Real-world effectiveness and safety of Vedolizumab for the treatment of Inflammatory Bowel Disease

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Title: Real-world effectiveness and safety of Vedolizumab for the treatment of Inflammatory Bowel Disease: The Scottish Vedolizumab Cohort

Short title: Real-world effectiveness and safety of vedolizumab for Inflammatory Bowel Disease

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NP study design, data collection, analysis and writing of manuscript. CSC data collection and writing of manuscript. GRJ, CWL study design, analysis and critical revision of manuscript. RMA, IDA, PB, PNB, SC, AMDC, SD, ED, DRG, MG, HMJ, PWJ, WLL, ML, JCM, MM, CM, GDN, LFP, ES, JPS, AS, PS, DIS, JAT, JV, AJMW, DAW data collection and critical revision of manuscript. All authors approved the final version of the manuscript.

ABSTRACT

Introduction

Vedolizumab is an anti-a4b7 monoclonal antibody that is licensed for the treatment of moderate to severe Crohn's disease and ulcerative colitis.

Aims

To establish the real-world efficacy and safety of vedolizumab in the treatment of inflammatory bowel disease.

Methods

Retrospective study involving six NHS health boards in Scotland between June 2015 and November 2017. Inclusion criteria included a diagnosis ulcerative colitis or Crohn's disease with objective evidence of active inflammation at baseline (HBI≥5 / Partial Mayo ≥2 plus CRP >5 g/L or faecal calprotectin ≥250 µg/g or inflammation on endoscopy / MRI) and at least one clinical follow up by 12 months. Kaplan-Meier survival analysis was used to establish 12-month cumulative rates of clinical remission (HBI <5 or Partial Mayo <2), mucosal healing (absence of ulceration/erosions on colonoscopy/MRI or Mayo score 0) and deep remission (clinical remission plus mucosal healing). Rates of serious adverse events were described quantitatively.

Results

Our cohort consisted of 180 patients with ulcerative colitis and 260 with Crohn's disease. Combined median follow up was 52 weeks (IQR 26-52 weeks). In ulcerative colitis, 12-month cumulative rates of clinical remission, mucosal healing and deep remission were 57.4%, 47.3% and 38.5% respectively. In Crohn's disease, 12-month cumulative rates of

clinical remission, mucosal healing and deep remission were 58.4%, 38.9% and 28.3% respectively. The serious adverse event rate was 15.6 per 100 patient years of follow up.

Conclusion

Vedolizumab is a safe and effective treatment for achieving both clinical remission and mucosal healing in ulcerative colitis and Crohn's disease.

Keywords: Vedolizumab, real-world, Crohn's disease, Ulcerative colitis, mucosal healing.

1. INTRODUCTION

The anti-TNF monoclonal antibodies have revolutionized the treatment of patients with inflammatory bowel disease (IBD). Clinical trials have clearly demonstrated their ability to induce and maintain clinical remission but also achieve mucosal healing in patients with IBD.[1,2,3] However, up to 30% and 45% of patients will experience a primary loss or secondary loss of response respectively.[4] Furthermore, the systemic immunosuppressive effect of anti-TNF agents is associated with significant morbidity.[5] Therefore, alternative treatments with different mechanisms of actions are required.

Vedolizumab is a human monoclonal antibody that targets a4b7 integrin and blocks lymphocyte trafficking to the gut via the MADCAM pathway.[6] Following the phase 3 GEMINI trials, that demonstrated efficacy in induction and maintenance of clinical remission in both ulcerative colitis (UC) and Crohn's disease (CD), vedolizumab was approved as the first gut selective biologic for the treatment of moderate to severe inflammatory bowel disease (IBD).[7,8,9] In GEMINI 1 and 2, 41.8% and 39.0% of UC and CD responders were in clinical remission at week 52 respectively.[7,8] However, because of the strict inclusion and exclusion criteria adopted in the seminal trials (e.g. age restrictions, exclusion of patients with stomas, stricturing disease or multiple small bowel resections) the populations treated are not always representative of those encountered in routine clinical practice.[10] Therefore, establishing the effectiveness and safety of vedolizumab in real-world settings is essential, especially when considering how it should be positioned in treatment algorithms.

To this date a number of real world studies have published data on the effectiveness and safety of vedolizumab.[11] However, limitations of several studies include their small sample size, small anti-TNF naive numbers, lack of long-term follow up and confinement to specialist tertiary centres.[11] Furthermore, with the paradigm shift of treating beyond clinical symptoms

to normalisation of faecal calprotectin (FC) and mucosal healing, increasing data is required on the ability of vedolizumab to achieve these objective end-points in the real world.[12] Therefore, in this study we aimed to assess the real-world effectiveness and safety of vedolizumab utilising a large multicentre Scottish cohort of patients with IBD, primarily looking to assess cumulative rates of clinical remission and mucosal healing by 12-months.

2. METHODS

2.1 Study Design

This was a multi-centre retrospective cohort analysis involving thirteen hospitals within six NHS health-boards across Scotland (NHS Lothian [co-ordinating site], NHS Greater Glasgow and Clyde, NHS Lanarkshire, NHS Fife, NHS Forth Valley, NHS Highlands). Data were retrospectively collected at each hospital by review of electronic medical records.

2.2 Data Collection

A standardised electronic data collection pro-forma was used at all sites. Baseline parameters for patient phenotyping were obtained. Follow up data on clinical disease activity (Harvey-Bradshaw Index [HBI] / Partial Mayo score/ Physician's global assessment [PGA]), faecal calprotectin (FC), endoscopy, radiology, surgery, steroid use and adverse events were collected where possible via review of electronic medical records. All data had been prospectively collected as part of routine clinical care.

2.3 Participants

Patients receiving vedolizumab for IBD between June 2015 and November 2017 were identified following review of prescribing, infusion suite and electronic medical records at each site. Inclusion criteria for our analysis were: (a) confirmed diagnosis of CD or UC (based on standard clinical, radiological, endoscopic and histological criteria); (b) active disease prior to starting vedolizumab defined by either a HBI ≥5 or Partial Mayo score ≥2 plus CRP ≥5 mg/L and/or endoscopic / radiographic assessment and/or FC ≥250 µg/g (c) completion of standard induction dosing (0, 2, 6 weeks); (d) at least one clinical follow up (assessment of disease activity score) within 12-months of initiation of vedolizumab. Patients with inflammatory bowel disease unknown (IBDU) were included in the UC analysis unless pathology favoured CD. Patients who did not complete induction were excluded.

Patients on vedolizumab but no objective evidence of active disease at baseline or receiving treatment for the indication of pouchitis and microscopic colitis were also excluded from the analysis.

