Ustekinumab for ulcerative colitis: a nationwide real-life observational cohort study

Pauliina Molander [a], Clas-Göran af Björkesten[a], Hans Henricson[b], Ritva Koskela[c], Heikki Nuutinen[d], Aki Käräjämäki[e], Jyrki Tillonen[f], Milla-Maria Tauriainen[g,h], Mikko Kellokumpu[i], Heli Eronen[j], Ulla-Maija Suhonen[k], Ilkka Vihriälä[l], Taru Hallinen[m], Minna Oksanen[m], Erkki Soini[m], Minni Koivunen[n], Mervi Kuronen[n], Daniel Wirth[o] and Taina Sipponen[a]

Objective This nationwide retrospective chart review study assessed ustekinumab treatment persistence and clinical outcomes of ustekinumab treatment in Finnish patients with ulcerative colitis in a real-world setting.
Methods Data was collected retrospectively until April 2022 from patient charts for all patients with ulcerative colitis who started ustekinumab between September 2019 and December 2021 in 16 Finnish inflammatory bowel disease centers. The primary outcomes were persistence on ustekinumab and clinical remission/steroid-free clinical remission, defined as partial Mayo score <3 and a combined stool frequency and rectal bleeding subscore of ≤1 at 16 weeks and 1 year.
Results The study included 221 patients with an average follow-up of 14.7 months and a median disease duration of 5.5 years. Disease status was endoscopically evaluated as severely active in more than 91% of the patients at baseline. Treatment persistence was 87% at 16 weeks and 63% at 1 year. The clinical/steroid-free remission rate was 49%/46% at 16 weeks and 68%/62% at 52 weeks, respectively. Decreases in fecal calprotectin and partial Mayo scores were observed. Concomitant corticosteroid use decreased from 60% at baseline to 28% at 16 weeks and to 16% at 1 year during ustekinumab maintenance therapy. Antibodies to ustekinumab were detected in very few patients (<5, <21%), and discontinuation was observed due to adverse effects even less frequently (<5, <6%).
Conclusion This real-world study demonstrated that ustekinumab has sustained efficacy in the treatment of ulcerative colitis in a real-world setting. Eur J Gastroenterol Hepatol XXX: XXXX–XXXX

European Journal of Gastroenterology & Hepatology XXX, XXX:XXXX–XXXX

Keywords: effectiveness, real-world evidence, treatment persistence, ulcerative colitis, ustekinumab

[a]Department of Gastroenterology, Abdominal Center, University of Helsinki and Helsinki University Hospital, Helsinki, [b]Department of Internal Medicine, Central Ostrobothnia Central Hospital, Kokkola, [c]Department of Internal Medicine, Oulu University Hospital, Oulu, [d]Division of Gastroenterology, Department of Medicine, Turku University Central Hospital, Turku, [e]Department of Internal Medicine, Vaasa Central Hospital, Vaasa, [f]Department of Internal Medicine, Päijät-Häme Central Hospital, Lahti, [g]Department of Internal Medicine, Central Finland Central Hospital, Jyväskylä, [h]Department of Internal Medicine, Kuopio University Hospital, Kuopio, [i]Department of Internal Medicine, Lapland Central Hospital, Rovaniemi, [j]Department of Internal Medicine, Kanta-Häme Central Hospital, Hämeenlinna, [k]Department of Internal Medicine, Kainuu Central Hospital, Kajaani, [l]Department of Internal Medicine, Etelä-Pohjanmaa Central Hospital, Seinäjoki, [m]ESiOR Oy, Kuopio, [n]Janssen-Cilag Oy, Espoo, Finland and [o]Janssen-Cilag GmbH, Neuss, Germany

Correspondence to Pauliina Molander, MD, PhD, Department of Gastroenterology, Abdominal Center, University of Helsinki and Helsinki University Hospital, P.O. Box 900, 00029 HUS Helsinki, Finland
Tel: +358 403593289; e-mail: pauliina.molander@hus.fi

Received 7 October 2024 **Accepted** 17 January 2025.

Supplemental Digital Content is available for this article. Direct URL citations appear in the printed text and are provided in the HTML and PDF versions of this article on the journal's website, www.eurojgh.com.

Introduction

Ulcerative colitis (UC) is a chronic inflammatory bowel disease (IBD) characterized by mucosal inflammation of the colon and rectum, potentially leading to a significant negative impact on patients' quality of life [1,2]. The goal of treatment is to avoid UC-associated disability and maintain patients' quality of life [3] by inducing and maintaining steroid-free clinical remission and endoscopic healing [3,4]. Up to 40% [5] of UC patients experience inadequate response or loss of response to first-line treatment options (i.e. 5-aminosalicylic acid, corticosteroids, or immunomodulators) for mild to moderate UC [3]. In patients with moderate to severe UC who are refractory to these options, biological therapies, and Janus kinase (JAK) inhibitors are recommended for induction and maintenance of remission [3]. During the past decades, advancements in UC treatment have reduced the need for surgery. However, it is estimated that approximately 13% of the patients diagnosed after 2010 will require surgery after a disease duration of 10 years [6].

Ustekinumab is a mAb that selectively inhibits interleukin-12 and interleukin-23 signaling pathways and has demonstrated efficacy in inducing and maintaining remission in patients with moderate to severe UC [7,8]. In the UNIFI clinical trial [7], the UC patients on ustekinumab had clinical remission rates of 15% after induction (week 8) and in maintenance 40% (week 44), both significantly higher than placebo (5 and 24%, respectively). In the UNIFI long-term extension, 55% of

patients who were randomized to ustekinumab at the maintenance baseline were in symptomatic remission after 4 years in the study [8]. Because clinical trial study populations and protocols may not completely reflect the general IBD population as well as local treatment practices, real-world data of effectiveness and safety are needed. In recent years, real-world evidence of ustekinumab has been published and supports its effectiveness in the real-world setting [9,10]. Our study aims to contribute to this body of evidence.

In Finland, ustekinumab has been granted a restricted reimbursement for the treatment of adult patients with active moderate to severe UC. To be entitled to reimbursement, the patients must have had an inadequate response to, lost response to, or be intolerant to either mesalamine, a thiopurine, or a biological or JAK inhibitors, or have medical contraindications to such therapies. Here, we report findings from the FINUSTE-UC study with the primary objective to assess ustekinumab treatment persistence and the clinical outcomes of ustekinumab treatment in UC in a Finnish real-world setting.

