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Vedolizumab induction therapy for inflammatory bowel disease in clinical practice – a nationwide consecutive German cohort study

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[1]See Appendix 1.

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SUMMARY

Background
Vedolizumab (VDZ) is a humanised monoclonal IgG1 antibody targeting $\alpha_4\beta_7$ integrin.

Aim
To investigate the real-world efficacy of vedolizumab for the treatment of Crohn's disease (CD) and ulcerative colitis (UC).

Methods
A consecutive cohort of 212 adult IBD patients with active disease (HBI >7/partial Mayo >4) newly receiving VDZ was prospectively recruited from 7 academic and 17 community centres. The primary endpoint was clinical remission (CRM) (CD HBI ≤4, UC pMayo ≤1) in week 14. Secondary endpoints included steroid-free remission (SFCRM), clinical response (CRS) (HBI/pMayo score drop ≥3), vedolizumab impact on CRP, calprotectin and haemoglobin.

Results
Data of 97 CD (71.1% female, HBI 11) and 115 UC (42.6% female, pMayo 6) patients were analysed. Only 5.2% CD and 24.3% UC were anti-TNFα naïve. Most had extensive mucosal involvement (Montreal L3 69.1%/E3 53.9%). At week 14, 23.7% vs. 23.5% of CD vs. UC patients achieved CRM, 19.6% vs. 19.1% SFCRM and 60.8% vs. 57.4% CRS, respectively (all based on NRI). Week 14 CRM in CD was significantly associated with no history of extraintestinal manifestations ($P = 0.019$), no prior adalimumab use ($P = 0.011$), no hospitalisation in the past 12 months ($P = 0.015$) and low HBI score ($P = 0.02$) and in UC with active or previous smoking ($P = 0.044/0.028$) and no anti-TNFα ($P = 0.023$) use. Low HBI ($P = 0.019$) and no hospitalisation in the past 12 months ($P = 0.01$) predict CD CRM. The three most common AE were joint pain, acne and nasopharyngitis.

Conclusion
Vedolizumab is effective in routine use.

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INTRODUCTION

Crohn's disease (CD) and ulcerative colitis (UC) are idiopathic inflammatory bowel diseases that cannot be cured and challenge patients and healthcare systems worldwide.[1, 2, 3] Leucocyte migration and retention are hallmark features of chronic inflammation including inflammatory bowel diseases.[4, 5]

Specifically, binding of the leucocyte $\alpha_4\beta_7$ integrin to its principal ligand, the mucosal addressin cellular adhesion molecule 1 (MAdCAM-1), which is expressed in high endothelial venules (HEV) of the gut lamina propria, gut-associated lymphoid tissue and mesenteric lymph nodes, has been shown to be pivotal in leucocyte homing to the gastrointestinal tract.[6–11] In inflammatory bowel diseases, the expression of MAdCAM-1 is highly upregulated in HEVs of inflammatory sites and promotes an increased capacity to bind leucocytes.[12, 13]

Vedolizumab (MLN0002, MLN02, LDP-02, anti-$\alpha_4\beta_7$) is a humanised monoclonal IgG_1 antibody targeting $\alpha_4\beta_7$ integrin.[14] Vedolizumab (VDZ) mostly binds to a subset of memory CD4+ cells (including T_h17 cells) and eosinophils.[14] Low-to-intermediate level binding was observed for naïve CD4+ cells, CD8+ cells, B cells, natural killer cells and basophils. Vedolizumab does not bind to neutrophils, the majority of memory CD4+ lymphocytes and most monocytes. Importantly, highly specific binding of vedolizumab to $\alpha_4\beta_7$ but not to $\alpha_4\beta_1$ or $\alpha_E\beta_7$ integrins was confirmed by a series of flow cytometry analyses. Interestingly, although $\alpha_4\beta_7$ integrin is a potential ligand for both MadCAM-1 and VCAM-1, vedolizumab selectively inhibits adhesion of $\alpha_4\beta_7$ integrin expressing cells to MAdCAM-1 but not to VCAM-1, even at high concentrations.[15]

Two pivotal trials have led to the approval of Vedolizumab for CD[16] and UC[17] in several jurisdictions including Germany. Since clinical trials in inflammatory bowel diseases rarely represent the real-world patient population,[18] we report the first real-life experience from a nationwide consecutive German patient cohort across all care levels.

METHODS

Patients

The study protocol was approved by University of Jena and Kiel's Institutional Review Boards. All patients gave written informed consent to the study. Adult, consenting patients eligible to receive treatment with Vedolizumab according to its German label were recruited from seven academic and 17 community centres in Germany. Patient's gender, age, disease duration, smoker status, previous inflammatory bowel diseases related surgeries, hospitalisation within the past 12 months, presence and type of extraintestinal disease manifestations, previous and current concomitant medications as well as phenotype according to the Montreal classification were recorded.[19]

The partial Mayo score[20] for UC and the Harvey–Bradshaw index[21, 22] for CD were used to assess disease activity. Active disease was defined as a Harvey–Bradshaw index score of >7 in CD and a partial Mayo score >4 in UC. Clinical response was defined as a Harvey–Bradshaw index score reduction ≥3 points in CD and a partial Mayo score reduction ≥3 points accompanied by a decrease of at least 30% from baseline in UC. Clinical remission was defined by a Harvey–Bradshaw index score of ≤4 in CD and partial Mayo score ≤1 plus a bleeding subscore of 0 in UC. Only patients with active UC or CD at baseline were included in the analysis.

