Perioperative Use of Vedolizumab is not Associated with Postoperative Infectious Complications in Patients with Ulcerative Colitis Undergoing Colectomy

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Abstract

Background and Aims: Preoperative use of vedolizumab has been associated with increased short-term postoperative infectious complications. We assessed this risk in a single-centre cohort of patients with ulcerative colitis undergoing colectomy.

Methods: Chart review was performed for all colectomies between 2006 and 2016. Short-term postoperative [non]infectious complications were evaluated within 30 days after colectomy. The comprehensive complication index was calculated based on all reported events.

Results: We identified 170 eligible patients [46% female, median age 40 years]. Thirty-four patients [20%] received vedolizumab within 16 weeks, 60 [35%] received anti-tumour necrosis factor [TNF] within 8 weeks, 32 [19%] received a moderate-to-high dose of prednisone and 71 [42%] received other therapies at colectomy. Pouch construction was performed at first stage in 47 patients [28%], and less frequently in patients under vedolizumab, anti-TNF or steroids [all p < 0.01]. Sixty-two short-term infectious and 75 noninfectious complications were reported in, respectively, 49 [29%] and 64 [38%] patients. Only pouch construction at first stage of surgery was independently associated with short-term postoperative infectious (odds ratio 2.40 [95% confidence interval 1.18–4.90], p = 0.016), overall complications (3.1 [1.52–6.40], p = 0.002) and more severe complications (comprehensive complication index 20.9 [0.0–30.8] vs 0.0 [0.0–20.9], p = 0.001). Perioperative medical therapy [including vedolizumab] did not influence short-term outcome, either in the overall population or in the subpopulation of patients with pouch construction at a second stage.

Conclusions: Perioperative use of vedolizumab was not associated with short-term postoperative [infectious] complications. However, postponing pouch construction to a second stage of surgery is advisable in patients under biological therapy or moderate-to-high doses of steroids.
1. Introduction

Ulcerative colitis [UC] is a chronic inflammatory bowel disease [IBD] characterized by inflammation of the colonic mucosa causing relapsing episodes of bloody diarrhoea. The introduction of anti-tumour necrosis factor [anti-TNF] agents dramatically impacted the treatment of UC, since they are not only able to induce and maintain [steroid-free] clinical remission, but are also associated with fewer relapses, lower hospitalization and colectomy rates, and increased quality of life.1-4 More recently, vedolizumab [EntyvioTM, Takeda Pharmaceuticals], a humanized monoclonal antibody to the α4β7-integrin, also showed efficacy in treatment of moderate-to-severe UC.6-7

In an integrated analysis of all pivotal trials with vedolizumab, its long-term safety was evaluated.8 In this cohort of 2 830 patients with 4811 person-years of vedolizumab exposure, no increased risk of [serious] infections was reported. Although vedolizumab can probably be regarded safer than anti-TNF therapy based on its gut-selective mode of action, data on surgical outcomes only recently became available. In a sub-analysis of the GEMINI 1 dataset, postoperative complications were reported in, respectively, 13.3% [2/15] and 33.3% [1/3] of patients who preoperatively had been treated with vedolizumab or placebo.9

Recent data from the Mayo Clinic [Rochester, MN, USA] suggested increased short-term infectious complications in patients with Crohn’s disease or UC undergoing abdominal surgery within 12 weeks of vedolizumab.10 Within 30 days of surgery, patients in the vedolizumab group more often had surgical site infections compared to patients in the anti-TNF and no biological group [37% vs 10% vs 6%, respectively, p < 0.01] and postoperative infections overall [53% vs 28% vs 33%, respectively, p < 0.01]. In multivariate analysis, use of vedolizumab within 12 weeks of surgery was the only independent predictor of surgical site infections. Although many methodological issues could be raised, it remains crucial for both patients and physicians to understand potential risks of biological therapies in patients who might need to undergo colectomy.

We assessed the risk of perioperative use of vedolizumab in development of short-term postoperative complications in patients with UC undergoing a colectomy.

