Digestive Diseases and Sciences (2022) 67:5220–5226
https://doi.org/10.1007/s10620-022-07440-9

ORIGINAL ARTICLE

Relationship Between Stages of Ileal Pouch-Anal Anastomosis, Timing of Restoration of Fecal Continuity, and Pouchitis

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Received: 23 September 2021 / Accepted: 7 February 2022 / Published online: 5 March 2022

Abstract

Background The most common complication following ileal pouch-anal anastomosis (IPAA) in patients with ulcerative colitis (UC) is pouchitis.

Aims We aimed to investigate whether a shorter period between pouch creation and restoration of fecal flow through an IPAA was associated with an increased risk of development of pouchitis within the first 2 years after IPAA.

Methods We performed a retrospective cohort study evaluating patients undergoing colectomy with IPAA for UC between January 1, 2004 and December 31, 2016. We used Kaplan–Meier testing and Cox Proportional Hazards Modeling to evaluate the relationship between the time between restoration of fecal continuity and time to subsequent development of pouchitis, adjusting for other clinical and demographic factors.

Results We identified 624 patients who underwent proctocolectomy with IPAA for UC, of whom 246 (39%) developed pouchitis within the first 2 years after IPAA. There was no difference when comparing the median time to restoration of continuity among those patients who developed pouchitis and those who did not (49 days vs. 49 days, $p=0.85$) or in multivariable analysis. Primary sclerosing cholangitis (Hazard Ratio [HR] 2.14, 95% CI 1.12–4.08), family history of inflammatory bowel disease (HR 1.49, 95% CI 1.08–2.06), and delayed pouch creation (HR 0.75, 95% CI 0.57–1.00) were significantly associated with time to development of pouchitis.

Conclusion Although a staged approach to IPAA may have benefits in the surgical management of UC, the timing interval between pouch creation and restoration of continuity did not impact the subsequent development of early pouchitis in this cohort.

Keywords Stage · Surgery · Inflammatory bowel disease · Ileal pouch-anal anastomosis · Delayed pouch

Introduction

Pouchitis is the most common complication following proctocolectomy with ileal pouch-anal anastomosis (IPAA) for ulcerative colitis (UC), affecting 40% of patients within the first year after IPAA [1] and up to 80% of patients within 30 years [2, 3]. Despite the high incidence and prevalence of pouchitis symptoms, risk factors for the development of pouchitis are poorly understood. Known risk factors include but are not limited to primary sclerosing cholangitis, [4–6]

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extraintestinal manifestations [7] and post-operative NSAID use [5]. The impact of surgical factors on the development of pouchitis remains an important area of clinical and research interest given the substantial impact of pouchitis and other pouch-related disorders.

Although restorative proctocolectomy with an IPAA is the most common surgical approach in patients with UC, [8] surgical decision making is often individualized. The surgeon may opt to create the pouch at the time of proctocolectomy or delay pouch creation until a subsequent surgery. Debate continues with regards to the necessity of delaying pouch construction, as used in a 3-stage or modified 2-stage approach to IPAA. Additionally, in the modified 2-stage approach, where the patient undergoes a total abdominal colectomy in the first stage with an end-ileostomy, the IPAA is created in the second stage without a diverting loop ileostomy [9]. Each of these decisions offers a different approach to potentially protecting the anastomotic site and allowing post-operative healing prior to the restoration of fecal continuity. A 2018 study by Kochar et al. [10] suggested that delayed pouch creation offers substantial benefits, including a lower 30-day adverse event rate in patients with delayed pouch creation. However, a 2021 study that included 371 children with UC undergoing IPAA showed no difference in adverse events between children undergoing early and late pouch creation [11]. The contrasting results of these studies outlines the lack of consensus regarding the best practice for timing of pouch construction.

In addition to short term complications in the perioperative setting, there are debates as to whether the surgical decision making regarding timing and stages of IPAA affects long-term complications such as pouchitis. Over time, significant shifts in the bacterial population of the pouch have been noted after proctocolectomy with IPAA, with significant differences also being noted when comparing samples from patients with UC with an ileostomy to those of patients with an IPAA [12]. These changes in the microbiota have been associated with significant differences in the risk of developing pouchitis among patients with an IPAA [13–15]. In patients undergoing IPAA, differences in the microbiota may be present even prior to colectomy, and may be a risk factor for future development of pouchitis [15]. However, it is not known whether the timing between surgical stages, and in particular, the time to restoration of fecal flow, accentuates or modifies these differences in the microbiota and the future risk of pouchitis.

