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A propensity score-matched, real-world comparison of ustekinumab vs vedolizumab as a second-line treatment for Crohn's disease. The Cross Pennine study II

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Summary

Background: The optimal choice of biological agents after failure of anti-tumour-necrosis-factor-(TNF)α agent in Crohn's disease (CD) is yet to be defined.

Aims: To assess the effectiveness and safety of ustekinumab compared to vedolizumab as second-line treatment in CD patients who failed anti-TNFα therapy.

Methods: Retrospective analysis of clinical response and remission at 14 and 52 weeks to ustekinumab by physician global assessment (PGA). A propensity score-matched analysis with a cohort treated with vedolizumab was performed.

Results: Of 282 patients (mean age 40 ± 15, F:M ratio 1.7:1) treated with ustekinumab, clinical response or remission was reached by 200/282 patients (70.9%) at 14 weeks, and 162/259 patients (62.5%) at 52 weeks. Overall, 74 adverse events occurred, of which 26 were labelled as serious (8.3 per 100 person-year). After exclusion of patients without prior anti-TNFα exposure and patients previously exposed to vedolizumab or ustekinumab, we analysed 275/282 patients (97.5%) on ustekinumab and 118/135 patients (87.4%) on vedolizumab. Propensity score analysis revealed that at 14 weeks, patients treated with ustekinumab were 38% (95% CI 25%-50%; $P < 0.001$) more likely to achieve clinical remission, while at 52 weeks, the difference of 9% (95% CI −15% to 33%; $P = 0.462$) was not significant.

Conclusions: Ustekinumab was effective and well tolerated in this real-world cohort. While ustekinumab proved more effective at 14-weeks, we found no statistically significant differences at 52 weeks compared to vedolizumab.

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The author's complete affiliation list are listed in Appendix 1.

1 | INTRODUCTION

Crohn's disease (CD) is a chronic, relapsing and progressive form of inflammatory bowel[1,2] disease associated with disabling symptoms[3] and often requiring lifelong medical treatments[4] and, in many cases, surgery.[5] Despite the recent advances in the pharmacological treatment of CD,[6] a number of uncertainties still exist regarding the effectiveness and safety of the available biologic therapies and, more importantly, their positioning in a real-life setting. In fact, the available treatment options have rapidly increased over the last two decades since the development of novel monoclonal antibodies. Anti-tumour necrosis factor (TNF) α agents, namely infliximab, adalimumab, and certolizumab, have been used for more than 20 years, and have dramatically improved the management of patients with CD, achieving and prolonging remission,[7] presenting an effective option for perianal disease,[8] and improving quality of life.[9] Vedolizumab, which blocks the α4β7 integrin impeding lymphocyte trafficking (gut homing), was the second class of monoclonal antibodies to be licensed after anti-TNF therapies. Its gut selectivity consequent better safety profile has been demonstrated in long-term extension studies and other data.[10] Vedolizumab proved effective and demonstrated a good safety profile in many real-world studies[11,12] with no new safety signals since the registrational trials. The latest monoclonal antibody to be approved for the induction and maintenance of CD was ustekinumab,[13] a monoclonal antibody directed against the shared p40 subunit of interleukins (IL)12 and IL23.[14] Ustekinumab targets a crucial inflammatory pathway in CD, and is also effective in treating some CD-related extra-intestinal manifestations,[15] especially dermatologic and rheumatologic, such as psoriasis and psoriatic arthritis.[16] Real-world data exploring its efficacy and safety in CD are still emerging,[17-23] as are comparative studies with vedolizumab in anti-TNFα-experienced patients.[24-26] In the absence of prospective, randomised clinical trials comparing available treatments, such studies are of particular interest, as they allow comparison after adjustment of potential confounding factors in a real-life setting. The studies published so far have included a limited number of patients and more data are needed.

On this basis, our primary aim was to describe the 3- and 12-month clinical effectiveness of ustekinumab, predictors of clinical response, and its safety profile in a large multicentre cohort of CD patients. As a secondary aim, we performed a propensity score-matched analysis between this cohort of CD patients and a previously described cohort (the Cross Pennine study)[11] treated with vedolizumab who failed any anti-TNFα agent.

2 | METHODS

2.1 | Patients

Eight inflammatory bowel disease (IBD) centres (both university and general hospitals) from the UK took part in this study (Leeds Teaching Hospitals; Manchester Royal Infirmary; Salford Royal Hospitals; Bolton NHS Trust; Bradford Teaching Hospital; The Royal Liverpool and Broadgreen University Hospitals; Wrightington, Wigan and Leigh NHS Trust and The Pennine Acute Hospitals NHS Trust). Data were retrospectively collected from all consecutive adult CD patients (age ≥18), who commenced ustekinumab (January 2017–January 2020; last follow-up available until 30 April 2020) through the electronic medical records. The diagnosis of CD was based according to internationally agreed diagnostic criteria.[27,28] Data of interest were extracted and semi-anonymised from patient records onto a pre-defined spreadsheet that was initially developed for the first Cross Pennine study (MVL),[11] and then implemented and centrally collated by the study coordinator (VD) at St. James's University Hospital, Leeds. Before study initiation, a meeting among all study investigators was held, in order to harmonise data abstraction across multiple sites. A small proportion of the patients recruited from Liverpool have already been described in a previous paper.[24] At the time of enrolment, all patients had either gastrointestinal symptoms or objective evidence of inflammation. Patients with incomplete data (i.e., missing medical history, 3- or 12-month clinical assessments not reported, lost to follow-up), uncertain diagnosis or IBD type-unspecified, or with a short follow-up (less than 3 months) were excluded. As per current recommendations, the first dose of ustekinumab was given as an intravenous infusion, diluted in a 0.9% saline solution. The dose was calculated depending on the body weight, according to the approved indication for CD patients. A subcutaneous injection was then administered after 8 weeks, at a dose of 90 mg. Thereafter, patients received a maintenance dose of 90 mg, subcutaneously, at either every 12 or every 8 weeks, as per clinical need, determined by supervising clinicians. Demographic (age, gender) and disease-related data (phenotype according to the Montreal classification, disease duration, previous medications, previous surgery and co-morbidities) were collected. Other variables of interest considered were concomitant steroid and immunosuppressive therapy use, bridging steroid therapy, smoking status, previous biologic exposure, and adherence to planned infusions.

