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Analysis of the effectiveness and safety of maintenance treatment with intravenous ustekinumab in inflammatory bowel disease

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ORIGINAL

ANALYSIS OF THE EFFECTIVENESS AND SAFETY OF MAINTENANCE TREATMENT WITH INTRAVENOUS USTEKINUMAB IN INFLAMMATORY BOWEL DISEASE

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ANALYSIS OF THE EFFECTIVENESS AND SAFETY OF MAINTENANCE TREATMENT WITH INTRAVENOUS USTEKINUMAB IN INFLAMMATORY BOWEL DISEASE

Methods

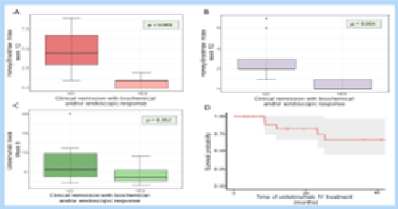
-Retrospective observational study

-22 patients with **Crohn´s Disease** or **Ulcerative Colitis**

-Maintenance therapy with **intravenous ustekinumab** after los of response to sc ustekinumab

- March 2017 – June 2024

Outcomes



ANALYSIS OF THE EFFECTIVENESS AND SAFETY OF MAINTENANCE TREATMENT WITH INTRAVENOUS USTEKINUMAB IN INFLAMMATORY BOWEL DISEASE

Conclusion

Maintenance therapy with intravenous ustekinumab appears to be **effective** and **safe** in rescuing patients with **CD** and **UC** who lost response to intensification of subcutaneous ustekinumab.

Pampín Sánchez, R. et al.
Revista Española de Enfermedades Digestivas (REED)
The Spanish Journal of Gastroenterology

Revista Española de Enfermedades Digestivas
The Spanish Journal of Gastroenterology

Analysis of the effectiveness and safety of maintenance treatment with intravenous ustekinumab in inflammatory bowel disease

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ABSTRACT

Background and purpose of the study: Ustekinumab is a monoclonal antibody approved for the treatment of moderate to severe Crohn's disease (CD) and ulcerative colitis (UC). In spite of being an effective treatment, patients may have suboptimal response, or lose it over time. In these cases, ustekinumab intravenous (IV) maintenance therapy has been explored as a rescue option.

Methods: Retrospective, monocentric, descriptive, observational study that included adult patients with inflammatory bowel disease who received maintenance therapy with intravenous ustekinumab after loss of response to intensified subcutaneous therapy. The primary outcome was a combination of clinical remission with biochemical and/or endoscopic response at week 12 after intravenous intensification.

Results: 22 patients were included. The primary outcome was achieved in 36.36% of patients. At week 12, clinical remission was achieved in 40.91% of patients, and biochemical remission in 63.64%. The median HBI score in patients with CD decreased from 6 to 3 points at week 12 ($p<0.001$), and to 2 points at week 52 ($p=0.004$). After a

Revista Española de Enfermedades Digestivas
The Spanish Journal of Gastroenterology

median follow-up period of 31.46 months, 81.82% of patients continued their treatment with ustekinumab. No adverse events were reported.

Conclusions: Maintenance therapy with intravenous ustekinumab seems to be effective and safe for the rescue of patients with CD and UC who lost response to intensified subcutaneous ustekinumab.

Key words: Ulcerative colitis. Intravenous dose. Effectiveness. Crohn's disease. Intensification. Ustekinumab.

