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Original Article

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Effectiveness and Safety of Ustekinumab in Ulcerative Colitis: Real-world Evidence from the ENEIDA Registry

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Abstract

Background and Aims: The development programm UNIFI has shown promising results of ustekinumab in ulcerative colitis [UC] treatment which should be confirmed in clinical practice. We aimed to evaluate the durability, effectiveness, and safety of ustekinumab in UC in real life.

Methods: Patients included in the prospectively maintained ENEIDA registry, who received at least one intravenous dose of ustekinumab due to active UC [Partial Mayo Score [PMS]>2], were included. Clinical activity and effectiveness were defined based on PMS. Short-term response was assessed at Week 16.

Results: A total of 95 patients were included. At Week 16, 53% of patients had response [including 35% of patients in remission]. In the multivariate analysis, elevated serum C-reactive protein was the only variable significantly associated with lower likelihood of achieving remission. Remission was achieved in 39% and 33% of patients at Weeks 24 and 52, respectively; 36% of patients discontinued the treatment with ustekinumab during a median follow-up of 31 weeks. The probability of maintaining ustekinumab treatment was 87% at Week 16, 63% at Week 56, and 59% at Week 72; primary failure was the main reason for ustekinumab discontinuation. No variable was associated with risk of discontinuation. Three patients reported adverse events; one of them had a fatal severe SARS-CoV-2 infection.

Conclusions: Ustekinumab is effective in both the short and the long term in real life, even in a highly refractory cohort. Higher inflammatory burden at baseline correlated with lower probability of achieving remission. Safety was consistent with the known profile of ustekinumab.

Key Words: Ustekinumab; ulcerative colitis; response; remission; durability; real-world evidence

1. Introduction

The UNIFI trial has demonstrated the superiority of ustekinumab over placebo in inducing and maintaining remission in patients with active ulcerative colitis [UC], not only in naïve patients but also in those who failed previous biologic agents with a good safety profile.[1] These promising results should be confirmed in clinical practice, where the experience with ustekinumab, in terms of both effectiveness and safety, is still limited.[2,3]

We performed the present study aiming to evaluate the durability of ustekinumab treatment in UC patients in clinical practice. Our secondary aims were to assess the short-term response [at Week 16] and the long-term effectiveness [at maximum follow-up], to identify predictive factors of response, to describe the schedules of ustekinumab administration in UC in real life and the need for dose adjustments, and finally, to assess the safety of ustekinumab in clinical practice.

2. Methods

2.1. Study design

This was an observational multicentre study carried out with data from ENEIDA project.[4] Patients 18 years of age or older, who received at least one intravenous dose of ustekinumab at least 16 weeks before data analysis due to active UC (Partial Mayo Score

[PMS] >2) were included. Patients who received ustekinumab for an indication other than UC while in remission or with a previous colonic resection were excluded. Patients were followed up until last ustekinumab administration or last visit, whichever came first. Data were remotely monitored to assess data quality. The ENEIDA project was approved by research ethics committees in all participating centres. Written informed consent to be enrolled in the ENEIDA registry was obtained from all patients. Variables collected and definitions used in the study are described in SupplementaryAnnexes 1 and 2, available as Supplementary data at *ECCO-JCC* online.

2.2. Evaluation of effectiveness

The assessment of ustekinumab effectiveness was based on the PMS. For the short-term efficacy analysis, the proportion of patients achieving remission or response after induction [Week 16] was calculated. In the long term, the proportions of patients in remission and steroid-free remission at Weeks 24 and 52 were calculated. Patients who discontinued ustekinumab owing to lack of therapeutic effect, an adverse event, or worsening of UC before their last visit were considered as not having achieved the endpoint [remission or response] at subsequent time points, and therefore they were considered failures. Dose adjustment was considered to be part of the treatment regimen [i.e. not included in treatment failure rules] unless otherwise indicated for dichotomous endpoints [remission vs no remission at a certain time point]. The statistical analysis is described in SupplementaryAnnex 3, available as Supplementary data at *ECCO-JCC* online.