For comparison, we have used a cohort of CD patients treated with vedolizumab whose clinical characteristics and clinical outcomes have already been described in the Cross Pennine study,[11] after the exclusion of those who had not been exposed to a previous anti-TNF or who had been previously treated with ustekinumab. In brief, these patients have been retrospectively enrolled in the same eight IBD centres between August 2014 and June 2017. Data were retrieved through the local electronic medical records by the treating physicians and all queries were resolved with the study coordinator (MVL). All consecutive patients initiated on vedolizumab in that time span have been included, with the exception of patients who had not yet reached the 3-month clinical assessment. As per current recommendations, vedolizumab was given as an intravenous infusion (300 mg) over 30 minutes at weeks 0, 2, 6, and every 8 weeks thereafter. Also, an additional week 10 dose was administered in 7 patients. The same outcomes were assessed in both the previous[11] and the current study, as detailed below.

2.1.1 | Outcomes

As for the first Cross Pennine study, the primary outcome of the study was to evaluate the 3- and 12-month short or medium-term clinical effectiveness of ustekinumab and to assess its safety. Clinical response or remission at 14 and 52 weeks (±2 weeks) were assessed using the physician global assessment (PGA) score. PGA outcomes were based on the clinical impression of the treating physician, defining remission as the complete relief or marked improvement of symptoms compared to baseline (score 0), and response as a partial (score 1), though significant, improvement. A PGA score of 2 indicated a moderately active disease, while a score of 3 a severely active disease. In order to support PGA results, the Harvey-Bradshaw Index (HBI) was also included in the statistical analysis, when available, and this was always concordant with the PGA (Spearman's rho 0.66; $P < 0.001$). HBI was not used as the primary outcome, as this was not available for all patients. Remission was defined with an HBI score ≤4, while a reduction of at least 3 or more points defined a clinical response. An HBI score 5-7, 8-16, and >16 were indicative of mild, moderate, or severe disease activity. Moreover, data on C reactive protein (CRP) and faecal calprotectin (FC) at baseline and at 14 weeks (±1 week) were collected. CRP was considered as elevated when >5 mg/dL, while FC was considered as significantly increased when >250 μg/g. A number of potential predictors of treatment failure were assessed, including bridging steroid therapy, concomitant use of immunosuppressant (azathioprine, 6-mercaptopurine, or methotrexate), previous anti-TNFα exposure, smoking status, disease duration, baseline FC and CRP, disease phenotype and location, and previous surgery.

Furthermore, we studied treatment discontinuation defined by the treating physician if ustekinumab was judged in their opinion to be ineffective, resulting in cessation of treatment. Specifically, primary failure was defined as inadequate clinical response after induction phase, leading to alternative treatment strategies, also including the need for surgery, while loss of response was defined as inadequate response to treatment occurring any time after the induction phase. Patients who stopped ustekinumab in weeks 14-52 were considered as treatment failure in the 52-week analysis. Data on other reasons for discontinuation, such as adverse events (serious and non-serious), infectious diseases, and other possible safety signals or conditions that were attributed to ustekinumab therapy were also collected. Finally, where applicable, we compared these data with those of the previously described vedolizumab cohort.[11]

As a secondary aim, we compared the 14- and 52-week remission and response rates according to the PGA in the ustekinumab vs the vedolizumab cohorts using a propensity score-matched analysis. For this purpose, patients who had been previously treated with ustekinumab (in the vedolizumab cohort) or with vedolizumab (in the ustekinumab cohort) were excluded. We have also excluded patients who had not been treated with any anti-TNFα agent as first-line therapy for CD.

As exploratory aims, we also reported 14- and 52-week steroid-free clinical remission, 52-week treatment persistence, 14-week CRP<5 mg/dL, and 52-week hospitalisation before and after matching.

2.2 | Statistical analysis

Given the observational, exploratory nature of the study, and in the absence of a pre-defined hypothesis, a sample size was not calculated *a priori*. A *post-hoc* calculation of the power showed that this was greater than 80% for the primary outcome, according to the method by Austin based on calculation of the variance inflation factor (VIF), which describes the extent to which the effective sample size has been reduced by weighting.[29] The *post-hoc* power of a chi-square test for the observed difference in proportion of success at 3 months is 0.99, while VIF is 1.15 based on a *c*-statistics of the model equal to 0.67 and a prevalence of treatment equal to 0.6. Hence, the resulting power is 86%.

Categorical variables were described as count and percentage; quantitative variables as mean and standard deviation (SD) or median and interquartile range (IQR) if not normally distributed. Percentages were calculated after exclusion of patients with missing data, and the analysis of the main outcomes was made on an intention-to-treat basis. Predictors of ustekinumab treatment failure were identified through univariable and multivariable (including only factors with $P < 0.05$ at univariable analyses) logistic regression models. In order to strengthen our results and to avoid possible biases, these models were also adjusted according to baseline PGA (2-3), inflammatory markers (increased CRP and/or FC), and previous exposure to vedolizumab. Results were expressed as odds ratio (OR) and 95% confidence interval (95% CI). For these subgroup analyses, a *P*-value below 0.01 was considered significant.

