Journal of Crohn's and Colitis, 2022, **16**, 1882–1892
https://doi.org/10.1093/ecco-jcc/jjac100
Advance access publication 27 July 2022
Original Article

Endoscopic Postoperative Recurrence in Crohn's Disease After Curative Ileocecal Resection with Early Prophylaxis by Anti-TNF, Vedolizumab or Ustekinumab: A Real-World Multicentre European Study

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Abstract

Background: Endoscopic-post-operative-recurrence [ePOR] in Crohn's disease [CD] after ileocecal resection [ICR] is a major concern. We aimed to evaluate the effectiveness of early prophylaxis with biologics and to compare anti-tumour necrosis factor [anti-TNF] therapy to vedolizumab [VDZ] and ustekinumab [UST] in a real-world setting.

Methods: A retrospective multicentre study of CD-adults after curative ICR on early prophylaxis was undertaken. ePOR was defined as a Rutgeerts score [RS] ≥ i2 or colonic-segmental-SES-CD ≥ 6. Multivariable logistic regression was used to evaluate risk factors, and inverse probability treatment weighting [IPTW] was applied to compare the effectiveness between agents.

Results: The study included 297 patients (53.9% males, age at diagnosis 24 years [19–32], age at ICR 34 years [26–43], 18.5% smokers, 27.6% biologic-naïve, 65.7% anti-TNF experienced, 28.6% two or more biologics and 17.2% previous surgery). Overall, 224, 39 and 34 patients received anti-TNF, VDZ or UST, respectively. Patients treated with VDZ and UST were more biologic experienced with higher rates of previous surgery. ePOR rates within 1 year were 41.8%. ePOR rates by treatment groups were: anti-TNF 40.2%, VDZ 33% and UST 61.8%. Risk factors for ePOR at 1 year were: past-infliximab (adjusted odds ratio [adj.OR] = 1.73 [95% confidence interval, CI: 1.01–2.97]), past-adalimumab [adj.OR = 2.32 [95% CI: 1.35-4.01] and surgical aspects. After IPTW, the risk of ePOR within 1 year of VDZ vs anti-TNF or UST vs anti-TNF was comparable (OR = 0.55 [95% CI: 0.25–1.19], OR = 1.86 [95% CI: 0.79–4.38]), respectively.

Conclusion. Prevention of ePOR within 1 year after surgery was successful in ~60% of patients. Patients treated with VDZ or UST consisted of a more refractory group. After controlling for confounders, no differences in ePOR risk were seen between anti-TNF prophylaxis and other groups.

Key Words: Crohn's disease; biologics; post-operative recurrence

1. Introduction

Bowel damage is present in one-fifth to one-third of patients with Crohn's disease [CD] at diagnosis and often leads to complications and surgery; up to 50% of the patients will have a surgical resection for CD, within 10 years of diagnosis, with up to a third requiring multiple surgeries during their lifetime.[1,2]

Ileocecal resection [ICR] is the most frequent operation performed in ileocolonic CD.[3] However, complete resection of the inflamed bowel segment does not imply a cure. It is well recognized that endoscopic postoperative recurrence [ePOR] precedes symptomatic recurrence and may reach 70% after 1 year.[4] This has influenced paradigms of management with

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one of two alternatives: either routine endoscopic monitoring within 6–12 months of surgery and initiation of treatment in the case of asymptomatic endoscopic recurrence based on the severity of the endoscopic findings (classified by the Rutgeerts Score [RS]),[5,6] or early postoperative pharmacological prophylaxis soon after surgery for high-risk patients.[7] The benefit of endoscopy-guided therapy over early prophylaxis or vice versa is uncertain.

Over the past decade, anti-tumour necrosis factor [anti-TNF]agents have become the mainstay of prophylaxis therapy for preventing postoperative recurrence in CD.[3,8–10] The landmark randomized controlled pilot trial by Regueiro *et al.*[11] that first paved the concept of postoperative prophylaxis with an anti-TNF demonstrated only 10% ePOR at 1 year in the infliximab-treated group vs almost 90% in the placebo arm. The concept was further confirmed in the PREVENT trial, demonstrating 22.4% ePOR 76 weeks after surgery in patients treated with infliximab, half of the risk of ePOR in the group treated by placebo [22.4% vs 51.3% $p < 0.001$].[12] Similarly, in a post hoc analysis of the POCER study, patients immediately treated with adalimumab had only 21% ePOR at 6 months after surgery.[13]

Despite the effectiveness of anti-TNF treatment in CD, many patients fail this strategy with time, develop immunogenicity, and become refractory or intolerant due to side effects.[14–16] The introduction of newer biological agents with novel mechanisms of action, namely vedolizumab [VDZ] and ustekinumab [UST], has increased medical options for disease control.[17,18] However, little is known about the efficacy of these newer biologics in preventing postoperative disease recurrence.[9,10]

Here, we aimed to evaluate the effectiveness of prophylactic therapy in preventing ePOR after curative ICR among patients with CD in a real-world setting and compare the effectiveness of VDZ or UST to that of anti-TNF.

2. Methods

2.1. Study design and population

This retrospective multicentre cohort study assessed ePOR after curative ICR. Data were collected from 38 centres in Europe, Australia and Israel. Patients aged >17 years with CD who underwent curative ICR between 2015 and 2019 were included.

All patients were assigned early prophylactic treatment within 6 months of surgery [not endoscopy-driven]. Prophylaxis included either an anti-TNF agent [infliximab, adalimumab, certolizumab pegol], VDZ or UST. Concomitant non-biologic therapies were allowed after surgery [aminosalicylates, corticosteroids, immunomodulators] and antibiotics as prophylaxis [imidazole]. We included only patients who had a follow-up ileocolonoscopy conducted at least 4 months after commencing prophylaxis [to enable the assessment of treatment impact]. All participants must have had at least 12 months of follow-up after surgery. Any exposure to immunomodulators [IMM], biologics or previous CD surgeries were assessed and recorded. Patients were excluded if they had a stoma, evidence of inflammation at remote sites outside the resected area including active perianal disease, if they underwent surgical procedure other than ICR [segmental small bowel resection, subtotal or total colectomy], if they were operated on for other indications than those related to refractory disease [i.e. malignancy] or if they were pregnant.