Treatment schedule and concomitant medications

Vedolizumab was applied according to label, that is, induction with 300 mg i.v. at week 0, 2 and 6 and maintenance every 8 weeks. Moreover, concomitant inflammatory bowel diseases medications such as 5-ASA derivatives (mesalazine or sulfasalazine), steroids (budesonide, beclomethasone, hydrocortisone or prednisolone), immunomodulators (azathioprine, mercaptopurine, methotrexate, tacrolimus and cyclosporin) and anti-tumour necrosis factor alpha (TNFα) biologics (adalimumab, golimumab, infliximab) were recorded.

Follow-up

Patients were seen at baseline and were prospectively followed in week 2, 6, 10 until week 14. All data were recorded into a database for analysis.

Primary and secondary endpoints

The primary endpoint of this study was clinical remission in week 14 as defined above. Secondary endpoints included clinical remission in week 6, steroid-free clinical remission in week 6 and 14, clinical response in week 6 and week 14, steroid sparing effect, impact on C-reactive protein (CRP), haemoglobin and where available calprotectin.

Safety

All adverse events were recorded and safety data are reported from the safety population, that is, the population of patients who received at least one dose of vedolizumab. The results are expressed using medical dictionary of regulatory activities (MedDRA) 18.1 terminology.[23]

Statistical analysis

All statistical analyses were performed with SPSS 23 (IBM, Armonk, NY, USA) software. For descriptive statistics, medians and interquartile ranges were reported where applicable. Categorical data are expressed in bar charts. Statistical significance was tested using the Wilcoxon test for ordinal or continuous and the Chi-squared test for binary variables. Missing values in effectiveness outcome (i.e. clinical remission, steroid-free clinical remission, clinical response, clinical remission in anti-TNFα naïve patients, steroid sparing effect) calculations were handled by nonresponder imputation (NRI). All other analyses are based on available data. All variables with a $P < 0.05$ at bivariate level were also tested in a logistic regression model for the primary endpoint of clinical remission in week 14 to identify independent predictors. Vector graphics were created using Prism 6 (GraphPad Software Inc., La Jolla, CA, USA).

RESULTS

Patient flow and recruitment

We recruited 212 patients for this study between 2014 and 2015. Patient disposition is depicted in a Consolidated Standards of Reporting Trials (CONSORT) style diagram (Figure 1).

Patient demographics and phenotype

Almost equal numbers of CD and UC patients were included in the analysis. Their median age and gender distribution was typical for inflammatory bowel diseases. Of note, the majority of patients had extensive mucosal involvement, that is, ileocolitis in CD or pancolitis in UC. More than 20% of CD patients had perianal fistulas. Almost a third of CD patients were active smokers. Almost one third of UC and one half of CD patients were diagnosed with an extraintestinal manifestation at some point during the course of their disease (Table 1).

Patient disease activity, disease- and treatment history

Approximately a third of CD and UC patients had been hospitalised within the past twelve months prior to vedolizumab treatment. More than 40% of CD patients had intestinal surgery in the past. Almost all CD and almost two thirds of UC patients had been exposed to anti-TNFα drugs before (Table 2, Figure 2a). The most commonly prescribed anti-TNFα compound prior to vedolizumab was adalimumab in CD and infliximab in UC (Table 2, Figure 2b). Most patients were receiving concomitant steroids, immunosuppressants or both at baseline.

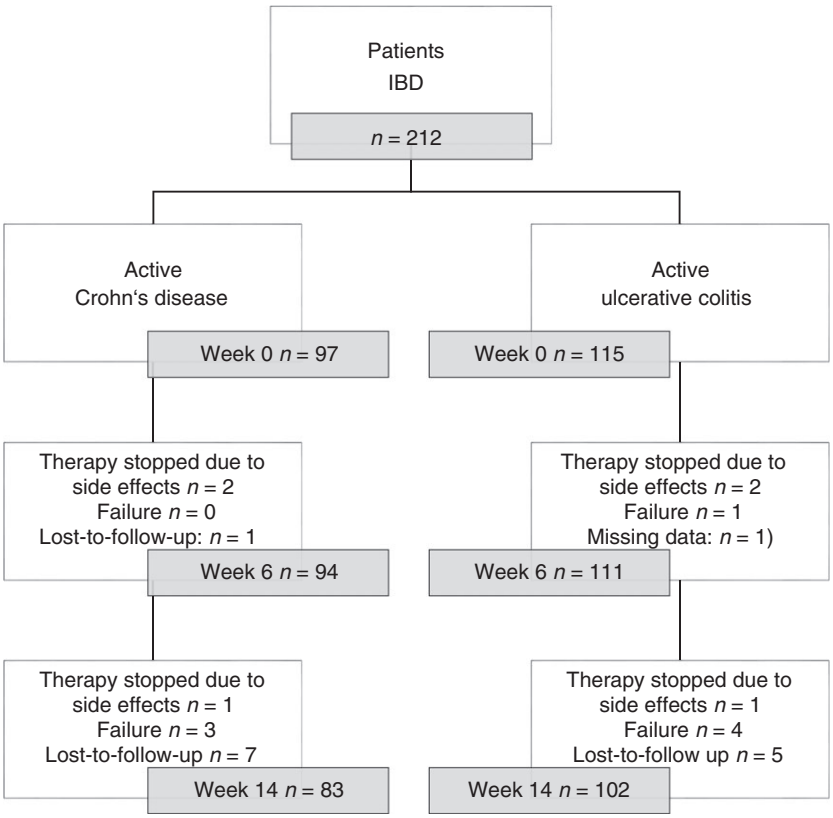


Figure 1 | Patient disposition.

