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Title:
Multicenter Spanish study on vedolizumab intravenous to subcutaneous switch in patients with inflammatory bowel disease in clinical remission

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Multicenter Spanish Study on Vedolizumab Intravenous to Subcutaneous Switch in Patients with Inflammatory Bowel Disease in Clinical Remission



24 Spanish hospitals

N=184 patients with IBD

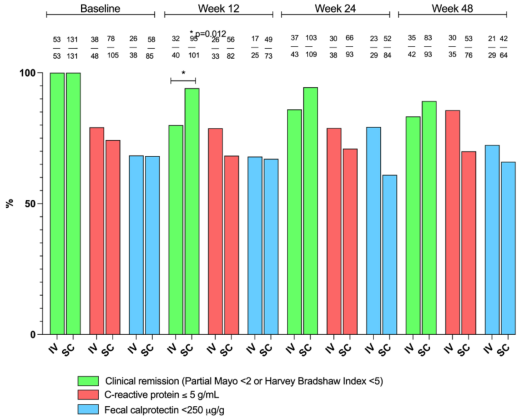
- 28.8% IV vedolizumab
- 71.2% SC vedolizumab

- Drug intensification:

  24.5% IV vs 0% SC, p<0.0001

- No differences in drug persistence, log-rank p=0.82

- No differences in safety among groups, p=0.06



Transitioning from IV to SC vedolizumab in patients with IBD in remission showed comparable effectiveness in maintaining disease remission and persistence. Patients on IV are more likely to need drug escalation during follow-up.

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Multicenter Spanish study on vedolizumab intravenous to subcutaneous switch in patients with inflammatory bowel disease in clinical remission

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Previous congress publications in abstract form

European Congress of Crohn's and Colitis Organization (ECCO year 2024). P989 Switching from intravenous to subcutaneous vedolizumab in patients with inflammatory bowel disease in clinical remission: a multicenter study from GETECCU

Authors' contributions

BG, YZ, MB, EI-F contributed to the design of the study. BG, NM, JG, IA-A, IR-L, RA, AP, FA, GR, FM, IG, MI, PB, FC, LM, JC, AC, LN, JMH, BC, FLR-S, BCS, CS, EA, YZ, MB, LGG, JO, contributed to the data collection. BG analysed the data. BG drafted the first version of the manuscript. All authors critically revised the manuscript for important intellectual content. All authors have approved the final version of this manuscript.

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ABSTRACT

BACKGROUND AND AIMS: Despite the established use of intravenous (IV) vedolizumab for treating inflammatory bowel disease, there's growing interest in exploring the advantages of the novel subcutaneous (SC) route. However, comprehensive real-world evidence regarding the extended safety and effectiveness of it remains scarce.

METHODS: IBD patients on IV vedolizumab treatment across 24 Spanish hospitals who were in clinical remission were given the option to transition to SC injections where this formulation was available or to remain on IV, while those in centers without access to SC vedolizumab remained on IV therapy. Data encompassing clinical disease activity, biochemical markers, adverse events, treatment persistence, and disease-related outcomes were retrospectively gathered from prospectively maintained clinical records at baseline, and at weeks 12, 24, and 48.

RESULTS: We identified 207 patients, with 23 excluded due to not being in clinical remission, resulting in a final inclusion of 184 patients. Of these, 53 (28.8%) remained on IV vedolizumab, while 131 (71.2%) transitioned to SC. There were 108 (58.7%) patients with ulcerative colitis and 76 (41.3%) with Crohn's disease. Both groups exhibited comparable demographic characteristics except for Crohn's disease behavior: non-inflammatory non-stricturing pattern (B1 Montreal classification) that was predominant among patients who transitioned to the SC (p=0.023). No differences were observed in drug persistence (log rank test p=0.82). Clinical, biochemical and fecal calprotectin remission at the different time-points were comparable at each time point with the exemption of clinical remission at week 12 favoring SC over IV. Drug intensification

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occurred in 24.5% of the patients on IV versus none on SC, p<0.0001. Safety was consistent with previously reported with no differences among groups 13 (8%) SC and IV 1 (2.1%), p=0.059; and most of them being mild in nature.

