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ORIGINAL ARTICLE

Comparative Persistence of Non-tumor Necrosis Factor (TNF) vs. TNF Antagonists for Post-operative Prophylaxis in Crohn's Disease (CD)

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Abstract

Background The comparative safety and effectiveness of available biologics for post-operative prophylaxis in Crohn's disease (CD) is uncertain. Drug persistence may serve as a real-world proxy for tolerability and effectiveness. We evaluated the comparative persistence of non-TNF and TNF antagonists for post-operative prophylaxis and their comparative effectiveness for preventing early endoscopic post-operative recurrence (POR).

Methods We conducted a single-center, retrospective study of surgically naïve CD subjects undergoing ileocecal or small bowel resection between 1/1/2000 and 12/31/2021 and prescribed a biologic for post-operative prophylaxis. We compared the risk of prophylaxis failure (requiring recurrent surgery or discontinuation of therapy due to persistent POR despite optimized drug level or dose escalation, immunogenicity, and/or adverse event) and early endoscopic POR (Rutgeert's score $\geq$ i2 within 15 months postoperatively) between non-TNF and TNF antagonist prophylaxis using Cox proportional hazard and logistic regression, respectively, adjusting for demographic and disease characteristics.

Results The study included 291 subjects (81% TNF antagonists). After multivariable adjustment, non-TNF antagonist prophylaxis was associated with a significantly lower risk of prophylaxis failure than TNF antagonists (hazard ratio 0.26; 95% confidence interval (CI) [0.13–0.53]). Prophylaxis with non-TNF and TNF antagonists had similar risk of early endoscopic POR (odds ratio 0.66; 95% CI [0.32–1.36]). Stratifying the non-TNF antagonists by anti-integrin and anti-IL12/23 yielded similar results.

Conclusion In a cohort of surgically naïve CD subjects prescribed a biologic for post-operative prophylaxis, non-TNF antagonists had greater persistence than TNF antagonists with similar risk for early endoscopic POR. If confirmed by large, prospective studies, these findings can inform post-operative management strategies in CD.

Keywords Crohn's disease · Post-operative recurrence · Drug persistence · Comparative effectiveness · Post-operative prophylaxis

Introduction

Despite advances in therapeutics and disease monitoring in Crohn's disease (CD), post-operative recurrence (POR) remains an unresolved challenge with the contemporary risk of recurrent surgery stagnant at 31% [1]. Presently, there are two strategies to mitigate POR: early post-operative pharmacologic prophylaxis, where high-risk patients for POR start/restart CD-directed therapy within 4–6 weeks after surgery, and endoscopy-guided pharmacologic therapy, where an ileocolonoscopy is performed within 6–12 months after surgery and CD-directed therapy is prescribed based on evidence of recurrence [2]. While the comparative effectiveness of these strategies is uncertain, current societal guidelines favor early post-operative pharmacologic prophylaxis for most patients but recognize the risk of therapy-related adverse events may outweigh the risk of POR in subset of low risk individuals [3]. Since the pivotal PREVENT trial,

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guidelines recommend first-line post-operative prophylaxis with Tumor Necrosis Factor (TNF) antagonists [3, 4]. However, surgical CD patients are increasingly TNF antagonist experienced or intolerant, but guidelines do not provide guidance on the role of non-TNF antagonists for post-operative prophylaxis [3]. This reflects the lack of data characterizing the safety and effectiveness of non-TNF antagonists for prophylaxis and how they compare to TNF antagonists [5–7]. Considering recent data suggesting non-TNF antagonists have more favorable safety profiles than TNF antagonists [8, 9], defining the safety and effectiveness of non-TNF antagonists for post-operative prophylaxis, especially as they compare to TNF antagonists, has important implications for post-operative risk stratification and management of CD.

Due to a lack of head-to-head randomized clinical trials (RCT) of the available biologics in IBD and their limited study durations, real-world studies play an important role for informing long-term safety and effectiveness of available therapies. Drug persistence can serve as a real-world proxy for the long-term tolerability (discontinuation of therapy due to adverse events) and effectiveness of a drug. Drug persistence is defined as the duration an individual remains on a prescribed therapy and assumes the individual continues the drug until it is no longer effective or develops an adverse event [10]. In IBD, several studies using this outcome have yielded important real-world evidence that have greatly informed our current practices, including data supporting concomitant immunomodulator therapy increases anti-tumor necrosis factor (TNF) agents persistence, first-line biologics have superior persistence to second-line agents, and HLA-DQQ1*05 decreases anti-TNF persistence [11, 12]. In fact, a recent study in active luminal IBD found non-TNF antagonists have superior drug persistence than TNF antagonists [12]. Drug persistence also has important implications for reducing healthcare expenditures in IBD [13]. In the context of post-operative prophylaxis, most of the available studies have limited follow-up of up to one year, so the long-term comparative tolerability and effectiveness of non-TNF and TNF antagonists are unclear. Drug persistence can help bridge this gap in knowledge. Therefore, we aim to evaluate the comparative persistence of non-TNF vs. TNF antagonists for post-operative prophylaxis in a cohort of surgically naïve CD patients. We also aim to evaluate the comparative effectiveness of non-TNF vs. TNF antagonists for preventing early endoscopic POR.