Methods

Study design

The FINUSTE-UC study was a nationwide retrospective, observational, noninterventional patient chart review of adult patients (≥18 years) with a diagnosis of UC (International Classification of Diseases, ICD10: K51.0, K51.1, K51.2, K51.3, K51.5, K51.8, K51.9), who initiated ustekinumab therapy with a single intravenous induction dose of ustekinumab (approximately 6 mg/kg) between 1 September 2019 and 31 December 2021 in one of the 16 participating Finnish hospitals. Patients with a history of panproctocolectomy, ileoanal anastomosis, or ileostomy, and patients with a current dual diagnosis of Crohn's disease were excluded.

The gastroenterologist at each hospital collected the data from electronic patient files using an electronic standardized case report form, which was implemented in a data collection system operated inside the SPESiOR secure processing environment (SPESiOR; ESiOR Oy, Kuopio, Finland). The data were collected from ustekinumab treatment initiation until relocation (i.e. change of service provider), death, or end of follow-up (i.e. 30 April 2022), whichever occurred first. Data collection started in January 2023 and was finalized in September 2023.

The data was collected at baseline, that is, at ustekinumab initiation, and at the time of outcomes assessment: at week 16 (±4 weeks), at 6 months (±1–3 months), at 12 months (±2 months), at 18 months (±3 months), and at 24 months (±2 months) after treatment initiation (if available). Baseline data included age, sex, smoking status, height, weight, year of diagnosis, age at diagnosis, specific UC diagnosis, Montreal classification for the extension of the disease, extraintestinal manifestations (arthritis, arthralgia, ankylosing spondylitis, uveitis, iritis, primary sclerosing cholangitis, pyoderma gangrenosum, erythema nodosum), history of psoriasis, hospitalization status at ustekinumab initiation, and previous and ongoing use of clinically relevant medications for UC.

Outcome measures

The primary objectives of the study were to assess ustekinumab treatment persistence (drug survival) and the clinical outcomes of ustekinumab treatment. Ustekinumab treatment persistence (drug survival) was assessed from the initiation of therapy (index date) until ustekinumab discontinuance or censoring (loss to follow-up or end of follow-up period).

The assessed clinical outcomes included disease severity, clinical response/remission, steroid-free clinical remission, clinical disease activity (CDA), endoscopic and histologic disease activity, biomarker assessment (fecal calprotectin, fCal), and biochemical (C-reactive protein, CRP) disease activity. Disease severity was assessed using the partial Mayo score (PMS) [11–13], and it was defined as severe when the score was 7–9, moderate when 5–6, mild when 2–4, and remission ≤1. Based on clinical convention, clinical response was defined as PMS reduction of ≥3 points and a decrease of at least 30% from the baseline score, and clinical remission as PMS of <3 plus a combined stool frequency and rectal bleeding subscore of ≤1. CDA was assessed using the Physician's Global Assessment (PGA), where remission, mild disease, moderate disease, and severe disease were defined as PGA = 0, PGA = 1, PGA = 2, and PGA = 3, respectively. Endoscopic status was assessed based on the Mayo endoscopic subscore, where a score of 0 or 1 suggested mucosal healing, a score of 2 moderately active disease, and a score of 3 severely active disease. Biomarker-assessed active disease was defined as fCal>250 µg/g, remission as fCal≤250 µg/g, normalization as fCal <100 µg/g, and response as a reduction in fCal of at least 50% from baseline [14,15]. Biochemical disease activity based on CRP was considered normal when CRP < 3 mg/L. Biochemical response was defined as a reduction in CRP of at least 50% from baseline. Ustekinumab serum concentrations and levels of therapeutic antibodies were assessed using validated ELISA assays (Sanquin, Amsterdam, The Netherlands).

The secondary outcome depicted the baseline positioning of ustekinumab in the treatment of UC in Finland. The available data regarding ustekinumab concentrations and antibodies were assessed as tertiary outcomes. In addition, reasons for assessing the concentrations as well as antibody status and treatment decisions based on them were assessed.

Statistical analysis

All analyses were performed with R (version 4.0.5; R Core Team, R: A language and environment for statistical computing, Vienna, Austria) in a secure operating environment. Treatment persistence and 95% confidence intervals (CIs) were calculated with the Kaplan–Meier estimator. Continuous variables were reported as median and interquartile range (IQR) or mean and SD, and categorical variables were reported as proportions (%). The significance of the change from baseline value in laboratory measures and clinical outcomes at different time points was tested with the Wilcoxon matched-pairs signed-rank test for continuous variables and the marginal homogeneity test for categorical variables. The log-rank test was used to test the significance of treatment persistence between groups. A *P*-value less than or equal to 0.050 was considered statistically significant. Factors associated with ustekinumab persistence were investigated with a Cox proportional

Table 1. Patient and disease characteristics at baseline

Patient characteristics	*N*	Value
Age, mean (SD)/median (IQR), years	221	40.3 (14.9) 37.5 (28.7–51.3)
Weight, mean (SD)/median (IQR), kg	206	80.1 (14.9)/80.0 (66.0–90.0)
Height, mean (SD)/median (IQR), cm	137	173.1 (9.6)/173.0 (167.0–179.0)
Male sex, *n* (%)	221	125 (57)
Current smoker, *n* (%)	169	8 (5)
Disease duration in years from UC diagnosis, mean (SD)/median (IQR)	214	7.6 (7.2)/5.5 (2.3–10.4)
Montreal classification, *n* (%)	221	
Proctitis		5 (2)
Left-sided colitis		72 (33)
Extensive colitis		144 (65)
Extraintestinal manifestations, *n* (%)	214	54 (25)
Arthritis		10 (5)
Arthralgia		28 (13)
Ankylosing spondylitis		5 (2)
Uveitis or iritis		6 (3)
Erytherma nodosum or pyoderma gangrenosum		<5 (<2)
Primary sclerosing cholangitis		10 (5)
Psoriasis	214	17 (8)
Prior biological/JAK treatment for UC, *n* (%)	221	215 (97)
1 biological		84 (38)
2 biologicals		92 (42)
≥3 biologicals		38 (17)
Adalimumab		86 (39)
Infliximab		174 (79)
Vedolizumab		106 (48)
Golimumab		21 (10)
Tofacitinib		40 (18)
Other		<5 (<3)
Nonbiological drugs at baseline, *n* (%)	221	192 (87)
Thiopurines		50 (23)
5-aminosalicylic acid		123 (56)
Budesonide		11 (5)
Oral corticosteroids		114 (52)
Intravenous corticosteroids		10 (5)

IQR, interquartile range; JAK, Janus kinase; UC, ulcerative colitis.

hazards model using baseline variables sex, duration of disease, number of prior advanced therapies (biological/JAK), disease severity (fCal/100), and presence of extraintestinal manifestations (yes/no). Missing data was treated as truly missing, and no imputation methods were used.

