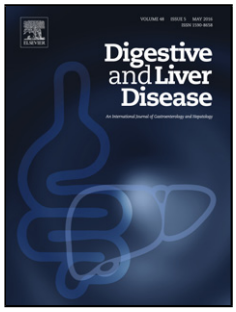

Title: A real-world, long-term experience on effectiveness and safety of vedolizumab in adult patients with inflammatory bowel disease: The Cross Pennine study

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A real-world, long-term experience on effectiveness and safety of vedolizumab in adult patients with inflammatory bowel disease: The Cross Pennine study

Running head: Real-world experience with vedolizumab

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Abstract

Background: Real-life data on vedolizumab effectiveness in inflammatory bowel disease (IBD) are still emerging. Data on the comparative safety of the gut selective profile are of particular interest.

Aims: To assess clinical outcome and safety in IBD patients treated with vedolizumab.

Methods: We retrospectively collected data of patients treated with vedolizumab at eight UK hospitals (August 2014-January 2018). Clinical response and remission at 14 and 52 weeks evaluated through Physician Global Assessment (PGA) and adverse events were recorded. Possible predictors of clinical response were examined.

Results: Two hundred and three IBD patients (mean treatment 16±8 months) were included. Of these, 135 patients (mean age 40.6±16.0 years; F:M 1.9:1) had CD and 68 (mean age 44.5±18.1 years; F:M 1:1.2) had UC. According to PGA, 106/135 (78.5%) CD and 62/68 (91.2%) UC patients (p=0.02) had a clinical response/remission at 14 weeks, whereas 76/119 (63.9%) CD and 52/63 (82.5%) UC patients (p<0.01) showed a sustained response or remission at 52 weeks, with a high adherence rate (97%). No predictors of clinical response were found. The cumulative incidence of infectious diseases was 11.9 per 100 person-years.

Conclusion: Vedolizumab is an effective therapy for inducing and maintaining remission of IBD, with better results for UC, and with a good safety profile.

Abbreviations: CD, Crohn's disease; CI, confidence interval; CRP, C reactive protein; EBV, Epstein-Barr virus; FC, faecal calprotectin; HBI, Harvey-Bradshaw Index; IBD, inflammatory bowel disease; IL, interleukin; PGA, Physician Global Assessment; PML, progressive multifocal leukoencephalopathy; TNF, tumour necrosis factor; UC, ulcerative colitis; VDZ, vedolizumab.

Keywords: biological therapy; clinical predictors; Crohn's disease; elderly; immunomodulator; ulcerative colitis.

Introduction

Inflammatory bowel disease (IBD) represents a group of chronic, immune-mediated conditions with multifactorial aetiology that encompasses two major phenotypes, namely

Crohn's disease (CD) and ulcerative colitis (UC).[1,2] The global burden of IBD is high, with approximately 3.5 million of people affected in Europe and the United States, and rapidly increasing in newly industrialised countries.[3] IBD increases the overall risk of death,[4] and adversely affects quality of life. All these considerations highlight the need for optimal management, comprising highly effective existing and novel medications with an acceptable risk-benefit profile.

Medical treatment of IBD has evolved over the last two decades, particularly since the introduction of biological therapies. Anti-tumour necrosis factor (TNF) α agents (infliximab, adalimumab, certolizumab pegol, and golimumab) were the first monoclonal antibodies used for the treatment of IBD.[5] A significant proportion of patients treated with anti-TNF agents experience primary non-response or secondary loss or response.[6-9] Further, there is a risk of relapse after discontinuation[10] and a small increase in the risk of infections and some types of cancer.[11] The evolving understanding of the immunopathogenesis of IBD has led to the development of other biological therapies. Natalizumab was the first anti-integrin monoclonal antibody to be used in the treatment of CD with moderate efficacy;[12,13] its use in clinical practice was limited by the death of a patient in the ENACT study due to progressive multifocal leukoencephalopathy (PML) from reactivation of the John Cunnigham (JC) virus as a consequence of non-selective $\alpha_4\beta_1$ inhibition.[14] Vedolizumab (VDZ) is a humanised, gut-selective monoclonal IgG1 antibody that targets the heterodimer $\alpha_4\beta_7$ integrin, inhibiting migration and leukocytes adhesion.[15] The landmark trials GEMINI 1,[16] 2,[17] and 3[18] showed that VDZ is effective in both CD and UC, with similar remission rates compared to anti-TNFs.[19] The long-term GEMINI safety studies and post hoc analyses confirmed an acceptable safety profile and efficacy,[20,21] regardless previous exposure to anti-TNFs[22,23] and age groups.[24] However, clinical trials do not necessarily reflect everyday practice, as real-life use may differ considerably in terms of patient selection. A number of real-life studies regarding VDZ have been published,