Participants were assessed for the first endoscopic, biochemical, and clinical POR up to 1, 2 and 3 years post-ICR. Participants without outcome data for any of the aforementioned time periods were excluded from that particular time period analysis to minimize bias. If a participant had reached a POR outcome at an early time period, this outcome was also considered a POR for the following time periods. The proportion of events was calculated as the number of patients with an event divided by the number of patients with data at that time point. The end of follow-up was determined by the last clinic visit, death or discontinuation/drug switch.

2.2. Data collection and definitions

Local investigators had access to all source documents, and patients were pseudo-anonymized. An appropriate case report form was designed to collect disease and patients' characteristics. Data included: patient demographics, smoking history, disease phenotype [Montréal classification], presence of extraintestinal manifestations, history of inflammatory bowel disease [IBD]-related medications, previous surgeries, indications for surgery, perioperative medications, surgical information, postoperative complications, postoperative regimen, postoperative endoscopic, clinical and biochemical assessment, postoperative IBD-related hospitalizations, surgeries and adverse events.

Curative ICR was defined as the resection of all macroscopic disease. Endoscopic recurrence was defined as a RS ≥ i2 [both i2a and i2b] or colonic segmental SES-CD ≥ 6 as specified by the sub-investigators at each participating site. Biochemical recurrence was defined as C-reactive protein [CRP] ≥ 10 mg/L or faecal calprotectin [FC] >150 mg/g stool. Clinical recurrence was defined as Harvey–Bradshaw index [HBI] > 4 or Physician Global Assessment [PGA] ≥ 1. To assess the impact of pre-surgical biologic exposure, patients were divided into four subgroups: [a] biologic naïve, [b] past biologic exposure, but off biologic at the time of ICR [defined as less than three consecutive months of biologic therapy before surgery], [c] treated with biologic therapy at the time of ICR and continued the same class for prophylaxis, and [d] treated with biologic therapy at the time of ICR and switch out of class for prophylaxis. For standardized analysis, the 1-, 2- and 3-year periods were defined: 6–18, 18–30 and 30–42 months after surgery, respectively.

2.3. Outcomes

The primary outcome was the ePOR rate within year1 after ICR. Secondary outcomes included: ePOR, clinical, biochemical and surgical recurrence rates at 24 and 36 months, and the safety profile of these treatment strategies.

2.4. Statistical analysis

Categorical variables were presented as frequency and percentage, while continuous variables were summarized as the median and interquartile range [IQR]. Comparison of categorical variables was performed using the Chi-square test or Fisher's exact test, and continuous variables were compared using the Mann-Whitney U test. The Bonferroni method was used to adjust for multiple comparisons.

Multivariable logistic regression using a backward stepwise method for variable selection [p >0.1 on Wald test was used for variable removal] was utilized to assess risk. Sex, age at surgery, disease duration, disease behaviour [B phenotype], extraintestinal manifestation, smoking status, biologic naïve

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at surgery, past infliximab, past adalimumab, past VDZ, past UST, past ICR, surgical properties (open vs laparoscopic and type of anastomosis [stapler vs handsewn]), anastomotic type [end-to-end vs end-to-side vs side-to-side anastomosis] and prophylactic treatment group [anti-TNF, VDZ or UST] were included in the initial analysis.

To better control for differences between groups, the propensity score was calculated by multivariable logistic regression for the probability of a patient being assigned a prophylactic treatment with either VDZ vs an anti-TNF therapy, UST vs an anti-TNF therapy, or VZD vs UST therapy. Sex, age at surgery, disease duration, extraintestinal manifestation, smoking status, past anti-TNF, past VDZ, past UST, history of two or more biologics and past ICR were included in the regression model for the propensity scoring. Next, inverse probability of treatment weighting [IPTW] with stabilized weights and truncation of 5% extreme scores was applied. All reported *p*-values are two-sided. *p*-values <0.05 were considered significant. Data were analysed using SPSS [IBM SPSS statistics, version 27.0, IBM].

3. Ethical Considerations

The study was approved by each participating centre's local institutional review board [Ethics committee], and the requirement for documented informed consent was waived. The investigators and the participating sites treated all information and data related to the study as confidential and did not disclose such information to any third parties or use such information for any purpose other than the performance of the study.

4. Results

4.1. Patients

4.1.1. Disposition

Overall, 522 patients were screened for eligibility, of whom 297 were eligible for analysis: 224 treated with anti-TNF, 39 with VDZ and 34 with UST. Patient data are presented in Supplementary Figure 1.

4.1.2. Characteristics

Of the 297 patients included, 44.1% [n = 131] were females, median age at CD diagnosis was 24 [IQR: 19–32] years, disease duration at surgery was 8 [IQR: 3–13] years, active smoking rate was 17.8% [n = 53], 72.4% of patients [n = 215] were experienced with biologics, of whom 28.6% [n = 85] received more than two biologics, 16.5% [n = 49] more than two classes of biologics, and 17.2% [n = 51] underwent previous CD-related surgery [seven patients more than one surgery]. Overall, 152/297 patients were operated on in the emergency or urgent setting [60 for a perforating complication]. Forty-three patients received steroids within 30 days before the ICR, while only six patients were on steroids after the surgery. Early [within 30 days] post-ICR leak occurred in three patients [10%], and two of these patients were treated with steroids before surgery. Of note, laparoscopic surgery was more common among patients who were operated on between 2017 and 2019 vs 2015 and 2016 [62.1% vs 48.5%, p = 0.027]. See Tables 1 and 2 for patients' characteristics before and after ICR.

