**COMPARATIVE EFFECTIVENESS AT 1 YEAR OF USTEKINUMAB OR VEDOLIZUMAB IN 130 PATIENTS WITH ANTI-TNF REFRACTORY CROHN’S DISEASE**

Short title: Comparative effectiveness of newer biologic therapy in Crohn’s disease

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**Summary**

**Background:** Anti-tumour necrosis factor (TNF) agents are effective in Crohn’s disease but a proportion of patients lose response and require alternative biologic therapy. Both ustekinumab and vedolizumab are used in this setting but there are few data on comparative effectiveness.

**Aim:** To compare the effectiveness of ustekinumab and vedolizumab in anti-TNF refractory Crohn’s disease over a 12- month period.

**Methods:** Patients commencing ustekinumab or vedolizumab for anti-TNF exposed Crohn’s disease patients with a minimum follow-up period of 12 months were included in this retrospective multi-centre cohort study. Disease activity was monitored serially with Harvey-Bradshaw Index for up to 12 months. Faecal calprotectin was recorded at baseline and follow-up, if available. The primary outcome measure was the difference in steroid free remission rates at end of induction (2 months) and at 12 months. We appropriately adjusted for confounders using propensity score matched analysis weighted by the inverse predicted probability of patients’ observed treatment. We also assessed clinical response and remission rates, treatment persistence rates, surgery rates and adverse events among the two groups. Finally, we performed a logistic regression analysis to assess factors associated with steroid-free remission and clinical response and remission.

**Results:** Eighty-five patients commencing vedolizumab and 45 commencing ustekinumab therapy were included. Baseline variables were comparable between the two groups. In an unadjusted model, the rates of steroid-free and clinical remission was significantly higher among ustekinumab treated patients. After adjusting for appropriate confounders, the rate of steroid-free remission was higher among ustekinumab treated patients at 2 months (odds ratio, OR 2.79, 95% confidence interval, CI 1.06-7.39, p=0.038) and 12 months (OR 2.01, 95% CI 0.89-4.56, p=0.095). In a logistic regression model, exposure to two prior anti-TNF agents was associated with lower probability of steroid-free remission (OR 0.27, 95% CI 01-0.74, p=0.011) and clinical remission (OR 0.32, 95% CI 0.12-0.86, p=0.024) at 12 months. There was a significant reduction in Harvey-Bradshaw Index and faecal calprotectin compared to baseline in both groups but ustekinumab treatment was associated with a greater reduction in Harvey-Bradshaw Index (OR -2.72, 95% CI -4.2 to -1.124, p<0.001). A significantly greater proportion of patients treated with ustekinumab remained on therapy at the end of 12 months (84.4% vs 61.5%, p=0.007).

**Conclusions:** Ustekinumab appeared to be more effective in treating anti-TNF refractory Crohn’s disease patients and more patients persisted with therapy in our real world cohort. Further data from prospective studies are warranted.

**Introduction**

Anti-tumour necrosis factor (TNF) therapies, such as infliximab and adalimumab, have transformed the treatment of Crohn’s disease. Around 10-30% of patients, however, fail to respond to initial therapy and up to 40% subsequently lose response or develop limiting side-effects requiring alternative biological therapy1. There are currently two classes of biological therapy that have been approved for use in anti-TNF refractory Crohn’s disease: the α4β7 antibody, vedolizumab, which blocks gut lymphocyte trafficking and the p-40 antibody ustekinumab, which targets interleukins-12 and 23 signalling. In a randomised trial of anti-TNF refractory Crohn’s disease, vedolizumab demonstrated efficacy for both induction and maintenance of remission2. Similarly, ustekinumab was superior to placebo in achieving clinical response and remission in randomised trials of anti-TNF refractory Crohn’s disease patients3,4. Data from clinical trials appear to suggest broadly comparable efficacy and safety for both agents in treating anti-TNF refractory Crohn’s disease. For instance, the induction response rates (defined by a reduction of 100 points in the Crohn’s disease activity index) was 39.2% (placebo 22.3%) for vedolizumab2 and 37.8% (placebo 20.2%) for ustekinumab3 respectively. Similarly, the overall serious adverse event rate was 6% (placebo 8%) for vedolizumab2 and 7.2% (placebo 6.1%) for ustekinumab3. There are no randomised controlled trials comparing the efficacy of these two agents in this setting. Emerging evidence from real world studies seems to suggest that ustekinumab treated patients achieve higher rates of clinical remission compared to vedolizumab treated patients during induction and maintenance therapy 5,6 We sought to compare the effectiveness of vedolizumab and ustekinumab in anti-TNF refractory Crohn’s disease with a view to substantiating existing studies.