Time to ustekinumab treatment discontinuation (also including comparison with vedolizumab) was represented by the Kaplan-Meier curve for interval data.

The propensity score-matched analysis is widely applied in medical sciences for reducing possible biases, from confounding variables, that may emerge by simply comparing two different treatments.[30] In the present study, the aim of the propensity score-matched analysis was to compare the 14- and 52-week clinical remission according to the PGA (score 0-1) between the ustekinumab and the vedolizumab cohorts.

Nearest-neighbour matching (NNM) was applied to the estimated propensity score. The NNM method of treatment-effect estimation imputes the missing potential outcome for each individual by using an average of the outcomes of similar subjects that receive the other treatment level. Each observation is matched with at least 1 observation from the other treatment level. Results are expressed as average treatment effect, computed by taking the average of the difference between the observed and potential outcomes for each subject.

The following pre-treatment variables were selected *a priori*, based on their clinical relevance as shown in previous studies,[24-27] for inclusion in propensity score estimation, namely gender, patient

age >65 years, active smoking, patient weight (as a continuous variable), previous CD surgery, colonic only vs small bowel involvement, presence of perianal disease, age at CD diagnosis, presence of extra-intestinal manifestations or psoriasis, disease behaviour, presence of at least one comorbidity other than CD, number of previous anti-TNFα therapies, concomitant immunosuppressive drug (i.e., azathioprine, methotrexate, 6-mercaptopurine), baseline HBI and PGA, baseline CRP and FC, need for steroids at any time as rescue therapy. The MeSH definition was used for defining the presence of comorbidity.[31] Psoriasis was included as a relevant variable, given that ustekinumab is the drug of choice in this condition in CD patients who failed anti-TNFα agents.[32] We have also performed a sensitivity analysis, only including variables that were significantly associated with the primary outcome at logistic regression.

As the use of steroids was included as a variable of interest, a separate analysis for steroid-free remission was not performed. As a sensitivity analysis, inverse probability weighting (IPW) regression adjustment was also performed.

The overlap assumption that requires that each individual has a positive probability of receiving each treatment was assessed graphically. This graph displays the estimated density of the predicted probabilities that a control patient (vedolizumab) is a control and the estimated density of the predicted probabilities that control is a treated patient (ustekinumab). Balancement instead was assessed through a box plot and by reporting the standardised mean difference (SMD) before and after matching each variable. There was no need for trimming, as the outliers were less than 5%.

The study was performed as a clinical audit using routinely 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. The results of the study are reported according to the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) recommendations for quality assurance and according to the Good Research for Comparative Effectiveness (GRACE) initiative.

3 | RESULTS

3.1 | Cohorts under study

Over the study period, 321 patients with CD commenced treatment with ustekinumab. Of these, we excluded 20 patients who did not reach the 14-week observation, 16 with incomplete or uncertain data, and 3 who were lost to follow-up. Hence, the final ustekinumab cohort included 282 patients (mean age 40 ± 15 years, F:M ratio 1.7:1) who had been treated with this drug for a mean period of 18 ± 5 months, and whose demographic and other relevant characteristics are reported in Table 1, along with the characteristics of the vedolizumab cohort. Almost all patients had already been exposed to a biologic agent, and roughly half of the patients had had CD-related abdominal surgery. Notably, at least one comorbidity was present in 222 patients (78.7%), with essential hypertension, ischaemic heart disease, psoriasis, and type 2 diabetes being the most common.

3.2 | Clinical effectiveness

The rates of 14- and 52-week clinical response or remission according to the PGA, as well as steroid-free response or remission, are reported in Figure 1. Clinical response or remission was reached by 200/282 patients (70.9%) at 14 weeks, and by 162/259 patients (62.5%) at 52 weeks. Of note, after induction, in 236 patients (83.7%) ustekinumab was escalated to every 8 weeks. Patients who discontinued ustekinumab and related reasons for discontinuation or loss of response are reported in Table 2. The most common reason for discontinuation was either primary failure or loss of response, followed by the occurrence of adverse events and by the need for surgery. Similar to the previously described vedolizumab cohort, non-adherence rate was rather low (1.4% in the ustekinumab vs 2.4% in the vedolizumab cohort). The Kaplan-Meier ustekinumab failure estimate is reported in Figure S1, while the Kaplan-Meier ustekinumab vs vedolizumab failure estimate is reported in Figure 2. Of note, no significant difference was noticed between the two groups at both 14 and 52 weeks. Finally, Table S1 reports data regarding 14- and 52-week assessment of CRP, FC, and HBI, when available. Of note, HBI and FC significantly decreased at both 14 and 52 weeks.

