REPORT SYNOPSIS

Project title:

A multi-centre observational study to describe the impact of vedolizumab on concomitant prescribing and quality of life in patients with ulcerative colitis and Crohn's disease in the UK and Ireland: OCTAVO.

Protocol: Sponsor Study Number MACS-2018-102427

Name of sponsor: Takeda

Participating centres and clinicians:

Six United Kingdom (UK) centres (Bristol Royal Infirmary [Bristol], Norfolk & Norwich University Hospital [Norfolk], Royal Derby Hospital [Derbyshire], St Marks Hospital [London], The Royal London Hospital [London], Western General Hospital [Somerset]) offering biologic naïve patients the choice of first-line treatment with either anti-tumour necrosis factor (anti-TNF) or vedolizumab (VDZ).

Number of patients (analysed):

Cohort 1: 112 patients with ulcerative colitis (56 initiated on biologic therapy with VDZ and 56 initiated on biologic therapy with anti-TNF).

Cohort 2: 61 patients (22 with Crohn's disease [CD] and 39 with ulcerative colitis [UC]).

Study period:

Cohort 1
Data were collected retrospectively for a 12-month period from the date of initiation on VDZ or anti-TNF. The overall 12-month study period was further split into an induction phase (week 0 to week 14) and a maintenance phase (week 14 to month 12).

Cohort 2
Baseline patient characteristics were collected retrospectively and patient reported outcomes (PROs) measured prospectively at pre-defined time-points during the 12-months post-initiation of VDZ (baseline, week 14, month 6 and month 12).

Project objectives:

Cohort 1

Primary objective
To evaluate changes in corticosteroid prescription during the first 12 months of first-line biologic therapy in patients with ulcerative colitis (UC) initiated on VDZ compared with patients initiated on an anti-TNF.

Secondary objectives

- To describe VDZ or anti-TNF escalation, de-escalation, switching or discontinuation during the first 12 months of first-line biologic therapy in patients with UC initiated on VDZ compared with patients initiated on anti-TNF.
- To evaluate prescription of immunomodulators and antibiotics during the first 12 months of first-line biologic therapy in patients with UC initiated on VDZ compared with patients initiated on anti-TNF.
- To describe the tolerability of VDZ compared with anti-TNF therapy.

- To describe the demographic and clinical characteristics of patients (duration of disease, inflammatory bowel disease [IBD]-related treatment history [all aminosalicylate {ASA}, corticosteroid, immunomodulator and biologic treatments prescribed in the 2 years prior to the index event] and baseline Montreal disease extent).

Cohort 2

Primary objective

To evaluate healthcare-related quality of life (HRQoL) in terms of IBD disease symptoms and work productivity and activity impairment during the first 12 months of VDZ therapy (initiated at any point in the treatment pathway) in patients with UC or CD.

Secondary objectives

- To describe the demographic and clinical characteristics of patients (demographics, type of IBD [UC or CD], duration of disease).
- To describe the impact of VDZ on different aspects of HRQoL during the first 12 months following treatment initiation.

Eligibility criteria:

Cohort 1

To be included in Cohort 1, patients were required to meet the following criteria:

Inclusion criteria:

- Have a diagnosis of UC.
- Be biologic naïve at the time they were initiated on first-line biologic treatment with VDZ or an anti-TNF as an outpatient.
- Be aged ≥18 years at initiation of first-line biologic treatment with VDZ or anti-TNF.
- Have data available for matching criteria (age, gender, baseline disease extent and corticosteroid use on the day of initiation of first-line biologic treatment with VDZ or an anti-TNF).
- Have at least 12 months of follow-up data after initiation of first-line biologic treatment with VDZ or an anti-TNF.

Exclusion criteria:

- Patients with primary fistulising disease.
- Patients with acute severe disease.
- Patients who were corticosteroid resistant or refractory at the time of initiation of first-line biologic treatment with VDZ or an anti-TNF.
- Patients whose hospital medical records were unavailable for review.
- Patients who declined consent for their primary and secondary care medical records to be accessed for the purposes of this study (except for deceased patients whose data were collected by members of the National Health Service [NHS] direct care team to preserve patient confidentiality).
- Patients enrolled in an interventional clinical trial of an investigational medicinal product during the study period.

Cohort 2

To be included in Cohort 2, patients were required to meet the following criteria:

Inclusion criteria:

- Have a diagnosis of CD or UC.
- Have initiated treatment with VDZ as an outpatient for the first time at the point of enrolment into the study.
- Be aged ≥18 years at initiation of VDZ.

