**COMPARATIVE EFFECTIVENESS OF ANTI-TUMOUR NECROSIS FACTOR AGENTS AND VEDOLIZUMAB IN ULCERATIVE COLITIS**

Short title: Comparative efficacy of biologic therapy in ulcerative colitis

Rebecca Davis1\*, Paula McParland1\*, Susanna Dodd2,Daniel Storey1Chris Probert,3 Paul Collins1, Thomas Skouras1, Alan Steel1, Edmund Derbyshire1, Martyn Dibb1, Sreedhar Subramanian1, ¶

1Department of Gastroenterology, Royal Liverpool University Hospital

2 Department of Biostatistics, Institute of Translational Medicine, University of Liverpool, L69 3GS, UK

\*Both authors contributed equally

¶Corresponding author:

Sreedhar Subramanian, MD, MRCP

Consultant Gastroenterologist and Honorary Senior Lecturer

Department of Gastroenterology

Royal Liverpool University Hospital

Prescot Street

Liverpool L7 8XP, UK

Tel: +44-151-706 3414

Fax: +44-151-706 5832

Email: [sreedhar.subramanian@rlbuht.nhs.uk](mailto:sreedhar.subramanian@rlbuht.nhs.uk)

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**Summary**

**Introduction:** Anti-tumour necrosis factor (TNF) agents and vedolizumab are used to treat UC but response is variable and there is little data on comparative effectiveness. Apart from prior exposure to anti- TNF agents, predictors of response have not been identified. We aimed to (i) compare the efficacy of anti-TNF agents and vedolizumab in UC and (ii) investigate the utility of clinical and biochemical parameters in predicting response.

**Methods:** Patients commencing any biological therapy for ambulant UC were included. Disease activity was monitored serially with Simple Clinical Colitis Activity Index (SCCAI) for up to 12 months. We compared the efficacy of anti-TNF agents and vedolizumab for induction and maintenance of response and remission on an intention-to-treat basis. We examined the utility of FC and early normalisation of FC to predict response.

**Results:** Ninety-seven patients commencing anti-TNF and 42 commencing vedolizumab therapy were included. Vedolizumab treated patients had significantly greater prior anti-TNF therapy exposure and a lower baseline FC. Response, remission and steroid free remission rates were comparable between both groups at 6 weeks, 6 and 12 months. Clinical remission but not steroid free remission at 12 months was higher in the vedolizumab group. There was a significant reduction in SCCAI and FC at 6 weeks, 6 and 12 months compared to baseline in both groups. Baseline FC and early normalisation did not predict response at 6 and 12 months.

**Conclusions:** The efficacy of anti-TNF and vedolizumab in UC appear comparable. We could not identify any predictors of response and remission.

**Keywords:** Inflammatory bowel disease, ulcerative colitis, vedolizumab, anti-tumour necrosis factor antibody, faecal calprotectin, comparative efficacy.

**Introduction**

There are currently two classes of biological therapy that have been approved for use in UC: anti-tumour necrosis factor (TNF) agents such as infliximab (1), adalimumab (2) and golimumab and the α4β7 antibody, vedolizumab, (3) which blocks gut lymphocyte trafficking. There are currently no trials comparing the efficacy and safety of anti-TNF agents and vedolizumab therapy to enable clinicians and patients to choose one therapy over another. There is also a paucity of real-world studies addressing the comparative effectiveness of these agents. A preliminary analysis from a recent multi-centre retrospective study (VICTORY) reported that vedolizumab treated patients had higher rates of mucosal healing (MH) and clinical remission rates compared to anti-TNF therapy at 12 months (4). However, this study was limited by several factors: (i) use of physician global assessment of symptoms to assess response as opposed to standardised disease activity instruments (ii) retrospective assessment of endoscopy findings and (iii) inclusion of only approximately 50% of the treated cohort. A further single centre study compared the induction response rates of a small number of patients treated with infliximab and vedolizumab and reported similar clinical response rates but long term maintenance efficacy was not assessed (5).

Given the variability in response to biological therapy, there is a need for predictors of response to biologic therapy to enable stratification of patients to the right therapy. Only a few studies have attempted to investigate predictors of response to anti-TNF agents and vedolizumab in UC. Short term clinical response, mucosal healing and absence of atypical perinuclear anti-neutrophilic cytoplasmic antibodies (pANCA) have been identified as independent predictors of sustained response to infliximab (6) but the predictive ability of these clinical variables is poor. Other studies have reported that active disease at baseline and IL-23 receptor variants predict response to infliximab therapy (7,8). However, such clinical parameters are not widely validated, have poor sensitivity and routine testing for IL-23 polymorphisms is not available in the clinic setting. No other predictor apart from prior anti-TNF exposure has been widely evaluated. Faecal calprotectin (FC) is a zinc and calcium binding neutrophilic protein, which is used to monitor disease activity in inflammatory bowel disease. In UC, several studies have shown that FC values <250μg/g correlate with mucosal healing and good clinical outcomes (9,10). Despite its widespread use in monitoring disease activity in IBD, only few studies have investigated the prognostic utility of FC. Higher FC values are associated with increased colectomy risk in acute severe ulcerative colitis (11). A subsequent analysis from the GEMINI cohort failed to note an association between baseline FC and subsequent clinical response. However, FC measured at week 6 from the same population appeared to correlate with clinical remission at 1 year (12). These findings have not been replicated in a real-life cohort and such data are not available for the anti-TNF agents.

