Objectively assessed disease activity and drug persistence during ustekinumab treatment in a nationwide real-world Crohn's disease cohort

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Objective Long-term evidence on ustekinumab treatment response and persistence in patients with Crohn's disease in a real-world setting is scarce. We performed a retrospective nationwide chart review study of long-term clinical outcomes in Crohn's disease patients treated with ustekinumab.

Methods The study was conducted in 17 Finnish hospitals and included adult Crohn's disease patients who received an initial intravenous dose of ustekinumab during 2017–2018. Disease activity data were collected at baseline, 16 weeks, and 1 year from health records.

Results The study included 155 patients. The disease was stricturing or penetrating in 69 and 59% had prior Crohn's disease-related surgeries, and 97% had a treatment history of at least one biologic agent. Of 93 patients with ≥1 year of follow-up, 77 (83%) were still on ustekinumab at 1 year. In patients with data available, from baseline to the 1-year follow-up the simple endoscopic score for Crohn's disease (SES-CD) decreased from 10 to 3 ($P=0.033$), C-reactive protein from 7 to 5 mg/L, ($P<0.001$) and faecal calprotectin from 776 to 305 µg/g ($P<0.001$).

Conclusions Ustekinumab treatment in patients with highly refractory Crohn's disease resulted in high long-term treatment persistence and significantly reduced disease activity, assessed with objective markers for intestinal inflammatory activity. Eur J Gastroenterol Hepatol 32: 1507–1513

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Introduction

The introduction of monoclonal antibodies against tumour necrosis factor (anti-TNFs), and α4β7 integrin (vedolizumab), has significantly improved the treatment of Crohn's disease. Nevertheless, a considerable proportion of Crohn's disease patients either fail to respond or lose response to these agents over time [1–3]. These refractory Crohn's disease patients are in urgent need of new treatment options with different modes of action. Ustekinumab is a fully human monoclonal IgG_{1k} antibody against the p40 subunit of interleukin 12 and 23. It was approved in the European Union and the United States in 2016 for the treatment of moderate to severe Crohn's disease after having demonstrated its efficacy in three phase III randomized controlled trials (RCTs) [4,5]. The efficacy of ustekinumab has also been demonstrated in long-term extensions of the RCTs and in a post-hoc endoscopic outcome analysis of the RCTs [6–8].

However, as the strict design and numerous exclusion criteria of RCTs tend to exclude a considerable portion of patients, patient populations in clinical trials may differ substantially from those in real-world routine practice [9]. Consequently, robust real-world effectiveness data are required to enable a reliable interpretation of the outcomes of new therapies in real-world settings. Due to the lack of clinical outcomes in administrative register-based studies, real-world long-term evidence on ustekinumab treatment response and persistence in Crohn's disease

patients receiving an intravenous induction dose followed by subcutaneously administered maintenance therapy is still scarce. Although there are several studies presenting real-world data on the results of ustekinumab in Crohn's disease patients, these mostly concern short-term effectiveness or exclude the intravenous induction regimen, introduced in clinical practice when the official label of ustekinumab was approved for Crohn's disease in 2016, thus much later than the subcutaneous regimen [10–15]. Only a few studies have utilized real-world data to assess the long-term effectiveness and persistence of ustekinumab maintenance therapy initiated with intravenous induction [16–21]. Long-term real-world data of objectively assessed disease activity, such as faecal markers and endoscopic outcomes, are even more limited, despite the fact that the disease activity measures have been pointed out to be central tools in order to prevent future structural bowel damage in the treat-to-target strategy [22].

We report the results of a retrospective noninterventional nationwide chart review study of dosing and long-term clinical outcomes in ustekinumab-treated patients with Crohn's disease in Finland (FINUSTE2, EUPAS30920). The aim is to increase the understanding on the use of ustekinumab in clinical practice and to assess patient outcomes during ustekinumab treatment in patients with Crohn's disease.

Methods

Study design

This retrospective chart review study, called FINUSTE2, captured data via gastroenterologists at 17 hospitals in Finland. All consecutive patients aged ≥18 years with a confirmed diagnosis of Crohn's disease who received an initial intravenous first dose of ustekinumab between 1 January 2017 and 31 December 2018 were included into the study. The study was an extension of the previous FINUSTE multicentre study of 48 adult Crohn's disease patients who initiated ustekinumab treatment in 2017 [13].

