Perioperative Use of Vedolizumab in Crohn’s Disease Patients and Surgical Outcomes

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The sole author designed, analysed, interpreted and prepared the manuscript.

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ABSTRACT

Despite advancement in managing Crohn’s disease (CD), a considerable proportion of cases still need surgical intervention, which is an essential means in therapy algorithms. Other drugs of the biologics are recently available, while most CD cases having operations have previously received a drug of this class. This class of agents has a direct association with higher postoperative complication rates, which raises a lot of controversies. In this review summarize the essential data concerning the vedolizumab effect on CD’s postoperative results. The previous data did not demonstrate a cause-effect absolute connection between the increased postoperative morbidities and vedolizumab. Many routing factors unquestionably affect CD's postoperative outcomes and complications, like malnutrition, unsuitable abdominal settings, and steroids' previous use. Using vedolizumab perioperatively seems safe. Nevertheless, a definitive relationship from the available data is controversial. Personalized, multidisciplinary evaluations and decisions should be made for each case independently, adjusting the surgical plan regarding the involved risk factors.

Keywords: Vedolizumab; gastroenterology; Crohn’s disease; preoperative period.

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1. INTRODUCTION

Crohn’s disease (CD) is a GI tract disease with idiopathic chronic inflammation. It occurs in the United States to around 800,000 subjects, while its incidence continuously increases without knowing the reason [1]. For Medical treatment, Biologics are known to be the primary choice for moderate to severe cases; however, the limitation by secondary response [2-10] loss and non-response, in addition to opportunistic infection risks, has been found to affect their benefit [11]. Almost 70 – 75% of cases undergo surgical intervention as a part of the treatment course despite receiving several immunosuppressives [12]. Morbidity rates postoperatively are up to 30%, while following anastomosis intraabdominal sepsis might happen in around 10% [13,14]. For better understanding the correlation between taking immunosuppressive agents perioperatively and the increased morbidity postoperatively, numerous studies have been made, particularly the morbidity of infectious type. Exacerbation of postoperative complications may be a risk with administering immunosuppressive agents like corticosteroids and biologics as anti-tumor necrosis factor-alpha (anti-TNFα) [15,16]. The current evidence is still indecisive, although many systematic reviews and meta-analyses concluded that an increased risk of complications might be seen postoperatively in patients with inflammatory bowel disease (IBD) receiving anti-TNFα preoperatively [13,17-23].

Biologics have made considerable advancements in the management and treatment of IBD and have turned to be the backbone in managing moderate to severe cases with Crohn’s disease [24]. Anti-TNFα agent (adalimumab, infliximab, and pegol), and the recent antibodies hindering α4β7 integrins (vedolizumab) on leukocytes, and the interleukins p40 subunit (IL)-12 and 23(ustekinumab) are very effective agents of biologics for CD [25], which can initiate remission with maintaining it, help the mucosa to heal, and diverse the disease of its standard course when using them on the right time evading the progression to fistula formation and stenosis [26]. Despite the therapeutic algorithms’ remarkable improvement, a critical number of CD patients still require surgery, but surgery rates have decreased with the biological agents [27,28].

Vedolizumab is a monoclonal antibody from Entyvio™, Takeda Pharmaceuticals America, and it got approval in May 2014 by the FDA for treating IBD. Due to vedolizumab’s gut selectivity, its introduction to the clinical world has raised significant enthusiasm [29-31]. It is essential to comprehend how to postoperatively alleviate the risk due to the considerable number of CD patients having abdominal procedures while taking immunosuppressive agents and the possibility of refractory disease. The data explaining the effect of perioperative vedolizumab using on surgical outcomes remain inconclusive. In this study, we aimed to review the perioperative use of vedolizumab in patients with Crohn’s disease and surgical outcomes.