Table 1 | Patient baseline demographics and phenotype*

	Crohn's disease (*N* = 97)		Ulcerative colitis (*N* = 115)	
	n	Median (95% CI)	*n*	Median (95% CI)
Age (years)	96	36 (34–42)	114	42 (37–46)
Disease duration (years)	96	9 (7–12)	114	7 (5–9)
	n	%	*n*	%
Gender				
Female	69	71.1	49	42.6
Male	28	28.9	66	57.4
Tobacco status				
Nonsmoker	45	46.4	79	68.7
Ex-smoker	21	21.6	24	20.9
Smoker	27	27.8	9	7.8
Montreal classification				
A1	14	14.4		
A2	72	74.2		
A3	10	10.3		
L1	7	7.2		
L2	16	16.5		
L3	67	69.1		
L4	9	9.3		
L4+	2	2.1		
B1	38	39.2		
B2	24	24.7		
B3	4	4.1		
B3p	21	21.6		
E1			7	6.1
E2			30	26.1
E3			62	53.9
History of extraintestinal manifestations				
Any	48	50	32	27.8
Arthralgia	41	42.3	27	23.5
Iritis	2	2.1	1	0.9
Erythema nodosum	3	3.1	1	0.9
Pyoderma gangrenosum	0	0.0	0	0
Primary sclerosing cholangitis	2	2.1	3	2.6
Oral aphthous lesions	0	0.0	1	0.9

* Percentages refer to the available data, i.e. *n*.

Outcomes and estimation

Clinical remission. Less than a quarter of all CD and UC patients achieved clinical remission as the primary endpoint in week 14. The percentage of patients achieving clinical remission increased in CD from 15.5% to 23.7% and in UC from 11.3% to 23.5%, respectively from week 6 to 14. Only the increase from week 6 to 14 in UC reached statistical significance ($P = 0.004$) (Figure 3a,b,d).

Steroid-free clinical remission. Less than a fifth of all CD and UC patients achieved steroid-free clinical remission at week 14. The percentage of patients achieving steroid-free clinical remission increased in CD from 11.3% to 19.6% and in UC from 8.7% to 19.1%, respectively from week 6 to 14. Only the increase in UC reached statistical significance ($P = 0.012$) (Figure 3a,b, d).

Clinical Remission in anti-TNFα naïve patients. Although the percentage of anti-TNFα naïve patients was very small in this cohort we decided to evaluate the full potential of the drug for both CD and UC when used as a first line biologic. Vedolizumab was significantly more effective for the induction of clinical remission in inflammatory bowel diseases at week 14. More anti-TNFα naïve CD (60%) and UC (39.3%) patients achieved clinical remission compared with anti-TNFα exposed CD (21.7%) and UC (18.5%) patients ($P = 0.05$ vs. 0.023, respectively) (Figure 3e).

Clinical response. In CD 66% vs. 60.8% of patients experienced a clinical response in week 6 and week 14, respectively. This drop was not statistically significant. The percentage of UC patients experiencing a clinical response significantly increased from 42.6% in week 6 to 57.4% in week 14 ($P = 0.008$) (Figure 3c).

Steroid sparing effect. It was possible to taper the steroids in many CD and UC patients. In CD 27.6%, 26.8% and 15.5% in UC 40.9%, 31.3% and 18.3% of patients were on steroids in weeks 0, 6 and 14, respectively. However, this drop was significant in CD only in week 6 vs. week 14 ($P = 0.019$) and week 0 vs. week 14 ($P = 0.012$), while in UC this reduction reached statistical significance in week 0 vs. week 6 ($P = 0.013$), week 6 vs. week 14 ($P = 0.001$), week 0 vs. week 14 ($P < 0.001$) (Figure 3f).

Impact of steroids at baseline and disease extent at baseline. We analysed clinical remission in week 14 stratified by steroid medication as well as disease extent by Montreal classification at baseline for both CD and UC. All patients in CD (26.8% vs. 0%), but not UC (21.9% vs. 31.3%) achieving remission in week 14 were on steroids at baseline (Figure 3g). While most patients enrolled in this study had extensive mucosal involvement

Table 2 | Patient disease activity, disease history and treatment data

	Crohn's disease (N = 97)		Ulcerative colitis (N = 115)	
	n	Median (95% CI)	*n*	Median (95% CI)
C-reactive Protein (mg/dL)	93	0.98 (0.64–1.25)	106	0.63 (0.47–0.90)
Haemoglobin (mmol/L)	51	7.7 (7.5–8.2)	64	8.3 (7.7–8.4)
Faecal calprotectin (mg/dL)	48	975.00 (547.62–2030.54)	61	1740.00 (820.13–2100.00)
Partial Mayo Score			115	6 (6–7)
Harvey–Bradshaw index Score	97	11 (10–12)		
Prior anti-TNFα therapy				
Number of previous anti-TNF therapies				
0	5	5.2	28	24.3
1	19	19.6	30	26.1
2	66	68.0	30	26.1
3	7	7.2	27	23.5
Infliximab	79	81.4	74	64.3
Adalimumab	86	88.7	61	53.0
Golimumab	7	7.2	36	31.3
Anti-TNFα naive	5	5.2	28	24.3
Anti-TNFα failure	80	82.5	85	73.9
Anti-TNFα side effects	9	9.3	1	0.9
	n	%	*n*	%
Concomitant medications				
5-ASA or Sulfasalazine	74	76.3	91	79.1
Steroids	82	84.5	96	83.5
Immunomodulators only*	78	80.4	88	76.5
Steroids and immunomodulators	60	61.9	74	64.3
	n	Median (95% CI)	*n*	Median (95% CI)
Prednisolone equivalent dose (mg/dL)	24	20 (20–30)	43	20 (10–22)
	n	%	*n*	%
Hospitalisation and surgery history				
Any bowel surgery	41	42.3	5	4.3
Hospitalisation within past 12 months	33	34.0	31	27.0

* Azathioprine, 6-MP, methotrexate, cyclosporine, tacrolimus.