We sought to (i) assess the comparative effectiveness of anti-TNF agents and vedolizumab in induction and maintenance therapy of UC and (ii) investigate the utility of routinely used clinical and variables including the role of baseline FC and early normalisation of FC in predicting response to anti-TNF agents and vedolizumab.

**Methods**

We conducted a single-centre study of ambulant moderate to severe UC patients treated with anti-TNF agents and vedolizumab at the Royal Liverpool University Hospital between January 2013 and September 2017. We excluded patients with acute severe colitis commencing infliximab therapy. All patients were treated with a standard induction regime: infliximab and vedolizumab at 0, 2 and 6 weeks and adalimumab and golimumab at 0, 2 and 4 weeks at standard doses. Dose escalation during the maintenance phase was dictated by clinical assessment. We collected baseline clinical information including concomitant immunomodulator and steroid therapy, body mass index (BMI), disease extent and duration, prior anti-TNF therapy, smoking status and simple clinical colitis activity index (SCCAI). SCCAI was prospectively collected at the point of clinic consultation or infusion and extracted from the case notes retrospectively. We collected SCCAI and FC (where available) at 6 weeks, 4 months, 6 and 12 months after initiation. We also recorded details of dose escalation, adverse events and discontinuation of biologic therapy if they occurred and need for surgery. Follow-up was curtailed at 12 months as the number of patients treated with vedolizumab beyond this period was limited.

Outcomes: The primary outcome was clinical response at end of induction therapy and 6 and 12 months after initiation of therapy. Clinical remission was defined as a SCCAI of ≤2 and clinical response was defined as a reduction SCCAI of ≥3 points from the baseline value.

Additional outcomes: We also assessed FC response to therapy and compared surgical rates, adverse event rates and treatment persistence rates between the two groups. Finally, we assessed the role of clinical variables (concurrent IM, prior anti-TNF therapy) and biochemical variables (baseline FC and early normalisation of FC as defined by a FC value of <250μg/g within 3 months of initiating therapy) for predicting response at 6 and 12 months.

*Statistical analysis*

Categorical variables have been summarized as frequency (%) and continuous variables as median (interquartile range, IQR). Baseline parameters were compared using Mann-Whitney test for non-parametric and students t-test for parametric variables. Binary outcomes (colectomy and treatment persistence rates) were compared using Fisher’s Exact test. Univariate logistic regression analysis was used to assess the influence of the following clinical and biochemical variables on steroid free response and remission: baseline FC, early normalisation of FC, prior anti-TNF exposure, disease extent and concomitant immunomodulatory therapy. A mixed effects linear regression was used to assess the effect of time on continuous outcomes (calprotectin and SSCAI), appropriately allowing for repeated measures on the same patient over time. Similarly, mixed effects logistic regression was carried out to assess the effect of time on binary outcomes (remission, response and steroid-free remission), adjusting for baseline variables (calprotectin, previous anti-TNF failure and drug) and appropriately allowing for repeated measures on the same patient over time. These models include an interaction between time and drug, which assesses the significance and magnitude of the difference in the effect of time for each drug. All analyses were carried out using Stata v13 software (Stata Statistical Software, Release 13; StataCorp LP, College Station, Texas, USA).

*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*

Ninety-seven patients commencing anti-TNF and 42 commencing vedolizumab therapy were included. The baseline characteristics of the included subjects are summarised in Table 1 and were comparable across the two groups apart from (i) patients treated with anti-TNF agent had a significantly higher baseline FC compared to vedolizumab (median 955μg/g, IQR 116-2100 vs 577μg/g, IQR 72-2100, P=0.005) and (ii) patients treated with vedolizumab had a higher rate of prior anti-TNF exposure (69% vs 11.3%, P=0.001). More than two-thirds of patients were on concomitant steroids at the time of initiating biologic therapy in both groups.

*Comparative effectiveness*

There were no significant differences in clinical response, clinical remission and corticosteroid free remission between anti-TNF and vedolizumab treated patients at week 6, 4, 6 and 12 month time points with the exception of clinical remission at 12 months (Figure 1a). The clinical remission rate was higher with vedolizumab (51.4%) compared to anti-TNF agents at 12 months (27.8%, difference 23.6%, 95% CI 4.8-42.4). However, response rates and steroid free remission rates were not significantly different at 12 months. Moreover, this difference was not observed in the anti-TNF naïve group. Notably, week 6 response was numerically equivalent between anti-TNF (72%) and vedolizumab (69%) treated patients. Exclusion of patients with prior anti-TNF exposure did not alter the clinical efficacy (Figure 1b).

