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Intravenous ustekinumab maintenance treatment in patients with loss of response to subcutaneous dosing

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Abstract

Background: Ustekinumab (UST) is indicated for the treatment of Crohn's disease (CD) and Ulcerative Colitis (UC). Despite having shown clinical effectiveness in the real world, some patients may lose response over time or need a higher dose to achieve it. In this context, UST intravenous (IV) maintenance has been proposed.

Objectives: The primary endpoint of our study was to evaluate the efficacy and safety of maintenance IV UST treatment in Inflammatory Bowel Disease (IBD) patients who present with partial response or loss of response to subcutaneous (SC) UST.

Design: We performed a monocentric observational retrospective study including patients with active IBD on maintenance treatment with IV UST.

Methods: The clinical response and remission was analyzed at week 12, defined as either Harvey–Bradshaw Index $\leqslant 4$ for CD or partial Mayo Score $\leqslant 2$ for UC. The reduction of objective markers of disease activity, fecal calprotectin, and C-reactive protein was evaluated. Moreover, UST trough levels were measured pre- and post-UST IV maintenance and any adverse events were assessed.

Results: We included 23 patients. Clinical remission at week 12 was achieved by 43.5% of the patients. The proportion of patients in clinical response after 12 weeks on UST IV maintenance was 82.6%. After a median follow-up of 9.3 months all patients remained on IV UST maintenance. No adverse events were recorded in any patient for the duration of the study.

Conclusions: IV UST maintenance treatment was able to recapture response in most of the patients who had lost response to SC maintenance.

Keywords: biologic therapy, Crohn's disease, effectiveness, intravenous dose, ustekinumab

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Introduction

Ustekinumab (UST) is a fully human immunoglobulin G1κ monoclonal antibody that blocks the cytokines interleukin (IL)-12 and IL-23.[1] It is indicated for the treatment of inflammatory bowel diseases (IBD), Crohn's disease (CD), and Ulcerative Colitis (UC), in adult patients who have failed to conventional therapy or anti-tumor necrosis factor (TNF) therapy, and for whom conventional therapy or anti-TNF therapy is contraindicated.[2,3] UST dosing as per the European label consists of an intravenous (IV) induction dose at week 0 of approximately 6 mg/kg and a maintenance dose of 90 mg subcutaneous (SC) every 8 weeks (q8w) or every 12 weeks (q12w).

Some real-world studies have been concluded that, 20–40% of patients with IBD treated with anti-TNF, may undergo dose escalation due to loss of response.[4,5] Approximately 60–80% of them achieve response again.[6,7] UST have also shown clinical effectiveness in real-world studies,[8,9] but as with anti-TNF drugs, some patients may lose response over time or need a higher dose

to achieve it, especially those refractories to several drugs. In this context, a range of strategies have been used, most commonly reducing the interval between doses, or giving a new dose of induction (reinduction), or a combination of both. Response rates reported with these strategies are variable, but most studies report recapture of response in around 60% of patients.[10] Alternatively, in clinical practice, UST IV maintenance has also been proposed,[11] but this strategy has been less studied.

Therefore, the aim of our study was to analyze how effective and safe is ustekinumab IV maintenance in patients with IBD with partial or complete loss of response to UST SC dosing.

Methods

Study design and patient population

This is a unicentric observational, descriptive, and retrospective study that included patients with IBD under UST IV maintenance treatment for at least 12 weeks. The patients included had received at least three maintenance doses of UST IV. Patients whose follow-up had been lost during these 12 weeks or whose data in the electronic story were not completed were not included in the study.

At baseline, all patients included had active disease, assessed with the Harvey–Bradshaw Index (HBI) for CD patients or partial Mayo Score (pMS) for UC patients. Clinical activity was defined as an HBI >4 or a pMS >2 points. All patients signed the written informed consent before study initiation and after that, signed their agreement for publication.

The study was approved by the local ethics committee. All the medical records were analyzed in an anonymous way to prevent any identification.

Sample size

All patients who met the inclusion criteria were included in the study. No sample size was calculated as this was a preliminary and descriptive study.

Outcomes and definitions

The primary endpoint of the study was clinical remission at week 12, defined as either HBI $\leqslant 4$ for CD or pMS $\leqslant 2$ for UC. Secondary endpoints included a reduction in objective markers of disease activity, fecal calprotectin (FCal) and C-reactive protein (CRP), and clinical response, defined as a decrease in HBI of at least 3 points for CD and a decrease in pMS of at least 3 points and 30% from baseline. FCal and CRP normalization were considered when levels were <250 mg/kg and <5 mg/L, respectively. UST trough levels were measured pre- and post-UST IV maintenance. Adverse events were collected.