Given these questions, we sought to examine the relationship between the staged approach to IPAA at our center and development of pouchitis. Specifically, our study aimed to investigate whether a shorter period between pouch creation and restoration of fecal flow through an IPAA (restoration of continuity) was associated with an increased risk of development of early pouchitis, defined as pouchitis occurring within the first 2 years of IPAA. In examining these relationships, we hypothesized that a delayed pouch creation would have decreased rates of pouchitis, and that longer delays between restoration of continuity may also impact pouchitis rates.

Methods

Patient Selection

We identified patients who underwent restorative proctocolectomy with IPAA for UC between January 1, 2004 and December 31, 2016 at the University of North Carolina at Chapel Hill (UNC). To be eligible for the study, patients were required to meet the following criteria: (1) age $\geq$ 18 years, (2) history of proctocolectomy with IPAA for UC at UNC during the study period, and (3) at least 2 years of complete follow-up after IPAA surgery. Any patient that did not have a full 2 years of follow-up after IPAA was excluded from the study. Additionally, any patient with a preoperative diagnosis of Crohn's disease (CD) or IBD-unclassified at the time of colectomy was excluded. All included patients had a J-pouch; no other conformations of an IPAA were included. Eligible patients were identified utilizing the Carolina Data Warehouse for Health (CDW-H). The CDW-H is a data repository that contains clinical and administrative data from electronic health records (EHR). We extracted pertinent clinical, demographic, and laboratory data from the EHR using a standardized case extraction form.

Outcomes of Interest

The primary outcome of this study was the development of pouchitis within the first 2 years after the final stage of IPAA surgery for UC. The 2-year time period was based on prior studies utilizing similar time assessments [16, 17], as well as the belief that any association between the time period between pouch creation and fecal restoration and the development of pouchitis would have the greatest impact in the early period after IPAA (as opposed to late-onset pouchitis). A diagnosis of pouchitis was based on clinical symptoms including frequency, urgency, abdominal pain, and a sense of malaise [18] as well as response to therapy. At least two of three expert gastroenterologists (ELB, BK, or HHH) reviewed the charts of all included patients to determine the clinical diagnosis of pouchitis. If a discrepancy existed between reviewers, the case was automatically re-reviewed with the assistance of a third reviewer to resolve any differences and make a final determination on the clinical diagnosis of pouchitis. The inter-rater and intra-rater reliability of the assessment of pouchitis was assessed using kappa

statistics and intra-class coefficients (ICCs) as directed by the Landis and Koch benchmarks (< 0.00 = poor, 0–0.2 slight, 0.21–0.40 fair, 0.41–0.60 moderate, 0.61–0.80 substantial, 0.81–1.00 almost perfect) [19]. In the assessment of inter-rater reliability, the kappa was 0.70 (95% Confidence Interval [CI] 0.64–0.76) indicating substantial agreement. For intra-rater reliability, the kappa was 0.86 (95% CI 0.76–0.96) indicating almost perfect agreement. Only the first episode of pouchitis was evaluated; we did not evaluate the development of chronic inflammatory conditions of the pouch in this study, including chronic antibiotic dependent pouchitis, chronic antibiotic refractory pouchitis, or Crohn's-like disease of the pouch in this study.

We performed multiple secondary analyses to further evaluate these relationships. Given that many definitions include endoscopic confirmation of pouchitis in the diagnostic algorithm, we performed a secondary analysis to evaluate the correlation between a clinical diagnosis of pouchitis and endoscopic findings of pouchitis within the pouch body based on the endoscopic subscore of the pouchitis disease activity index (edema, friability, granularity, loss of vascularity, mucus exudate, and ulcerations [18]. This secondary analysis was performed among patients with available pouchoscopy data at the time of pouchitis diagnosis. In a separate analysis, we evaluated the development of pouchitis among only those patients who underwent a diverting ileostomy as part of their staged approach to IPAA (2-, 3-, and modified 2-stage approaches). We also evaluated the relationship between time period of surgery and the risk of pouchitis, controlling for other factors.

