Vedolizumab and early postoperative complications in nonintestinal surgery: a case-matched analysis

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Abstract

Background: Vedolizumab (VDZ) is a gut-specific α4-β7 integrin antagonist that has demonstrated efficacy in Crohn’s disease (CD) and ulcerative colitis (UC). The safety of VDZ in the perioperative period remains unclear. The aim of this study was to evaluate postoperative complications and perioperative safety in VDZ-treated patients undergoing nonintestinal operations.

Methods: A case-matched study was performed at two inflammatory bowel disease (IBD) referral centers. Adult patients with CD and UC who underwent a nonintestinal surgical procedure during treatment with VDZ were included. Patients who had their last VDZ infusion up to 12 weeks before the procedure were considered exposed and were matched in a 1:1 ratio to patients without VDZ therapy, according to type of surgical procedure, age, and sex. The primary outcome was overall risk of early postoperative infectious complications (up to 30 days after surgery), readmissions, reoperations, surgical site infections, and other infections. The VDZ and control groups were subsequently compared using the Pearson χ² test and Wilcoxon rank sum.

Results: We identified 34 patients treated with VDZ who underwent 36 nonintestinal surgical procedures. These patients were matched with 36 control procedures. Postoperative complications were not different between the VDZ-treated and control cohorts for all outcomes analyzed: infectious complications occurred in 14% versus 8% (p = 0.45), superficial surgical site infections 6% versus 0% (p = 0.15), reoperations 6% versus 3% (p = 0.56) and readmissions 11% versus 6% (p = 0.37).

Conclusions: VDZ-treated patients with IBD undergoing nonintestinal procedures did not have an increased risk of overall postoperative infections or other complications compared with matched controls.

Keywords: antibodies, infection, inflammatory bowel diseases, integrins, monoclonal, postoperative complications

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Introduction

The incidence and prevalence of inflammatory bowel diseases (IBDs), including Crohn’s disease (CD) and ulcerative colitis (UC), seem to be increasing over time, both in the western world as well as in developing countries.1 In parallel, the management of patients with moderate to severe IBD has advanced substantially over the last decades, especially with the approval and widespread adoption of antitumor necrosis factor (TNF) monoclonal antibodies and other biological agents with different mechanisms of action, as well as innovative therapeutic strategies.2,3

Vedolizumab (VDZ) is a human immunoglobulin G anti-α4β7 monoclonal antibody with gut-specific properties that blocks leucocyte trafficking from the circulation to the bowel. The efficacy of VDZ...
in the management of both CD and UC was proved in pivotal trials,\(^4,5\) as well as in real world experiences with the drug,\(^6\) both in patients naïve to or with previous exposure to anti-TNF agents. Furthermore, the favorable safety profile of VDZ has been demonstrated in two different large studies, as a gut-specific agent that tends not to cause systemic immunosuppression.\(^7,8\)

A significant portion of patients with IBD will need surgery during the disease course, although the rates of IBD-related surgery seem to be decreasing in the biological era.\(^9,10\) The impact of preoperative exposure to biological agents on postoperative surgical outcomes is controversial.\(^11\) Two prospective studies have demonstrated that anti-TNF agents can be related to higher rates of postoperative infections after CD-related abdominal surgery.\(^12,13\) However, this has not been confirmed in other meta-analyses and cohort studies.\(^14–16\)

An early study from Mayo Clinic suggested that there may be an increase in overall postoperative infections and surgical site infections (SSIs) after major IBD-related abdominal surgery in VDZ-exposed patients, although this may have been confounded by the impact of severe underlying disease activity.\(^17\) In a cohort of 100 patients with CD, Lightner and colleagues have also found preoperative VDZ exposure to be a risk factor for postoperative infections compared with patients treated with anti-TNF or conventional therapy.\(^18\) In contrast, retrospective cohorts from other jurisdictions have actually demonstrated the opposite effect, with preoperative VDZ not increasing postoperative complication rates.\(^19,20\) A recent meta-analysis, with five studies and 307 patients exposed to VDZ preoperatively, did not show an increased risk for overall postoperative complications or infectious complications.\(^21\) The conclusions of these studies led to controversy regarding this topic, as the mechanism of action and gut specificity of VDZ theoretically would not impair systemic healing or independently increase overall infection risks.\(^22\)

To date, all studies that have analyzed the perioperative impact of VDZ in IBD included IBD-related intestinal surgical procedures. Whether systemic healing could possibly be affected is unclear and there are insufficient data evaluating surgical procedures not related to IBD during VDZ therapy. Therefore, the aim of the present study was to evaluate postoperative complications and perioperative safety in VDZ-treated patients submitted to nonintestinal operations.

