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Ustekinumab for Crohn's Disease: Two-Year Results of the Initiative on Crohn and Colitis (ICC) Registry, a Nationwide Prospective Observational Cohort Study

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Abstract

Aims: Ustekinumab is a monoclonal antibody that selectively targets p40, a shared subunit of the cytokines interleukin [IL]-12 and IL-23. It is registered for the treatment of inflammatory bowel diseases. We assessed the 2-year effectiveness and safety of ustekinumab in a real world, prospective cohort of patients with Crohn's disease [CD].

Methods: Patients who started ustekinumab were prospectively enrolled in the nationwide Initiative on Crohn and Colitis [ICC] Registry. At weeks 0, 12, 24, 52 and 104, clinical remission Harvey Bradshaw Index≤ 4 points], biochemical remission (faecal calprotectin ≤ 200 μg/g and/or C-reactive protein ≤5 mg/L], perianal fistula remission, extra-intestinal manifestations, ustekinumab dosage and safety outcomes were determined. The primary outcome was corticosteroid-free clinical remission at week 104.

Results: In total, 252 CD patients with at least 2 years of follow-up were included. Of all included patients, the proportion of patients in corticosteroid-free clinical remission was 32.3% [81/251], 41.4% [104/251], 39% [97/249] and 34.0% [84/247] at weeks 12, 24, 52 and 104, respectively. In patients with combined clinical and biochemical disease activity at baseline [*n* = 122], the corticosteroid-free clinical remission rates were 23.8% [29/122], 35.2% [43/122], 40.0% [48/120] and 32.8% [39/119] at weeks 12, 24, 52 and 104, respectively. The probability of remaining on ustekinumab treatment after 52 and 104 weeks in all patients was 64.3% and 54.8%, respectively. The main reason for discontinuing treatment after 52 weeks was loss of response [66.7%]. No new safety issues were observed.

Conclusion: After 104 weeks of ustekinumab treatment, one-third of CD patients were in corticosteroid-free clinical remission.

Key Words: Ustekinumab; Crohn's disease; real-world; ICC Registry

1. Introduction

Crohn's disease [CD] is a chronic inflammatory bowel disease [IBD] with heterogeneous symptoms including abdominal pain, diarrhoea, rectal bleeding and malnutrition. To prevent disease-related gastrointestinal damage, it is essential to obtain deep [endoscopic] remission, which usually requires long-term medical therapy.[1] None of the currently available medical therapies are effective in all CD patients and all medical therapies are associated with possible severe side effects.

One of the newer therapeutic options for CD is ustekinumab, a fully human monoclonal antibody targeting the p40 subunit of interleukin [IL]-12 and IL-23. This inhibits T-helper 1 and T-helper 17 pathways involved in CD. The effectiveness of ustekinumab in inducing and maintaining clinical remission in CD patients has been demonstrated in the IM-UNITI trials.[2] The long-term extension [LTE] trial revealed that treatment with ustekinumab every 8 or 12 weeks was effective in maintaining corticosteroid-free remission through week 92 in 63.4% [52/82] and 67.9% [57/84] of patients, respectively, and that treatment was well tolerated.[3] However, patients could only enter the IM-UNITI LTE when achieving clinical response (decrease in Crohn's Disease Activity Index [CDAI] score ≥100 points or a total CDAI score<150) after 8 weeks of treatment and continued treatment after 52 weeks. Notwithstanding that ustekinumab has demonstrated its effectiveness in formal trials, it is estimated that only one-third of IBD patients meet the strict inclusion and exclusion criteria to participate in clinical trials.[4] Hence, it can be questioned whether the results of the UNITI trials can be extrapolated to the real-world IBD population. Real-world data with long-term follow-up to assess effectiveness, safety and loss of response is required given the need for continued treatment in CD. Furthermore, the ability to predict response to ustekinumab is important because the number of treatment options for patients with CD is increasing. If predictors of response or intolerance are identified, therapy can be applied more specifically to those patients who are likely to benefit, which leads to improved outcomes of IBD.

To date, a considerable number of cohorts have described the experience of ustekinumab up to 1 year.[5–13] Only a few cohorts have described the long-term [>52 weeks] results regarding the effectiveness and safety of ustekinumab in a real-world population.[14–16] However, these cohorts consisted of a small number of patients, had a retrospective study design and were unable to identify predictors of clinical response.

Using the Dutch Initiative on Crohn and Colitis [ICC] Registry, a prospective, observational registry for novel IBD therapies, we aimed to evaluate the long-term effectiveness and safety of ustekinumab in a real-world setting with a follow-up of 2 years. Secondly, we aimed to assess predictors of clinical response.

2. Methods

2.1. Study design and setting

The ICC Registry is a prospective, nationwide and observational registry of IBD patients starting novel IBD therapies in regular care in the Netherlands. The design and rationale as well as the ustekinumab results up to 1 year have previously been described in detail.[5] Currently, the eight academic and seven non-academic centres participate in this registry. IBD patients aged ≥18 years were included and followed for 2 years according to a pre-defined schedule of out-patient visits designed to closely follow regular care [at initiation of therapy and during maintenance at weeks 12, 24, 52 and 104 or until medication is discontinued]. Electronic case report forms [eCRFs] were used for data collection with automated reminders to ensure adherence to the protocol. Monitoring of data entrance takes place by the treating physician or IBD nurse specialist. Validation of data takes place by the investigator.

2.2. Participants

Patients ≥18 years old with an established CD diagnosis starting ustekinumab in regular care were enrolled in 12 participating centres. The decision to start ustekinumab was at the discretion of the treating physician. The initial intravenous [IV] infusion with ustekinumab at baseline was weight-adjusted [260 mg ≤55 kg, 390 mg between 55 and 85 kg, 520 mg ≥85 kg]. According to the label, the first subcutaneous [SC] 90 mg induction dose was administered at week 8

followed by a maintenance dose of 90 mg SC every 8 or 12 weeks, at the discretion of the physician.

Since this is an ongoing registry, we included patients starting therapy at least 2 years ago for the current evaluation.