(Table 1), patients with limited disease (i.e. L1 and E1) more frequently achieved clinical remission in week 14 (L1 28.6%, L2 18.8% L3 23.9% and E1 42.9% E2 30% and E3 21% respectively; Figure 3h). There were no statistically significant differences in these groups.

Impact on biochemical surrogates of inflammation.
C-reactive protein: While the CRP values successively decreased from week 0 to week 6 and 14 in both CD 0.98 vs. 0.898 vs. 0.72 mg/dL and UC 0.63 vs. 0.52 vs. 0.43 mg/dL patients, this trend did not achieve statistical significance (Figure 4a).

Calprotectin: Calprotectin levels in CD decreased successively from week 0, to week 6 and 14 975 vs. 860 vs. 370 mg/dL. However, only the drop from week 0 to week 14 reached statistical significance (n = 13, P = 0.003). In UC calprotectin levels significantly decreased at all time points 1740 vs. 825 vs. 273 mg/dL (n = 23, P = 0.023 vs. n = 12 P = 0.033 vs. n = 20, P < 0.0001) respectively (Figure 4b).

Haemoglobin: Haemoglobin levels minimally increased from week 0 to week 6 and 14 both in CD 7.70 vs. 7.75 vs. 7.9 mmol/L and UC 8.3 vs. 8.20 vs. 8.51 mmol/L. However, only the increase from week 6 to week 14 in UC was statistically significant (n = 47, P = 0.020) (Figure 4c).

Safety

Most adverse events fell equally into three MedDRA system organ classes (SOC): skin and subcutaneous tissue disorders (n = 6), infections and infestations (n = 6) and gastrointestinal disorders (n = 6). The five most commonly reported adverse events were arthralgia, acne,

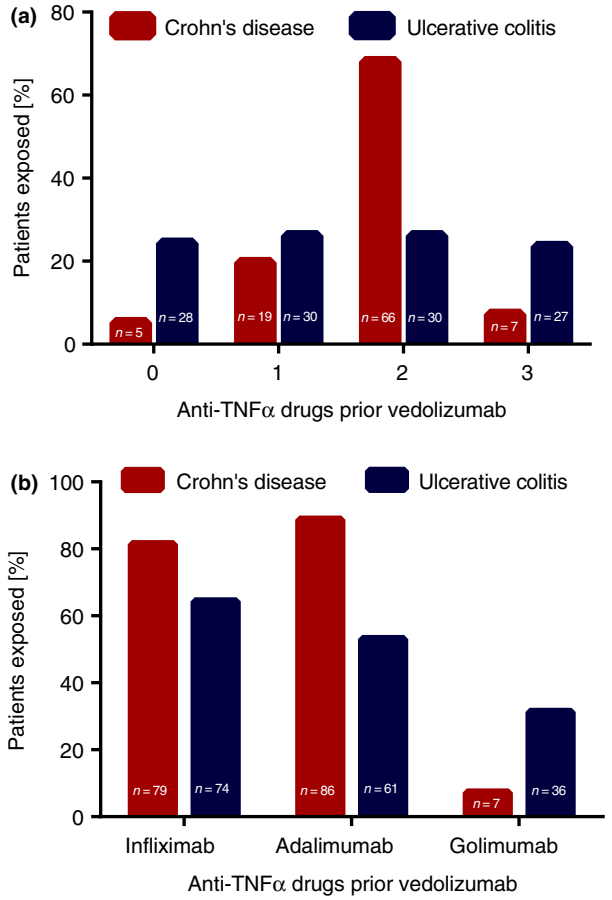


Figure 2 | Anti-TNFα exposure prior to vedolizumab. (a) Number of anti-TNFα drugs prior to vedolizumab. (b) Type of anti-TNFα drugs prior to vedolizumab.

arthritis and nasopharyngitis. Table 3 summarises the safety data.

Predictors of clinical effectiveness

At bivariate level using baseline values (week 0) in CD no history of extraintestinal manifestations, a low Harvey–Bradshaw index score, no adalimumab use, no hospitalisation in the past 12 months and in UC active or previous smoking, no infliximab use and no-anti-TNFα use at all, were significantly associated with clinical remission in week 14 (Table S1).

At logistic regression with stepwise variable selection (CD $R^2 = 0.224$) (Nagelkerke) (UC $R^2 = 0.079$) (Nagelkerke) using only significant variables from Table S1 only low Harvey–Bradshaw index ($P = 0.019$) and no recent hospitalisations ($P = 0.01$) in CD remained significant. Thus, low Harvey–Bradshaw index and no recent hospitalisations in CD can be classified as independent predictors of clinical remission in week 14.

