eligible to participate in any of the selected RCTs. Patients would have been excluded because they had stricturing or penetrating CD, took high doses of steroids, had comorbidities or prior exposure to biologics, or received topical therapies. Of the trial-ineligible patients with ulcerative colitis, 23.3% had colectomies, and 31.7% received infliximab, with a 63.2% response rate. Approximately half (49.4%) of the 82 trial-ineligible patients with CD received biological therapies, with lower response rates (60%) than trial-eligible patients (89%; $P = .03$). **CONCLUSIONS: Most patients with moderate–severe IBD evaluated in an outpatient practice would not qualify for enrollment in a pivotal RCT of biological reagents; this finding raises important questions about their therapeutic efficacy beyond the clinical trial populations. Additional evaluation of the transparency of RCT design and selection criteria is needed to determine whether trial results can be generalized to the population.**

Keywords: Inflammation; Intestine; Efficacious; Validate.

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Crohn's disease (CD) and ulcerative colitis (UC) are chronic inflammatory diseases of the gastrointestinal tract characterized by symptomatic relapses often requiring escalation of medical therapy. The introduction of the biologic anti–tumor necrosis factor alpha (anti-TNF) agents has transformed the management of the inflammatory bowel diseases (IBD) during the past decade. The evidence supporting their use for patients with moderate–severe IBD is compelling, with demonstrated efficacy at inducing and maintaining remission for CD and UC compared with placebo.[1,2] In addition to symptom improvement, these agents also might promote mucosal healing and other favorable longer-term clinical outcomes such as decreased hospitalizations, surgeries, and improved quality of life.[3–10] There is also evidence supporting the use of anti-alpha4 integrin therapy for the treatment of patients with moderate–severe CD.[11,12] Since 2002, there have been at least 8 major randomized controlled trials (RCTs) for the Food and Drug Administration (FDA) approved biologics. The results from these pivotal RCTs form the basis for regulatory agency approval, expert recommendations, and evidence-based practice guidelines for the management of patients with clinically active IBD.[13,14]

RCTs are currently the best approach available to study treatment effect. By means of prespecified patient enrollment criteria, these trials aim to minimize the potential bias of confounding variables to preserve the internal validity of the study results. It is assumed that the findings obtained from these studies carry a high level of external validity with applicability to general clinical practice. However, by limiting the

Abbreviations used in this paper: ACCENT 1, A Crohn's Disease Clinical Study Evaluating Infliximab in a New Long-Term Treatment Regimen; ACT 1 and 2, Active Ulcerative Colitis Trials; anti-TNF, anti–tumor necrosis factor alpha; CD, Crohn's disease; CHARM, Crohn's Trial of the Fully Human Antibody Adalimumab for Remission Maintenance; CLASSIC 1, Clinical Assessment of Adalimumab Safety and Efficacy Studied as Induction Therapy in Crohn's Disease; ENACT, Efficacy of Natalizumab as Active Crohn's Therapy; ENCORE, Efficacy of Natalizumab in Crohn's Disease Response and Remission; FDA, Food and Drug Administration; HBI, Harvey–Bradshaw Index; IBD, inflammatory bowel diseases; PRECISE1, Pegylated Antibody Fragment Evaluation in Crohn's Disease; RALES, Randomized Aldactone Evaluation; RCT, randomized controlled trial; SONIC, Study of Biologic and Immunomodulator Naive Patients in Crohn's Disease; UC, ulcerative colitis.

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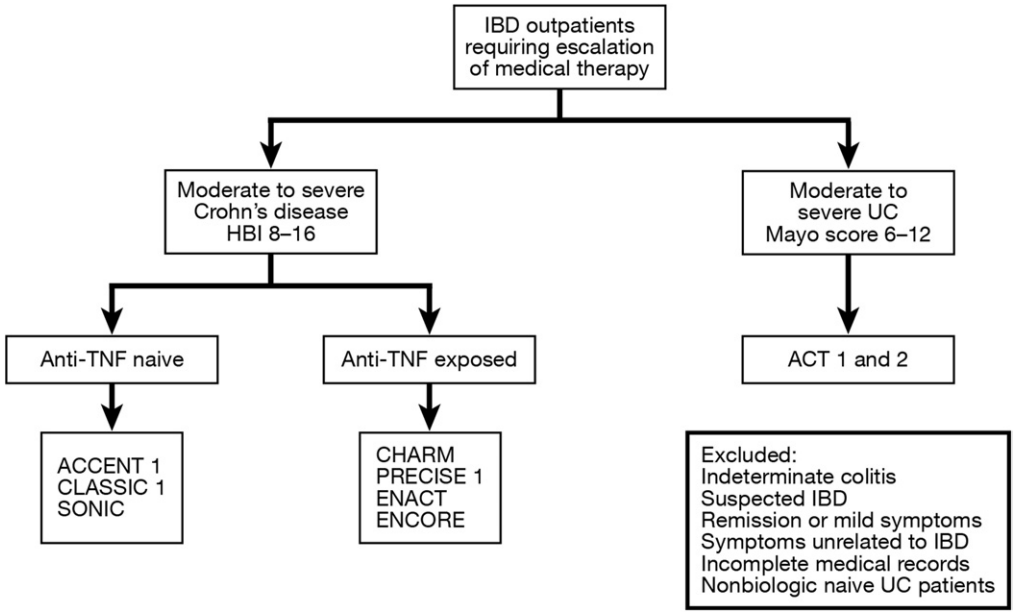