After ICR, the majority (224/297 [75.4%]) were assigned an anti-TNF for prophylaxis. Of these, 112 patients [50%] had received an anti-TNF therapy before the ICR [81/112 patients continued the same therapy, and 31/112 were switched in class]. When comparing treatment groups, patients treated with VDZ and UST were more biologic-experienced and more likely to have had previous surgery compared to those receiving an anti-TNF [biologic experience: VDZ 87.2% and UST 94.1% vs anti-TNF 66.5%, p < 0.001; previous surgery: VDZ 25.6% and UST 38.2% vs anti-TNF 12.5%, p < 0.001]; see Table 1 for baseline characteristics. Patients in the VDZ and UST groups had more stricturing complications leading to surgery than those treated with anti-TNF [obstructive complication: VDZ 79.5% and UST 76.5% vs anti-TNF 60.3%, p = 0.021]. Combination with an IMM was similar across treatment groups: anti-TNF 22.3%, VDZ 25.6% and UST 14.7% [p = 0.499]. After ICR, most of this cohort were treated with standard dosing of biologics for CD [274/297]. Twenty patients were on an escalated dose [17 on anti-TNF and three on VDZ], while three on UST were given psoriatic dosing [45 mg every 8 weeks]. Later, and following the first index endoscopy, three patients who did not have evidence of ePOR underwent dose escalation within 3 months of that colonoscopy: two with mild endoscopic activity [designated RSi1]. Active smoking after ICR and time to prophylaxis were also similar between all treatment groups (smoking rates: anti TNF 19.2%, VDZ 23.1%, UST 8.8% p = 0.257, median time to prophylaxis in months: anti-TNF- 1.6 [IQR 1.0–2.6], VDZ 2.1 [IQR 1.1–3.3], UST 1.5 [IQR 1.0–3.2], p = 0.137). See Table 2 for surgical characteristics.

4.2. Postoperative endoscopic recurrence rates

Within 1 year after surgery, 41.8 % of the cohort [124/297] had ePOR. This rate did not increase significantly with longer follow-up (48.6% [129/263] and 48.6% [90/185] within 24 and 36 months, respectively). The 1-year RS was: 36.6% i0, 22.1% i1, 28% i2, 7.3% i3 and 5.9% i4. Only five patients [1.6%] out of the cohort had an endoscopic recurrence in the colon.

When comparing 1-year ePOR rates per prophylactic agents we noted that there were no significant differences between patients treated with anti-TNF vs UST [40.2% vs 61.8%, p = 0.054], or anti-TNF vs VDZ [40.2% vs 33.3%, p = 0.999], but patients treated with VDZ had significantly lower ePOR rates compared to patients treated with UST [33.3% vs 61.8%, p = 0.045]. See Figure 1 for ePOR rates per treatment group.

Combining IMM was not associated with lower ePOR within 1 year after ICR [IMM 36.9% vs no IMM 43.1%, p = 0.396]. Only one of the three patients given UST prophylaxis at a lower dose than standard had an ePOR at the index colonoscopy.

The 1-year ePOR based on the RS showed similar distribution between anti-TNF and VDZ, while in the UST group [p = 0.074], there was a numerically higher proportion of RS i2 [anti-TNF 27.8%, VDZ 17.9%, UST 41.2%; see Figure 2]. When analysing only patients with no/minimal ePOR [RS i0 or i1] vs significant ePOR [RS i3 or i4], results were similar between treatment groups [p = 0.123]; however, patients treated with anti-TNF had numerically lower rates of significant ePOR [16.0%] compared to UST [35.0%; p = 0.059]. Comparing patients' sub-groups based on RS i0 vs RS i1 vs RS i ≥ 2 revealed several differences: more prevalent penetrating phenotype among patients with RS i ≥ 2 [42.5, 40.5 and 57.1%, respectively, p = 0.035], more extraintestinal

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Table 1. Baseline characteristics

	Entire cohort, *N* = 297 [100]	Anti-TNF, *n* = 224 [75.4]	VDZ, *n* = 39 [13.1]	UST, *n* = 34 [11.4]	*p*-value*
Age at diagnosis, years, median [IQR]	24 [19–32]	23 [19–31]	25 [19–40]	25 [19–33]	0.634
Male sex, *n* [%]	166 [55.9]	122 [54.5]	26 [66.7]	18 [52.9]	0.343
Montreal—location, *n* [%]					
L1, ileal disease	151 [50.8]	119 [53.1]	16 [41.0]	16 [47.1]	0.339
L3, ileocolonic disease	146 [49.2]	105 [46.9]	23 [59.0]	18 [52.9]	
L4, upper GI	26 [8.7]	17 [7.6]	3 [7.7]	6 [17.6]	0.199
Montreal—behaviour, *n* [%]					
B1, inflammatory	15 [5.1]	9 [4.0]	1 [2.6]	1 [2.9]	0.247
B2, stricturing	205 [69.0]	100 [44.6]	17 [43.6]	22 [64.7]	
B3, penetrating	147 [49.5]	115 [51.3]	21 [53.8]	11 [32.4]	
Perianal disease, *n* [%]	67 [22.6]	52 [23.2]	8 [20.5]	7 [20.6]	0.894
Extraintestinal manifestation, *n* [%]	70 [23.6]	49 [21.9]	11 [28.2]	10 [29.4]	0.480
Smoking status—ever, *n* [%]	109 [36.7]	84 [39.3]	15 [38.5]	10 [29.4]	0.546
Treatment history, *n* [%]					
Past immunomodulator	182 [61.3]	137 [61.2]	20 [51.3]	25 [73.5]	0.153
Biologic naïve	82 [27.6]	75 [33.5]	5 [12.8]	2 [5.9]	$<0.001_{a,b}$
Past anti-TNF	195 [65.7]	130 [58.0]	34 [87.2]	31 [91.2]	$<0.001_{a,b}$
More than 2 anti-TNFs	67 [22.6]	36 [16.1]	13 [33.3]	18 [52.9]	$<0.001_{a,b}$
More than 2 classes of biologics	49 [16.5]	25 [11.2]	8 [20.5]	16 [47.1]	$<0.001_{b,c}$
More than 2 biologics	85 [28.6]	47 [21.0]	16 [41.0]	22 [64.7]	$<0.001_{a,b,c}$
Surgical history, *n* [%]					
Previous CD-related surgery	51 [17.2]	28 [12.5]	10 [25.6]	13 [38.2]	$<0.001_{a,b}$
More than one CD-related surgery	7 [2.4]	2 [0.9]	3 [7.7]	2 [5.9]	$0.013_{a,b}$

**p*-values for comparison between the three treatment groups; statistical significance ($p < 0.05$): a, anti-TNF vs VDZ; b, anti TNF vs UST; c, VDZ vs UST. CD, Crohn's disease; UST, ustekinumab; VDZ, vedolizumab; ICR, ileocecal resection; Immunomodulator, a thiopurine or methotrexate; IQR, interquartile range.

manifestations among RS i ≥ 2 [21.7% vs 12.5% vs 31.1%, respectively, $p = 0.016$] and more than two anti-TNFs and two classes of biologics among the RS i ≥ 2 [15.1% vs 10.9% vs 34.5%, respectively, $p < 0.001$, and 22.6% vs 14.1% vs 40.3%, respectively, $p < 0.001$]. The entire set of comparisons between these sub-groups is presented in Supplementary Table 1.