Due to the anonymization requirements of the Finnish Social and Health Data Permit Authority Findata, nonzero numbers of observations that are recorded for less than five patients cannot be reported exactly or be indirectly deducible from other observations [16]. Thus, they were reported as less than five or as the respective proportion.

Ethical considerations

This study was approved by Findata (permit number THL/102/14.02.00/2021). Patients were not contacted as this was a retrospective observational study and did not affect the treatment of patients. The Ethics Committee of Tampere University Hospital reviewed the study protocol and approved the study. This study was registered in an electronic health records (EHR) system (EUPAS1000000222).

Results

Patient characteristics

Overall, 221 patients were included in the study population originating from the 16 Finnish IBD treating centers, with 6–39 (3–18%) patients from each center.

Patient characteristics at the baseline are summarized in Table 1. The average age was 40.3 (SD: 14.9) years and disease duration was 7.6 (SD: 7.2) years. Typically, ustekinumab was positioned as a second- or third-line advanced treatment ($n = 74$, 34% and $n = 86$, 39%, respectively). Almost all patients ($n = 215$, 97%) had previously been treated with at least one biological therapy or JAK inhibitor, and almost two-thirds ($n = 141$, 64%) had used two or more biologicals as well as JAK inhibitors. At baseline, half of the patients ($n = 113$, 51%) were corticosteroid-dependent (corticosteroid use could not be reduced without worsening of UC) and 10 patients (5%) were hospitalized. The reported reason for ustekinumab initiation was most commonly related to previous biological therapies: lack of effectiveness ($n = 157$, 71%), loss of response ($n = 102$, 46%), and side effects or problems with adherence ($n = 43$, 20%). At baseline, most patients had extensive ($n = 144$, 65%) or left-sided colitis ($n = 72$, 33%). Seven (3%) patients had IBD unclassified.

Follow-up and ustekinumab treatment persistence

Intravenous ustekinumab induction dosing was performed in line with the summary of ustekinumab product characteristics: 117 (53%) of patients received 390 mg, 88 (40%) 520 mg, and 16 (7%) either 260 mg or a modified dose. Almost all patients ($n = 214/221$; 97%) received a subcutaneous ustekinumab induction dose after the intravenous induction (Fig. 1). Maintenance treatment with subcutaneous ustekinumab was initiated in 91% of the patients ($n = 201/221$) with 90 mg every 8 weeks ($n = 162/201$; 81%), 90 mg every 12 weeks ($n = 18/201$; 9%), or 90 mg every 6 weeks ($n = 15/201$; 8%).

The mean follow-up time was 14.7 months (SD: 7.1; median: 13.9; IQR: 8.8–20.4 months). Follow-up data at 16 weeks, 6 months, 1, 1.5, and 2 years were available for 219 (99%), 207 (94%), 157 (71%), 99 (45%), and 38 (17%) patients, respectively. The Kaplan–Meier graph in Fig. 2 depicts ustekinumab treatment persistence over time. At the end of follow-up, 136 (62%) patients were still on ustekinumab maintenance treatment, and 85 (39%) patients had discontinued ustekinumab (Fig. 2). The mean time to ustekinumab discontinuation was 10.9 months (SD: 7.5; median: 9.1; IQR: 5.1–15.7 months). Discontinuation was highest during the first 6 months, and persistence plateaued at around 60% after 1 year, with a 63% (95% CI: 57–70%) persistence at 12 months. The Kaplan–Meier-estimated median persistence was 25.9 months.

In the multivariable Cox model, baseline fCal/100 and the presence of an extraintestinal manifestation were statistically significantly associated with treatment persistence, with respective hazard ratios of 1.01 (95% CI: 1.00–1.03, $P = 0.04$) and 0.43 (95% CI: 0.22–0.85, $P = 0.02$). A more detailed description is provided in Supplementary 1, Supplemental digital content 1, *http://links.lww.com/EJGH/B124*.

Ustekinumab was discontinued in 44% ($n = 37/84$) of the patients with only one prior biological failure and in 36% ($n = 47/130$) of the patients with more than one biological failure. Between these groups, the persistence was 85% (95% CI: 77–93) and 93% (95% CI: 89–98) at 16 weeks. At 1 year, the persistence was 60% (95% CI: 50–72) and 63% (95% CI: 53–73), respectively ($P = 0.20$).