**Materials and methods**

**Study design and patient population**

A retrospective case-matched study of patients with IBD treated with VDZ from two tertiary academic care centers (Mayo Clinic, Rochester, MN, USA and University of Calgary, Canada) was conducted. Adult (\(\geq 18\) years) patients were eligible for inclusion if they had a confirmed diagnosis of IBD (CD or UC) by standard endoscopic, radiologic, or histopathologic criteria; subsequently underwent a nonintestinal surgical procedure between 1 January 2014 and 1 November 2017; and had a VDZ infusion up to 12 weeks before the nonintestinal surgical procedure. All patients were evaluated at a minimum of two visits at their respective institution.

Patients undergoing any intestinal surgery (involving any segments of the small bowel, appendix, colon, or rectum), including perianal procedures (whether related or not to the diagnosis of IBD) were excluded. Patients treated with VDZ who had only a single encounter visit at the involved institution (for example, for a second opinion), but were not followed after the initial appointment, were excluded due to insufficient data for analysis.

VDZ-treated patients were compared with a matched control cohort of patients without IBD who underwent a similar nonintestinal surgical procedure over the same period of time in a 1:1 ratio. Patients from the control group were also matched to the included patients according to age and sex. All control patients and procedures were randomly selected from electronic databases.

**Data collection**

Data were collected independently by four authors (PGK, NM, AA, and AL) from electronic databases from both institutions via chart review. Informed consent was waived by the ethical boards from both institutions, in accordance with requirements for retrospective analysis of patients from internal databases. Patient demographics
including age, sex, subtype of IBD (CD or UC), disease phenotype as defined by the Montreal Classification, smoking status, disease duration from diagnosis to the surgical procedure, body mass index (BMI) at time of surgery, laboratory parameters (albumin, C-reactive protein, hemoglobin and complete blood count) within 1 month preoperatively, and types of surgical procedures were collected. Medication history including biologic exposure and perioperative immunosuppression (corticosteroids, azathioprine, or methotrexate) were additionally recorded.

**Outcomes**
The primary outcome was the 30-day postoperative infectious complication rate as defined by both medical postoperative infections (urinary tract infections, pneumonia, positive serum blood cultures) and surgical infectious complications (superficial and deep space SSIs). Superficial SSI was defined by clinical assessment, need for opening a wound due to concern for infection, or prescription of antibiotics for a wound infection. Deep space SSIs were defined as an intracompartmental abscess. Other postoperative data included need for unplanned hospital readmission, unplanned return to the operating room, and 30-day postoperative mortality.

**Statistical analysis**
Statistical analysis was performed using JMP, version 10.0.0 (SAS Institute Inc., Cary, NC, USA). Baseline patient characteristics were analyzed using standard descriptive statistics; medians with interquartile ranges (IQRs) were calculated for continuous data and proportions were calculated for categorical data. Comparisons between baseline characteristics and postoperative outcomes between the VDZ-treated and control cohorts were performed using the Pearson χ² test or Fisher exact test for categorical data and Wilcoxon rank sum for nonparametric continuous variables. A p value less than 0.05 was considered to be statistically significant.

**Ethical considerations**
This study was approved by the Institutional Review Board and Human Research Ethics Board at Mayo Clinic (reference number 17-010043) and the University of Calgary (reference number REB16-1779_MOD1), respectively.

**Results**

**Patient identification**
The study flow diagram is illustrated in Figure 1. A total of 377 patients with IBD treated with VDZ were initially considered for the study (155 from Mayo Clinic and 222 from the University of Calgary). Of these, 34 patients underwent nonintestinal surgical procedures during VDZ therapy and were included in the study. These 34 patients underwent 36 nonintestinal surgical procedures (two patients underwent two different, unrelated surgical procedures each, occurring greater than 1 year apart). The control cohort was matched to the VDZ-treated cohort by type of surgical procedure, and then by patients’ age and sex.