2. Materials and methods

2.1. Patient population

Through a prospectively maintained surgical database, we identified all patients with UC undergoing a colectomy at the University Hospitals of Leuven [Leuven, Belgium]. The 10-year selection period ran from September 2006 [initiation of vedolizumab studies in our referral centre] to September 2016. Diagnosis of UC was confirmed after review of medical and pathological records.11,12 Exclusion criteria were the anticipated construction of a permanent ileostomy and the preoperative use of other investigational products than vedolizumab within 16 weeks of first stage of surgery. Clinical charts of all patients were reviewed to trace sex, age at diagnosis, age and disease duration at first stage of surgery, presence of primary sclerosing cholangitis, smoking behaviour, familial history of IBD, extent of disease prior to colectomy, body weight, body mass index [BMI], medical therapy at first stage of surgery, indication for surgery [intractable disease vs dysplasia or cancer], haemoglobin, C-reactive protein [CRP] and serum albumin at first stage of surgery.

Surgical characteristics included type of surgery [open vs laparoscopy, urgent vs elective colectomy], type of pouch–anal anastomosis [stapled vs hand-sewn], pouch design [J-pouch or other], number of stages [one-, two-, modified two- or three-stage procedure]. An urgent surgical procedure was defined as a procedure performed during a hospitalization which was initially planned to start or optimize medical therapy. The first stage consisted of either a restorative proctocolectomy and ileal pouch–anal anastomosis [IPAA] without [one-stage] or with a diverting ileostomy [two-stage], or consisted of a total colectomy with ileostomy. In the latter scenario, a restorative proctectomy with IPAA was only performed during a second stage, without [modified two-stage] or with diverting ileostomy [three-stage].

Over the study period, surgery was performed by three experienced abdominal surgeons [AD, AdBvO, AW]. The decision to perform a total colectomy with ileostomy was based on the clinical appreciation of the severity of disease. Follow-up data were obtained by standardized and regular outpatient visits which included detailed history, clinical examination and further imaging if indicated.

2.2. Preoperative medical therapy

Based on their half-lives, preoperative use of vedolizumab was defined as a last infusion within 16 weeks, and preoperative use of anti-TNF as a last administration of anti-TNF within 8 weeks of first stage of surgery.13 Preoperative corticosteroid use was divided into three groups: high dose [intravenous or oral methylprednisolone ≥40 mg/day], moderate dose [oral ≥20 mg/day for more than 2 months] and low-dose [oral < 20 mg/day or oral ≥20 mg/day for less than 2 months].14 Patients who had stopped methylprednisolone prior to colectomy were not classified in the steroids group, regardless of the duration between last administration and colectomy. Based on previous observations we looked specifically at the subgroup of patients using a moderate-to-high dose of steroids.15 Patients who did not receive one of the aforementioned medical therapies were defined as ‘other therapy group’. This group included patients on mesalamine, topical steroids, a low dose of systemic steroids, thiopurines, methotrexate, calcineurin inhibitors, antibiotics or no therapy.

To facilitate comparison with the data published by Lightner et al., we also performed a separate analysis for patients who had received vedolizumab, infliximab or no biological therapy within 12 weeks of surgery.10

2.3. Short-term postoperative complications

Short-term postoperative complications were recorded within the first 30 days after first stage of surgery. Infectious complications were divided into pouch-specific, surgical site and nonsurgical site infectious complications. Pouch-specific complications included anastomotic leaks with or without need for antibiotics or re-laparotomy,16 while surgical site infections included superficial and deep wound infections.17 Nonsurgical site infections included gastroenteritis, respiratory tract infections, urinary tract infections, catheter sepsis, fever of unknown origin, oral candidiasis, oral aphthous ulcers, toxic exanthema and spondylodiscitis. Short-term noninfectious
complications included prolonged ileus, [sub]obstruction, anaemia with or without need for transfusion, dehydration, venous thrombo-
sis, urinary retention, pneumothorax, compression neuropathy, liver
decompensation and arrhythmias.

Each short-term postoperative complication was classified
according to Clavien–Dindo criteria.28 Furthermore, the compre-
hensive complication index [CCI] was calculated based on all complica-
tions reported within 30 days of first stage of surgery.25 The recently
developed CCI is based on the Clavien–Dindo classification for post-
operative morbidity and is calculated using a predefined formula,
resulting in a number between 0 and 100. This number reflects severity
of complications and has the advantage to include all occurring
complications in contrast to the ‘classical’ Clavien–Dindo classifica-
tion, which only takes the most severe complication into account,
omitting all concurrent morbidity. A Clavien–Dindo I complication
[minor complication] would, for example, result in a score of 8.7
on the CCI scale, while a Clavien–Dindo IIIa complication [major
complication] is represented by 26.2 on the same scale. CCI was cal-
culated by using the online CCI calculator [www.assesssurgery.com].