Exclusion criteria:

- Patients with primary fistulising disease.
- Patients with acute severe disease.
- Patients whose hospital medical records were unavailable for review.
- Patients who declined consent for their hospital medical records to be accessed for the purposes of this study.
- Patients enrolled in an interventional clinical trial of an investigational medicinal product during the study period.
- Patients unwilling or unable to complete web-based PRO questionnaires.

Project design and methodology:

This United Kingdom (UK)-based, multi-centre, observational study was designed and conducted according to the requirements of the European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP) and International Society for Pharmacoepidemiology (ISPE) guidance[1,2], as appropriate.

Cohort 1

Data were collected between 31st July 2018 and 15th November 2019 by OPEN VIE or the NHS research teams at the centres via an electronic data capture (EDC) system using electronic data collection forms. Primary care prescription data for corticosteroid and antibiotic use were requested from the patients' general practitioner and anonymised data were subsequently entered into the electronic case report form (eCRF) by OPEN VIE. Patients were identified in all study records by a unique study code to link multiple study records for each participant (if applicable) and preserve patient confidentiality.

CRF data were managed using the Food and Drug Administration (FDA)-validated MACRO™ data management system. Data collection was completed by trained staff with source data verification performed on 10% of CRFs at each study centre to ensure accuracy and data quality; all clinical data submitted were checked for eligibility, completeness, and accuracy.

Cohort 2

Data collection occurred between 31st July 2018 and 30th June 2020. Clinical data from secondary care medical records were collected by OPEN VIE or the NHS direct care team at the centres via an EDC system using eCRFs. PRO data, including HRQoL data, and data on patient experiences and preferences when choosing IBD treatment were collected directly from patients via a bespoke online survey, with the following questionnaires administered at baseline, and at the date occurring 14 weeks, 6 months and 12 months post-initiation of VDZ:

- Short Inflammatory Bowel Disease Questionnaire (SIBDQ);
- IBD-Control-8 questionnaire (IBD-C-8);
- Work Productivity and Activity Impairment questionnaires specific to Crohn's disease and ulcerative colitis (WPAI-CD/UC);
- Rating Form of IBD Patient Concerns (RFIPC).

In addition, a bespoke questionnaire was administered at baseline that addressed the patient's preferred and actual level of involvement in the decision-making process when choosing their IBD treatment.

Data analysis methodology:

Data from all centres were pooled for analyses which were performed by OPEN VIE. Distributions and descriptive statistics of central tendency (medians and arithmetic means) and dispersion (standard deviation [SD], interquartile range [IQR]) were presented for quantitative variables as applicable. Categorical variables were described with frequencies and percentages.

Cohort 1 analyses

Between-group differences for quantitative variables were compared using unpaired t-tests or Wilcoxon rank-sum tests. Between-group differences for categorical variables were compared using the Chi-square test. Within-group differences for quantitative variables were compared using a paired sample t-test, the Wilcoxon matched-pairs signed-ranks test, or a repeated-measures analysis of variance test. Within-group differences for categorical variables were compared by the McNemar test. Estimates of proportions and means of distributions are presented with 95% confidence intervals (CIs), as appropriate. Statistical analyses were carried out using Stata 14.2 (StataCorp LLC) and Microsoft excel.

Where data were missing from the original medical record, the affected analyses were conducted using only the results of those patients with data available and the number included in each analysis (i.e. the denominator) is stated. Where no denominator is reported in the results, the denominator is the total number of patients in that cohort (i.e. n=56).

The following assumptions were made:

- The induction period is defined as the time-period beginning at initiation of VDZ/anti-TNF (week 0) until just before the start of week 14 (i.e. week 13 + 6 days).
    - All results relating to the induction period are described as "week 0 to week 14" in the relevant sections of this report.
- The maintenance period is defined as the time-period beginning at the start of week 14 until the end of month 12.
    - All results relating to the maintenance period are described as "week 14 to month 12" in the relevant sections of this report.
- A patient was said to have started a new course of treatment if there was a gap of at least 7 days between stopping a medication and starting a new one, unless the patient switched to a different medication (in which case it would be automatically classified as a new treatment course, even if the patients started the new medication less than 7 days after ending the previous medication).
- If the end date of a patient's medication was not recorded, it was derived from the days' supply.
- If corticosteroids resumed within 7 days of the previous end date, this was not considered a new course. Where corticosteroid start or stop dates were not available or could not be derived, the number of courses was not derived.
- Where data on the same course of corticosteroids were available from hospital and primary care records, data from hospital records were used in the analyses.
- For treatments in the 2-year period prior to index event, summary statistics were produced for each type of drug (ASA, corticosteroids, immunomodulators, biologics) rather than for each individual medication.
- The dose regimen is described at baseline, week 14, and months 6, 9 and 12.
  The following logic was used to account for missing end date information when evaluating whether a patient was receiving antibiotics during the induction and maintenance periods: if a patient started an antibiotic course between week 14 and month 12 but did not have an end date

recorded, it was assumed that they received an antibiotic during that time-period. If a patient started an antibiotic course between week 0 and week 14 and did not have an end date recorded, it was assumed they were receiving antibiotics between week 0 and week 14 but their antibiotic status was classified as 'not known' for week 14 to month 12.