**Materials and Methods**

We conducted a multi-centre study of Crohn’s disease patients treated with vedolizumab and ustekinumab for anti-TNF refractory or intolerant Crohn’s disease across 4 hospitals in the North West of England. Patients were excluded if previously exposed to either drug or if receiving either drug for an indication other than luminal Crohn’s disease. Patients were also excluded if they had not yet completed 12 months of follow-up, had insufficient baseline data, had an ostomy, or were taking the medication for prevention of post-operative recurrence. All patients were treated with a standard induction regime for each of the respective agents. Maintenance dosing was 8 weekly for both ustekinumab and vedolizumab after completion of induction therapy. Additional vedolizumab dosing at week 10 and dose escalation during the maintenance phase were at the discretion of the treating clinician. Steroid taper was at the choice of the treating clinician but budesonide 9mg tapered over 12 weeks and prednisolone 40mg once daily with step-wise reduction over the course of eight weeks is standard practice in our region. We collected baseline clinical information including concomitant immunomodulator and steroid therapy, body mass index, disease extent and duration, prior anti-TNF therapy and surgery, smoking status and Harvey-Bradshaw Index. Follow-up data included Harvey-Bradshaw Index, C-reactive protein and faecal calprotectin (where available) at months 2, 4, 6 and 12 after initiation. Data were included if collected within two weeks of each specified time point (four weeks at the 12 month time point). Harvey-Bradshaw Index was routinely assessed whenever patients attended for vedolizumab infusion. For patients receiving ustekinumab, Harvey-Bradshaw Index was routinely monitored by inflammatory bowel disease specialist nurses as part of drug response monitoring. We also recorded details of dose escalation, adverse events and discontinuation of biologic therapy if they occurred and need for surgery. Dose optimisation of vedolizumab or ustekinumab to 4 weekly was based on clinical grounds of suboptimal response combined with biochemical markers of active disease (elevated C-reactive protein or faecal calprotectin). Follow-up was curtailed at 12 months as the number of patients treated with ustekinumab beyond this period was limited. Clinical remission was defined as a Harvey-Bradshaw Index of <5 and clinical response was defined as a reduction Harvey-Bradshaw Index of ≥3 points from the baseline value7,8. We consulted the STROBE statement checklist for observational studies.

Outcomes of interest: The primary outcome measure was rate of steroid-free clinical remission at end of induction therapy and during maintenance therapy. We also assessed rates of clinical response and remission. All patients who had at least an induction dose of either agent were used to calculate response and remission rates even if they had discontinued therapy. We also assessed response of faecal calprotectin to therapy, surgical rates, adverse events and treatment persistence rates. Finally, we assessed the role of clinical variables and biochemical variables (baseline C-reactive protein) in predicting response and remission at 2 and 12 months.

*Statistical analysis*

Categorical variables have been summarized as frequency (%) and continuous variables as median (interquartile range, IQR). We compared remission, response and treatment persistence rates using Fisher’s Exact test. We conducted further sensitivity analyses taking in to account patients who had discontinued therapy for primary non-response, secondary loss of response and loss to follow-up. The numbers at risk for these analyses were the number of patients who remained on therapy at each time point. In order to reduce the effects of treatment selection bias and confounding factors, we initially performed a multiple logistic regression model. We only examined the effect of clinical variables on the end points of steroid-free remission, clinical remission and response at end of induction (2 months) and end of follow-up (12 months). We subsequently performed a propensity score matched analysis weighted by the inverse predicted probability of patients’ observed treatment9,10, stabilised and truncated at the 1st and 99th centiles. The denominators of the stabilised weights were adjusted for baseline confounders (predictors of treatment and outcome), namely perianal disease, disease location, disease severity, smoking and disease duration. The confounders for the propensity score matching were identified on the basis of baseline co-variate differences and factors commonly known to impact on treatment outcome. The numerators of the stabilised weights were equal to the probability of receiving the patient’s treatment without considering covariates. The weighted remission/response/steroid-free remission models included only the treatment variable.

Mixed effects linear regression was used to assess the effect of time and drug on continuous outcomes (faecal calprotectin and Harvey-Bradshaw Index), appropriately allowing for repeated measures on the same patient over time. These models include baseline measures of the outcome and an interaction between time and drug, which assesses the significance and magnitude of the difference in the effect of time for each drug.

Sample size estimation: A two group χ² test with a 5% two-sided significance level will have 68% power to detect the difference between a Group 1 proportion, π₁, of 0.4 and a Group 2 proportion, π₂ of 0.2 (odds ratio of 0.375) when the sample sizes are 45 and 85, respectively (a total sample size of 130).

All analyses were carried out using Stata v16 software (Stata Statistical Software, Release 16; StataCorp LP, College Station, Texas, USA).

*Ethical standards*

The project used anonymized, routinely collected data extracted by clinical teams as part of local quality improvement activities at the participating centres and analysed for the purpose of local audit of compliance with relevant guidance from the National Institute for Health and Care Excellence and to generate benchmarking data for clinical outcome and safety achieved for different agents at the participating centres. Each site registered the biologics audit with their respective institutional audit department and received approval. As routinely collected data it is exempt from the need for ethics committee approval in the United Kingdom and the need to take written informed consent. All data were fully anonymised before pooled analysis.