Methods

Study Population

We conducted a retrospective, single-center study of a cohort of surgical CD subjects enrolled in the Cedars-Sinai Medical Center (CSMC) MIRIAD Research repository (IRB #3358). From this cohort, we included subjects ≥ 16 years with ileal or ileocolonic disease with predominantly ileal disease (confirmed in most recent ileocolonoscopy prior to surgery by chart review) undergoing their first ileocecal or small bowel resection (ICR and SBR, respectively) between 1/1/2000 and 12/31/2021 and were prescribed a biologic for post-operative pharmacologic prophylaxis (Fig. 1). Colonic or colonic predominant ileocolonic CD was excluded to avoid confounding from potential differences in the disease biology compared to ileal predominant CD [14]. Post-operative prophylaxis was defined as a biologic started after the primary anastomosis or ileostomy reversal with restoration of bowel continuity without objective evidence by imaging or endoscopic exam demonstrating recurrence. Timing of post-operative prophylaxis was defined by when a subject received the first dose based on provider documentation. Subjects who discontinued their prophylaxis for the following reasons were excluded: self-discontinuation/poor adherence, insurance denial, de-escalation of therapy, and unknown reasons. Through manual chart review, reasons for discontinuation were classified as persistent POR (POR was defined according to standard clinical practices through imaging and ileocolonoscopy (Rutgeert's ≥ i2), and these diagnostics were sometimes ordered in response to elevated inflammatory markers to confirm presence of recurrence) despite optimized drug concentration level or dose escalation (in those without available drug levels), immunogenicity (defined as undetectable drug concentration level with detectable anti-drug antibodies in addition to stated reason for discontinuation by treating physician), and adverse events (i.e., infection, allergic reaction, infusion reaction, malignancy, or paradoxical immune reactions, such as TNF-induced psoriasis). Patients who had POR and found to have low drug level on reactive therapeutic drug monitoring and received dose escalation or had empiric dose escalation were followed until their IBD provider switched the individual to another biologic agent because of persistent POR. Of note, there were a small group of subjects ($n = 12$) who initially did not have POR (confirmed by ileocolonoscopy) on prophylaxis with a biologic but later developed POR and discontinued their biologic without dose optimization or available drug concentration and anti-drug antibody levels. As such, the reason for discontinuation was classified as indeterminate for these subjects. This study was approved by the Institutional Review Board at CSMC.

Exposure

Subjects were grouped into those on TNF antagonist (infliximab, adalimumab, or certolizumab) and non-TNF antagonist prophylaxis (anti-integrin or anti-IL12/23).