4.3. Secondary outcomes

The biochemical recurrence rate at 1 year was 43.5% [110/253], and a comparison between treatment groups revealed a higher biochemical recurrence rate in the VDZ group [anti-TNF 40.0%, VDZ 65.7%, UST 39.3%, $p = 0.017$]. Seventy-six patients had an elevated CRP with a median level of 15.9 mg/L [IQR: 13.1–25.0], and 82 patients had elevated FC with a median level of 440 mg/g [IQR: 297–750]. CRP levels in the VDZ group were numerically higher compared to the other treatment groups although not reaching statistical significance (anti-TNF 15.8 mg/L [IQR: 13.0–24.5], VDZ 20.5 mg/L [IQR: 4.0–27.3], UST 15.3 mg/L [IQR: 10.6–19.0], $p = 0.421$). Similarly, FC levels were significantly higher among patients treated with VDZ (anti-TNF 405 mg/g [IQR: 288-750], VDZ 465 mg/g [IQR: 360-725], UST 180 mg/g [IQR: 160-622], $p = 0.025$).

The 1-year clinical recurrence rate was 64.1% and comparable between treatment groups: anti-TNF 62.0%, VDZ 78.1%, UST 60.9% [$p = 0.201$]. Rates of biochemical and clinical recurrence slightly increased from 1 to 2 years [43.5% vs 51% and 61.4% vs 70.6%, respectively]. These rates remained stable for 3 years. Surgical recurrence during follow-up occurred in 9/297 [3.0%] patients within a median follow-up of 9.1 [IQR: 3.4–23.4] months. CD-related hospitalization was reported in 17/297 [5.7%] patients within a median of 8.6 [IQR: 2.1–24.8] months [see Supplementary Table 2].

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Table 2. Surgical characteristics

	Entire cohort, N = 297 [100]	Anti TNF, *n* = 224 [75.4]	VDZ, *n* = 39 [13.1]	UST, *n* = 34 [11.4]	*p*-value*
Age at surgery, years, median [IQR]	34 [26–43]	33 [26–42]	36 [22–50]	38 [28–46]	0.462
Disease duration at surgery, years, median [IQR]	8 [3–13]	8 [3–13]	8 [3–11]	11 [5.7–17.2]	0.132
Smoking status—active, *n* [%]	53 [17.8]	41 [19.2]	9 [23.1]	3 [8.8]	0.257
Indication for surgery, *n* [%]					
Refractory inflammation	37 [12.5]	32 [14.3]	2 [5.1]	3 [8.8]	0.275
Stricturing complication [obstruction]	192 [64.6]	135 [60.3]	31 [79.5]	26 [76.5]	0.021_{a}
Penetrating complication [abscess]	95 [32.0]	75 [33.5]	12 [30.8]	8 [23.5]	0.503
Surgical properties, *n* [%]					
Open [vs laparoscopic]	122 [41.1]	88 [41.1]	13 [33.3]	21 [61.8]	$0.036_{b,c}$
Stapling [vs handsewn]	187 [63.0]	144 [72.0]	17 [44.7]	26 [83.9]	$0.001_{a,c}$
Anastomosis type, *n* [%]					
End to end	36 [12.1]	27 [13.3]	5 [13.2]	4 [12.5]	0.065_{a}
Side to side	192 [64.6]	135 [66.5]	32 [84.2]	25 [78.1]	
End to side	45 [15.2]	41 [20.2]	1 [2.6]	3 [9.4]	
Elective surgery [vs urgent or emergency]#	141 [48.1]	109 [49.5]	15 [38.5]	17 [50.0]	0.431
Time to prophylaxis, months, median [IQR]	1.7 [1.0-2.8]	1.6 [1.0-2.6]	2.1 [1.1-3.3]	1.5 [1.0-3.2]	0.137
Combination with an immunomodulator, *n* [%]	65 [21.9]	50 [22.3]	10 [25.6]	5 [14.7]	0.499
Combination with an azole antibiotics, *n* [%]	105 [35.6]	74 [33.2]	20 [51.3]	11 [33.3]	0.090

**p*-values for comparison between the three treatment groups; statistical significance: a, anti TNF vs VDZ; b, anti-TNF vs UST; c, VDZ vs. UST.
Immunomodulator, a thiopurine or methotrexate; UST, ustekinumab; VDZ, vedolizumab; IQR, interquartile range.
#Urgent surgery, within 2 months from admission; emergency surgery, at the index hospitalization.

Adverse events after prophylactic therapy were reported in 19/224 [5.8%] patients. All were treated with an anti-TNF; four patients had severe infectious complications: *Legionella* pneumonia, catheter sepsis, staphylococcal skin abscess, and a leak after surgery with pelvic collection requiring drainage and antibiotics. One patient developed Hodgkin's lymphoma while treated with UST; this patient was previously treated with azathioprine and anti-TNF. Supplementary Table 3 gives details of adverse events.

4.4. Risk factors associated with endoscopic recurrence

In univariate analysis prophylaxis treatment group was associated with ePOR at 1 year, [anti-TNF 40.2% vs VDZ 33.3% vs UST 61.8%, $p = 0.031$]. However, in the last step of the multivariable analysis, only past exposure to either infliximab or adalimumab and side-to-side and end-to-side anastomoses compared to end-to-end anastomosis were associated with the risk of ePOR at 1 year: adjusted odds ratio [OR]: 1.73 (95% confidence interval [CI] 1.01–2.97], 2.32 [95% CI 1.35–4.01], 0.38 [95% CI 0.17–0.83] and 0.34 [95% CI 0.13–0.92], respectively; see Table 3 for risk factors for ePOR at 1 year. Neither prophylaxis with VDZ vs anti-TNF, UST vs anti-TNF, nor active smoking were associated with significant risk for ePOR at 1 year and therefore were not included in the final model (adjusted OR: 0.59 [95% CI 0.25–1.38], 1.55 [95% CI 0.62–3.85] and 1.15 [95% CI 0.56–2.36], respectively). There were no differences in risk between patients with stricturing [B2] vs penetrating phenotype [B3] (0.97 [95% CI 0.55–1.71]). Still, it was not possible to properly assess the risk between B2 or B3 vs B1 as only a few patients in this cohort were operated on while having an inflammatory phenotype [B1]. Results of multivariable analysis for risk factors to ePOR after 2 and 3 years are presented in Supplementary Table 4, and risk factors for biochemical POR are presented in Supplementary Table 5.