Exposures of Interest

The primary exposures of interest in this study were centered on the surgical approach to IPAA in our patient population. This included the number of stages used in IPAA surgery and the time between IPAA and restoration of fecal flow. In our analyses, a 1-stage procedure was defined as a total proctocolectomy with IPAA construction, without a diverting ileostomy. A traditional 2-stage IPAA was defined as a total proctocolectomy IPAA with loop ileostomy followed by an ostomy takedown. Based on definitions utilized at our center, a modified 2-stage IPAA was defined as follows: a total abdominal colectomy with end ileostomy is completed in the first operation and after a recovery interval, a second surgery is performed including completion proctectomy and IPAA (without a diverting loop ileostomy) [9]. A 3-stage approach was defined as a total abdominal colectomy with end ileostomy followed by a completion proctectomy and IPAA (with a diverting loop ileostomy) and subsequent ileostomy closure. In all analyses, delayed pouch creation was defined as the use of a modified 2-stage or 3-stage approach to IPAA surgery.

Covariates

We examined the EHR of each patient to extract demographic and clinical factors that might be associated with the development of pouchitis. These factors included disease extent, a concomitant diagnosis of primary sclerosing cholangitis (PSC), and the number and types of medications used prior to colectomy.

Statistical Analysis

Continuous variables were summarized using median and interquartile range (IQR) and compared using the Wilcoxon-Rank-Sum test. Categorical variables were expressed as proportions and compared using Fisher's exact and Chi-square testing as appropriate. We used Kaplan–Meier testing and Cox Proportional Hazards Modeling to evaluate the relationship between the time between stages of surgery (evaluated in quartiles of the total study population) and time to subsequent development of pouchitis, adjusting for other clinical, and demographic factors. All covariates included in the Cox Proportional Hazard Modeling were identified a priori based on suspected association with disease activity in ulcerative colitis preoperatively or the subsequent development of pouchitis after IPAA. All statistical analyses were performed using SAS (version 9.4) statistical software (SAS Institute, Cary, NC, USA). The study protocol was approved by the Institutional Review Board at UNC.

Results

Development of Pouchitis

A total of 624 patients were identified who underwent restorative proctocolectomy with IPAA for UC during the study period. Among all patients in the cohort, 52% were male and the median age at the time of surgery was 40.6 years (IQR 29.5–52.5). During the first 2 years after IPAA, 246 (39.4%) patients developed pouchitis. Patients who developed pouchitis were significantly more likely to have a family history of CD or UC than patients without pouchitis (21.2% vs. 13.8%, $p = 0.02$, Table 1). All patients diagnosed with pouchitis were treated with ciprofloxacin, metronidazole, or a combination of these antibiotics per the standard protocol of the UNC Multidisciplinary Pouch Clinic.

Surgical Decision Making and Pouchitis

In the assessment of the impact of surgical decision making and the development of pouchitis, the number of stages involved in IPAA surgery was significantly associated with the development of pouchitis (Table 2). Patients undergoing

Table 1 Univariate comparison of demographic and clinical characteristics of patients with and without pouchitis in the 2 years following an ileal pouch-anal anastomosis

	Patients without pouchitis ($n=378$)		Patients with pouchitis ($n=246$)		p value
	n	%	n	%	
Age at surgery, in years (Median, IQR)	41.2	28.6–51.9	42.5	30.7–54.3	0.11
Disease duration prior to surgery (Median, IQR)	9.8	2.2–15.31	9.8	2.21–13.1	0.98
Male Sex	200	52.9	123	50	0.47
Race	326	86.2	218	88.6	0.53
White	52	13.8	28	11.3	
Non-White					
Hispanic	6	1.6	7	2.9	0.56
Family history of CD or UC	49	13	48	19.5	0.04
Indication for surgery	296	78.3	197	80.1	0.55
Medically-refractory colitis	55	14.6	28	11.4	
Dysplasia or cancer	27	70.1	21	8.5	
Other indication					
Disease extent prior to surgery	17	4.8	9	3.9	0.22
Proctitis	95	26.9	78	33.5	
Left-sided colitis	241	68.3	146	62.7	
Extensive colitis					
Abscess or pelvic sepsis after IPAA surgery	70	18.5	46	18.7	0.95
Evidence of an IPAA leak immediately after surgery	28	7.4	18	7.3	0.96
Primary Sclerosing Cholangitis	8	2.1	11	4.5	0.09
Medications Prior to Colectomy					
Systemic aminosalicylate	291	77	204	82.9	0.07
Topical aminosalicylate	174	46	127	51.6	0.17
Thiopurine	225	59.5	165	67.1	0.06
Methotrexate	43	11.4	24	9.8	0.52
Anti-TNF	195	51.6	125	50.8	0.85
Vedolizumab	7	1.9	10	4.1	0.10
Cyclosporine	12	3.2	14	5.7	0.12
Prednisone use at the time of last stage of surgery	149	39	101	41	0.63