FINUSTE2 extended the FINUSTE study by further including Crohn's disease patients who initiated ustekinumab treatment in 2018 and by collecting data from five additional hospitals using the same inclusion criteria as in the FINUSTE study. Furthermore, the study follow-up time was extended by one year until 30 April 2019 for all patients. Identical to the FINUSTE study, the data were collected from health records using electronic standardized health questionnaires. In the FINUSTE2 study, one electronic standardized health questionnaire was used for Crohn's disease patients included in the FINUSTE study ($n=48$) and another health questionnaire was used for new eligible Crohn's disease patients.

The primary objectives of the FINUSTE2 study were to describe the current treatment patterns and the positioning of ustekinumab in the treatment of Crohn's disease in Finland by investigating clinical outcomes and dosing patterns in a real-world setting. Secondary objectives were to determine the proportion of patients continuing treatment with ustekinumab at the time of data collection and to evaluate the change in endoscopic activity and laboratory tests during follow-up. This article addresses clinical outcomes, ustekinumab treatment persistence and changes in endoscopic activity and laboratory tests during follow-up. Details of dosing patterns and concomitant medications are reported elsewhere (Sipponen *et al*., submitted).

The objective of the study was not to assess the safety of ustekinumab. However, due to the pharmacovigilance obligations of drug manufacturers, the investigators received instructions to report directly to Janssen-Cilag Oy if they encountered notations related to adverse events possibly, probably or very likely attributed to ustekinumab while reviewing the patient charts within the scope of the information required by the protocol.

Study variables

Baseline data included age, sex, smoking status, height, weight, year of diagnosis, history of bowel surgery, comorbidities (psoriasis, ankylosing spondylitis, hidradenitis suppurativa), age at diagnosis, disease location and behaviour according to the Montreal classification, and clinically relevant medication for Crohn's disease. Disease activity was measured at baseline, at week 16 (±4 weeks), at 12 months (±1 month), at 18 months (±1 month) and 24 months (±1 month) with a modified Harvey–Bradshaw index (mHBI) not taking notice of the abdominal palpation finding [23,24] the Simple Endoscopic Score for Crohn's Disease (SES-CD) [25] and routine follow-up laboratory tests, such as haemoglobin, leukocytes, platelets, albumin, serum C-reactive protein (CRP) and faecal calprotectin (fCal). The SES-CD is implemented in standard endoscopic assessment recommendations and, hence, in routine daily use in several hospitals in Finland.

Definitions and ustekinumab treatment

We defined biomarker-assessed active disease as fCal >250 µg/g, biomarker remission as fCal ≤250 µg/g [26] and biomarker response as a reduction in fCal of at least 50% from baseline. SES-CD >2 indicated endoscopically active disease and SES-CD ≤2 endoscopic remission [27], whereas a reduction in SES-CD of at least 50% from baseline indicated endoscopic response. Furthermore, clinically active disease and clinical remission were defined as mHBI >4 and mHBI ≤4, respectively, whereas clinical response was defined as a reduction in mHBI of ≥3 points from baseline [28]. The definition of clinical benefit includes both patients with clinical response (a reduction in mHBI of ≥3 points from baseline) and patients with clinically active disease at baseline who reached clinical remission during follow-up.

The patients received the first dose of ustekinumab intravenously and weight-based (<55 kg: 260 mg, 55–85 kg: 390 mg, >85 kg: 520 mg) according to label [14]. Until the 16-week timepoint, the patients had received the first 1–2 subcutaneous injections of ustekinumab 90 mg subcutaneously. The patients who continued ustekinumab therapy beyond the 16-week timepoint started the maintenance treatment by receiving the 90 mg subcutaneous ustekinumab injections with a dosage interval of 8 or 12 weeks [14].

Ethical statement

The FINUSTE2 study was registered in the European Union electronic Register of Post-Authorization Studies (EU PAS Register, EUPAS30920). The ethics committee of Tampere University Hospital reviewed the amended study protocol (R18055) and all involved local register holders approved the study.