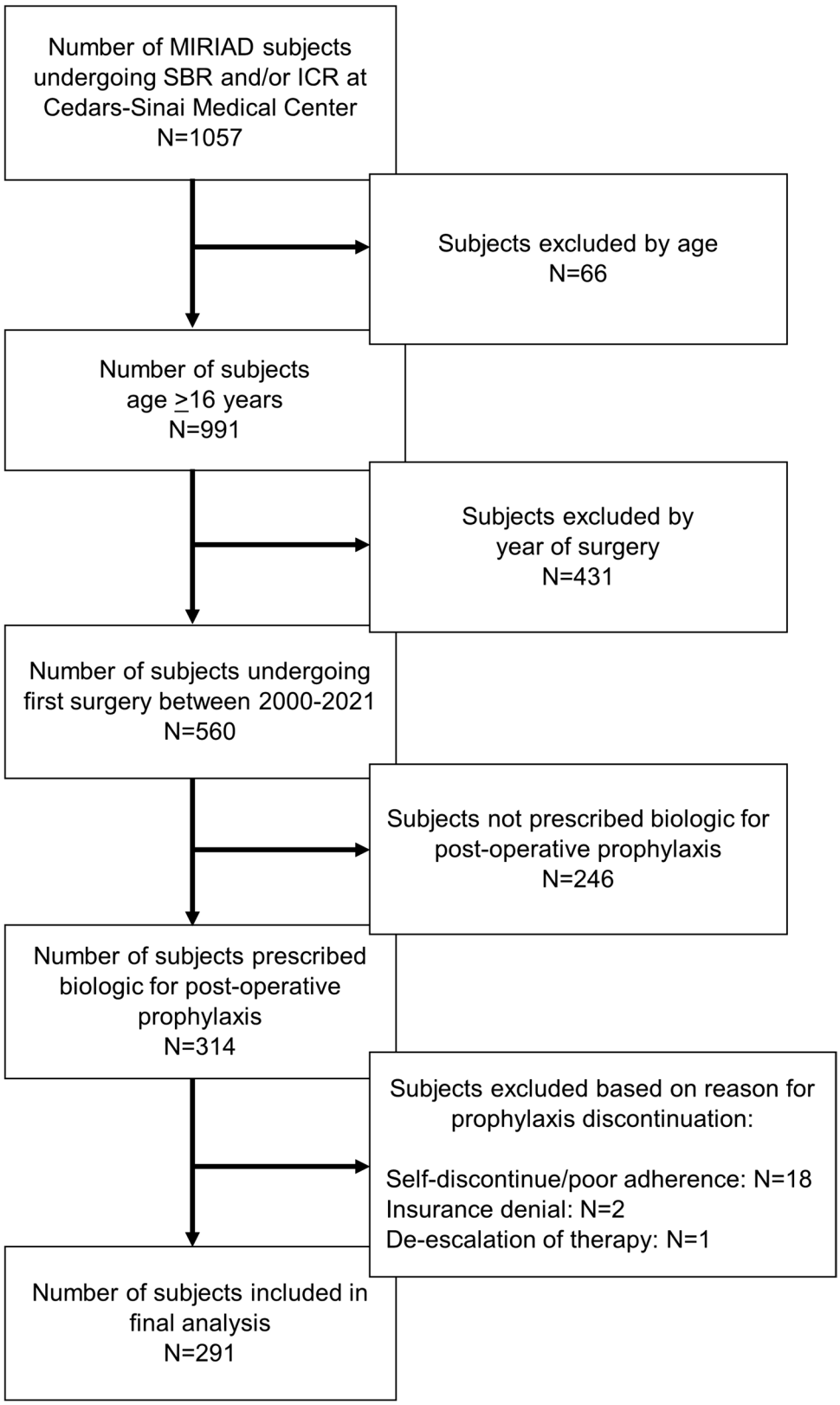

Fig. 1 Inclusion/exclusion flowchart

Outcomes

The primary outcome was time to prophylaxis failure, a composite outcome defined as requiring recurrent surgery for POR or discontinuation of therapy due to persistent POR despite optimized drug concentration level or dose escalation, immunogenicity, and/or adverse event. The secondary outcome was early endoscopic POR defined as Rutgeert's score ≥ i2 on the first endoscopic exam performed within 15 months after primary anastomosis or ileostomy reversal with restoration of bowel continuity [15]. Endoscopy reports were reviewed, and if a Rutgeert's score was not recorded, text and imaging were retrospectively applied by a trained IBDologist (PG). Due to evolving practice patterns during the study period, Rutgeert's score i2a and i2b were not routinely reported, and many endoscopy reports early in the study period did not provide adequate description to differentiate i2 into i2a or i2b, so they were not incorporated into the outcome definition for endoscopic POR. Patients were followed from time of starting post-operative prophylaxis until occurrence of primary study outcome, lost to follow-up, or study completion (12/31/2021).

Statistical Analysis

We used descriptive statistics to compare baseline demographic, disease, and treatment characteristics among subjects prescribed TNF and non-TNF antagonist prophylaxis. We performed Mann–Whitney *U* and χ [2] to compare continuous and categorical variables, respectively. To evaluate the comparative persistence of TNF and non-TNF antagonists, we performed a survival analysis using multivariable Cox proportional hazard regression adjusting for age, sex, CD disease duration, pre-operative smoking status, pre-operative biologic mechanism, and number of prior biologic exposures [16], which were determined a priori. Because changes in practice patterns over the study period is a potential confounding factor, we performed a sensitivity analysis excluding subjects who underwent surgery before 1/1/2014, which was the year vedolizumab was FDA approved for CD. Similarly, patient non-adherence to early post-operative colonoscopy could confound the results, so a sensitivity analysis was performed excluding patients who did not undergo a colonoscopy within 15 months postoperatively. To evaluate the comparative risk for early endoscopic POR between TNF and non-TNF antagonists, we performed a multivariable logistic regression, adjusting for age, sex, CD disease duration, pre-operative smoking status, and internal penetrating disease behavior, which were determined a priori. Stratified analyses comparing TNF antagonists to anti-integrins and anti-IL12/23, respectively, were performed for both outcomes. All statistical analyses were performed using SPSS (IBM Corp. Released 2016. IBM SPSS Statistics for Windows, Version 24.0. Armonk, NY: IBM Corp).

Results

Patient Characteristics

Of the 291 subjects included, 81% ($n=236$) were prescribed a TNF antagonist for post-operative prophylaxis. Of the 55 subjects prescribed non-TNF antagonist for post-operative prophylaxis, 18 were prescribed an anti-integrin and 37 anti-IL12/23. The median follow-up time was 55.7 months [interquartile range (IQR) 28.3–100.0], and the median time to start post-operative prophylaxis was 4.4 weeks (IQR 3.4–8.1) after surgery. Compared to TNF antagonist prophylaxis (Table 1), subjects prescribed a non-TNF antagonist for prophylaxis had longer disease duration ($p=0.001$), were less likely to be active smokers ($p=0.015$), less likely biologic naive ($p=3.02e^{-13}$), less pre-operative steroid use ($p=0.019$), and less likely to be prescribed a concomitant immunomodulator ($p=0.034$). Also, subjects prescribed non-TNF antagonist prophylaxis were more likely to use non-TNF antagonists preoperatively ($p=2.61e^{-30}$). There were no differences among subjects prescribed TNF and non-TNF antagonist prophylaxis regarding age at surgery ($p=0.76$), disease location ($p=0.62$), internal penetrating disease behavior ($p=0.89$), and time to start prophylaxis after surgery ($p=0.92$).