2. METHODS

The authors conducted a thorough literature search till march 2021 in the PubMed dataset. We used the Medline subheadings and keywords “Vedolizumab”, “Entyvio”, “MLN0002”, “MLN02”, “MLN-002”, “MLN-02”, “Crohn’s Enteritis”, “Regional Enteritis”, “Crohn’s Disease”, “Crohns Disease”, “Granulomatous Enteritis”, “Ileocolitis”, “Granulomatous Colitis”, “Terminal Ileitis”, “Regional Ileitis”, “Perioperative”, “complications”, “Post-surgical” and “surgical”.

2.1 Pathophysiology

Vedolizumab is an anti-integrin biological agent. It prevents leukocyte integrin α4β7 from combining with addressin MADCAM-1 that blocks its effect in the endothelial wall, leukocyte migration from the endothelial layer to the other intestinal layers [32]. It is gut selective, being the first of its kind. Vedolizumab got approved for the management and treatment of ulcerative colitis (UC) and CD with increasing its use globally [33]. The impairment of anastomotic healing by preoperative vedolizumab in CD surgery is still controversial.

2.2 Evidence of Perioperative Consequences of Vedolizumab

We investigated ten studies with different methodologies (mostly multicenter cohorts or retrospective single-center) and comparison groups. Definitive evidence is still unclear and controversial. The expected outcomes showed no statistical difference in most studies. However, due to nonuniformity between the groups analyzed in each study, these outcomes can not represent hard evidence for vedolizumab’s impact on surgical results.
A posthoc analysis by Shen et al. [34] of safety from GEMINI 1 and 2 in addition to studies investigating long-term safety for patients undergoing bowel surgery or colectomy reported postoperative complications, in 58 surgeries of GEMINI 1 and GEMINI 2, for 5.9% of vedolizumab-receiving patients (3/51) and 14.3% of the placebo group (1/7). While in the study of long-term safety, 7% of patients (157/2,243) underwent bowel resection/surgery or colectomy; 11 of these 157 patients developed postoperative complications. Twenty-three days was the median time from the final preoperative dose of vedolizumab and surgery in GEMINI 1, in GEMINI 2 was 20 days, and 39 to 40 days for the study for long-term safety. While in the postmarketing phase, postoperative complications appeared in 19 patients out of 46,978 patients receiving vedolizumab for years from the postmarketing Vedolizumab Global Safety Database.

Lightner et al. [35] investigated 712 CD cases in a retrospective observational cohort study. One hundred twenty-seven patients received vedolizumab, 272 received anti-TNFα, 38 received ustekinumab, and 275 did not take any biological agents; through the 12 weeks prior to the abdominal surgery. No statistical difference was concluded between the groups regarding infectious complication rates or intraabdominal septic complications incidence, which increased with adjuvant corticosteroid therapy to biologics and former abdominal resection. Additionally, Yamada et al. [36] showed different results comparing 64 subjects with previous vedolizumab with 129 cases on anti-TNFα and 250 on conventional therapy. The results did not demonstrate any statistical significance in postoperative complications rates between the vedolizumab group and the two patients set (p = 0.35). The authors found that anemia and preoperative steroid administration were dominant factors in multivariate analysis for increasing the complications. A study conducted by Park et al. [37] showed the same results - no complication risk increased with previous vedolizumab, using a similar methodology. The authors investigated two groups; vedolizumab and anti-TNFα groups. At the same time, they concluded no variations amongst them in surgical site infections (SSI) (14.9% in vedolizumab and 12% in anti-TNFα). However, considering these results, they found vedolizumab to be safe preoperatively. Meanwhile, the authors of Kotze et al. [38] investigated 34 vedolizumab-receiving IBD cases undergoing 36 nonintestinal surgeries matched with 36 control interventions. The study was cross-matched. The analyzed outcomes demonstrated no differences between the vedolizumab group and the control group in postoperative complications. These results between the vedolizumab group and the control group include SSI (6% to 0%, the p was 0.15), infections (14% to 8%, the p was 0.45), readmissions (11% to 6%, the p was 0.37) and reoperations (6% to 3%, the p was 0.56).