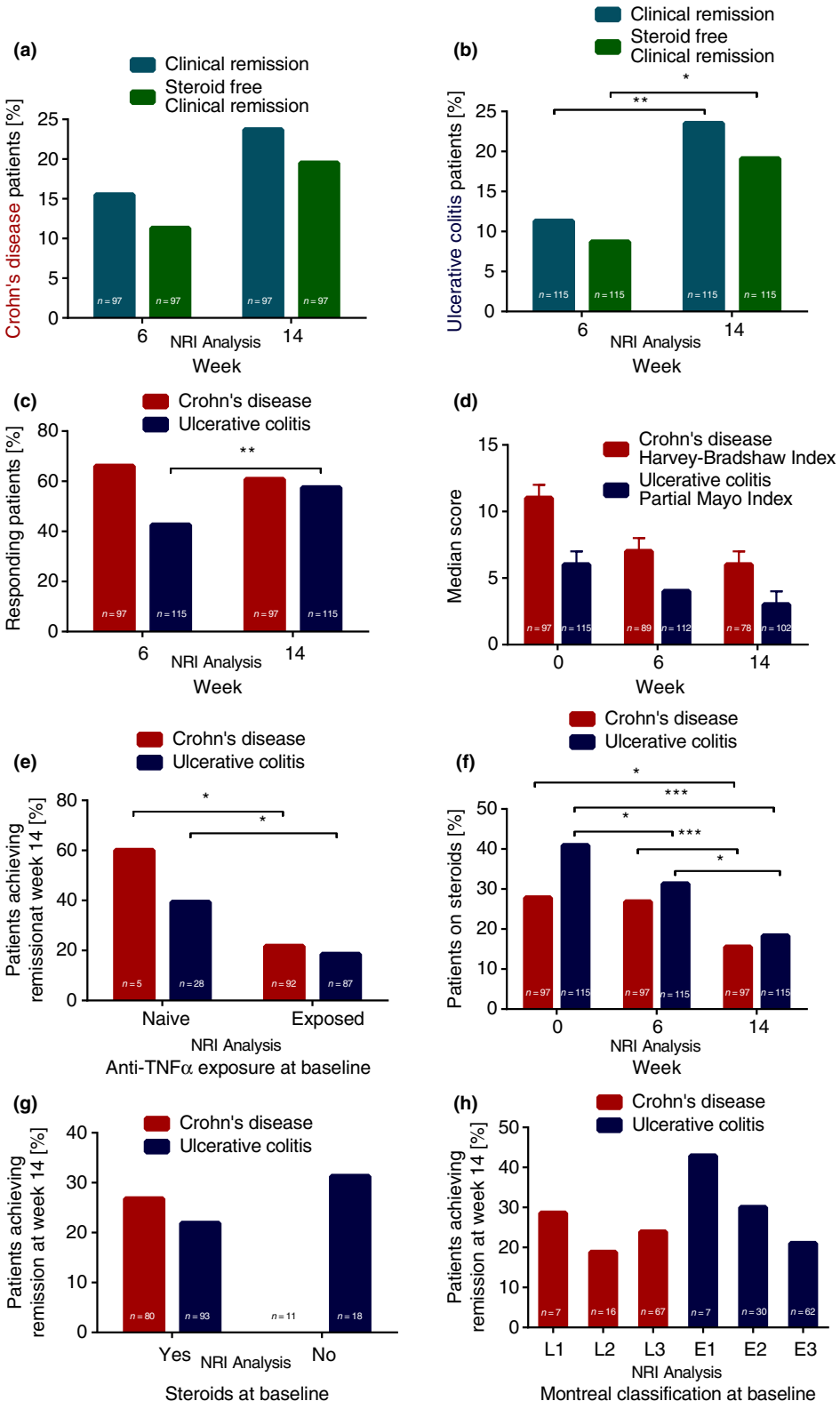
DISCUSSION

This is the first industry independent, multicentre, prospective real-world study of vedolizumab in inflammatory bowel diseases in clinical practice across all care levels.

Compared with the pivotal CD trial,[16] we saw a greater than twofold higher clinical response rate (66% vs. 31.4%) in week 6, while the clinical remission data looked very similar (15.5% vs. 14.5%). This could result from including CD patients based on a relatively high Harvey–Bradshaw index of >7 and thus greater likelihood of a drop from an elevated level. Age, disease duration and mucosal involvement have probably not contributed to these differences, as they were more favourable in the original trial population. We cannot rule out that carry-over effects from concomitant medications may have contributed to the higher response rate in week 6 since the percentages of patients on steroids (84.5% vs. 34.2%) and immunosuppressants plus steroids (61.9% vs. 17%) at baseline were higher in our cohort. The use of different indices that is, CDAI in the pivotal trial and Harvey–Bradshaw index in our study does not appear to be major factor based on an analysis of 1000 data pairs that concluded that a CDAI drop of 100 points equals a 3 point Harvey–Bradshaw index drop and remission based on a CDAI of <150 points equals an Harvey–Bradshaw index of ≤4.[22]

In UC, our results match the pivotal trial[17] more closely with slightly lower clinical response (42.6% vs. 47.1%) and clinical remission (11.3% vs. 16.9%) rates in week 6, respectively. A female dominated, younger (40.3 years vs. 42.6 years) original trial population with less extensive mucosal involvement (pancolitis 37% vs. 59%) and less inflammation based on an almost 50% lower calprotectin value (899 mg/L vs. 1740 mg/L) may account for these differences.

As known from previous trials with anti-TNFα biologics, effectiveness does depend on previous biologic use. Consistent with that notion vedolizumab performed significantly better in anti-TNFα-naïve inflammatory bowel diseases patients of our cohort. While the manufacturer has not directly analysed the efficacy of vedolizumab in anti-TNFα-naïve vs. anti-TNFα-exposed patients in its pivotal trial, data from a placebo controlled sub-study in CD patients who had experienced an inadequate response, loss of response or intolerance to TNF antagonists, immunosuppressives or corticosteroids within the past 5 years are available.[24] This sub-study did not detect a statistically significant difference for clinical remission



in week 6 between vedolizumab and placebo. The actual clinical remission rate in this sub-study at week 6 is similar to the pivotal trial was comparable (15.2% vs. 14.5%).