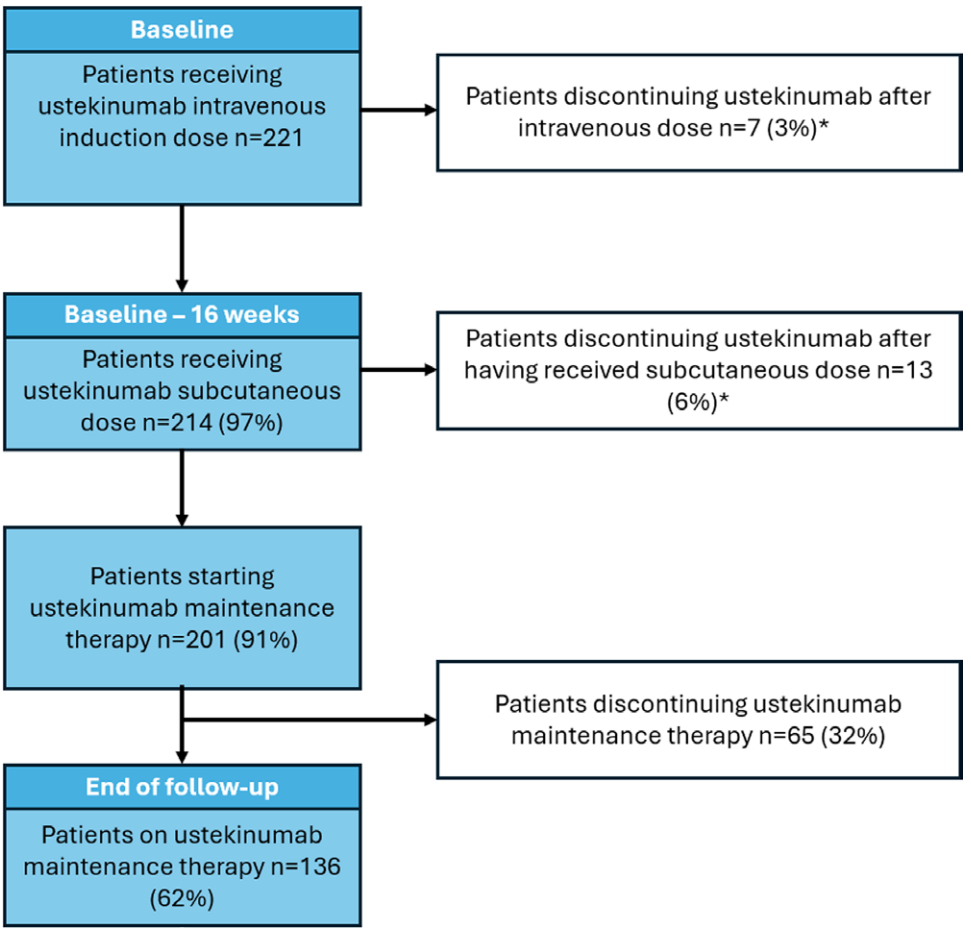

Fig. 1. Flowchart of ustekinumab treatment in the study population. *Of the 20 patients who did not continue to maintenance therapy, eight (40%) had surgery on average 5.1 months after the intravenous induction (SD: 6.5), 14 (70%) were primary nonresponders, and five (25%) had nonadherence, an adverse event, an economic reason, as well as patient wish. Five (25%) patients continued to another biological or Janus kinase treatment.

The most common reasons for discontinuation were primary nonresponse ($n = 64$, 75%), secondary loss of response ($n = 18$, 21%), and patient decision ($n = 6$, 7%). Economic, adherence, adverse effects, remission, and other discontinuation reasons were reported for each in less than five patients. The development of neutralizing ustekinumab antibodies was not reported as a reason for discontinuation.

Disease activity and clinical outcomes during follow-up

During ustekinumab treatment, significant decreases were seen in disease severity and biomarkers reflecting disease activity already 16 weeks after treatment initiation. At baseline, 23 (12%) of 189 patients with available data were in clinical remission and 13 (7%) were in steroid-free clinical remission. The proportion of patients with clinical remission increased to 49% (74/150) at 16 weeks, 55% (70/127) at 6 months, and 68% (48/71) at 1 year (Fig. 3). Of these, 93% (69/74), 84% (59/70), and 92% (44/48) achieved steroid-free clinical remission. Clinical response was observed in 46% (63/136) of the patients at 16 weeks, and it increased to 51% (57/111) at 6 months, and 52% (33/64) at 1 year. Biomarker-assessed response was seen in 52% (65/125), 59% (63/107), and 63% (36/57) of the patients at 16 weeks, 6 months, and 1 year, respectively. During the follow-up, 29 patients (13%) underwent pan-proctocolectomy and ileoanal anastomosis with/without temporary ileostomy.

The greatest decreases in disease severity were seen during 16 weeks after the treatment initiation (Fig. 4). The median PMS decreased from 5.0 (IQR: 4.0–7.0) at baseline to 2.0 (IQR: 1.0–5.0) ($P < 0.001$) at 16 weeks. At the same time the median fCal reduced from 1262 (IQR: 587–2608) at baseline to 662 (IQR: 155–1544) at 16 weeks ($P < 0.001$). Both PMS and fCal continued to decrease until the 1-year time point, when median PMS and fCal were 1.0 (IQR: 0.0–3.0) and 215 (IQR: 41–678), respectively ($P < 0.001$ in both). Only minor improvements in both were observed thereafter. Changes in categorical PMSs are reported in Supplementary 2, Supplemental digital content 1, *http://links.lww.com/EJGH/B124*.

Disease status was endoscopically assessed to be severely active in more than 91% (>105/115) at baseline. In addition, more than 96% (>106/110) had histologically evaluated active disease. Changes over time in these outcomes are reported in Supplementary 3, Supplemental digital content 1, *http://links.lww.com/EJGH/B124*.