Finally, readmission rates within 30 days of first stage of surgery
were also assessed.

2.4. Statistical analysis
Chi-square, Fisher exact, Mann–Whitney and backward Wald mul-
tiple binary logistic regression were performed using the IBM SPSS
Statistics 23.0 software package. Besides some predefined variables
[perioperative use of vedolizumab, anti-TNF or a moderate-to-high
dose of steroids], variables associated with postoperative complica-
tions in univariate analysis were first assessed for collinearity and
examined in multivariate analysis thereafter to define independent
contributions of each of these factors. The threshold for statistical
significance was predefined at \( p < 0.05 \).

3. Results
3.1. Study population
Overall, 192 patients with UC underwent acolectomy. Eight patients
were excluded because they underwent proctocolectomy with perma-
nent ileostomy [Figure 1]. Fourteen patients were excluded because
they participated in a clinical trial and may have received another
anti-adhesion molecule than vedolizumab within 16 weeks of first
stage of surgery. The population of interest consisted of 170 patients
[46% female, median [interquartile range, IQR] age 40.1 [30.5–52.0]
years, median disease duration 7.2 [2.4–15.1] years]. The subpopula-
tion consisted of 123 patients who underwent pouch construction at
a second stage. All patients’ characteristics are listed in Table 1.

3.2. Preoperative medical therapy
As shown in Figure 2 and Supplementary Table S1, 32 patients
[19%] were using a moderate-to-high dose of systemic steroids at
first stage of surgery, 60 patients [35%] had received anti-TNF ther-
apy within 8 weeks and 34 patients [20%] had received vedolizumab
within 16 weeks of first stage of surgery. Five patients received both
anti-TNF therapy and vedolizumab in the preoperative setting, but
always as consecutive but not concomitant therapies. The remaining
71 patients [42%] received no or other medical therapy at first stage
of surgery. Details on the preoperative medical therapy in the sub-
population are described in Supplementary Figure S1.

3.3. Surgical characteristics
By September 2016, 160 out of 170 patients had completed all surgi-
cal stages with construction of an IPAA and restoration of the faecal
stream [Table 1]. In four patients the final surgical procedure was
planned after September 2016. In another three patients the final
procedure was postponed due to postoperative complications \( n = 2 \)
or diagnosis of a lymphoma in the resection specimen \( n = 1 \). Finally,
in three patients the IPAA had not yet been constructed on a specific
patient’s request.

In 47 patients [28%] the pouch was constructed during first stage
of surgery. As shown in Supplementary Table S2, pouch construction
was more often postponed to a second stage in patients with intract-
able disease, an urgent procedure or in the presence of other factors
suggesting disease severity [increased CRP, low haemoglobin, low
serum albumin]. Furthermore, pouch construction was more often
postponed to a second stage in patients under moderate-to-high
doses of steroids [100% vs 66%, odds ratio 1.52 [95% confidence
interval [CI] 1.35–1.71], \( p < 0.001 \), anti-TNF [85% vs 65%, odds
ratio 2.99 [1.35–6.73], \( p = 0.006 \)] or vedolizumab [91% vs 68%,
odds ratio 4.94 [1.43–17.05], \( p = 0.005 \)].

3.4. Short-term postoperative complications
During the first 30 days after surgery, 86 out of 170 patients [51%]
developed at least one complication. In 64 patients [38%] this was
at least one noninfectious complication, in 49 patients [29%] at least
one infectious complication. A detailed overview of all short-term
postoperative complications is provided in Supplementary Table
S3. Anastomotic leakage was observed in seven patients [grade A in
two, grade B in two and grade C in three patients]. Six patients who
underwent total colectomy with temporary ileostomy developed
postoperative peritonitis requiring antibiotics. One patient developed
dehiscence of the rectal stump requiring laparotomy. Wound
infections were observed in ten patients [superficial in three, and
deep in seven]. Nineteen patients [11%] needed readmission within
30 days of surgery. The median [IQR] CCI was 8.7 [0.0–22.6]. No
short-term mortality was observed.