CONCLUSIONS: Transitioning from IV to SC vedolizumab in patients with IBD in remission showed comparable effectiveness in maintaining disease remission and persistence. Patients on IV are more likely to need drug intensification during follow-up.

Keywords: Ulcerative colitis. Biologics. Real-world data. Vedolizumab.

Lay summary: Vedolizumab is a medication used to treat inflammatory bowel diseases (IBD). Traditionally, it has been given through intravenous (IV) infusions at the hospital. A newer option allows patients to receive the treatment as subcutaneous (SC) injections, which can be done at home. In this study, 184 patients with IBD who were in clinical remission while on IV vedolizumab were followed in 24 hospitals across Spain. Some patients switched to SC injections, while others continued with IV infusions. The results showed that patients who switched to SC vedolizumab maintained their remission as effectively as those who stayed on IV treatment. Importantly, none of the patients who switched to SC needed to increase their dose, while about a quarter of those on IV did. Both forms of treatment showed a good safety profile, with no serious safety concerns.

INTRODUCTION

The transition from intravenous (IV) to subcutaneous (SC) vedolizumab for the maintenance treatment of inflammatory bowel disease (IBD) has attracted growing interest due to its potential advantages, including enhanced patient convenience, cost-effectiveness, and comparable clinical outcomes. Vedolizumab, a gut-selective integrin antagonist, remains a cornerstone therapy for both Crohn's disease (CD) and ulcerative

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colitis (UC) (1) valued for its well-established efficacy and safety profile.

After VISIBLE 1 and 2 trials were published, proving the efficacy of vedolizumab SC route both in CD and UC,(2,3) emerging real-world evidence supports the safety and effectiveness of switching from IV to SC vedolizumab. Some studies have demonstrated that this transition maintains clinical and biochemical stability in patients with CD and UC(4–6) while significantly increasing median serum vedolizumab concentrations post-switch.(7)

Longer-term data have reinforced these findings. Sustained therapeutic effectiveness and safety over 12 months, coupled with high patient satisfaction and reduced treatment costs.(4)

The preference for SC administration among patients has also addressed, proving that most patients find it more convenient after having been on SC route. (7) Collectively, these studies highlight that transitioning from IV to SC vedolizumab is a practical and effective option for maintaining disease control in IBD patients, offering a favorable safety profile, improved convenience, and potential economic benefits.

Our aim was to confirm the effectiveness and safety of switching to vedolizumab SC in patients with IBD who were in clinical remission in Spain.

MATERIAL AND METHODS

2.1 Study design

We performed a multicentre, retrospective, observational, cohort study performed at 24 Spanish hospitals. The study was publicly available to all Spanish centres affiliated with the Spanish group of the study of Crohn's disease and ulcerative colitis (GETECCU).

2.2 Participants

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IBD patients receiving IV vedolizumab who were in clinical remission defined as partial Mayo score <2 for UC patients, and Harvey-Bradshaw Index (HBI) <5 for CD at the time of transition to SC vedolizumab were included. Patients who transitioned to SC formulation comprised the main cohort, while those who did not transition and stayed on IV formulation (either due to no SC formulation available in their center or due to patient's preference) served as the control cohort. When SC was available, the decision to switch was based on patient preference after clinician counseling; no additional clinical eligibility criteria were applied beyond remission at baseline. We note that availability varied by center and calendar time as SC was implemented locally at different dates.

There was no minimum time requirement for IV treatment before transitioning, with the only prerequisite being clinical remission at the time of study inclusion.

2.3 Data collection

Baseline demographic, phenotyping and follow-up data were collected by reviewing electronic medical records. Data regarding clinical disease activity scores (partial Mayo score, and HBI); C-reactive protein (CRP); faecal calprotectin (FC); dose intensification; steroid prescriptions; hospitalization rates; surgery need and adverse events were retrospectively gathered from prospectively maintained clinical records at baseline, and at weeks 12, 24, and 48 and were collected via review of electronic medical records. Available CRP and FC data at baseline, 12± 4 weeks and 24± 4 weeks and 48± 4 weeks from baseline were analysed. Study data were collected using the Research Electronic Data Capture (REDCap), which is hosted by the Spanish Gastroenterology Association (AEG; www.aegastro.es). REDCap is a secure, web-based application designed that supports data capture for research studies and provides an intuitive interface for validated data entry, audit trails for tracking data manipulation and export procedures.(8)