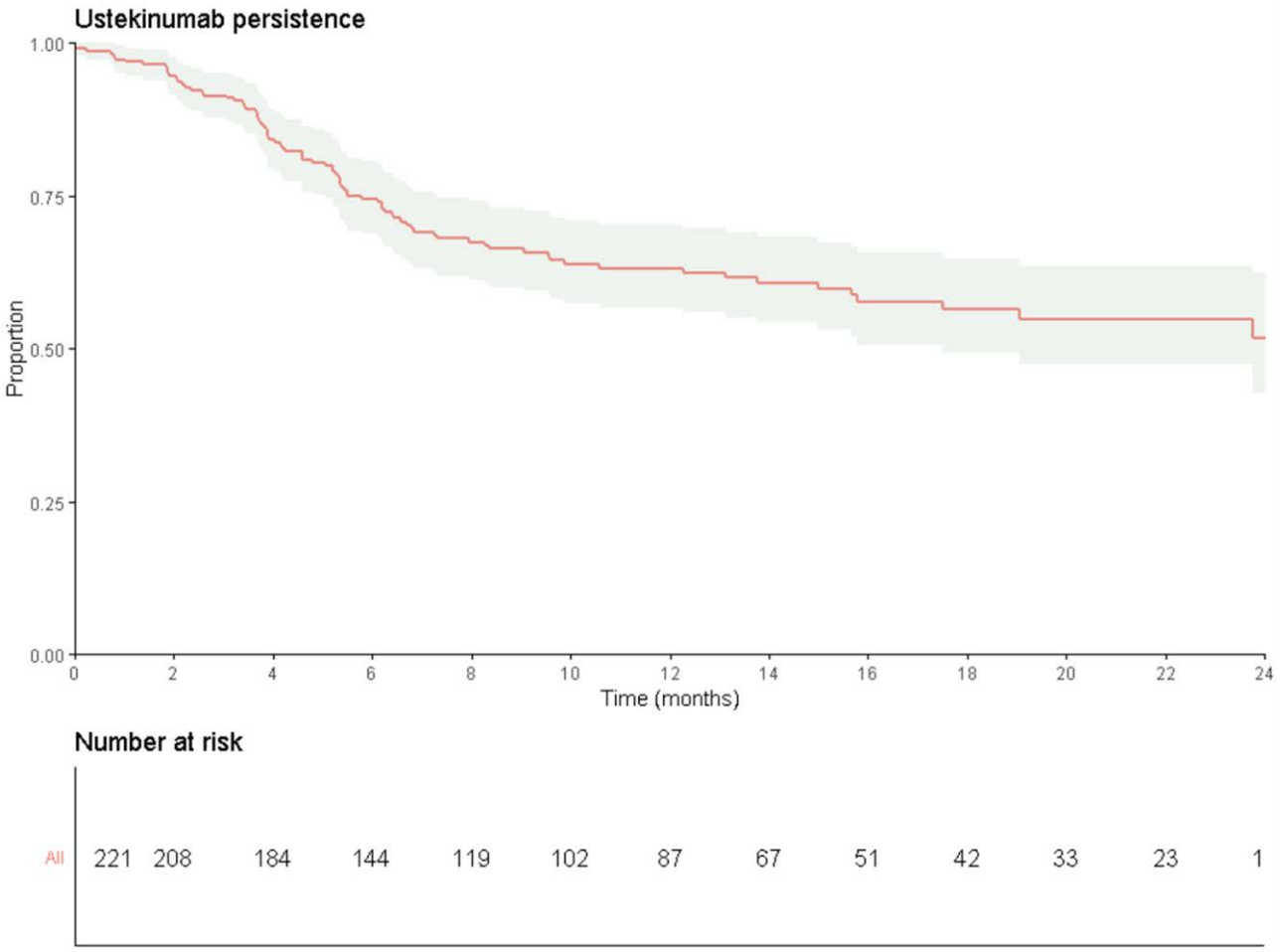

Fig. 2. Ustekinumab treatment persistence.

Concomitant drugs

At baseline, 192 (87%) patients used at least one concomitant drug for treatment of UC (Table 1). During ustekinumab therapy, the use of concomitant drugs reduced to 75% (150/201) at 16 weeks and remained rather unchanged thereafter. Correspondingly, the proportion of patients with ustekinumab monotherapy increased from 13% (29/221) at baseline to 25% (51/201) at 16 weeks, 33% (54/166) at 6 months, 33% (34/102) at 1 year, 42% (25/60) at 1.5 years, and 39% (9/23) at 2 years. Decreases were seen in the use of mesalamine, thiopurines, and corticosteroids (Supplementary 4, Supplemental digital content 1, *http://links.lww.com/EJGH/B124*). In particular, the proportion of patients using corticosteroids (budesonide, other oral corticosteroids, or intravenous corticosteroids) reduced from 60% (133/221) at baseline to 28% (57/201) at 16 weeks, 25% (42/166) at 6 months, 16% (16/102) at 1 year, 10% (6/60) at 1.5 years, and <22% (<5/23) at 2 years. In total, 42 (19%) patients initiated another biological therapy or tofacitinib for the treatment of UC during follow-up.

Ustekinumab concentrations, dosing adjustments, and antibodies

Ustekinumab concentrations were measured in 125 patients at different time points. The most common reasons for assessing drug concentrations were routine measurement (40%), poor treatment response (55%), and monitoring after dose change (8%). Mean (SD) ustekinumab concentrations before 12 weeks, at 16 weeks, 6 months, 1, 1.5, and 2 years were 5.7 µg/ml (4.2; $n = 9$), 3.8 µg/ml (2.8; $n = 43$), 2.8 µg/ml (1.9; $n = 50$), 3.1 µg/ml (1.9; $n = 25$), and 3.7 µg/ml (2.8; $n = 13$), respectively. In most cases (67%), the measurement of ustekinumab concentrations led to no changes in the treatment, but in 15% the dosing interval was shortened.

Dosing adjustments were made in 62 (31%) patients, the first one on average 6.9 (SD: 4.9) months after ustekinumab initiation. Extension of dosing intervals occurred (at any time) in 13 (7%, 13/201) patients and shortening in 49 (24%, 49/201) patients, the first time on average 9.8 and 6.7 (SD: 6.8 and 4.5) months after ustekinumab initiation, respectively. Of those who started with a 12-week dosing interval, 50% (9/18) were adjusted to 8-week or eventually to 6-week intervals ($n < 5$). Of those who started with an 8-week dosing interval, 26% (42/162) were adjusted to either 4- ($n = 8$), 6- ($n = 28$), or 7-week ($n = 6$) intervals. Ustekinumab was paused for more than 2 months in only less than five patients.

Ustekinumab antibodies were assessed with a total of 31 measurements at different timepoints taken from 24