reporting novel - but sometimes conflicting - results, including possible clinical predictors of response and new safety signals.[25-35]

The aim of this study was to describe our clinical experience with VDZ, defining its effectiveness and safety in inducing and maintaining remission in IBD patients treated in eight different hospitals across northern England.

Methods

Patients

Eight IBD centres (belonging to both university and general hospitals) from the UK participated in this study (Leeds Teaching Hospitals; Manchester Royal Infirmary; Salford Royal Hospitals; Bolton NHS Trust; Bradford Teaching Hospital; The Royal Liverpool and Broadgreen University Hospitals; Wrightington, Wigan and Leigh NHS Trust; The Pennine Acute Hospitals). We retrospectively collected data of all IBD patients (age ≥ 18) initiated on VDZ (August 2014 – June 2017; last follow up January 2018) through the local electronic medical records. All patients had an established diagnosis of CD or UC according to internationally agreed diagnostic criteria.[36,37] Data were extracted and anonymised from patient records onto a pre-defined spreadsheet that was centrally collated at the coordinating site (St. James's University Hospital, Leeds). All queries regarding uncertain data were resolved via email through consensus with the study coordinator (MVL). VDZ was given as an intravenous infusion (300 mg) over thirty minutes at week 0, 2, 6, and every 8 weeks thereafter. A number of centres gave an additional week 10 dose for the indication of CD only (12 patients), if clinically indicated, and in a few patients, the infusion interval was shortened to 4 weekly. Demographic (age, gender) and disease data (phenotype according to the Montreal classification,[38] disease duration, previous medications, previous surgery) were evaluated. Other variables of interest

considered were concomitant steroid and immunosuppressive therapies, bridging steroid therapy, smoking status, previous exposure to any biologic therapies, and adherence to planned infusions. All the required items for observational cohort studies were included according to STROBE recommendations.

Outcomes

Our primary outcome measure was clinical response or remission at 14 (just before commencing maintenance therapy) and 52 weeks (±2 weeks) assessed using the Physician Global Assessment (PGA) score. PGA outcomes were based on the clinical impression of the local investigator, defining remission as the complete relief or marked improvement of symptoms compared to baseline, and response as a partial, though significant, improvement. In order to corroborate PGA results, we also evaluated the Harvey-Bradshaw Index (HBI)[39] for CD and the partial Mayo score for UC,[40] when available (either prospectively, recorded in clinic letters, or retrospectively, derived from clinic letters). Compared to the baseline, remission was defined with a HBI ≤ 4 or a partial Mayo score ≤ 1 without any bleeding, while a reduction of 3 or more points of both scoring systems defined clinical response. Furthermore, we collected data on C reactive protein (CRP) and faecal calprotectin (FC) at baseline and at 14 weeks (±1 week), when available. As secondary outcome, we assessed potential predictors of clinical response, including, among others, bridging steroid therapy, concomitant use of immunosuppressant (azathioprine, 6-mercaptopurine, or methotrexate), previous anti-TNF exposure, smoking status, disease duration, baseline FC and CRP, disease phenotype and location for CD, disease extension for UC, and previous surgery. As third outcome, we looked at reasons for discontinuation, all the adverse events, infectious diseases, and other safety signals or disorders that were related to VDZ therapy that occurred from overall exposure to VDZ until end of follow-up. A sub-analysis of elderly patients (≥ 65 years old) was performed.