2.4 Primary and Secondary Outcomes

Our primary outcomes were the proportion of patients achieving clinical remission and mucosal healing. Secondary outcomes included: proportion of patients achieving deep remission (clinical remission plus mucosal healing); change in FC during follow up; rates of resectional surgery; baseline predictors of outcome; and serious adverse events. Achievement of mucosal healing was determined from endoscopy or radiology reports. Serious adverse events were defined as any event leading to disruption or discontinuation of therapy, hospitalisation or death.

2.5 Ulcerative Colitis Definitions

Clinical remission was defined as a Partial Mayo score <2 and complete tapering of steroids. Mucosal healing was assessed either by flexible sigmoidoscopy or ileo-colonoscopy and defined as an Endoscopic Mayo score of 0 with complete tapering of steroids. Where a score was not documented it was determined by review of endoscopy reports / photos. At least one assessment of mucosal healing by flexible sigmoidoscopy or ileo-colonoscopy was available in 101/180 UC patients (56.1%).

2.6 Crohn's Disease Definitions

Clinical remission was defined as a HBI <5 off steroids (PGA used in patients with stoma). Mucosal healing was defined as the absence of mucosal ulceration / erosions on ileo-colonoscopy and off steroids. In patients where ileo-colonoscopy was not possible mucosal healing was assessed by MRI (defined according to local site radiologist) or capsule

endoscopy (defined according to local site physician) where available. We were unable to apply any validated MRI scoring indices, therefore a sensitivity analysis was performed excluding individuals who had a mucosal assessment based on radiology alone. At least one assessment of mucosal healing was available in 140/260 CD patients (53.8%), performed via; ileo-colonoscopy in 114 (81.4%); MRI in 25 (17.9%) because of stricturing disease (n=21) or proximal small bowel disease (n=4); and capsule endoscopy in 1 (0.7%) because of proximal small bowel disease.

2.7 Statistical Analysis

SPSS Version 24 (IBM Inc., Chicago, IL, USA) and Prism Version 7.0 (Graphpad Software, San Diego, CA, USA) were used for statistical analyses and generation of graphs. Descriptive statistics are presented as medians with interquartile range (IQR) for continuous variables and frequencies with percentages for categorical variables. For comparison of non-parametric continuous variables, the Mann-Whitney U or Kruskall-Wallis test was used where appropriate. For comparison of categorical variables, the Chi-squared test was used. Primary and secondary outcomes were assessed using Kaplan-Meier survival analysis and comparisons made using the log-rank test. Patients were censored at failure, last follow up (if less than 365 days) or at 365 days follow up. To try and account for some of the possible bias introduced from retrospective observational data with varying follow up, we performed a non-responder imputation (NRI) analysis to obtain a conservative estimate of outcomes at 12 months. Cox proportional hazard regression analyses were carried out to identify possible baseline predictors of clinical remission, mucosal healing and deep remission. Variables for analysis were chosen a-priori and are listed in Supplementary table 1. Variables from the univariable analysis with a p-value <0.20 were fitted and a stepwise backward selection approach was adopted to identify significant predictors. A p-value <0.05 was considered significant for all statistical tests.

2.8 Ethics

This study was considered a retrospective audit by the local ethics committee as all data was collected as part of routine clinical care; hence no formal ethical approval was necessary. Caldicott guardian approval (NHS Lothian) was granted for data collection, storage and submission for publication (Application ID: 1845).

3. RESULTS

3.1 Patient Cohort

A total of 481 patients receiving vedolizumab were identified. Of these, 180 UC and 260 CD patients fulfilled our inclusion criteria for analysis (Figure 1, Table 1). The median follow up (time from initiation to last infusion or discontinuation) was 51 weeks (IQR 26-52 weeks) for CD and 52 weeks (IQR 26-52 weeks) for UC. Patient demographics and disease characteristics are shown in Table 1. Amongst the CD patients, 230 (88.5%) had been previously exposed to anti-TNF with 62.7% receiving vedolizumab as either 3rd or 4th line biologic. Amongst the UC patients, 111 (61.7%) had been previously exposed to anti-TNF.

3.2 Ulcerative colitis outcomes

The cumulative rates of clinical remission (Partial Mayo score <2) were 20.0%, 43.3% and 57.4% at 3, 6 and 12 months respectively. The median time to first endoscopic assessment was 13 weeks (IQR 13-51 weeks). Cumulative rates of mucosal healing (Endoscopic Mayo score of 0) were 17.9% and 47.3% after 6 and 12 months of treatment respectively. In those achieving outcome, median time to clinical remission and mucosal healing was 14 weeks (IQR 13-26 weeks) and 26 weeks (IQR 22-51 weeks) respectively. The cumulative rates of deep remission (mucosal healing plus clinical remission) at 6 and 12 months were 14.3% and 38.5% respectively. Utilising a NRI analysis at 12 months; clinical remission, mucosal healing and deep remission was achieved in 19.4% (n=35/180), 15.8% (n=16/101) and 10.9% (n=11/101) of patients respectively. Cumulative clinical remission rates were significantly higher in patients without endoscopic follow up compared to those with (74.6% vs 43.6% at 12 months, log-rank p<0.01) (Supplementary Figure 1). A significant drop in faecal calprotectin levels was observed after 3, 6 and 12 months of treatment compared to baseline (Figure 2).

Cumulative rates of colectomy were 6.0% and 12.4% after 6 and 12 months of vedolizumab treatment. Amongst these patients, n=7 had received IV steroids for severe disease (n=2/7 also started on concomitant cyclosporine) and underwent colectomy within 4 months of starting vedolizumab due to non-response.

3.3 Predictors of treatment outcomes in ulcerative colitis

Multivariable Cox regression analysis identified receiving vedolizumab as first line treatment as the only independent predictor of clinical remission (HR 1.9, 95% CI 1.24-2.91, p<0.01), mucosal healing (HR 2.32, 95% CI 1.11-4.89, p=0.03) and deep remission (HR 3.78, 95% CI 1.55-9.22, p<0.01) (Table 2). Stratifying patients by previous TNF exposure revealed significantly higher cumulative rates of clinical remission (71.4% vs 48.0% at 12 months, log-rank p<0.01), mucosal healing (61.6% vs 34.3% at 12 months, log-rank p=0.03) and deep remission (58.4% vs 20.0% at 12 months, log-rank p<0.01) in patients who were anti-TNF naïve (Table 2, Figure 3). No significant difference was observed in cumulative rates of colectomy between anti-TNF naïve and exposed patients (7.2% vs 15.5%, p=0.15) (Figure 2). Comparison of baseline disease activity measures showed no difference in median partial Mayo scores (6 vs 6, p=0.33) (*partial Mayo scores available in n=120*) or median CRP levels (4.0 vs 5.0 mg/L, p=0.11) (*CRP available in n=164*) between anti-TNF naïve and exposed patients. However, anti-TNF patients had significantly lower median FC levels at baseline (745 vs 1050 µg/g) (*FC available in n=116*) but higher rates of concomitant steroid use (62.3% vs 43.2%, p=0.01) compared to those who were anti-TNF exposed.