**Patient characteristics**
Of the 34 patients, 28 (82.4%) had a diagnosis of CD and 6 UC (17.6%). In total, 8 of the 36 procedures (22.2%) were performed in patients with UC and 28 in those with CD (77.8%). Demographic characteristics of the patients are described in detail in Table 1. Patients in the VDZ-treated group had lower median BMI compared with controls (24.0 versus 31.4 kg/m², p = 0.0003) while patients in the control group had a higher prevalence of diabetes mellitus (14% versus 0%, p = 0.02).

**Surgical procedures**
Table 2 demonstrates the types of surgical procedures that were included in the analysis. A myriad of different surgical procedures in different systems were performed, from simpler operations (e.g. septoplasty or ureteric stenting) to major surgery (e.g. liver transplant, radical vulvectomy, mastectomy, neck dissection).

**Postoperative complications**
A comparison of postoperative complications between the VDZ-treated and control groups is summarized in Table 3. The mean period between the last dose of VDZ and the surgical procedure was 5.11 weeks (ranging from 1 to 8 weeks). VDZ-treated patients had similar frequency of complications compared with controls in overall infectious complications (14% versus 8%, p = 0.45), surgical infectious complications (11% versus 3%, p = 0.16), and nonsurgical infectious complications (6% versus 6%, p = 1.00).
**Figure 1.** Study flowchart, patients and distribution of procedures. VDZ, vedolizumab.

**Table 1.** Demographic characteristics of the 34 included patients, ASA (American Society of Anesthesiologists) scores adapted for 36 procedures.

| Variable                      | Vedolizumab     | Non-vedolizumab | p value |
|-------------------------------|-----------------|-----------------|---------|
| Age (years), median (IQR)     | 51 [37–63]      | 55 [38–66]      | 0.55    |
| Female, n (%)                 | 26 (72)         | 26 (72)         | 1.0     |
| Median BMI, kg/m² (IQR)       | 24.0 [21.3–28.3] | 31.4 [26.3–39.3]| 0.0003  |
| Smoking, n (%)                |                 |                 |         |
| Yes                           | 1 [3]           | 2 [6]           | 0.36    |
| No                            | 30 [83]         | 24 [67]         |         |
| Former                        | 5 [14]          | 10 [28]         |         |
| Diabetes mellitus, n (%)      | 0               | 5 [14]          | 0.02    |
| ASA physical status, n (%)    |                 |                 |         |
| I                             | 4 [11]          | 2 [6]           | 0.17    |
| II                            | 21 [58]         | 13 [38]         |         |
| III                           | 10 [28]         | 15 [44]         |         |
| IV                            | 1 [3]           | 4 [12]          |         |
| Missing                       | 0               | 2               |         |

BMI, body mass index; IQR, interquartile range.
Additionally, no differences were found in terms of superficial SSI (6% versus 0%, \( p = 0.15 \)), reoperations (6% versus 3%, \( p = 0.56 \)), or readmissions (11% versus 6%, \( p = 0.37 \)). As seen, despite higher absolute numbers and percentages in the VDZ-treated patients, no statistical differences were found. No cases of postoperative pneumonia and no postoperative deaths occurred.

Two patients in the VDZ group had postoperative urinary tract infections (one after a robotic hysterectomy for endometriosis and another after left ureteric stenting). Two cases of superficial SSI were also observed (one after a total abdominal hysterectomy that required drainage and packing, and another case after a radical vulvectomy that required drainage and systemic antibiotics). Two cases with intra-abdominal abscesses (one after a robotic hysterectomy and another after a Stoppa conventional hernia repair) were treated with percutaneous drainage and antibiotics. Two patients required return to the operating room: one case for thoracocentesis due to extensive pleural effusion after a bone marrow transplantation, and another case for restenting of the ureter after obstruction and urinary tract infection. Four VDZ-treated patients required readmission, the aforementioned two cases of pelvic abscess (after robotic