2.4 Definitions

Clinical remission, biochemical remission and faecal calprotectin remission were defined

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as a partial Mayo score <2 or HBI <5; CRP ≤ 5 mg/L and FC <250 µg/g, respectively.(9) Normal albumin level was defined as ≥ 36g/L. Steroid prescription during follow-up was defined as oral prednisone or oral budesonide prescribed at any point after baseline. Serious adverse events were defined as any event leading to permanent discontinuation of therapy, hospitalisation, or death. Drug intensification was done as per clinician discretion with vedolizumab intensified up to 300 mg every 4 or 6 weeks or SC intensified to weekly dose. Date of drug intensification was recorded.

2.5 Primary and secondary outcomes

The primary outcome of this study was clinical remission at week 48. Secondary outcomes included drug persistence, adverse events; biochemical and calprotectin remission at weeks 12, 24 and 48.

2.6. Statistical analysis

Descriptive statistics are presented as medians with interquartile range [IQR] for continuous variables, and frequencies with percentages for categorical variables. For comparison of non-parametric continuous variables, the Mann–Whitney U test was used. For comparison of categorical variables, the chi-squared test was used. Kaplan-Meier survival curve was generated to assess drug persistence. Cox proportional hazard regression analyses were carried out to identify possible baseline predictors of drug survival. Variables for analysis were chosen a priori. In case of a p-value of < 0.1 in univariable analysis, variables were included in the multivariable analysis. The model included the duration of prior IV vedolizumab exposure at baseline as a covariate to account for differences in time on treatment before allocation to SC vs continued IV.

A per-protocol analysis was used for the effectiveness outcomes. A p-value <0.05 was considered significant.

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SPSS Version 25 [IBM Inc., Armonk, NY] and Prism Version 9.0 [Graphpad Software, San Diego, CA, USA] were used for statistical analyses and generation of graphs.

2.7 Ethics

The study was carried out in accordance to the European General Data Protection Regulation (GDPR) 2016/679 and the Spanish Data Protection Organic Law 3/2018.
The protocol was approved by the Research Ethic Committee of Cordoba (code: SUBVE. Internal code: 0387-N-23). The study complies with the ethical guidelines of the 1975 Declaration of Helsinki.(10)

RESULTS

Study population

We identified 207 patients, with 23 excluded due to not being in clinical remission, resulting in a final inclusion of 184 patients for analysis. Of these, 53 (28.8%) remained on IV vedolizumab, while 131 (71.2%) transitioned to SC vedolizumab. Median age of the cohort was 51 years (37-61) and 97 (52.7%) were female. Regarding IBD type, 108 (58.7%) had UC/IBDU and 76 (41.3%) had CD and 41 (22.3%) had extraintestinal manifestations (EIMs). The majority of the patients had previously been exposed to any biologic or small molecule 129 (70.1%). Time on IV vedolizumab before study baseline was 16.8 months (1.8- 42.4).
Both groups exhibited comparable demographic characteristics including age, gender, disease type, disease duration and extent, previous therapy, presence of extraintestinal manifestations and comorbidities (Table 1). However, there was a significant disparity in CD behavior: non-inflammatory non-stricturing pattern (B1 of Montreal classification) was predominant among patients who transitioned to the SC formulation (p=0.023).

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Efficacy outcomes

Regarding clinical, biochemical and fecal calprotectin remission at the different time-points, we found significant difference in clinical remission at week 12 favoring SC vedolizumab vs IV (94.1% vs 80%, p=0.01), but no other differences (Figure 1). No differences were observed in FC and CRP at the different time-points when these are analyzed as continuous variables, Figure 4.

We then analyzed both CD and UC separately. No differences were observed in CD outcomes at the different time-points, whereas we found similar finding than in the overall cohort among UC patients, with clinical remission at week 12 being higher in those on SC vs IV (89.7% vs 69.2%, p=0.02), Figure 2.