3.3 Crohn's disease outcomes

Cumulative rates of clinical remission were 21.9%, 39.9% and 58.4% after 3, 6 and 12 months of vedolizumab treatment respectively. The median time to first mucosal assessment was 28 weeks (IQR 14-48 weeks). Cumulative rates of mucosal healing were

10.1% and 38.9% after 6 and 12 months of treatment respectively. In those achieving remission, median time to clinical remission and mucosal healing was 14 weeks (IQR 12-26 weeks) and 39 weeks (IQR 21-50 weeks), respectively.

Analysis of mucosal healing, including only patients with endoscopic follow up (n=114), revealed cumulative rates of 12.2% and 42.6% at 6 and 12 months respectively. Furthermore, cumulative rates of deep remission at 6 and 12 months were 7.4% and 28.3% respectively. Utilising a NRI analysis at 12 months; clinical remission, mucosal healing and deep remission was achieved in 16.2% (n=42/260), 9.3% (n=13/140) and 7.1% (n=10/140) of patients respectively. Cumulative clinical remission rates were similar in patients without follow up for mucosal healing compared to those with (62.5% vs 55.3% at 12 months, log-rank p=0.25) (Supplementary Figure 1). We observed a significant drop in faecal calprotectin levels after 3, 6 and 12 months of treatment compared to baseline (Figure 2).

Cumulative rates of resectional surgery were 5.4% and 13.1% after 6 and 12 months of vedolizumab respectively (pan-proctocolectomy with ileostomy n=10; subtotal colectomy n=1; ileocaecal resection n=8; ileocaecal resection for stricturing disease n=2; ileocaecal resection for penetrating disease n=3; ileocaecal resection for perforation n=2). Surgical procedures for perianal disease were performed in 11 patients (fistulotomy n=1; fistulectomy n=2; examination under anaesthesia with drainage of abscess and seton insertion n=8).

3.4 Predictors of treatment outcomes in Crohn's disease

Multivariable Cox regression analysis revealed individuals with an IBD related hospitalisation in the last 12 months were less likely to achieve clinical remission (HR 0.59, 0.40-0.86, p<0.01) (Table 3). However, no predictive factors were identified for achieving mucosal healing or deep remission (Table 3). Stratifying patients by prior IBD admissions

revealed significantly higher cumulative rates of clinical remission in those that had not been hospitalised due to their IBD in the 12 months prior to vedolizumab (65.3% vs 49.1% at 12 months, log-rank p<0.01). However, no difference was seen in cumulative mucosal healing (61.6% vs 34.3% at 12 months, log-rank p=0.03), deep remission (58.4% vs 20.0% at 12 months, log-rank p=0.003) or resectional surgery. Comparison of baseline disease activity measures showed no difference in median HBI (7 vs 6, p=0.07) (*HBI available in n=130*) and FC levels (540 vs 780 µg/g, p=0.30) (*FC available in n=130*) but did show higher CRP levels (7.5 vs 7.0 mg/L, p=0.02) (*CRP available in n=256*) between patients with previous IBD related hospitalisations versus those without.

Stratifying patients by previous TNF exposure revealed no significant difference for cumulative clinical remission (61.3% vs 57.8% at 12 months, log-rank p=0.27), mucosal healing (37.0% vs 39.4% at 12 months, log-rank p=0.92), deep remission (27.3% vs 28.5% at 12 months, log-rank p=0.91) and resectional surgery (3.0% vs 14.6% at 12 months, log-rank p=0.13) between patients who were anti-TNF naïve and exposed (Supplementary Figure 3).

3.4 Safety

The combined CD and UC cohort had over 333 patient years of follow-up (PYF). Dose escalation to Q4 vedolizumab was carried out in 9 UC patients (after 3 months due to sub-optimal response) and 6 CD patients (after 6 months due to loss of response [n=3] and sub-optimal response [n=3]). The rate of serious adverse events was 15.6 per 100 PYF (Table 2). The rate of serious infections was 6.3 per 100 PYF, however the majority continued vedolizumab following treatment of their infection. There was a total of 4 (0.9%) infusion reactions and 2 (0.5%) delayed hypersensitivity reactions, all requiring discontinuation of vedolizumab. Arthralgia was the most common non-infective severe adverse event (3.3 per

100 PYF). No deaths occurred during follow-up. Three malignancies were reported during treatment. One patient was diagnosed with a cholangiocarcinoma following 4 doses of vedolizumab. However, he was thought to also have concurrent PSC. Another patient was diagnosed with metastatic ovarian cancer after 3 doses of vedolizumab. The final patient underwent a colectomy due to non-response to vedolizumab and upon review of his pathology was found to also have a colonic neuro-endocrine tumour. In patients undergoing surgery following vedolizumab, post-operative complications (30-day) were observed in 22.2% (Clavien Dindo Grade 1: n=2; Grade 2: n=2) and 19.2% (Clavien Dindo Grade 1: n=1; Grade 2: n=2; Grade 3: n=2) of the UC and CD patients respectively.

4. DISCUSSION

Here we present results from a large, multi-centre, real-world cohort investigating the effectiveness and safety of vedolizumab in the treatment of patients with IBD. To our knowledge, this is the largest UK cohort published to date, with data not only on clinical outcomes but also assessment of mucosal healing. In our cohort, we observed 12-month cumulative clinical remission, mucosal healing and deep remission rates of 57.4%, 47.3%, 38.5% in UC respectively; and 58.4%, 38.9%, 28.3% in CD respectively. We were also able to show a significant drop in FC for both CD and UC after 3-months of treatment. Furthermore, with over 333 patient years of follow-up no new safety signals were observed. These results are in keeping with other previously reported experiences and add to the growing body of literature on the effectiveness and safety of vedolizumab in the real world.