Statistical analyses

All analyses were performed with Stata MP 14 statistical software (StataCorp 2015, Stata Statistical Software: Release 14. StataCorp LP, College Station, Texas, USA). Continuous variables are reported as median and interquartile range (IQR) due to potential skewness and censoring of distributions and categorical valuables are reported as proportions (%). The significance of the change from baseline value in laboratory measures and clinical outcomes was tested with the Wilcoxon matched-pairs signed-rank test. Results with a *P* value below 0.05 were considered statistically significant. At all assessment time points, only patients with continued ustekinumab use were included into the analyses. Due to the low number of patients with follow-up data beyond the 1-year timepoint, statistical analyses were based on the data at baseline, 16 weeks and 1 year.

Results

Baseline characteristics

A total of 155 Crohn's disease patients received an intravenous dose of ustekinumab. Table 1 summarizes patient characteristics at baseline. The patients had a median age of 37.3 and a median disease duration of 12.6 years. A vast majority ($n = 150$, 96.8%) had a treatment history of at least one biologic agent and two-thirds ($n = 103$, 66.5%) had used two or more biologic agents. Most frequently used biologic therapies were infliximab (80.0%), adalimumab (66.5%) and vedolizumab (39.4%). A patient could have several reasons for ustekinumab initiation, the most reported reasons being lack of effectiveness of previous biologics ($n = 130$, 83.9%), side effects of previous biologics ($n = 50$, 32.3%) and immunization to previous biologics ($n = 21$, 13.5%). The disease was stricturing in 54.2% of the patients and had required surgery in 59.4%. At baseline, 93 patients (75.6%) had biomarker-assessed active disease (fCal > 250 µg/g), whereas all 43 patients who underwent baseline endoscopy had endoscopically active disease (SES-CD > 2). Of 130 patients with baseline data on fCal and/or SES-CD, 21 patients (16.2%) had no objectively detectable disease activity. In 97 patients with baseline data on mHBI, 63 (64.9%) had clinically active disease (mHBI > 4).

Table 1. Baseline patient and disease characteristics

Patient characteristics	*N*	Value
Age, years, median (IQR)	155	37.3 (29.3–53.0)
Weight, kg, median (IQR)	155	70 (60–83)
Height, cm, median (IQR)	133	171 (165–179)
Disease duration, years, median (IQR)	148	12.6 (5.0–19.2)
Male gender, *n* (%)	81	52.3
Current smoking, *n* (%)[a]	32	20.7
Prior surgery for Crohn's disease, *n* (%)	92	59.4
Prior biological therapy for Crohn's disease, *n* (%)		
No biologics	5	3.2
1 biologic	47	30.3
2 biologics	66	42.6
3 or more biologics	37	23.9
Nonbiological drugs at baseline, *n* (%)		
Corticosteroids[b]	64	41.3
Thiopurines	36	23.2
Methotrexate	21	13.6
5-aminosalicylic acid	20	12.9
Age at diagnosis, *n* (%)		
<17 years (A1)	36	23.2
17–40 years (A2)	87	56.1
>40 years (A3)	32	20.7
Location, *n* (%)		
Ileal (L1) and/or upper gastrointestinal tract (L4)	39	25.2
Colonic (L2)	26	16.8
Ileocolonic (L3)	78	50.3
Ileocolonic (L3) with upper gastrointestinal involvement (L4)	12	7.7
Disease behaviour, *n* (%)		
Inflammatory (B1)	48	31.0
Stricturing (B2)	84	54.2
Penetrating (B3)	23	14.8
Perianal disease (p)	49	31.6

IQR, interquartile range.
[a]Smoking status not known in 13 patients.
[b]Budesonide, prednisone, prednisolone, methylprednisolone.