3.5. Predictors of short-term postoperative complications
As shown in Figure 3 and Supplementary Table S4, none of the
preoperative medical therapies of interest was associated with an

![Figure 1. Patient disposition. IMP: investigational medical product; IPAA: ileal pouch–anal anastomosis; UC: ulcerative colitis.](https://academic.oup.com/ecco-jcc/article-abstract/11/11/1353/3957970)
increased risk of postoperative infectious or noninfectious complications. Patients who had received vedolizumab within 16 weeks of surgery did not have an increased risk of developing short-term anastomotic leakage (3% vs 4%, odds ratio 0.66 [95% CI 0.08–5.64], p = 1.000), pouch-related infectious complications (3% vs 6%, 0.49 [0.06–4.01], p = 0.689), surgical site infectious complication (12% vs 15%, 0.73 [0.23–2.29], p = 0.788), nonsurgical site infectious complications (12% vs 21%, 0.51 [0.17–1.58], p = 0.328), infectious complications overall (24% vs 30%, 0.71 [0.30–1.71], p = 0.446) or noninfectious complications (24% vs 41%, 0.44 [0.19–1.04], p = 0.057). Patients who had received vedolizumab within 16 weeks of first stage of surgery even had a significantly lower risk of developing any short-term postoperative complication (35% vs 54%, 0.44 [0.19–1.04], p = 0.057). Furthermore, in patients who had received preoperative therapy with vedolizumab, we could not observe a difference in disease
duration between last infusion of vedolizumab and colectomy in patients with and without postoperative complications [data not shown].

The frequency of short-term postoperative complications did not differ when dividing the study period into four consecutive quartile periods of 2.5 years [Supplementary Figure S2]. Also, the median [IQR] CCI remained stable over time (0 [0–20.9] for period 1, 20.9 [0–26.2] for period 2, 0 [0–20.9] for period 3 and 8.7 [0.0–29.6] for period 4, \( p = 0.479 \)). However, pouch construction at first stage of surgery significantly decreased over time [50% in period 1, 42% in period 2, 26% in period 3, 11% in period 4, \( p < 0.001 \)]. The number of patients under vedolizumab [0% for period 1, 10% for period 2, 12% for period 3, 40% for period 4, \( p < 0.001 \)] and the median [IQR] number of biological therapies received prior to colectomy (1 [1–1] for period 1, 1 [1–2] for period 2, 1 [1–2] for period 3, 2 [1–3] for period 4, \( p < 0.001 \)) increased significantly.

For the multivariate analysis, we included not only all preoperative medical therapies of interest, but also the construction of the pouch at first stage of surgery. Other variables associated with short-term postoperative [infectious or noninfectious] complications in univariate analysis were excluded due to co-linearity with construction of the pouch at first stage of surgery [e.g. primary sclerosing cholangitis, dysplasia or cancer] or preoperative medical therapy of interest [mesalamine, topical steroids]. As shown in Table 2, the only variable independently associated with short-term postoperative [infectious or noninfectious] complications was the construction of the pouch at first stage of surgery.

The 30 day CCI and postoperative hospital stay were influenced only by construction of the pouch at first stage of surgery and not by anti-TNF or moderate-to-high dose of steroids [Figure 4]. Patients who had received vedolizumab tended to have a lower CCI and had a significantly lower postoperative hospitalization stay. Similarly, readmission rates were significantly lower in patients who had received vedolizumab (3% vs 21%, odds ratio 0.12 [0.02–0.89], \( p = 0.011 \)).

Also, if we looked at the subpopulations of patients in whom the pouch was constructed at first or second stage, preoperative use of vedolizumab was not associated with short-term postoperative complications [Supplementary Figure S3 and Table S5]. In patients in whom the pouch was constructed at a second stage of surgery, a haemoglobin below 10 mg/dl was the only factor independently associated with short-term infectious complications [Supplementary Table S6]. For short-term noninfectious complications and complications overall in this subpopulation, no independent predictor could be determined. Both CCI and hospitalization stay were not negatively influenced by perioperative therapy [data not shown]. However, patients with a haemoglobin below 10 mg/dl had a higher short-term CCI (20.9 [0.0–29.6] vs 0.0 [0.0–20.9], \( p = 0.044 \)) and a longer postoperative hospitalization stay (9 [7–14] vs 7 [5–10], \( p = 0.001 \)).

Finally, we also performed a similar analysis as in the original paper by the Mayo clinic. As shown in Figure 5, neither preoperative vedolizumab nor preoperative anti-TNF therapy was associated with short-term postoperative [infectious or noninfectious] complications.