**Results**

*Cohort*

We identified 213 candidate patients from local inflammatory bowel disease treatment databases. We included 85 patients treated with vedolizumab and 45 patients treated with ustekinumab after excluding ineligible patients (Figure 1). Approximately half of excluded patients were those not previously treated with anti-TNF therapy (n=23), or patients taking ustekinumab who were previously exposed to vedolizumab (n=17). Further excluded patients had not yet reached 12 months follow-up or had insufficient baseline data (n=30). Of the remaining patients, a further 13 were excluded after scrutinising case notes and found to have an ostomy or meeting the other exclusion criteria. The baseline characteristics of the included subjects are summarised in Table 1. There were more vedolizumab treated patients by virtue of its earlier license for Crohn’s disease treatment. Approximately a third of patients were on concomitant steroids at the time of initiating biologic therapy in both groups. More patients in the vedolizumab group were exposed to two prior anti-TNF agents (55.3% vs 26.7%, p=0.002).

*Comparative effectiveness*

Unadjusted steroid-free remission rates were significantly higher for ustekinumab at all time points for patients who received at least their induction dosing (Figure 2A and Table 2A). A significant difference was also noted for clinical remission rates except at 12 months, p=0.057 (Figure 2B and Table 2B). There was, however, no significant difference in clinical response rates between vedolizumab and ustekinumab during both induction and maintenance phase (Figure 2C and Table 2C).

We additionally performed sensitivity analyses excluding patients who had discontinued treatment (complete case basis) and the results were similar apart from no significant difference in clinical and steroid-free remission rates at 12 months (Supplementary Table 1A-C).

In a propensity score adjusted analysis, the rates of steroid-free remission rates were significantly higher among ustekinumab treated patients at 2 months (odds ratio, OR 2.79, 95% CI 1.06-7.39, p=0.038) and tended towards significance at12 months (OR 2.01, 95% CI 0.89-4.56, p=0.095, Table 3). There were no significant differences among clinical remission and response rates in the adjusted model apart from clinical remission at 2 months favouring ustekinumab therapy (OR 2.38, 95% CI 0.99-5.75, p=0.053)

*Predictors of efficacy*

We next examined the effect of baseline clinical variables in an unweighted logistic regression model (Tables 4-6). Exposure to two prior anti-TNF agents were associated with a lower probability of both steroid-free (OR 0.27, 95% CI 01-0.74, p=0.011) and clinical remission (OR 0.32, 95% CI 0.12-0.86, p=0.024) at 12 months (Tables 4 and 5). Concomitant steroid therapy at baseline was associated with a lower chance of clinical response at 12 months (OR 0.43, 95% CI 0.19-0.97, p=0.042, Table 6) but this was not associated with clinical or steroid-free remission at 12 months.

*Trends in Harvey-Bradshaw Index and faecal calprotectin*

There was a significant reduction in Harvey-Bradshaw Index from baseline to the end of treatment across the two treatment groups (Figure 3A and B). Ustekinumab was associated with a greater reduction in Harvey-Bradshaw Index compared to vedolizumab (co-efficient -2.72, 95% CI -4.20 to -1.24, P<0.001, Table 7A). This was mirrored by a reduction in faecal calprotectin for both treatment groups though follow-up faecal calprotectin results were not available for all treated patients (Figure 3C and D). No significant difference was noted between vedolizumab and ustekinumab in faecal calprotectin reduction (Table 7B).

*Treatment persistence, surgery, dose escalation and safety outcomes*

At the end of 12 months, a significantly greater proportion of patients continued on ustekinumab (N=38, 84.4%) compared to vedolizumab (N=51, 61.5%, p=0.007). Adverse events leading to discontinuation of therapy are summarised in Table 8. Two patients (one vedolizumab and one ustekinumab) died during the treatment period. One patient had surgery in the vedolizumab group (1.1%) and four in ustekinumab group (8.9%) during the follow-up period. Eighteen (21%) and 10 patients (22.2%) were escalated to 4 weekly dosing of vedolizumab and ustekinumab respectively. One patient who received two doses of vedolizumab died following a recurrence of lung cancer, who was previously thought to have had a curative resection. One patient treated with ustekinumab, underwent a laparotomy for small bowel obstruction and died post-operatively following an ischaemic stroke and aspiration pneumonia.

**Discussion**

In this multi-centre retrospective study, we report superior steroid-free remission rates and treatment persistence rates for ustekinumab during the induction and maintenance phase compared to vedolizumab in patients with anti-TNF refractory Crohn’s disease, adjusting for potential confounding using inverse probability weighting. It is unlikely that this difference could be solely accounted for by a slower onset of action for vedolizumab as a significant difference was apparent until 12 months. Previous studies suggest a slower onset of action for vedolizumab in both randomised trials2 and observational studies11. The peak effect of vedolizumab was achieved 10-14 weeks after initiation of therapy and therefore unlikely to have accounted for the difference observed for up to 12 months in our study.