3.3 | Predictors of ustekinumab treatment failure

Potential predictors of failure to ustekinumab treatment were assessed in univariable and multivariable analyses, at both 14 and 52 weeks. Besides considering the whole cohort of patients, in order to mitigate the possible bias related to the use of the sole PGA, we also performed alternative analyses pooling together patients with a PGA 2-3 and a PGA 0-1 with either raised CRP or FC (biochemical disease activity). We also performed a separate analysis for patients who had been previously exposed to vedolizumab. All results are reported in Tables S2–S4. Of note, considering the whole sample, at multivariable analysis, high baseline HBI (OR 1.12; 95% CI 1.01-1.24; $P = 0.024$), Montreal B2 (OR 1.47; 95% CI 0.33-6.47; $P = 0.608$), and Montreal B3 (OR 3.49; 95% CI 1.01-12.1; $P = 0.05$) were associated with treatment failure at 14 weeks. At 52 weeks, current smoking, baseline HBI or PGA, and use of steroids were found to be correlated, in almost all subanalyses (Tables 3 and 4), including vedolizumab-experienced patients, with treatment failure. In the previously published data regarding our vedolizumab cohort, no predictors of treatment failure were found, including bridging steroid therapy, concomitant use of immunosuppressors, smoking status, disease duration, and baseline CRP and FC.[11]

3.4 | Safety outcomes

Overall, 74 adverse events occurred during the study period in 69 patients (24.5%) treated with ustekinumab, of which 26 were labelled as serious (i.e., life threatening or requiring hospital admission; Table S3). Of note, among serious adverse events, six neoplastic disorders and one obstetric complication (premature rupture of membranes) were recorded. In contrast to what we reported in the vedolizumab

TABLE 1 Demographic and other relevant characteristics of patients with Crohn's disease treated with ustekinumab

	Ustekinumab cohort	Vedolizumab cohort
N. patients	282	118
Age (years), mean ± SD	40 ± 15	41 ± 16
F:M ratio	1.7:1	1.8:1
Start weight (kg), mean ± SD	71 ± 15	NA
Duration of disease (years), mean ± SD	12 ± 9	9 ± 8
Disease phenotype, n (%)	A1, 61 (21.6)	A1, 34 (32.4)
	A2, 162 (57.4)	A2, 57 (54.3)
	A3, 59 (20.9)	A3, 14 (13.3)
	L1, 63 (22.3)	L1, 14 (13.3)
	L2, 69 (24.5)	L2, 32 (30.5)
	L3, 150 (53.2)	L3, 59 (56.2)
	B1, 95 (33.7)	B1, 40 (38.1)
	B2, 90 (31.9)	B2, 38 (36.2)
	B3, 97 (34.4)	B3, 27 (25.7)
	Perianal disease, 86 (30.5)	Perianal disease, 14 (13.3)
Smoking status, n (%)		
Never smoker	123/238 (51.7)	62/90 (68.9)
Former smoker	62/238 (26.1)	10/90 (11.1)
Active smoker	53/238 (22.2)	18/90 (20.0)
Missing datum, n (%)	44/282 (15.6)	28/118 (23.7)
Previous bowel resection, n (%)	131 (46.4)	27 (23.5)
At least one comorbidity, n (%)	222 (78.7)	94 (79.7)
Extra-intestinal manifestations, n (%)	55 (19.5)	22 (18.6)
Psoriasis, n (%)	31 (11.0)	8 (6.8)
Any prior biologic drug exposure, n (%)	275 (97.5)	115 (97.4)
At least two previous biologics, n (%)	172 (61.0)	70 (59.3)
Previous infliximab, n (%)	202 (71.6)	102 (88.7)
Previous adalimumab, n (%)	224 (79.4)	79 (67.0)
Previous vedolizumab, n (%)	80 (28.4)	–
Concomitant immunosuppressive therapy, n (%)	93 (32.9)	66 (55.9)
Concomitant steroid therapy, n (%)	100 (35.5)	43 (36.4)

For the vedolizumab cohort, disease phenotype according to the Montreal classification was not specified in 12/118 (10.2%) cases.

Abbreviation: SD, standard deviation.

cohort,[11] most patients reporting an adverse event were on ustekinumab monotherapy (81.1%; 28.6% in the vedolizumab cohort), while a minority was also taking an immunosuppressant or systemic steroid (18.9%; 71.4% in the vedolizumab cohort). The cumulative incidence of severe adverse events and infectious diseases were 8.3 per 100 person-year and 17.2 per 100 person-years, respectively.

3.5 | Propensity score-matched analysis

For the purposes of this analysis, we compared the ustekinumab cohort with a cohort of ustekinumab-naïve CD patients who were treated with vedolizumab after failing any anti-TNFα agent and whose characteristics have already been described.[11] Following the criteria established for this analysis, we included 275/282 patients (97.5%; mean age 41 ± 14 years, F:M ratio 1.7:1) from the ustekinumab cohort and 118 (Table 1) from the vedolizumab cohort. The propensity score balance plot (before and after adjustment for potential confounders) is reported in Figure S2, while the SMD before and after matching for the variables included is reported in Figure S3. The overlap plot is shown in Figure S4. Neither curve indicates too much probability mass near 0 or 1, and the two estimated densities have most of their respective masses in regions in which they overlap with each other. Thus, there is no evidence that the overlap assumption is violated.