In a sub-analysis, patients were divided into four subgroups based on pre-surgical therapeutic exposure: biologic naïve [$n = 82$]; exposed, but off biologics at the time of ICR [$n = 43$]; on biologic at the time of ICR and continued the same biologic for prophylaxis [$n = 125$]; and on biologic at the time of ICR but switched out of class for post-surgical prophylaxis [$n = 47$]. The proportions of ePOR within 1 year were: 32.9, 51.2, 42.4 and 46.8%, respectively [$p = 0.196$]. When comparing disease duration between these sub-groups, it was noted that biologic naïve patients before surgery had significantly shorter disease duration compared with patients who were pre-surgically exposed to biologics (naïve 5 years [IQR: 1–13], exposed but off biologics 11 years [IQR: 7–15], same class 8 years [IQR: 4–13], switched out of class 9 years

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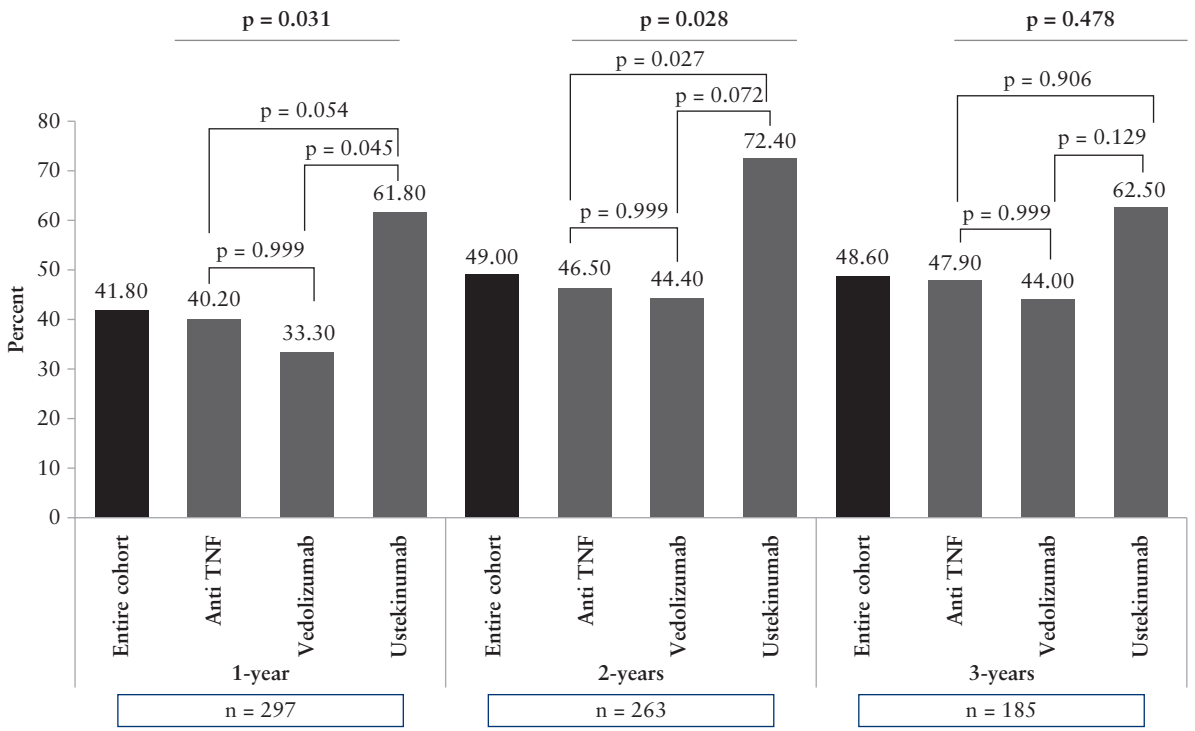

Figure 1. Endoscopic postoperative recurrence [ePOR]. ePOR rates were stratified by time from surgery and by treatment groups. ePOR rates are defined as Rutgeerts score [RS] i2–i4 or simple endoscopic score for Crohn's disease [SES-CD] ≥ 6. Anti-TNF, anti-tumour necrosis factor; UST, ustekinumab; VDZ, vedolizumab.

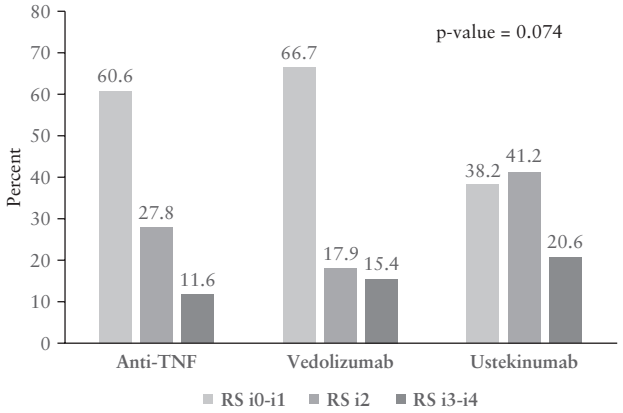

Figure 2. The Rutgeerts score at year. Rutgeerts score [RS] stratified by treatment groups; RS i0–i1, endoscopic remission; RS i2, endoscopic postoperative recurrence [ePOR]; RS i3 or i4, significant ePOR. Anti-TNF, anti-tumor necrosis factor; UST, ustekinumab; VDZ, vedolizumab.

[4–11], $p = 0.006$). There were no differences in disease duration between patients who continued the same class after surgery and patients who were switched out of class [$p = 0.963$].