Follow-up time and ustekinumab drug survival

After one intravenous induction dose, one subcutaneous dose at 8 weeks, and in a proportion of patients ($n = 73$) with a delayed response, another subcutaneous dose until the 16-week follow-up, 140 patients (90.3%) continued to maintenance therapy with subcutaneous ustekinumab. The median follow-up time was 14.2 months (IQR 7.8–17.4 months). Follow-up data at 16 weeks, 1 and 2 years were available for all 155 patients, 93 patients (60.0%) and 18 patients (11.6%), respectively. At the end of the follow-up period (30 April 2019), 122 patients (79.7%) were on ustekinumab maintenance therapy and 31 patients (20.3%) had discontinued ustekinumab treatment, whereas two patients were lost to follow-up (Fig. 1). In 93 patients with follow-up time of at least 1 year, 77 (82.8%) were still on ustekinumab 1 year after treatment initiation. The Kaplan–Meyer graph in Fig. 2 depicts ustekinumab treatment persistence over time.

Disease activity markers during follow-up

During ustekinumab treatment, statistically significant decreases were observed in fCal, CRP and SES-CD already at 16 weeks from treatment initiation (Table 2 and Fig. 3). The proportion of patients with biomarker-assessed active disease decreased from 75.6% (93/123) at baseline to 64.2% (70/109, $P = 0.0582$ vs baseline) at 16 weeks and 51.7% (30/58, $P = 0.001$ vs baseline) at 1 year (Fig. 4). Hence, 48.3% (28/58) of the patients were in biomarker remission at one year. Of these, 24 patients were in corticosteroid-free biomarker remission, meaning a corticosteroid-free biomarker remission rate of 41.4% at 1 year. The biomarker response increased from 37.1% (36/97) at 16 weeks to 53.9% (28/52) at 1 year. In the subgroup of patients who underwent endoscopic assessment, the proportion of patients with endoscopically active disease decreased from 100% (43/43) at baseline to 64.7% (11/17, $P < 0.001$ vs baseline) at 16 weeks but remained after that unchanged with 66.7% (12/18, $P < 0.001$ vs baseline) at 1 year. The proportion of patients with clinically active disease (mHBI > 4) decreased, from 64.9% (63/97) at baseline to 29.5% (23/78, $P < 0.001$ vs baseline) at 16 weeks and remained after that similarly unchanged with 30.2% (13/43, $P < 0.001$ vs baseline) at 1 year. Clinical benefit, defined as having clinical response or reaching clinical remission during follow-up, was found for 82.6% (38/46) at 16 weeks and 77.8% (21/27) at 1 year in patients with clinically active disease at baseline.

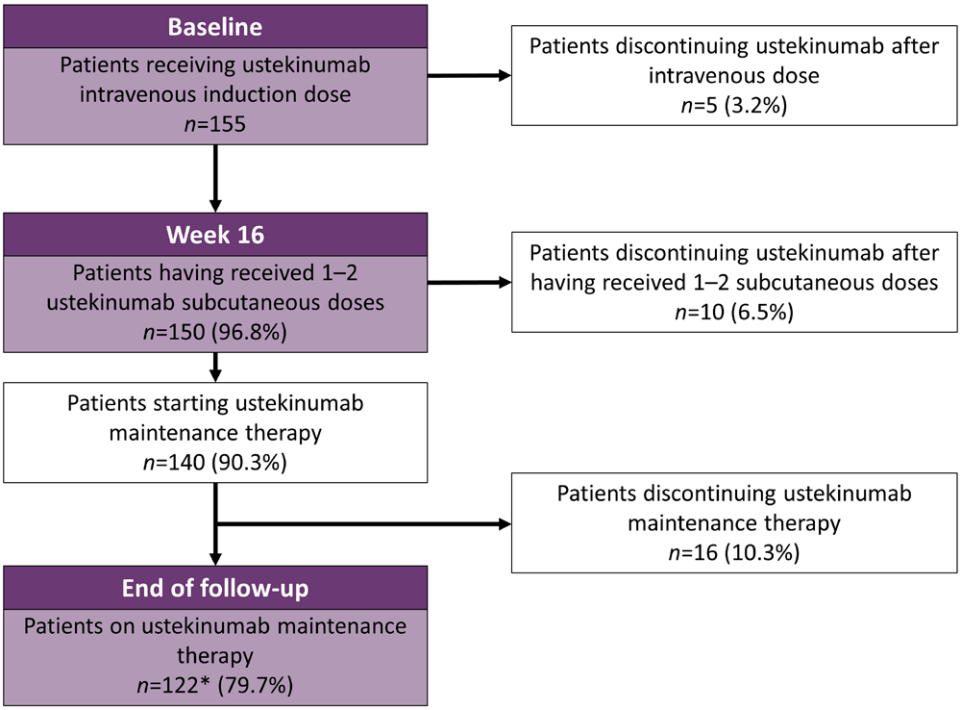

Fig. 1. Flowchart of ustekinumab treatment in the study population. *Two patients lost to follow-up.