2.3. Outcomes and definitions

The primary objective of this study was to determine the proportion of patients treated with ustekinumab in corticosteroid-free clinical remission (Harvey Bradshaw Index [HBI] ≤ 4) at week 104 compared to baseline. Secondary outcomes included: clinical response [at least 3 points HBI reduction], clinical remission [HBI ≤ 4], biochemical remission (faecal calprotectin [FC] level of ≤200 µg/g and/or C-reactive protein [CRP] concentration ≤5 mg/L, when available), ulcerative disease during endoscopy, absence of extra-intestinal manifestations [EIMs], general wellbeing [as part of the HBI, reported by the patient on a scale of 0–10] and ustekinumab discontinuation rate. When biochemical data were missing, patients were considered non-responders. Clinical and biochemical predictors associated with disease severity or refractory disease [disease behaviour, disease location, perianal disease, active fistula, prior intestinal resections, anti-integrin exposure, clinical and biochemical disease activity and concomitant medication] were included in the regression analyses.

Corticosteroid-free clinical remission was compared between patients on concomitant immunosuppressant therapies [thiopurines or methotrexate] and without concomitant immunosuppressant medication at baseline. Furthermore, corticosteroid-free clinical remission was compared between patients with every 8 weeks vs every 12 weeks interval dosing from week 12.

EIMs that were assessed included arthralgia/arthritis, uveitis, aphthous stomatitis, erythema nodosum and pyoderma gangrenosum. The presence and/or absence of EIMs was assessed by the treating physician.

Reasons for treatment discontinuation were documented at the discretion of the treating physician. Patients who discontinued ustekinumab treatment due to a primary or secondary non-response, adverse events, or at the patient's request without clinical remission were considered as a treatment failure and classified as non-responders. Patients who discontinued ustekinumab because of pregnancy or at their own request with long-term sustained clinical and biochemical remission were considered censored cases. When patients changed treatment facility while continuing treatment, follow-up information of remaining visits were collected through contacting patient's new treatment facility. Follow-up time was determined based on the date of the initial IV infusion with ustekinumab until the last IV infusion.

All safety analyses were performed based on a per-protocol principle. Safety outcomes included the number of drug-related adverse events, infections and disease-related hospitalizations per 100 patient-years. Adverse events were classified as possibly, probably and not related to ustekinumab. Infections not requiring medical treatment were classified as mild, infections treated with oral antibiotics or antiviral medication were classified as moderate, and infections requiring hospitalization or IV administered antibiotic or antiviral medication were classified as severe.

2.4. Statistical methods

All effectiveness analyses were performed based on an intention-to-treat principle. Depending on the normality of the underlying distribution, continuous variables were presented as means with standard deviation [SD] of as median with interquartile range [IQR]. Categorical variables were presented as percentages and compared by using the χ^2 test. Dichotomous variables were analysed using a chi-square test or Fisher's exact test and continuous variables using an independent *t*-test or Mann–Whitney *U* test according to distribution. Kaplan–Meier plots were used to illustrate time to ustekinumab discontinuation. Binary logistic regression analyses were used to assess variables associated with week 104 corticosteroid-free clinical remission. Multivariate analysis was performed on variables with $p < 0.2$ on univariate analysis. Two-sided p-values < 0.05 were considered statistically significant. All analyses were performed with IBM SPSS Statistics version 26.0.0.1.

2.5. Ethical consideration

This study was reviewed and approved by the Committee on Research Involving Human Subjects at the Radboudumc, Nijmegen [institutional review board: 4076].

3. Results

3.1. Baseline characteristics

On October 1, 2020, a total of 315 CD patients were included in the ICC Registry. Of these patients, 252 completed at least 2 years of follow-up and were included in this study. The median treatment duration was 95 weeks [IQR 31–104]. Baseline characteristics of these 252 patients are summarized in Table 1. Most patients were female [60.3%] and the median age at inclusion was 41 years [IQR 32–55]. At inclusion, patients had a median disease duration of 15 years [IQR 10–22]. Around one-third of patients [35.7%, n = 90/252] had ileocolonic disease and 16.7% [42/252] had penetrating disease behaviour. Almost all patients [99.2%] were exposed to at least one anti-tumour necrosis factor [anti-TNF] treatment and 73% were exposed to two or more. In total, 108 patients [42.9%] were previously treated with vedolizumab. There were no significant different baseline characteristics between patients who were vedolizumab-naive and patients who were vedolizumab-experienced. A history of intestinal resections was documented in 60.3% of patients and 21.0% had undergone previous perianal surgery. Ninety-one patients [36.1%] used corticosteroids at initiation of therapy and 55 patients [21.8%] were already in corticosteroid-free clinical remission.

At baseline 171 patients [67.9%] had clinical disease activity with a median HBI of 9 [IQR 7–12]. These patients showed a median FC of 610 µg/g [IQR 288–1595] and a median CRP of 9 mg/L [IQR 3–21] at baseline. In total, 173 patients [68.7%] had biochemical disease activity [FC > 200 µg/g and/or CRP > 5 mg/L] at baseline and 222 [88.1%] patients had either clinical or biochemical disease activity. In total, 122 patients had both clinical and biochemical disease activity. Before initiation of therapy, 140 patients [55.6%] underwent endoscopy of whom 138 showed disease activity. The most common reasons to initiate ustekinumab therapy in patients without clinical or biochemical disease activity were adverse events caused by previous biological therapy and stricturing disease due to inflammation without clinical disease activity [HBI > 4]. Other reasons to start therapy were prevention after surgery, perianal disease, wishes of the patient or unclear.