3. Results

3.1. Patient characteristics

A total of 95 patients were included, with a median time of exposure to ustekinumab of 31 weeks (interquartile range [IQR] = 18–59 weeks]. The main characteristics of the study population are summarised in Table 1.

Table 1. Characteristics of the study population.

Characteristics	
Mean age [SD] [years]	47 [16]
Median time of follow-up [IQR] [weeks]	82 [41–153]
Female gender, *n* [%]	55 [56]
UC extent	53 [56]
Extensive colitis, *n* [%]	55 [58]
Left-sided colitis, *n* [%]	37 [39]
Proctitis, *n* [%]	3 [3]
Extraintestinal manifestations, *n* [%]	27 [28]
Smokers, *n* [%]	4 [4]
Family history, *n* [%]	7 [8]
Median Partial Mayo Score at baseline [IQR]	6 [4–8]
Endoscopic assessment at baseline, *n* [%]	68 [72]
Mild, *n* [%]	3 [4]
Moderate, *n* [%]	20 [30]
Severe, *n* [%]	45 [66]
Baseline CRP over the upper limit of normal range, *n* [%]	61 [64]
Anaemia at baseline, *n* [%]	38 [40]
Median faecal calprotectin at baseline [IQR] [μg/g]	1,564 [795–2,998]
Previous biologic treatment or tofacitinib, *n* [%]	95 [100]
Anti-TNF, *n* [%]	93 [98]
Vedolizumab, *n* [%]	78 [82]
Tofacitinib, *n* [%]	28 [30]
Anti-TNF and vedolizumab, *n* [%]	76 [80]
Anti-TNF, vedolizumab and tofacitinib, *n* [%]	27 [28]
Number of previous biologic agents	
1–2 previous biologics, *n* [%]	40 [42]
≥3 previous biologics, *n* [%]	55 [58]
Concomitant immunosuppresants, *n* [%]	16 [17]
Steroids during induction, *n* [%]	53 [56]

Ulcerative colitis, UC; standard deviation, SD: interquartile range, IQR; C-reactive protein, CRP; tumour necrosis factor, TNF.

3.2. Short-term effectiveness

After the induction [Week 16], 33 patients [35%] reached clinical remission and 50 [53%] reached clinical response [including patients with remission] [Figure 1].

The schedule for the induction varied widely between patients. All of them received a first intravenous dose of approximately 6 mg/kg. A total of 91 patients received a second dose of ustekinumab, whereas four interrupted the treatment before administration of the second dose; 51 patients [56%] received the second dose between Weeks 6 and 10, eight [9%] before Week 6, 21 [23%] at Week 11, five [5%] at Week 12, and six [6%] after Week 12.

In all, 84 patients received a third dose of ustekinumab. In most of the cases [80%], administration was between Weeks 16 and 20. Fourteen patients [17%] received the third dose before Week 16, and three patients [3.5%] after Week 20.

At baseline, the proportions of patients with elevated C-reactive protein [CRP] [above the normal range limit] and the proportion of patients with severe endoscopic activity were significantly lower in patients who achieved remission at Week 16 than in those who did not achieve remission, [52% vs 75%, $p<0.05$, and 50% vs 74%, $p<0.05$, respectively] [Table 2]. In the multivariate analysis, CRP above the normal range limit at baseline was the only variable associated with lower probability of achieving remission at Week 16 (odds ratio [OR] = 0.3, 95% confidence interval [CI] = 0.1–0.7) .

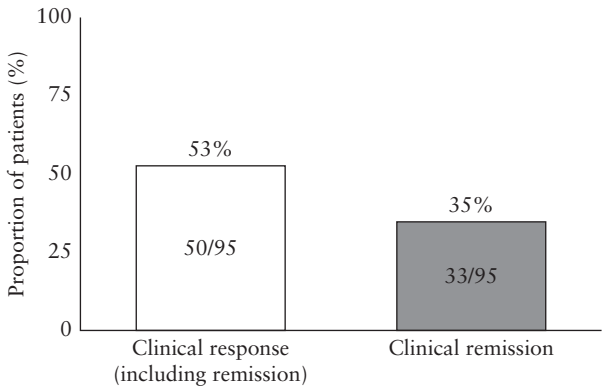

Figure 1. Effectiveness of ustekinumab for the induction of clinical remission in ulcerative colitis [Week 16].