Novello et al. [39] included 980 IBD patients for comparing morbidity rates after surgery following receiving vedolizumab versus other biological agents or non. One hundred forty-one patients received vedolizumab. 59% of cases underwent abdominal procedures, including diverting or end ostomy formation. The primary multivariate analysis showed that receiving vedolizumab was separately related to higher morbidity incident (p<0.001), but not to infectious morbidity (p=0.30). They conducted a case-matched assessment for 95 vedolizumab-receiving cases compared to 95 cases taking infliximab or adalimumab. It did not demonstrate any variation in the general morbidity (p=0.32), SSI (p=0.12), or infectious complications (p=0.15).

Novello et al. [40] conducted a matched-case analysis comparing the total postoperative complications in ustekinumab-receiving patients preoperatively with vedolizumab-receiving patients. The authors investigated 103 CD subjects; 30 cases took ustekinumab preoperatively, and 73 received vedolizumab. Using univariate analysis, vedolizumab-receiving patients showed a higher incidence of postoperative complications (p = 0.009) and ileus incidence (p = 0.015), the analysis showed no significant statistical difference in the main outcomes. Moreover, Lightner et al. [41] performed a cohort study of adult IBD cases, which was multicenter retrospective. A total of 435 patients had abdominal surgery; 146 patients took vedolizumab through 12 prior to the abdominal intervention, and 289 patients took anti-TNFα treatment. Vedolizumab-receiving subjects had a higher risk of any postoperative SSI (P < 0.01), deep space SSI (the P was 0.39), superficial SSI (the P was less than 0.01), and diverting mucocutaneous stoma separation (the P was less than 0.00) in comparison with cases on anti-TNFα agents. On multivariate assessment, after regulating body mass index, steroids at the time of surgery, and institution, receiving vedolizumab continued to be a considerable predictor for postoperative SSI (P <
Lightner et al. [42] investigated 94 subjects from the Mayo Clinic with former vedolizumab use. They were divided into groups; the anti-TNFα therapy groups and the conventional treatment group, compared retrospectively for postoperative complications. Vedolizumab group had a higher incidence of SSI (p < 0.001) and postoperative infections than the rest of the groups. These outcomes made vedolizumab perioperative safety use questionable. However, the vedolizumab-receiving cases with refractory CD were severe with laparoscopic approaches and less initial anastomoses. Lightner et al. [43] performed a retrospective cohort for adult IBD cases who had abdominal surgeries. The study included 94 subjects taking vedolizumab 12 weeks prior to their surgery and subjects taking either anti-TNFα or no biologics as the control group. Fifty patients underwent postoperative complications representing 53%; 35 were SSIs representing 36%. The vedolizumab-receiving group showed higher rates of postoperative complications. Nonspecific postoperative infections occurred 53% with vedolizumab versus 33% with anti-TNFα and 28% with no biologics use (P<0.001) while SSI occurred 37% versus 10% and 13% (P< 0.001), respectively. And yet, vedolizumab exposure is related to a significantly higher incidence of SSI postoperatively (P<0.001) on multivariate and univariate evaluation.

Other systematic reviews with meta-analyses [33,44,45] were also conducted and no statistically significant difference in cases with preoperative vedolizumab use was observed concerning an increased incidence of postoperative complications. A summary of these studies is described in more detail in Table 1.

### Table 1. Main characteristics and outcomes of studies assessed the influence of vedolizumab in postoperative complications.