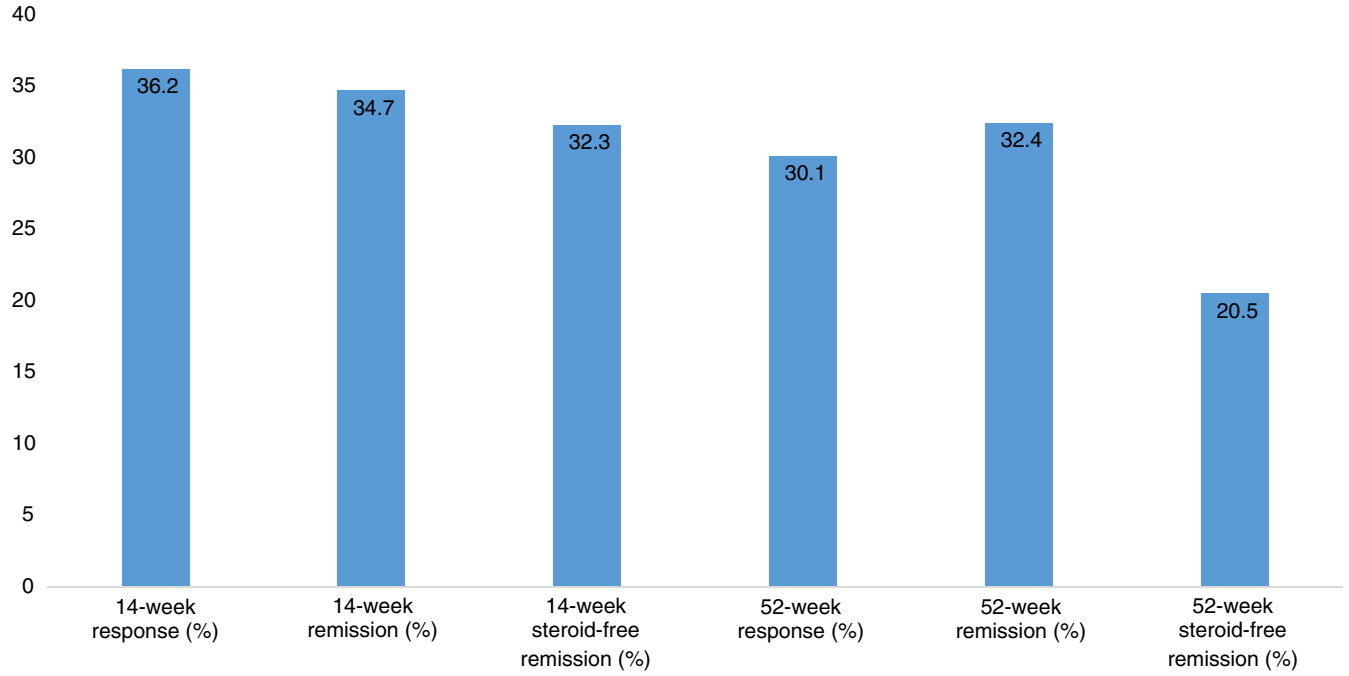

FIGURE 1 Rates of 14- and 52-week clinical response or remission and steroid-free response or remission (expressed as %) according to the physician global assessment [Colour figure can be viewed at wileyonlinelibrary.com

TABLE 2 Patients who discontinued ustekinumab and related reasons for discontinuation or loss of response during the study period

Discontinuation ≤14 weeks, n (%)	23/282 (8.2)
Ineffective (primary non-responder)	15
Adverse effect	6
Need for intestinal surgery	1
Non-adherence	1
Discontinuation >14 and ≤52 weeks, n (%)	49/259 (18.9)
Loss of response	32
Adverse effect	6
Need for intestinal surgery	8
Pregnancy	1
Non-adherence	2
Discontinuation >52 weeks, n (%)	29/210 (13.8)
Loss of response	15
Achieved remission	2
Need for intestinal surgery	4
Need for non-intestinal surgery	2
Infection	2
Pregnancy	3
Non-adherence	1
Total discontinuations	101/282 (35.8%)

Besides the variables chosen *a priori*, the analysis was also matched with baseline HBI and CD behaviour, being significantly associated with the outcome. At 14 weeks, patients treated with ustekinumab were 38% (95% CI 25%-50%; $P < 0.001$) more likely to achieve a PGA 0-1 score (i.e., clinical remission). Instead, at 52 weeks, patients treated with ustekinumab were 9% (95% CI −15% to 33%; $P = 0.462$) more likely to achieve a PGA 0-1 score.

Sensitivity analysis, only including variables that were statistically significantly associated with primary outcome at logistic regression (namely baseline HBI, age greater than 65, and number of previous anti-TNFα therapies) show that patients treated with ustekinumab were 23% (95% CI 8%-38%; $P = 0.003$) more likely to achieve a PGA 0-1 score at 3 months.

The sensitivity IPW analysis gave similar results at both 14 weeks (33%; 95% CI 17%-48%; $P < 0.001$) and 52 weeks (19%; 95% CI −3% to 42%; $P = 0.093$).

In Table S4, we reported data of the other exploratory outcomes, showing a significant increase in the 14-week steroid-free clinical remission and in the 52-week treatment persistence in patients treated with ustekinumab (after matching).

4 | DISCUSSION

According to our real-life, multicentre study involving eight IBD centres from the UK, ustekinumab proved effective in inducing and maintaining remission in a substantial proportion of CD patients who had, in most cases, failed previous biological therapies and had a long disease duration. Important predictors of treatment failure were found at multivariable analysis, including CD behaviour, smoking status, and use of steroids. We have also performed the largest propensity score-matched analysis so far, comparing ustekinumab and vedolizumab, showing that, at induction,