A mixed effect logistic regression analysis did not demonstrate an independent effect of biological agent class (vedolizumab or anti-TNF) on overall response and remission rates (Tables 2a and b).

Four patients each in the anti-TNF (4.1%) and vedolizumab (9.5%) treated groups underwent colectomy but this difference was not significant.

*Trends in SCCAI and calprotectin*

There was a significant reduction in SCCAI from baseline to week 6, 4, 6 and 12 months across the two treatment groups (Figure 1c and d). This was mirrored by a reduction in FC at the same time points though follow-up FC results were not available for all treated patients (Figure 1e and f).

There was a significant average weekly reduction in SCCAI for both vedolizumab (0.06, 95% CI 0.04 to 0.09, P<0.001) and anti-TNF agents (0.06, 95% CI 0.04 to 0.07, P<0.001). Similarly, the average weekly calprotectin reduction was significant for both vedolizumab (7.64 μg/g, 95% CI 2.45-12.82, P=0.004) and anti-TNF agents (17.43 μg/g, 95% CI 11.08-23.79, P<0.001).

*Predictors of efficacy*

None of the clinical and biochemical variables predicted clinical response at 6 and 12 months. Interestingly, early normalisation of FC did not predict clinical response to either anti-TNF agents (Tables 2A and B) or vedolizumab (Tables 2C and D) at 6 months and 12 months. A baseline calprotectin of >500 μg/g was associated with a significantly lower steroid free response or remission to vedolizumab at 12 months (Table 2D) but not all patients had available data. A similar trend was seen with anti-TNF agents at both 6 and 12 months but this effect was not statistically significant.

*Treatment persistence and safety outcomes*

At the end of 12 months, 73% of vedolizumab and 71% of anti-TNF treated patients remained on therapy. Adverse events leading to discontinuation of therapy are summarised in Table 3. Two patients treated with vedolizumab developed abnormal liver function tests resulting in treatment discontinuation. Two patients (1 vedolizumab and 1 anti-TNF) died during the treatment period. The vedolizumab treated patient died due to a pre-existing progressive pulmonary fibrosis and the anti-TNF treated patient died 5 months after cessation of therapy from cerebrovascular disease.

**Discussion**

In this single centre study, we report similar efficacy rates for vedolizumab and anti-TNF agents both during induction and maintenance phase in patients with UC. The overall efficacy figures observed in our study are consistent with that of other real world cohort studies of UC patients treated with anti-TNF agents (13-15) and vedolizumab (16-17). Our findings of comparable efficacy for both biologic agents are broadly similar to findings from other investigators. Preliminary findings from a multi-centre study from the US (VICTORY) reported higher remission rates and mucosal healing rates at 12 months in vedolizumab treated patients (4). This is comparable to our findings where we noted a 2-fold increase in remission rates in vedolizumab treated patients compared to anti-TNF treated patients at 12 months. However, there were no differences in response or steroid free remission at 12 months between the two agents. We did not routinely perform endoscopic assessment at follow up and therefore do not have evaluable mucosal healing data. It is noteworthy, however, that median calprotectin values at 6 and 12 month time points were comparable between the two treatment groups. Our finding of comparable early efficacy after the induction period is also consistent with a smaller study which reported comparable induction response rates between infliximab and vedolizumab (5). Equivalent efficacy of anti-TNF agents and vedolizumab has also been observed in a recently published network meta-analysis (18).

We looked at potential predictors of clinical response to biological agents but our analysis failed to demonstrate any statistical association with any of the evaluated variables. Notably, prior anti-TNF exposure did not influence the response and remission rates to vedolizumab. This stands in contrast to post-hoc GEMINI trial analyses (3). However, it is noteworthy that subsequent cohort studies have yielded contradictory results with some supporting the notion that prior anti-TNF use is associated with lower response (16,17) whilst other studies concur with our findings (19, 20). FC at baseline and its subsequent normalisation failed to discriminate patients who were likely to achieve remission or response. A post-hoc analysis from the GEMINI study similarly failed to note an association between baseline FC and subsequent clinical response (21). However, early normalisation of FC at week 6 predicted remission at 1 year in an analysis of the cohort from GEMINI study (12) and a subsequent German cohort study (17). We noted a trend towards improved remission rates to vedolizumab in patients with a baseline FC<500 μg/g but this effect was not observed at 6 months. Sample size differences are likely to account for ~~this~~ the observed differences. We report that the use of concomitant immunosuppressants is not associated with a better response to vedolizumab. Similar results were noted for both UC and CD in the registration trials (3) and a Swedish National Registry (5). In contrast, one retrospective analysis reported for Crohn’s disease patients that the addition of an immunomodulator after induction improved odds of clinical response at 52 weeks but this effect was not observed in UC (19).