3.3. Ustekinumab durability

A total of 34 patients [36%] discontinued ustekinumab over time; median time of exposure to ustekinumab was 31 weeks [IQR = 18–59]. The probability of maintaining ustekinumab treatment was 87% at Week 16, 63% at Week 56, and 59% at Week 72 [Figure 2]. The reasons for ustekinumab discontinuation were: primary non-response in 21 patients [22%], loss of response in 12 patients [13%], and adverse event in one patient [1%]. Neither the univariate nor the multivariate analysis found any variable

Table 2. Distribution of different variables according to achievement of remission at Week 16.

Variable	No remission *n* = 62	Remission *n* = 33	*p*
Mean age [years] [SD]	46.5 [2]	47 [3]	n.s.
Female gender, *n* [%]	34 [55]	19 [59.4]	n.s.
Extensive colitis, *n* [%]	32 [52]	22 [69]	n.s.
Extraintestinal manifestations, *n* [%]	17 [27]	10 [30]	n.s.
Smokers, *n* [%]	1 [1.7]	3 [10]	n.s.
Family history, *n* [%]	4 [6.9]	3 [10.7]	n.s.
Median Partial Mayo Score at baseline [months] [IQR]	6 [5–8]	6 [3–6]	n.s.
Endoscopic assessment at baseline, *n* [%]	46 [74]	22 [67]	
Mild, *n* [%]	0 [0]	3 [14]	
Moderate, *n* [%]	12 [26]	8 [36]	<0.05
Severe *n* [%]	34 [74]	11 [50]	
Baseline CRP over the upper limit of normal range, *n* [%]	45 [79]	16 [52]	<0.05
Anaemia at baseline, *n* [%]	25 [42]	13 [43]	n.s.
Median faecal calprotectin at baseline [μg/g]	1625	1281	n.s.
Previous biologic treatment or tofacitinib			
Anti-TNF, *n* [%]	61 [98]	32 [97]	n.s.
Vedolizumab, *n* [%]	53 [86]	25 [76]	n.s.
Tofacitinib, *n* [%]	19 [31]	9 [27]	n.s.
Median previous number of biologic agents, *n* [IQR]	3 [2–3]	2 [2–3]	n.s.
Concomitant immunosuppresants, *n* [%]	11 [18]	5 [15]	n.s.
Steroids during induction, *n* [%]	36 [58]	17 [52]	n.s.

Standard deviation, SD; interquartile range, IQR; C-reactive protein, CRP; tumour necrosis factor, TNF; not significant, n.s.