Statistical analysis

Statistical analysis was performed using GraphPad Prism 6 (GraphPad Software, Inc., California, USA). Non-parametric tests were used to analyse continuous variables, and absolute and relative frequencies to describe categorical variables. Categorical data were summarised as the percentage of the total group according to disease type (CD, UC). Differences in continuous variables between two groups were analysed using the nonparametric Mann-Whitney U-test for unpaired samples (as not all variables were available in all patients). Chi-squared test was used for comparison of proportions. The degree of correlation between HBI or partial Mayo score and PGA (1=remission; 2=partial response; 3=non-response or worsening) at 14 and 52 weeks was assessed with nonparametric two-tailed Spearman's rank correlation coefficient. Two-sided Fisher's exact test was used to compare categorical data between the two groups, along with the 95% confidence interval (CI) and odds ratio. A p-value of <0.05 was considered as statistically significant. Effectiveness outcomes for 14 weeks were reported on an intention-to-treat basis, while 52-week effectiveness data used the number of patients entered into maintenance therapy as the denominator.

Ethical standards

The study was performed as a clinical audit using routine collected clinical data and as such is exempt from the need for ethics committee approval in the UK and the need to take written informed consent.

Results

Cohort

After excluding 22 patients with insufficient data, we included 203 patients with IBD (mean age 41.9±16.8 years; F:M 1.4:1) treated with VDZ for a mean period of 16±8 months (range 1-37 months). Demographic and relevant clinical characteristics are reported in Table 1. Notably, 27/203 patients (13.3%; mean age 72.4±4.7 years, 17 females; 14 CD and 13 UC) were ≥ 65 years old (elderly subgroup) and 13/27 (48.1%) had at least two associated chronic diseases, namely essential hypertension, chronic heart failure, diabetes mellitus type 2, and chronic obstructive pulmonary disease. Among all patients with CD, 27/135 (20.0%) had at least one previous abdominal IBD-related surgical intervention (including partial colectomy, small-bowel resections), 56/135 (41.5%) had been exposed to one anti-TNF α, and 73/135 (54.1%) had been exposed to at least two different biological therapies (any anti-TNF α agents or/and ustekinumab). Among patients with UC, 40/68 (58.8%) have been exposed to one anti-TNF α, and 5/68 (7.3%) have been exposed to two different anti-TNF α agents.

Clinical effectiveness

According to PGA, 106/135 (78.5%) CD and 62/68 (91.2%) UC patients (p=0.02) had a clinical response or remission at 14 weeks, whereas 76/119 (63.9%) CD and 52/63 (82.5%) UC patients (p<0.01) showed a sustained response or remission at 52 weeks. Steroid-free remission was particularly high in the studied population (Figure 1). Figure 1 shows the 14- and 52-week response rates and steroid-free remission according to disease type and Table 2 reports the trend of HBI or partial Mayo score, along with the inflammatory markers (CRP, FC). Clinical activity indexes (HBI and partial Mayo score) had a decreasing trend over time (p<0.01) (Supplementary Table 1). Moreover, a significant positive correlation between HBI/partial Mayo score and PGA was found at both 14 (r=0.588, 95% CI 0.469-0.687, p<0.01) and 52 (r=0.728, 95% CI 0.608-0.816, p<0.01) weeks, thus confirming PGA results. Similarly, both FC and CRP showed a decreasing

trend at 14 weeks, even if this was statistically significant only for FC. In five patients VDZ therapy was intensified (one escalated to six weekly, four escalated to four weekly). Furthermore, 13/135 (9.6%) CD patients had an additional dose at week 10. In the elderly subgroup, 12/14 (85.7%) CD and 12/13 (92.3%) UC patients had a clinical response to the induction therapy (p=ns), whereas 11/14 (78.6%) CD and 10/13 (76.9%) UC patients maintained response at 52 weeks (p=ns). The rate of concomitant immunosuppressant in the elderly group was 13/27 (48.1%) *vs* 88/176 (50.0%) of the adult group (p=ns), whereas the rate of steroid use at baseline was 16/27 (59.2%) *vs* 78/176 (44.3%), respectively (p=ns).