Finally, as patients treated with VDZ and UST consisted of a more refractory group, we further performed a propensity score analysis applying the IPTW to compare groups and account for these confounders. There were no differences in 1-year ePOR risk when comparing the VDZ vs the anti-TNF groups (OR 0.55 [95% CI 0.25–1.19, $p = 0.131$]) and the UST vs the anti-TNF groups (OR 1.86 [95% CI 0.79–4.38], $p = 0.156$). However, significantly increased 1-year ePOR risk was observed among UST- compared with VDZ-treated patients (OR 3.75 [95% CI 1.33–10.6, $p = 0.012$]).

5. Discussion

In this large multicentre real-life cohort of patients with CD after curative ICR who received early postoperative prophylaxis with a biologic agent, ePOR was observed in 41.8, 49 and 48.6% within 1, 2 and 3 years, respectively. Most patients in this cohort [75%] were treated with an anti-TNF for prophylaxis. Rates of ePOR within the first year after ICR per prophylactic agent were 40, 33 and 61% among patients on anti-TNF, VDZ and UST, respectively. Patients treated with VDZ and UST prophylaxis comprised a distinct and more refractory group, highly experienced with biologics and more likely to have had previous CD-related surgeries.

The overall rate of ePOR observed at 1 year in our cohort is double that previously reported in both the PREVENT and POCER trials.[12,13] This higher ePOR rate could be explained by a relatively high number of risk factors for disease recurrence in our cohort: 49.5% operated while having penetrative disease phenotype, 17.2 % with a previous ICR, and the majority were biologic experienced [65% had failed an anti-TNF, and 16.5% failed two lines of biologic therapy]. By contrast, patients included in the PREVENT trial had a shorter median disease duration: 5.2 vs 8 years in our cohort, and only 25.3% were treated with an anti-TNF before surgery.[12] Previous exposure to an anti-TNF in the POCER trial cohort was also lower than in our cohort [39% vs 65%]. Notably, patients included in POCER and PREVENT were not exposed to any other class of biologic.[13]

Several real-world studies have addressed the issue of ePOR, most reporting higher ePOR rates compared with the results in randomized control trials, ranging between 30 and 70%.[19–22] In fact, in some studies, ePOR rates were as high as the rates reported in the seminal studies by Rutgeerts *et al.*, when no prophylactic treatment was administered.[23] Most of

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Table 3. Risk factors associated with ePOR at 1 year by multivariable logistic regression analysis

Risk factor	Adjusted OR	95% CI		*p*-value
Female sex	1.6	0.93	2.75	0.091
Past infliximab	1.73	1.01	2.97	0.045
Past adalimumab	2.32	1.35	4.01	0.002
Stapling vs handsewn anastomosis	1.737	0.96	3.16	0.071
Anastomosis type				
End to end	1			
Side to side	0.38	0.17	0.83	0.015
End to side	0.34	0.13	0.92	0.032

ePOR, endoscopic post operative recurrence; anti-TNF, anti-tumour necrosis factor; UST, ustekinumab; VDZ, vedolizumab.
Multivariable logistic regression adjusted for: sex, age at surgery, disease duration, disease behaviour (B phenotype), extraintestinal manifestation, smoking status, biologic naïve at the time of ICR, past infliximab, past adalimumab, past VDZ, past UST, past ICR, surgical properties (open vs laparoscopic and type of anastomosis [stapler vs. handsewn]), anastomotic type (end-to-end vs end-to-side vs side-to-side anastomosis) and prophylactic treatment group (either anti-TNF, VDZ or UST).

these studies have significant methodological heterogeneity; thus, these cohorts cannot be directly compared. However, one study from the ENEIDA Registry investigated the impact of early prophylaxis with anti-TNF following ICR [a median time of 29 days after surgery]. It demonstrated an overall lower rate of ePOR, reaching 34%.[20] This observation, together with the 40% ePOR rate in our cohort, where most patients also started prophylaxis early after ICR [a median time of 1.7 months from surgery], may suggest an advantage to the strategy *early prophylactic therapy* vs *endoscopy-driven management* for high-risk patients in the postoperative setting.

Data on VDZ and UST as POR prophylaxis are scarce.[9,10] In our real-world cohort, only 25% received prophylactic therapy with either VDZ [n = 39] or UST [n = 34]. These groups were relatively small and consisted of distinct refractory patients different from the anti-TNF group; thus, we used a propensity score analysis considering all relevant variables. We used the IPTW approach to compare the risk of ePOR at 1 year. After controlling for disease severity characteristics, we showed that postoperative treatment with UST or VDZ resulted in a similar ePOR risk to prophylaxis with anti-TNF. A comparison of the UST vs VDZ groups revealed an increased 1-year ePOR risk among UST-treated patients (OR 3.75 [95% CI 1.33–10.6, p = 0.012]). These findings should be interpreted with caution as the numbers were small, and our analysis allows only for approximation of randomization. Further investigation of larger populations in a prospective randomized trial is required to address effects of UST vs VDZ on ePOR.

Discordant endoscopic, biochemical and clinical recurrence rates were noted for the various agents, specifically the VDZ and UST groups. Several factors could account for the discordant biochemical and endoscopic recurrence rates in our cohort; first, it is well established that there is high variability in FC levels in patients with CD.[24] Likewise, it has been previously shown that the sensitivity of FC for assessing either endoscopic healing or endoscopic inflammation in the postoperative setting is only moderate.[25–27] In fact, it was shown that the trajectory of serial FC measures is a better indicator of ePOR compared with a single FC measure [as was taken in our cohort].[28] Furthermore, endoscopic healing may miss residual histological inflammation,[29] possibly explaining some of the discrepancies in FC measurements. Regarding CRP, levels were only mildly elevated [up to 3–4 times the upper limit of normal], and we had only one measurement at each time period, while data regarding the trajectory of repeated CRP levels were missing. While postoperative endoscopy only reaches the anastomosis, it is possible that more proximal inflammation may confound endoscopic measures of inflammation that were reflected by either elevated FC and/or CRP.[30] Ultimately, it is important to acknowledge that both the VDZ and UST groups were very small, and we believe that most of this variability is explained by the small sample size in these groups and, therefore, clear conclusions cannot be drawn. Inconsistency between clinical and endoscopic recurrence is a well-known phenomenon in CD, and other factors may contribute to the symptoms reported by the patients in this cohort, including bile acid diarrhoea, bacterial overgrowth, infections and functional factors.