Overall, we encountered low rates of colectomy and adverse events in our study. The colectomy rate was numerically higher in the vedolizumab group and this is likely to reflect an exhaustion of therapeutic medical options. The rates of adverse events were generally low in our study and the spectrum of events is consistent with that noted in the literature. Two patients developed abnormalities in liver function tests (LFT) which resulted in cessation of vedolizumab therapy. LFT abnormalities have been reported with vedolizumab therapy though this did not result in therapy discontinuation in the pivotal clinical trials (22). There were two deaths in our study: one vedolizumab treated patient died due to worsening of a pre-existing idiopathic pulmonary fibrosis and one anti-TNF treated patient died from cerebrovascular disease five months after therapy discontinuation.

Our study has ~~some~~ several limitations. The study is retrospective and non-randomised and does not account for inherent treatment selection bias. The comparisons were indirect and we did not conduct a propensity score matching as (1) a large proportion of vedolizumab treated patients had been exposed to anti-TNF agents and (2) channelling bias: vedolizumab was only licensed several years after approval of anti-TNF agents for UC. Therefore, treatment choice of biologic was restricted to anti-TNF for some of our cohort. However, baseline characteristics including clinical disease activity indices and steroid intake at baseline were both well matched and justify the comparison. We did note a higher baseline calprotectin level among anti-TNF treated subjects which may imply a physician bias of treating patients with worse disease activity with an anti-TNF agent. The sample size is limited by the number of patients with UC treated at a single centre and was not powered to address equivalence or superiority. We pooled all anti-TNF treatment agents for efficacy analyses and this approach does not take in to account the structural and efficacy differences between the agents. However, previous network meta-analysis (23) and cohort studies (24) show broad equivalence among the anti-TNF agents. Our centre does not mandate endoscopic follow up and therefore we do not have data on mucosal healing. This limitation is slightly overcome by the availability of FC data but not all of the patients had follow up FC results. Another limitation is that 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 of adverse events.

In summary, we report that anti-TNF agents and vedolizumab appear equally efficacious in UC treatment. We were unable to identify any predictors of efficacy. Overall, our findings offer support to the notion of choosing any agent from an efficacy perspective though cost, route of administration, speed of onset, safety and patient preference should also be accounted for. Further prospective studies with larger sample size are required to inform clinicians regarding the optimal positioning of biological therapies in UC.

**Funding**

This research was not directly funded.

**Conflict of interest**

RD, PM, SD, TS and DS report no conflicts of interest. CP is/has been on the speaker bureau and/or an advisory board member for Dr Falk pharmaceuticals, Ferring, MSD, Takeda, Warner Chilcott, MSD, Hospira and Abbvie. MD has received an educational grant from Abbvie and MSD and speaker honorarium from Abbvie. PC has received speaker fee from Dr Falk pharmaceuticals, MSD, Ferring and educational support from Dr Falk, MSD, Ferring and Given. ED has received an educational grant from Janssen. SS has received speaker fee from MSD, Actavis, Abbvie, Dr Falk pharmaceuticals, Shire and received educational grant from MSD, Abbvie, Actavis and is an advisory board member for Abbvie, Dr Falk pharmaceutics and Vifor pharmaceuticals. SA has received an educational grant from Tillotts, speaker fees from Teva pharmaceuticals and is an advisory board member for Abbvie. DS has received a speaker fee from Janssen and is an advisory board member for Dr Falk pharmaceuticals.

Author contributions: PM, RD, DS, ED, AS, MD, ED and TS were involved in data collection and drafting of the manuscript. SD and SS were involved in data analysis. PC and CP were involved in drafting and final revision of the manuscript. SS was involved in study design, data collection, analysis, drafting and revision of the manuscript.

**Figure legends**

Table 1. Baseline characteristics of included subjects

Figure 1a and b: Response, remission and corticosteroid-free remission (CFR) defined by SCCAI improvement in all patients (Fig 1a) and biologic naïve patients (Fig 1b)

Figure 1c and d: SCCAI trend in anti-TNF (Fig 1c) and vedolizumab (Fig 1d) treated patients. The dots represent outlier values. (Anti-TNF: N=97, N=95, N=79, N=72, N=60, Vedolizumab: N=42, N=40, N=36, N=36, N=30 at baseline, week 6, 4, 6 and 12 months respectively)

Figure 1e and f: Faecal calprotectin (FC) trend in anti-TNF (Fig 1e) and vedolizumab (Fig 1f) treated patients. Horizontal line represents median and whiskers represent inter-quartile range. Horizontal line represents median and whiskers represent inter-quartile range. The dots represent outlier values. (Anti-TNF: N=75, N=43, N=23, N=21, N=16, Vedolizumab: N=39, N=33, N=22, N=22, N=16 at baseline, week 6, 4, 6 and 12 months respectively)

Table 2a and b: Mixed effects logistic regression model of factors associated with overall clinical response (2a) and remission (2b)

Table 3a-d: Univariate analysis of variables associated with response to anti-TNF (Table 3a) and vedolizumab (Table 3b) at 6 months and 12 months (Table 3c and 3d)