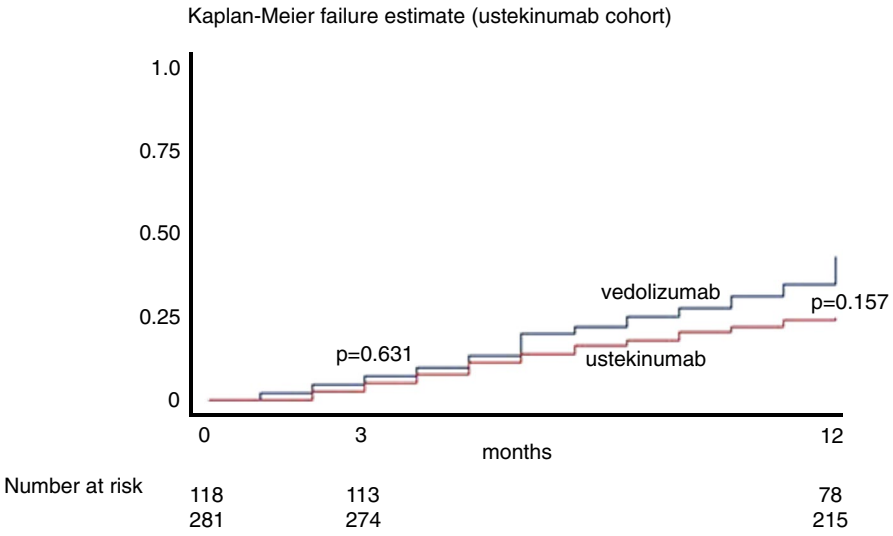

FIGURE 2 Kaplan-Meier ustekinumab vs vedolizumab failure estimate. Of note, no significant difference was noticed between the two drugs at both 3- and 12-month follow-up [Colour figure can be viewed at wileyonlinelibrary.com

TABLE 3 Univariable and multivariable analysis of baseline characteristics in relation to the 52-week clinical outcome in the whole sample vs baseline PGA 2-3 in the ustekinumab cohort

	Whole sample, OR (95% CI), *P*-value	Whole sample, OR (95% CI), *P*-value	Baseline PGA 2-3, OR (95% CI), *P*-value	Baseline PGA 2-3, OR (95% CI), *P*-value
	Univariable analysis	Multivariable analysis	Univariable analysis	Multivariable analysis
Age	0.99 (0.98-1.01) $P = 0.84$	–	0.99 (0.97-1.02) $P = 0.88$	–
Female sex	1.34 (0.77-2.33) $P = 0.28$	–	1.30 (0.62-2.71) $P = 0.47$	–
Disease duration	0.98 (0.96-1.01) $P = 0.46$	–	0.98 (0.94-1.02) $P = 0.37$	–
Previous smoker	1.53 (0.77-3.03) $P = 0.22$	–	0.86 (0.34-2.16) $P = 0.75$	–
Current smoker	2.72 (1.36-5.42) $P = 0.004$	2.48 (1.13-5.44) $P = 0.02$	2.00 (0.81-4.96) $P = 0.13$	–
Baseline CRP	1.01 (0.99-1.02) $P = 0.10$	–	1.00 (0.99-1.02) $P = 0.27$	–
Baseline HBI	1.21 (1.12-1.31) $P < 0.001$	NA[a]	1.13 (1.02-1.24) $P = 0.01$	1.13 (1.02-1.25) $P = 0.009$
Baseline PGA	2.52 (1.72-3.70) $P < 0.001$	2.4 (1.55-3.69) $P < 0.001$	–	–
Increased CRP or FC	0.96 (0.52-1.77) $P = 0.90$	–	0.84 (0.36-194) $P = 0.68$	–
Montreal L2	0.84 (0.39-1.82) $P = 0.67$	–	1.14 (0.39-3.27) $P = 0.80$	–
Montreal L3	1.18 (0.61-2.25) $P = 0.61$	–	0.74 (0.32-1.73) $P = 0.49$	–
Montreal B2	0.64 (0.33-1.25) $P = 0.19$	–	1.02 (0.43-2.43) $P = 0.95$	–
Montreal B3	1.12 (0.60-2.06) $P = 0.71$	–	1.31(0.58-2.91) $P = 0.50$	–
Perianal disease	1.53 (0.88-2.68) $P = 0.13$	–	1.5 (0.72-3.11) $P = 0.27$	–
Previous bowel resection	1.36 (0.80-2.29) $P = 0.24$	–	1.22 (0.62-2.41) $P = 0.55$	–
Previous infliximab	1.06 (0.60-1.89) $P = 0.82$	–	0.97 (0.45-2.05) $P = 0.93$	–
Previous adalimumab	2.06 (1.00-4.25) $P = 0.04$	1.92 (0.82-4.52) p=0.134	1.39 (0.54-3.58) $P = 0.48$	–
Previous vedolizumab	1.24 (0.70-2.19) $P = 0.45$	–	0.72 (0.34-1.49) $P = 0.38$	–
Concomitant immunosuppressant	0.83 (0.48-1.46) $P = 0.53$	–	1.05 (0.51-2.15) $P = 0.88$	–
Concomitant steroids	1.90 (1.11-3.25) $P = 0.01$	2.42 (1.26-4.65) $P = 0.008$	2.46 (1.21-5.00) $P = 0.01$	2.27 (1.03-5.00) $P = 0.04$

Abbreviations: CI, confidence interval; CRP, C-reactive protein; FC, faecal calprotectin; HBI, Harvey-Bradshaw index; NA, not assessable; OR, odds ratio; PGA, physician global assessment.

[a]Not assessable because HBI and PGA are collinear.

remission was more likely to be achieved in those treated with ustekinumab, while no statistically significant difference was noticed at one-year follow-up.