### Table 2. Nonintestinal surgical procedures performed.

| Procedure performed          | Number of cases | Details                                                                 |
|------------------------------|-----------------|------------------------------------------------------------------------|
| Hernia repair                | 8               | 3 laparoscopic, 2 umbilical, 2 Stoppa, 1 incisional                     |
| Hysterectomy                 | 4               | 2 robotic, 1 vaginal, 1 conventional [this is for cervical carcinoma]  |
| Liver transplant             | 4               | 3 cadaveric (for PSC), 1 living donor [for cholangiocarcinoma]         |
| Ureteroscopy and stone removal | 3     | 2 left sided and 1 right sided                                       |
| Total knee replacement        | 2               |                                                                        |
| Hysteroscopy                 | 2               |                                                                        |
| Hip replacement               | 2               |                                                                        |
| Open cholecystectomy          | 1               |                                                                        |
| C-section                    | 1               |                                                                        |
| Allogenic bone marrow transplant | 1           | For aplastic anemia. Sibling as a donor                               |
| Septoplasty                  | 1               |                                                                        |
| Mastectomy                   | 1               | For invasive breast cancer                                           |
| Implantation of cardiac defibrillator | 1            |                                                                        |
| Laparotomy and muscle flap   | 1               | For incarcerated ventral hernia                                       |
| Neck dissection              | 1               | For recurrent laringeal squamous cell carcinoma                       |
| Radical vulvectomy           | 1               | For squamous cell carcinoma                                          |
| Salpingo oophorectomy        | 1               | For ruptured ovarian cist                                            |
| Thyroid lobectomy            | 1               | For goiter                                                            |

C-section, cesarean section; PSC, primary sclerosing cholangitis.
hysterectomy and postoperative Stoppa hernia repair), the case of restenting the ureters as well as one patient who suffered a stroke 2 weeks after radical vulvectomy.

**Discussion**

The perioperative safety of VDZ in patients with IBD undergoing intestinal surgical procedures remains controversial, with conflicting data from different tertiary care centers as to whether preoperative VDZ exposure increases the risk of postoperative infectious complications in IBD surgery. Lightner and colleagues reported that 36% of the 94 patients with IBD with previous VDZ exposure developed postoperative SSIs, and VDZ patients experienced higher rates of overall infectious complications compared with patients treated with anti-TNF or conventional therapy (37% versus 10% and 13% respectively, \( p < 0.001 \)). Similarly, experiences from other institutions demonstrated the opposite effect. The experience from Leuven, Belgium, in 34 surgical patients with IBD showed that 26 of 34 (76%) experienced SSIs, 22 of whom had previous VDZ exposure. This study suggests that the higher rate of SSIs in the VDZ group was not due to the influence of VDZ per se, but rather due to the increased risk of SSIs and postoperative infections: Lightner and colleagues reported that 36% of the 94 patients with IBD with previous VDZ exposure developed postoperative SSIs, and VDZ patients experienced higher rates of overall infectious complications compared with patients treated with anti-TNF or conventional therapy (37% versus 10% and 13% respectively, \( p < 0.001 \)).

| Variable                        | VDZ n (%) | Non-VDZ control n (%) | \( p \) value |
|---------------------------------|-----------|-----------------------|---------------|
| Overall infectious complications | 5 (14)    | 3 (8)                 | 0.45          |
| Surgical infectious complications| 4 (11)    | 1 (3)                 | 0.16          |
| Nonsurgical infectious complications | 2 (6)    | 2 (6)                 | 1.0           |
| Urinary tract infection         | 2 (6)     | 1 (3)                 | 0.56          |
| Pneumonia                       | 0         | 0                     | –             |
| Positive blood cultures         | 0         | 1 (3)                 | 0.31          |
| Superficial SSI                 | 2 (6)     | 0                     | 0.15          |
| 30-day return to operating room | 2 (6)     | 1 (3)                 | 0.56          |
| 30-day unplanned hospital readmission | 4 (11) | 2 (6)                 | 0.37          |
| Mortality                       | 0         | 0                     | –             |

SSI, surgical site infection; VDZ, vedolizumab.
UC and previous VDZ did not find an association between anti-integrin use and short-term postoperative infections. Only pouch construction at the first stage was significantly associated with postoperative complications. Similarly, when analyzing postoperative complications in 443 patients treated at the University of Chicago (64 patients with previous VDZ), a propensity-score matched analysis did not demonstrate differences in postoperative complications between patients previously exposed to VDZ, anti-TNF, or conventional therapy, in CD ($p = 0.40$) or in UC ($p = 0.35$).