Table 4: Reasons for therapy discontinuation across treatment groups

|  |  |  |
| --- | --- | --- |
|  | **Anti-TNF (N=97)** | **Vedolizumab (N=42)** |
| Age, mean (SD) | 40.4 (17.3) | 44.9 (19.2) |
| Sex, male % | 46.3% | 54.7% |
| BMI kg/m2, mean (SD) | 26.5 (5.3) | 26.5 (5.6) |
| Smoking status:  Current  Ex/never  Unknown | 4.0%  86.7%  9.3% | 2.4%  91%  7% |
| Disease extent:  Pancolitis, N (%)  Left sided, N (%)  Proctitis, N (%)  Unknown, N (%) | 38 (39%)  51 (53%)  7 (7.3%)  1 (1%) | 11 (26%)  24 (57%)  7 (17%)  - |
| Disease duration:  <2 years, N (%)  2-5 years, N (%)  5-10 years, N (%)  >10 years, N (%) | 10 (10.3%)  28 (29%)  33 (34%)  26 (26.7%) | 1 (2.4%)  10 (24%)  15 (36%)  16 (38%) |
| Anti-TNF agent:  Infliximab, N (%)  Adalimumab, N (%)  Golimumab, N (%) | 52 (53%)  26 (27%)  19 (20%) | **-** |
| Concomitant IM, N (%) | 63 (65%) | 24 (57%) |
| Previous anti-TNF, N (%)\* | 11 (11.3%) | 29 (69%) |
| Steroids at baseline, % | 66 (68%) | 33 (79%) |
| Baseline SCCAI, median (range) | 7 (1-15) | 6 (0-12) |
| FC, μg/g, median (range), N\*\* | 955 (116-2100), N=75 | 577 (72-2100), N=39 |
| CRP mg/dl, median (range), N | 8 (5-58), N-94 | 5 (5-47), N=42 |