Statistical analysis

Demographic data and baseline disease characteristics were reported for all patients. Categorical variables were presented as percentages and continuous variables were presented as mean with standard deviation or as median with interquartile range (IQR) depending on the normality of the underlying distribution. Normal distribution was determined using the Shapiro–Wilk test. Statistical differences for HBI, pMS, FCal, CRP, and UST levels were assessed *versus* baseline using the Student's t test or Wilcoxon rank sum test, according to the normality criteria. A two-sided p value of 0.05 or less was considered statistically significant. All data analyses were performed using IBM SPSS Statistics for Windows, version 24.0. [IBM]. The reporting of this study conforms to the STROBE statement[12] (Supplemental Appendix 2).

Results

We included 23 patients with a median age of 43 years (IQR 32–50) and a median duration of disease of 12 years (IQR 5–21). A total of 82.6% (19/23) of patients had a diagnosis of CD, 53.5% were active smokers, 30.4% had perianal disease, and 39.1% had a previous history of intestinal resection. Most patients (87%, 20/23) had been previously exposed to other biologics/small molecules and only three were bionaïve. Prior to UST IV maintenance 69.5% (16/23) of patients were treated with a reduced SC dosing interval, 56.5% (13/23) were treated with 90 mg q4w and 13% (3/23) with 90 mg q6w (Table 1).

Patients were escalated to IV UST dosing after a median duration of 14.7 months on SC maintenance. Most patients were escalated to 130 mg IV every 4 weeks (18/23, 78.3%), three patients were treated with 260 mg IV q4w (13%), one patient

Table 1. Clinical and demographic characteristics.

Baseline characteristics	Patients ($n = 23$)
Age (years), median [IQR]	43 [32–50]
Gender, *n* (%)	
Male	11 (47.8)
Female	12 (52.2)
Duration of disease (years), median [IQR]	12 [5–21]
IBD type	
Crohn's disease, *n* (%)	19 (82.6)
Ulcerative colitis, *n* (%)	4 (17.4)
Smoking, *n* (%)	10 (43.5)
Perianal disease, *n* (%)	7 (30.4)
Previous surgical interventions, *n* (%)	9 (39.1)
Steroids, *n* (%)	17 (73.9)
Concomitant immunosuppressors, *n* (%)	3 (13.0)
Previous treatments, *n* (%)	
Infliximab	16 (69.6)
Adalimumab	14 (60.9)
Vedolizumab	9 (39.1)
Tofacitinib	3 (13.0)
Certolizumab	1 (4.3)
Golimumab	1 (4.3)
Number of biologics or previous JAKi, *n* (%)	
0	3 (13.0)
1	6 (26.1)
2	7 (30.4)
3	5 (21.7)
4	1 (4.3)
5	1 (4.3)
Previous ustekinumab subcutaneous UST dosage frequency, *n* (%)	
Every 4 weeks	13 (56.5)
Every 6 weeks	3 (13.0)
Every 8 weeks	7 (30.4)
Albumin, median [IQR]	4.1 [3.7–4.4]
Alkaline phosphatase, median [IQR]	76.5 [64.8–110.3]
HBI, median [IQR]	10 [8–12]
pMS, median [IQR]	8.5 [7.5–9]
CRP basal (mg/L), median [IQR]	7.9 [5.0–13.3]
FCal Basal (mg/kg), median [IQR]	1497.4 [666–3970]
Subcutaneous UST trough levels (mcg/mL), median [IQR]	3.02 [0.7–5.8]
Subcutaneous UST treatment duration (months), median [IQR]	14.7 [5–26]

CPR, C-reactive protein; FCal, fecal calprotectin; HBI, Harvey–Bradshaw Index; IBD, Inflammatory Bowel Disease; IQR, interquartile range; JAKi, Janus kinase inhibitors; pMS, partial Mayo Score; UST, Ustekinumab.

with 130 mg IV q6w (4.3%) and one patient with 130 mg IV q8w (4.3%) (Table 2).

For CD patients, median baseline HBI was 10 (IQR 8–12), after 12 weeks of treatment with UST IV, median HBI was reduced to 4 (IQR 4–7) ($p < 0.001$) (Figure 1(a)). Four UC patients were included in the study and had a median pMS of 8.5 (IQR 7.5–9) at baseline, that decreased to 5.5 (IQR 4.75–6) after 12 weeks of treatment with UST IV ($p = 0.002$) (Figure 1(b)).