Consistent with the lower clinical effectiveness of vedolizumab in CD are the identified significant associations of clinical remission with surrogates of lower disease activity or a less complicated disease course,

Figure 3 | Clinical effectiveness of vedolizumab. (a) Clinical remission and steroid-free clinical remission in Crohn's disease determined by Harvey–Bradshaw index score. (b) Clinical remission and steroid-free clinical remission in ulcerative colitis determined by partial Mayo index score. (c) Clinical response in Crohn's disease and ulcerative colitis determined by Harvey–Bradshaw and partial Mayo index scores, respectively. (d) Median disease activity score in Crohn's disease (Harvey–Bradshaw index) and ulcerative colitis (partial Mayo index) respectively. Error bars show 95% CI. (e) Clinical remission in week 14 in anti-TNFα naïve patients in Crohn's disease and ulcerative colitis. (f) Steroid sparing effect of vedolizumab assessed as percentage of patients of prednisolone or equivalent. (g) Clinical remission in week 14 stratified by steroid medication at baseline in Crohn's disease and ulcerative colitis. (h) Clinical remission in week 14 stratified by disease extent (Montreal classification) in Crohn's disease and ulcerative colitis. Significant differences are shown with brackets. Asterisks denote statistical significance: $*P \leq 0.05$, $**P \leq 0.01$, $***P \leq 0.001$, $****P \leq 0.0001$. NRI, nonresponder imputation.

such as a low Harvey–Bradshaw index score at baseline, the absence of a recent hospitalisation and no history extraintestinal manifestation. It was not surprising to see active or previous tobacco use associated with clinical remission in UC as a milder disease course of UC in smokers is long known from epidemiological studies[25, 26] At logistic regression only low Harvey–Bradshaw index and no recent hospitalisations in CD were identified as independent predictors of clinical remission in week 14.

Our study did not detect any alarming new safety signals. Of note compared with the pivotal trials was the high(er) frequency of arthralgia and skin reactions.[27] Nasopharyngitis seen in our study was also common in the pivotal trials.[16, 17] Unlike with anti-TNFα biologics, where psoriasiform skin lesions[28] occur, we saw mostly acneiform lesions and dry skin. Since vedolizumab does not affect the cross-regulation of TNFα and IFNα,[29, 30] which mechanistically contributes to psoriasis pathogenesis, such lesions would not be expected with vedolizumab. In fact the successful use of vedolizumab to treat a UC patients with an infliximab associated psoriasiform rash has been reported.[31] The higher frequency of acne and nasopharyngitis with vedolizumab could result from its immunosuppressive effect on target receptor expression outside the gut. Vedolizumab is not gut exclusive, but rather gut focused.[5, 32] Infections including serious infections were also more common in vedolizumab treated patients in the pivotal trials. One meta-analyses comparing natalizumab, vedolizumab and etrolizumab reported higher absolute numbers of opportunistic infections with these anti-integrin antibodies, but this difference was not statistically significant.[33] There is also a new case report of pseudomonas meningitis associated with vedolizumab treatment for CD.[34] There is no mechanistic explanation for the higher rates of arthralgia yet. It is important to stress, that all comparisons with the pivotal studies should be interpreted with caution, because a randomised controlled trial setting can never be directly compared with real-world data.[18]

Our study has limitations. Although a nationwide effort, the number of patients eventually enrolled and the observation period were limited compared with the pivotal trials. This precludes advanced statistical modelling and any meaningful additional analyses of combined endpoints and outcomes. A significant proportion of patients was lost to follow-up. This is not surprising in an observatory study that is not supported by the manufacturer and therefore is limited in its investment in patient and centre retention strategies. Because we do not know why patients discontinued we used NRI as our primary analysis strategy. With this approach, every endpoint relevant data point that is missing is declared to represent a therapeutic failure and estimates for effectiveness are maximally pessimistic. Using a censored analysis ("as observed") as in most other observatory studies (in which the missing follow-ups are disregarded and therefore the relevant denominator (n) keeps declining over time) we see clinical responses at week 6 in CD of 71.9% (64, $n = 89$) and UC of 43.8% (49, $n = 112$) and at week 14 in CD of 75.6% (59, $n = 78$) and UC of 74.7% (66, $n = 102$), respectively. The corresponding data for clinical remission are at week 6 for CD 16.9% (15, $n = 89$) and UC of 11.4% (13, $n = 114$) and at week 14 CD of 29.5% (23, $n = 78$) and UC of 26.5% (17, $n = 102$) respectively. The principal findings that the onset of action appears to be comparable between CD and UC and that the magnitudes of effectiveness rates in the two forms of inflammatory bowel diseases are also similar, are independent of the analytical scenario. Therefore, we suggest that further analyses of vedolizumab effectiveness data (in particular future meta-analyses of open label observational cohorts or a re-analyses of the clinical trial program) could use the inflammatory bowel diseases