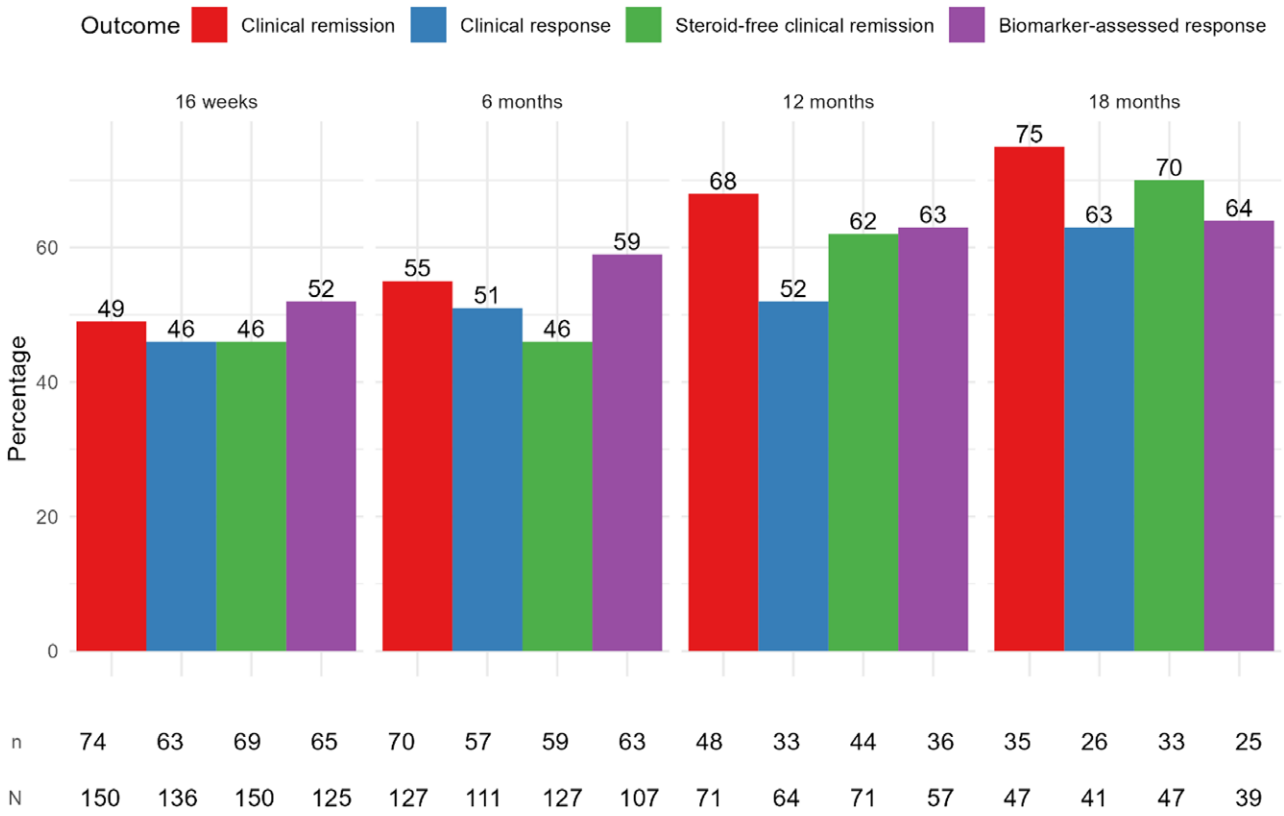

Fig. 3. Clinical outcomes over time. Clinical remission = partial Mayo score <3 plus a combined stool frequency and rectal bleeding subscore of ≤1, clinical response = partial Mayo score reduction of ≥3 points and a decrease of at least 30% from the baseline score, steroid-free clinical remission = clinical remission with no concurrent steroid treatment, biomarker-assessed response = a reduction in fecal calprotectin of at least 50% from baseline. *n*, yes; *N*, available data among ustekinumab users.

patients during the study. Ustekinumab antibodies were detected in less than five patients at 6 months, but these results did not lead to drug discontinuation.

Discussion

This FINUSTE-UC study conducted in a representative nationwide cohort of Finnish UC patients demonstrated that real-world persistence on ustekinumab was 87% at 16 weeks and 63% at 1 year. The patients had an average disease duration of nearly 8 years. Most patients had endoscopically assessed moderate or severe disease and had failed other advanced UC therapies prior to ustekinumab initiation. Discontinuations were mostly due to primary nonresponse (75%) and secondarily due to secondary loss of response. Adverse events causing ustekinumab discontinuations were rare, indicating that ustekinumab is well-tolerated also in this patient population.

Clinical remission and steroid-free clinical remission are critical outcomes in evaluating the effectiveness of UC therapies. Less than 30% of anti–tumor necrosis factor experienced patients with moderate-severe UC have been estimated to succeed in the achievement of clinical remission on tofacitinib, vedolizumab, or adalimumab [17]. In our study clinical remission rates in patients on ustekinumab maintenance therapy ranged from 49 to 75%, supporting ustekinumab as an effective option when prior therapies have failed. The clinical remission rates in our study were in line with those reported for ustekinumab-treated patients in other recent real-world studies [18–20]. Similar rates have also been reported in a recent systematic review of observational studies, with 33–79% of patients achieving clinical remission at 52 weeks while on ustekinumab therapy [10]. However, the observed remission rates in our study were higher than in the UNIFI trial ([7], 38.4–43.8% at 44 weeks), which used a stricter definition of remission and did not intensify dosing intervals during the maintenance phase.

In our study, steroid-free clinical remission was achieved by 46% of patients at 16 weeks, and the proportion was observed to increase over time. Steroid-free clinical remission rates were slightly higher than in the recent study conducted in France by Amiot *et al.* [18], where 35% achieved steroid-free clinical remission at 8 weeks with almost the same definition of clinical remission. UNIFI long-term trial data showed that ustekinumab symptomatic remission rates were 55.2% at week 200, and of those 96.4% were steroid-free [8].

In addition to the clinical parameters, we recorded the biochemical markers of UC during ustekinumab treatment. Of note is fCal, which is routinely measured in Finnish clinical practice and has been proven to be a reliable surrogate marker of endoscopic remission in UC [21]. Decreases over time were seen in fCal values, which were similar in magnitude to those observed for patients with an initial 8-week dosing interval in the UNIFI trial [our median of 215 (IQR: 41–678) at 52 weeks vs. 205.0 (IQR: 57.0–936.5) at 44 weeks [7]]. In addition, the reduction