The primary endpoint of the study, clinical remission at week 12, was achieved by 43.5% of the patients (10/23). A total of 10 out of 19 patients with CD achieved clinical remission after 12 weeks, and none with UC. The proportion of patients in clinical response after 12 weeks on ustekinumab IV maintenance was 82.6% (19/23) (Figure 2).

Regarding the 16 patients who had already failed increased SC dosing (either q4 or q6), 81.2% (13/16) experienced a clinical response and

Table 2. Ustekinumab intravenous maintenance treatment.

IV Dose and frequency, *n* (%)	Patients (*n* = 23)
130 mg q4w	18 (78.3)
130 mg q6w	1 (4.3)
130 mg q8w	1 (4.3)
260 mg q4w	3 (13)

IV, intravenous.

43.8% (7/16) achieved clinical remission with IV maintenance at week 12.

Objective markers of response were also evaluated. FCal was decreased from a median baseline FCal of 1198.7 µg/g (IQR 638.5–3688.8) to a median value of 520.5 µg/g (IQR 276.0–1389.5) at week 12 ($p = 0.005$) (Figure 3(a)). Similarly, a significant decrease in serum CRP was observed, at baseline median CRP was 7.9 mg/L (IQR 5.0–13.3), decreasing to a median of 3.9 mg/L (IQR 0.9–9.0) at week 12 ($p = 0.004$) (Figure 3(b)).

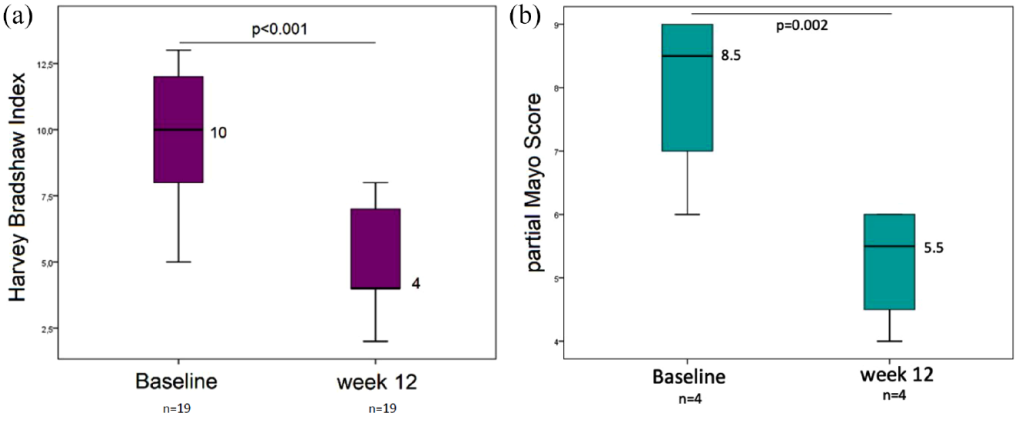

Figure 1. Clinical effectiveness of ustekinumab intravenous maintenance. (a) Median HBI index concentration with interquartile range from baseline to week 12 in CD patients and (b) median partial Mayo Score concentration with interquartile range from baseline to week 12 in UC patients.
CD, Crohn's disease; HBI, Harvey–Bradshaw Index; UC, Ulcerative Colitis.

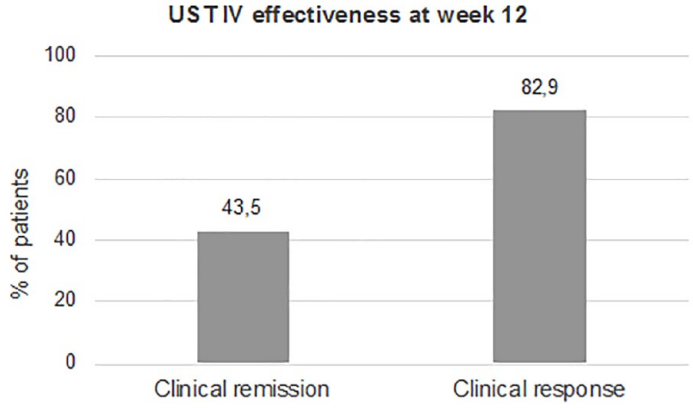

Figure 2. Proportion of patients in clinical remission and clinical response after 12 weeks of IV UST maintenance.
IV, intravenous; UST, Ustekinumab.