3.2. Effectiveness outcomes

3.2.1. Corticosteroid-free clinical remission

The proportion of patients in corticosteroid-free clinical remission was 32.3% [81/251], 41.4% [104/251], 39% [97/249] and 34.0% [84/247] at weeks 12, 24, 52 and 104, respectively [Figure 1]. Of the

Table 1. Baseline characteristics

		Total, *n* = 252
Age at inclusion [years] [a]	Median [IQR]	41 [32–55]
Female	*N* [%]	152 [60.3%]
Disease duration [years]	Median [IQR]	15 [10–22]
Follow-up since start ustekinumab [weeks]	Median [IQR]	95 [31–104]
Body mass index[b]	Mean [SD]	24 [4.9]
Perianal disease	*N* [%]	33 [13.1%]
Active smoking	*N* [%]	53 [21.0%]
Disease activity		
HBI score	Median [IQR]	7 [4–11]
CRP [mg/L]	Median [IQR]	8.0 [2.5–20.0]
FC [mg/kg]	Median [IQR]	633.5 [260.8–1524.8]
Medical history		
Disease location[b]		
Ileum	*N* [%]	72 [28.6%]
Colon	*N* [%]	90 [35.7%]
Ileocolonic	*N* [%]	90 [35.7%]
Upper gastrointestinal involvement	*N* [%]	12 [4.8%]
Disease behaviour[b]		
Inflammatory	*N* [%]	181 [71.8%]
Stricturing	*N* [%]	25 [9.9%]
Penetrating	*N* [%]	42 [16.7%]
Unknown	*N* [%]	4 [1.6%]
Prior intestinal resection[s]	*N* [%]	152 [60.3%]
Prior perianal interventions	*N* [%]	53 [21%]
Prior treatment		
Failed ≥ 1 anti-TNF	*N* [%]	250 [99.2%]
Failed ≥ 2 anti-TNF	*N* [%]	184 [73.0%]
Failed vedolizumab	*N* [%]	108 [42.9%]
Concomitant treatment[b]		
Oral prednisone	*N* [%]	47 [18.7%]
Oral prednisone dose	mg [IQR]	20 [20–30]
Thiopurine	*N* [%]	49 [19.4%]
Methotrexate	*N* [%]	15 [6.0%]

Abbreviations: IQR, interquartile range; anti-TNF, anti-tumour necrosis factor; HBI, Harvey–Bradshaw Index; CRP, C-reactive protein; FC, faecal calprotectin.
[a]At inclusion.
[b]Maximum extent until inclusion.

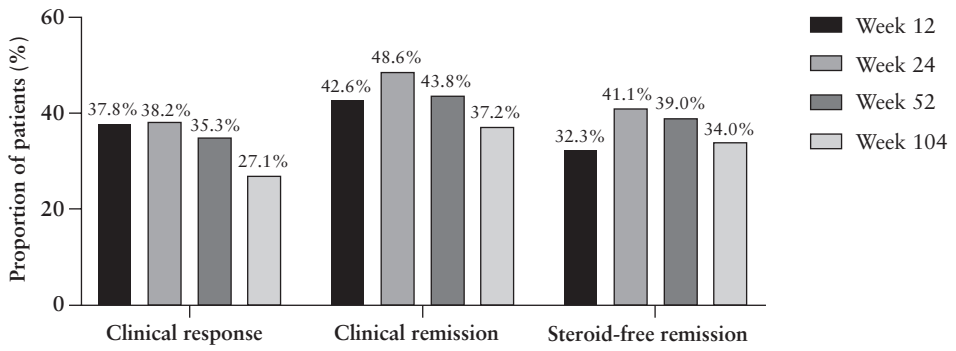

Figure 1. Clinical outcomes in all patients. Percentage of patients with clinical response, clinical remission and steroid-free remission at weeks 12, 24, 52 and 104. All patients included in the ustekinumab series who initiated therapy at least 2 years previously were included [intention-to-treat]. Remission was defined as an Harvey Bradshaw Index [HBI] score ≤4 points. Response was at least 3 points HBI reduction. Missing data were considered non-responders.

104 patients in corticosteroid-free clinical remission at week 24, 50 patients [48.1%] were still in corticosteroid-free clinical remission at week 104.

In patients with combined clinical and biochemical disease activity at baseline, the corticosteroid-free clinical remission rates were 23.8% [29/122], 35.2% [43/122], 40.0% [48/120] and 32.8% [39/119] at weeks 12, 24, 52 and 104, respectively [Figure 2].

Of the patients who were treated with prednisone at baseline, 5/47 [10.6%], 14/47 [29.8%], 16/47 [34.0%] and 16/47 [34.0%] were in corticosteroid-free clinical remission at weeks 12, 24, 52 and 104 respectively.

The course of clinical outcomes between initiation of therapy, week 52 and 104 is displayed in a Sankey diagram for both patients with and without clinical disease activity at baseline [Figure 3].

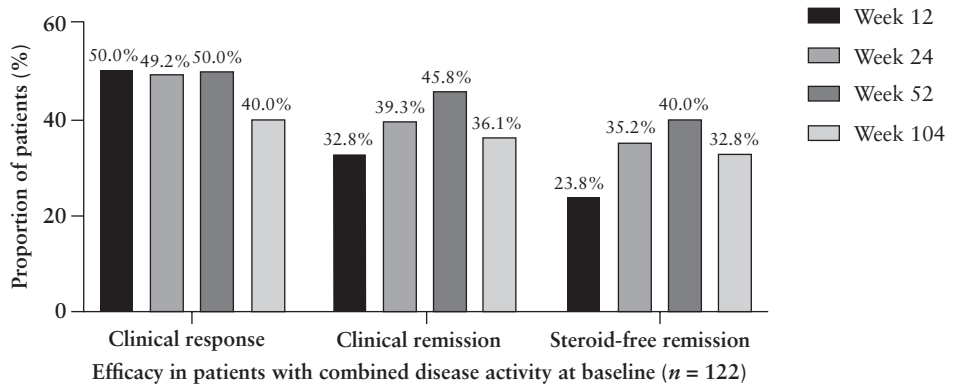

Figure 2. Clinical outcomes in patients with clinical and biochemical disease activity at baseline. Percentage of patients with clinical response, clinical remission and steroid-free remission at weeks 12, 24, 52 and 104. Patients with combined clinical disease activity (Harvey Bradshaw Index [HBI] > 4) and biochemical disease activity (faecal calprotectin [FC] level > 200 μg/g and/or C-reactive protein [CRP] > 5 mL/L) were included.