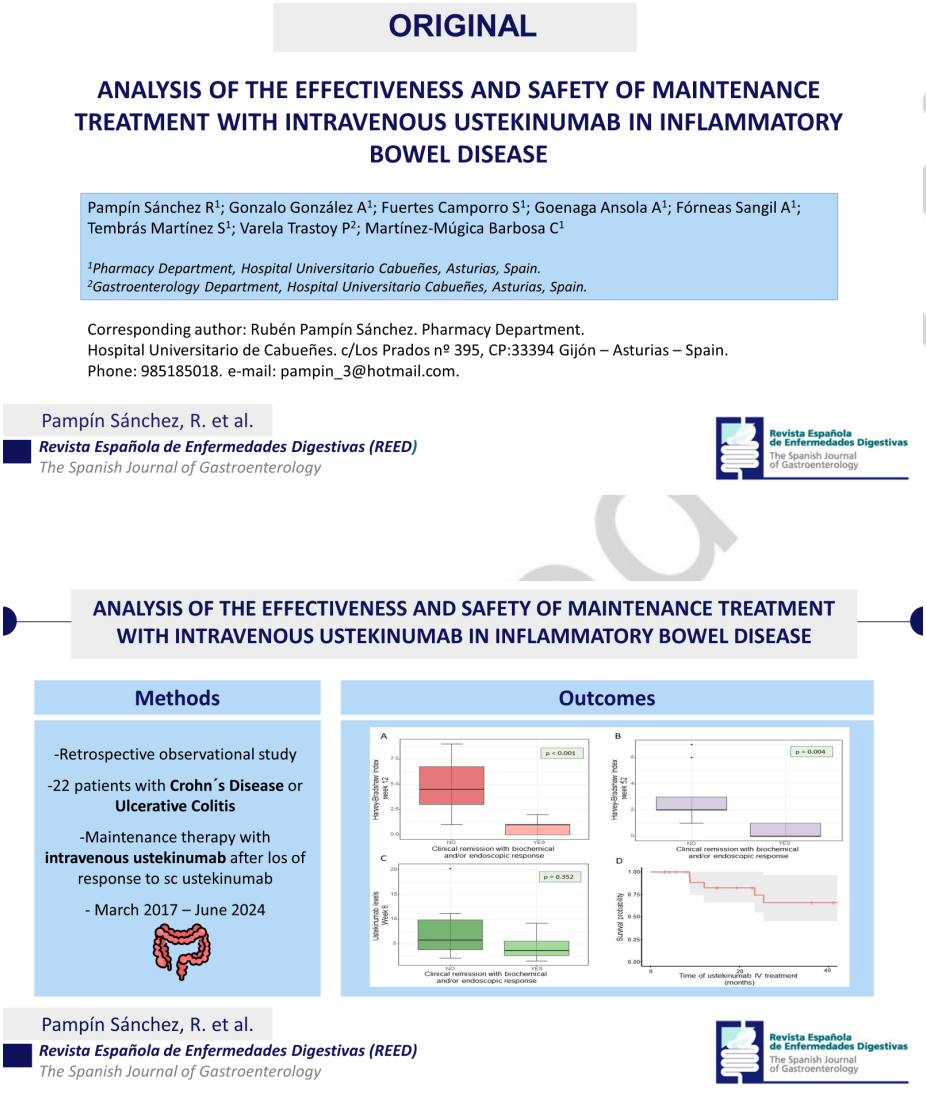
***Lay Summary*:**

In spite of the approval of new drugs for the treatment of inflammatory bowel diseases, therapeutic options are still limited. Many patients do not achieve adequate control of their disease with the currently available treatments, which highlights the need to optimize them. This study focused on assessing the efficacy and safety profile of an intensified treatment with intravenous ustekinumab as maintenance therapy for patients who responded poorly to subcutaneous doses. The outcomes of patients treated with maintenance intravenous ustekinumab were analyzed, observing their clinical responses and treatment persistence over time. Intensified therapy with intravenous ustekinumab allowed for a high percentage of patients who did not respond to typical doses to regain response. In our study, 81.82% of patients continued the treatment in the long term. Additionally, blood drug levels were observed to improve, although some statistical analyses showed no statistically significant differences. In conclusion, intensified intravenous ustekinumab is an effective and safe option for patients who lose response to the subcutaneous form over time. This strategy must be considered before switching to different drugs. Further studies are needed in order to identify which patients benefit the most from this approach, as well as to determine the best dosing regimen.

CRediT Author Statement:

RPS, AGG, SFC, AGA, AFS, STM, PVT, CMM have contributed to the design, writing, critical review, and final approval of the submitted version of this work, taking responsibility of every aspect of it in order to guarantee the resolution of every question that could possibly arise.