4. Discussion

We performed a cohort study of all 170 patients with UC undergoing a colectomy over a 10-year period looking at postoperative

![Figure 2. Preoperative medical therapy, TNF: tumour necrosis factor.](https://academic.oup.com/ecco-jcc/article-abstract/11/11/1353/3957970/1111357357970)

![Figure 3. Short-term postoperative complications. The vedolizumab group consisted of patients who received a last infusion of vedolizumab within 16 weeks of first stage of surgery. The anti-TNF group consisted of patients who received a last administration of anti-TNF within 8 weeks of first stage of surgery. The moderate-to-high dose of steroids group consisted of patients who received a moderate [at least 20 mg prednisone for at least 2 weeks] or high dose [at least 40 mg prednisone] of steroids at first stage of surgery. The other group consisted of all other patients receiving no or other medical therapy. TNF: tumour necrosis factor.](https://academic.oup.com/ecco-jcc/article-abstract/11/11/1353/3957970/1111357357970)
Table 2. Factors associated with short-term postoperative complications after binary logistics multivariate analysis in the total population

<table>
<thead>
<tr>
<th></th>
<th>Infectious Complications, odds ratio [95% CI]</th>
<th>Non-infectious complications, odds ratio [95% CI]</th>
<th>Any Complication, odds ratio [95% CI]</th>
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<tbody>
<tr>
<td></td>
<td><em>p</em>-value</td>
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<tr>
<td>Moderate-to-high dose of steroids at first stage</td>
<td>NS</td>
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<td>NS</td>
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<tr>
<td>Anti-TNF therapy within 8 weeks of first stage</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
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<tr>
<td>Vedolizumab within 16 weeks of first stage</td>
<td>NS</td>
<td>NS</td>
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<tr>
<td>Pouch construction at first stage</td>
<td>2.40 [1.18–4.90], <em>p</em> = 0.016</td>
<td>2.77 [1.39–5.53], <em>p</em> = 0.004</td>
<td>3.11 [1.52–6.40], <em>p</em> = 0.002</td>
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NS: not significant; TNF: tumour necrosis factor; 95% CI: 95% confidence interval.

Figure 4. The 30 day comprehensive complication index (CCI, panel A) and postoperative hospitalization stay after first stage of surgery (panel B). The vedolizumab group consisted of patients who received a last infusion of vedolizumab within 16 weeks of first stage of surgery. The anti-TNF group consisted of patients who received a last administration of anti-TNF within 8 weeks of first stage of surgery. The moderate-to-high dose of steroids group consisted of patients who received a moderate [at least 20 mg prednisone for at least 2 weeks] or high dose [at least 40 mg prednisone] of steroids at first stage of surgery. The other group consisted of all other patients receiving no or other medical therapy. TNF: tumour necrosis factor.
complications. Based on a recent alarming article by Lightner et al.,\textsuperscript{13} we aimed to evaluate the effect of perioperative vedolizumab on the occurrence of both short-term postoperative infectious and noninfectious complications. Furthermore, we compared outcome with that of patients who received anti-TNF therapy, a moderate-to-high dose of steroids or other therapy. In contrast to the recent findings of the Mayo Clinic, we were not able to demonstrate a higher risk of postoperative infectious complications in patients who had received vedolizumab within 16 weeks of first stage of surgery. Furthermore, none of the medical therapies of interest was associated with short-term postoperative [infectious] complications. The only independent risk factor for short-term postoperative infectious and noninfectious complications was pouch construction at first stage of surgery. However, in this subpopulation, perioperative anemia was associated with short-term postoperative infectious complications, a higher CCI and a longer postoperative hospitalization stay.

Although many authors reported no increased safety risk with vedolizumab, short-term postoperative [infectious] complications were mostly not addressed.\textsuperscript{9,20-23} The recent results highlighted in the paper by the Mayo Clinic reflected the surgeons’ concern about blocking leucocyte migration to the intestine in the perioperative setting.\textsuperscript{10} Indeed, leucocytes are a major component of wound healing and failure of appropriate intestinal healing may contribute to anastomotic leaks and organ space surgical site infections. However, vedolizumab mainly blocks lymphocyte trafficking, while mainly neutrophils and macrophages play an important role in wound healing.\textsuperscript{24} These leucocyte subsets are probably not affected by an anti-α4β7-integrin antibody.

As for all retrospective studies, it is unclear if the observed association with perioperative use of vedolizumab proves causality.