Our results support the use and effectiveness of vedolizumab for the treatment of both UC and CD. Despite both cohorts being mature with high anti-TNF exposure (61.7% in UC; 88.5% in CD) by 12-months over 50% of patients were able to achieve clinical remission. Adopting a NRI analysis, clinical remission rates of 19.4% and 16.2%; and mucosal healing rates of 15.8% and 9.3% were observed in UC and CD at 12 months respectively. However, these estimates are conservative and several patients who had missing data at 12 months or had less than 12 months follow up, had already achieved the end point of clinical remission and/or mucosal healing. Furthermore, we did observe in both cohorts that FC dropped significantly by 3-months (Figure 2). When assessing cumulative mucosal healing, superior rates were observed in UC, possibly due to the greater number of anti-TNF naive patients (Table 1). For both cohorts, the greatest benefit was observed after >6 months of treatment. This observation has been reported by others and suggests that in many patients

vedolizumab may have a slower onset of action and persistence to >6 months of therapy is required to achieve optimum outcomes.[12-15]

In UC, our results are in keeping with other real-world cohorts from the US (12-month cumulative clinical remission, 51.0%; 12-month cumulative endoscopic remission, 41.0%; NRI 12-month clinical remission, 20.0%; NRI 12-month mucosal healing, 17.0%), France (12-month clinical remission, 42.1%), Sweden (12-month clinical remission, 64.0%), Canada (12-month: clinical remission 62.0%; endoscopic remission 47.8%) and Germany (NRI 12-month clinical remission, 25.0%).[13-18] Again in CD our results are similar to those reported by others, although there appears to be more variation in published outcomes.[11,13-18] For example, in the US VICTORY consortium (n=221) which was analysed in a similar way to our study, cumulative 12-month clinical remission was 35.0% and mucosal healing much higher at 63.0%.[14] Their higher mucosal healing rates compared to clinical remission may suggest that a number of the patients had symptoms unrelated to active IBD, especially as patients could be included based on symptoms alone.[14] Individuals may not always have active IBD driving their symptoms (e.g. bile salt malabsorption in patient with small bowel resection, irritable bowel syndrome) or have disproportionate symptoms for the degree of mucosal inflammation. As such, treatments aimed at treating inflammation may show poor efficacy for achieving clinical remission but superior mucosal healing as baseline inflammation is not as severe as expected. In contrast to this our inclusion criteria necessitated objective evidence of inflammation (HBI ≥5 or Partial Mayo score ≥2 plus CRP ≥5 mg/L and/or endoscopic / radiographic assessment and/or FC ≥250 µg/g) which might explain some of the differences observed. Other reasons for differences in reported outcomes between our study and the US VICTORY consortium include; differences in the patient populations examined; the use of the PGA to assess efficacy rather than validated

disease activity scores; and the definition of mucosal healing necessitating being off steroids.[14]

Optimum positioning of vedolizumab for the treatment of IBD is still unknown and highly debated. Currently in the UK, NICE guidelines allow the use of vedolizumab first line in patients with moderate to severe UC but in CD stipulate its use only after anti-TNF failure or if there are contraindications to anti-TNF use.[19,20] Results from the GEMINI trials indicated higher efficacy in bio-naive patients for both UC and CD, something that has been echoed in other real-world cohorts.[7-9,11] In the VICTORY consortium study they showed that previous anti-TNF exposure was associated with a reduced probability of achieving clinical remission (HR 0.53 [95% CI 0.38-0.75] for UC; HR 0.40 [95% CI 0.20-0.81] for CD) and mucosal healing (HR 0.51 [95% CI 0.29-0.88] for UC; HR 0.29 [95% CI 0.12-0.73] for CD).[13,14] We observed similar results in patients with UC, where Cox regression analysis identified first line use of vedolizumab as the only independent predictor of clinical remission (HR 1.9, 95% CI 1.24-2.91, p<0.01), mucosal healing (HR 2.32, 95% CI 1.11-4.89, p=0.03) and deep remission (HR 3.78, 95% CI 1.55-9.22, p<0.01) (Table 2). Although, anti-TNF exposed patients had a higher baseline FC; partial Mayo scores and CRP were similar between the two groups. Furthermore, the proportion of patients on concomitant steroids was higher in the anti-TNF naïve group suggesting significant disease. Interestingly, in a recent network meta-analysis of randomised controlled trials published by Singh et al., vedolizumab and infliximab were ranked highest as first line agents for induction of remission and mucosal healing in patients with moderate to severe UC.[21] No difference was observed in our CD cohort but our analysis was likely underpowered due to the small number of bio-naive patients (Supplementary Figure 2). Despite data showing superior efficacy with first line use for both CD and UC, in the absence of head to head trials no definite conclusions can be

made as to its positioning compared to anti-TNF therapy. However, factors such as safety and cost, especially in the advent of biosimilar anti-TNF agents, may also influence health trusts and providers.

In our CD cohort, we were unable to identify any independent predictors of mucosal healing or deep remission (Table 3). However, we did find that in patients who had an IBD related hospitalisation in the prior 12 months to vedolizumab, there was a significantly lower probability of achieving clinical remission (HR 0.59, 0.40-0.86, p<0.01) (Table 3). This observation may be due to more severe disease in those with prior hospitalisation. Other studies have also identified severe disease, active perianal disease and smoking history as independent predictors of clinical remission in CD.[14]

The mechanism of action of vedolizumab theoretically results in reduced systemic immunosuppression and thus superior safety profile when compared to other agents like anti-TNF or azathioprine.[6] Recently, Colombel et al. published safety data from six vedolizumab trials including 2830 patients with over 4800 patient years of follow up.[22] Authors found no increased risk of any infection or serious infection with vedolizumab exposure compared to placebo.[22] Furthermore, infusion reactions were described in ≤5% of patients and reported malignancy rates of <1%, in keeping with background risk.[22] In our cohort, rates of SAEs were low (15.6 per 100 PYF) and in keeping with the published literature. Infusion reactions were also uncommon and no deaths occurred during follow up. Three malignancies were reported but these all occurred soon after therapy was initiated and thought to be unrelated to vedolizumab.

There are several strengths to our study. Firstly, we present results from the largest CD and second largest UC cohort published to date with data gathered from multiple centres within different NHS health boards in Scotland. This allows representation of a diverse patient population, capturing practices from both tertiary referral centres and district general hospitals treating patients with IBD. In contrast to others, we have also used standardised and validated disease activity scores to assess clinical remission. Furthermore, in the paradigm shift of treating to normalisation of FC and mucosal healing, we present data on the ability of vedolizumab to achieve these important objective end points. However, we also acknowledge certain limitations within our study. The retrospective nature of patient identification and data collection may have influenced our results. We have tried to overcome this by creating a standardised data collection proforma and using objective outcome measures where possible. Furthermore, variability in follow-up intervals and both assessment and reporting of mucosal healing may have introduced bias. To account for differences in follow-up, Kaplan-Meier analysis was used although our results may have been influenced by heavy censoring and / or lack of independence between censoring and events. Furthermore, we performed a NRI analysis to provide conservative outcomes following the use of vedolizumab. In addition, when we compared cumulative clinical remission rates depending on whether patients had a follow up for mucosal healing we found that in UC cumulative clinical remission rates were significantly higher in patients who did not have endoscopic follow up (Supplementary Figure 1). This suggests a possible selection bias for performing endoscopy in more unwell patients, therefore outcomes may be underestimated. Finally, as our study was multi-centre, encompassing different types of hospitals, we would expect some variations in patient populations and practice patterns. Although, as previously stated, our aims were to assess real-world outcomes that are generalisable to all practice.