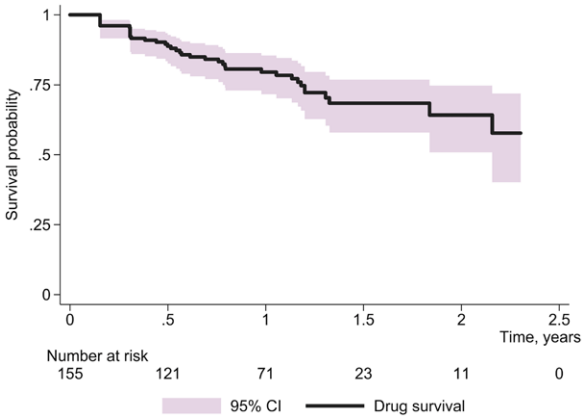

Fig. 2. Kaplan–Meier curve of ustekinumab continuation. CI, confidence interval.

The proportion of patients on corticosteroids decreased statistically significantly from 41.4% at baseline to 18.6% at 16 weeks ($P < 0.001$) and 13.0% at 1 year ($P < 0.001$) in patients on ustekinumab maintenance therapy.

Lack of response during follow-up and ustekinumab tolerability issues

Of 155 patients, 26 (16.8%) underwent surgery during follow-up. Overall, 31 patients (20.3%) discontinued ustekinumab. The main reasons for treatment discontinuation were lack or loss of response ($n = 17$), followed with economic reasons or patient's own wish ($n = 7$). Diagnosis of diffuse large B-cell lymphoma within a year from ustekinumab treatment initiation, pregnancy and other physician's advice were reasons for treatment discontinuation in less than five patients. Events more directly interpreted as related to tolerability (elevated liver enzymes, abdominal abscess, perianal fistula complications and septicaemia and prolonged respiratory infection) were reasons for ustekinumab discontinuation in less than five patients. According to Finnish legislation, this registry study is prevented from reporting data that would further identify individual patients.

Discussion

In this nationwide real-world long-term follow-up study, ustekinumab treatment of patients with highly refractory and long-standing Crohn's disease effectively reduced inflammatory activity, assessed with endoscopy, CRP and fCal. In addition, the study showed long-term drug persistence in patients on ustekinumab treatment.

The study population differs from patients included in RCTs but have similarities with other European real-world study cohorts. The majority of patients in the FINUSTE2 study (96.8%) had been previously treated with biologics including anti-TNFs and vedolizumab, and more than half (59.4%) had undergone Crohn's disease-related surgery. This indicates a more severe disease phenotype than observed in the ustekinumab maintenance therapy RCTs, where as many as 41.9% of the patients were anti-TNF naïve [8]. Instead, the patient population demographics in the FINUSTE2 study show numerous similarities with German [16,17] Belgian [19,20] and Dutch [21] real-world studies. However, heterogeneous study endpoints and definitions of response and remission complicate the direct comparison of the results with other real-world studies. For example, in a retrospective study of 93 Crohn's disease patients with disease activity at baseline by Kubesch *et al.* [16], the disease activity was assessed by combining the HBI and CRP, and, when available (number of observations not mentioned), fCal. The authors reported a remission rate of 51.6% and a response rate of 26.9% at 48 weeks [16].