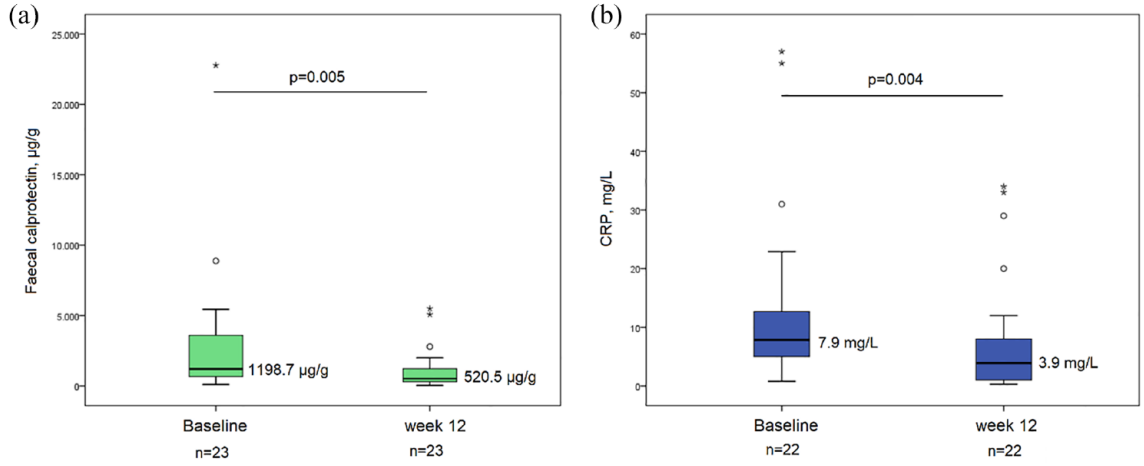

Figure 3. (a) Median fecal calprotectin concentration with interquartile range at baseline and week 12 and (b) median C-reactive protein concentration with interquartile range at baseline and week 12.

Median UST trough levels before IV maintenance were 3.02 µg/mL (IQR 0.7–5.8), after IV maintenance median UST trough levels were increased to 11.45 µg/mL (IQR 7.2–19.9) ($p < 0.001$) (Figure 4).

The median duration of follow-up was 9.3 months (IQR, 4.4–13.6). At the end of follow-up all patients remained on IV UST maintenance. There were no adverse events recorded in any patient for the duration of the study.

Discussion

To our knowledge this is the study with the largest population published with the main aim to assess the effectiveness and safety of UST IV dosage as maintenance treatment for patients with IBD who have lost response to SC ustekinumab treatment.

Ustekinumab is indicated for the treatment of CD and UC, and in real-word studies, it has been reported to have a clinical and endoscopic remission rate of 63% and 55%, respectively, for a year of follow-up.[13] In two recent meta-analysis[14,15] this clinical remission rate for UC patients and for CD patients has been 37% and 31–47% at 1 year, respectively. Most patients included in these studies had already failed other biologics. In contrast, in bio-naive patients, clinical remission at 1 year was higher, 82.2%.[16]

Similar to other biologic drugs, primary or secondary loss of response has been published with ustekinumab. In a recent meta-analysis,[17] it has been estimated that in CD patients, the annual risk of loss of response to ustekinumab and dose escalation among primary responders was 21% and 25% per person-year, respectively. To maintain the response, some strategies have been described, reducing the interval between doses, giving a new dose of induction (reinduction), or a combination of both. Using these approaches, clinical response was regained in 50–58% (interval reduction or IV reinduction) both in CD and UC patients.[18,19] In the study by Heron *et al.*,[20] 65 patients underwent only IV UST reinduction, and clinical remission off corticosteroids with biochemical and/or endoscopic response was achieved in 31% of patients, and no serious adverse events were reported.

Nevertheless, maintenance with the IV UST dose has been less studied. The longest work is by Garcia-Alvarado *et al.*,[21] who have also looked at this; it is a poster published at European Crohn´s and Colitis Organisation (ECCO) in 2022. A total of 79 patients were included. After, 12 weeks of the first IV dose, 43% of patients achieved clinical remission and 59.5% achieved it at the end of follow-up. At the end of the follow-up, 81% of patients maintained the treatment. In the study by Hermida *et al.*,[11] 12 CD patients were included at weeks 26 and 52, and 60% and 64% of the patients were in clinical remission, respectively, using this strategy and without serious adverse events. In our study, most patients had been previously exposed to other biologics or small molecules, and prior to ustekinumab IV maintenance, 69.5% of patients were treated with a reduced SC dosing interval. 43.5% of the patients regained