Cohort 2 analyses

Total scores and relevant sub-scores were calculated for each patient in accordance with the published manuals for each of the study questionnaires and the study statistical analysis plan.

Scores derived from each measure were summarised using descriptive statistics at baseline, and at week 14, month 6 and month 12, respectively. Total scores and relevant sub-scores and responses to individual questionnaire items were described separately for patients with CD and UC.

For the SIBDQ, IBD-C-8, WPAI-CD/UC and RFIPC questionnaires, respectively, within-person change in scores between baseline and follow-up time points were also calculated for each patient.

A repeated-measures analysis of variance (ANOVA) test was used to test for statistically significant effects of time on changes in questionnaire scores post initiation of VDZ. Where a violation of Mauchly's test of sphericity was observed, appropriate corrections were applied (e.g. for epsilon >0.75, the Huynh-Feldt correction was applied and for epsilon <0.75, the Greenhouse-Geisser correction was applied).

In order to ensure that any changes in patient responses for SIBDQ, IBD-C-8, WPAI-CD/UC and RFIPC observed from baseline at post-index time-points were related to use of VDZ and not another treatment, patients who had discontinued VDZ prior to the relevant post-index time-point were excluded from analyses.

Summary of key findings:

Cohort 1

Matching and previous therapies

- A total of 56 patients initiated on VDZ were matched with 56 patients initiated on anti-TNF based on age (median [IQR] age at index 47.0 [31.0 to 60.8] and 41.0 [32.0 to 61.5] years, respectively), gender (55% of each group were male), corticosteroid use (55% of each group were using corticosteroids at index) and extent of disease (9%, 52% and 39% of each group had E1, E2 and E3 disease extent, respectively, at baseline according to Montreal classification).
- In the 2-year pre-index period, most patients initiated on VDZ and anti-TNF were prescribed at least one course of corticosteroids (84% and 95%, respectively), immunomodulators (77% and 79%, respectively) and ASAs (89% and 91%, respectively).

Corticosteroids prescribed during the study period

- The proportion of patients prescribed at least one corticosteroid during the week 14 to month 12 maintenance phase was significantly lower for patients initiated on VDZ (37% [95% CI 23%–50%; n=19/52]) compared with those initiated on anti-TNF (57% [95% CI 43%–70%; n=30/53]; P=0.039). There were no statistically significant differences in the proportions of patients initiated on VDZ compared with patients initiated on anti-TNF who were prescribed at least one course of corticosteroids between: week 14 and month 6 (VDZ: 26% [95% CI 14%–38%; n=13/50]; anti-TNF: 43% [95% CI 30%–57%; n=22/51]; P=0.070); between month 6 and month 9 (VDZ: 20% [95% CI 9%–32%; n=10/49]; anti-TNF: 35% [95% CI 22%–48%; n=18/51]; P=0.213); and between month 9

and month 12 (VDZ: 24% [95% CI 12%–37%; n=12/49]; anti-TNF: 36% [95% CI 23%–49%; n=18/50]; P=0.213).

- Mean (SD) total dose of corticosteroids during the maintenance period (the primary endpoint) was 1658.5 (3392.0) mg for patients initiated on VDZ (n=14) and 1252.9 (2722.6) mg for patients initiated on anti-TNF (n=15; P=0.305); no statistically significant difference in corticosteroid dose was observed for any time period assessed during the overall 12-month study period.
- A similar proportion of patients initiated on VDZ and anti-TNF were corticosteroid-free at 12 months (82% [n=40/49] vs 79% [n=37/47]; P=0.721) or were corticosteroid dependant at any point during the 12-month study period (34% [n=16/47] vs 41% [n=15/37]; P=0.540).
- Prednisolone was the most commonly prescribed corticosteroid in patients initiated on VDZ and anti-TNF (78% [n=28/36] and 83% [n=34/41], respectively), and was most commonly prescribed due to disease flare (47% [n=17/36] and 60% [n=28/47], respectively).