In the study by the Mayo Clinic, the cut-off value for preoperative exposure to vedolizumab and anti-TNF therapy was exactly the same, namely 12 weeks.\textsuperscript{25} We decided to categorize the eligible patients differently and based these categories on the clearly different half-life of the biologicals, being 10–14 days for anti-TNF and 25 days for vedolizumab.\textsuperscript{26} We also repeated our analysis using the criteria proposed by Lightner et al., but this did not influence our results.

Meanwhile, two other centres evaluated the risk of vedolizumab in the perioperative setting. Stringfield et al. reported their experience in 26 IBD patients who underwent intra-abdominal or anorectal surgeries while treated with vedolizumab.\textsuperscript{27} The overall rate of infectious complications was 44% with an anastomotic leak rate of 15%. The authors did not observe significant differences in the number of vedolizumab doses, time of surgery since last dose of vedolizumab or number of failed biologic therapies prior to vedolizumab between those with and without postoperative complications. Koh et al. reported their experience in 15 patients with IBD who had failed vedolizumab and required surgery.\textsuperscript{28} Only two patients had a short-term postoperative complication [one wound abscess and one readmission for ileus]. The authors concluded that vedolizumab had a promising safety profile for patients on salvage therapy prior to surgery.

The only independent risk factor for short-term postoperative [infectious and noninfectious] complications in our cohort was the development of the pouch at first stage of surgery. If there is indeed an increased risk linked to preoperative use of vedolizumab, anti-TNF therapy and moderate-to-high doses of corticosteroids, this risk might be overcome by maintaining a more conservative surgical approach and postponing pouch construction to a second stage. Also, in the subpopulation of patients in whom pouch construction was postponed, perioperative medical therapy was not associated with short-term postoperative [infectious or noninfectious] complications. After our previous cohort study, pouch surgery is indeed mostly postponed to a second stage in patients under immunosuppressive therapy.\textsuperscript{14} Other authors have also described lower short-term postoperative infectious complications if pouch construction is postponed.\textsuperscript{29,30}
In the subpopulation of patients in whom the pouch construction was postponed to a second stage of surgery, the only variable independently associated with short-term postoperative infectious complications was perioperative anaemia [haemoglobin below 10 g/dl]. Furthermore, anaemia was also associated with a higher CCI and a longer postoperative hospitalization stay. Perioperative anaemia is a well-known risk factor for postoperative complications, and in this specific situation may be a surrogate marker for severe disease.

Our cohort study has some limitations. First, as for all similar retrospective studies, the sample size was too small to draw any strong conclusions. Furthermore, as for most retrospective studies, we were lacking a good assessment of preoperative disease activity, such as Mayo score or Trueove–Witts index. We only had indirect evidence of increased disease activity, measured by CRP, serum albumin, haemoglobin and concomitant therapies. All these indirect factors of disease severity were associated with a more frequent construction of the pouch in a second stage, but not with an increased risk of postoperative complications. Similarly, we lacked data on serum levels of biological therapies at colectomy. A previous study has suggested increased postoperative complications in patients with higher preoperative anti-TNF serum levels. Next, the inclusion period of 10 years may be associated with different surgical techniques and experience, potentially causing a bias.

We also must consider that our study may be underpowered to detect a difference in short-term postoperative infectious complications. Although our sample size is larger than those in previously published trials, we certainly need large multicentre studies to conclude on the exact detrimental role of preoperative therapy. Such trials should ideally be prospective and take into account all confounding factors, such as disease severity and type of surgery.

In conclusion, in this large retrospective analysis evaluating patients with UC undergoing colectomy, we did not observe an increased risk of postoperative [infectious or noninfectious] complications in patients who recently received vedolizumab. However, a more conservative approach, with pouch construction only at a second stage, seems advisable in patients under biological therapy.

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Conflict of Interest
MF receives financial support for research from Takeda, lecture fees from Tillotts, Ferring, Boehringer-Ingelheim, Janssen, Chiesi, Falk, Zeria, Mitsubishi, MSD, Takeda and Abbvix, and does consultancy for Abbvix, Ferring, MSD, Boehringer-Ingelheim and Janssen. ABO has no financial disclosures. NS has no financial disclosures. MA has no financial disclosures. SV has no financial disclosures. AW has no financial disclosures.

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Author Contributions
MF: study concept and design, data acquisition, data analysis and interpretation, statistical analysis, and manuscript writing; AdBvO, NS, AM, GVA, AW, SV and AD: data acquisition, and critical revision of the manuscript.

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

References