In conclusion, we have shown in a large, real-world, multi-centre cohort that vedolizumab is effective at achieving not only clinical remission but mucosal healing at 12-months for both UC and CD. In addition, we add to the body of evidence that in UC, first line use results in superior outcomes. Finally, our safety data further supports the favourable safety profile of vedolizumab in the treatment of IBD. Further real-world prospective as well as head to head trials are now required.

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Table 1. Patient demographics and disease characteristics of cohort. CD, Crohn's disease; UC, ulcerative colitis; IFX, infliximab; ADA, adalimumab; UST, ustekinumab.

	CD (n=260)		UC (n=180)	
Median age, years (IQR)	39 (29-54)		41 (30-56)	
Median disease duration, years (IQR)	9 (5-14)		6 (3-11)	
Female gender, n (%)	160 (61.5)		77 (42.8)	
Smoking, n (%)				
Current	23 (8.8)		7 (3.9)	
Ex	33 (12.7)		30 (16.7)	
Disease location / extent, n (%)	L1	50 (19.2)	E1	15 (8.3)
	L2	83 (31.9)	E2	68 (37.8)
	L3	127 (48.8)	E3	97 (53.9)
Disease behaviour n (%)	B1	150 (57.7)	-	
	B2	57 (21.9)	-	
	B3	53 (20.4)	-	
Perianal disease, n (%)	52 (20.0)		-	
Extra-intestinal manifestations, n (%)	83 (31.9)		44 (24.4)	
IBD hospitalisations in last year, n (%)	106 (40.8)		61 (33.9)	
Previous Resectional Surgery, n (%)	108 (41.5)		-	
Previous anti-TNF exposure, n (%)	226 (86.9)		111 (61.7)	
Position of vedolizumab, n (%)				
1st Line	34 (13.1)		69 (38.3)	
2nd Line	86 (33.1)		86 (47.8)	
3rd Line	132 (50.8)		24 (13.3)	
4th Line	8 (3.1)		1 (0.6)	
Reason for vedolizumab, n (%)				
-Failure of IFX and/or ADA	199 (76.5)		100 (55.6)	
-Failure of IFX and/or ADA plus UST	8 (3.1)		-	
-Contraindication to anti-TNF	32 (12.3)		30 (16.7)	

-Intolerance of anti-TNF	24 (9.2)	6 (3.3)
-Patient preference	3 (1.2)	15 (8.3)
-Clinician preference	-	29 (16.1)
Vedolizumab dosing, n (%)		
Week 10 dose	53 (20.4)	4 (2.2)
8-weekly	253 (97.3)	180 (100)
4-weekly	7 (2.7)	0
Concomitant immunosuppressant, n (%)	77 (13.0)	58 (32.2)
Concomitant steroids, n (%)	100 (38.5)	91 (50.6)
Median Harvey-Bradshaw Index, (IQR)*	6 (5-10)	-
Median Partial Mayo Score, (IQR)**	-	6 (3-8)
Median CRP, mg/L (IQR)	7 (4-15)	5 (2-10)**
Median Faecal Calprotectin*, µg/g (IQR)	690 (250-1065)*	840 (500-1500)**

**Harvey Bradshaw Index, CRP and faecal calprotectin available in n= 130, 256 and 130 at baseline respectively*

***Partial Mayo Score, CRP and faecal calprotectin available in n= 120, 164 and 116 at baseline respectively*

Table 2. Univariable and multivariable predictors of outcomes in ulcerative colitis. HR, hazard ration; CI, confidence interval

	Univariable analyses			Multivariable analyses		
	HR	**95% CI**	**p-value**	**HR**	**95% CI**	**p-value**
Clinical Remission						
First line treatment	1.99	1.30-3.04	<0.01	1.90	1.24-2.91	<0.01
Age >60 years	0.51	0.27-1.00	0.04			
Mucosal Healing						
First line treatment	2.19	1.05-4.59	0.04	2.32	1.11-4.89	0.03
IBD related hospitalisation in the prior 12 months	0.51	0.21-1.27	0.15			
Deep Remission						
First line treatment	3.52	1.45-8.58	<0.01	3.78	1.55-9.22	<0.01
Female	0.46	0.17-1.24	0.12			
Age >60 years	1.96	0.77-4.98	0.16			
IBD related hospitalisation in the prior 12 months	0.42	0.14-1.23	0.11			
Left sided disease (E2)	0.41	0.11-1.54	0.18			

Table 3. Univariable and multivariable predictors of outcomes in Crohn's disease. HR, hazard ration; CI, confidence interval

	Univariable analyses			Multivariable analyses		
	HR	**95% CI**	**p-value**	**HR**	**95% CI**	**p-value**
Clinical Remission						
Female	0.73	0.51-1.05	0.09			
Age >60 years	1.39	0.90-2.14	0.14			
IBD related hospitalisation in the prior 12 months	0.60	0.41-0.88	<0.01	0.59	0.40-0.86	<0.01
Disease duration >5 years	0.74	0.49-1.12	0.15			
Smoking	0.57	0.27-1.23	0.15			
Ileo-colonic disease (L3)	1.76	1.03-2.99	0.04			
Mucosal Healing						
Age >60 years	2.01	0.95-4.26	0.07			
Disease duration >5 years	2.54	0.77-8.36	0.12			
Penetrating disease (B3)	0.44	0.16-1.26	0.13			
Deep Remission						
Age >60 years	1.83	0.80-4.21	0.16			
Concomitant steroids	1.96	0.90-4.27	0.09			
Penetrating disease (B3)	0.31	0.07-1.30	0.11			

Table 4. Cumulative rates of clinical remission, mucosal healing and deep remission stratified by **(A)** previous TNF exposure in ulcerative colitis **(B)** IBD related hospitalisations in the 12 months prior to vedolizumab in Crohn's disease.

A.

	Overall			**anti-TNF naive**			**anti-TNF exposed**		
	3M	6M	12M	3M	6M	12M	3M	6M	12M
Clinical Remission	20.0%	43.3%	57.4%	23.8%	53.1%	71.4%	17.6%	29.7%	48.0%
Mucosal Healing	4.2%	17.9%	47.3%	8.6%	20.9%	61.6%	1.6%	11.8%	34.3%
Deep Remission	4.2%	14.3%	38.5%	8.6%	20.9%	58.4%	1.6%	8.0%	20.0%

B.