Comparative Persistence of Post-operative Pharmacologic Prophylaxis

On follow-up, 50.2% ($n=146$) subjects experienced prophylaxis failure with median time to prophylaxis failure of 88.9 weeks (IQR 38.0–206.9). The most common reason for prophylaxis failure was persistent POR despite optimized drug concentration level or dose escalation (43.8%, $n=64$) followed by adverse event (24.7%, $n=36$) and immunogenicity (18.5%, $n=27$, Table 2). There were 5 subjects prescribed TNF antagonist for prophylaxis who developed immunogenicity and an adverse event to the drug, so both were included as reasons for discontinuation. On multivariable Cox proportional hazard regression, subjects prescribed non-TNF antagonist prophylaxis were significantly less likely to experience prophylaxis failure than those prescribed TNF antagonists [adjusted hazard ratio (aHR) 0.26; 95% confidence interval (CI) (0.13–0.53), Fig. 2]. When stratifying non-TNF antagonists by drug mechanism, subjects prescribed anti-integrins (aHR 0.32; 95% CI [0.14–0.76]) and anti-IL12/23 (aHR 0.21; 95% CI [0.09–0.51]) for prophylaxis were significantly less likely to experience prophylaxis failure compared to those prescribed a TNF antagonist

Table 1 Differences between post-operative prophylaxis with non-TNF and TNF antagonists

Variable	TNF antagonist ($n=236$)	Non-TNF antagonist ($n=55$)	p value
Median age [years, interquartile range (IQR)]	28.5 (22.3–38.6)	33.0 (21.1–46.3)	0.755
Female, *n* (%)	119 (50.4)	25 (45.5)	0.507
European ancestry, *n* (%)	206 (87.3)	52 (94.5)	0.126
Median BMI at surgery (kg/m^2, IQR)	22.3 (19.0–26.1) Missing $n=68$	22.1 (18.4–24.3) Missing $n=4$	0.343
Median disease duration (months, IQR)	**65.3 (18.3–121.1)** Missing $n=4$	**106.6 (58.1–168.0)** Missing $n=0$	**0.001**
Median age at diagnosis (years, IQR)	21.8 (16.4–29.2) Missing $n=4$	20.7 (12.8–32.5) Missing $n=0$	0.225
Active smoking at surgery, *n* (%)	**23 (10.1)** Missing $n=8$	**0** Missing $n=1$	**0.015**
Crohn's disease location, *n* (%)			
Ileal (L1)	107 (45.3)	27 (49.1)	0.615
Ileocolonic (L3)	129 (54.7)	28 (50.9)	0.615
Upper GI (L4)	25 (10.6)	8 (14.5)	0.405
Crohn's disease behavior, *n* (%)			
Non-fibrostenosing, non-penetrating (B1)	18 (7.7)	2 (3.6)	0.292
Fibrostenosing (B2)	112 (47.7)	30 (54.5)	0.344
Internal penetrating (B3)	41 (17.4)	10 (18.2)	0.887
Fibrostenosing/penetrating (B2/3)	64 (22.2)	13 (23.6)	0.598
Perianal Crohn's disease, *n* (%)	48 (20.3)	16 (29.1)	0.158
No. of biologic exposures prior to immediate pre-operative biologic agent, *n* (%)*			
0	**175 (74.2)**	**12 (21.8)**	**3.02e^{-13}**
1	**53 (22.5)**	**19 (34.5)**	**0.061**
≥ 2	**8 (3.4)**	**24 (43.6)**	**8.56e^{-18}**
Pre-operative steroid use, *n* (%)	**71 (30.2)**	**8 (14.5)**	**0.019**
Pre-operative biologic mechanism, *n* (%)			**2.61e^{-30}**
None	**81 (34.5)**	**9 (16.4)**	
TNF antagonist	**152 (64.7)**	**15 (27.3)**	
Non-TNF antagonist	**2 (0.9)**	**31 (56.4)**	
Prophylaxis: concomitant immunomodulator	**51 (21.6)**	**5 (9.1)**	**0.034**
Azathioprine/6-mercaptopurine	37 (72.5)	1 (20.0)	–
Methotrexate	14 (27.5)	4 (80.0)	–
Surgical resection histopathology			
Median length of small bowel resected (cm, IQR)	23.5 (15.2–35.3) Missing $n=26$	20.1 (10.7–33.0) Missing $n=2$	0.086
Histologically clean resection margins, *n* (%)	153 (85.5) Missing $n=57$	43 (87.8) Missing $n=12$	0.684
Lymph node granuloma, *n* (%)	30 (16.9) Missing $n=58$	10 (20.0) Missing $n=13$	0.605
Median time to start prophylaxis postoperatively (weeks, IQR)	4.4 (3.5–7.9)	4.7 (2.9–8.6)	0.922
Early endoscopic POR, *n* (%)	61 (37.2) Missing $n=72$	14 (29.8) Missing $n=8$	0.350

Bold values indicate statistically significant differences between treatment groups

*Biologic agents used immediately prior to surgery were not counted due to difficulty ascertaining if subjects had true non-response or disease too advanced to respond to medical therapy and biologics used immediately preoperatively are often resumed postoperatively

Table 2 Comparative incidence of prophylaxis failure during the study period and reasons for prophylaxis failure with TNF vs. non-TNF antagonist prophylaxis