Since the introduction of ustekinumab for the treatment of CD, a number of real-life studies[17-23] have shown effectiveness for either inducing or inducing and maintaining remission in line with that

TABLE 4 Univariable and multivariable analysis of baseline characteristics in relation to the 52-week clinical outcome in PGA 2-3 or 0-1 with raised inflammatory markers and in vedolizumab-experienced patients in the ustekinumab cohort

	Baseline PGA 2-3 or 0-1 with ↑ CRP or FC, OR (95% CI), *P*-value	Baseline PGA 2-3 or 0-1 with ↑ CRP or FC, OR (95% CI), *P*-value	Vedolizumab experienced, OR (95% CI), *P*-value	Vedolizumab experienced, OR (95% CI), *P*-value
	Univariable analysis	Multivariable analysis	Univariable analysis	Multivariable analysis
Age	1.0 (0.98-1.01) $P = 0.87$	–	1.01 (0.98-1.04) $P = 0.40$	–
Female sex	1.41 (0.79-2.51) $P = 0.24$	–	1.66 (0.61-4.47) $P = 0.31$	–
Disease duration	0.99 (0.96-1.02) $P = 0.64$	–	0.96 (0.90-1.02) $P = 0.25$	–
Previous smoker	1.38 (0.67-2.84) $P = 0.37$	–	4.66 (1.13-19.1) $P = 0.03$	3.73 (0.42-33.5) $P = 0.24$
Current smoker	2.64 (1.28-5.43) $P = 0.008$	2.32 (1.00-5.37) $P = 0.05$	5.0 (1.37-18.1) $P = 0.01$	8.09 (0.78-8.3) $P = 0.07$
Baseline CRP	1.0 (0.99-1.02) $P = 0.16$	–	1.0 (0.97-1.03) $P = 0.86$	–
Baseline HBI	1.21 (1.12-1.32) $P < 0.001$	1.21 (1.10-1.32) $P < 0.001$	1.28 (1.07-1.53) $P = 0.006$	1.70 (1.16-2.51) $P = 0.007$
Baseline PGA	–	–	1.29 (0.62-2.7) $P = 0.48$	–
Increased CRP or FC	–	–	1.41 (0.46-4.27) $P = 0.53$	–
Montreal L2	1.0 (0.44-2.25) $P = 1.0$	–	2.18 (0.34-13.75) $P = 0.40$	–
Montreal L3	1.03 (0.53-2.01) $P = 0.91$	–	2.57 (0.49-13.5) $P = 0.26$	–
Montreal B2	0.79 (0.39-1.60) $P = 0.52$	–	0.56 (0.15-2.08) $P = 0.39$	–
Montreal B3	1.34 (0.70-2.58) $P = 0.37$	–	0.58 (0.18-1.82) $P = 0.35$	–
Perianal disease	1.64 (0.90-2.96) $P = 0.10$	–	1.10 (0.41-2.96) $P = 0.84$	–
Previous bowel resection	1.39 (0.80-2.41) $P = 0.23$	–	0.80 (0.28-2.22) $P = 0.67$	–
Previous infliximab	1.12 (0.62-2.04) $P = 0.69$	–	1.12 (0.30-4.17) $P = 0.85$	–
Previous adalimumab	1.87 (0.86-4.04) $P = 0.10$	–	1.34 (0.31-5.7) $P = 0.69$	–
Previous vedolizumab	1.25 (0.68-2.29) $P = 0.45$	–	–	–
Concomitant immunosuppressant	0.77 (0.43-1.39) $P = 0.39$	–	0.32 (0.10-0.99) $P = 0.04$	0.2 (0.02-1.81) $P = 0.15$
Concomitant steroids	2.02 (1.15-3.56) $P = 0.01$	1.99 (0.99-4.00) $P = 0.05$	3.41 (1.25-9.28) $P = 0.01$	21.1 (1.7-26.5) $P = 0.01$

Abbreviations: CI, confidence interval; CRP, C-reactive protein; FC, faecal calprotectin; N/A, not assessable; OR, odds ratio; PGA, physician global assessment.

reported in the UNITI-1 and -2 trials.[13] We have included a large number of patients who had, in most cases, a long history of CD, who failed prior immunosuppressive or biological therapies, and who suffered from multimorbidity (i.e., the co-occurrence of at least 2 chronic conditions). Despite this, we found a high rate of clinical response or remission at both 14 weeks (70.9%) and 52 weeks (62.5%), and this finding was corroborated by concomitant biochemical remission (Table S1). However, most patients were immediately escalated to an 8-week schedule, as judged by the treating physician. A meta-analysis including six real-world studies including a total of 578 CD patients, most of whom (97.7%) were anti-TNF experienced, described a pooled clinical response rate of 60%, 62%, 49% at 12, 24 and 52 weeks, respectively, and a pooled remission rate of 39% at 24 weeks.[17] To note, some real-life studies have only reported data regarding the induction phase,[19,22] while data regarding long-term effectiveness are still scant.[18,20,21]

Interesting variables that may be useful for predicting failure to ustekinumab have emerged from our analysis. Of note, considering the whole sample of 282 patients, at multivariable analysis, a high baseline HBI, Montreal B2 (stricturing behaviour), and Montreal B3 (penetrating behaviour) were associated with treatment failure at 14 weeks, while current smoking, baseline HBI or PGA, and use of steroids were found to be correlated, in almost all sub-analyses, with treatment failure at 52 weeks. Little is known regarding specific predictors of failure to ustekinumab. According to a study including 123 CD patients, HBI and perianal disease were associated with failure to achieve remission after ustekinumab dose intensification.[33] Other putative factors have been called into question in different study types. For example, in the registrational UNITI-1 trial, younger age was associated with clinical response,[13] while older age was associated with poor response in a real-world study.[34] Disease extension, in particular ileal or ileocolonic localisations, has been associated with both good[13] and poor[20] clinical responses. Regarding disease behaviour, both stricturing and penetrating behaviours were associated with poor response.[21,35,36] Summarising the available evidence, we conclude that more data are needed for drawing firm conclusions, as many other predictive factors still need to be studied.[37]