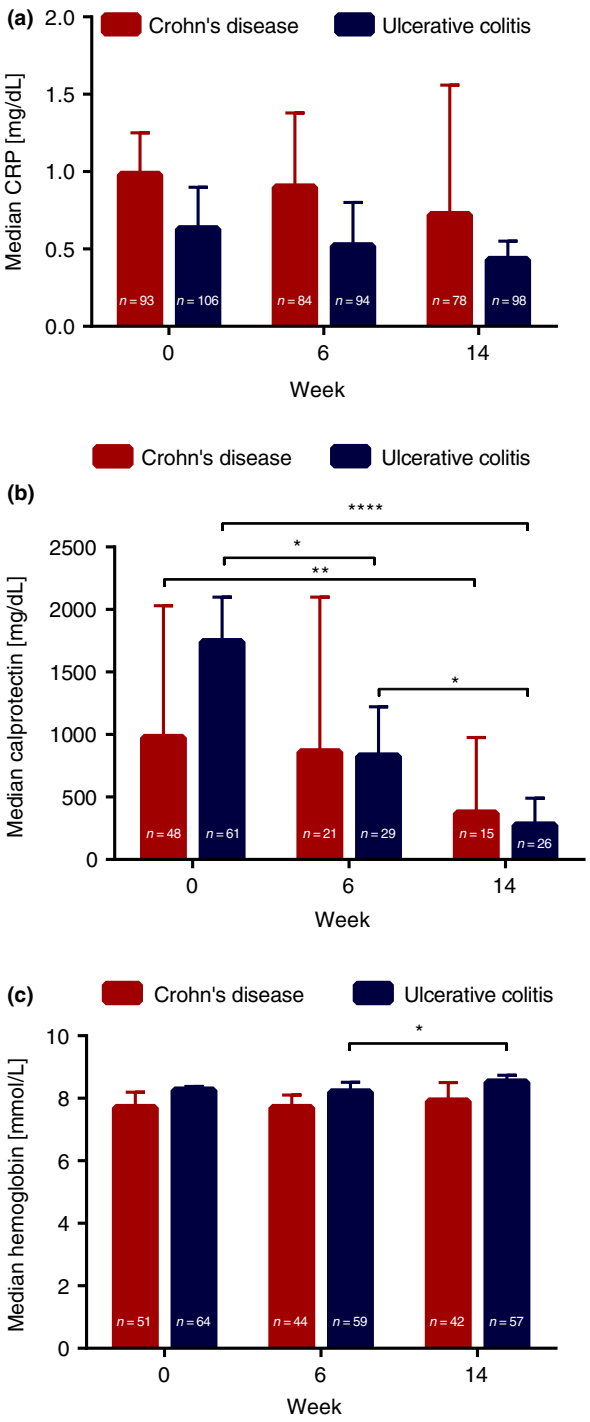


Figure 4 | Vedolizumab impact on biochemical surrogate parameters of inflammation. (a) Median CRP levels. Error bars show 95% CI. (b) Median Calprotectin. Error bars show 95% CI. (c) Median haemoglobin levels. Error bars show 95% CI. Significant differences are shown with brackets. Asterisks denote statistical significance: *$P \leq 0.05$, **$P \leq 0.01$, ***$P \leq 0.001$, ****$P \leq 0.0001$.

phenotype in contrast to splitting the population according to treatment protocol and indication. Such an approach could result in a greatly enhanced statistical power to detect subgroups and model parameters to identify patients with long term benefits.

Our study was also too small to pick- up any low frequency safety signals. Moreover, while originally intended, insufficient week 6 and week 14 data prevented the analysis of quality of life and endoscopic data. Thus, we cannot make any statements on patient reported outcomes (PROs), quality of life or mucosal healing. However, as calprotectin is a surrogate of mucosal disease activity and we found a significant drop towards week 14, it can be hypothesised that at least some reduction of mucosal inflammation and damage took place. This was most pronounced in UC where the difference between week 0 and 14 reached a maximum significance level of $P < 0.0001$.

To date, only data from one other real-world cohort are fully published.[35] In this retrospective pooled analysis from one institution 59 patients with UC, 42 with CD and 6 with unclassified disease were included. The authors reported for CD, 48.9% and 23.9% and UC, 53.9% and 29.3% clinical response and clinical remission at week 14, respectively. We saw slightly higher response rates especially in CD, but substantially lower remission rates in UC at week 14. Their lower response to vedolizumab in CD rate could relate to an older, male dominated CD population (39.7 years vs. 36 years) with longer disease duration (16.4 years vs. 9 years). Their Harvey–Bradshaw index determined disease activity, although apparently lower (6 vs. 11) cannot directly be compared with ours because it was only collected in less than half of their patients. This group's CD patients had more frequently surgery in the past (58.8% vs. 42.3%), while exposure to approximately two anti-TNFs in the past was very similar to our cohort. The higher remission rates for UC in week 14 probably relates to their female dominated, younger UC patient population, the use of a different assessment instrument (simple clinical colitis activity index vs. partial Mayo index) and less inflammatory mucosal involvement (54.6% vs. 59%). On the other hand their patients were more frequently exposed to anti-TNFα drugs (61.5% vs. 26.1%) prior to vedolizumab than our patients. The authors identified as the only statistically significant independent predictor for a response to vedolizumab in inflammatory bowel diseases: a CRP of greater 8 mg/L at baseline. Reported side effects in this cohort were similar to our experience, with