3.2.2. Clinical remission and response

The proportion of patients in clinical remission was 42.6% [107/251], 48.6% [122/251], 43.8% [109/249] and 37.2% [92/247] at weeks 12, 24, 52 and 104, respectively [Figure 1]. Of the 122 patients in clinical remission at week 24, 62 [50.8%] were still in remission at week 104. In patients with combined clinical and biochemical disease activity at baseline [*n* = 122], the clinical remission rates were 32.8% [40/122], 39.3% [48/122], 45.8% [55/120] and 36.1% [43/119] at weeks 12, 24, 52 and 104, respectively [Figure 2].

The proportion of patients with clinical response was 37.8% [95/251], 38.2% [96/251], 35.3% [88/249] and 27.1% [67/247] at weeks 12, 24, 52 and 104, respectively [Figure 1]. Of the 96 patients with clinical response at week 24, 49 [51.0%] still had clinical response at week 104. In patients with combined clinical and biochemical disease activity at baseline, the clinical response rates were 50.0% [61/122], 49.2% [60/122], 50.0% [60/120] and 40.0% [44/119] at weeks 12, 24, 52 and 104, respectively [Figure 2].

3.2.3. Biochemical disease activity

The proportion of patients in biochemical remission was 17.9% [45/252], 23.5% [59/251], 21.1% [53/251], 27.3% [68/249] and 21.5% [53/247] at baseline and weeks 12, 24, 52 and 104, respectively. Of the 53 patients with biochemical remission at week 24, 22 [41.5%] were still in biochemical remission at week 104. In patients with combined clinical and biochemical disease activity at baseline [*n* = 122], the biochemical remission rates were 23.0% [28/122], 21.3% [26/122], 25.8% [31/120] and 21.0% [25/119] at weeks 12, 24, 52 and 104, respectively.

Median FC levels of patients still on treatment were 663.5 μg/g [IQR 260.8–1524.8], 389.5 μg/g [IQR 124.3–917.8], 263 μg/g [IQR 96–818], 175 μg/g [IQR 69.5–672.5] and 105 μg/g [IQR 48.3–233.3] at baseline and weeks 12, 24, 52 and 104, respectively. Median CRP levels of all patients were 8 mg/L [IQR 2.5–20], 5 mg/L [IQR 2–12], 5.6 mg/L [IQR 2–13], 3.4 mg/L [IQR 1.4–9] and 3 mg/L [IQR 1.3–6.4] at baseline and weeks 12, 24, 52 and 104, respectively.

3.2.4. Combined clinical and biochemical remission

The proportion of patients with combined corticosteroid-free clinical and biochemical remission was 5.2% [13/252], 7.6% [19/251], 12.4% [31/251], 17.7% [44/249] and 15.8% [39/247] at baseline and weeks 12, 24, 52 and 104, respectively. Of the 31 patients with combined remission at week 24, nine [29.0%] were still in combined remission at week 104.

In patients with combined clinical and biochemical disease activity at baseline, combined clinical and biochemical remission was 9.0% [11/122], 13.1% [16/122], 20.0% [24/120] and 18.5% [22/119] at weeks 12, 24, 52 and 104, respectively.

3.2.5. Endoscopic disease activity

Endoscopy was not mandatory in our cohort, but was performed at the discretion of the treating physician. Forty-six patients had endoscopic disease activity at baseline and underwent at least one endoscopy during follow-up, after a median duration of 8 months [5.5–9]. Ten of 46 patients [21.7%] showed remission of ulcers. Seventeen of these 46 patients underwent a second endoscopy during follow-up. One patient showed remission of ulcers in the second endoscopy, 19 months after initiation of therapy. Two of 17 patients [11.8%] were considered secondary treatment failures after a treatment duration of 12 and 14 months. The 14 patients with persisting ulceration underwent their second endoscopy after a mean treatment duration of 14 months [SD 5.6].

Overall, in 20 of 46 patients, endoscopy was performed shortly before withdrawal of therapy. Ulcers were seen in 80% [16/20] of these patients.

3.2.6. Ustekinumab interval

After the first subcutanous (SQ) injection, 82 [32.5%] patients started SQ therapy at a 12-week interval [q12w], 146 [57.9%] patients at an 8 week [q8w] interval, two patients at a 6 week interval and two patients at a 4 week interval. The remaining 20 patients discontinued treatment before 12 weeks after initiation. Preference for a q8w or q12w interval was centre-dependent. Patients with a q8w interval had a significantly longer follow-up compared to patients with a q12w interval [Supplementary Table 1]. Further baseline characteristics were comparable between patients on a q8w interval and a q12w interval [Supplementary Table 1]. The proportion of patients in corticosteroid-free clinical remission was not significantly different at weeks 52 and 104 between patients on a q8w or a q12w interval: 45.2% [q8w] vs 35.4 [q12w], $p = 0.80$; and 39.7% [q8w] vs 29.3% [q12w], $p = 0.68$, respectively. Patients on a q12w interval at 12 weeks of treatment discontinued treatment after a significantly shorter period when compared to patients on a q8w interval [37 weeks vs 29 weeks respectively, $p = 0.01$]. In both groups, lack of response was the main reason for treatment discontinuation.