Table 1: Baseline characteristics of included subjects. \*P=0.005 \*\*P=0.001

Fig 1A

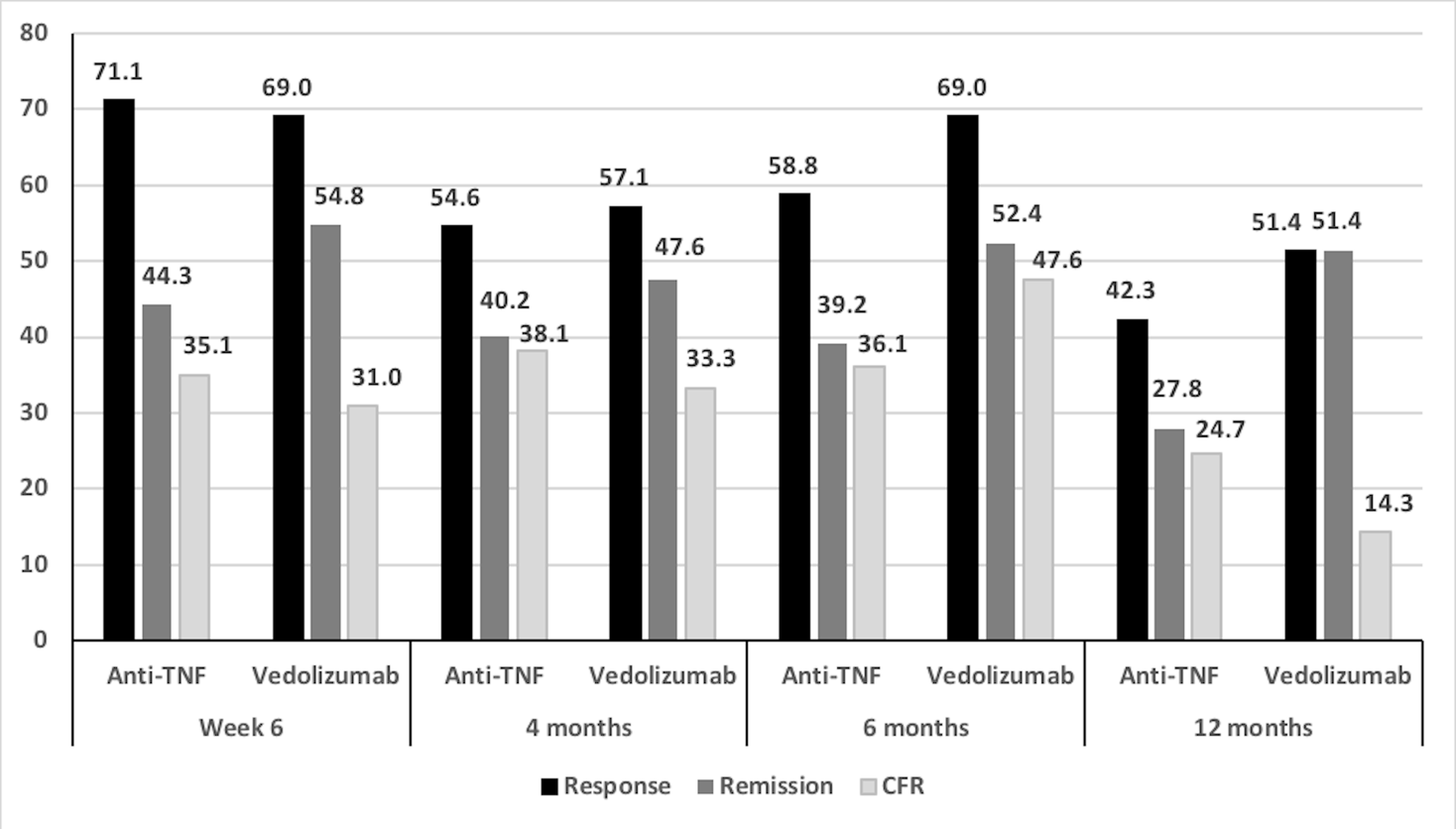


Fig 1B

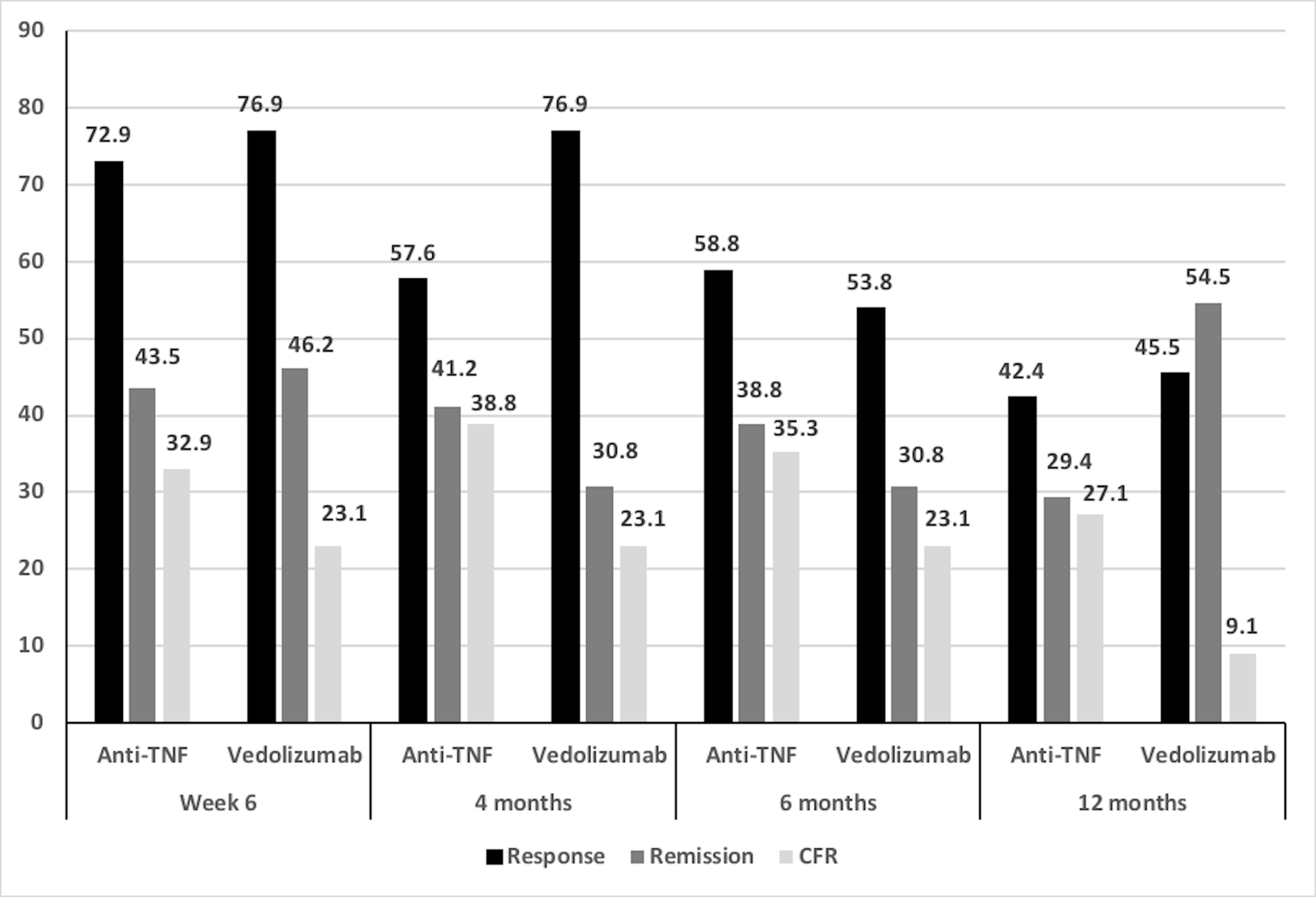


Table 2a

**Outcome: Response**

|  |  |  |  |
| --- | --- | --- | --- |
| **Variables** | **Co-efficient** | **95% CI** | **p-value** |
| Baseline calprotectin | 0.0002 | (-0.0004, 0.0009) | 0.499 |
| Previous anti-TNF exposure | -0.48 | (-1.61, 0.65) | 0.407 |
| Drug: Vedolizumab (vs Anti-TNF) | 0.85 | (-0.43, 2.14) | 0.194 |
| Time (weeks) | 0.002 | (-0.018, 0.022) | 0.824 |
| Drug\*time interaction | -0.031 | (-0.065, 0.003) | 0.072 |
| Intercept | 0.86 | (-0.12, 1.85) | 0.086 |