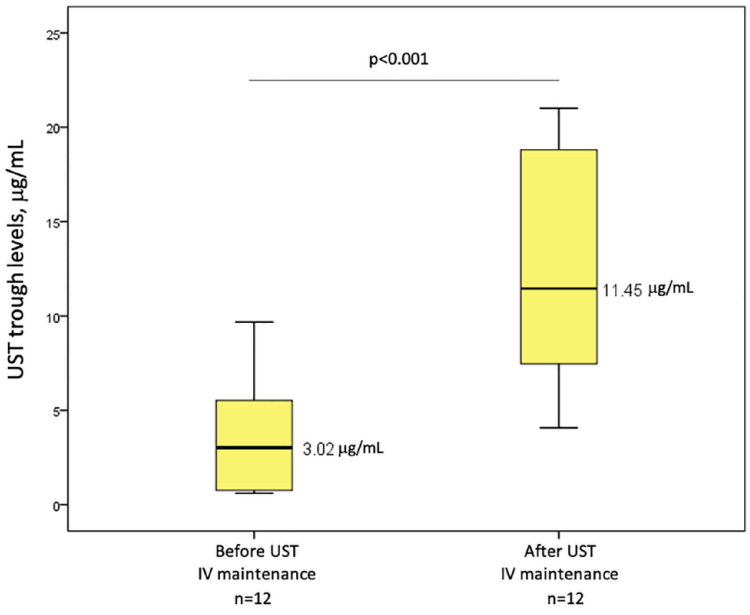

Figure 4. Median UST through levels with interquartile range before and after UST IV maintenance.
IV, intravenous; UST, Ustekinumab.

remission and 82.6% had a clinical response at 12 weeks, which is the main relevance of this study. On the contrary, these patients would have had to switch to another treatment, and some of them had no other option. Obviously, it is a drawback for the patient to have to go to hospital but, on the other hand, the improvement in their condition outweighs this disadvantage. The other question is how long you must keep up this dosage instead of changing back to SC. However, we consider that more patients are likely to regain clinical remission if the IV treatment is continued longer. We are currently following this cohort of patients to answer this question. There are other issues to consider: the dose to use as well as the interval of administration. Most patients were administered one vial of 130 mg with a 4-week interval, following the previous SC schedule. Only three patients received 260 mg, due to disease severity and only two patients were administered treatment less regularly, due to a mild flare-up and patient's preference so we maintained the same time interval. Also, it is important to emphasize that no adverse events were recorded in any patient for the duration of the study.

In our work, median UST trough levels were increased almost four-fold. This higher trough levels of UST in patients treated with the IV maintenance could explain the recapture of clinical remission of patients who had lost response. It has been reported that a drug exposure–response relationship exists both in CD and UC patients treated with UST.[22]

Our study has some limitations that should be considered when interpreting the findings. First, like other real-world studies, it is a retrospective study, which could have led to overestimation of the positive response rate and underestimation of adverse events. Second, the small sample size and heterogeneity of UST IV infusions (dose and frequency) impacts the validity of conclusions. Third, the follow-up period is limited, and there is not a SC ustekinumab comparative group. Fourth, there were no endoscopic or Magnetic Resonance data available for the assessment of mucosal healing or improvement. Furthermore, fecal calprotectin, PCR, and UST trough levels data were only available for a limited number of patients.

Conclusion

To conclude, our findings confirmed the effectiveness and good safety profile of IV UST as maintenance treatment in IBD patients who have lost response to SC treatment due to its ablility to

recapture response in 82.6% of the patients. Consequently, even though IV maintenance therapy is outside the product license, it could be considered in this group of patients and proposed in hospital pharmacies. Nevertheless, new studies comparing the efficacy of both dosages are needed to establish the best option.

Declarations

Ethical approval and consent to participate

The study was conducted at the Digestive System Department of the University Hospital Virgen Macarena (Spain). The protocol was reviewed and approved by the Institutional Review board/Independent Ethics Committee (CEIm Provincial Sevilla, Spain) on March 10th, 2023 (Supplemental Appendix 1). The ethical approval number is: 0700-N-23 and the code: 2023/149. All patients signed the written informed consent before study initiation. The study was conducted in full conformity with appropriate local laws and regulations and the Declaration of Helsinki.

Consent for publication

Not applicable.

Author contributions

Federico Argüelles-Arias: Conceptualization; Investigation; Project administration; Supervision; Validation; Visualization; Writing – review & editing.

Teresa Valdés Delgado: Conceptualization; Data curation; Formal analysis; Funding acquisition; Investigation; Methodology; Project administration; Resources; Software; Supervision; Validation; Visualization; Writing – original draft; Writing – review & editing.

Belén Maldonado Pérez: Investigation; Visualization.

Jaime González Antuña: Formal analysis; Investigation.

Luisa Castro Laria: Visualization.

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Competing interests

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Availability of data and materials

Not applicable.

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Supplemental material

Supplemental material for this article is available online.

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