Drug survival, steroid prescription, hospitalization and dose optimization

At the end of follow-up (48-weeks) 4 (8.3%) patients on IV and 6 (4.5%) on SC discontinued vedolizumab, p=0.804. There were 6 (4.5%) patients who were switched back from SC to IV. Considering also patients who switched back to IV formulation as a drug withdrawal for survival analysis, 11 (9.6%) patients on SC either stopped the drug or switched back to IV, (one switched back to IV but ended up withdrawing the drug), with no differences in drug survival (log rank test p=0.82), Figure 3. Additionally, corticosteroids were needed in 6 (12.8%) patients on IV vs 10 (8.7%) on SC formulation (p=0.43). Regarding drug dosage, 13 (24.5%) patients who were on IV vedolizumab needed drug intensification during follow-up, whereas no patients on SC required it, p<0.0001. There were 2 (1.7%) IBD related admissions documented in the SC group vs 1 (2.1%) in the IV group (p=0.868) and one patient (1.8%) on IV needed an IBD related surgery during follow-up.

Predictors for drug persistence

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Univariable cox regression analysis identified the presence of immune-mediated inflammatory diseases (IMID) (hazard ratio [HR] 6.23, 95% confidence interval [CI] 1.75-22.14, p=0.005) and upper CD location (L4 Montreal classification) (HR 18.61, 95% CI 4.33-80.51, p<0.001) as associated with worse drug persistence. Multivariable cox regression analysis identified only L4 location as associated with worse drug persistence (HR 13.94, 95% CI 2.58-75.13, p=0.002) (Table 2). Neither vedolizumab formulation nor the time on IV formulation prior switch were associated to drug persistence.

Safety

During follow-up a total of 14 (8.6%) adverse events were documented. Patients on SC experiencing an adverse event were 13 (8%) and on IV 1 (2.1%), p=0.06. Out of the 14, 4 were due to skin reaction to the injection, 1 was due to joint pain, 1 chest infection and 9 of another cause. There were 6 patients whose drug was withdrawn due to an adverse event: 1 joint pain, 1 chest infection, 1 skin reaction and 3 of another cause. There were not allergic reactions documented and no deaths.

DISCUSSION

Our study provides valuable insights into the real-world effectiveness, safety and drug persistence of IV and SC vedolizumab formulations in patients with IBD. The primary endpoints of clinical, biochemical, and calprotectin remission rates were achieved, with a significant difference favoring SC vedolizumab in clinical remission at week 12 (94.1% vs 80%, p=0.012). The observed superiority of SC vedolizumab at this time point, particularly in patients with UC, aligns with prior studies suggesting that SC formulations can enhance treatment convenience and adherence.(11,12) However, caution is warranted when interpreting this finding, as the lack of differences at week 24 and 48 along with the absence of significant differences in CRP and FC remission at all time points.

The transition to SC vedolizumab potentially empowers patients by offering greater autonomy, which could improve psychosocial well-being and explain the observed clinical

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benefit at week 12. This could explain why CRP and FC did not differ at this timepoint. This aligns with the growing recognition of the importance of patient-centric approaches in chronic disease management.(13)

Drug survival analysis revealed no significant differences between SC and IV vedolizumab, proving that both formulations are viable options for long-term management of IBD. However, it is notable that none of the patients in the SC group required dose intensification during follow-up, compared to 24.5% of patients on IV. This finding suggest that the SC formulation may offer advantages maintaining stable disease activity without additional therapeutic adjustments, which warrants further investigation. Supporting this observation, Volkers et al., reported higher median serum vedolizumab concentrations with SC administration (7) although the real relevance of vedolizumab level variation and its relation to IBD outcomes has conflicting data.(14–16)

The only variable identified as a risk factor for drug withdrawal was upper CD location (L4). This aligns with the understanding that upper GI involvement in CD often correlates with more severe disease and suboptimal treatment responses and also there is a lower density of alpha-4-beta-7 receptors in the upper gastrointestinal tract.(17) However, this result should be interpreted cautiously due to the small number of patients with L4 in our cohort. Similarly, while univariable analysis identified the presence of IMID as a predictor of worse drug persistence, this was not confirmed in multivariable analysis, likely due to the low prevalence of IMIDS (3.8%), most of which were psoriasis. Vedolizumab, being the only approved drug in the IBD pipeline with a gut-specific target, does not work in any other immune-mediated conditions for which this finding is not surprising. It is perhaps more interesting to note, that 22.3% of patients had EIMs and this was not associated to drug withdrawal, this supports the notion that many EIMs parallel bowel inflammation and may improve with effective control of intestinal disease. Notably, neither the vedolizumab formulation nor the time on IV therapy prior to switching impacted drug persistence, suggesting that the choice of formulation does not compromise long-term outcomes.