More recently, a meta-analysis including 307 VDZ-exposed patients did not find VDZ as a risk factor for postoperative complications. In a pooled analysis, the relative risks (RRs) in VDZ-treated patients for overall postoperative complications [RR 1.00; 95% confidence interval (CI) 0.46–2.15] and postoperative infectious complications (RR 0.99; 95% CI 0.37–2.65) were not significantly different from patients without previous biologic exposure. The same pattern was observed compared with patients with previous exposure to anti-TNF agents (RR 0.92; 95% CI 0.44–1.92 for overall postoperative complications, and RR 0.99; 95% CI 0.34–2.90 for infectious postoperative complications). In addition, it is difficult to account for disease severity and the many combinations of concurrent immunosuppressive agents. Thus, definitive conclusions regarding the independent impact of VDZ on postoperative complications have not been determined.

What could be the rationale to explain a possible increase in postoperative SSIs and overall infections in patients with VDZ? Although VDZ is purported to be a gut-specific agent with no or very limited systemic action, blocking $\alpha_4\beta_7$ integrin has previously been demonstrated to also affect systemic (nonclassical) M2 macrophages. These specific cells are deeply involved in systemic healing and tissue restitution. Impairing these ‘repair’ macrophages with VDZ may predispose patients to superficial SSIs, poor wound healing, and mucocutaneous separation in stomas. However, this purported mechanism requires further validation with both animal models and examination of human tissue at the time of operation.

A dose–response relationship for VDZ levels and risk of postoperative complications has not been substantiated. Lopez and colleagues measured serum levels of VDZ before surgery and analyzed their relation to postoperative complications. In 42 patients with IBD, 30 had detectable serum levels of VDZ. The authors found no association between the preoperative level of VDZ and overall postoperative morbidity ($p = 0.61$), 30-day readmissions ($p = 0.66$), or comprehensive complication index ($p = 0.11$) after surgery. Drug-level monitoring was not routinely available in our study, although given the long half life of VDZ, we hypothesize that most patients would have detectable serum levels if they received VDZ within 8–12 weeks of surgery. In our analysis, the mean time from the last infusion of VDZ until the surgical procedure was 5.11 weeks, and no specific comparison was made between these patients in terms of shorter versus longer time from infusion to surgery, due to the reduced number of complications that were found, which could represent important bias.

Our study comprises the first cohort in the literature evaluating postoperative outcomes in VDZ-treated patients undergoing nonintestinal surgical procedures. Although the sample size is small, despite higher numbers and percentages in the VDZ group, we did not observe any statistically significant differences in postoperative infections and SSIs in patients with previous VDZ compared with controls, who were matched on surgical procedure. This could be a consequence of a reduced number of procedures included, and powered studies with larger numbers of patients are needed, with proper sample calculation. Importantly, a specific limitation of our study was that a minority of included procedures did require large skin incisions (e.g. urological procedures, nasal operations, bone marrow transplantation). This limits the study power for detecting superficial surgical site infections.

The impact of biologics on postoperative complications for nonintestinal operations in patients with IBD is poorly described. Syed and colleagues evaluated the outcomes in patients treated with anti-TNF agents undergoing nonintestinal abdominal operations. However, they did not report outcomes separately from the IBD intestinal procedures, and therefore, no conclusions could be drawn in this specific group of individuals. Extrapolating from rheumatology and dermatology, there is no clear evidence that patients on anti-TNF agents undergoing nonintestinal operations, primarily orthopedic
surgery or minor cosmetic procedures, are at increased risk for postoperative complications. For daily practice, further guidance is required to direct therapeutic decisions and proper timing of surgery, particularly as the proportion of patients with CD and UC treated with VDZ increases over time. Larger prospective studies sufficiently powered to detect relatively rare postoperative complications are needed to answer this practical dilemma.

Our study has some important limitations. First, this was a retrospective analysis, which introduce the risk of recall bias, performed in a convenience sample, possibly underpowered to identify slight differences in complications. Furthermore, this restricted our ability to evaluate postoperative complications using a validated scoring system such as the Clavien-Dindo classification. Matching 1:1 to controls was primarily based on surgical indication, although some minor differences in procedure type or technique remain. Third, because we analyzed nonintestinal surgeries, a small proportion of patients were included who did not require extensive skin incisions. Despite these limitations, this cohort study is the first study to evaluate an important clinically relevant question: what is the postoperative risk associated with VDZ use in patients with IBD who require nonintestinal non-IBD-related operations?