In our cohort, pre-surgical exposure to an anti-TNF was a predictor of ePOR. A similar finding was observed in other real-world cohorts.[22] Pre-surgical exposure to anti-TNF is a marker for more refractory and long-standing disease. Continuation of anti-TNF treatment after surgery resulted in a similar numerical rate of ePOR as switching to a different mechanism of action. Our findings corroborate the previous report by Assa and colleagues, showing that re-introduction of the same anti-TNF agent that had failed to prevent surgery is an effective strategy for preventing postoperative recurrence.[31]

Our study also showed that surgical technique might be a factor in the risk of ePOR; a side-to-side anastomosis was shown to be a protective factor for ePOR (adj. OR 0.38 [95% CI 0.17–0.83, p < 0.015]). Indeed, in the past decade, evidence in favour of a side-to-side anastomosis has emerged and been confirmed.[3] Similarly, a network meta-analysis of 11 trials and 1113 patients confirmed the superiority of stapled side-to-side anastomosis in overall complications, clinical recurrence and reoperation for recurrence.[32] Moreover, we noted that patients who underwent laparoscopic surgery trended towards a better outcome with lower ePOR rates compared with patients who underwent an open surgery [37% vs 47.5%, p = 0.072]; this was probably driven by the fact that patients with the less complicated disease are referred for laparoscopy rather than open surgery.

Our study has several important strengths. It is a large multicentre study focusing on a select population who underwent curative ICR and started early prophylaxis therapy. It

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contributes novel data on the use of newer biologics in the setting of early postoperative prophylaxis with a biologic in a real-world environment. This study also demonstrates the complexity of preventing disease recurrence in treatment-experienced patients. Limitations include the relatively small sample of patients treated with newer biologic agents, the retrospective study design, variability in the timing of endoscopic evaluation, the lack of central reading, and missing data for the 2- and 3-year periods, as well as lack of data regarding the reason for biologic failure before surgery. We also acknowledge potentially missing some patients who did not complete a colonoscopy after starting prophylaxis [either complete remitters or treatment failures]; however, facing the nature of this refractory population and the standards of care in the participating centres, we assume that these cases represent the minority. Similarly, Kaplan–Meyer analysis was not performed in this study as the nature of endoscopic evaluation in the postoperative setting is a follow-up examination that is scheduled based on physician/patient preferences/willingness and health insurance coverage, and it is not conducted to assess clinical exacerbation to confirm or exclude active disease. We do not report rates of endoscopic progression [the transition rates from RS i2 to RS i3–4] through time, and we do not report other risk factors associated with ePOR such as myenteric plexitis as these data were not collected. Finally, this study was underpowered for an insightful comparison of the effectiveness of the three studied prophylactic agents.

6. Conclusion

In this real-world cohort of patients with CD who underwent curative ICR, rates of ePOR at 1 year were 40% and remained stable through 3 years. Patients treated with VDZ or UST prophylaxis comprised a more refractory group. After controlling for disease severity characteristics, there were no differences in ePOR risk between anti-TNF prophylaxis and the other treatment groups. Our findings highlight the need for more effective therapeutic strategies in the postoperative setting, particularly for refractory patients.

Funding

This work was not supported by any financial contribution.