Visual Abstract



Revista Española de Enfermedades Digestivas
The Spanish Journal of Gastroenterology

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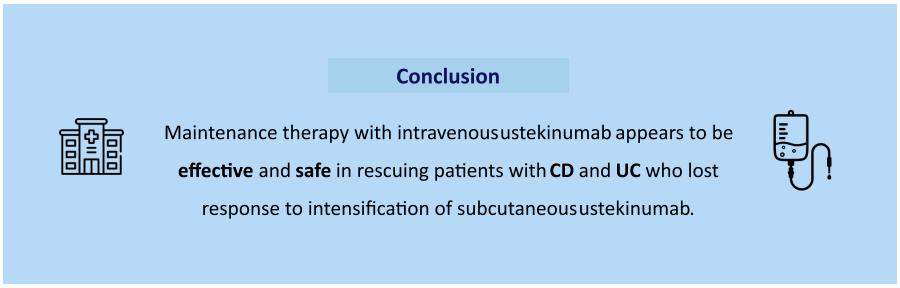

Pampín Sánchez, R. et al.
Revista Española de Enfermedades Digestivas (REED)
The Spanish Journal of Gastroenterology

Revista Española de Enfermedades Digestivas
The Spanish Journal of Gastroenterology

***Highlights*:**

- ✓ Nearly 50% of patients with inflammatory bowel disease fail to achieve adequate control of the disease with currently available therapies.
- ✓ Intensified intravenous therapy with maintenance ustekinumab is safe and effective in patients experiencing secondary loss of response to subcutaneous administration.
- ✓ This strategy allows for high drug persistence rates, rescuing 81.82% of treated patients.
- ✓ Further prospective studies are needed in order to identify which patient profiles may benefit the most from intravenous ustekinumab.

Conflict of interest statement: The authors have no conflict of interest to declare.

Diversity and inclusion statement: We support inclusive, diverse and equitable research.

AI use statement: The authors have not used any type of artificial intelligence tools or services for the writing and/or review of this work, and assume full responsibility for the content of this publication.

Revista Española de Enfermedades Digestivas
The Spanish Journal of Gastroenterology

INTRODUCTION

Ustekinumab is a fully human IgG1κ monoclonal antibody that inhibits the activity of interleukins (IL) 12 and 23, which are central to the pathology of Crohn's disease (CD) and ulcerative colitis (UC), among others (1). It is indicated in adult patients with moderate-to-severe active disease who have either failed to adequately respond or lost response to standard therapy or Tumor Necrosis Factor-alpha (TNFα) antagonists, as well as those who are intolerant or contraindicated to receive them. It was approved after UNITI (CD) (2) and UNIFI (UC) (3) studies with single-dose intravenous induction, based on the patient's body weight, followed by a 90-mg subcutaneous maintenance dose at week 8, and subsequently every 8 to 12 weeks, depending on treatment response.

The data generated by IM-UNITI (CD) (4) and UNIFI-M (UC) (5) studies showed that around 40% and 30% of patients, respectively, experienced loss of response to the drug at week 44 (52 weeks after the induction dose).

Secondary loss of response to ustekinumab is frequently found also in clinical practice, and its management is not clearly established in intensification guides (6). Between 40% (CU) and 50% (CD) of patients experience loss of response after treatment (7-9). Therefore, many of these patients receive rescue therapy with intensified treatment regimens every 4 or 6 weeks (10), empirically and based on clinical criteria, given the lack of data to support therapeutic monitoring of ustekinumab (11). Studies have been recently published showing positive results on the use of maintenance intravenous (IV) ustekinumab with the aim of rescuing patients who have either lost response or partially responded to intensified therapy with subcutaneous ustekinumab (12-14).

In our study, we plan to evaluate the efficacy and safety of rescue therapy with maintenance intravenous ustekinumab after secondary loss of response in patients with

CD or UC.

PATIENTS AND METHODS

Study design

A retrospective, monocentric, descriptive, observational study was developed in a third-level hospital, which included adult patients with inflammatory bowel disease (IBD) who received maintenance therapy with intravenous ustekinumab after loss of response to the intensified subcutaneous form of the drug. The follow-up period lasted from March 2017 to June 2024. The study included all the patients who had received at least three doses of maintenance intravenous ustekinumab as rescue therapy. Patients lost to follow up and those with insufficient clinical records were excluded.

Variables and response evaluation

Demographic data (sex, age, weight, height, body mass index) were collected, as well as those related to patients' baseline characteristics, such as smoking habits, type of IBD, Montreal Classification, disease duration, presence of perianal disease, previous surgeries, previous therapies, concomitant intensified intravenous treatments, and previous subcutaneous ustekinumab regimens.