Immunomodulators prescribed during the study period

- During the overall study period, 38% (95% CI 25%–50%; n=21) of patients initiated on VDZ and 30% (95% CI 18%–42%; n=17) of patients initiated on anti-TNF were prescribed immunomodulators (P=0.425). The proportion of patients receiving immunomodulators did not differ significantly between patients initiated on VDZ and anti-TNF during any post-initiation time periods (week 0 to week 14: 34% [95% CI 22%–46%; n=19] and 25% [95% CI 14%–36%; n=14], respectively [P=0.300]; week 14 to month 12: 34% [95% CI 22%–46%; n=19] and 30% [95% CI 18%–42%; n=17], respectively [P=0.686]).
- Immunomodulators were most frequently prescribed due to ongoing treatment in patients initiated on VDZ (65% [n=17/26]) and disease flare in patients initiated on anti-TNF (33% [n=8/24]).

Antibiotics prescribed during the study period

- During the overall study period, 18% (95% CI 8%–28%; n=10/56) of patients initiated on VDZ were prescribed antibiotics compared with 25% (95% CI 14%–36%; n=14/56) of patients initiated on anti-TNF (P=0.357). The proportion of patients prescribed antibiotics was also similar in patients initiated on VDZ and anti-TNF between week 0 and week 14 (8% [95% CI 0%–15%; n=4/53] and 7% [95% CI 0%–14%; n=4/54], respectively; P=0.978) and between week 14 and month 12 (16% [95% CI 7%–26%; n=9/55] and 20% [95% CI 9%–30%; n=11/56], respectively; P=0.202).
- Urinary tract infection was the most common reason for antibiotic prescription (33% [n=5/15] for patients initiated on VDZ and 31% [n=5/16] for patients initiated on anti-TNF).

Changes in biologic treatment during the study period

- Significantly fewer patients initiated on VDZ switched or permanently discontinued first-line biologic therapy during the overall 12-month study period compared with patients initiated on anti-TNF (13% [n=7] and 45% [n=25], respectively; P<0.001). Between week 0 and week 14, 4% (n=2) patients initiated on VDZ and 9% (n=5) of patients initiated on anti-TNF permanently discontinued first-line biologic therapy (P=0.242). Significantly fewer patients initiated on VDZ compared to anti-TNF also switched or discontinued first-line biologic therapy between week 14 and month 12 (9% [n=5] and 36% [n=20], respectively; P<0.001).
- VDZ was the most commonly prescribed biologic therapy (65% [n=11/17]) switched to, for patients initiated on anti-TNF.
- Significantly fewer patients initiated on VDZ had treatment escalations or interval shortenings during the overall 12-month study period compared with patients initiated on anti-TNF (9% [n=5] and 23% [n=13], respectively; P=0.040). Between week 0 and week 14, 5% (n=3) of patients initiated on VDZ and 16% (n=9) patients initiated on anti-TNF (P=0.067) had treatment escalations or interval shortenings while 4% (n=2) patients initiated on VDZ and 11% (n=6) patients initiated

on anti-TNF (P=0.142) had treatment escalations or interval shortenings between week 14 and month 12.

- None of the patients initiated on VDZ had de-escalations during the 12-month study period. Conversely, 4% (n=2) of patients initiated on anti-TNF had de-escalations during the study period, which both occurred between week 14 and month 12.
- When considering all changes between (switches and discontinuations) and within (escalations, de-escalations and interval shortening) treatment during the 12-month study period, 82% (n=46) of patients initiated on VDZ had no change to their treatment whereas 46% (n=26) of patients initiated on anti-TNF had no change.

Treatment-related adverse events (AEs)

- Treatment-related AEs during the 12-month study period were reported in 14% (n=8) of patients initiated on VDZ and 25% (n=20) of patients initiated on anti-TNF; the difference was not significant (P=0.154).
- The total number of treatment-related AEs was similar for patients initiated on VDZ compared with patients initiated on anti-TNF (11 vs 20, respectively; P=0.154).
- Of the 8 patients initiated on VDZ with treatment-related AEs, the most common AEs were infections and infestations (40% [n=4/8] of patients), and general disorders and administration site conditions (20% [n=2/8 of patients). Of the 14 patients initiated on anti-TNF with treatment-related AEs, the most common were skin and subcutaneous tissue disorders (33% [n=6/14] of patients) and infections and infestations (22% [4/14) of patients).