| ID    | Disease   | Number of patients treated | Design        | Type of surgery                  | Main outcomes                                              | Main finding                                                                                          |
|-------|-----------|----------------------------|---------------|----------------------------------|------------------------------------------------------------|--------------------------------------------------------------------------------------------------------|
| Shen  | CD, UC    | GEMINI 1: UC, Vedolizumab (n=15), Placebo (n=3) | Post hoc analysis | Colectomy and bowel surgery/resection | Post-operative complications | In clinical trials, complications were infrequent with a slight difference. In the post-marketing phase, the frequency of complications was low. |
| Shen  | CD, UC    | GEMINI 2: CD, Vedolizumab (n=36), Placebo (n=4) GEMINI LTS study: all vedolizumab-treated: UC (n=55), CD (n=102). | Post hoc analysis | Colectomy and bowel surgery/resection | Post-operative complications | In clinical trials, complications were infrequent with a slight difference. In the post-marketing phase, the frequency of complications was low. |
| Novello | CD, UC | 980; 141 vedolizumab | A case-matched analysis | Abdominal surgery for IBD | Postoperative morbidity of IBD surgery following treatment with vedolizumab. | Preoperative vedolizumab was not associated with an increased morbidity rate. |
| Lightner | CD | 712; 272 anti-TNF, 127 vedolizumab, 38 ustekinumab, and 275 no biologic therapy | Retrospective Single-center | Major abdominal operation | Thirty-day overall postoperative infectious complications and intraabdominal septic complications. | The intended outcomes rate did not increase with preoperative biologics exposure. Increased rates were noted with corticosteroids |
| ID     | Disease | Number of patients treated | Design                      | Type of surgery     | Main outcomes                                                                 | Main finding                                                                                     |
|--------|---------|----------------------------|-----------------------------|---------------------|------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------|
| Novello 2018 | CD      | 103; 30 ustekinumab, 73 vedolizumab | A case-matched analysis    | Colorectal surgery | Short-term postoperative complication rate.                                   | The analysis showed no significant statistical difference in the main outcomes.                  |
| kotze 2018 | CD, UC  | 70; 34 vedolizumab, 36 control | A case-matched study       | Non intestinal surgical procedure | overall risk of early postoperative infectious complications (up to 30 days after surgery), readmissions, reoperations, surgical site infections, and other infections. | Vedolizumab-receiving IBD patients showed no increased risk of complications over the matched controls. |
| Lightner 2018 | CD, UC  | 435; 146 vedolizumab, 289 anti-TNF | Retrospective Multicenter Cohort | major abdominal or pelvic colorectal operation. | The rate of 30-day postoperative surgical site infection.                       | Vedolizumab-receiving subjects had a higher risk for postoperative SSIs compared with anti-TNFα.    |
| Yung 2018 | CD, UC  | 1080; 281 vedolizumab, 364 anti-TNF, 435 no biologics | systematic review and meta-analysis | Abdominal surgery for IBD | Overall postoperative complications, infectious complications, surgical site infections, need for repeat surgery, and major postoperative complications | There was no increased risk of postoperative complications. The overall complications' risk may be lower in UC with vedolizumab. |
| Law 2018 | CD, UC  | 1332; 307 vedolizumab, 490 anti-TNF, 535 no biologics | systematic review and meta-analysis | Abdominal surgery for IBD | Postoperative infectious complications and overall postoperative complications. | There was no increased risk of postoperative infections or other complications with vedolizumab. |
| Park 2018 | CD, UC  | 186; 94 vedolizumab, 92 anti-TNF | Retrospective cohort       | Abdominal surgery for IBD | The risk of surgical site infections.                                         | There was no increased risk of SSI with perioperative vedolizumab.                                |
| Yamada 2017 | CD, UC  | 443; 64 vedolizumab, | Retrospective cohort       | Major abdominal operation | The rates of 30-day postoperative complications.                             | There was no effect on the                                                                         |
| ID     | Disease | Number of patients treated | Design                   | Type of surgery        | Main outcomes                                         | Main finding                                                                 |
|--------|---------|----------------------------|--------------------------|------------------------|-------------------------------------------------------|-----------------------------------------------------------------------------|
|        |         | 129 anti-TNF, 250 no biologics |                          | postoperative complications | risk of 30-day postoperative complications with perioperative vedolizumab in UC and CD. |
| Lightner 2017 | CD      | 312; 100 vedolizumab, 107 anti-TNF, 105 no biologics | Retrospective cohort | Major abdominal operation | The rates of 30-day postoperative complications | 62% of CD patients receiving vedolizumab within 12 weeks before the abdominal operation experienced a significantly higher risk of 30-day postoperative SSI. |
| Engel 2017 | CD, UC  | 1565; 571 UC, 994 CD         | Systematic review        | Major abdominal operation | Efficacy and safety data with vedolizumab in induction and maintenance treatment in adults with IBD. | Vedolizumab is effective in CD and UC. It has a good safety profile in the Real-world Experience. |
| Lightner 2016 | CD, UC | 392; 94 vedolizumab, 126 anti-TNF, 172 no biologics | Retrospective cohort | Major abdominal operation | The rates of 30-day postoperative complications | 37% of IBD patients receiving vedolizumab within 12 weeks before an abdominal operation experienced a significantly higher risk of 30-day postoperative SSI. |