The safety profile seems to be in line with the published literature. According to the aforementioned meta-analysis, 134 adverse events were reported in total, of which 19 were labelled as serious.[17] In our study, we found a cumulative incidence of severe

adverse events and infectious diseases of 8.3 per 100 person-years and 17.2 per 100 person-years, respectively. The rate of infectious diseases was higher than that reported in the vedolizumab cohort (11.9 per 100 person-years).[11] Also, most of the reported serious adverse events were infectious events, mostly directly related to CD (abscesses, abdominal/perianal sepsis), but six neoplastic disorders (one melanoma leading to death and four with poor prognosis/advanced oncological disease) and one obstetric complication (premature rupture of membranes) were recorded. Indeed, the risk of developing (or relapsing) neoplasia on biological therapy is an important issue that must be continuously monitored, and most data regarding ustekinumab derives from the experience of patients treated for psoriasis. In fact, in nested case-control analyses of roughly 12 000 patients with psoriasis, the use of ustekinumab did not increase the risk of developing neoplasia, contrary to the use of anti-TNF drugs.[38] A case report of a CD patient, also having dysplastic nevus syndrome, and developing melanoma while treated with ustekinumab has been reported.[39] The authors hypothesised that IL12 blockade may theoretically promote photocarcinogenesis and hence ustekinumab should be avoided in patients at high risk of developing melanoma. Pregnancy outcomes are another important research area for all patients with IBD. According to a recently published retrospective study comparing vedolizumab and ustekinumab, the authors found a similar rate of prematurity, spontaneous abortion, congenital malformations, and maternal complications between the two groups.[40]

Another pressing need in the research IBD agenda is the correct positioning of the available drugs. In the absence of head-to-head trials, the propensity score-matched analysis can be considered as a useful tool for comparing different treatments after correction for potential confounding factors. We found ustekinumab to be superior in inducing remission, while no difference was noticed between ustekinumab and vedolizumab at 52 weeks. This finding is in contrast with three previously published propensity score-matched analyses including 45 (Liverpool study),[24] 85 and 224 (two French studies),[26,41] and 107 (Dutch study)[25] ustekinumab-treated CD patients, respectively, in which they found (although with some important differences), ustekinumab to be superior in maintaining remission at 1-year follow-up. There might be a number of reasons for this apparent discrepancy, and one reason is that propensity score-matched analysis may underperform when the number of included patients is low, increasing the risk of overfitting. In addition, in all cases, the primary endpoint was steroid-free remission, even if other sub-analyses were also included. For example, in one of the French studies,[26] there was no significant difference between ustekinumab and vedolizumab with regard to steroid-free clinical remission (44.7% vs 34.0%; OR = 1.57), while ustekinumab was superior in patients with ileal localisation (OR = 3.49) and with penetrating disease (OR = 6.58). Second, we have corrected our analysis for important factors that were not considered in the previous studies, namely multimorbidity (i.e., 2 or more concomitant chronic diseases), the presence of extra-intestinal manifestations or psoriasis, and the need for steroids. Indeed, all these factors are important clinical characteristics which drive the choice of treatment and hence must be considered as confounders. Additionally, in order to strengthen our results and to avoid overfitting, we have also run a separate analysis including variables which turned out to be significantly associated with the main outcome at multivariable analysis, and a similar result was noticed.

Summarising our results, we could hypothesise the use of either vedolizumab or ustekinumab in different settings, which must take into account patient, disease, and drug-related variables. Our findings confirm that ustekinumab allows a more rapid achievement of clinical remission compared to vedolizumab, which may take a few more weeks for reaching this goal, as is already known.[42] However, at 52 weeks, both drugs are effective in maintaining remission, although some predictors of treatment failure were found for ustekinumab, and these should be taken into account when choosing therapy. According to our data, while vedolizumab should be first considered in older patients with multimorbidity, and maybe with other negative prognostic factors, ustekinumab may be preferred in younger patients with psoriasis and in patients whose primary goal is to achieve remission more rapidly.

Indeed, our study has some limitations that must be considered, and our results should be carefully interpreted on the basis of the following considerations. The retrospective nature has inherent limitations, as indeed the lack of standard approach for CRP and FC detection methods. The PGA is another limitation, as it is open to subjectivity with interpretation, as also the lack of endoscopic assessment which has impeded the analysis of an important endpoint, i.e., endoscopic and histological remission. Finally, adverse events between the ustekinumab and the vedolizumab cohorts could not be compared more in depth because a more rigorous, clinical trial-style, approach was used for ustekinumab safety reporting, and most patients had been previously exposed for long time to other biologics and/or immunosuppressants. Nonetheless, we have here reported data from the largest propensity score-matched analysis looking at vedolizumab- vs ustekinumab-treated CD patients, reflecting day-by-day clinical practice outside a controlled, randomised head-to-head trial. Also, we tried to overcome the aforementioned limitations by doing additional analyses corrected for baseline PGA and biochemical inflammatory markers, and the propensity score-matched analysis included the largest possible number of confounding factors.

To conclude, ustekinumab proved effective in a real-life setting, although early treatment failure was associated with penetrating and stricturing disease behaviour, and high baseline HBI, while smoking, use of steroids, and high baseline HBI/PGA were associated with long-term treatment failure. While ustekinumab was more effective in inducing remission, no difference was noticed between vedolizumab and ustekinumab at one-year follow-up. Further studies addressing safety issues are needed.

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AUTHORSHIP

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DATA AVAILABILITY STATEMENT

Data are not publicly available as there is no patient consent for this. Summary data are available on request.

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SUPPORTING INFORMATION

Additional supporting information will be found online in the Supporting Information section.

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APPENDIX 1

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