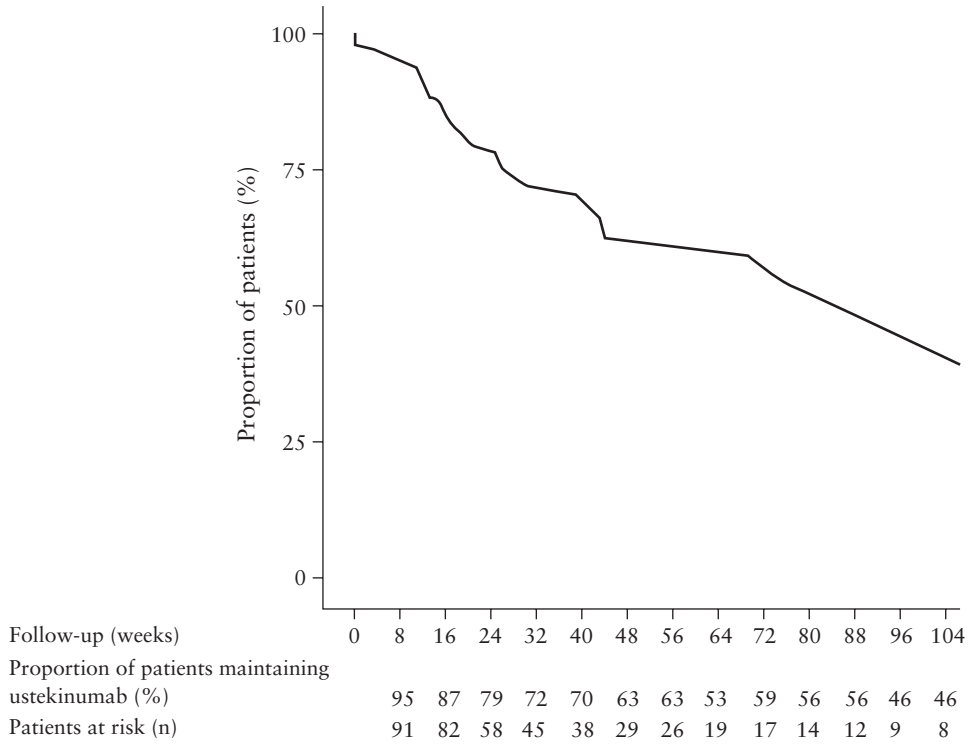

Figure 2. Survival curve of the durability of ustekinumab treatment in patients with ulcerative colitis.

associated with ustekinumab discontinuation; 53 patients were receiving steroids at baseline, and 35 [66%] were able to stop them.

3.4. Long-term effectiveness and dose adjustments

Of 83 patients who started ustekinumab at least 24 weeks before data analysis, 32 [39%] were in remission at Week 24, and 25 [30%] in steroid-free remission. A total of 54 patients started ustekinumab at least 52 weeks before data analysis; at Week 52, 18 [33%] of these were in remission and 17 [32%] in steroid-free remission [Figure 3].

In all, 81 patients started the maintenance phase [at Week 16]; 30 patients were in remission at that moment. Three patients [10%] started the maintenance phase with every 12 weeks schedule, 24 patients [80%] with every 8 weeks schedule, and three [10%] with intensified schedule [every 6 weeks or every 4 weeks]. Two patients

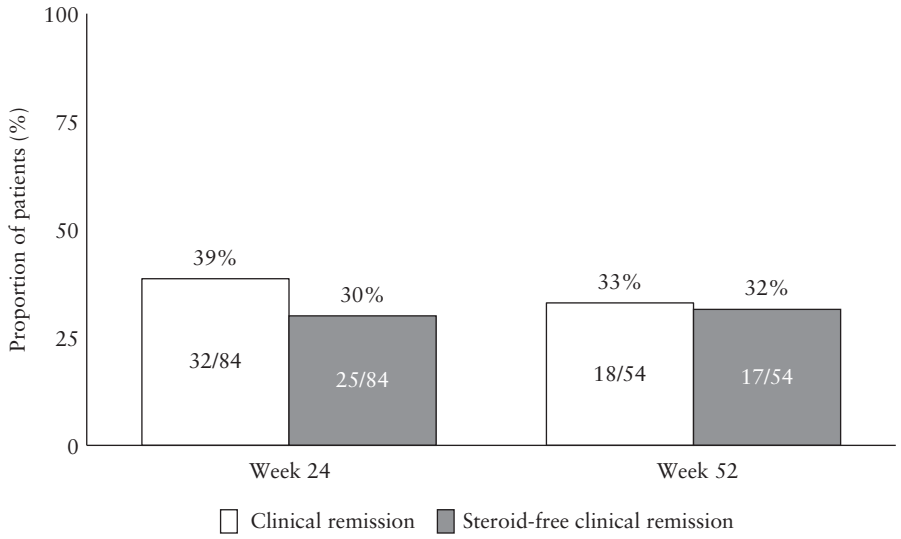

Figure 3. Proportion of ulcerative colitis patients under ustekinumab treatment with clinical remission and steroid-free clinical remission at Weeks 24 and 52.

had to interrupt the treatment due to loss of response and one patient due to clinician's choice during follow-up. Ten patients relapsed during follow-up: four intensified the dose [two reached remission again], two interrupted the treatment, and in four the change in treatment was unknown.