The overall efficacy figures for ustekinumab in our study are comparable to other real world cohort studies in Crohn’s disease. For instance, in a German cohort study of 180 patients, the induction clinical response and remission rates were 55% and 25% respectively and at the end of 1 year the rates were 52% and 27% respectively12. Furthermore, in a meta-analysis of 13 observational studies of Crohn’s disease patients treated with ustekinumab, the pooled induction response and remission rates were 56% and 34% respectively and maintenance response and remission rates were 62% and 40% respectively13. Our efficacy outcomes for vedolizumab are also consistent with observations from other cohorts. In a large real-world cohort of Crohn’s disease patients treated with vedolizumab, the induction and maintenance steroid-free clinical remission rates were 31% and 27.2% respectively14. These figures are broadly consistent with those noted in our study.

A multi-centre French retrospective study reported findings of superior efficacy for ustekinumab at week 48 in achieving clinical remission5. This is consistent with our findings of higher steroid-free remission with ustekinumab after 1 year of follow-up. In keeping with this, a recent Dutch study also confirmed superior effectiveness for ustekinumab compared to vedolizumab for treating anti-TNF refractory patients15. To the contrary, another preliminary small Dutch study (n=42 in each group) showed comparable effectiveness between vedolizumab and ustekinumab in treating anti-TNF refractory Crohn’s disease6. Similar to cohort studies, the observation from indirect comparisons of randomised trials is also conflicting. For instance, Pacou et al suggested a higher likelihood for superior efficacy with ustekinumab compared to vedolizumab in anti-TNF refractory Crohn’s disease in an indirect treatment comparison of patients from randomised trials of various biologics though the results failed to achieve statistical significance16. Another indirect comparison study noted no significant differences in safety or efficacy between the two agents in treating anti-TNF refractory Crohn’s disease17. Taken together, these findings emphasise the need for further clinical data to guide informed decision-making.

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. Previous studies have examined several clinical variables as predictors of response to both ustekinumab and vedolizumab. Prior anti-TNF exposure is probably the best studied and is well known to influence response to both vedolizumab18 and ustekinumab18. In our study, exposure to more than one anti-TNF agent adversely affected outcomes. Several studies including sub-group analyses from randomised trials and observational studies suggest disease activity to be an independent predictor of poor response to both vedolizumab18,19 and ustekinumab20. Similarly, an elevated C-reactive protein was noted to adversely affect response rates to both vedolizumab21 and ustekinumab22. Disease related characteristics such as longer disease duration18 and perianal disease23 were previously shown to be associated with negative outcomes with vedolizumab whereas ileocolonic disease was associated with a higher likelihood of response to ustekinumab20. We were unable to confirm associations with clinically active disease or an elevated C-reactive protein and response to ustekinumab or vedolizumab in our study. These discrepancies are likely due to differences in sample size and patient characteristics. We were unable to assess the influence of disease location on response to ustekinumab or vedolizumab given the limited number of subjects in each category. Finally, we noted that a higher proportion of patients in the vedolizumab group were active smokers though this difference was not statistically significant. The effect of smoking on response to novel biological therapy is not well established. In a retrospective multi-centre cohort study of Crohn’s disease patients treated with vedolizumab, active smoking was negatively associated with clinical remission23. To the contrary, other cohort studies do not report an association between response to vedolizumab and smoking11,24,25.

Overall, we encountered low rates of surgery and adverse events in our study. The surgical rate was numerically higher in the ustekinumab 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 died during the follow-up period, one in each group and neither were directly related to the treatment.

Our study has some limitations. The study is retrospective and non-randomised and does not account for inherent treatment selection bias. We attempted to adjust for potential confounding between treatment groups by applying inverse probability weighting to provide unbiased treatment effect estimates, but the validity of this analysis relies on the untestable assumption that we have accounted for all confounders. Baseline characteristics including clinical disease activity indices and steroid intake at baseline were both well matched and therefore justify the comparison. There were no mandated steroid-tapering regimes for patients requiring steroids, but most patients were prescribed the typical regime described in the methods section for prednisolone and budesonide therapy. It is possible but unlikely that our universal policy of treating patients with 8 weekly and not 12 weekly ustekinumab in anti-TNF refractory Crohn’s disease may have accounted for some of the efficacy differences. However, it is noteworthy that other real world cohorts which utilised a 8 or 12 weekly ustekinumab dosing schedule also showed superior effectiveness of ustekinumab compared to vedolizumab6,26. Moreover, dose titration to 4 weekly vedolizumab was also allowed within our study. Comparison between the two treatment groups is limited by the small number of patients. It is unlikely, however, that our findings are reflective of sample size limitations as our findings are consistent with that reported previously15,26. 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 faecal calprotectin data but not all of the patients had follow-up faecal calprotectin 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. The duration of follow-up is also limited and ideally studies with longer follow-up duration are required to confirm outcomes over a prolonged period.

In summary, we report that ustekinumab was superior to vedolizumab in achieving steroid-free remission and clinical remission at both early time points and up to 1 year of treatment. We were unable to identify any predictors of efficacy. Further prospective studies are required to confirm our findings.