Cohort 2

Patient characteristics

- A total of 61 patients were included in Cohort 2; 36% (n=22) had CD and 64% (n=39) had UC.
- The median (IQR) age at index was 40.5 (34.8 to 52.0) years for patients with CD and 39.0 (30.0 to 56.0) years for patients with UC; 59% (n=13) of patients with CD and 44% (n=17) of patients with UC were female.
- The median (IQR) disease duration at index was 11.5 (5.3 to 17.5) years for patients with CD and 5.6 (1.3 to 17.4) years for patients with UC.

Patient experiences and preferences for IBD treatment

- When asked if they wanted to be involved in choosing their own treatment, 64% (n=14) of patients with CD 'totally agreed' and 23% (n=5) of 'somewhat agreed', while 56% (n=22) of patients with UC 'totally agreed' and 31% (n=12) of patients with UC 'somewhat agreed' that they wanted to be involved in choosing their treatment.
- When asked if they had been involved in choosing their current IBD treatment, 41% (n=9) of patients 'totally agreed' and 55% (n=12) of patients 'somewhat agreed'. For patients with UC, 41% (n=16) of patients 'totally agreed' and 31% (n=12) 'somewhat agreed' that they had been involved in choosing their current IBD treatment.
- When asked if they had been given information on all treatment options available, 33% (n=7/21) of patients with CD 'totally agreed' while 43% (n=9/21) 'somewhat agreed'. For UC, 53% (19/36) patients 'totally agreed' and 19% (n=7/36) 'somewhat agreed' that they had been given information on all treatment options available before a treatment decision was made.
- When asked if they had received enough information on different treatment options 'to help [them] choose the best treatment for me', 32% (n=6/19) of patients with CD 'totally agreed' and 42% (n=8/19) 'somewhat agreed'. For patients with UC, 43% (n=16/37) patients 'totally agreed'

and 22% (n=8/37) 'somewhat agreed' that they had been given enough information on different treatment options to make the best decision.

- When asked which factors were most important to them (when making a decision about treatment), the majority of patients with CD and UC responded that 'managing symptoms in the long term' was most important (68% [n=15] of patients with CD and 59% [n=23] of patients with UC), followed by the 'risk of (serious) side effects' (CD: 18% [n=4]; UC: 26% [n=10]) and a 'quick improvement in symptoms' (CD: 14% [n=3]; UC: 15% [n=6]). None of the respondents said that 'receiving treatment at home' was the most important factor.

SIBDQ

- For patients with CD, the mean (SD) overall SIBDQ score at baseline (n=22) was 36.9 (14.5). The mean (SD) overall scores at the post-index time-points were 46.6 (11.0) at week 14 (n=18), 40.6 (12.9) at month 6 (n=18), and 49.2 (10.7) at month 12 (n=14). For patients with CD, there was a mean (SD) increase in overall SIBDQ score from baseline of 6.1 (10.2) at week 14 (n=18), 2.2 (12.3) at month 6 (n=18) and 8.6 (7.9) at month 12 (n=14). The effect of time on change in overall SIBDQ score post-index was statistically significant for patients with CD, signifying an overall improvement in scores from baseline over the 12 months post-index (P=0.018, n=14).
- For patients with UC, the mean (SD) overall SIBDQ score at baseline (n=38) was 40.1 (14.8). The mean (SD) overall scores at the post-index time-points were 47.7 (16.2) at week 14 (n=33), 49.5 (13.4) at month 6 (n=32) and 50.9 (14.8) at month 12 (n=29). There was a mean (SD) increase in overall SIBDQ score from baseline of 7.2 (12.9) at week 14 (n=33), 8.3 (11.1) at month 6 (n=32) and 8.1 (12.0) at month 12 (n=29). The effect of time on change in total SIBDQ scores post-index was statistically significant for UC, signifying an overall improvement in scores from baseline over the 12 months post-index (P<0.001, n=29).
- There were statistically significant overall improvements observed for certain SIBDQ sub-scores during the 12 months post-index. For example, there was a statistically significant effect of time on change in the SIBDQ bowel system sub-score for patients with CD (P=0.037, n=14) and UC (P<0.001, n=29). There was also a statistically significant effect of time on changes in the emotional health sub-score for patients with CD (P=0.017, n=14) and UC (P=0.001, n=29). The effect of time on change in the systemic symptoms sub-score post-index was statistically significant for patients with CD (P=0.027, n=14) but not for patients with UC (P=0.287, n=29). There was also a statistically significant effect of time on change in the social function sub-score for patients with UC (P<0.001, n=29) although this did not reach statistical significance for patients with CD (P=0.087, n=14).