Anti-tumor necrosis factor alpha (anti-TNF); Crohn's disease (CD); ileal pouch-anal anastomosis (IPAA); interquartile range (IQR); ulcerative colitis (UC)

Table 2 Comparison of surgical approach among patients who developed pouchitis and those who did not after ileal pouch-anal anastomosis for ulcerative colitis

	Patients without pouchitis ($n=378$)		Patients with pouchitis ($n=246$)		p value
	n	%	n	%	
Type of IPAA Surgery	75	19.9	41	16.7	0.03
1-Stage (n = 116)	119	31.6	105	42.7	
2-Stage ($n=224$)	153	40.6	79	32.1	
Modified 2-Stage (n = 232)	30	8	21	8.5	
3-Stage ($n=51$)					
Delayed Pouched Creation[a]	183	48.5	100	40.7	0.05
Time between pouch creation and fecal restoration of fecal flow (in days, median, IQR)	49	0–80	49	41–77	0.85

Ileal pouch-anal anastomosis (IPAA); interquartile range (IQR)

[a]Delayed pouch creation defined as a modified 2 stage or 3 stage approach to ileal pouch-anal anastomosis

a traditional 2 stage procedure demonstrated the highest rate of pouchitis within the first 2 years after IPAA (47%). Additionally, those patients undergoing delayed pouch creation (modified 2-stage or 3-stage IPAA) demonstrated less pouchitis than patients without delayed pouch creation 35% vs. 43%, $p=0.045$). Additionally, when excluding patients with a 1-stage procedure and comparing only patients the modified 2-stage or 3-stage IPAA to those with a traditional 2-stage IPAA, those patients with a delayed pouch procedure still demonstrated less pouchitis (35% vs. 47%, $p=0.007$) The median time between IPAA and restoration of fecal flow was 49 days (IQR 33.5–78.5) among all patients in the cohort, with no significant difference among patients who developed pouchitis and those who did not (median 49 vs. 49 days, $p=0.85$). When analyzing the number of days between pouch creation and restoration of fecal flow in quartiles, there was also no significant difference in the rate of pouchitis ($p=0.63$).

There was also no significant difference when evaluating the relationship between the timing of restoration of fecal flow and the time to development of pouchitis when analyzed via Kaplan–Meier testing (Fig. 1). Similarly, there was no significant association between the timing of restoration of fecal flow and the time to development of pouchitis in a Cox-Proportional Hazards model adjusting for other potential factors. However, the other factors thought to influence the development of pouchitis were significantly associated with the time to development of pouchitis including delayed pouch creation (Hazard Ratio [HR] 0.75, 95% CI 0.57–1.00), PSC (HR 2.14, 95% CI 1.12–4.08), and a family history of CD or UC (HR 1.49, 95% CI 1.08–2.06, Table 3).

Secondary Analyses

In a secondary analysis removing patients with 1-stage IPAAs, there remained no significant difference between the timing of restoration of fecal flow and the risk for development of pouchitis. Multiple previously identified risk factors remained significantly associated with increased risk for development of pouchitis in this analysis, including delayed pouch formation and a diagnosis of primary sclerosing cholangitis (Supplemental Table 1). There was no difference in the rate of pouchitis when evaluating the time period of surgery, evaluating all patients undergoing IPAA (Supplemental Table 2) and when removing patients with 1-stage IPAAs (Supplemental Table 3).