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**Table 1. Baseline characteristics of patients who were treated with ustekinumab or vedolizumab who received at least induction dosing of vedolizumab or ustekinumab for anti-tumour necrosis factor therapy refractory Crohn’ disease. P-values calculated from two sample T-tests, Mann Whitney U tests and chi-square tests for normally distributed continuous variables, non-normally distributed variables and categorical variables, respectively.**

|  | **Vedolizumab (N=85)** | **Ustekinumab (N=45)** | **p-value** |
| --- | --- | --- | --- |
| Age, mean (SD) | 44.1 (15.8) | 41.7 (14.9) | 0.402 |
| Sex, male N (%) | 37 (43.5) | 14 (31.1) | 0.168 |
| BMI kg/m2, mean (SD) | 24.8 (5.6) | 26.3 (7.5) | 0.205 |
| Smoking status N (%)  Current  Ex/never  Unknown | 20 (23.5)  65 (76.5)  1 (1.2) | 6 (13.3)  39 (86.7)  0 (0) | 0.157 |
| Disease extent:  Colonic, N (%)  Ileal, N (%)  Ileal-colonic, N (%) | 20 (23.5)  16 (18.8)  49 (57.7) | 11 (24.4)  10 (22.2)  24 (53.3) | 0.870 |
| Disease duration\*:  <2 years, N (%)  2-5 years, N (%)  5-10 years, N (%)  >10 years, N (%) | 0 (0)  12 (14.1)  24 (28.2)  49 (57.7) | 2 (4.4)  11 (24.4)  10 (22.2)  22 (48.9) | 0.125 |
| Perianal disease, N (%) | 29 (34.1) | 14 (31.1) | 0.729 |
| Behaviour:  B1, N (%)  B2, N (%)  B3, N (%) | 31 (36.5)  32 (37.7)  22 (25.9) | 17 (37.8)  14 (31.1)  14 (31.1) | 0.719 |
| Concomitant immunomodulator, N (%) | 40 (47.1) | 16 (35.6) | 0.208 |
| Immunomodulator use:  MP, N (%)  AZA, N (%)  MTX, N (%)  None, N (%)  Unknown, N (%) | 11 (12.9)  22 (25.9)  7 (8.2)  43 (50.6)  2 (2.4) | 6 (13.3)  8 (17.8)  2 (4.4)  20 (44.4)  9 (20.0) | 0.866 |
| Previous anti-TNF exposure  One  Two | 85 (100)  47 (55.3) | 45 (100)  12 (26.7) | 0.002 |
| Previous anti-TNF 1:  Adalimumab, N (%)  Infliximab, N (%) | 26 (30.6)  59 (69.4) | 24 (53.3)  21 (46.7) | 0.011 |
| Anti-TNF failure 1, N (%) | 40 (47.1) | 28 (62.2) | 0.100 |
| Cause for anti-TNF failure\*\* N(%)  Adverse event  Intolerance  Primary non-response  Secondary non-response | 30 (35.3)  15 (17.7)  10 (11.8)  30 (35.3) | 15 (33.3)  2 (4.4)  12 (26.7)  16 (35.6) | 0.050 |
| Previous anti-TNF 2, N (%)  Adalimumab, N (%)  Infliximab, N (%)  Certolizumab, N (%)  None, N (%) | 39 (45.9)  7 (8.2)  1 (1.2)  38 (44.7) | 8 (17.8)  4 (8.9)  0 (0)  33 (73.3) | 0.010 |
| Anti-TNF failure 2  Yes, N (%)  No, N (%)  N/A, N (%) | 30 (35.3)  17 (20.0)  38 (44.7) | 8 (17.8)  4 (8.9)  33 (73.3) | 0.855 |
| Cause for anti-TNF, N (% out of those on previous anti-TNF 2)  Adverse event  Intolerance  Primary non-response  Secondary non-response  N/A | 11 (12.9)  7 (8.2)  8 (9.4)  21 (24.7)  38 (44.7) | 3 (6.7)  1 (2.2)  6 (13.3)  2 (4.4)  33 (73.3) | 0.085 |
| Steroids at baseline, N (%)  Budesonide, N (%)  Prednisolone, N (%) | 30 (35.3)  15 (17.7)  15 (17.7) | 20 (44.4)  5 (11.4)  14 (31.8) | 0.308 |
| HBI, median (range) | 9 (0, 25) | 7 (1, 20) | 0.240 |
| Baseline CRP, mg/L, median (range) | 8 (1, 103) | 6 (1, 64) | 0.798 |
| Baseline faecal calprotectin, µg/g, median (range) | 320 (15, 2100) | 449 (41, 2100) | 0.430 |

SD= standard deviation, BMI = Body mass index, AZA = azathioprine, MP = mercaptopurine, MTX = methotrexate, TNF = tumour necrosis factor, HBI = Harvey Bradshaw Index, CRP = C-reactive protein. \*P-value calculated for <5, 5-10 and >10 years disease duration \*\*Reason for failure of 1st anti-TNF agent.