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The safety profile of vedolizumab remained favorable across both formulations, with low rates of adverse events and no allergic reactions or deaths reported. Most of the adverse events recorded were mild in nature and slightly higher in the SC group, particularly transient local injection reactions which consistent with previous studies.(6,18)

The cost-effectiveness of SC vedolizumab, with a reported 15% reduction in annualized treatment costs, is an important consideration for healthcare systems.(4,19,20) This not only translates into fewer infusions and reduced day-hospital demands but also contributes to a lower environmental footprint by decreasing the frequency of hospital visits and reducing the need for treatment intensification. Furthermore, SC administration aligns with patient' preferences, as many patients favor SC delivery over IV. (11,12) This economic benefit, combined with the high drug persistence rates in our study which is in line with the persistence rates reported by Lim et al. at 52 weeks,(6) support the convenience of SC switching. Additionally, as IBD prevalence continues to increase SC therapies are gaining interest due to their ability to reduce the need for infusion suites and pharmacist-led drug preparation, thereby alleviating hospital saturation.

Several limitations of our study should be acknowledged. First, its retrospective design and selection bias due to non-random allocation. This introduces potential selection bias that may not be fully captured by measured covariates. Although our analyses adjust for baseline characteristics, residual and unmeasured confounding and secular trends across centers and calendar time could still influence comparative estimates of effectiveness and persistence. Second, the relatively short follow-up period might underestimate long-term differences in drug survival or safety profiles, especially in rare adverse events. Third, our study population included a high proportion of biologic-experienced patients, which might influence outcomes compared to biologic-naïve populations. Finally, as this is not generally assessed in clinical practice vedolizumab levels were not available and we could not perform an economic analysis of the strategy due to the drugs having different cost depending on the hospital and regional area in Spain.

But our study has a number of strengths, first this is a multicenter study across Spain, second unlike some of the published studies, all the patients included were in clinical

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remission which facilitates comprehension of drug behavior and comparison at the different timepoints.

Therefore, our study supports the transition from IV to SC vedolizumab as a viable option for maintaining therapeutic effectiveness and safety in IBD patients, with added benefits of patient convenience and reduced healthcare costs and perhaps decrease drug IV intensification need. These findings are consistent with the broader body of real-world evidence, reinforcing the clinical utility of SC vedolizumab in routine practice. Future studies would benefit from patient-reported outcome measures (PROMs) for better understanding of quality-of-life impact and drug adherence.

CONCLUSIONS

This study supports the use of SC vedolizumab as an effective and safe alternative to IV therapy in IBD, with the added benefit of reduced need for drug intensification. Drug intensification is more frequently needed among patients on IV than on SC. Future prospective studies should focus on patient-reported outcomes and pharmacoeconomic analyses to better understand the implications of transitioning to SC formulations in clinical practice.

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Table 1. Baseline characteristics of patients

N=184	Total	Vedolizumab IV (n=53)	Vedolizumab SC (n=131)	*p*
Age, years, median (IQR)	51 (37-61)	52 (42-63)	50 (35-59)	0.329
Gender, female, n (%)	97 (52.7)	32 (60.4)	65 (49.6)	0.186
IBD type, n (%) • UC/IBDU • CD	 108 (58.7) 76 (41.3)	 33 (62.3) 20 (37.7)	 75 (57.3) 56 (42.7)	0.532
Disease duration, years, median (IQR)	9 (3-18)	6 (2-19)	9 (4-18)	0.285
Smokers, n (%)	23 (12.5)	12 (22.6)	11 (8.5)	0.032
Ulcerative colitis, n (%) • Proctitis (E1) • Left sided (E2)	 3 (1.6) 34 (18.5)	 0 9 (17.0)	 3 (2.3) 25 (19.1)	0.327