In total, 49 patients underwent dose intensification from a q12w interval to a q8w interval after 12 weeks of treatment. Of these

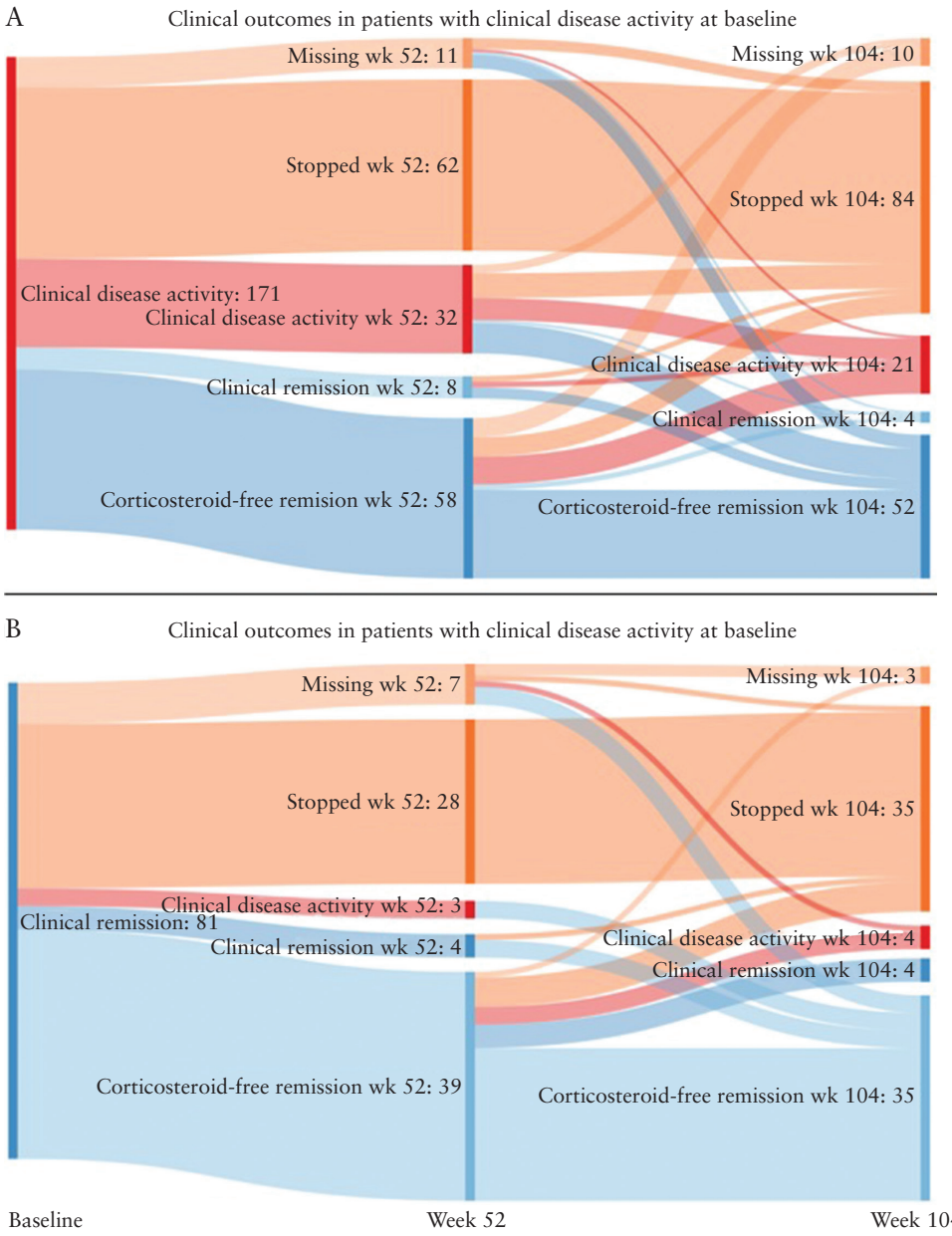

Figure 3. Sankey diagram, depicting the course of clinical outcomes between initiation of therapy and weeks 52 and 104 of all patients. [A]The course of clinical outcomes in patients with clinical disease activity (Harvey Bradshaw Index [HBI] > 4) at baseline. [B]The course of clinical outcomes in patients without clinical disease activity at baseline.

patients, 71.4% [35/49] achieved corticosteroid-free clinical remission. Eight patients underwent dose intensification from a q12w interval to a q8w interval after 52 weeks of treatment, of whom five [62.5%] achieved clinical remission at 104 weeks of follow-up. Eleven patients underwent dose de-escalation from a q8w to q12w interval after 12 weeks of SC treatment. Of these patients, 63.6% [7/11] achieved corticosteroid-free clinical remission at week 104.

3.2.7. Concomitant immunosuppressants

At initiation of therapy, 64 patients [25.4%] used concomitant immunosuppressant therapy [either methotrexate or thiopurine]. Patients treated with a concomitant immunosuppressant at baseline had undergone significantly more intestinal resections. Further baseline characteristics were comparable [Supplementary Table 2].

The proportion of patients in corticosteroid-free clinical remission was not significantly different at weeks 52 and 104 between patients treated with monotherapy vs patients treated with concomitant immunosuppressant therapy: 36.2% [monotherapy] vs 45.3% [combined], $p = 0.23$; and 31.4% [monotherapy] vs 39.1% [combined], $p = 0.28$. There was no significant difference in discontinuation rate between the two groups. Of the patients treated with monotherapy, 45,7% [86/188] discontinued treatment vs 45.3% [29/64] of patients with concomitant immunosuppressant use [$p = 0.54$].

3.2.8. Clinical factors associated with corticosteroid-free clinical remission

Possible predictors of corticosteroid-free clinical remission at week 104 are displayed in Table 2. There were no predictive factors

associated with corticosteroid-free clinical remission at week 104 in univariate and multivariate analysis.

3.2.9. Perianal manifestations

At baseline, 29 patients [11.5%] with perianal Crohn's disease [pCD] had one or more active fistulas. In 18 patients [62.1%] fistulas had spontaneous drainage and in 11 patients [37.9%] fistulas drained after gentle manual pressure. Fistula remission was seen in 17.2% [5/29], 37.9% [11/29], 37.9% [11/29] and 20.7% [*n* = 6/29] of patients after 12, 24, 52 and 52 weeks of treatment. Six of these patients had undergone perianal surgery during follow-up, mostly seton placement. Two of these six patients underwent perianal surgery after 52 weeks while in clinical remission. Seven patients developed new perianal fistulas during follow-up, of whom five developed fistulas within 24 weeks after initiation of treatment. Five of these patients achieved fistula remission within the 2 years of follow-up. One patient developed perianal fistula after 52 weeks of therapy while the patient was in corticosteroid-free clinical remission. Four patients had perianal abscesses at baseline. All of these abscesses were absent at week 12 and all four patients achieved corticosteroid-free clinical remission.