Continuation of VDZ and safety outcomes

Table 2 shows the timing of VDZ discontinuation (≤14 weeks, >14 and ≤52 weeks, >52 weeks) and the related reasons or subsequent management. Overall, 71 patients (34.9%) discontinued VDZ after an average time of 7±4 months (7±4 months for CD; 7±5 months for UC; p=ns). We reported one case of death, which occurred in a 39-year old male patient with a longstanding history of CD, who had had multiple intestinal resections and a permanent ileostomy, due to intestinal obstruction. This patient had been on VDZ for 29 months and had previously experienced primary or secondary non-response to three different anti-TNF α agents and ustekinumab. Non-adherence to VDZ was reported in 6/203 (2.9%) patients. We considered a number of potential predictive factors of clinical response at 14 and 52 weeks (Supplementary Tables 2 and 3), and only the use of bridging steroid therapy in CD patients showed a negative association at 14 weeks (OR 0.403; 95% CI 0.1746-0.9332; p=0.0339) with steroid exposed patients less likely to experience response to VDZ. However, after adjusting this variable for disease severity at baseline (mean HBI 10.2±4.7 *vs* 8.4±4.1; p=0.03), the association was lost. Moreover, gender, disease behaviour, disease location, and previous surgery for CD, and gender and

disease extension for UC were not predictive of clinical response (p=ns). Finally, Table 3 summarises all the adverse events, infectious diseases, and other disorders or safety signals attributed to VDZ therapy. Adverse events and infectious diseases were fatal, though led to VDZ discontinuation in 16 patients (7.8%, Table 2). At least one infection occurred in 8/52 (15.4%) patients on VDZ monotherapy compared to 20/151 (13.2%) patients on any concomitant immunosuppressive drug (including steroids; p=0.692). However, among the 28 patients who had at least one infection, this occurred in 8 (28.6%) who were on VDZ monotherapy and in 20 (71.4%) who were also taking another immunosuppressive drug (p<0.01; 10/28 [35.7%] an immunomodulator, 6/28 [21.4%] steroid therapy, and 4/28 [14.3%] both immunomodulator and steroid therapy). Admission at hospital for infectious diseases occurred in 11/28 (39.3%) patients. The cumulative incidence of non-infective adverse events and infectious diseases were 5.1 per 100 person-year and 11.9 per 100 person-years, respectively. No cases of PML were reported in our cohort. No infectious diseases were seen in the elderly subgroup.

Discussion

Our multicentre experience of eight IBD Units across Northern England is the largest study from the United Kingdom to date showing that VDZ is an effective and safe therapy in real-world practice for both the induction and maintenance of remission of CD and UC. Patients with UC had a better clinical response at both 14 and 52 weeks compared to CD. VDZ demonstrated high effectiveness and safety even in the subgroup of elderly patients with multiple co-morbidities. Unlike previous studies,[26,27,29,31,33,41] we have not found possible predictors of clinical response.

Since VDZ was approved for the treatment of IBD in 2014, further evidence has demonstrated long-term efficacy and safety. However, many unresolved issues require further clarification, in particular regarding the usefulness of concomitant immunosuppressive therapy and steroids, and the definition of possible predictors of clinical response. Ongoing debate over its placement in the biological treatment algorithm requires further effectiveness and safety data. In our cohort, we found a cumulative induction and maintenance response/remission rate for both CD and UC, generally higher than previous registration trials and in keeping with other long-term analyses.[16,17,20,21] However, in our series UC patients experienced higher maintained response rates than those with CD. Compared to a recent pooled analysis of real-world data,[42] 52-week response/remission rate was lower in our series (63.9% *vs* 86%) for CD. This finding may have different explanations. Our CD population had a high rate of patients who failed to multiple biological therapies or had bowel resections. On the contrary, our UC population had a high rate of anti-TNFs naïve patients with a disease extension limited to the left colon. HBI and Mayo score significantly decreased at 14 weeks, with a further decrease at 52 weeks ($p<0.01$ *vs* baseline, Supplementary Table 1). Accordingly, CRP and FC decreased at 14 weeks, but this was statistically significant for FC only.