IBD, inflammatory bowel diseases; LTS, long-term safety; UC, ulcerative colitis; CD, Crohn’s disease; TNF, tumor necrosis factor; SSI, surgical site infections

3. CONCLUSION

Using vedolizumab perioperatively seems safe; however, more prospective interventional studies are needed to clarify the effect of vedolizumab use in the preoperative period. Although most of the mentioned studies showed no statistically significant increase in CD patients’ postoperative outcomes, a definitive relationship from the accessible data is still contentious. Personalized, multidisciplinary evaluations and decisions should be made for each case independently, adjusting the surgical plan giving to the involved risk factors.

4. RECOMMENDATIONS

So far, a definitive conceptual proof explaining the postoperative effect of biological agents on the CD course has not been clearly shown. The cause-effect relationship that may be established by drug serum levels, as an example, was not evident in the most critical prospective study till now. Moreover, records that could explain tissue
diffusion of these drugs in the surgical specimens are also missing.

The database, including biological agents with different action mechanisms, is still in its initial years in international literature due to the relatively recent vedolizumab approval in the clinical practice. As presented in this review, in spite of the initial warning record [43] that demonstrated the possibility of complications increases with previously taking vedolizumab, most of the recently published studies showed opposite outcomes [36,37]. More prospective trials are required to confirm the vedolizumab effect in the preoperative period.

Additionally, it is essential to state that a study conducted in Germany showed decreased systemic circulation classical monocytes (M2 macrophages) with inhibiting the integrin α4-β7, caused by vedolizumab, which could impact wound healing [46]. Therefore, owing to this essential basic scientific concept, added to the fact that no prospective studies with vedolizumab were published to date, personalized, multidisciplinary evaluations and decisions should be made for each case independently in the clinical practice.

We recommend that prospective analysis and trials enroll a significant case sample with strict details and more comparison groups to design an appropriate study to generate more meaningful results to resolve the controversy and aim for more reliable and high-quality evidence.

5. LIMITATIONS

The studies included have different methodologies (mostly multicenter cohorts or retrospective single-center), which may have information biases. Some records studied IBD patients, not CD alone, and nonuniformity existed in the comparisons made between the different groups’ studies.

Additionally, many routing factors unquestionably affect CD’s postoperative outcomes and complications in patients undergoing intestinal resection, like impaired nutritional condition [47], unsuitable abdominal settings, and steroids’ previous use [48]. One of these or more might exist for patients indicated for surgery who are already on these biological agents. Therefore, in patients with malnutrition, with prior steroids, and/or anemia, the surgical strategy can be impacted. More significantly, when unsuitable abdominal settings are present in operation, such as bowel dilatation, abscesses, and intestinal incomplete or complete obstruction, the operational plan needs to be redefined.

The novel global surgical direction towards the creation of stomas rather than primary anastomoses has become the rule for cases with these conditions, not due to using the biological drugs per se, but for more critical patients with the higher risk of complications by definition.

CONSENT

It is not applicable.

ETHICAL APPROVAL

It is not applicable.

COMPETING INTERESTS

Author has declared that no competing interests exist.

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