	TNF antagonist ($n=236$)	Non-TNF antagonist ($n=55$)	p value
Prophylaxis failure, n (%)	130 (55.1)	16 (29.1)	0.001
Reason for prophylaxis failure, n (%)			
Indeterminate	12 (9.3)	0	0.203
Failure despite optimized dose/drug level	55 (42.3)	9 (56.3)	0.289
Immunogenicity	25 (19.2)	2 (12.5)	0.317
Adverse event	34 (26.2)	2 (12.5)	0.232
Recurrent surgery	9 (6.9)	3 (18.8)	0.104

(Fig. 2). Sensitivity analyses after excluding subjects who underwent surgery before 2014 and after excluding subjects who did not undergo colonoscopy within 15 months of surgery yield similar results (Table 1, Supplementary Data Content). When comparing reasons for prophylaxis failure, TNF antagonist prophylaxis had nominally higher rates of adverse events (26% vs.12%, $p=0.232$) compared to non-TNF antagonist prophylaxis (Table 2). Among subjects who discontinued a TNF antagonist for adverse events, the most common adverse event was infection (23.5%, $n=8$) followed by infusion reaction to infliximab (20.6%, $n=7$, Table 2, Supplementary Data Content).

Comparative Effectiveness for Preventing Early Endoscopic POR

After their index surgery, 85.3% ($n=214$) subjects had an endoscopic exam within 15 months and 35.2% ($n=74$) of these subjects developed early endoscopic POR. Median time to first ileocolonoscopy was similar between the TNF antagonist and non-TNF antagonist groups (32.1 vs. 31.5 weeks, $p=0.84$). Of those with early endoscopic POR, 24.8% ($n=52$) had Rutgeert's score i2, 5.2% ($n=11$) i3, and 5.2% ($n=11$) i4. On multivariable logistic regression, non-TNF antagonist prophylaxis had similar risk for early endoscopic POR as TNF antagonist prophylaxis [adjusted odds ratio (aOR) 0.66; 95% CI (0.32–1.36), Fig. 3]. When stratifying non-TNF antagonists by drug mechanism, prophylaxis with anti-integrins [aOR 0.71; 95% CI (0.21–2.39)] and anti-IL12/23 [aOR 0.64; 95% CI (0.27–1.49)] had similar risk for early endoscopic POR as TNF antagonists (Fig. 3).

Risk Factors for Decreased Persistence of Post-operative Prophylaxis with Biologics

In the overall cohort, on multivariable Cox proportional hazard regression, pre-operative active smoking (aHR 1.98; 95% CI [1.14–3.43]), number of prior biologic exposures [1 prior biologic: aHR 1.85; 95% CI (1.24–2.77); ≥2 prior biologics: aHR 1.98; 95% CI (1.10–3.56)], ileocolonic CD [aHR 1.57; 95% CI (1.11–2.22)], and longer resection length (aHR 1.02; 95% CI [1.01–1.02]) were associated with increased risk of prophylaxis failure (Table 3, Supplementary Data Content). Pre-operative steroid use [aHR 0.78; 95% CI (0.54–1.12)], internal penetrating disease behavior [aHR 1.03; 95% CI (0.52–2.03)], concomitant immunomodulator use [aHR 0.93; 95% CI (0.63–1.37)], and time to start prophylaxis after surgery [aHR 1.00; 95% CI (0.99–1.02)] were not associated with risk of post-operative prophylaxis failure.

Risk Factors for Early Endoscopic POR in CD Subjects Prescribe Biologics for Post-operative Prophylaxis

In the overall cohort, on multivariable logistic regression, European ancestry was associated with risk of early endoscopic POR (aOR 5.78; 95% CI [1.28–26.21], Table 3, Supplementary Data Content). Male sex [aOR 1.56; 95% CI (0.86–2.81)], pre-operative active smoking [aOR 0.69; 95% CI (0.20–2.42)], internal penetrating disease behavior [aOR 0.49; 95% CI (0.14–1.70)], length of bowel resected [aOR1.01; 95% CI (0.99–1.03)], and presence of lymph node granulomas [aOR 1.43; 95% CI (0.61–3.34)] were not associated with risk of early endoscopic POR.

Discussion

In a cohort of previously surgically naïve CD patients undergoing ICR or SBR who were prescribed a biologic for post-operative prophylaxis, we made several key observations on the comparative persistence and effectiveness of preventing early endoscopic POR between non-TNF vs. TNF antagonists. First, we observed that non-TNF antagonists were associated with increased drug persistence than TNF antagonists for post-operative prophylaxis, and, in stratified analyses, similar findings were observed for anti-integrin and anti-IL12/23 compared to TNF antagonists, respectively. Second, we observed that non-TNF and TNF antagonists have similar effectiveness in preventing early endoscopic POR. Third, to explain the differences in drug persistence, we observed nominally higher rates of adverse events with TNF antagonists. Overall, our findings provide real-world evidence supporting the tolerability and effectiveness of non-TNF antagonists for post-operative prophylaxis.