The co-primary endpoint established was clinical remission with biochemical and/or endoscopic response at week 12 after intensification of intravenous ustekinumab.

The evaluation of clinical activity was performed before the switch to rescue therapy with maintenance intravenous ustekinumab, and also at week 12 and week 52 after the switch. The Harvey-Bradshaw index (HBI) was used in patients with CD, and the partial Mayo score (pMS) in patients with UC. Clinical activity was defined as HBI >4 or pMS >2 points. Clinical response was considered with a ≥3-point reduction in HBI and pMS, and clinical remission with values of HBI ≤4 or pMS ≤2 points at week 12.

Biochemical response was assessed by fecal calprotectin (FC) values and blood C-reactive protein (CRP) before the switch to intravenous ustekinumab, as well as at weeks 12 and 52 after the switch. Serum FC levels below 250 µg/g and PCR levels below 5 mg/l were

considered as biochemical remission. When available, endoscopic and radiological activity was assessed by bowel ultrasound or magnetic resonance enterography. The tests used were performed during the last 3 months prior to the switch to intravenous ustekinumab, and the 6 months subsequent to it. The SES-CD score (Simple Endoscopic Score for Crohn's Disease) was used in order to assess endoscopic response. Response was defined as a 50% reduction from baseline (or a reduction of at least 2 points from baseline in patients with isolated ileal disease and a baseline SES-CD of 4), and a ≤3-point reduction and at least a 2-point reduction from baseline and no >1 subscores in any individual variable. In UC, the Mayo Endoscopic Score was used considering a reduction of at least 1 point from baseline, and remission when Mayo 0 is reached.

Additionally, ustekinumab plasma levels were determined before intravenous intensification and in weeks 8 and 24 in those patients in which they were available. Other complementary parameters used were intravenous ustekinumab dosing regimens and drug persistence rate. Drug persistence rate was evaluated at weeks 24 and 52. Ustekinumab-related adverse events were also collected.

Statistical analysis

The percentage of patients who had had a positive primary assessment criterion were compared to those who had had a negative one for each of the variables of interest.

Chi-square test was used in categorical variables in order to obtain the p-value for difference in proportions in those cases in which expected frequencies were higher than 5, and the non-parametric Fisher's test in cases when some of the expected frequencies were lower than 5.

The Mann-Whitney U test was used for numerical variables in order to obtain the p-value associated with mean differences.

Failure-free survival with ustekinumab was assessed by the Kaplan-Meier method.

Missing data were not imputed for the analysis. Instead, only the patients whose data were fully recorded for the analyzed variables were considered.

Statistical analysis was performed using R version 4.3.2.

Revista Española de Enfermedades Digestivas
The Spanish Journal of Gastroenterology

RESULTS

A total of 22 patients were included, 19 diagnosed with CD and 3 with UC. 68% were female, with a mean age of 47 years (IQR 30-77) and a median duration of disease of 10 years (IQR 3-42). 68.2% (15/22) were active smokers (2/22) or former smokers (13/22), 40.9% had perianal disease, 50% had extraintestinal features, and 59.1% had a history of bowel resection. Patients had been treated with subcutaneous ustekinumab during a median period of 11.2 months (IQR 1.4-37.3). 72,73% were on a 90-mg intensified regimen every 4 weeks, and 4 patients were receiving concomitant immunosuppression at the time of intravenous intensification. 90.91% had been treated with anti-TNF drugs and 40.91% had experienced failure to 2 previous treatments. The reason for intensified therapy with intravenous ustekinumab was the loss of secondary response in all the included patients. Different maintenance regimens were used with intravenous ustekinumab, the most frequent being 260 mg every 4 weeks (22.73%) and 390 mg every 6 weeks (18.18%) (*Table 1*).