In summary, our study demonstrated that VDZ-treated patients with IBD undergoing nonintestinal surgical procedures did not have an increased risk of overall postoperative infectious complications, readmission, or reoperation compared with controls. For now, there does not appear to be a need to undergo a washout period or delay in surgical intervention related to VDZ exposure. This may be attributed to VDZ’s gut-selective mechanism, but further mechanistic research is needed.

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Conflict of interest statement
Paulo Kotze is a speaker and consultant for Abbvie, Janssen, Pfizer and Takeda. Remo Panaccione has disclosed that he has served on the speaker’s bureau of AstraZeneca, Abbott, Byk Canada, Solvay, Janssen-Ortho, Schering-Plough, Centocor, Elan, and Prometheus; as a consultant for AstraZeneca, Ferring, Abbott, Schering-Plough, Shire, Centocor, Elan, GlaxoSmithKline, UCB, P&G Pharmaceuticals, and Bristol-Myers Squibb; on the advisory board of Ferring, Abbott, Schering-Plough, Shire, Elan, UCB, and P&G Pharmaceuticals. Dr Panaccione has also disclosed that he has received speaker honoraria from Axcan Pharma, Shire, and P&G Pharmaceuticals; research support from Abbott, Schering-Plough, Centocor, Millennium Pharmaceuticals, Elan, P&G Pharmaceuticals, and Bristol-Myers Squibb; and educational support/honoraria from Ferring, Axcan Pharma, Janssen-Ortho, and Schering-Plough. Edward Loftus reports receiving personal fees from Janssen, Takeda, Abbvie, UCB Pharma, Genentech, Celgene, Amgen, Bristol-Myers Squibb, Eli Lilly, Mesoblast, Theradigm, Sun Pharma, and Seres Therapeutics and grant support from Janssen, Takeda, Abbvie, UCB Pharma, Genentech, Amgen, Bristol-Myers Squibb, Pfizer, Receptos, Gilead Sciences, and Robarts Clinical Trials. Amy Lightner is a consultant for Takeda. All other authors have no disclosure.

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References
1. Ng SC, Shi HY, Hamidi N, et al. Worldwide incidence and prevalence of inflammatory bowel disease in the 21st century: a systematic review of population-based studies. Lancet 2017; 390: 2769–2778.
2. Khanna R, Bressler B, Lefvesque BG, et al. Early combined immunosuppression for the management of Crohn’s disease (REACT): a cluster randomised controlled trial. Lancet 2015; 386: 1825–1834.
3. Colombel J-F, Panaccione R, Bossuyt P, et al. Effect of tight control management on Crohn’s disease (CALM): a multicentre, randomised, controlled phase 3 trial. Lancet 2017; 390: 2779–2789.
4. Feagan B, Rutgeerts P, Sands B, et al. Vedolizumab as induction and maintenance therapy for ulcerative colitis. N Engl J Med 2013; 369: 699–710.
5. Sandborn WJ, Feagan BG, Rutgeerts P, et al. Vedolizumab as induction and maintenance therapy for Crohn’s disease. N Engl J Med 2013; 369: 711–721.

6. Engel T, Ungar B, Yung DE, et al. Vedolizumab in IBD—lessons from real-world experience; A systematic review and pooled analysis. J Crohns Colitis 2018; 12: 245–257.

7. Bye W, Jairath V and Travis S. Systematic review: the safety of vedolizumab for the treatment of inflammatory bowel disease. Aliment Pharmacol Ther 2017; 46: 3–15.

8. Colombel J, Sands BE, Rutgeerts P, et al. The safety of vedolizumab for ulcerative colitis and Crohn’s disease. Gut 2017; 66: 839–851.

9. Rungoe C, Langholz E, Andersson M, et al. Changes in medical treatment and surgery rates in inflammatory bowel disease: a nationwide cohort study 1979–2011. Gut 2014; 63: 1607–1616.

10. Frolkis AD, Dykeman J, Negron ME, et al. Risk of surgery for inflammatory bowel diseases has decreased over time: a systematic review and meta-analysis of population-based studies. Gastroenterology 2013; 145: 996–1006.

11. Kotze PG, Ghosh S, Bemelman WA, et al. Preoperative use of anti-tumor necrosis factor therapy in Crohn’s disease: promises and pitfalls. Intest Res 2017; 15: 160–165.