The medical therapy of IBD poses a particular challenge in the elderly population that is more likely to suffer from multimorbidity with a higher risk of negative outcomes. We therefore sub-analysed the efficacy and safety of VDZ in the subgroup of patients ≥ 65 years. VDZ proved to be effective, and no infectious diseases were reported. In a previous small case series of elderly patients, a few adverse events, including respiratory tract and gastrointestinal infections, were reported. [43] VDZ may represent a good choice for these patients, but more prospective studies are needed.

Additionally, we looked at potential predictors of clinical response (Supplementary Tables 2 and 3) according to the literature,[26,27-29,31,32,41,42] but the analysis failed to demonstrate any statistical association. In contrast to post hoc GEMINI trials analyses being anti-TNF α naïve was not associated with a better response.,[22,23] Data from real-world series show conflicting results.[26,27,30,31,41] For CD our analysis may lack statistical power but for UC a greater proportion of patients were anti-TNFs naïve. Also, CRP and FC at baseline failed to discriminate patients who were more likely to achieve remission or response. A few real-world studies found a negative association between high disease activity and high CRP at baseline and clinical remission.[26,27,29,33]

Whether bridging steroid therapy and/or immunosuppressants increase VDZ response rate is still a matter of debate. Similar to the registration trials,[16,17]the retrospective consortium study from the US,[31] and the Swedish National Registry[30] we found no association of concomitant immunosuppressants with response. In contrast, one retrospective analysis in CD patients reported that the addition of an immunomodulator after induction improved odds of clinical response at 52 weeks, acting as salvage therapy.[41] In The risk-benefit balance of immunomodulator therapy needs to be considered and as the majority of infections occurred in patients on combination therapy clinicians should routinely re-evaluate the need for immunosuppressive therapy in patients on VDZ.

The role of dose escalation or intensification with VDZ remains unresolved. Five patients achieved remission after escalation of therapy (to six weekly in one patient and to four weekly in the others) and 13 CD patients had an additional dose at week 10. Data regarding dose escalation are still scanty, but this strategy proved efficacious in the long-term GEMINI studies.[20,21]

Primary or secondary non-response were the leading causes (Table 2) for VDZ discontinuation (46/203, 22.6%), while six patients (2.9%) were not adherent to the planned VDZ infusions. This is the first report of non-adherence in patients treated with VDZ. Non-adherence to medication is an essential, though often underestimated, problem in IBD patients, where beliefs and concerns may have a negative impact.[44,45]

Overall, we encountered low rates of adverse events. Among these, five led to discontinuation (four urticarial rash and one supraventricular tachycardia during VDZ infusion). The cumulative incidence of non-infective adverse events of 5.1 per 100 person-year is much lower than that found in long-term GEMINI studies,[20,21] (we did not include disease progression as an adverse event however). We reported a relatively high occurrence of headache and paraesthesia, in keeping with other studies.[33,46] The single case of miscarriage occurred in a 27-year old female with CD who had received 6 VDZ infusions and voluntarily decided to stop the infusions and subsequently flared. Pregnancy outcomes in patients treated with VDZ are still largely unknown.[42]

Unsurprisingly, among the infectious diseases, nasopharyngitis and pneumonia were the most represented. We reported a cumulative incidence of infectious diseases of 11.9 per 100 person-year (13.7% of the whole cohort), that is comparable to the other real-life studies (range 1.7%-12.6%).[46] We reported two VDZ discontinuation in relation to significant viral infections in our cohort: a case of viral meningitis and a case of Epstein-Barr virus (EBV) infection with acute hepatitis. Both of these patients were on concomitant immunosuppressive therapy. A life-threatening case of fungal sepsis occurred in a 23-year old male who was on concomitant methotrexate and systemic steroid therapy. The only case of tuberculosis reactivation affecting the central nervous system occurred in a 57-year old female suffering from type 2 diabetes.