	Overall			**Hospitalised**			**Not Hospitalised**		
	3M	6M	12M	3M	6M	12M	3M	6M	12M
Clinical Remission	21.9%	39.9%	58.4%	13.7%	28.0%	49.1%	27.4%	40.3%	65.3%
Mucosal Healing	2.3%	10.1%	38.9%	0%	4.4%	31.1%	4.0%	12.6%	43.0%
Deep Remission	1.5%	7.4%	28.3%	0%	4.2%	27.6%	2.6%	9.7%	28.6%

Table 5. Serious adverse events. PYF, patient years of follow-up.

Serious Adverse Events	Incidence, n (%)	Event rate per 100 PYF
Serious Infection	21 (4.7)	6.3 per 100 PYF
-Intra-abdominal collection	1 (0.2)	
-Tonsillitis	1 (0.2)	
-Nasopharyngitis	2 (0.5)	
-Cellulitis	2 (0.5)	
-Shingles	1 (0.2)	
-Pneumonia	5 (1.1)	
-Cholecystitis	2 (0.5)	
-Urogenital Infection	4 (1.0)	
-Septic Arthritis	1 (0.2)	
-Dental Abscess	1 (0.2)	
-Clostridium Difficile	1 (0.2)	
Arthralgia	11 (2.5)	3.3 per 100 PYF
Infusion reaction	4 (1.0)	1.2 per 100 PYF
Deranged LFTs	4 (1.0)	1.2 per 100 PYF
Delayed Hypersensitivity	2 (0.4)	0.6 per 100 PYF
Malignancy	3 (0.7)	0.9 per 100 PYF
Bowel Perforation	2 (0.4)	0.6 per 100 PYF
Headache	3 (0.7)	0.9 per 100 PYF
Depression	1 (0.2)	0.3 per 100 PYF
Neutropenia	1 (0.2)	0.3 per 100 PYF

Figure 1. Study flowchart of patients included in analysis. IBD, inflammatory bowel disease; UC, ulcerative colitis; CD, Crohn's disease.

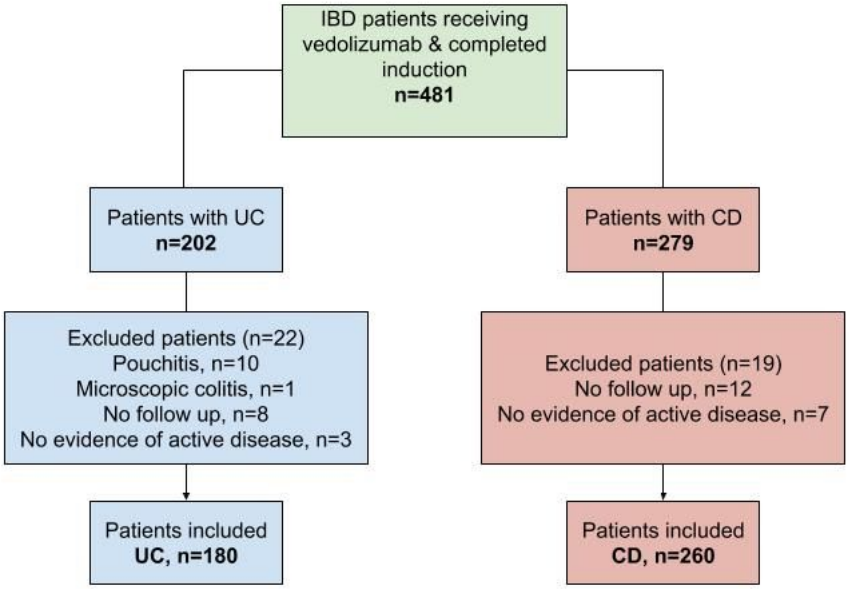


Figure 2. Effect of vedolizumab on faecal calprotectin after 3, 6 and 12 months of therapy in (A) ulcerative colitis and (B) Crohn's disease (faecal calprotectin value used if within +/- 1 month of specified time interval). Dotted line indicates faecal calprotectin cut-off of 250 µg/g.

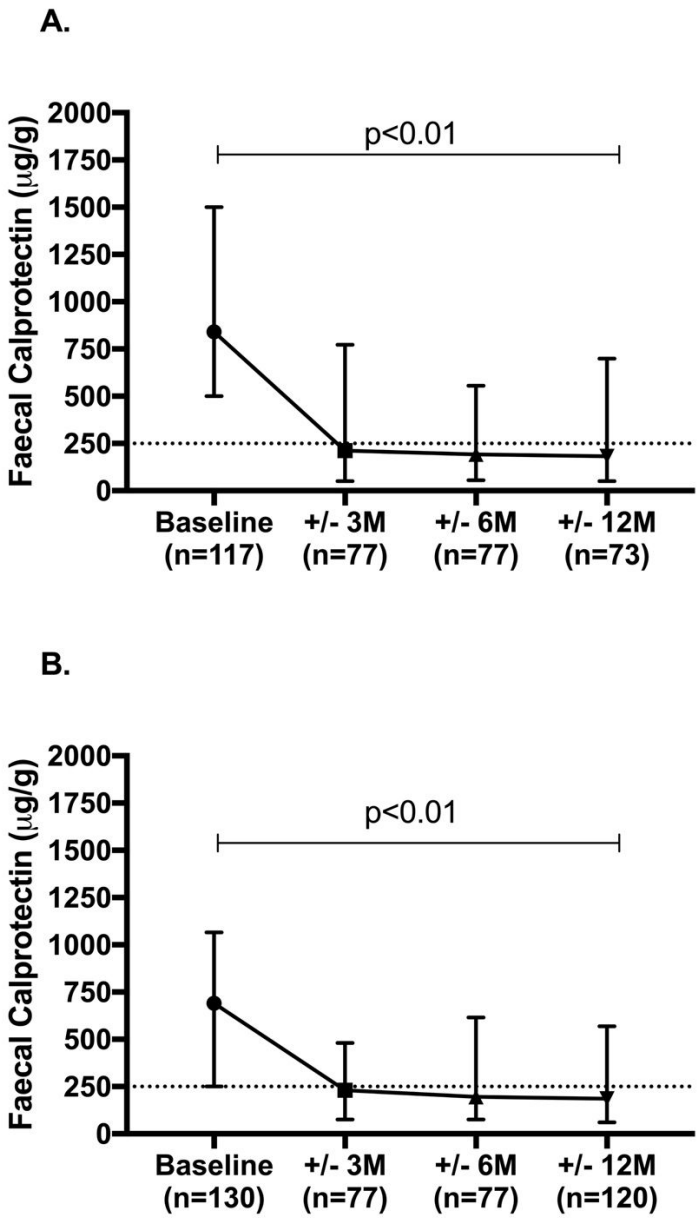


Figure 3. Kaplan-Meier curves for ulcerative colitis treatment outcomes stratified by previous anti-TNF exposure. **A**, cumulative rates of clinical remission; **B**, cumulative rates of mucosal healing; **C**, cumulative rates of deep remission; **D**, cumulative rates of colectomy.