On the other hand, 51 patients started the maintenance phase despite having active disease at Week 16. Three patients [6%] started with an every 12 weeks schedule, 36 [71%] with every 8 weeks, and 12 [23%] an with intensified schedule. Of those patients who were not in remission at Week 16, 21 [41%] ended up stopping the treatment during follow-up, 13 [25%] maintained the treatment during follow-up despite never reaching remission, and 17 [34%] reached remission later on during follow-up.

A total of 66 patients started the maintenance phase with the standard dose [either every 12 weeks or every 8 weeks schedule]; of these, 18 patients intensified the treatment—10 [55%] due to primary failure, three [17%] due to partial response, and five [28%] due to loss of response. One among 10 patients with primary failure and two among five patients with loss of response achieved remission after dose intensification. None of the three patients who intensified the dose due to partial response reached remission. Finally, one patient escalated the dose from every 12 weeks to every 8 weeks due to loss of response and reached remission after dose optimisation.

A total of nine patients [9.5%] needed to undergo colectomy due to ustekinumab failure. Median time from ustekinumab start to surgery was 14 weeks [IQR = 7.5–18].

3.5. Adverse events

Three adverse events were reported in our cohort. A patient developed dry skin and itching probably related with ustekinumab. The symptoms were mild and did not lead to treatment discontinuation. Another patient had pneumonia probably not related to ustekinumab treatment, which did not cause treatment discontinuation. Finally, a 54-year-old male with extensive UC and no comorbidities, who had been exposed to ustekinumab for 43 weeks, developed severe SARS-Cov-2 pneumonia and died. At the time of infection, the patient had been treated with ustekinumab 90 mg every-6 weeks for 43 weeks without steroids or immunomodulators, after previously failing infliximab, adalimumab, golimumab, vedolizumab, and tofacitinib.

4. Discussion

To our knowledge this is the largest study to date providing real-life evidence on the long-term benefit of ustekinumab treatment in UC patients. In our cohort, one-third of patients were able to achieve remission after the induction [Week 16], despite being highly refractory patients [80% had failed both anti-TNF agents and vedolizumab, and 30% had failed anti-TNF agents, vedolizumab, and tofacitinib]. In addition, one-third of patients achieved steroid-free remission during follow-up [Week 24 and Week 52].

To date, only one previous real-life study has assessed the short-term effectiveness of ustekinumab in UC patients.[2] In this study, at Weeks 12–16, 39.8% of patients had clinical remission. This figure is quite similar to ours: 34.7% of patients were in remission at Week 16.

We found that CRP serum concentration over the normal range upper limit was the only factor significantly associated with lower probability of achieving remission. Similarly, Amiot *et al.* observed that patients with PMS >6 had significantly lower chance of achieving remission in the short term.[2] Those findings suggest that the inflammatory burden has a significant impact on ustekinumab effectiveness during induction in UC patients. Other factors, such as concomitant treatment with immunomodulators or the number of previous biologics, do not seem to have an impact on treatment response.

The long-term effectiveness of ustekinumab in UC in real life has hardly been studied. Ochsekühn *et al.* published a retrospective series of 19 UC patients treated with ustekinumab.[3] The main aim was to know the proportion of patients in clinical remission at 1 year; 53% of patients [10/19] had clinical remission after 12 months of treatment.

Our study provides some relevant findings on the long-term real-life effectiveness of ustekinumab treatment in UC. With respect to drug survival, we observed that the proportion of patients maintained under ustekinumab treatment was over 60% at 12 months, primary failure being the main reason for ustekinumab discontinuation. These results are similar to those reported for other drugs in particularly refractory patient populations.[5–7] We acknowledge that ustekinumab might have been maintained in some patients, despite not reaching clinical remission, as the last medical option to avoid

surgery. However, ustekinumab might have exerted some effect even in those patients avoiding colectomy [less than 10% of our patients ended up undergoing surgery].