Our study has some limitations. First, the retrospective nature may lead to possible biases, such as the over- or underestimation of PGA. We tried to overcome this obstacle using a standardised spreadsheet with uniform data, also comprising HBI and partial Mayo score that showed a significant positive correlation with PGA. A similar method has already been used for the retrospective assessment of clinical efficacy of a biological therapy.[48] Second, it is known that FC may have a between-assay variability[49] and the hospitals that took part in the study may have used different FC assays, thus producing variations in results. Minor adverse events and infections might have not been reported by patients or have not been recorded in local electronic records, therefore our results may underestimate the incidence as described in clinical trials. Nevertheless, we have reported novel and interesting insights that should be further investigated.

In summary, we have here described our 2-year long, real-life, multicentre experience with VDZ since it was approved for the treatment of IBD. Based on clinical and laboratory grounds, VDZ proved to be an effective and safe drug, even in this cohort of predominantly anti-TNF α exposed patients and in a subgroup of elderly patients.

Guarantor of the article: Christian P Selinger

Statement of author contributions: All authors significantly participated in the drafting of the manuscript or critical revision of the manuscript for important intellectual content and provided approval of the final submitted version. Individual contributions are as follows: MVL coordinated the study, collated, analysed, and interpreted data and wrote the manuscript. All the other authors diagnosed and followed-up patients over time, locally collected data, and reviewed the paper for final approval. CPS supervised MVL, reviewed the paper and made final critical revision for important intellectual contents.

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We herein declare the potential conflict of interest of the submitting authors (Article title: A real-world, long-term experience on effectiveness and safety of vedolizumab in adult patients with inflammatory bowel disease: The Cross Pennine study):

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Figure legend

Figure 1. 14- and 52-week remission and response rates and steroid-free remission according to the Physician Global Assessment.

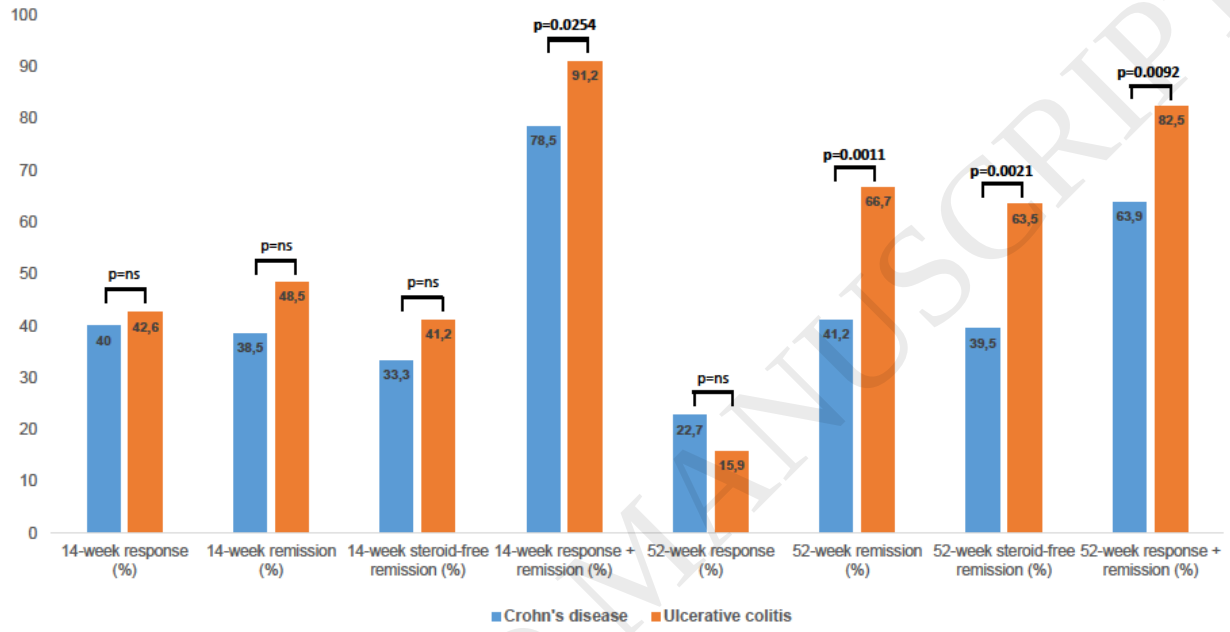

Table 1. Demographic and other relevant characteristics of patients treated with vedolizumab.