Among the 246 patients who developed pouchitis, 124 (50%) had a pouchoscopy available at the time of pouchitis diagnosis. Of these, all 124 had both clinical symptoms and corresponding findings on pouchoscopy to confirm a diagnosis of pouchitis. An additional 27 patients underwent

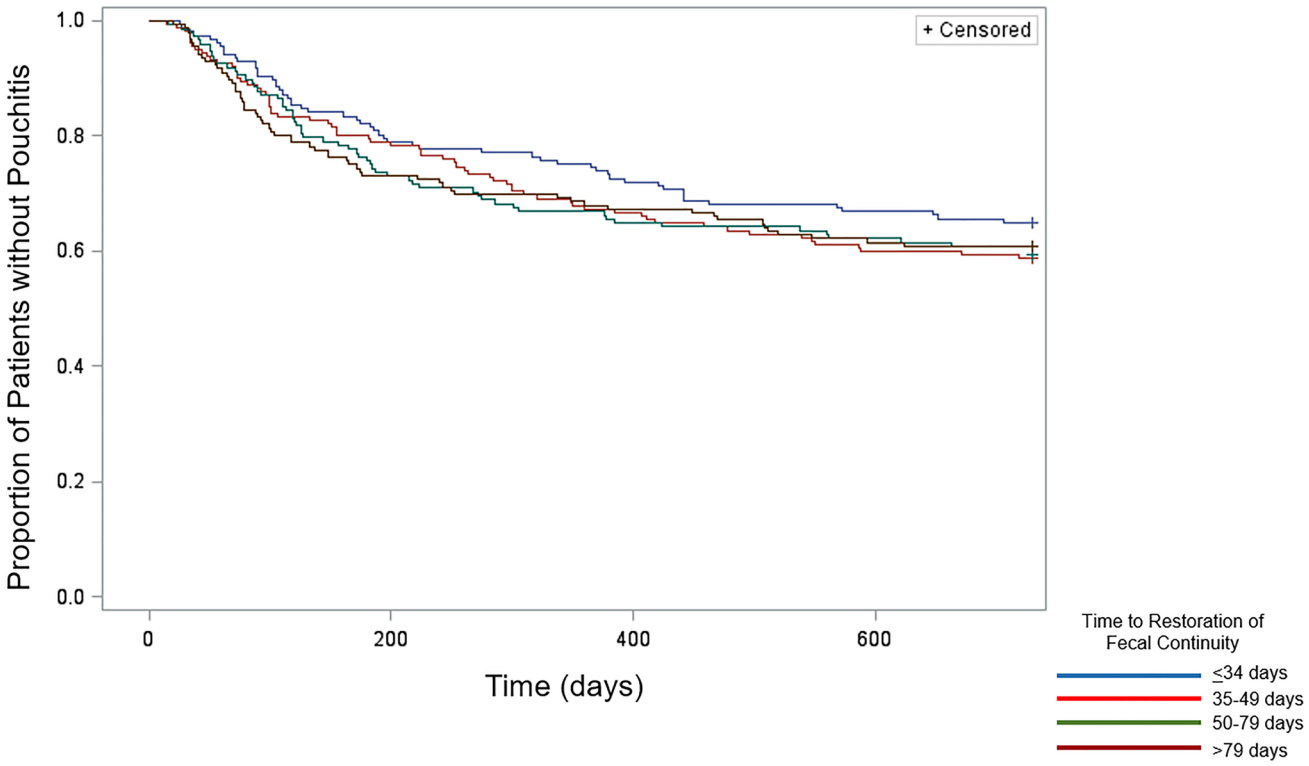

Fig. 1 Time to development of pouchitis, with patients grouped in quartiles by time between pouch creation and restoration of fecal flow through ileal pouch-anal anastomosis

Table 3 Risk for development of pouchitis within the first 2 years following an ileal pouch-anal anastomosis

	Hazard ratio	95% CI
Delayed pouch creation[a]	0.75	0.57–1.00
Time between pouch creation and restoration of fecal flow evaluated in quartiles	0.70 0.95	0.47–1.05 0.71–1.51
0–34 days	Reference	Reference
35–49 days	1.00	0.69–1.37
50–79 days		
> 79 days		
Family history of Crohn's disease or ulcerative colitis	1.49	1.08–2.06
Primary sclerosing cholangitis	2.14	1.12–4.08

All factors included in the Cox-Proportional Hazards model are shown above

[a]Delayed pouch creation defined as a modified 2 stage or 3 stage approach to ileal pouch-anal anastomosis

pouchoscopy during the study period, of whom only 2 had endoscopic evidence of pouchitis with no clinical symptoms.