Conflict of Interest

HY: reports receiving research grants from Pfizer; consultancy, advisory, and speakers' fees from: AbbVie, Janssen Pharmaceuticals, Pfizer and Takeda. JS: Speaker's fees: Abbvie, Falk, Takeda, Janssen, and Fresenius. Consultancy fees: Janssen, Ferring. Research support: Galapagos. GJM: Advisor/lecturer for AbbVie, Celgene, Celtrion, Ferrirng, Genesis, Hospira, Janssen, MSD, Mylan, Pfizer, Takeda, Vianex, Falk Pharma; Consultation fees for AbbVie, MSD and Takeda; research support from AbbVie, Genesis, Vianex, MSD, and Ferring. AA: consulting and/or advisory board fees from AbbVie, Allergan, Amgen, Arena, Biogen, Bristol-Myers Squibb, Celgene, Celltrion, Ferring, Gilead, Janssen, Lilly, MSD, Mylan, Pfizer, Samsung Bioepis, Sandoz, Takeda; lecture and/or speaker bureau fees from AbbVie, Amgen, Biogen, Ferring, Gilead, Janssen, MSD, Mitsubishi-Tanabe, Nikkiso, Novartis, Pfizer, Sandoz, Samsung Bioepis, Takeda; and research grants from MSD, Pfizer, Takeda, Biogen. DP: speaker fees from Janssen, Pfizer, Takeda and Galapagos; Advisory Board from Pfizer. FF: Janssen, Pfizer, MSD, Abbvie. GF: Janssen, Takeda, Pfizer, Amgen, Sandoz, Ferring, Samsung Bioepis, Galapagos, Vifor. DD: speaker, a consultant and an advisory board member for MSD, Abbvie, Takeda, Pfizer, Janssen, Amgen, Biogen and Krka. TK: speaker for Takeda, Abbvie, Pfizer, Janssen and Amgen. NM: speaking and/ or consulting fees from Pfizer, Takeda, Janssen, Ferring, BiomX, BMS, Nestle and grant support from Takeda, Janssen, Abbott, Pfizer, BMS, Corundum Innovation Ltd. FC: speaker, a consultant and an advisory board member from Abbvie, Takeda, Jansen, Pfizer, Biogen, Fresenius, Sandoz. OMN: speaker fees from Janssen, Ferring, Pfizer. KF: speaker's honoraria from AbbVie, Janssen, Ferring, Takeda and Goodwill Pharma. TM: speaker's honoraria from MSD, AbbVie, Egis, Goodwill Pharma, Takeda, Pfizer and Teva. ZK: Janssen, Abbvie, Takeda, Celltrion, Pfizer- speaker honoraria. MB: Janssen, Abbvie, Takeda, Pfizer- speaker honoraria. CB: Janssen, Abbvie, Takeda. MC: speaker, as consultant or has received research or education funding from MSD, Abbvie, Hospira, Pfizer, Takeda, Janssen, Ferring, Shire Pharmaceuticals, Dr. Falk Pharma, Tillotts Pharma, Biogen and Gilead. SN: Janssen, Abbvie, Takeda, MSD, Pfizer, Tillots Pharma, Novartis. TL: Financial support for research from Abbvie, Viatris, MSD, Mundipharma, Biogen, Janssen, Pfizer and Takeda; Speaker fees from Ferring, MSD, Abbvie, Janssen, Amgen, Fresenius Kabi, Galapagos, Viatris and Takeda; Consultancy fee from Janssen, Galapagos, Amgen, Bristol Myers Squibb Fresenius Kabi and Takeda. JPG: speaker, a consultant and advisory member for or has received research funding from MSD, Abbvie, Pfizer, Kern Pharma, Biogen, Mylan, Takeda, Janssen, Roche, Sandoz, Celgene, Gilead, Ferring, Faes Farma, Shire Pharmaceuticals, Dr. Falk Pharma, Tillotts Pharma, Chiesi, Casen Fleet, Gebro Pharma, Otsuka Pharmaceutical, and Vifor Pharma. SS: AbbVie, Takeda, Janssen, Arena, Gilead. PB: financial support for research from AbbVie, Mundipharma, Pfizer, Janssen, Amgen and Mylan; lecture fees from AbbVie, Takeda, Pfizer and Janssen; advisory board fees from Abbvie, Arena pharmaceuticals, BMS, Takeda, Hospira, Janssen, MSD, Mundipharma, Roche, Pfizer, Sandoz, Galapagos, PSI-CRO and Pentax. FH: speaker for Abbvie, Janssen-Cilag, MSD, Takeda, Celltrion, Teva, Sandoz and Dr Falk. Funding [Grants/Honoraria]: Dr Falk, Janssen-Cilag, Abbvie, Takeda. Consulting Fees: Celgene. CV: Janssen. JT: speaker fees from Janssen and consulting fees from Arena Pharmaceuticals, Pfizer, Gilead and Galapagos. KK: speaker fees from Abbvie, Aenorasis, Janssen, MSD, Pfizer and Takeda. Consultation or advisory board member fees from Abbvie, Amgen, Ferring, Galenica, Genesis, Janssen, MSD, Pfizer and Takeda. ES: lecture or consultancy fees from Abbvie, Amgen, Bristol-Myers Squibb, Fresenius Kabi, Janssen, Merck & Co, Sandoz, Sofar, Takeda. CCS: Janssen. RW: speaker for Takeda, AbbVie and Janssen. CE: speaker, a consultant or an advisory board member for Takeda, Janssen Cilag, Pfizer, Abbvie, and has received research funding from the Regional Agreement on Medical Training and Clinical Research between Region Örebro County and Örebro University: ALF. IEK: Advisory board member for Abbvie, Astelas, Genesis, Janssen, MSD, Pharmacosmos, Pfizer, Shire and Takeda; Speaker for AbbVie, Astelas, Genesis, Janssen, MSD, Takeda and Mylan; research support Abbvie and Ferring. JKL: Speaker and connsultancy fees: Abbvie, Arenna pharma, Galapagos, Janssen, MSD, Pfizer, Takeda and Tillots. Reserarch support: Galapagos

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and Takeda. EL: Speaker fee: Janssen, Research support: GalapagosEC: lecture fees for Abbvie, Takeda, Pfizer, Sandoz and Janssen. FZ: lecture fees for Janssen, Takeda. DGR: Janssen, Abbvie. ID: Advisory board, consultation and speaking fees from: Janssen, Abbvie, Takeda, Pfizer, Genentech/Roche, Arena, Neopharm, Gilead, Galapagos, Celltrion, Rafa Laboratories, Ferring, Falk Pharma, Cambridge Healthcare, Sublimity, Sandoz, Sangamo, Nestle, Wild bio, Food industries organization, Integra Holdings, Athos, Iterative Scopes, Celgene/BMS, Abbott. UK: Research support: Takeda Medtronic Jannsen. Advisory/speaker fees- Abbvie Jannsen BMS Takeda Novartis Medtronic Rafa Pfizer. ABS: reports consulting/advisory fees from Takeda, Janssen, Neopharm Pfizer and AbbVie; Speaking and teaching fees from Takeda, Janssen, AbbVie, Neopharm, and Pfizer; and research support from Takeda and Janssen. HAB, AK, OK, SH, KM, SY, RS, EC, MLM, ML, MT, IAB, JEO, SS, PB, JS, AP, JR, MV, PM, ET, PE, DBH, TN, KF, GS, RF, YS, IG, HBE, YB, MAG: none.

Acknowledgments

The authors thank Ms Vardit Shay, the study research coordinator, who greatly contributed to data collection.

Author Contributions

Guarantor of the article: HY. Study concept and design: HY. Data integration and project manager: MAG. Statistical analysis, data analysis and interpretation: HY and MAG. Writing the manuscript: HY, MAG, IAB, KEO. Data acquisition and manuscript critical revision: HY, HAB, AK, OK, JS, SH, GJM, KM, DP, AA, FF, GF, DD, TK, SY, NM, FC, OMN, RS, KF, TM, ZK, MB, EC, MLM, UK, CB, ABS, ML, MC, MT, SN, IAB, JO, ID, TL, JPG, SS, PB, PB, JS, FH, CV, AP, JT, JR, KK, MV, ES, PM, ET, PE, CCS, RW, DBH, TN, CE, IEK, KF, JKL, EL, GS, EC, FZ, RF, DGR, YS, IG, HBE, YB, MAG. All authors approved the final version of the manuscript.

Conference Presentation

Oral Abstract presentation at Israeli Week of Gastroenterology July 2021 [virtual], Poster presentation at ECCO Congress February 2022, Vienna, Austria.

Data Availability

The data underlying this article were provided by the ePOR study group collaborators. The data cannot be shared publicly for the privacy of individuals who participated in the study. The data will be shared on reasonable request to the corresponding author with the permission of ePOR collaborators.

Supplementary Data

Supplementary data are available online at *ECCO-JCC* online.

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