IBDC-8

- For patients with CD, the mean (SD) overall IBDC-8 score was 5.7 (4.3) at baseline (n=22), 9.3 (4.1) at week 14 (n=18), 7.6 (4.3) at month 6 (n=18) and 10.4 (3.9) at month 12 (n=14). There was a mean (SD) increase in overall IBDC-8 score from baseline of 2.6 (4.2) at week 14 (n=18), 1.7 (4.8) at month 6 (n=18), and 3.9 (4.1).at month 12 (n=14) for patients with CD. A statistically significant effect of time on change in total IBDC-8 score was observed for CD, signifying an overall improvement in scores from baseline over the 12 months post-index (P=0.010, n=14).
- For patients with UC, the mean (SD) overall score was 7.1 (5.0) at baseline (n=38), 10.4 (5.2) at week 14 (n=33), 11.4 (4.5) at month 6 (n=32), and 11.7 (4.9) at month 12 (n=29). There was a mean (SD) increase in overall score from baseline of 3.4 (5.8) at week 14 (n=33), 4.3 (4.6) at month 6 (n=32), and 4.1 (4.4) at month 12 (n=29) for patients with CD. There was a statistically significant effect of time on change in total IBDC-8 score observed for patients with UC, signifying an overall improvement in scores from baseline over the 12 months post-index (P<0.001, n=29).

WPAI-CD/UC

- Of the patients with CD who were working at that time, the median (IQR) percentage of work time missed due to their disease (absenteeism) was 20% (0 to 33%) at baseline (n=11), 4% (0 to 5%) at week 14 (n=7), 0% (0 to 17%) at month 6 (n=7) and 0% (0 to 0%) at month 12 (n=5). There was a mean (SD) reduction in absenteeism of 18% (39%) at week 14 (n=7); however, the mean (SD) work time missed increased by 11% (24%) at month 6 (n=7). At month 12 (n=5), the mean (SD) was reduced by 9% (14%). The effect of time on change in absenteeism post-index was not statistically significant for CD (P=0.426, n=5).
- For patients with UC who were working at that time, the median (IQR) absenteeism was 0% (0 to 25%) at baseline (n=23), 0% (0 to 22%) at week 14 (n=17), 0% (0 to 0%) at month 6 (n=19) and 0% (0 to 10%) at month 12 (n=17). There was a mean (SD) reduction in absenteeism from baseline of 5% (21%) at week 14 (n=17), 8% (18%) at month 6 (n=19) and 7% (27%) month 12 (n=17) for UC. The effect of time on change in absenteeism post-index was not statistically significant for UC (P=0.283, n=17).
- For patients with CD who were working at that time, the median (IQR) percentage of working time that was impaired due to disease (presenteeism) was 45% (18 to 73%) at baseline (n=10), 60% (20 to 60%) at week 14 (n=7), 20% (15 to 48%) at month 6 (n=6) and 30% (15% to 50%) at month 12 (n=5). For patients with CD, there was a mean (SD) increase in presenteeism of 14% (17%) at week 14 (n=7), 15% (22%) at month 6 (n=6) and 10% (19%) at month 12 (n=5). The effect of time on change in presenteeism post-index was not statistically significant for CD according to the repeated-measures ANOVA analysis (P=0.428, n=5).
- For patients with UC who were working at that time, the median (IQR) presenteeism was 40% (20 to 70%) at baseline (n=22), 30% (10 to 50%) at week 14 (n=16), 10% (0 to 35%) at month 6 and 20% (0 to 65%) at month 12 (n=17). There was a mean (SD) reduction in presenteeism of 8% (32%) at week 14 (n=16), 20% (21%) at month 6 (n=18) and 6% (30%) at month 12 (n=17). For patients with UC, there was a statistically significant effect of time on change in presenteeism, signifying an overall reduction in presenteeism from baseline over the 12 months post-index (P=0.021, n=17).
- For patients with CD, the median (IQR) overall work impairment was 49% (20 to 81%) at baseline (n=10), 60% (20 to 62%) at week 14 (n=7), 20% (15 to 51%) at month 6 (n=6) and 30% (15 to 50%) at month 12 (n=5). There was a mean (SD) increase in overall work impairment from baseline of 13% (21%) at week 14 (n=7), 15% (25%) at month 6 (n=6) and 6% (23%) at month 12 (n=5) for patients with CD. The effect of time on change in work impairment post-index was not statistically significant for CD (P=0.534, n=5).
- For patients with UC, the median (IQR) overall work impairment was 44% (20 to 77%) at baseline (n=22), 34% (10 to 63%) at week 14 (n=16), 10% (0 to 46%) at month 6 (n=18) and 20% (10 to 65%) at month 12 (n=17). For patients with UC, there was a mean (SD) reduction in overall work impairment of 11% (35%) at week 14 (n=16), 24% (24%) at month 6 (n=18), and 8% (33%) at month 12 (n=17). There was a statistically significant effect of time on change in overall work impairment for patients with UC, signifying an overall reduction in work impairment over the 12 months post-index (P=0.005, n=17).
- For patients with CD, the median (IQR) activity impairment was 50% (20 to 80%) at baseline (n=22), 50% (20 to 73%) at week 14 (n=18), 45% (20 to 63%) at month 6 (n=18) and 35% (18 to 53%) at month 12 (n=14). For patients with CD, activity impairment increased by a mean (SD) of 1% (27%) at week 14 (n=18), and reduced by a mean (SD) of 7% (28%) at month 6 (n=18) and 16% (17%) at month 12 (n=14). The effect of time on change in activity impairment post-index was not statistically significant for CD (P=0.120, n=14).
- For UC, the median (IQR) activity impairment was 40% (20 to 60%) at baseline (n=38), 30% (10 to 55%) at week 14 (n=33), 20% (0 to 50%) at month 6 (n=32) and 20% (3 to 48%) at month 12 (n=28). For patients with UC, there was a mean (SD) reduction in activity impairment of 9% (31%) at week