Discussion

In this retrospective evaluation of over 600 patients undergoing proctocolectomy with IPAA for UC, we demonstrated that patients undergoing a delayed pouch creation, defined as using a 3-stage or modified 2-stage surgical approach, were less likely to develop pouchitis in the first 2 years after IPAA than those patients without delayed pouch creation. However, the time between pouch creation and restoration of fecal continuity was not associated with the development of early pouchitis. Taken together, these findings would suggest that a delayed pouch creation is a more important factor in preventing pouchitis than the ultimate timing of ileostomy takedown and restoration of continuity. In addition to these examinations of surgery-related factors, we also confirmed previously demonstrated associations between clinical risk factors and the development of pouchitis, including an increased risk of pouchitis among patients with a concomitant diagnosis of PSC.

Our findings build on prior literature including a 2008 study by Hoda et al. examining 237 patients with UC that underwent total colectomy with subsequent IPAA. In this analysis, they found that a 2-stage IPAA demonstrated a numerically but non-statistically significant association with increased risk for development of pouchitis [20]. Perhaps more pertinent to our current study, the authors also found that the duration of diverting ileostomy after pouch formation had no association with the development of pouchitis ($p = 0.304$). Kochar et al. also noted that patients with pouch creation at the time of colectomy experienced higher rates of minor/major adverse events, readmissions, and reoperations in the first 30 days following surgery when compared to patients who had delayed pouch creation [10]. Although this study did not specifically examine pouchitis as an outcome, there was evidence of improved safety with delayed pouch creation.

Multiple prior authors have suggested that delayed pouch creation utilizing a modified-2 stage or 3-stage IPAA may be safer than a traditional 2-stage surgery, and preferred in the current management of patients with UC [10, 20, 21]. Luo et al. showed lower complication rates among adults undergoing the modified 2-stage surgical approach than those undergoing the traditional 2-stage approach. This was particularly significant in adult cohorts with less preoperative biologic exposure. They also suggested the 3-stage approach is over-utilized in adults with UC, resulting in increased costs and the risks associated with a diverting ileostomy.

It has been noted that there are significant shifts in the bacterial population of the pouch after IPAA for UC, [12] and it has been hypothesized that pouchitis is associated with decreased microbial diversity of the pouch [22]. Importantly, pouchitis only develops once fecal continuity has been restored [23, 24]. We reasoned that an increased length of time between diverting ileostomy and restoration of fecal continuity would lead to greater shifts in the bacterial population of the pouch, and hypothesized that this would cause increasing frequency of pouchitis in patients with greater duration of diverting ileostomy. Although we did not specifically analyze changes in the microbial composition among patients after IPAA, we found no significant relationship between pouchitis and time to restoration of fecal continuity, perhaps indicating that the timing of pouch creation is a more important risk factor for development of pouchitis.

Our study benefited from a relatively large sample size and the requirement of 2 years of complete follow-up for all included patients. However, our study does have limitations. All patient information was obtained via review of electronic medical records, and the amount of information available in each patient's chart was variable. Given the retrospective nature of this study, we were unable to account for the reasons behind surgical decision making. Data was collected on patients undergoing IPAA from 2003 to 2016. We were unable to account for improvements in surgical technique

over this time period, which could have skewed outcomes data towards patients that had surgery more recently. Lastly, all patients were seen at a single academic medical center, creating a possibility for selection bias.

In conclusion, we demonstrated that delayed pouch creation in the form of a modified 2-stage or 3-stage IPAA decreased the odds of developing pouchitis while the time between IPAA and restoration of fecal flow was not associated with the development of pouchitis. These findings add to the growing body of medical literature indicating improved safety outcomes with a modified 2-stage or 3-stage IPAA for UC. Given these findings, it would appear that the timing of the pouch creation itself, and not the timing of restoration of fecal flow, has the greatest impact on pouchitis rates, and these findings and the etiology of this relationship should be investigated in further large cohorts.

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s10620-022-07440-9.

Funding This research was supported by the National Institutes of Health [K23DK127157-01 (ELB)].

Declarations

Conflict of interest ELB has served as a consultant for AbbVie, Pfizer, and Target RWE. BK has served as a consultant for Pfizer. HHH has served as a consultant for Alivio, AMAG, Finch, Gilead, Lycera, Merck, Otsuka, Pfizer, PureTech, Seres and research support from Pfizer and Artizan Biosciences. GCS, JH, and SE have no relevant disclosures.

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