3.2.10. Extra-intestinal manifestations

At baseline there were 67 reported EIMs in 59 patients: 53 patients with artralgia, eight with aphtous stomatitis, three with uveitis, two with erythema nodosum and one with pyoderma gangrenosum. Five patients reported both artralgia and aphtous stomatitis at baseline. Three patients reported both arthralgia and uveitis. During follow-up, 32.8% of patients [22/67] with arthralgia achieved EIM remission. All patients with uveitis, apthous stomatitis and pyoderma gangrenosum achieved EIM remission and one of the two patients with erythema nodosum achieved EIM

Table 2. Univariate and multivariate predictors of corticosteroid-free clinical remission at week 104

	Univariate analyses			Multivariate analyses		
	OR	95% CI	*p* value	OR	95% CI	*p* value
Age at inclusion	0.99	0.97–1.02	0.66			
BMI per point	0.97	0.88–1.07	0.59			
Weight	0.98	0.96–1.01	0.21			
Sex						
Male	*Ref*					
Female	1.13	0.38–2.03	0.77			
Disease duration	1.00	0.96–1.04	0.99			
Disease location[a]			0.64			
Ileum	*Ref*					
Colon	1.36	0.46–3.99	0.58			
Ileocolonic	1.54	0.62–3.85	0.35			
Disease behaviour[a]			0.65			
Inflammatory disease	*Ref*					
Stricturing disease	1.21	0.11–13.96	0.88			
Penetrating disease	4.50	0.19–106.82	0.35			
Perianal disease						
No	*Ref*					
Yes	0.31	0.07–1.46	0.14	0.27	0.06–1.29	0.10
Active fistula						
No	*Ref*					
Yes	0.75	0.22–2.49	0.64			
Prior intestinal resections						
No	*Ref*					
Yes	1.89	0.80–4.47	0.15	2.14	0.89–5.13	0.09
Anti-integrin exposure						
No	*Ref*					
Yes	0.96	0.43–2.16	0.92			
Clinical disease activity[b]			0.37			
Mild [HBI 5–7]	*Ref*					
Moderate [HBI 8–16]	2.22	0.30–16.56	0.44			
Severe [HBI > 16]	1.02	0.15–6.75	0.98			
Biochemical disease activity[b]						
CRP, mg/L	1.00	0.98–1.02	0.87			
Leukocytes, ×109/L	1.01	0.88–1.15	0.92			
Faecal calprotectin, µg/g	1.00	1.00–1.00	0.60			
Concomitant medication[b]						
Corticosteroids	0.78	0.35–1.75	0.55			
Immunosuppressant	1.16	0.36–3.77	0.80			

Abbreviations: CI, confidence interval; BMI, body mass index; HBI, Harvey–Bradshaw Index.

[a]At inclusion.

[b]Maximum extent until inclusion.

remission during follow-up. When EIM remission was achieved, 65.7% [23/35] of patients were also in clinical remission. Thirty-nine patients developed new arthralgias during follow-up, of whom 66.7% [26/39] achieved EIM remission before week 104. Three patients developed transient aphthous stomatitis during follow-up, two patients uveitis, two patients erythema nodosum and one patient pyoderma gangrenosum.

3.2.11. General well-being

At baseline, 244 patients reported a mean well-being score of 6.3 out of 10 [SD 1.76]. The mean well-being score was 7.3 [SD 1.51], 7.4 [SD 1.71], 8.0 [SD 1.26] and 8.1 [SD 1.26] at weeks 12, 24, 52 and 104, respectively in patients still treated with ustekinumab. Median well-being score at the time of therapy discontinuation was 5.9 [SD 1.62]. The mean well-being score at weeks 52 and 104 was significantly higher compared to baseline (95% confidence interval [CI]: −1.94 to −1.26, $p = 0.00$ and 95% CI −2.11 to −1.41, $p < 0.001$, respectively). There was no significant difference between the mean well-being score at week 104 compared to week 52.

3.3. Safety outcomes

3.3.1. Adverse events

In total, 252 patients were treated for 348 patient-years. Eight patients [3.2%] stopped treatment due to adverse events after a median treatment duration of 14 weeks [IQR 1.75–34.50]. Two patients stopped ustekinumab due to an infection after 8 and 30 weeks of treatment [mild fever syndrome and moderate upper airway infection, respectively]. Six patients discontinued treatment due to non-infectious adverse events, mostly musculoskeletal [$n = 3/6$] and headache [2/6]. During follow-up, 81 possibly and 18 probably related adverse events were noted [Table 3]. The most common adverse events were headache, skin reaction and musculoskeletal complaints. In total, 48 moderate and 13 severe infections were observed [Table 3]. More than half of the severe infections occurred while patients were on concomitant immunosuppressant therapy [53.8%, $n = 7/13$] and almost half of the severe infections were gastrointestinal infections [46.2%, $n = 6/13$].

During follow-up, three patients were diagnosed with malignancies [squamous cell carcinoma at week 7, melanoma after week 52 and metastatic colorectal cancer after week 52]. Two of these patients were treated with concomitant thiopurines alongside ustekinumab. One death was reported in a 59-year-old patient who was treated with ustekinumab for 52 weeks. She died shortly after she was diagnosed with metastatic colorectal cancer, due to an abdominal sepsis after a colonoscopic perforation.

During follow-up, 22 patients required intestinal resection. Fifteen patients continued ustekinumab treatment postoperatively, of whom ten [66.7%] had a combined biochemical and corticosteroid-free clinical remission during follow-up. In total, 66 patients required hospitalization and six patients were hospitalized at initiation of therapy.