**Table 2b**

**Outcome: Remission**

|  |  |  |  |
| --- | --- | --- | --- |
| **Variable** | **Co-efficient** | **95% CI** | **p-value** |
| Baseline calprotectin | 0.0003 | (-0.0002, 0.0009) | 0.209 |
| Previous anti-TNF exposure | 0.39 | (-0.60, 1.37) | 0.442 |
| Drug: Vedolizumab (vs Anti-TNF) | 0.87 | (-0.35, 2.09) | 0.162 |
| Time (weeks) | 0.016 | (-0.004, 0.036) | 0.126 |
| Drug\*time interaction | -0.019 | (-0.049, 0.012) | 0.229 |
| Intercept | -1.12 | (-1.94, -0.29) | 0.008 |

Figure 1C

C:\Users\Susie\DatAnywhere\Sync\SDodd\Sree\Vedo study\Box plots\AntiTNF Index.tif

Figure 1D

Box%20plots/Vedo%20Index.tif

Figure 1EBox%20plots/AntiTNF%20Cal.tif

Figure 1F

Box%20plots/Vedo%20Cal.tif

Table 3a

Predictors of steroid-free remission or response to anti-TNF agents at 6months

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Variables** | **Steroid-free remission or response at 6m** | | **OR (95% CI)** | **p-value** |
|  | **No (n=46)** | **Yes (n=51)** |
| Baseline calprotectin: baseline ≥ 500 μg/g | 28 (77.8) | 23 (59.0) | 0.41 (0.15, 1.13) | 0.085 |
| Week 6 Calprotectin <250 μg/g | 6 (25.0) | 8 (40.0) | 2.00 (0.55, 7.24) | 0.291 |
| Disease duration: ≥5yr | 27 (58.7) | 32 (62.8) | 1.19 (0.52, 2.68) | 0.683 |
| Concurrent IM | 30 (65.2) | 35 (68.6) | 1.17 (0.50, 2.72) | 0.721 |
| Disease extent: pancolitis | 22 (47.8) | 16 (31.4) | 0.50 (0.22, 1.14) | 0.099 |

Table 3b

Predictors of steroid-free remission or response to anti-TNF agents at 12months

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Variables** | **Steroid-free remission or response at 12m** | | **OR (95% CI)** | **p-value** |
|  | **No (n=61)** | **Yes (n=36)** |
| Baseline calprotectin: baseline ≥ 500 μg/g | 35 (76.1) | 16 (55.2) | 0.39 (0.14, 1.05) | 0.062 |
| Week 6 Calprotectin <250 μg/g | 10 (35.7) | 4 (25.0) | 0.60 (0.15, 2.36) | 0.465 |
| Disease duration: ≥5yr | 34 (55.7) | 25 (69.4) | 1.80 (0.76, 4.31) | 0.184 |
| Concurrent IM | 41 (67.2) | 24 (66.7) | 0.98 (0.41, 2.34) | 0.956 |
| Disease extent: pancolitis | 28 (45.9) | 10 (27.8) | 0.45 (0.19, 1.10) | 0.080 |

Table 3c

Predictors of steroid-free remission or response to vedolizumab at 6months

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Variables** | **Steroid-free remission or response at 6m** | | **OR (95% CI)** | **p-value** |
|  | **No (n=16)** | **Yes (n=26)** |
| Anti-TNF failure | 6 (46.2) | 15 (68.2) | 2.50 (0.61, 10.26) | 0.203 |
| Baseline calprotectin: baseline ≥ 500 μg/g | 9 (64.3) | 12 (48.0) | 0.51 (0.13, 1.97) | 0.331 |
| Week 6 Calprotectin <250 μg/g | 4 (28.6) | 11 (57.9) | 3.44 (0.79, 15.02) | 0.101 |
| Disease duration: ≥5yr | 11 (68.8) | 20 (76.9) | 1.52 (0.37, 6.12) | 0.560 |
| Concurrent IM | 10 (62.5) | 14 (53.9) | 0.70 (0.20, 2.50) | 0.583 |
| Disease extent | 0 (0.0) | 11 (42.3) | - | - |

