HHS Public Access

Author manuscript

Clin Gastroenterol Hepatol. Author manuscript; available in PMC 2021 November 23.

Published in final edited form as:

Clin Gastroenterol Hepatol. 2021 July ; 19(7): 1491–1493.e3. doi:10.1016/j.cgh.2020.07.008.

Recycling of Precolectomy Anti-Tumor Necrosis Factor Agents in Chronic Pouch Inflammation Is Associated With Treatment Failure

Maia Kayal[*], **Thomas Lambin**[‡], **Michael Plietz**[§], **Anam Rizvi**[*], **Marlana Radcliffe**[*], **Sergey Khaitov**[§], **Patricia Sylla**[§], **Alexander J. Greenstein**[§], **Jean Frederic Colombel**[*], **Marla C. Dubinsky**[*], **Ryan C. Ungaro**[*]

[*]Division of Gastroenterology, Department of Medicine, Icahn School of Medicine at Mount Sinai, New York, New York

[‡]Division of Gastroenterology, Lille University Hospital, Lille, France

[§]Department of Surgery, Icahn School of Medicine at Mount Sinai, New York, New York

Despite improvements in medical management, 10%–15% of patients with ulcerative colitis (UC) require total proctocolectomy (TPC) with ileal pouch anal anastomosis (IPAA) for refractory disease.[1] Acute pouchitis is the most common post-IPAA inflammatory condition, with cumulative incidence of 45% at 5 years.[2] Up to 20%–30% of patients develop chronic pouch inflammation (CPI), categorized as antibiotic responsive, antibiotic refractory, or Crohn's disease–like (CDL).[3]

There is no current consensus regarding the medical management of CPI. Clinical response rates for CPI range from 20% to 60% with anti-tumor necrosis factor (TNF) therapy, from 50% to 80% with anti-interleukin therapy, and from 30% to 70% with anti-integrin therapy.[4–6] Therapies used post-IPAA for CPI are often the same as those used pre-TPC for refractory colitis. The utility of recycling prior therapies is uncertain.

The aim of this study was to assess if the effectiveness of biologic therapy for CPI differs among patients exposed to the same biologic class pre-TPC and post-IPAA.

Methods

This was a single center, retrospective study of patients 18 years of age or older with medically refractory UC who underwent TPC with IPAA complicated by CPI on biologic therapy. CPI included chronic pouchitis and CDL pouch inflammation, definitions are provided in Supplementary Material. The primary outcome of clinical remission was assessed by physician global assessment and incorporated improvement in symptoms

Reprint requests Address requests for reprints to: Maia Kayal, MD, The Henry D. Janowitz Division of Gastroenterology, Icahn School of Medicine at Mount Sinai, One Gustave L. Levy Place, PO Box 1069, New York, New York 10029. maia.kayal@mountsinai.org; fax: (347) 328-3419.

Supplementary Material

Note: To access the supplementary material accompanying this article, visit the online version of *Clinical Gastroenterology and Hepatology* at www.cghjournal.org, and at https://doi.org/10.1016/j.cgh.2020.07.008.

(frequency, urgency, hematochezia, abdominal or pelvic pain), endoscopy when available (ulcerations), and laboratory indices when available (C-reactive protein, erythrocyte sedimentation rate) assessed at 12 months after biologic initiation. Secondary outcomes included endoscopic improvement of pouch ulceration by 12 months after biologic initiation and pouch failure at any time during follow-up. Description of statistical analysis is provided in Supplementary Material.

Results

A total of 83 patients on biologic therapy for CPI were identified. Patient demographics and disease characteristics are presented in Table 1. Forty-four (53.0%) patients used anti-TNF therapies for UC before TPC. In all 44 patients, anti-TNF failure was deemed secondary to mechanistic loss of response based on drug concentration and anti-drug antibody testing. For CPI, adalimumab was initiated in 43 (51.8%) patients, infliximab in 24 (28.9%), vedolizumab in 7 (8.4%), ustekinumab in 6 (7.2%), and certolizumab in 3 (3.6%). All patients on biologics were previously refractory to antibiotics or steroids for treatment of CPI.

Among the 30 (36.1%) patients in clinical remission, 12 (38.7%) were on adalimumab, 10 (32.3%) on infliximab, 4 (12.9%) on ustekinumab, and 4 (12.9%) on vedolizumab. Outcome rates stratified by biologic type are provided in Supplementary Figure 1. Full univariable and multivariable results for clinical remission, endoscopic remission, and pouch failure are provided in Supplementary Table 1. On univariable and multivariable analysis, patients exposed to anti-TNF agents pre- and postcolectomy were less likely to experience clinical remission compared with those who were anti-TNF agent–naïve precolectomy or exposed to a different class postcolectomy (adjusted odds ratio [OR]: 0.20; 95% confidence interval [CI], 0.06–0.61). Age, sex, and pouch duration were not significantly associated with clinical remission. Endoscopic data within 12 months of biologic initiation were available for 45 (54.2%) patients, and improvement occurred in 11 (24.4%). On univariable and multivariable analysis, exposure to anti-TNF agents pre- and postcolectomy was associated with less endoscopic improvement of CPI, although this did not reach statistical significance (adjusted OR: 0.66; 95% CI, 0.11–4.08). Pouch failure occurred in 16 (19.3%) patients a median 1.22 (IQR, 0.74–3.39) years after biologic initiation. On univariable and multivariable analysis, patients who recycled anti-TNF postcolectomy were more likely to experience pouch failure compared with those who were anti-TNF agent naïve preoperatively or exposed to a different biologic class postoperatively (OR, 4.9; 95% CI, 1.34–18.13).