	Crohn's disease	**Ulcerative colitis**
N. patients	135	68
Age (years), mean ± SD	40.6 ± 16.0	44.5 ± 18.1
F:M ratio	1.9:1	1:1.2
Duration of disease (months), mean ± SD	107 ± 96	84 ± 62
Disease phenotype, n (%)	Ileal, 15 (11.1%)	Proctitis, 3 (4.4%)
	Colonic, 34 (25.2%)	Left sided colitis, 44 (64.7%)
	Ileocolonic, 67 (47.4%) Upper, 11 (8.1%) Perianal, 16 (11.9%)	Pancolitis, 18 (26.5%) N/A= 3
	Inflammatory, 35 (25.9%)	
	Stricturing, 31 (22.9%)	
	Penetrating, 27 (20.0%)	
	N/A= 17	
Smoking status		
Current smoker, n (%)	20 (14.8%)	1 (1.5%)
Former smoker, n (%)	13 (9.6%)	23 (33.8%)
Any prior anti-TNF α exposure, n (%)	129 (95.5%)	45 (66.2%)
*Concomitant immunosuppressive therapy, n (%)	70 (51.8%)	31 (45.6%)
Bridging steroid therapy	51 (37.7%)	46 (67.6%)

*This includes: azathioprine, methotrexate, or 6-mercaptopurine. Abbreviations: N/A, not available; SD, standard deviation; TNF, tumour necrosis factor.

Table 2. Patients who discontinued vedolizumab and related reasons for discontinuation or loss of response.

	Crohn's disease	**Ulcerative colitis**
Discontinuation ≤14 weeks, n (%)	9/135 (6.6%)	3/68 (4.4%)
Adverse effect	2	/
Abscess development	2	/
Need of surgery	3	3
Infection	1	/
Non-adherence	1	/
Discontinuation >14 and ≤52 weeks, n (%)	39/107 (36.4%)	10/61 (16.4%)
Adverse effect	5	1
Loss of response (switch to other agent)	16	4
Need of surgery	11	3
Infection	4	1
Non-adherence	3	1
Discontinuation >52 weeks, n (%)	8/80 (10.0%)	2/53 (3.8%)
Adverse effect	1	/
Loss of response (switch to other agent)	1	1
Need of surgery	3	1
Infection	1	/
Death (intestinal obstruction)	1	/
Non-adherence	1	/
Total discontinuations	56/135 (41.5%)	15/68 (22.1%)

Table 3. Adverse events, infectious diseases, and other disorders reported during vedolizumab therapy, regardless its discontinuation. More than one event may have occurred within the same patient.

	Crohn's disease	**Ulcerative colitis**	**Total**
Adverse events, n	13	1	14
Urticarial rash	3	1	
Itching (without rash)	2	/	
Paresthesia	2	/	
Hypotension	1	/	
Supraventricular tachycardia	1	/	
Headache	3	/	
Miscarriage	1	/	
Infectious diseases, n	23	8	31
Nasopharyngitis	6	3	
Pneumonia	5	3	
Perianal sepsis	3	/	
Skin bacterial infection	2	/	
Scarlett fever	/	1	
Urinary tract infection	1	1	
Viral meningitis	1	/	
Herpes zoster (shingles)	1	/	
Epstein-Barr infection	1	/	
Fungal sepsis	1	/	
Cryptosporidium gastroenteritis	1	/	
Central nervous system tuberculosis	1	/	
Other disorders, n	4	3	7
Lichen planus	1	/	
Iron deficiency anaemia	1	/	
Abnormal liver function tests	1	1	
Rectal muscle spasm	/	1	
Worsening of psoriasis	1	/	
Atrial mixoma	/	1	