To mitigate POR in CD, current societal guidelines favor post-operative pharmacologic prophylaxis for most patients. Yet, recent studies suggest 30–56% of patients prescribed post-operative prophylaxis with a biologic develop endoscopic POR within 18 months after surgery [4, 6, 17–19]. This highlights gaps in knowledge surrounding accurate

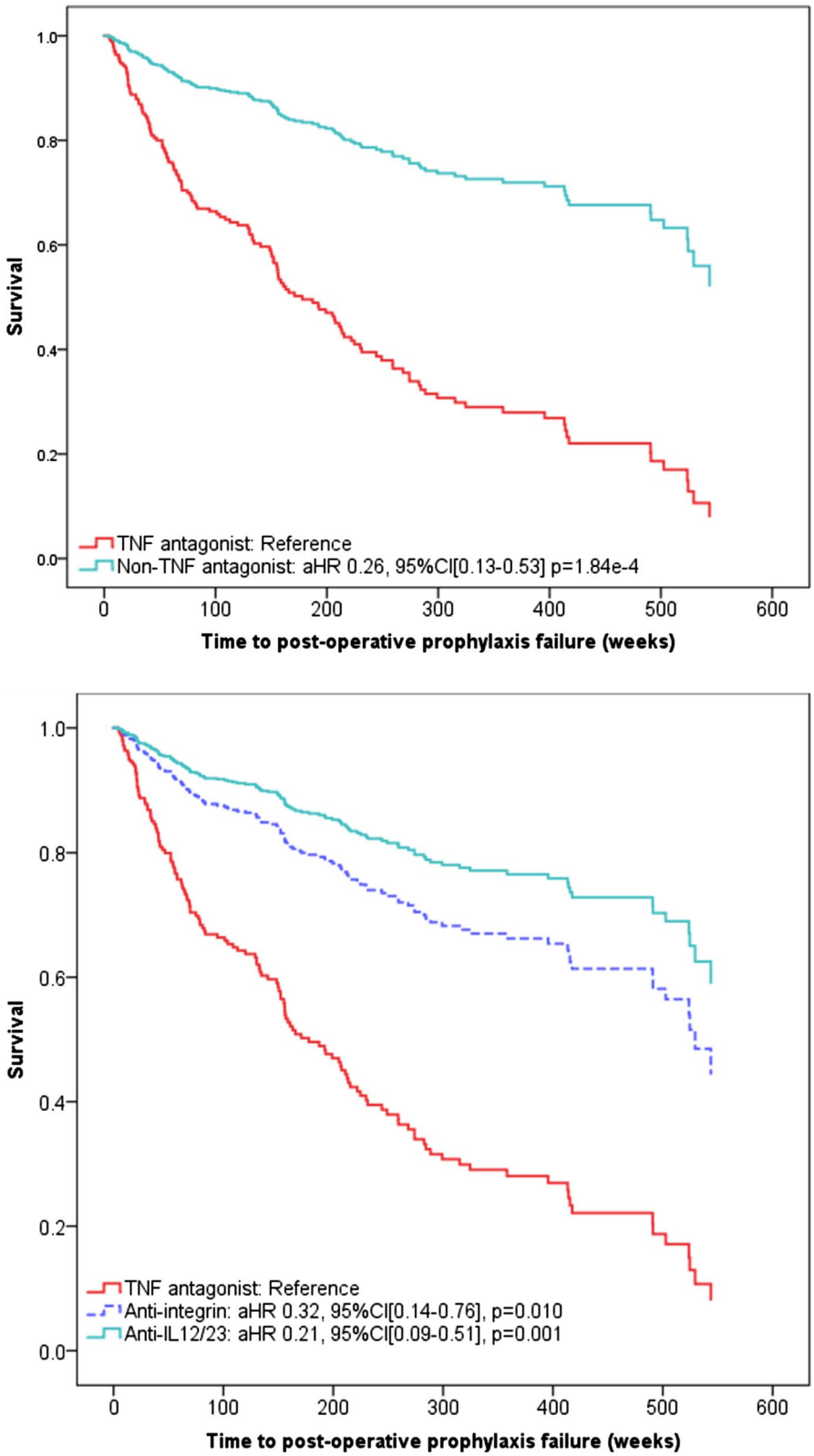

Fig. 2 Adjusted[α] survival curve comparing persistence of non-TNF vs. TNF antagonist (reference) for post-operative prophylaxis

aHR: adjusted hazards ratio, CI: confidence interval
[α]Adjusted for age, sex, disease duration, smoking status, pre-operative biologic mechanism, and # of prior biologic exposure

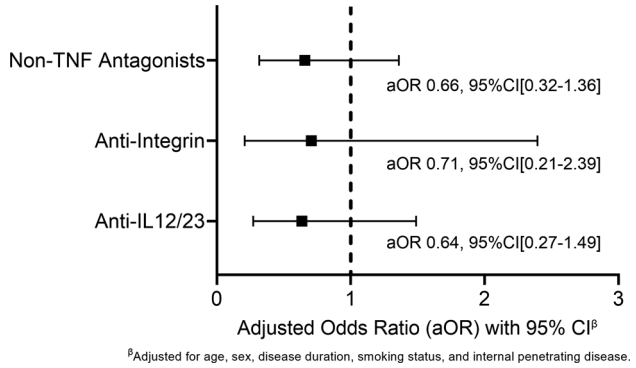

Fig. 3 Post-operative prophylaxis with non-TNF or TNF antagonists (reference) has comparable risk for early endoscopic POR