14 (n=33), 16% (30%) at month 6 (n=32) and 18% (27%) at month 12 (n=28). There was a statistically significant effect of time on change in activity impairment post-index for UC, signifying an overall reduction in activity impairment from baseline over the 12 months post-index (P=0.010, n=28).

RFIPC

- For patients with CD, the mean (SD) overall RFIPC score at baseline (n=22) was 58.5 (18.1), 44.9 (21.4) at week 14 (n=18), 50.4 (20.5) at month 6 (n=18) and 45.8 (24.9) at month 12 (n=14). For patients with CD, there was a mean (SD) reduction in overall score from baseline of 10.0 (14.8) points at week 14 (n=18), 7.8 (13.0) points at month 6 (n=18) and 6.6 (18.7) points at month 12 (n=14). While there was a general trend suggesting that overall RFIPC scores improved post-index, the effect of time on change in overall RFIPC score post-index did not reach statistical significance (P=0.055, n=14).
- For patients with UC, the mean (SD) overall score at baseline (n=38) was 58.9 (20.5), 46.4 (26.3) at week 14 (n=33), 43.4 (24.1) at month 6 (n=32) and 43.7 (26.9) at month 12 (n=29). There was a mean (SD) reduction in overall score from baseline of 11.5 (20.3) points at week 14 (n=33), 14.1 (20.1) points at month 6 (n=32), and 14.7 (20.0) points at month 12 for UC (n=29). For patients with UC, there was a statistically significant effect of time on change in overall RFIPC score, signifying an overall improvement in scores from baseline over the 12 months post-index (P<0.001, n=29).

Conclusions:

To our knowledge this was the first real-world study that described the impact of VDZ on corticosteroid, immunomodulator and antibiotic prescribing in anti-TNF naïve patients with UC treated in routine clinical practice.

Notably, the study found that patients initiated on VDZ were significantly less likely to be prescribed a course of corticosteroids during the maintenance phase than patients initiated on anti-TNF therapy. This finding is of importance given recent calls to include the reduction or discontinuation of systemic corticosteroids as a treatment goal due to the known adverse consequences of chronic steroid use for patients. Furthermore, significantly fewer patients initiated on VDZ switched or discontinued first-line biologic treatment compared with patients initiated on anti-TNF during the study and a lower proportion of patients initiated on VDZ had dose-escalations or interval shortenings compared with anti-TNF treatment.

Generally, these results are broadly consistent with other evidence suggesting that VDZ is a well-tolerated treatment for adult patients with UC. Since the patients in this study were anti-TNF naïve at initiation, the results also provide some support for the use of VDZ in the first-line setting, instead of reserving VDZ solely for patients who have failed or are intolerant of or contraindicated for anti-TNF therapy. The differences observed in this study may also suggest a therapeutic advantage of treatment with VDZ compared to anti-TNF therapy for patients initiating biologic therapy for UC.

The study also demonstrated that VDZ may lead to real-world benefits during the first 12 months of treatment from a patient perspective, with results from PRO measures administered at key time-points post-initiation of treatment demonstrating statistically significant improvements in scores for a variety of areas relating to overall HRQoL, perceived IBD control, work and activity impairment and disease concern for patients with UC and CD.