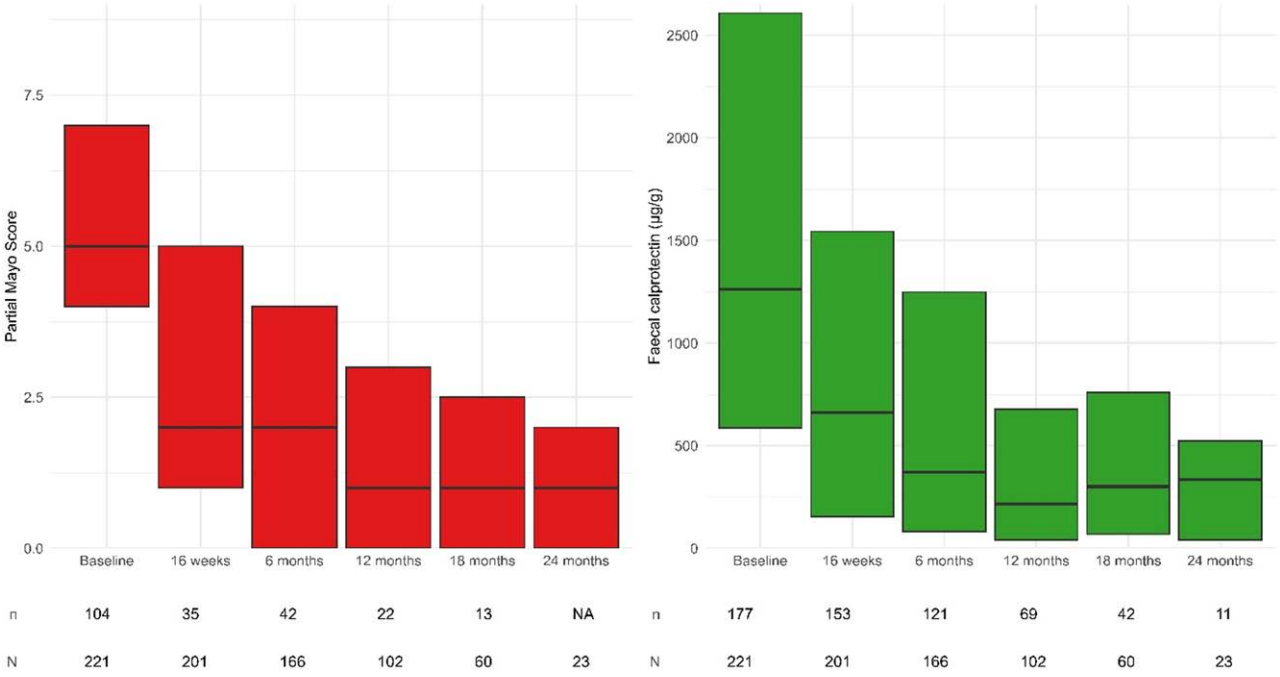

Fig. 4. Partial Mayo score and fecal calprotectin values over time. The median and interquartile range are shown. *n*, number of observations; *N*, patients still using ustekinumab.

in fCal values observed in our study aligns with findings reported in real-world studies conducted in Sweden and Italy [22,23].

In our cohort, most patients started maintenance therapy with 8-week dosing intervals (81%, 162/201), even though the SPC (Summary of Product Characteristics) recommends maintenance dosing to start every 12 weeks [24] (European Medicines Agency). Despite this, a considerable proportion (24%, 49/201) had dose escalations during the follow-up. Notably, 50% (9/18) of patients who initially started with 12-week dosing intervals were later intensified to 8-week intervals. A similar proportion (19%) of patients with dose escalations at 12 months has been reported in a large patient cohort from the USA [25], although their patients were more commonly bionaive. In the UNIFI long-term trial, the proportion of patients with dose escalation from a 12-week dosing interval to 8-week intervals was 42.6% [26], but escalations were allowed only after week 56. Taking this into account, it is reasonable to consider ustekinumab treatment at an 8-week interval, especially for therapy-resistant UC.

The strength of our study is the relatively large patient population and excellent geographical coverage as nearly all eligible patients in Finland were included in the study. However, some centers originally planned for inclusion into the study did not complete the data collection, and therefore an estimated 11% of the total population who received ustekinumab is missing. The retrospective nature of our study also meant that incomplete data was collected for some outcome measures as these had not been reported in the patient charts for all subjects as part of regular clinical practice. Since our study focused on assessing outcomes of patients with continued use of ustekinumab, no conclusions on ustekinumab's relative effectiveness versus other treatment alternatives can be drawn based on our study.

Conclusion

Taken together, our findings demonstrate that ustekinumab has sustained effectiveness in real-life clinical practice. Despite the patients being biological- as well as JAK-experienced, corticosteroid use decreased substantially. Ustekinumab dosing is generally more frequent than recommended in the SPC. The high level of persistence and efficacy of ustekinumab in real-life clinical practice should be considered when evaluating different treatment options for a UC patient.

Acknowledgements

The authors thank Fredrik Forsström, MD, and Karri Utriainen, MD, for patient data collection; Inka Koskinen, MD, for assistance in patient data collection; Tuomas Lundström (ESiOR) for technical implementation and management of data collection; as well as Petri Mankinen (ESiOR), Christina Wennerström, and Johanna Koponen (Janssen) for their expertise in the study management. Dr. Sandra Hänninen is acknowledged for native speaker language review.

This study was funded by Janssen-Cilag Oy, Espoo, Finland.

ESiOR Oy received funding from Janssen-Cilag Oy (Finland) to carry out the study.

Conflicts of interest

P.M. has received speaker and consultancy fees from Abbvie, Lilly, Orion Pharma, Pfizer, Sandoz, Takeda, and Tillotts Pharma; and advisory board member fees from BMS, Gilead, and Janssen-Cilag. C.-G.a.B. has received speaker and consultancy fees from Abbvie, BMS, Galapagos, Johnson & Johnson, Lilly, Pfizer, and Takeda, and advisory board member fees from Lilly. H.H. has

received fees for travel expenses from Janssen, Abbvie, Ferring, and Tillots Pharma. A.K. owns stock in Orion and has received fees for travel expenses from Ferring. M.-M.T. has received speaker and consultancy fees from Abbvie, Orion Pharma, MSD, and Takeda. M. Kellokumpu has received speaker and consultancy fees from Janssen and BMS, and fees for training and travel expenses from Janssen, Abbvie, and Pfizer. H.E. has received speaker fees from Abbvie, Takeda, and Tillots Pharma; and advisory board member fees from Lilly. E.S. is a partner of ESiOR Oy and Chairman of the Board at the Kuopio Health Cooperative. M. Koivunen is an employee of Janssen-Cilag Oy, Espoo, Finland, a Johnson & Johnson company, and owns stock in Johnson & Johnson. M. Kuronen is an employee of Janssen-Cilag Oy, Espoo, Finland, a Johnson & Johnson company. D.W. is an employee of Janssen-Cilag Oy, Neuss, Germany, a Johnson & Johnson company. T.S. has received speaker and consultancy fees from Abbvie, Lilly, Pfizer, and Takeda; and advisory board member fees from Abbvie, BMS, Janssen-Cilag, and Pfizer. For the remaining authors, there are no conflicts of interest.