Table 3 | Adverse events using MedDRA 18.1 terminology

Preferred term	System organ class	Crohn's disease (*n*)	Ulcerative colitis (*n*)
Arthralgia	Musculoskeletal and connective tissue disorders	9	12
Acne	Skin and subcutaneous tissue disorders	9	6
Arthritis	Musculoskeletal and connective tissue disorders	9	4
Nasopharyngitis	Infections and infestations	2	4
Erythema nodosum	Skin and subcutaneous tissue disorders	1	2
Dry skin	Skin and subcutaneous tissue disorders	2	1
Acute generalised exanthematous pustulosis	Skin and subcutaneous tissue disorders	1	1
Nausea	Gastrointestinal disorders	2	
Paraesthesia	Nervous system disorders		2
Oral herpes	Infections and infestations		2
Rash	Skin and subcutaneous tissue disorders	1	1
Anal fissure	Gastrointestinal disorders	1	
Helicobacter gastritis	Infections and infestations	1	
Pruritus	Skin and subcutaneous tissue disorders	1	
Headache	Nervous system disorders	1	
Abdominal pain	Gastrointestinal disorders	1	
Acute renal failure	Renal and urinary disorders	1	
Malnutrition	Metabolism and nutrition disorders	1	
Crohn's disease	Gastrointestinal disorders	1	
Colitis ulcerative	Gastrointestinal disorders		1
Clostridium difficile colitis	Infections and infestations		1
Sweating fever	Infections and infestations		1
Infection	Infections and infestations		1
Cough	Respiratory, thoracic and mediastinal disorders		1
Fatigue	General disorders and administration site conditions		1
Memory impairment	Nervous system disorders		1
Aphthous ulcer	Gastrointestinal disorders		1

many patients complaining of arthralgia and a variety of skin problems. However, they also reported serious adverse events, we did not see such as perianal abscesses and thromboembolic events such as a retinal vein occlusion.

Additional real-world data are currently only available in abstract format from both Digestive Disease Week and United European Gastroenterology Week earlier this year. A small series from Saint Louis, MO, USA series involving 18 CD and 15 UC patients reported their monocentric effectiveness data in week 6.[36] None of their patients had achieved clinical remission by then, but Harvey–Bradshaw index and partial Mayo scores dropped significantly ($P < 0.01$ vs. 0.05, respectively). A group from Chicago, IL, USA reported monocentric clinical effectiveness data for 42 CD and 27 UC patients.[37] Here 38.5% of their CD and 40% of their UC patients achieved clinical remission in week 14. They identified colon involvement and bio-naïve patients as predictors for vedolizumab response. As Swedish prospective, multicentre cohort based on their national register (SWIBREG) reported a clinical response in 33% of their 33 CD and 40% of their 64 UC patients, 90% of which had previously been exposed to anti-TNFα drugs.[38] Lastly, a manufacturer financed real-world study reported prospective, multicentre cohort data collected from 170 CD patients and 121 UC patients in France.[39, 40] The authors reported response and remission as well as steroid-free response and remission rates for CD 59% vs. 38%/47% vs. 32% and UC 52 vs. 35%/45% vs. 31% respectively. There are some potential explanations for the apparent higher effectiveness compared with our data. Their younger (40.4 vs. 42 years) UC population had a slightly shorter disease duration (6.5 vs. 7 years) and less extensive mucosal involvement compared with our patients. Carry-over effects from co-administered drugs, which may have contributed to the greater effectiveness, may also have been a factor. While the sociodemographics of their CD population were very similar (female dominance, age 36.3 vs. 36 years, disease duration 10.7 vs. 9 years) to our cohort, they defined active CD by an Harvey–Bradshaw index of >5 compared with

>7 in our study, that is, included CD patients with less active disease in their analysis. Furthermore, while demographic data were reported as medians assuming a non-normal data distribution of their cohort based on sample size, their effectiveness data although were reported in means which may have skewed their outcome data. Also, further differences may have resulted from a different handling of missing values, which was most likely not NRI based like in our effectiveness analysis. Their safety analysis reported mostly infectious complications including opportunistic infections, skin problems, paraesthesia as well as also thromboembolic events and one adenocarcinoma of the rectum.

In summary, our data and the limited currently available evidence from other cohorts in Europe and North America discussed suggest that vedolizumab is effective in bio-experienced and even more so in bio-naïve real-life inflammatory bowel diseases patients. Its gradual onset of action was confirmed. Based on our data, a meta-analysis and systematic review of biologic therapies for CD, vedolizumab is not the first line choice for bio-naïve CD patients.[41] Larger and longer prospective, multicentre studies and registers including formal evaluation with validated PRO instruments, endoscopic studies to assess mucosal healing and quality of life are needed to render reliable safety data, especially regarding risk of (serious) infection and malignancy as well as determine its position in relation to other anti-integrins currently in development such as etrolizumab[42] or anti-MAdCAM (PF-00547,659).[43] If vedolizumab and the evolving anti-integrins expected improved safety profile compared with anti-TNFα biologics is confirmed long term they may assume an earlier role in the inflammatory bowel diseases treatment algorithm.

SUPPORTING INFORMATION

Additional Supporting Information may be found in the online version of this article:

Table S1. Association of Baseline (Week 0) Patient Characteristics, Disease and Treatment History with the Primary Endpoint of Clinical Remission in Week 14 at Bivariate Level. Significant p values appear bold.

AUTHORSHIP

Guarantor of the article: D.C.B. on behalf of the Vedolizumab Germany Consortium.

Author contributions: D.C.B., B.B., S.S. and A.S. had the idea, designed and led the project. A.D., B.B. and D.C.B. developed the CRF. A.D. programmed the database and performed the statistical analyses. All authors interpreted the results. D.C.B. presented the data at United European Gastroenterology Week 2015 in Barcelona, Spain and wrote the first draft. All authors edited and finally approved the manuscript prior to submission.

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APPENDIX 1

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