Table 3d

Predictors of steroid-free remission or response to vedolizumab at 12 months

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Variables** | **Steroid-free remission or response at 12m** | | **OR (95% CI)** | **p-value** |
|  | **No (n=24)** | **Yes (n=18)** |
| Anti-TNF failure | 12 (63.2) | 9 (56.3) | 0.75 (0.19, 2.92) | 0.678 |
| Baseline calprotectin: baseline ≥ 500 μg/g | 15 (68.2) | 6 (35.3) | 0.25 (0.07, 0.97) | 0.045 |
| Week 6 Calprotectin <250 μg/g | 9 (47.4) | 6 (42.9) | 0.83 (0.21, 3.34) | 0.797 |
| Disease duration: ≥5yr | 16 (66.7) | 15 (83.3) | 2.5 (0.56,11.23) | 0.232 |
| Concurrent IM | 16 (66.7) | 8 (44.4) | 0.40 (0.11, 1.41) | 0.154 |
| Disease extent | 7 (29.2) | 4 (22.2) | 0.69 (0.17, 2.86) | 0.613 |

Table 4

|  |  |  |
| --- | --- | --- |
| **Category** | **Vedolizumab (n=42)** | **Anti-TNF (n=97)** |
| Death | 1 (2.4%) | 1 (1%) |
| Abnormal liver function tests | 2 (4.8) |  |
| Headaches | 1 (2.4%) |  |
| Infections | - | Pneumonia 1 (1%)  Recurrent URTI (2%) |
| Infusion reactions | - | Acute infusion reaction 1 (1%)  Delayed hypersensitivity 2 (2%) |
| Neurological | - | Paresthesiae 1 (1%) |
| Cutaneous | - | Eczema 1 (1%)  Psoriasiform 1 (1%) |

STROBE Statement—checklist of items that should be included in reports of observational studies

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
|  | Item No. | Recommendation | Page  No. | Relevant text from manuscript |
| **Title and abstract** | 1 | (*a*) Indicate the study’s design with a commonly used term in the title or the abstract | [page 2] |  |
| (*b*) Provide in the abstract an informative and balanced summary of what was done and what was found | [page 2] |  |
| Introduction | | | |  |
| Background/rationale | 2 | Explain the scientific background and rationale for the investigation being reported | [pages 4,5] |  |
| Objectives | 3 | State specific objectives, including any prespecified hypotheses | [page 5] |  |
| Methods | | | |  |
| Study design | 4 | Present key elements of study design early in the paper | [pages 5,6] |  |
| Setting | 5 | Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection | [pages 5,6] |  |
| Participants | 6 | (*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up  *Case-control study*—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls  *Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants | [pages 5,6] |  |
| (*b*)*Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed  *Case-control study*—For matched studies, give matching criteria and the number of controls per case | [n/a] |  |
| Variables | 7 | Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable | [page 6] |  |
| Data sources/ measurement | 8\* | For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group | *[n/a]* |  |
| Bias | 9 | Describe any efforts to address potential sources of bias | [page 11] |  |
| Study size | 10 | Explain how the study size was arrived at |  |  |

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| --- | --- | --- | --- | --- |
| Quantitative variables | 11 | Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why | [pages 6,7] |  |
| Statistical methods | 12 | (*a*) Describe all statistical methods, including those used to control for confounding | [pages 6,7] |  |
| (*b*) Describe any methods used to examine subgroups and interactions | [pages 6, 7] |  |
| (*c*) Explain how missing data were addressed | [n/a] |  |
| (*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed  *Case-control study*—If applicable, explain how matching of cases and controls was addressed  *Cross-sectional study*—If applicable, describe analytical methods taking account of sampling strategy | [n/a] |  |
| (*e*) Describe any sensitivity analyses | [n/a] |  |
| Results | | | | |
| Participants | 13\* | (a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed | [table 1] |  |
| (b) Give reasons for non-participation at each stage | [table 4] |  |
| (c) Consider use of a flow diagram |  |  |
| Descriptive data | 14\* | (a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders | [table 1] |  |
| (b) Indicate number of participants with missing data for each variable of interest | [n/a] |  |
| (c) *Cohort study*—Summarise follow-up time (eg, average and total amount) | [page 5] |  |
| Outcome data | 15\* | *Cohort study*—Report numbers of outcome events or summary measures over time | *[page 9]* |  |
| *Case-control study—*Report numbers in each exposure category, or summary measures of exposure | *[n/a]* |  |
| *Cross-sectional study—*Report numbers of outcome events or summary measures | *[n/a]* |  |
| Main results | 16 | (*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included | [n/a] |  |
| (*b*) Report category boundaries when continuous variables were categorized | [n/a] |  |
| (*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period | [n/a] |  |

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| Other analyses | 17 | Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses | [n/a] |  |
| Discussion | | | | |
| Key results | 18 | Summarise key results with reference to study objectives | [page 12] |  |
| Limitations | 19 | Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias | [pages 11,12] |  |
| Interpretation | 20 | Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence | [pages 11, 12] |  |
| Generalisability | 21 | Discuss the generalisability (external validity) of the study results | [pages 11, 12] |  |
| Other information | |  | | |
| Funding | 22 | Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based | n/a |  |

\*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

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