**Table 2A-C: Rates of steroid-free remission (2A), clinical remission (2B) and clinical response (2C) at 2, 4, 6 and 12 months in patients who were treated with ustekinumab or vedolizumab who received at least induction dosing of vedolizumab or ustekinumab for anti-tumour necrosis factor therapy refractory Crohn’ disease**

**Table 2A: Steroid-free remission**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Time Point** | **Ustekinumab** | **Vedolizumab** | **Difference in percentages**  **(95% CI)** | **p-value** |
| 2 months | 13/45 (28.9%) | 10/85 (11.8%) | 17.1 (2.2, 32.0) | 0.015 |
| 4 months | 17/45 (37.8%) | 17/85 (20.0%) | 17.8 (1.3, 34.3) | 0.028 |
| 6 months | 17/45 (37.8%) | 13/85 (15.3%) | 22.5 (6.4, 38.6) | 0.004 |
| 12 months | 19/45 (42.2%) | 21/85 (24.7%) | 17.5 (0.4, 34.6) | 0.040 |

**Table 2B: Clinical remission**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Time Point** | **Ustekinumab** | **Vedolizumab** | **Difference in percentages**  **(95% CI)** | **p-value** |
| 2 months | 16/45 (35.6%) | 14/85 (16.5%) | 19.1 (3.0, 35.1) | 0.014 |
| 4 months | 18/45 (40.0%) | 18/85 (21.2%) | 18.8 (2.1, 35.6) | 0.023 |
| 6 months | 18/45 (40.0%) | 14/85 (16.5%) | 23.5 (7.2, 39.9) | 0.003 |
| 12 months | 19/45 (42.2%) | 22/85 (25.9%) | 16.3 (-0.8, 33.5) | 0.057 |

**Table 2C: Clinical response**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Time Point** | **Ustekinumab** | **Vedolizumab** | **Difference in percentages**  **(95% CI).55** | **p-value** |
| 2 months | 22/45 (48.9%) | 30/85 (35.3%) | 13.6 (-4.2, 31.4) | 0.132 |
| 4 months | 25/45 (55.6%) | 33/85 (38.8%) | 16.7 (-1.1, 34.6) | 0.068 |
| 6 months | 22/45 (48.9%) | 33/85 (38.8%) | 10.0 (-7.8, 28.0) | 0.269 |
| 12 months | 24/45 (53.3%) | 37/85 (43.5%) | 9.8 (-8.2, 27.8) | 0.287 |

CI=confidence interval

**Table 3: Propensity score adjusted rates of steroid-free remission, clinical remission and response at 2 and 12 months comparing ustekinumab to vedolizumab**

|  |  |  |  |
| --- | --- | --- | --- |
| **Ustekinumab vs vedolizumab** | **Odds Ratio** | **95% CI** | **p-value** |
| Steroid-free remission at 2 months | 2.79 | (1.06, 7.39) | 0.038 |
| Steroid-free remission at 12 months | 2.01 | (0.89, 4.56) | 0.095 |
| Clinical remission at 2 months | 2.38 | (0.99, 5.75) | 0.053 |
| Clinical remission at 12 months | 1.78 | (0.79, 4.02) | 0.167 |
| Clinical response at 2 months | 1.76 | (0.81, 3.85) | 0.155 |
| Clinical response at 12 months | 1.34 | (0.62, 2.91) | 0.457 |

CI=confidence interval

**Table 4: Logistic regression of variables associated with steroid-free remission at 2 months and 12 months in patients who received at least induction dosing of vedolizumab or ustekinumab for anti-tumour necrosis factor therapy refractory Crohn’s disease**

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| **Variables** | **Steroid-free remission at 2 months** | | | **Steroid-free remission at 12 months** | | |
| **Odds Ratio** | **95% CI** | **p-value** | **Odds Ratio** | **95% CI** | **p-value** |
| Drug: Ustekinumab (vs Vedolizumab) | 2.94 | (1.03, 8.35) | 0.043 | 1.88 | (0.77, 4.60) | 0.167 |
| Disease duration (baseline <=5 years) |  |  | 0.725 |  |  | 0.364 |
| 5-10 | 1.04 | (0.26, 4.18) |  | 1.20 | (0.31, 4.57) |  |
| > 10 | 0.66 | (0.17, 2.53) |  | 2.15 | (0.65, 7.13) |  |
| Current smoker | 0.59 | (0.13, 2.60) | 0.482 | 0.54 | (0.16, 1.77) | 0.310 |
| Disease extent (baseline colonic) |  |  | 0.277 |  |  | 0.444 |
| Ileal | 1.02 | (0.31, 3.36) |  | 0.58 | (0.19, 1.80) |  |
| Ileo-colonic | 0.26 | (0.04, 1.53) |  | 1.29 | (0.35, 4.78) |  |
| Perianal disease | 2.10 | (0.46, 9.55) | 0.337 | 1.01 | (0.32, 3.19) | 0.984 |
| Steroids at baseline | 0.99 | (0.34, 2.89) | 0.982 | 0.46 | (0.18, 1.20) | 0.111 |
| HBI at baseline | 0.94 | (0.82, 1.08) | 0.382 | 0.91 | (0.82, 1.01) | 0.080 |
| Two previous anti-TNF (baseline one) | 0.60 | (0.18, 1.99) | 0.409 | 0.27 | (0.10, 0.74) | 0.011 |
| Intercept | 0.17 | (0.02, 1.74) | 0.137 | 1.05 | (0.19, 5.69) | 0.954 |