The primary goal, consisting of clinical remission with biochemical and/or endoscopic response, was achieved in 36.36% of patients (8/22). Clinical remission was achieved at week 12 after intravenous intensification in 40.91% of patients (7/19 with CD and 2/3 with UC). 77.27% of the patients who received maintenance therapy with IV ustekinumab achieved clinical response after 12 weeks of treatment (*Table 2*). In patients with CD, the median HBI decreased from a baseline of 6 points to 3 points at week 12 ($p<0.001$) and 2 points at week 52 (p: 0.004) (*Figure 1*). In patients with UC, the median pMS also decreased from a baseline of 5 points to 0 points at weeks 12 ($p<0.001$) and 52 ($p<0.001$). 2 patients in the CD group experienced a flare during the follow-up year after intravenous intensification. 63.64% of patients showed biochemical remission at week 12. FC decreased from a mean baseline of 624 µg/g (IQR 10-5.390) to a median level of 223 µg/g (IQR 9-8.000) at week 12 (p: 0.402). PCR also showed a decrease from a mean baseline of 9 mg/L (IQR 0.5-185) to 6 mg/L (IQR 0.5-21.1) at week 12 (p:0.07). Radiological data are

only available from 9 patients, 6 of which achieved endoscopic response, and only 1 endoscopic remission.

Ustekinumab plasma levels were recorded in 9 patients. The median ustekinumab levels increased from 1.34 µg/mL (IQR 0.13-5.52) to 5.52 µg/mL (IQR 1.59-20.26) at week 8 after intravenous intensification of ustekinumab (p: 0.352) (*Figure 1*).

After a median follow-up period of 31.46 months (IQR 3.00-70.37), 81.82% of patients continued their treatment with ustekinumab. The 4 patients (18.18%) who discontinued ustekinumab were considered as treatment failures. This line of therapy continued for a median of 3.2 years IQR 0.4-6.5; p: 0,365), with treatment persistence rates during the intravenous maintenance regimen of 81.82% and 68.18% at weeks 24 and 52, respectively (*Figure 1*).

DISCUSSION

In spite of the recent approval of new molecules for the treatment of inflammatory bowel diseases, there are still some studies showing that nearly 50% of patients fail to achieve adequate disease control (15). As a consequence, it is essential to find ways to optimize the available lines of therapy. All this combined with an increasingly ambitious treatment goal, that is, to aim for deep disease remission (clinical, biochemical and endoscopic), demands a personalized medicine approach to inflammatory bowel disease.

Ustekinumab has proved to be a safe and effective drug in the treatment of inflammatory bowel diseases. Intensification, at shortened intervals (every 4-6 weeks), showed response recovery data in 50-70% of patients (9,16). However, when these intensified regimens do not achieve their goal, options are limited. Diverse studies (*Table 3*) have published data on intravenous intensification resulting in clinical remission in around 45% of patients.

The clinical response and remission data presented in our study are in line with other published real-world practice studies. García-Alvarado et al presented data from 79 patients with CD and UC, with insufficient response or loss of response to the intensified regimen of intravenous ustekinumab every 4-6 weeks. After switching to maintenance therapy with intravenous ustekinumab, they reached clinical remission data of 43% at

week 12 (17). Subsequently, Argüelles et al, in their 23-patient cohort, presented response rates of 82.6% and clinical remission rates of 43.5% at week 12 for the patients who had received maintenance IV ustekinumab (13). Furthermore, Suárez-Ferrer et al published data on 27 patients in which, in spite of the lack of statistically significant changes in HBI as a whole (70% vs 67%) at week 12, subgroup analysis showed 14.8% reduction in patients with severe activity (14). In our patient cohort, intensified therapy with IV ustekinumab allowed us to rescue 81.82% of the patients who had experienced failure to the maximum intensification regimens used in their subcutaneous form.

Despite the lack of statistical significance, possibly caused by the reduced sample size, biochemical response showed considerably reduced biomarker levels, both in PCR and fecal calprotectin

Long-term sustained response is one more condition that must be considered in IBD. Certain studies on the persistence of the available therapies for IBD showed better persistence data at one year for ustekinumab than for anti-TNF drugs and vedolizumab in patients with CD (18). In our study, the intravenous intensification approach allowed for a prolonged treatment persistence with ustekinumab by a median of 3.2 years, with 81.82% of patients continuing the treatment by the end of the follow-up period. An optimal management of these treatments allows us to rescue a high percentage of patients that would otherwise experience treatment failure and need to progress to a further line of therapy, thus limiting their future therapeutic options.