Table 2. Markers reflecting disease activity over time among ustekinumab users

	Baseline	16 weeks	1 year	1.5 years
Markers of disease activity	*N* = 155	*N* = 146	*N* = 77	*N* = 27
Faecal calprotectin, µg/g	776 (253–1944) *n* = 123	554 (175–1011)** *n* = 109	305 (92–972)*** *n* = 58	253 (43–529)** *n* = 14
C-reactive protein, mg/L	7.2 (3–15) *n* = 154	5 (2–13)*** *n* = 141	5 (2–11)*** *n* = 72	6 (2–13) *n* = 25
Haemoglobin, g/L	133 (124–141) *n* = 155	133 (123–142) *n* = 143	135 (126.5–147)* *n* = 79	134 (125–147) *n* = 27
Leukocytes, E9/L	7.8 (6.5–10) *n* = 155	7.4 (5.6–9)** *n* = 143	7.1 (5.9–8.8)*** *n* = 76	7.5 (6.3–9.3) *n* = 27
Platelets, E9/L	330 (280–404) *n* = 155	323 (276–383)* *n* = 143	307 (265.5–375)* *n* = 76	328 (295–374) *n* = 27
Albumin, g/L	35 (31–37) *n* = 111	35 (32–37) *n* = 93	34 (31.1–38.1)* *n* = 44	35 (32–38)* *n* = 15
SES-CD	10 (8–15) *n* = 43	5 (0–6)** *n* = 17	3 (0–9)* *n* = 18	*n* < 5

All values given as median (interquartile range), number of patients with available data. *P < 0.05, **P < 0.01, ***P < 0.001 based on the Wilcoxon matched pairs signed rank test.
SES-CD, simple endoscopic score for Crohn's disease.

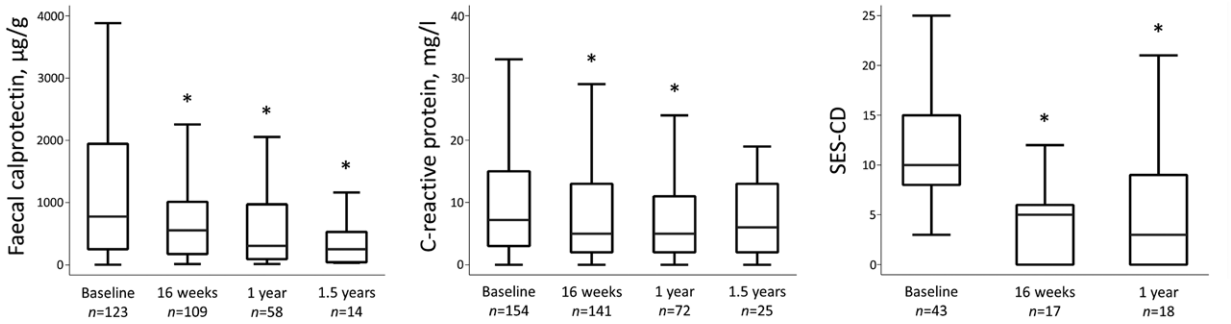

Fig. 3. Markers of disease activity at baseline and during follow-up. SES-CD, simple endoscopic score for Crohn's disease. *P < 0.05 vs baseline.