CI=confidence interval, HBI=Harvey-Bradshaw Index, TNF = tumour necrosis factor,

**Table 5: Logistic regression of variables associated with clinical remission at 2 months and 12 months in patients who received at least induction dosing of vedolizumab or ustekinumab for anti-tumour necrosis factor therapy refractory Crohn’s disease**

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| **Variables** | **Clinical remission at 2 months** | | | **Clinical remission at 12 months** | | |
| **Odds Ratio** | **95% CI** | **p-value** | **Odds Ratio** | **95% CI** | **p-value** |
| Drug: Ustekinumab (vs Vedolizumab) | 2.37 | (0.92, 6.15) | 0.075 | 1.72 | (0.71, 4.18) | 0.233 |
| Disease duration (baseline <=5) |  |  | 0.935 |  |  | 0.527 |
| 5-10 | 1.15 | (0.31, 4.26) |  | 0.89 | (0.24, 3.34) |  |
| > 10 | 0.93 | (0.27, 3.19) |  | 1.59 | (0.50, 5.09) |  |
| Current smoker | 0.37 | (0.09, 1.58) | 0.179 | 0.47 | (0.14, 1.54) | 0.211 |
| Disease extent (baseline colonic) |  |  | 0.761 |  |  | 0.752 |
| Ileal | 1.46 | (0.35, 6.12) |  | 0.76 | (0.19, 2.98) |  |
| Ileo-colonic | 1.63 | (0.44, 5.95) |  | 1.21 | (0.39, 3.71) |  |
| Disease behaviour (baseline B1) |  |  | 0.206 |  |  | 0.310 |
| B2 | 0.77 | (0.26, 2.28) |  | 0.48 | (0.16, 1.47) |  |
| B3 | 0.24 | (0.05, 1.16) |  | 1.14 | (0.31, 4.17) |  |
| Perianal disease | 1.02 | (0.27, 3.87) | 0.972 | 0.95 | (0.30, 2.97) | 0.933 |
| Steroids at baseline | 1.78 | (0.68, 4.63) | 0.238 | 0.43 | (0.17, 1.12) | 0.085 |
| HBI at baseline | 0.91 | (0.80, 1.03) | 0.139 | 0.90 | (0.81, 1.00) | 0.051 |
| Two previous anti-TNF (baseline one) | 0.66 | (0.19, 1.61) | 0.280 | 0.32 | (0.12, 0.86) | 0.024 |
| Intercept | 0.55 | (0.08, 3.88) | 0.550 | 1.93 | (0.35, 10.78) | 0.451 |

CI=confidence interval, HBI=Harvey-Bradshaw Index, TNF = tumour necrosis factor

**Table 6: Logistic regression of variables associated with clinical response at 2 months and 12 months in patients who received at least induction dosing of vedolizumab or ustekinumab for anti-tumour necrosis factor therapy refractory Crohn’s disease**

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| **Variables** | **Clinical response at 2 months** | | | **Clinical response at 12 months** | | |
| **Odds Ratio** | **95% CI** | **p-value** | **Odds Ratio** | **95% CI** | **p-value** |
| Drug: Ustekinumab (vs Vedolizumab) | 1.58 | (0.68, 3.66) | 0.288 | 1.32 | (0.56, 3.11) | 0.525 |
| Disease duration (baseline <=5) |  |  | 0.458 |  |  | 0.147 |
| 5-10 | 1.22 | (0.39, 3.83) |  | 0.45 | (0.13, 1.49) |  |
| > 10 | 0.69 | (0.24, 1.99) |  | 0.33 | (0.11, 1.00) |  |
| Current smoker | 0.60 | (0.22, 1.69) | 0.338 | 0.44 | (0.16, 1.22) | 0.115 |
| Disease extent (baseline colonic) |  |  | 0.689 |  |  | 0.374 |
| Ileal | 1.69 | (0.50, 5.68) |  | 0.52 | (0.14, 1.85) |  |
| Ileo-colonic | 1.38 | (0.49, 3.93) |  | 1.16 | (0.42, 3.23) |  |
| Disease behaviour (baseline B1) |  |  | 0.406 |  |  | 0.048 |
| B2 | 0.52 | (0.20, 1.36) |  | 0.32 | (0.11, 0.88) |  |
| B3 | 0.74 | (0.22, 2.47) |  | 1.13 | (0.32, 3.99) |  |
| Perianal disease | 0.74 | (0.25, 2.16) | 0.579 | 0.86 | (0.28, 2.59) | 0.785 |
| Steroids at baseline | 1.36 | (0.61, 3.05) | 0.450 | 0.36 | (0.15, 0.87) | 0.023 |
| HBI at baseline | 1.11 | (1.01, 1.21) | 0.033 | 1.08 | (0.98, 1.19) | 0.106 |
| Two previous anti-TNF (baseline one) | 0.69 | (0.29, 1.62) | 0.390 | 0.60 | (0.25, 1.45) | 0.257 |
| Intercept | 0.35 | (0.07, 1.71) | 0.194 | 3.02 | (0.60, 15.14) | 0.179 |