The use of intravenous ustekinumab is suggested with the aim of increasing the drug's bioavailability in order to improve clinical response. This hypothesis is based on the fact that during maintenance phase, concentrations equal to or higher than 1 µg/mL are associated with clinical response and clinical remission, whereas concentrations equal to or higher than 4.5 µg/mL are associated with higher endoscopic response (11). Recent studies also affirm that there seems to be a link between a higher minimum concentration of ustekinumab and clinical outcomes, as well as achieved healing and mucosal response regardless of previous exposition to biologic agents (19-20). In spite of this, the interpretation of plasma levels could vary depending on the patient, and there are

currently no established therapeutic ranges. Our study analyzed intensification with intravenous ustekinumab during maintenance in order to achieve patients' clinical, biochemical and endoscopic stabilization. Although plasma levels appeared to be four times higher in the 9 patients with records, statistical analysis showed no statistically significant differences at week 8 between the patients who achieved the primary goal and those who did not. Additionally, body mass index was analyzed as a possible predictor of negative response, with no statistically significant differences observed. (p:0.973).

Regarding study limitations, the small sample size may be worth highlighting, which results in low statistical power. Further studies, preferably multicenter ones, would be necessary in order to obtain a larger sample size that would allow to compare patient profiles that could benefit the most from the intravenous use of the drug. Additionally, the irregular intensification pattern may affect the validity of conclusions. Furthermore, the lack of therapeutic alternatives at the beginning of the study period created the need to optimize the use of ustekinumab to the maximum.

Intensification with intravenous ustekinumab has proved to be a safe and effective rescue therapy in patients who experience loss of response to the standard regimen or subcutaneous intensification, allowing for high drug-persistence rates. This strategy must be taken into account for those patients who have experienced secondary failure to ustekinumab before considering a therapeutic target change.

Conducting larger prospective studies could help to understand which patient profiles may benefit the most from this strategy, as well as the optimal dose regimen for intravenous ustekinumab.

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Revista Española de Enfermedades Digestivas
The Spanish Journal of Gastroenterology

Table 1. Clinical and demographic characteristics.

Patient characteristics	Data	p-value
Median age at IV intensification (years, IQR)	47 (30-77)	0.561
Sex (n, %)		1
Male	7 (31.82%)	
Female	15 (68.18%)	
Median Body Mass Index	23.8	0.973
Smoking status (n, %)		0.421
No	7 (31.82%)	
Current	2 (9.1%)	
Former	13 (59.1%)	
IBD type (n, %)		0.527
Crohn´s disease diagnostic	19 (86.4%)	
Ulcerative Colitis	3 (13.6%)	
Median age at diagnosis (years, IQR)	38 (17-67)	
Median duration of the disease (years, IQR)	10 (3-42)	0.891
Disease location (CD) (n, %)		0.606
Ileal	8 (42.11%)	
Colonic	3 (15.79%)	
Ileocolonic	7 (36.84%)	
Upper GI	1 (5.26%)	
Disease behaviour (CD) (n, %)		0.372
Non-stricturing, non penetrating	11 (57.89%)	
Stricturing	2 (10.53%)	

Revista Española de Enfermedades Digestivas
The Spanish Journal of Gastroenterology

Penetrating	6 (31.58%)	
Perianal disease (n, %)	9 (40.91%)	0.662
Extraintestinal manifestations (%)	50%	1
Baseline índices (n, IQR)		
Median HBI	6 (0-10)	<0.001
Median pMAYO	5 (2-8)	<0.001
Median CRP level (mg/L)	9 (0.5-185)	0.07
Median calprotectin level (mcg/g)	624 (10-5390)	0.402
Prior therapy (n, %)		1
Prior anti-TNFα therapy	20 (90.91%)	1
Failed 2 biologics	9 (40.91%)	
Failed 3 or more biologics	3 (13.64%)	
Previous IBD-related surgery	13 (59.09%)	0.662
Corticosteroid use at the time of IV intensification (n, %)	2 (9.09%)	1
Inmunosupressant use at the time of IV intensification (n, %)	2 (9.09%)	1
Previous UST SC dosage frecuency (n, %)		0.352
Every 4 week	17 (77.27%)	
Every 6 week	1 (4.55%)	
Every 8 week	4 (18.18%)	
Subcutaneous UST treatment duration (months), median [IQR]	11.2 (1.4-37.3)	0.26
Subcutaneous UST through levels (mcg/mL) median [IQR]	1.34 (0.13-5.52)	0.583
Dose and frequency of IV UST (n, %)		
130 mg q4w	3 (13.64%)	
130 mg q6w	1 (4.55%)	
130 mg q8w	1 (4.55%)	