LAY SUMMARY

Ulcerative colitis (UC) and Crohn's disease (CD) are types of bowel disease which can cause bloody diarrhoea, abdominal pain, and in more severe cases, ulcers and obstructions in the intestinal system. The exact causes of UC and CD are unknown, but are thought to involve parts the body's immune system attacking itself (a flare) due to various triggers (e.g. stress and different food types). Tumour necrosis factor (TNF) is a molecule released during a flare which causes the immune system to attack itself; several drugs inhibiting TNF (anti-TNFs) are used to treat UC and CD. Another molecule involved in the activation of the immune system is the protein α4β7 integrin, which is present on the surface of immune cells. Vedolizumab (VDZ) is a monoclonal antibody which inhibits the activity of α4β7 integrin to activate an immune response and acts primarily in the gut (rather than throughout the body). This may mean it acts more specifically, thus having fewer side-effects than anti-TNFs.

This study used medical records to identify patients who started receiving VDZ or any anti-TNF for UC (56 patients in each group), and then followed their medication use throughout the next 12 months. Drugs assessed included corticosteroids, immunomodulators and antibiotics, classes of drugs commonly prescribed alongside anti-TNFs or VDZ to treat UC and CD. Reductions in how often these drugs are prescribed, and the average doses, are an indication of how well VDZ or the anti-TNF is working.

The results of the study showed that fewer patients initiated on VDZ (37% [n=19]) were prescribed a corticosteroid during the study compared with patients initiated on anti-TNF (57% [n=30]), although there was no statistical difference in the average dose of corticosteroid prescribed (1658.5 mg for patients initiated on VDZ and 1252.9 mg for patients initiated on anti-TNF). The number of patients who did not require corticosteroids after a year of treatment was similar between groups (82% [n=40/49] for patients initiated on VDZ and 79% [n=37/47] for patients initiated on anti-TNF were not receiving steroids at month 12), as was the number of patients who were dependant on corticosteroids to control disease at any point during the year (34% [n=16/47] for patients initiated on VDZ and 41% [n=15/37] for patients initiated on anti-TNF). Use of immunomodulators was also similar between groups, with around a third of patients initiated on VDZ and anti-TNF being prescribed at least one immunomodulator during the study. Antibiotics were also prescribed for 18% patients initiated on VDZ compared with 25% patients initiated on anti-TNF, although the difference between groups was not statistically significant. The potential benefits of VDZ for lowering infections and therefore antibiotic usage in patients with UC may however be a topic that is worthy of further investigation.

Changes to treatment are another indicator of how well a drug works, as patients not responding to a drug may switch to another drug, stop the drug entirely due to side effects or require changes to the dose. The study found that there were significantly fewer patients initiated on VDZ who either switched or discontinued therapy (13% [n=7] vs 45% [n=25]) compared with patients who were initiated on anti-TNF. In addition, fewer patients initiated on VDZ required their dose to be increased or for the time between treatments to be reduced compared with those initiated on anti-TNF (9% [n=5] vs 23% [n=13]). Overall, less than half the patients initiated on VDZ (46% [n=26]) required any changes to medication (switches, discontinuations, escalations, de-escalations and interval shortening) compared with 82% [n=46] of patients initiated on anti-TNF.

In addition, the study also demonstrated that VDZ may lead to real-world benefits during the first 12 months of treatment from a patient perspective for patients with CD and UC. Results from various questionnaires administered to patients at the time they started treatment with VDZ (baseline) and at different time-points after starting treatment (week 14, month 6 and month 12) showed that patients with UC and CD experienced statistically significant improvements in their HRQoL and the level of control they felt they had over their IBD during the 12 months after starting treatment with VDZ. Statistically significant improvements were also observed for patients with UC during the 12 months after starting

treatment in other areas, such as their productivity (i.e. percentage of work time and general activities that were impaired due to their UC) and also in terms of the amount of worries and concerns they had in relation to their UC.

Overall, this study shows that fewer patients with UC initiated with VDZ required corticosteroids and changes to their therapy than patients initiated with anti-TNF. These findings are important because steroids can often lead to negative effects for patients, and so clinicians have been encouraged to reduce their use where possible. The results also suggest that VDZ is well-tolerated by patients with UC who have not previously received treatment with another anti-TNF and that it could even be a more favourable treatment option over other anti-TNFs in certain situations. In addition, the study found that there may be additional benefits of VDZ from a patient perspective for patients with CD and UC, with patients reporting improvements in the 12 months after starting treatment across different areas such as their HRQoL, IBD control, work and activity impairment and amount of disease-related worries and concerns.