HBI=Harvey-Bradshaw Index, TNF = tumour necrosis factor

**Table 7A-B: Mixed effects linear regression model demonstrating effect of time and drug on Harvey Bradshaw Index (Table 7A) and faecal calprotectin (Table 7B)**

**Table 7A: Harvey Bradshaw Index**

|  |  |  |  |
| --- | --- | --- | --- |
|  | **Co-efficient** | **95% CI** | **p-value** |
| Baseline Harvey Bradshaw Index | 0.45 | (0.34, 0.57) | <0.001 |
| Drug: Ustekinumab (vs Vedolizumab) | -2.72 | (-4.20, -1.24) | <0.001 |
| Time (months) | -0.15 | (-0.27, -0.02) | 0.025 |
| Drug\*time interaction | 0.07 | (-0.14, 0.27) | 0.527 |
| Intercept | 4.34 | (2.92, 5.76) | <0.001 |

**Table 7B: Faecal calprotectin**

|  |  |  |  |
| --- | --- | --- | --- |
|  | **Co-efficient** | **95% CI** | **p-value** |
| Baseline faecal calprotectin (µg/g) | 0.50 | (0.37, 0.64) | <0.001 |
| Drug: Ustekinumab (vs Vedolizumab) | 14.36 | (-254.53, 283.24) | 0.917 |
| Time (months) | -11.51 | (-30.77, 7.74) | 0.241 |
| Drug\*time interaction | -4.51 | (-37.23, 28.21) | 0.787 |
| Intercept | 311.19 | (118.45, 503.94) | 0.002 |

CI=confidence interval

**Table 8: Reasons for therapy discontinuation across treatment groups, N (%)**

|  | **Vedolizumab (N=85)** | **Ustekinumab (N=45)** |
| --- | --- | --- |
| Adverse reaction leading to treatment cessation | 5 (5.9%) | 1 (2.2%) |
| Lack of response | 19 (22.4%) | 1 (2.2%) |
| Death | 1 (1.2%) | 1 (2.2%) |
| Surgery | 1 (1.2%) | 4 (8.9%%) |

**Figure legends**

**Figure 1: Study flowchart**

**Figure 2A-C: Steroid-free remission (Fig 2A) and clinical remission (Fig 2B) rates defined by a Harvey Bradshaw Index of <5 and clinical response rates (Fig 2C) defined by Harvey Bradshaw Index improvement of ≥3 in patients treated with ustekinumab or vedolizumab for anti-tumour necrosis factor refractory Crohn’s disease. Fig 2A: All P<0.05, Fig 2B: All P<0.05 at all time points except 12 months, P=0.057. Fig 2C: All P=non-significant**

**Figure 3A-B: Harvey Bradshaw Index trend in patients treated for anti-tumour necrosis factor refractory Crohn’s disease with vedolizumab (Fig 3A) and ustekinumab (Fig 3B) at baseline, 2, 4, 6 and 12 months (m). Horizontal line represents median and boxes represent inter-quartile range**

**Figure 3C-D: Faecal calprotectin trend in patients treated for anti-tumour necrosis factor refractory Crohn’s disease with vedolizumab (Fig 3C) and ustekinumab (Fig 3D) at baseline, 2, 4, 6 and 12 months (m). Horizontal line represents median and boxes represent inter-quartile range**

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 1] |  |
| (*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 3] |  |
| Objectives | 3 | State specific objectives, including any prespecified hypotheses | [page 3] |  |
| Methods | | | |  |
| Study design | 4 | Present key elements of study design early in the paper | [pages 4,5] |  |
| Setting | 5 | Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection | [pages 4,5] |  |
| 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 4,5] |  |
| (*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 5] |  |
| 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 10] |  |
| Study size | 10 | Explain how the study size was arrived at |  |  |

Continued on next page

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| Quantitative variables | 11 | Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why | [pages 5, 6] |  |
| Statistical methods | 12 | (*a*) Describe all statistical methods, including those used to control for confounding | [pages 5, 6] |  |
| (*b*) Describe any methods used to examine subgroups and interactions | [pages 5, 6] |  |
| (*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, figure 1] |  |
| (b) Give reasons for non-participation at each stage | [table 7, figure 1] |  |
| (c) Consider use of a flow diagram | [Figure 1] |  |
| 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] |  |

Continued on next page

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| 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 11,12] |  |
| 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 10,11] |  |
| Interpretation | 20 | Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence | [pages 10,11, 12] |  |
| Generalisability | 21 | Discuss the generalisability (external validity) of the study results | [pages 10,11, 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.