3.3.2. Drug survival

Of 252 patients included, 115 [45.6%] discontinued ustekinumab after a median treatment duration of 28 weeks [IQR 11–48]. The probability of remaining on ustekinumab treatment after 52 and 104 weeks was 64.3% and 54.8%, respectively [Figure 4]. The main reasons for discontinuing treatment were lack of response [61.7%], loss of response [18.3%] and adverse events [7.0%]. Three patients discontinued treatment early due to a malignancy, two patients due to pregnancy and one patient discontinued on its own initiative after

Table 3. Ustekinumab-related adverse events

Mild infections	**65 [18.7 per 100 patient-years]**
Upper respiratory tract	23
Flu-like symptoms	10
Gastrointestinal	9
Herpes simplex	6
Skin	6
Urinary tract	6
Soft tissue	3
Fever of unknown origin	1
Gynaecological	1
Moderate infections	**48 [13.8 per 100 patient-years]**
Upper respiratory tract	13
Urinary tract	10
Soft tissue	6
Flu-like symptoms	5
Skin	5
Gastrointestinal	4
Lower respiratory tract	3
Gynaecological	1
Herpes zoster	1
Severe infections	**13 [3.7 per 100 patient-years]**
Gastrointestinal	6
Central venous catheter	2
Flu-like symptoms	1
Herpes zoster	1
Skin	1
Soft tissue	1
Upper respiratory tract	1
Possibly related	**81 [23.3 per 100 patient-years]**
Other	30
Skin	23
Musculoskeletal	6
Eye condition	3
Exacerbation IBD	3
Gastrointestinal	3
Vascular	3
Infusion-related	2
Malignancy	2
Psychiatric	2
Cardiac	1
Hepatobiliary	1
Nerve system	1
Respiratory	1
Probably related	**18 [5.2 per 100 patient-years]**
Other	6
Infusion related	4
Skin	3
Musculoskeletal	2
Exacerbation IBD	1
Eye condition	1
Vascular	1
Serious adverse events	**9 [2.6 per 100 patient-years]**
Musculoskeletal	2
Skin	2
Arthralgia	1
Eye condition	1
Severe headache	1
Infusion related	1
Vascular	1

Abbreviations: IBD, inflammatory bowel disease.

achieving clinical remission. Of the 97 patients in corticosteroid-free clinical remission at week 52, 11 patients [11.3%] stopped treatment after a median duration of 89 weeks [IQR 80–94]. Nine of these patients stopped due to loss of response and two due to a malignancy.

4. Discussion

We assessed real-world effectiveness and safety of maintenance ustekinumab treatment for CD patients over a period of 2 years in a prospective, nationwide clinical practice cohort. The corticosteroid-free clinical remission rate after 104 weeks of ustekinumab treatment was 34.0%. Of the patients in corticosteroid-free clinical remission at week 52, 59.8% were still in corticosteroid-free clinical remission at week 104. The main reason for drug withdrawal after 52 weeks of treatment was loss of response and no new safety issues were witnessed.

The IM-UNITI LTE trial demonstrated clinical remission and clinical response rates of 67.5% and 77.6% at week 92, respectively.[3] These high remission and response rates, compared to our corticosteroid-free remission rate of 34.0% after 104 weeks, can be explained by the fact that patients could only enter the IM-UNITI LTE when achieving clinical response [decrease in CDAI score ≥100 points or a total CDAI score <150] after 8 weeks of treatment and were only analysed in patients continuing treatment after 52 weeks. In contrast, we included all patients initiating ustekinumab treatment in the effectiveness analysis. Furthermore, approximately 40% of patients included in the IM-UNITI LTE were anti-TNF-naïve, while in our cohort only two patients were anti-TNF-naïve [0.8%].

Several real-world retrospective cohorts evaluated the effectiveness and safety of ustekinumab in CD patients. Only three real-world cohorts retrospectively described the effectiveness and safety of ustekinumab with a follow-up of at least 2 years.[14–16] When comparing these cohorts, differences in study design and endpoints must be acknowledged. A French study included 88 anti-TNF-experienced patients with a median follow-up of 26.6 months.[14] They observed a failure-free persistence [no need for surgery, intolerance of withdrawal due to loss of response] in 66% of patients [58/88] after 2 years of treatment. It must be taken into account that only patients with clinical benefit at 3 months of treatment or late responders with clinical benefit during the first year were included in the later analysis. A retrospective German cohort described 93 patients with disease activity at baseline of whom ten patients were followed until 88 weeks of treatment.[15] After 88 weeks, eight patients [8.6%] responded [defined as a significant HBI reduction by at least

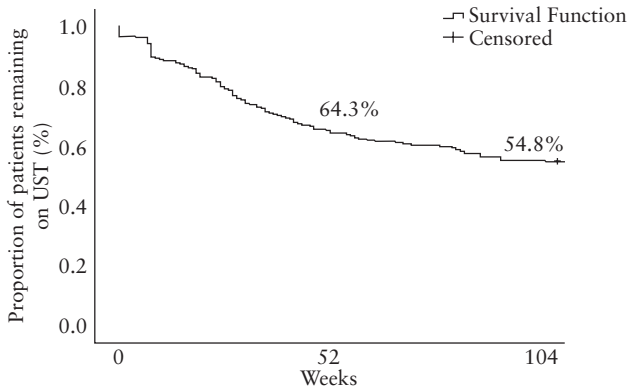

Figure 4. Drug survival. Kaplan–Meier probability curve of ustekinumab treatment survival during a 104-week follow-up period.

three points or an FC reduction of at least 50% or <250 µg/g] to ustekinumab and five patients [5.4%] were in remission [HBI ≤ 4 and/or FC < 250 µg/g, if available]. A Canadian cohort described 29 patients with follow-up data available after 12 months.[16] Twenty-one patients had ongoing response at the time of most recent assessment [range of 12–42 months]. Retrospective data collection was used to assess response, which was based on physician documentation of resolution or reduction of CD-associated symptoms, improvement in subjective assessment of quality of life, withdrawal of steroids and continuation of therapy. The cause of treatment withdrawal in the remaining eight patients who ceased therapy during this follow-up interval was not described. Differences in outcomes should be interpreted with caution due to the retrospective nature and different endpoints as compared to our systematic and prospective cohort. Furthermore, the definitions of remission and response used in other real-world studies differ considerably.

