HHS Public Access

Author manuscript

Aliment Pharmacol Ther. Author manuscript; available in PMC 2020 October 12.

Published in final edited form as:

Aliment Pharmacol Ther. 2018 December ; 48(11-12): 1313–1314. doi:10.1111/apt.15032.

Editorial: treating inflammatory bowel disease strictures - authors' reply

Florian Rieder[1], **Brian G. Feagan**[2,3,4], **Vipul Jairath**[2,3,4]

[1]Department of Gastroenterology, Hepatology and Nutrition, Digestive Diseases and Surgery Institute; Department of Inflammation and Immunity, Lerner Research Institute; Cleveland Clinic Foundation, Cleveland, OH, USA

[2]Robarts Clinical Trials Inc., University of Western Ontario, London, ON, Canada

[3]Department of Medicine, University of Western Ontario, London, ON, Canada

[4]Department of Epidemiology and Biostatistics, University of Western Ontario, London, ON, Canada.

We thank Professor Kamm for his interest in our paper[1,2]. We agree that limited attention that has been given to developing therapies to prevent or treat stricturing Crohn's disease (CD). Although earlier data suggested an association between treatment with TNF antagonists and development of strictures[3,4], this relationship was not confirmed in subsequent cohort studies, including CREOLE [5,6], and was likely the result of bowel damage already present at initiation of treatment.

A major obstacle in this field is the lack of definitions and appropriate clinical trial endpoints for testing drugs in stricturing CD, which fueled the development of a global initiative: the CrOhN'S disease anti-fibrotic STRICTure Therapies (CONSTRICT) study group's expert RAND/UCLA panel[2]. We agree with the comment by Professor. Kamm that the proposed definitions of luminal narrowing, prestenotic dilation and wall thickening will mainly capture patients with severe strictures. Our intent was to ensure that patients entering trials of anti-fibrotics have sufficient disease severity at baseline in order to maximize the chance of detecting a true treatment difference in an efficient manner. Furthermore, these patients arguably have the most to gain through administration of anti-fibrotic therapy and avoidance of surgery. We however respectfully disagree with the notion that an inability to pass a stricture with an endoscope is a more objective measure of severity compared to cross sectional imaging definitions because this definition is naturally confounded by operator related factors. We note that this approach has previously been documented to have poor reliability during the validation of endoscopic indices for Crohn's disease[7].

CORRESPONDENCE: Dr. Florian Rieder, Department of Gastroenterology, Hepatology and Nutrition, Digestive Diseases and Surgery Institute, 9500 Euclid Avenue – NC22, Cleveland, OH, 44195; Phone: ++49 941 9440; Fax: ++49 941 944 7036; riederf@ccf.org.

AUTHORSHIP

Development of the study concept and design: FR, BGF and VJ; Drafting of the manuscript: FR, BGF and VJ. All authors performed critical revision of the manuscript for intellectual content and approved the final draft.

DECLARATIONS OF PERSONAL AND FINANCIAL INTERESTS

The authors' declarations of personal and financial interests are unchanged from those in the original article[2].

Bouhnik and colleagues in the CREOLE trial selected relief of obstruction-related symptoms as one of their endpoints[5]. Our consensus panel recommended a co-primary endpoint criterion should be selected consisting of recurrence or worsening of clinical symptoms and documented intestinal obstruction on magnetic resonance enterography (MRE), with inclusion of experimental sequences signaling the need for endoscopic intervention or surgery[2]. We agree with Professor. Kamm's opinion that symptom relief or worsening may be an endpoint sensitive to change with therapy. However, a validated patient reported outcome (PRO) instrument specific for stricturing CD is not available. MRE was considered the preferred imaging modality due to high specificity and sensitivity and lack of radiation exposure[2]. This assessment does not discount the role of abdominal ultrasound in the scenario of routine clinical care, but rather weights the appropriateness of imaging modalities for clinical trial endpoints.

Taken together, the development of a pathway towards testing anti-fibrotics in CD is a major unmet need. The CONSTRICT study group has established stricture definitions, defined optimal diagnostic tools, and proposed clinical trial endpoint configurations which may be acceptable to regulators. Nascent projects by the group focus on index development for PRO, radiology and histopathology to provide the necessary building blocks for testing anti-fibrotic drugs in CD.

ACKNOWLEDGEMENTS

All authors approved the final version of the manuscript. This work was supported by grants from the National Institutes of Health [T32DK083251, P30DK097948 Pilot, K08DK110415] (held by FR).

REFERENCES

1. Kamm M Editorial: treating inflammatory bowel disease strictures. Aliment Pharmacol Ther 2018; in press.
2. Rieder F, Bettenworth D, Ma C, et al. An expert consensus to standardise definitions, diagnosis and treatment targets for anti-fibrotic stricture therapies in Crohn's disease. Aliment Pharmacol Ther 2018.
3. Vasilopoulos S, Kugathasan S, Saeian K, et al. Intestinal strictures complicating initially successful infliximab treatment for luminal Crohn's disease. Am J Gastroenterol 2000;95:2503.
4. Toy LS, Scherl EJ, Kornbluth A, et al. Complete bowel obstruction following initial response to infliximab therapy for Crohn's disease: a series of a newly described complication. Gastroenterology 2000;118(4):A569.
5. Lichtenstein GR, Olson A, Travers S, et al. Factors associated with the development of intestinal strictures or obstructions in patients with Crohn's disease. Am J Gastroenterol 2006;101(5):1030–8. [PubMed: 16606351]
6. Bouhnik Y, Carbonnel F, Laharie D, et al. Efficacy of adalimumab in patients with Crohn's disease and symptomatic small bowel stricture: a multicentre, prospective, observational cohort (CREOLE) study. Gut 2018;67(1):53–60. [PubMed: 28119352]
7. Khanna R, Zou G, D'Haens G, et al. Reliability among central readers in the evaluation of endoscopic findings from patients with Crohn's disease. Gut 2016;65(7):1119–25. [PubMed: 25935574]