12. Lau C, Dubinsky M, McGovern D, et al. The impact of preoperative serum anti-TNF α therapy levels on early postoperative outcomes in inflammatory bowel. Ann Surg 2015; 261: 487–496.

13. Brouquet A, Maggiori L, Zerbib P, et al. Anti-TNF therapy is associated with an increased risk of postoperative morbidity after surgery for ileocolonic Crohn disease. Ann Surg 2018; 267: 221–228.

14. Yang Z, Hong L, Wu Q, et al. Preoperative infliximab use and postoperative complications in Crohn’s disease: a systematic review and meta-analysis. Int J Surg 2014; 12: 224–230.

15. Billioud V, Ford AC, Del E, et al. Preoperative use of anti-TNF therapy and postoperative complications in inflammatory bowel diseases: a meta-analysis. J Crohns Colitis 2013; 7: 853–867.

16. Kotze P, Saab M, Saab B, et al. Tumor necrosis factor alpha inhibitors did not influence postoperative morbidity after elective surgical resections in Crohn’s disease. Dig Dis Sci 2017; 62: 456–464.

17. Lightner AL, Raffals LE, Mathis KL, et al. Postoperative outcomes in vedolizumab-treated patients undergoing abdominal operations for inflammatory bowel disease. J Crohns Colitis 2017; 11: 185–190.

18. Lightner AL, McKenna NP, Tse CS, et al. Postoperative outcomes in vedolizumab-treated Crohn’s disease patients undergoing major abdominal operations. Aliment Pharmacol Ther 2018; 47: 573–580.

19. Yamada A, Komaki Y, Patel N, et al. Risk of postoperative complications among inflammatory bowel disease patients treated preoperatively with vedolizumab. Am J Gastroenterol 2017; 112: 1423–1429.

20. Ferrante M, de Buck Van Overstraeten A, Schils N, et al. Perioperative use of vedolizumab is not associated with postoperative infectious complications in patients with ulcerative colitis undergoing colectomy. J Crohns Colitis 2017; 11: 1353–1361.

21. Law CC, Narula A, Lightner AL, et al. Systematic review and meta-analysis: preoperative vedolizumab treatment and postoperative complications in patients with inflammatory bowel disease. J Crohns Colitis 2018; 12: 538–545.

22. Kotze PG and Yamamoto T. Preoperative vedolizumab and postoperative outcomes in inflammatory bowel disease: does smoke always mean fire? J Crohns Colitis 2017; 11: 643.

23. Satsangi J, Silverberg MS, Vermeire S, et al. The Montreal classification of inflammatory bowel disease: controversies, consensus, and implications. Gut 2006; 55: 749–753.

24. Lightner AL, McKenna NP, Moncrief S, et al. Surgical outcomes in vedolizumab-treated patients with ulcerative colitis. Inflamm Bowel Dis 2017; 23: 2197–2201.

25. Schleier L, Wiendl M, Binder M, et al. 4β/7 Integrin-dependent gut homing of non-classical monocytes is essential for intestinal wound healing mediated by M2 macrophages. J Crohns Colitis 2018; 12(Suppl. 1): S005–S007.

26. Lopez N, Zaghhiyan K, Melmed G, et al. Preoperative serum vedolizumab levels do not predict postoperative outcomes in inflammatory bowel disease (IBD). J Crohns Colitis 2018; 12(Suppl. 1): S303–S304.

27. Syed A, Cross RK and Flasar MH. Anti-tumor necrosis factor therapy is associated with infections after abdominal surgery in Crohn’s disease patients. Am J Gastroenterol 2013; 108: 583–593.
28. George MD, Baker JF, Hsu JY, et al. Perioperative timing of infliximab and the risk of serious infection after elective hip and knee arthroplasty. *Arthritis Care Res* 2017; 69: 1845–1854.

29. Choi YM, Debbaneh M, Weinberg JM, et al. From the Medical Board of the National Psoriasis Foundation: perioperative management of systemic immunomodulatory agents in patients with psoriasis and psoriatic arthritis. *J Am Acad Dermatol* 2016; 75: 798–805.e7.

30. Dindo D, Demartines N and Clavien P-A. Classification of surgical complications. *Ann Surg* 2004; 240: 205–213.