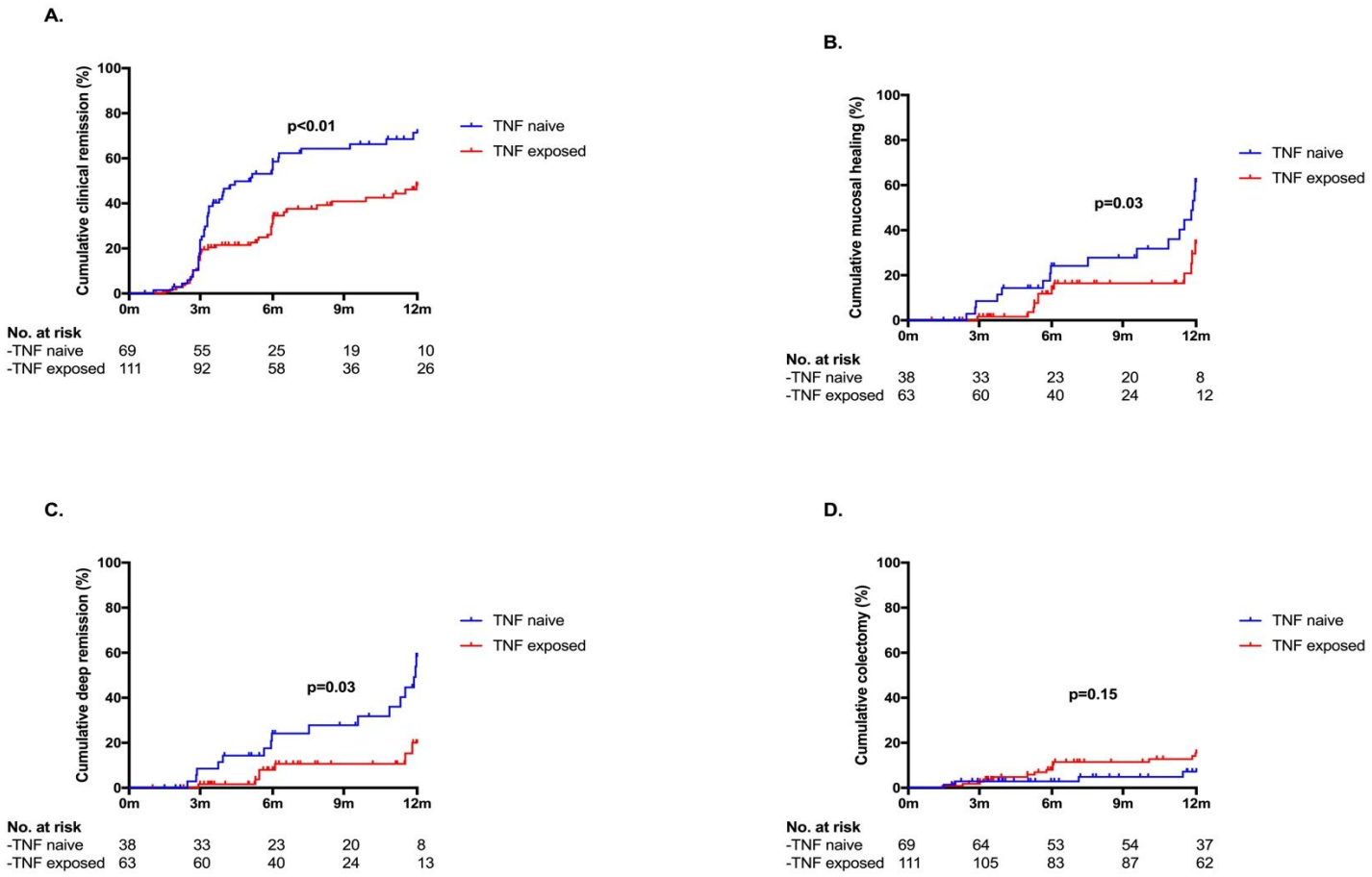
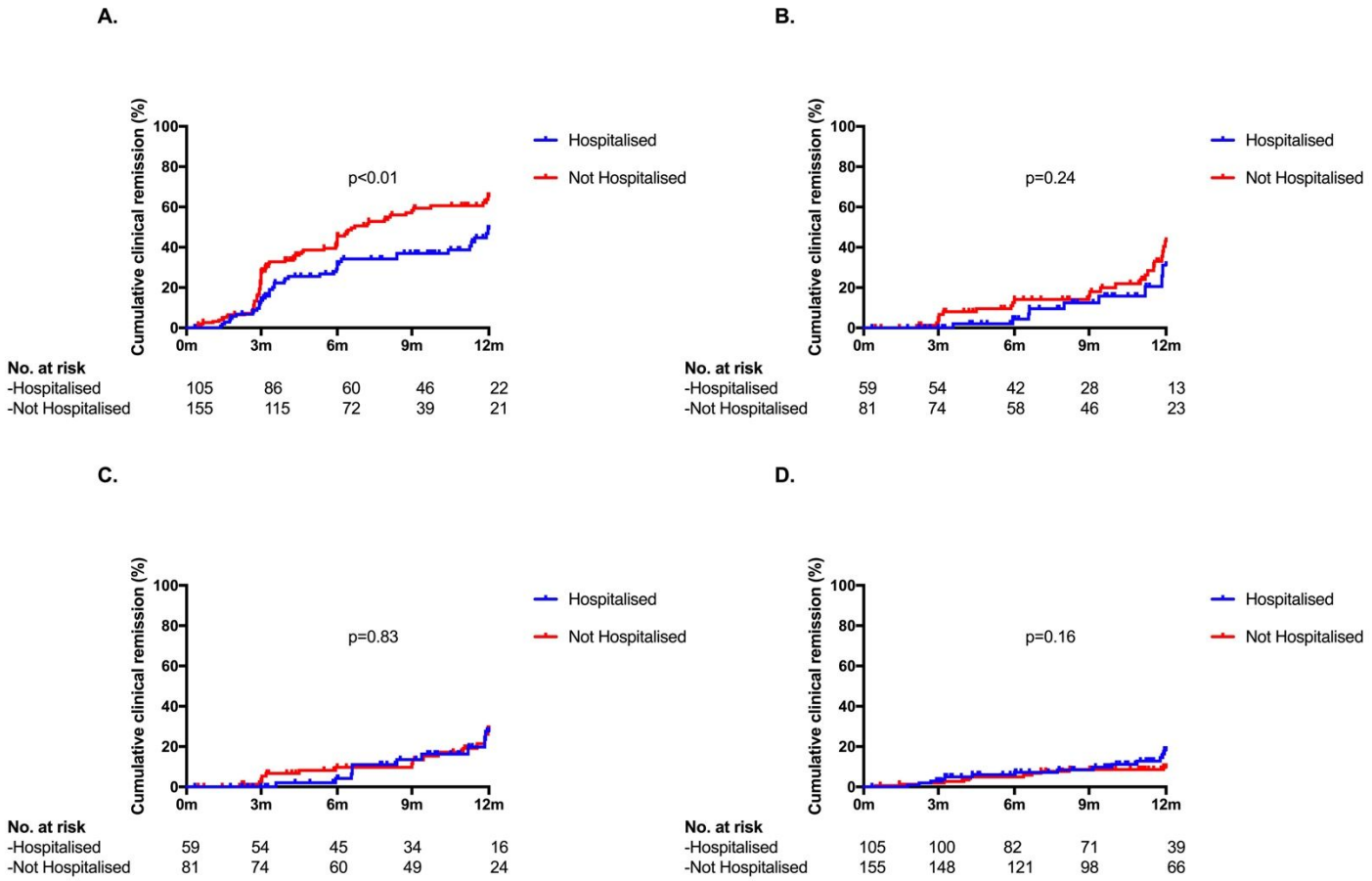


