Editorial: clinical trials in IBD—how much of a difference is enough?

The therapeutic pipeline for IBD is rapidly expanding, however, from recent registration trials differences between active treatment arms and placebo in achieving primary endpoints vary greatly; from 12.9% to 29% in CD trials and from 8.8% to 29.5% in ulcerative colitis (UC) trials. What then is a clinically meaningful result from an IBD clinical trial? To address this issue 46 members of the International Organization for the Study of Inflammatory Bowel Diseases (IOIBD) completed a web-based survey on the interpretation of IBD clinical trial results in six domains: placebo-controlled trials, head-to-head trials, bioequivalence studies, non-inferiority studies, safety and cost. In UC placebo-controlled trials for both clinical and endoscopic remission, respondents considered a 15%-20% difference to be clinically relevant in biologic-naïve and a 10%-15% difference in biologic-experienced patients. In CD placebo-controlled trials of biologic-naïve patients the differences deemed relevant were 15%-20% for clinical remission, and 10%-15% for endoscopic remission. For biologic-experienced patients a 10%-15% difference was considered relevant for both clinical and endoscopic remission. Therefore, amongst biologic-naïve UC patients, relevant clinical and endoscopic remission rates were considered the same, reflecting the high validity of endoscopic endpoints in UC studies. For both CD and UC patients, relevant clinical and endoscopic remission rates were 5% lower in biologic-experience patients. When viewed overall, relevant clinical differences were lower for both head-to-head trials (10%-15%) and non-inferiority studies (5%-10%). For bioequivalence studies relevant clinical and pharmacokinetic differences were considered to be 5%-10%; this is significantly less than the non-inferiority margin of 15% employed in the NOR-SWITCH study. The difference in safety between two therapies considered clinically relevant ranged from 0.5% to 7.5%, while a cost difference of 10%-15% was considered relevant enough to change clinical practice.

These survey results have practical importance to clinicians treating IBD. The 15% differences considered clinically relevant for clinical and endoscopic remission rates in UC and CD placebo-controlled trials are largely consistent with results from registration trials. However, agreement for this exact result of 15% was only present in 30%-40% of cases, and few individual responses had agreement from the majority of respondents. This lack of clear consensus amongst this highly qualified group demonstrates the need for further research, especially as the number and complexity of clinical trials continues to increase with more head-to-head, non-inferiority and bioequivalence studies anticipated in coming years. Clinicians can, however, be reassured that a 15% difference in a clinical trial will translate to significantly higher response rates and differences between treatment groups in real-world practice. Responses from this survey indicate that relevant clinical differences are less for head-to-head and non-inferiority trials compared to placebo-controlled trials, meaning that larger, and potentially unobtainable, sample sizes will be required to achieve adequately powered studies with these designs. Most pivotal clinical trials included in this survey utilised clinical disease activity indices to assess the primary endpoint of clinical remission. Future similar initiatives should include more studies with pre-specified endpoints incorporating deep remission, an increasingly obtainable endpoint as IBD management strategies adopt a treat-to-target approach.

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Intestinal fibrosis is associated with chronic intestinal inflammation in IBD, generally reflecting long-lasting illness, where persistent tissue damage and result in scar tissue formation. It has been stated that inflammation is required for the initiation of fibrosis, as both share the same distribution. However, inflammation seems to play a minor role in fibrosis progression. Transmural inflammation and fibrosis are common features of stricturing Crohn’s disease (CD), however, in ulcerative colitis (UC), both inflammation and extracellular matrix (ECM) deposition are generally restricted to the colonic mucosal and submucosal layers, affecting deeper layers only after profound ulcers below to submucosa. Fibrosis in UC is characterised by marked thickening of muscularis mucosae and excessive ECM deposition in the submucosa, seldom leading to strictures. In UC, fibrosis has been related with ulcers and longer disease duration—the latter linked to higher risk of malignancy. UC is now seen as a potentially progressive disease where fibrosis may lead to diffuse increased wall stiffness, resulting in motility abnormalities, anorectal dysfunction, rectal urgency and incontinence.

In a recent issue of AP&T, Gordon and colleagues depicted the first comprehensive assessment of fibrosis in UC. They studied 706 H&E and Masson Trichrome stained sections of 89 UC total colectomy or proctocolectomy specimens, which were compared to those of Crohn’s colitis, diverticular disease and normal colons. Inflammation was graded according to Geboes score and fibrosis over a new UC submucosal fibrosis score (grading 0 to 4) for each segment, with the average designated as “fibrosis burden score.” They further correlated the section studies results with histological findings on mucosal biopsies taken <4 weeks prior to surgery matched for colon location, with no endoscopic biopsy features predicting the degree of submucosal fibrosis.

The systematic approach used allowed the identification of clinical and pathological associations supporting the concept of inflammation-driven fibrogenesis in UC: submucosal fibrosis and muscularis mucosae thickening were restricted to involved segments of the colon, showing a gradient from proximal to distal colon; refractory disease was associated with higher degrees of fibrosis and muscularis mucosae thickening; and the degree, severity and histological aspects of active inflammation and chronic mucosal injury correlated with the grade of fibrosis. Importantly, the amount of fibrosis was not associated with disease duration but with severity of inflammation, which contrasts with previous studies. Likewise, no relation was found between the degree of fibrosis or average muscularis mucosae thickening and the length of the colon specimen, which contradicts the traditional view that submucosal fibrosis is responsible for the so-called “lead pipe colon.”

In summary, this paper comprehensively demonstrates that UC is a progressive disease characterised by submucosal fibrosis and muscularis mucosae thickening associated with both severity and chronicity of inflammation. We now have evidence to support that inflammation in UC drives not only an increased risk of colorectal neoplasia, but also of intestinal fibrosis, reinforcing the importance of deep remission (including histological remission) as a therapeutic target in UC.

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