In the current study, clinical remission of perianal fistulas was seen in 17.2% [5/29], 37.9% [11/29], 37.9% [11/29] and 20.7% [n = 6/29] after 12, 24, 52 and 104 weeks, respectively. The effectiveness of ustekinumab on fistulas is poorly studied, especially in the long term. A pooled study of patients with active fistula at inclusion in both CERTIFI and UNITI-1/UNITI-2s showed a consistent signal for effectiveness of ustekinumab in fistula healing. These studies showed non-significant but higher numerical rates of fistula closure after 8 weeks of treatment for the 161 [24.7%] patients in the ustekinumab group compared to the 77 [14.1%] patients in the placebo group.[17] A French multicentre retrospective cohort demonstrated that about 40% of patients with active pCD at initiation of treatment reached success [assessed by physician judgment; no need for dedicated medical treatment for perianal lesions nor unscheduled surgical treatment] after 6 months of treatment.[18] Three other retrospective studies described clinical remission, clinical improvement and clinical response rates of 66% [6/9], 61% [11/18] and 48.9% [22/45], respectively, in pCD in a small number of patients after 6 months of treatment.[8,9,14] Due to the small numbers of patients and mostly retrospective study designs, we cannot conclude whether ustekinumab is effective in treating perianal CD. Currently, anti-TNF therapy is the first-line medical treatment for perianal fistulas in CD.[19] In the ACCENT II study, at week 54, 36% of patients who had responded to induction therapy and received maintenance infliximab therapy maintained complete fistula closure compared with 19% of patients receiving placebo [p = 0.009].[21] To determine the precise role of ustekinumab in the treatment of perianal CD, further dedicated prospective randomized studies are warranted.

In our cohort, ustekinumab treatment was generally well tolerated with comparable rates of adverse events as in the IM-UNITI trial.[3] A similar spectrum of adverse events including headaches, musculoskeletal complaints and cutaneous reactions was reported in other observational cohorts.[8,13,14,16] The number of severe infections was low and mostly occurred while patients were on concomitant immunosuppressive therapy.

When comparing drug survival rates of treatment options in CD, interesting differences can be found. Our cohort shows that the probability of remaining on ustekinumab treatment after 52 and 104 weeks remains fairly stable [64.3% and 54.8%, respectively]. With vedolizumab treatment, a decrease in the probability of continuing vedolizumab treatment from 54% to 38% in patients with CD was seen between the first and second year after treatment.[22] In line with these results, a French cohort showed a decrease in the overall rate of steroid-free clinical remission from 27.2% to 19.9% between weeks 52 and 162.[22] Moreover, we saw that of the

97 patients in corticosteroid-free clinical remission after 52 weeks, 11 patients [11.3%] stopped treatment after a median duration of 89 weeks. Loss of response rates in both infliximab and adalimumab treatment in CD patients are 13% every year after the first year of treatment.[23] Although these results might favour use of ustekinumab, additional cohorts with long-term follow-up are needed to confirm these observations.

No predictors of ustekinumab effectiveness at 2 years of treatment were found in univariate or multivariate analysis. Several cohort trials found that colonic disease was associated with better responses to ustekinumab.[7,9–11,24] Furthermore, in phase 3 clinical trials, the rates of clinical response and remission at induction were higher in patients who had failed or were intolerant of conventional therapy than in patients who had failed anti-TNF therapy.[2] Since only two patients were anti TNF-naïve, our study was not powered to assess this difference in response. Moreover, clinical data regarding the cause of anti-TNF failure before start of ustekinumab were missing. Further studies are warranted to assess possible predictors of response to determine the optimal positioning of ustekinumab in the treatment of CD.

The systematic prospective follow-up is one of the main strengths of our study. All patients were treated by a dedicated IBD team and seen on predetermined time points up to 2 years of follow-up. Furthermore, due to the nationwide coverage of not only academic but also general hospitals, we feel that our outcomes can be generalized to the whole IBD population.

One of the limitations of our study is the limited amount of objective evaluation of remission and response as endoscopic assessment was not mandatory in our study design. Most participating centres do not perform endoscopy systematically to assess response but only perform endoscopy if clinical and biochemical parameters are inconclusive. The endoscopic outcomes should be interpreted with caution because endoscopies were not performed systematically and most frequently in patients to confirm clinical disease activity, which might have led to selection bias. Also, biochemical data were missing in a substantial number of patients, which may possibly lead to underestimated biochemical remission rates as all missing data were considered non-response. Although we included patients in both academic and non-academic hospitals, a relatively refractory population was analysed because all patients initiated ustekinumab treatment shortly after the approval of ustekinumab for the treatment of CD. It is possible that refractory patients, with little treatment options left, were waiting for ustekinumab to be approved for the treatment of CD and directly started after it became available. This may limit the external validity of our observations to a less treatment-refractory patient population but is consistent with the general patient population exposed to ustekinumab [>85% exposed to at least one anti-TNF].[25]

In conclusion, ustekinumab was effective and relatively safe in our real-world cohort of CD patients. One-third of patients were in corticosteroid-free clinical remission after 2 years of ustekinumab treatment and 60% of the patients who were in corticosteroid-free clinical remission after 1 year were still in remission after 2 years. These results underline the value of ustekinumab in managing refractory CD patients. However, head-to-head trials are warranted to determine the optimal positioning of ustekinumab in the treatment of CD.

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Conflict of Interest

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Author Contributions

M.P., F.H., V.B., T.S., A.M. and M.D. designed the study. All authors collected data. T.S., A.M and M.D. analysed the data and drafted the manuscript. All authors critically revised the manuscript and approved the final version of the manuscript.

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The manuscript, including figures and tables, has not been previously published and is not under consideration elsewhere.

Data Availability Statement

The data underlying this article were provided by the ICC Registry under licence/by permission. Data will be shared on request to the corresponding author with permission of the ICC Registry.

Supplementary Data

Supplementary data are available at *ECCO-JCC* online.

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