individualized risk stratification and effective use and positioning of biologics for post-operative prophylaxis. Since the PREVENT trial, TNF antagonists have been the mainstay for post-operative prophylaxis [4]. However, with the expanding menu of available advanced therapies for CD, surgical CD patients are increasingly TNF antagonist experienced or intolerant, but the role of non-TNF antagonists for post-operative prophylaxis is poorly characterized. Preliminary data from the REPREVIO study, a randomized placebo-controlled trial, suggested vedolizumab is effective for preventing POR [20]. There have been three retrospective studies describing the comparative effectiveness of non-TNF vs TNF antagonists for post-operative prophylaxis with conflicting results. In a retrospective single-center study, Yamada, et al. found vedolizumab was associated with an increased risk for endoscopic POR within 12 months after surgery compared to TNF antagonists [aOR 5.58, 95% CI (1.51–24.3)]. Conversely, in a retrospective multicenter study, Yanai et al. found prophylaxis with vedolizumab [aOR 0.55, 95% CI (0.25–1.19)] and ustekinumab [aOR 1.86, 95% CI (0.79–4.38)] yielded similar risk as TNF antagonists for endoscopic POR within 1 year after surgery [6]. In a dual-center retrospective study, Axelrad et al. observed TNF antagonist prophylaxis was associated with reduction in POR [aHR 0.61, 95% CI (0.40–0.93)], while vedolizumab and ustekinumab were not [7]. The discrepancy among the available studies are potentially due to variable definitions of POR and follow-up time. Additionally, the studies were limited by heterogeneous cohorts because they included CD subjects with prior resections, who arguably have a different underlying disease biology compared to surgically naïve subjects. In our study, we exclusively included previously surgically naïve subjects to avoid prior surgery as a confounding variable and found non-TNF antagonists had similar effectiveness in preventing early endoscopic POR. However, the available data should be interpreted with caution because none of the studies, including the present study, were adequately powered to detect a difference for endoscopic POR. Nonetheless, in our study, the rate of early endoscopic POR for each drug class was 30–40%, which is similar to the PREVENT and POCER trial as well as recent observational data [4, 6, 17–19]. While the available data provides reassuring evidence that non-TNF and TNF antagonists have similar effectiveness for preventing endoscopic POR, the data also suggest there may be a therapeutic ceiling for POR prevention with currently available agents. Large, prospective studies are required to further evaluate the comparative effectiveness of non-TNF and TNF antagonists for preventing early endoscopic POR.

In addition to effectiveness, long-term tolerability is an equally important consideration for positioning biologics for CD. Like treating luminal CD, the benefit of post-operative prophylaxis for preventing POR should outweigh the risk of therapy-related adverse events, but there are very limited data on the rates of adverse events for different interventions in this context. Current guidelines draw estimated rates of adverse events from population-based studies and RCTs in patients with active luminal CD. However, individuals with active luminal CD are arguably a different patient population than CD patients with surgically induced remission. Moreover, several studies have suggested patient-related factors play a significant role in the tolerability of biologic therapy in CD, including severity of disease activity, opioid exposure, steroid exposure, nutritional status, and frailty, which may not be all applicable in a post-surgical population [8, 9, 21]. Thus, despite its importance in post-operative management of CD, data for the tolerability of available biologics for post-operative prophylaxis are scarce. Drug persistence can help fill this gap in knowledge and indirectly assesses a drug's long-term effectiveness and tolerability. In our study, we observed non-TNF antagonists have greater persistence than TNF antagonists, suggesting non-TNF antagonists are more favorable long-term options than TNF antagonists for post-operative prophylaxis. To account for potential confounders due to changes in practice patterns over the study period such as a treat-to-target approach and use of therapeutic drug monitoring, we performed a sensitivity analysis of subjects who underwent surgery after 2014 when the non-TNF antagonists were first FDA approved for CD. The sensitivity analysis also demonstrated greater persistence of non-TNF antagonists than TNF antagonists for prophylaxis, providing further supporting of the primary findings of the study. Additionally, a recent large population-based study in Australia reported similar findings with non-TNF antagonists having greater persistence than TNF antagonists in non-surgical subjects with active IBD [12]. Interestingly, in our study, non-TNF antagonist prophylaxis had increased persistence despite having longer disease duration and greater number of prior biologic exposures, but these findings could have been offset by more active smokers

in the TNF antagonist group. To explain the differences in drug persistence, we sought to compare reasons for discontinuation between the two groups. While not statistically significant likely owing to the limited sample size of the non-TNF antagonist group, we observed a larger proportion of subjects discontinue TNF antagonists due to adverse events than non-TNF antagonist prophylaxis. Infection was the most common adverse event result in discontinuation in the TNF antagonist group. Our findings are in line with large observational studies and network meta-analyses in non-surgical IBD patients that have found non-TNF antagonists are associated with lower rates of adverse events than TNF antagonists [8, 22]. Our data also suggests the comparative long-term tolerability and effectiveness of non-TNF vs TNF antagonists in post-surgical CD patients may parallel the experience of CD patients with active luminal disease. Thus, using risk estimates from therapeutic studies in subjects with luminal CD may be appropriate for developing post-operative CD management guidelines. However, large, prospective studies are required for accurate risk estimates of adverse events and tolerability to better inform post-operative management of CD. Additionally, the comparative risk of immunogenicity will be important to elucidate in this CD patient population as well. Finally, it is worth noting that 22 subjects (Fig. 1) were excluded from the final analysis owing to prophylaxis discontinuation due to self-discontinuation ($n=18$), insurance denial ($n=2$), and de-escalation of therapy ($n=1$).