Discussion

Approximately 40% of patients on biologic therapy for CPI achieved clinical remission in this single-center study. Patients exposed to anti-TNF pre-TPC and post-IPAA were less likely to experience clinical remission and more likely to experience pouch failure compared with those who were biologic naïve preoperatively or exposed to a different class postoperatively.

Previous studies have noted higher rates of adverse events related to immunogenicity in patients exposed to anti-TNF agents pre-TPC and post-IPAA, and higher rates of postoperative CD recurrence in patients exposed to anti-TNF agents pre– and post–small bowel resection.[78] In this study, the decreased rates of clinical remission and increased rates of pouch failure among patients with CPI exposed to the same biologic class are likely related to mechanistic loss of response and transformation of the disease target, rather than immunogenicity, because most patients were on a different anti-TNF agent pre-TPC and post-IPAA.

Our data suggest that selection of biologic therapy for CPI should take into consideration previous class exposure, and initiation of an alternative biologic class may be warranted.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Funding

Thomas Lambin is supported by a grant from the Digest Science Foundation (Lille, France). Ryan C. Ungaro is supported by a National Institutes of Health K23 Career Development Award (K23KD111995-01A1).

Conflicts of Interest

Thomas Lambin has received travel accommodations from Adacyte Therapeutics. Jean Frederic Colombel has served as a consultant for AbbVie, Amgen, Arena Pharmaceuticals, Boehringer Ingelheim, Celgene Corporation, Celltrion, Eli Lilly, Enterome, Ferring Pharmaceuticals, Genentech, Janssen Pharmaceuticals, Landos, Ipsen, Medimmune, Merck, Novartis, Pfizer, Shire, Takeda, and Tigenix; and received research grants from AbbVie, Janssen, and Takeda. Marla C. Dubinsky has served as a consultant for Janssen, Takeda, Pfizer, Celgene, and AbbVie; and received research grants from Pfizer and AbbVie. Ryan C. Ungaro has served as an advisory board member or consultant for Janssen, Pfizer, and Takeda; and received research grants from AbbVie, Boehringer Ingelheim, and Pfizer. The remaining authors disclose no conflicts.

References

1. Fumery M, Singh S, Dulai PS, et al. Natural history of adult ulcerative colitis in population-based cohorts: a systematic review. Clin Gastroenterol Hepatol 2018;16:343–356.e3. [PubMed: 28625817]
2. Ferrante M, Declerck S, De Hertogh G, et al. Outcome after proctocolectomy with ileal pouch-anal anastomosis for ulcerative colitis. Inflamm Bowel Dis 2008;14:20–28. [PubMed: 17973304]
3. Shen B. Acute and chronic pouchitis–pathogenesis, diagnosis and treatment. Nat Rev Gastroenterol Hepatol 2012;9:323–333. [PubMed: 22508158]
4. Colombel JF, Ricart E, Loftus EV Jr, et al. Management of Crohn's disease of the ileoanal pouch with infliximab. Am J Gastroenterol 2003;98:2239–2244. [PubMed: 14572574]
5. Weaver KN, Gregory M, Syal G, et al. Ustekinumab is effective for the treatment of crohn's disease of the pouch in a multicenter cohort. Inflamm Bowel Dis 2019;25:767–774. [PubMed: 30295784]
6. Gregory M, Weaver KN, Hoversten P, et al. Efficacy of vedolizumab for refractory pouchitis of the ileo-anal pouch: results from a multicenter US cohort. Inflamm Bowel Dis 2019; 25:1569–1576. [PubMed: 30810748]
7. Verstockt B, Claeys C, De Hertogh G, et al. Outcome of biological therapies in chronic antibiotic-refractory pouchitis: a retrospective single-centre experience. United European Gastroenterol J 2019;7:1215–1225.
8. Collins M, Sarter H, Gower-Rousseau C, et al. Previous exposure to multiple anti-TNF is associated with decreased efficiency in preventing postoperative Crohn's disease recurrence. J Crohns Colitis 2017;11:281–288. [PubMed: 27578800]

Table 1.

Patient Demographics and Disease Characteristics (N = 83)

Age at time of biologic initiation, y	36.8 (27.7–47.4)
Pouch duration at time of biologic initiation, y	3.76 (1.3–7.0)
Sex	
Male	49 (59.0)
Female	34 (41.0)
Tobacco use	
Former	11 (13.3)
Current	4 (4.8)
Never	68 (81.9)
Precolectomy biologic type[a]	44 (53.0)
Infliximab	36 (81.8)
Adalimumab	7 (15.9)
Golimumab	1 (2.23)
Precolectomy immunomodulator use	49 (59.0)
Post-IPAA biologic use indication	
CDL pouch inflammation	64 (77.1)
Chronic antibiotic refractory pouchitis	19 (22.9)
Post-IPAA biologic type	83 (100)
Infliximab	24 (28.9)
Adalimumab	43 (51.8)
Vedolizumab	7 (8.4)
Ustekinumab	6 (7.2)
Certolizumab	3 (3.6)
Post-IPAA immunomodulator use	18 (21.7)
Post-IPAA immunomodulator discontinuation	36 (73.5)
Length of follow-up, y	3.0 (1.5–5.0)
Clinical remission	30 (36.1)
CDL pouch inflammation	21 (70)
Chronic pouchitis	9 (30)
Pouch failure	16 (19.3)
CDL pouch inflammation	12 (75)
Chronic pouchitis	4 (25)

NOTE. Values are median (interquartile range) or n (%).

CDL, Crohn's disease–like; IPAA, ileal pouch anal anastomosis.

[a]Two patients were on 2 biologics precolectomy, both pre- and postoperative biologics were within a different class.