Figure 4. Kaplan-Meier curves for Crohn's disease treatment outcomes stratified by IBD related hospitalisations in the 12 months prior to vedolizumab. **A**, cumulative rates of clinical remission; **B**, cumulative rates of mucosal healing; **C**, cumulative rates of deep remission; **D**, cumulative rates of surgery.



Supplementary Table 1. (A) Covariates selected for Cox regression model in UC. **(B)** Covariates selected for Cox regression model in CD.

A.

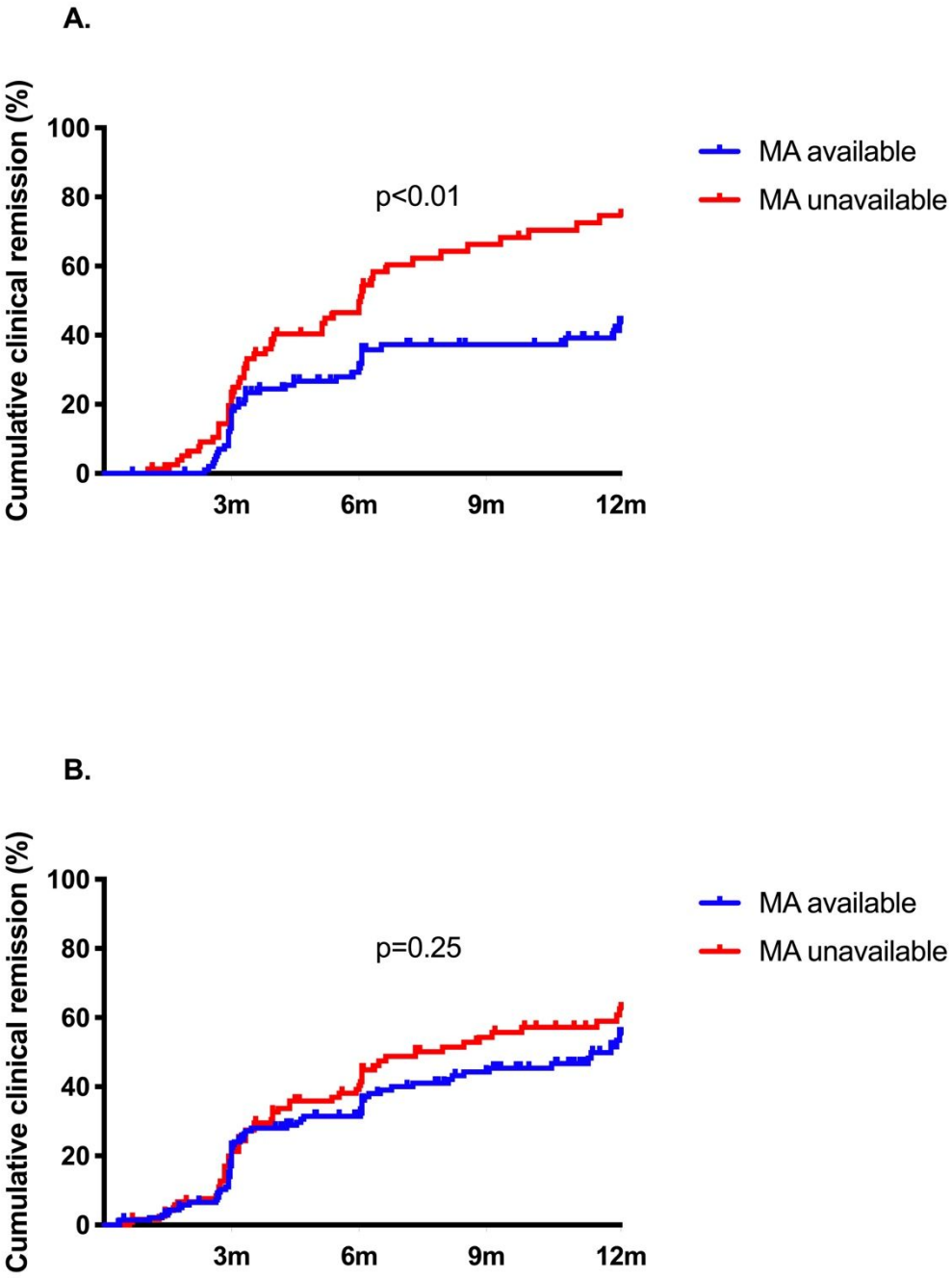
1	First line treatment
2	Female
3	Age >60 years
4	Disease duration >5 years
5	Disease extent (E1, E2, E3; reference E1)
6	Concomitant steroids
7	Concomitant immunosuppressant
8	IBD related hospitalisation in the prior 12 months

Smoking was not included as a covariate as there were only n=7 documented active smokers in the UC cohort.

B.

1	First line treatment
2	Female
3	Age >60 years
4	Disease duration >5 years
5	Disease distribution (L1, L2, L3; reference L1)
6	Concomitant steroids
7	Concomitant immunomodulator
8	IBD related hospitalisation in the prior 12 months
9	Peri-anal disease
10	Week 10 dose
11	Previous surgery
12	Smoking
13	Penetrating disease (B3)

Supplementary Figure 1. Cumulative clinical remission rates in UC (**A**) and CD (**B**). depending on whether endoscopic / MRI follow up was available. MA, mucosal assessment.



Supplementary Figure 2. Kaplan-Meier curves for Crohn's disease treatment outcomes stratified by previous anti-TNF exposure. **A**, cumulative rates of clinical remission; **B**, cumulative rates of mucosal healing; **C**, cumulative rates of deep remission; **D**, cumulative rates of surgery.