Our study has several notable strengths. First, we included a large cohort of exclusively surgically naïve CD subjects, which avoids prior resections as a confounding variable. Additionally, there was a long follow-up period to better characterize the long-term tolerability and effectiveness of non-TNF and TNF antagonists for post-operative prophylaxis. On the other hand, there are several important limitations to consider. First, this was a retrospective, single-center study. As such, determining if a subject had medically untreatable CD (such as fibrostenostic CD) or progressive CD despite medical therapy that required surgery could not be consistently concluded from clinical progress notes. While this could potentially influence selecting the agent for prophylaxis, we attempted to adjust for this variable by controlling for the pre-operative biologic mechanism of action in the multivariable regression model. Similarly, due to the limitations of a retrospective study design, there could have potentially been unmeasured variables of disease severity that could have influenced the treating provider's choice for post-operative prophylaxis. Second, the sample size of non-TNF antagonists was limited and unbalanced with the TNF antagonist group, which was potentially underpowered to provide insightful comparison for the effectiveness of preventing early endoscopic POR. In post hoc power analysis, this would require $n=1274$ to detect a 7% risk difference in incidence of early endoscopic POR with 80% power. However, our primary focus was comparative long-term drug persistence, which our study had > 90% power to detect a 26% risk difference in incidence of prophylaxis failure. Nonetheless, while future larger studies are needed to confirm our findings, our data provide additional insights into a gap in knowledge in post-operative management of CD. Third, since drug concentration level and anti-drug antibody labs were not consistently available for every subject, we could not differentiate between those who failed despite optimized drug concentration level or immunogenicity for every subject in our cohort. Thus, the rate of immunogenicity may be underestimated. Nevertheless, our findings reflect real-world practice patterns where obtaining drug concentration levels and antibodies may not be feasible or cost effective in every individual. Fourth, we could not retrospectively differentiate Rutgeert's i2a from i2b recurrence accurately, and the limited sample size precluded restricting recurrence to Rutgeert's i3-4. However, our primary endpoint was not risk of endoscopic POR. Finally, the treating providers' decision to prescribe a non-TNF vs. TNF antagonist for prophylaxis could not be easily discerned by chart review, so there is risk for selection bias. However, our institutional practice is to continue the biologic agent that was prescribed prior to surgery if patient tolerated it, so we adjusted for this in our multivariable model as well as prior biologic failures prior to surgery.

In conclusion, in a single-center cohort of previously surgically naïve CD subjects undergoing ICR and/or SBR who were prescribed a biologic for post-operative prophylaxis, we found non-TNF antagonists may be more favorable long-term prophylactic therapies than TNF antagonists with similar effectiveness for preventing early endoscopic POR. If confirmed by larger, prospective studies, these findings can better inform post-operative management strategies in CD and potentially further mitigate the risk of POR.

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Author's contributions PG is the guarantor of the article and was involved in concept and design, data collection, statistical analysis, drafting of manuscript, and final approval of manuscript. SD was involved in statistical analysis, drafting of manuscript, and final approval of manuscript. YL was involved in data collection, drafting of manuscript, and final approval of manuscript. SY was involved in data collection, drafting of manuscript, and final approval of manuscript. DL was involved in statistical analysis, drafting of manuscript, and final approval of manuscript. TH was involved in statistical analysis, drafting of manuscript, and final approval of manuscript. EV was involved in drafting of manuscript and final approval of manuscript. NB was involved in drafting of manuscript and final approval of manuscript. GS was involved in drafting of manuscript and final approval of manuscript. AY was involved in concept and design, drafting of manuscript, and final approval of manuscript. DZ was involved in drafting of manuscript and final approval of manuscript. ST was involved in concept and design, drafting of manuscript, and final approval of manuscript.

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Declarations

Conflict of interest PG had no conflicts of interests to disclose. SD had no conflicts of interest to disclose. YL had no conflicts of interest to disclose. SY had no conflicts of interest to disclose. DL has received consulting fees from Prometheus Biosciences Inc.. TH had no conflicts of interest to disclose. EV had no conflicts of interest to disclose. NB had no conflicts of interest to disclose. GS receives research support from Pfizer. AY has received consulting fees from Bristol Myers Squibb, Arena, Pfizer, Takeda, and Landos. DZ is on the speaking bureau for AbbVie, Prometheus Labs, and Regeneron. ST serves on the scientific advisory board for Seaver Foundation for Austim and has stock options in Promethus Biosciences Inc. PF has received consulting fees from Takeda. SR has received advisory fees from Prometheus and Janssen. GYM has received consulting fees from Abbvie, Arena Pharmaceuticals, Bristol Myers Squibb, Boehringer Ingelheim, Celgene, Dieta, Entasis, Fresenius Kabi, Genentech, Gilead, Janssen, Medtronic, Merck, Oshi, Prometheus Labs, Pfizer, Takeda, and Techlab. DPBM has received consulting fees from Gilead, Takeda, Pfizer, Boehringer Ingelheim, Qu Biologics, Bridge Biotherapeutics, Prometheus Biosciences Inc. (now owned by MERCK), and Prometheus Labs.

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