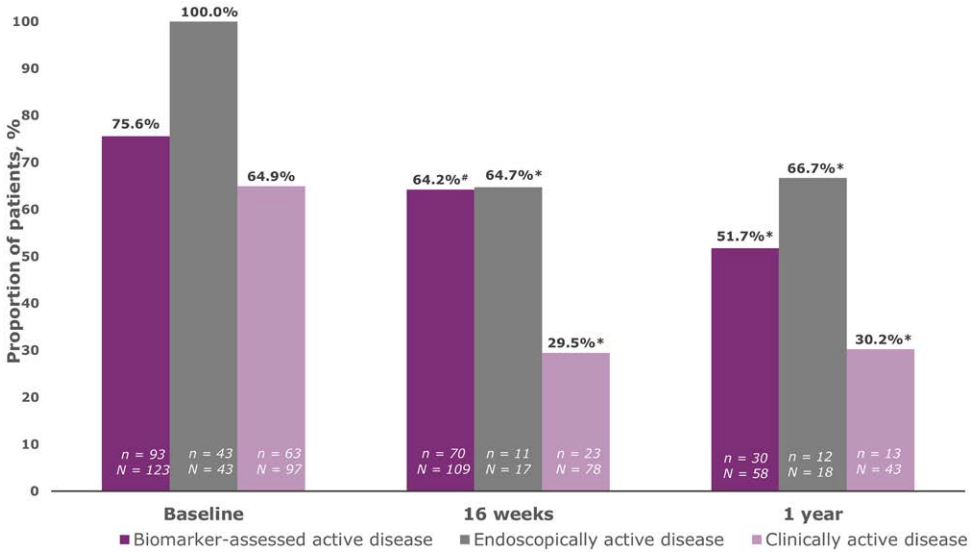

Fig. 4. Proportions of patients in biomarker-assessed, endoscopically, and clinically active disease during follow-up. Biomarker-assessed active disease: faecal calprotectin >250 µg/g; endoscopically active disease: the simple endoscopic score for Crohn's disease > 2; clinically active disease: modified Harvey–Bradshaw index > 4, #P = 0.0582 vs baseline, *P ≤ 0.001 vs baseline.

Our study separates clinical symptoms measured with the mHBI from objectively assessed biomarker response and remission. Moreover, subjective symptoms correlate poorly with the grade of inflammation and may complicate the interpretation of inflammatory response to treatment even though both symptoms and potentially asymptomatic inflammation should be considered in clinical practice. Liefferinckx *et al*. retrospectively studied 152 patients with clinically active disease at baseline, and defined clinically active disease as HBI >4, clinical response as reduction in HBI of ≥3 points, and remission as HBI ≤4 [20]. The study observed a steroid-free clinical response rate of 42.1% and clinical remission rate of 25.7% at 1 year. Verstockt *et al*. performed a prospective real-world

study in 86 Crohn's disease patients with follow-up data of at least 24 weeks for every patient [19]. In line with the results of our study, a significant decrease in the SES-CD from baseline (11.5) to 24 weeks (9.0) occurred with an endoscopic response rate (≥50% SES-CD decrease from baseline) and remission rate (SES-CD ≤ 2) of 20.5 and 7.1%, respectively. However, the investigators observed a significant decrease in fCal levels from baseline to 8 weeks followed by an increase which reapproached the baseline values at 24 weeks. A recent prospective real-world follow-up study by Biemans *et al*., however, showed continuous improvement of biochemical activity markers of CRP and fCal during a 52-week follow-up [21]. The authors found that 26.4% of patients achieved biochemical remission at 52 weeks defined as CRP ≤5 mg/L and fCal ≤200 µg/g. These findings are comparable to our results showing biomarker remission defined as fCal ≤250 µg/g of 48.3% at 1 year.

Despite a doubled proportion of patients in biomarker remission and a statistically significant decrease in fCal levels and SES-CD from baseline to the 1-year timepoint, 51.7 and 66.7% of our patients still had biomarker-assessed active disease and endoscopically assessed active disease, respectively, at 1 year. In addition, most patients were on ustekinumab therapy at the end of the whole follow-up even though only a minority of patients reached biomarker remission. This may reflect the lack of treatment options in this population including patients with a history of highly refractory disease, but it may also be due to the undisputable clinical benefit. Our study findings suggest that Crohn's disease patients on ustekinumab treatment have high treatment persistence as 82.8% were on ustekinumab 1 year after treatment initiation. In previous real-world long-term studies with similar patient characteristics and intravenous induction, the probability of continuing ustekinumab at 1 year after treatment initiation has been lower, ranging from 58.5 to 62.9% [16,20,21].

We found that endoscopic response (40.0%) and endoscopic remission (33.3%) at one year were clearly higher compared to endoscopic response (17.4%) and endoscopic healing (10.9%) at 44 weeks in a post-hoc endoscopy analysis of the RCTs [8]. These findings were surprising because of the markedly lower number of biologically naïve patients in our study. However, the results should be taken with great caution due to the limited number of SES-CD data in our study [8].

Additionally, an important finding of our study is the statistically significant reduction of patients using corticosteroids after starting ustekinumab, regardless of remission status. The 1-year corticosteroid-free biomarker remission rate of 41.4% is not directly comparable with the results from other real-world studies on long-term ustekinumab therapy as these have dealt with corticosteroid-free objective remission only as a part of a broader combined entity of clinical and objective markers. For example, steroid-free combined remission (HBI ≤ 4 and fCal < 250 µg/g) at 48 weeks used by Kubesch *et al*. [16] occurred in 20.4%, whereas Biemans *et al*. [21] reported 18.2% of their patients having achieved combined corticosteroid-free clinical and biochemical remission (HBI ≤ 4, CRP < 5 mg/L and, if available, fCal ≤ 200 µg/g) at 52 weeks.