References

1 Ungaro R, Mehandru S, Allen PB, Peyrin-Biroulet L, Colombel JF. Ulcerative colitis. *Lancet* 2017; 389:1756–1770.
2 Armuzzi A, Liguori G. Quality of life in patients with moderate to severe ulcerative colitis and the impact of treatment: a narrative review. *Dig Liver Dis* 2021; 53:803–808.
3 Raine T, Bonovas S, Burisch J, Kucharzik T, Adamina M, Annese V, *et al*. ECCO guidelines on therapeutics in ulcerative colitis: medical treatment. *J Crohns Colitis* 2022; 16:2–17.
4 Burri E, Maillard MH, Schoepfer AM, Seibold F, Van Assche G, Rivière P, *et al*; Swiss IBDnet, an Official Working Group of the Swiss Society of Gastroenterology. Treatment algorithm for mild and moderate-to-severe ulcerative colitis: an update. *Digestion* 2020; 101(Suppl 1):2–15.
5 Park SC, Jeen YT. Current and emerging biologics for ulcerative colitis. *Gut Liver* 2015; 9:18–27.
6 Musallam R, Rahman SH, Shweikeh F, Daaboul R, Beran A, Mohan B, *et al*. S969 risk of surgery for inflammatory bowel diseases has decreased over time: a systematic review and meta-analysis of population-based studies. *Am J Gastroenterol* 2023; 118(Suppl 10):S730.
7 Sands BE, Sandborn WJ, Panaccione R, O'Brien CD, Zhang H, Johanns J, *et al*; UNIFI Study Group. Ustekinumab as induction and maintenance therapy for ulcerative colitis. *N Engl J Med* 2019; 381:1201–1214.
8 Afif W, Arasaradnam R, Abreu M, Danese S, Sandborn W, Miao Y, *et al*. Efficacy and safety of ustekinumab for ulcerative colitis through 4 years: final results of the UNIFI long-term maintenance study. *Am J Gastroenterol* 2024; 119:910–921.
9 Uchida G, Nakamura M, Yamamura T, Tsuzuki T, Kawashima H. Real-world effectiveness of ustekinumab for patients with ulcerative colitis: a systematic review and meta-analysis. *Nagoya J Med Sci* 2023; 85:402–427.
10 Gisbert JP, Parody-Rúa E, Chaparro M. Efficacy, effectiveness, and safety of ustekinumab for the treatment of ulcerative colitis: a systematic review. *Inflamm Bowel Dis* 2024; 30:292–302.
11 Schroeder KW, Tremaine WJ, Ilstrup DM. Coated oral 5-aminosalicylic acid therapy for mildly to moderately active ulcerative colitis. *N Engl J Med* 1987; 317:1625–1629.
12 Lewis JD, Chuai S, Nessel L, Lichtenstein GR, Aberra FN, Ellenberg JH. Use of the noninvasive components of the Mayo score to assess clinical response in ulcerative colitis. *Inflamm Bowel Dis* 2008; 14:1660–1666.
13 Turner D, Seow CH, Greenberg GR, Griffiths AM, Silverberg MS, Steinhart AH. A systematic prospective comparison of noninvasive disease activity indices in ulcerative colitis. *Clin Gastroenterol Hepatol* 2009; 7:1081–1088.
14 D'Haens G, Ferrante M, Vermeire S, Baert F, Noman M, Moortgat L, *et al*. Fecal calprotectin is a surrogate marker for endoscopic lesions in inflammatory bowel disease. *Inflamm Bowel Dis* 2012; 18:2218–2224.
15 af Björkesten CG, Ilus T, Hallinen T, Soini E, Eberl A, Hakala K, *et al*. Objectively assessed disease activity and drug persistence during ustekinumab treatment in a nationwide real-world Crohn's disease cohort. *Eur J Gastroenterol Hepatol* 2020; 32:1507–1513.
16 Findata. Producing anonymous results. https://findata.fi/en/services-and-instructions/producing-anonymous-results/. [Accessed 16 August 2024].
17 Singh S, Fumery M, Sandborn WJ, Murad MH. Systematic review with network meta-analysis: first- and second-line pharmacotherapy for moderate-severe ulcerative colitis. *Aliment Pharmacol Ther* 2018; 47:162–175.
18 Amiot A, Filippi J, Abitbol V, Cadiot G, Laharie D, Serrero M, *et al*; UC-USK-GETAID Study Group. Effectiveness and safety of ustekinumab induction therapy for 103 patients with ulcerative colitis: a GETAID multicentre real-world cohort study. *Aliment Pharmacol Ther* 2020; 51:1039–1046.
19 Uchida G, Nakamura M, Yamamura T, Maeda K, Sawada T, Ishikawa E, *et al*. Real-world effectiveness and risk factors for discontinuation of ustekinumab in ulcerative colitis. *Inflamm Intest Dis* 2023; 8:60–68.
20 Solitano V, Narula N, Ma C, Nanayakkara A, Suarez KE, Zoughlami A, *et al*. Effectiveness of ustekinumab for patients with moderate to severe ulcerative colitis: a multi-center real-world Canadian study. *Am J Gastroenterol* 2024; 10:14309.
21 Sipponen T, Kolho KL. Fecal calprotectin in diagnosis and clinical assessment of inflammatory bowel disease. *Scand J Gastroenterol* 2015; 50:74–80.
22 Sabhan H, Bello F, Muhsen S, Borin A, Johansson F, Höög C, *et al*. Long-term real-world data of ustekinumab in ulcerative colitis: the Stockholm Ustekinumab Study (STOCUSTE). *Eur J Gastroenterol Hepatol* 2024; 36:1419–1425.
23 Tursi A, Mocci G, Scaldaferri F, Napolitano D, Maresca R, Pugliese D, *et al*. Ustekinumab safety and effectiveness in patients with ulcerative colitis: results from a large real-life study. *Expert Opin Biol Ther* 2024; 24:101–109.
24 Janssen Pharmaceutical Companies. *Summary of product characteristics, SmPC*. 2016. https://www.janssenlabels.com/package-insert/product-monograph/prescribing-information/STELARA-pi.pdf. [Accessed 16 August 2024].
25 Zhdanava M, Zhao R, Manceur AM, Kachroo S, Lefebvre P, Pilon D. Persistence and dose escalation during maintenance phase and use of nonbiologic medications among patients with ulcerative colitis initiated on ustekinumab in the United States. *Crohns Colitis 360* 2023; 5:otad045.
26 Abreu MT, Rowbotham DS, Danese S, Sandborn WJ, Miao Y, Zhang H, *et al*. Efficacy and safety of maintenance ustekinumab for ulcerative colitis through 3 years: UNIFI long-term extension. *J Crohns Colitis* 2022; 16:1222–1234.