Approximately one-third of patients who were in remission at Week 16 in our cohort, relapsed during follow-up [median time of exposure to ustekinumab was 31 weeks]. Dose was optimised in four patients, and two of them regained remission. Ustekinumab dose intensification seems to be useful to regain remission in CD patients[8,9]; however, data in UC patients are lacking. The role of dose intensification in UC patients losing response to ustekinumab needs to be further studied.

Finally, the potential role of concomitant therapy with immunomodulators is of great interest to optimise the treatment in clinical practice. Evidence from CD studies supports that combined treatment with thiopurines does not increase either the short- or the long-term effectiveness of ustekinumab.[10] In our cohort, combined treatment was not associated either with the probability of achieving short-term remission or with the durability of ustekinumab treatment in the long term. With respect to the safety profile, our results are consistent with those previously reported for ustekinumab.[11]

In conclusion, ustekinumab is effective in inducing remission in up to one-third of UC patients, even in a highly refractory population. Patients with higher inflammatory burden are less likely to achieve short-term remission. Over 60% of patients maintained ustekinumab treatment at 12 months, suggesting that it also provides benefit in the long term. The safety profile is similar to that previously described for ustekinumab.

The data underlying this article will be shared on reasonable request to the corresponding author.

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Conflict of Interest

MC has served as a speaker, as consultant, or has received research or education funding from MSD, Abbvie, Hospira, Pfizer, Takeda, Janssen, Ferring, Shire Pharmaceuticals, Dr Falk Pharma, Tillotts Pharma, Biogen, and Gilead. MBA has served as a speaker, consultant, and advisory member for or has received research funding from MSD, AbbVie, Janssen, Kern Pharma, Celltrion, Takeda, Gillead, Pfizer, Ferring, Faes Farma, Shire Pharmaceuticals, Dr Falk Pharma, Chiesi, Gebro Pharma, Adacyte, and Vifor Pharma. MJCa has received research or education funding from Pfizer, Takeda, Shire Pharmaceuticals, Janssen, MSD, Ferring, Biogen, and Abbvie. Fiorella Cañete has served as a speaker or has received research or education funding or advisory fees from Takeda, Janssen, MSD, Pfizer, and Ferring. JB has served as a speaker, as consultant, or has received research or education funding from MSD, Abbvie, Takeda, Janssen, and Ferring. VH has served as speaker and has received travel support or research funding from MSD, AbbVie, Ferring, FAES Farma, Shire Pharmaceuticals, Dr Falk Pharma, Tillotts Pharma, Otsuka Pharmaceutical, Pfizer, Takeda, Jansen, KernPharma Biologics, Gebro Pharma, Adacyte, Sandoz, and Fresenius-Kabi. Elena Ricart has served as a speaker or has received research or education funding or advisory fees from MSD, Abbvie, Takeda, Ferring, Pfizer, Janssen, Fresenius Kabi. MMa has served as a speaker or has received research or education funding or advisory fees from FAES, Ferring MSD, AbbVie, Takeda, Pfizer, and Janssen. MR has served as a speaker, a consultant, and advisory member for Merck Sharp and Dohme, Abbvie, Pfizer, and Janssen. ED has served as a speaker and has received research and educational funding and advisory fees from MSD, AbbVie, Takeda, Kern Pharma, Pfizer, Janssen, Celgene, Adacyte Therapeutics, Otsuka Pharmaceuticals, Ferring, Shire Pharmaceuticals, Tillots, Thermofisher, Grifols, and Gebro. JPG has served as a speaker, a consultant, and advisory member for or has received research funding from MSD, Abbvie, Pfizer, Kern Pharma, Biogen, Mylan, Takeda, Janssen, Roche, Sandoz, Celgene, Gilead, Ferring, Faes Farma, Shire Pharmaceuticals, Dr Falk Pharma, Tillotts Pharma, Chiesi, Casen Fleet, Gebro Pharma, Otsuka Pharmaceutical, and Vifor Pharma.

Author Contributions

MC and JPG: study design, data collection, data analysis, data interpretation, writing the manuscript. AG: data monitoring. Rest of authors: patient inclusion. All authors approved the final version of the manuscript.

Supplementary Data

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

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