According to the number and severity of reported adverse events in our study, the safety of ustekinumab is comparable to the safety profile of ustekinumab reported in RCTs and other real-world studies in Crohn's disease patients.

The major strength of our study is the nationwide coverage of all major inflammatory bowel disease treatment centres in Finland including a vast majority of Crohn's disease patients in Finland who have initiated ustekinumab treatment with intravenous induction during 2017–2018. The study confirms and complements previous real-world studies by providing extensive information on objectively assessed disease activity markers, particularly by the very large amount of fCal measurements. The high number of patients with baseline and follow-up data on fCal reflects the widespread use of fCal in monitoring treatment response in clinical practice in the Finnish centres. In addition, it indicates consistency of national treatment routines. As a descriptive, noninterventional real-world study, we find it important to report for all patients included, regardless of disease activity status at baseline. Although the major reason for ustekinumab initiation was active, treatment-refractory disease, a small proportion of patients initiated ustekinumab due to other reasons, such as tolerability issues, with no detectable baseline disease activity. The use of the mHBI in a clinical setting is justified, since the correlation between the complete HBI and the mHBI is strong. Furthermore, this should allow for both self-reporting and chart review of the variables required for calculation of clinical activity [24]. The retrospective design is by far the biggest limitation, leading to patient heterogeneity and incomplete follow-up data, particularly on the endoscopic assessment of disease activity. We are also aware that fCal values may differ due to variation of laboratory tests provided by different manufacturers. Due to the retrospective nature of our study, we cannot rule out the effect of this variation in the results, but we consider it to be minor and unlikely.

In conclusion, this study provides further robust real-world evidence on the long-term persistence and effectiveness of ustekinumab treatment objectively assessed with disease activity markers, such as fCal, CRP and the SES-CD.

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Conflicts of interest

C.-G.a.B. reports personal fees from Janssen-Cilag during the conduct of the study and personal fees from AbbVie, Janssen-Cilag, MSD, Mylan, Pfizer and Vifor Pharma outside the submitted work. T.I. reports grants from Janssen Cilag during the conduct of the study and personal fees from Takeda and Tillotts Pharma outside the submitted work. T.H. is a partner, employee and chairman of the board of ESiOR Oy, and reports grants and nonfinancial support from Janssen-Cilag during the conduct of the study. E.S.

is a partner, employee and CEO of ESiOR Oy, and reports grants and non-financial support from Janssen-Cilag Oy during the conduct of the study. A.E. reports grants from Janssen-Cilag, personal fees from Janssen-Cilag, MSD, Pfizer and Takeda outside the submitted work. A.J. reports personal fees from Abbvie, Ferring, Janssen-Cilag, MSD, Pfizer, Takeda and Tillotts Pharma outside the submitted work. R.K. reports grants from Janssen-Cilag during the conduct of the study, personal fees from Ferring, Tillotts Pharma, Janssen-Cilag, MSD, Pfizer, and nonfinancial support from Ferring, MSD, Takeda, Tillotts Pharma and Vifor Pharma outside the submitted work. I.K. reports personal fees from Janssen-Cilag during the conduct of the study, personal fees and nonfinancial support from Abbvie, MSD and Tillotts Pharma, and non-financial support from Ferring, Janssen-Cilag, Medans/Pharmacosmos and Takeda outside the submitted work. H.N. reports personal fees from Janssen-Cilag during the conduct of the study and personal fees from Abbvie, Janssen-Cilag, MSD, Pfizer, Roche, Takeda and Tillotts Pharma outside the submitted work. J.T. reports personal fees from Janssen-Cilag during the conduct of the study and personal fees from Janssen-Cilag and Pfizer outside the submitted work. T.S. reports grants from Janssen-Cilag during the conduct of the study, grants from Takeda, personal fees from AbbVie, Ferring, Janssen-Cilag, Pfizer, Takeda and Tillotts Pharma outside the submitted work. C.W., A.B., R.N. and M.R.K. are all employees of Janssen-Cilag. There are no conflicts of interest for the remaining authors.

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