260 mg q4w	5 (22.73%)	
260 mg q6w	3 (13.64%)	
260 mg q8w	1 (4.55%)	
390 mg q4w	1 (4.55%)	
390 mg q6w	4 (18.18%)	
390 mg q8w	2 (9.09%)	
520 mg q6w	1 (4.55%)	

CD, Crohn´s Disease; CRP, C-reactive protein; HBI, Harvey-Bradshaw Index; IBD, Inflammatory Bowel; IV, intravenous; IQR, interquartile range; SC, subcutaneous; TNF, tumor necrosis factor; UST, Ustekinumab

Table 2. Outcomes of clinical activity, CRP, fecal calprotectin and UST levels before and after switching to intravenous Ustekinumab

Variables	Basal	12 weeks	52 weeks
Clinical activity	Median	Median	Median
Harvey-Bradshaw Index	6	3	2
p-Mayo Score	5	0	0
C-reactive protein (mg/L)	9	6	5
Fecal Calprotectin (mcg/g)	624	223	116
Median UST through levels	1.34	5.02*	9.27*

**Ustekinumab leves were determinated at baseline and in weeks 8 and 24*

Revista Española
de Enfermedades Digestivas
The Spanish Journal
of Gastroenterology

Table 3. Studies of the use of intravenous ustekinumab as maintenance treatment in refractory inflammatory bowel disease.

Authors, year	Study design	Sample, size (n)	Age years (median)	Disease duration (years)	UST SC duration (months)	Therapeutic indication	Disease behabiour	Risk factors	Previous biological /iJAK therapies (n, %)	Dose IV UST	Clinical response (%; week)	Clinical remission (%; week)
García-Alvarado et al, 2022	Monocentric retrospective observational study*	79	47 (21-80)	12,46 (1-43)	14,65	CD (73/79) and UC (6/79)	B2 (21/73) B3 (24/73)	PI (28/79)	1 (42%); 2 (37%); 3 (16%); 4 (1,3%)	NA (c/4-6 weeks usually)	NA	43%, week 12
Hermida et al, 2023	Letter to the editor	12	42	NA	NA	CD	B2 (2/12) B3 (4/12)	PI (7/12)	ND (12/12 anti-TNF previously)	Dose (390mg 50%; 260mg 42%; 130mg 8%). Frequency (8week 67%; 6week 8%; 4week 25%)	63%, week 8	25%, week 8

Argüelles-Arias et al, 2023	Monocentric retrospective observational study	23	43 (32-50)	12 (5-21)	14,7 (5-26)	CD (19/23) and UC (4/23)	NA	PI (7/23) PS (9/23)	1 (26%); 2 (30%); 3 (22%); 4 (4%); 5 (4%)	130mg: c/4week (78%); c/6week (4,3%); c/8week (4,3%). 260mg/4week (13%)	82,6%, week 12	43,5% (CD 10/19; UC 0/4), week 12
Suárez-Ferrer et al, 2024	Monocentric retrospective observational study	27	NA	NA	NA	CD	B2 (15/27) B3 (6/27)	PI (9/27) PS (9/27)	1 (37%); 2 (33%); 3 (15%)	130 mg/ 4 week	No changes; severe reduction basal activity 14,8%, week12	NA
Valdés-Delgado et al, 2024	Multicentric retrospective observational study*	59	41 (32-52)	13 (9-21)	25 (15-17)	CD (50/59) and UC (9/59)	NA	PI (23/59) PS (24/59)	1 (32%); 2 (41%); 3 (12%); 4 (5%); 5 (1,7%)	NA	NA	47,5%, week 12
López-Sáez et al, 2024	Monocentric retrospecti	29	NA	NA	NA	CD (24/29) and UC	NA	NA	NA	130 mg/ 4 week	CD: 87,5% (week 8) and 83,3% (week	NA

	ve observational study*					(5/29)					16) UC: 60% (weeks 8 and 16)	