Figure 1. Clinical trial selection and study enrollment algorithm.

available pool of potential study patients with strict inclusion and exclusion criteria in an effort to maximize internal validity, trial results might have limited external validity. The generalizability of these studies might be further compromised by the heterogeneity of the IBD patient population. The success or failure of clinical trials informs the clinician about the effect of that agent on the included patients but is unable to comment on the probable benefits to an individual patient. In addition, many patients with clinically active disease present with symptoms and circumstances that would preclude entry into a clinical trial, yet there is little information available regarding the applicability of the individual trial data for these patients.

With these potential limitations of RCTs in mind, we hypothesized that only a small percentage of patients seen in a consultative IBD practice would have been eligible for study participation. Therefore, the aim of this study was to estimate the percentage of IBD patients with moderate–severe disease who would have been eligible for enrollment into a pivotal biologic RCT and to assess the enrollment criteria most likely to impact trial eligibility.

Methods

Study Population and Data Collection

We performed a retrospective chart review of consecutive adult IBD patients with moderate–severe disease activity presenting to the Mount Sinai Medical Center for an escalation or adjustment of their medical therapy from January 2008 to June 2009. Moderate–severe disease activity was defined as a Harvey–Bradshaw Index (HBI) score between 8 and 16 for CD and a Mayo UC disease activity index score between 6 and 12 for UC.[7,15] Patients with indeterminate colitis, suspected but not established IBD, mild symptoms, symptoms thought to be unrelated to IBD, disease remission, or with incomplete records for review were excluded. Because there is currently only one FDA-approved biological therapy for UC, UC patients currently on or previously exposed to biologics were also excluded from the study. The Program for the Protection of Human Subjects at the Mount Sinai School of Medicine in New York approved this study.

Data collection included routine demographics, IBD phenotype, extent, disease activity assessments, comorbidities, medication, and surgical histories. Additional data collected included subsequent medical treatments and surgical interventions as well as therapeutic response determined by physician's global assessment by 4–12 weeks after the initial visit.

Trial Selection

For the CD patients, we selected 7 published RCTs of biological therapy for patients with moderate–severe disease activity: ACCENT 1 (A Crohn's Disease Clinical Study Evaluating Infliximab in a New Long-Term Treatment Regimen),[16] CLASSIC 1 (Clinical Assessment of Adalimumab Safety and Efficacy Studied as Induction Therapy in Crohn's Disease),[17] CHARM (Crohn's Trial of the Fully Human Antibody Adalimumab for Remission Maintenance),[18] PRECISE1 (Pegylated Antibody Fragment Evaluation in Crohn's Disease),[19] ENCORE (Efficacy of Natalizumab in Crohn's Disease Response and Remission),[11] ENACT (Efficacy of Natalizumab as Active Crohn's Therapy),[12] and SONIC (Study of Biologic and Immunomodulator Naïve Patients in Crohn's Disease).[20] For the UC patients, we selected the ACT 1 and 2 trials (Active Ulcerative Colitis Trials) for infliximab in moderate–severe UC[7] (Figure 1).

Inclusion and exclusion criteria were extracted from the published manuscripts of these CD and UC trials and applied to our study population to determine overall percentage of trial eligibility. Exclusion criteria from the studies were further subcategorized on the basis of disease complications, comorbid conditions, and concomitant medications to identify variables that most affect trial eligibility.

Outcomes and Analysis

The primary outcome of interest was to determine the RCT eligibility of our study population. Secondary outcomes of interest included identification of the selection criteria that more commonly impact trial eligibility among outpatient refer-