						CD (24/29) and UC (5/29)						
Fernández-Prada et al, 2024	Monocentric retrospective observational study*	60	46	NA	3,5 (2-4)	CD	B2 (6/60) B3 (17/60)	PI (14/60)	NA (1 or more 56/60)	NA	NA	79,6%; week 8 (48,3% at the begining)
CD, Crohn´s Disease; iJAK, Janus Kinase inhibitor; NA, Not available; PI, Perianal involvement; PS, Previous surgeries; TNF, Tumor necrosis factor; UC, Ulcerative Colitis												
**Preliminar data from studies published as Abstracts in Congresses*												

FIGURES

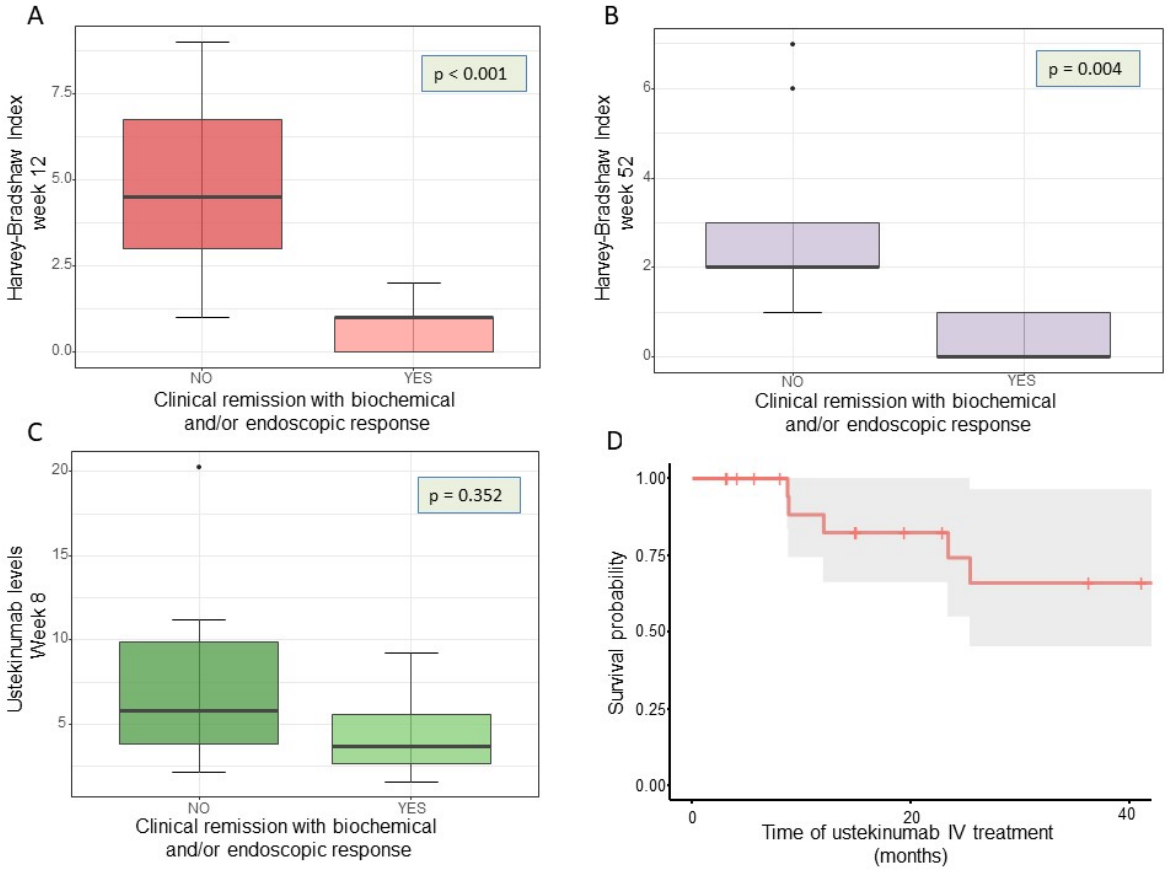

Figure 1. Clinical effectiveness of intravenous maintenance of ustekinumab. Clinical remission with biochemical and/or endoscopic response in patients with Crohn's disease at weeks 12 (A) and 52 (B), as well as ustekinumab levels at week 8 (C). (D) Survival probability (drug persistence rates) of intravenous ustekinumab treatment.