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N=184	Total	Vedolizumab IV (n=53)	Vedolizumab SC (n=131)	*p*
• Extensive/pancolitis (E3) *missing data 2	68 (37)	24 (45.3)	44 (33.6)	
Crohn's disease behavior, n (%) • B1 • B2 • B3	43 (23.4) 22 (12) 11 (6)	7 (13.2) 9 (17.0) 4 (7.5)	36 (27.5) 13 (9.9) 7 (5.3)	0.023 0.065 0.413
Crohn's disease location, n (%) • Ileal (L1) • Colonic (L2) • Ileocolonic (L3)	32 (17.4) 7 (3.8) 37 (20.1)	10 (18.9) 2 (3.8) 8 (15.1)	22 (16.8) 5 (3.8) 29 (22.1)	0.405 0.887 0.365
Aditional/ Isolated Upper location (L4)	4 (2.2)	2 (3.8)	2 (1.5)	0.269
Perianal disease, n (%)	23 (12.5)	6 (11.3)	19 (13.0)	0.758
EIMS, n (%)	41 (22.3)	9 (17.0)	32 (24.4)	0.272
Comorbidities, n (%) • Active cancer • Past cancer • Cardiac disease • Demyelinating disease	51 (27.7) 8 (4.3) 26 (14.1) 5 (2.7) 3 (1.6) 17 (9.2)	14 (26.4) 2 (3.8) 9 (17) 1 (1.9) 1 (1.9) 1 (1.9)	37 (28.2) 6 (4.6) 17 (13) 4 (3.1) 2 (1.5) 16 (12.2)	0.802

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N=184	Total	Vedolizumab IV (n=53)	Vedolizumab SC (n=131)	*p*
• Other				
Previous therapy, n (%) • AntiTNF • Ustekinumab • JAK inhibitors	 129 (70.1) 24 (13) 3 (1.6)	 38 (71.7) 5 (9.4) 0	 91 (69.5) 19 (14.5) 3 (2.3)	 0.765 0.355 0.267
Time on IV prior to switch/no switch, months, median (IQR)	16.8 (1.8-42.4)	29.5 (7.3-47.4)	13.4 (1.4-37.7)	0.193

AntiTNF: anti tumour necrosis factor. B1: non-stricturing no penetrating; B2: stricturing; B3: penetrating; CD: Crohn's disease. EIMS: extra-intestinal manifestations. IBD: inflammatory bowel disease. IQR: inter quartile range. IV: intravenous. JAK inhibitors: Janus kinase inhibitors. SC: subcutaneous. UC: ulcerative colitis.

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Table 2. Variables associated with vedolizumab withdrawal

Variable	Univariable Cox Regression			Multivariable Cox Regression		
	HR	95% CI	p	HR	95% CI	p
Age	0.98	0.95-1.01	0.189			
Gender, male	0.39	0.13-1.23	0.11			
IBD type	0.61	0.22-1.68	0.340			
Smokers	1.03	0.20-5.30	0.874			
UC extent (Ref E1)	0.91	0.24-3.49	0.890			
Perianal disease	1.03	0.23-4.55	0.972			
CD Behavior (Ref B1) B2 B3	1.32 0.95	0.29-5.91 0.11-8.52	0.715 0.965			
CD Location (Ref						

L1) L2 L3 L4	0.04 1.05 18.68	0.01-1434 0.26-4.18 4.33-80.51	0.553 0.95 <0.001	13.94	2.58-75.13	0.002
Previous CD surgery	0.65	0.15-2.90	0.576			
EIMs	2.03	0.46-8.97	0.353			
IMID	6.23	1.75-22.14	0.005	2.21	0.33-14.69	0.410
Previous antiTNF	0.98	0.31-3.07	0.969			
SC formulation	1.19	0.38-3,75	0.762			
Time on IV	1.01	0.99-1.03	0.241			

AntiTNF: anti tumour necrosis factor. CD: Crohn's disease. EIMS: extra-intestinal manifestations. IBD: inflammatory bowel disease. IMID: immune-mediated inflammatory diseases. IV: intravenous. SC: subcutaneous. UC: ulcerative colitis.

Figure 1. Clinical, biochemical and fecal calprotectin remission

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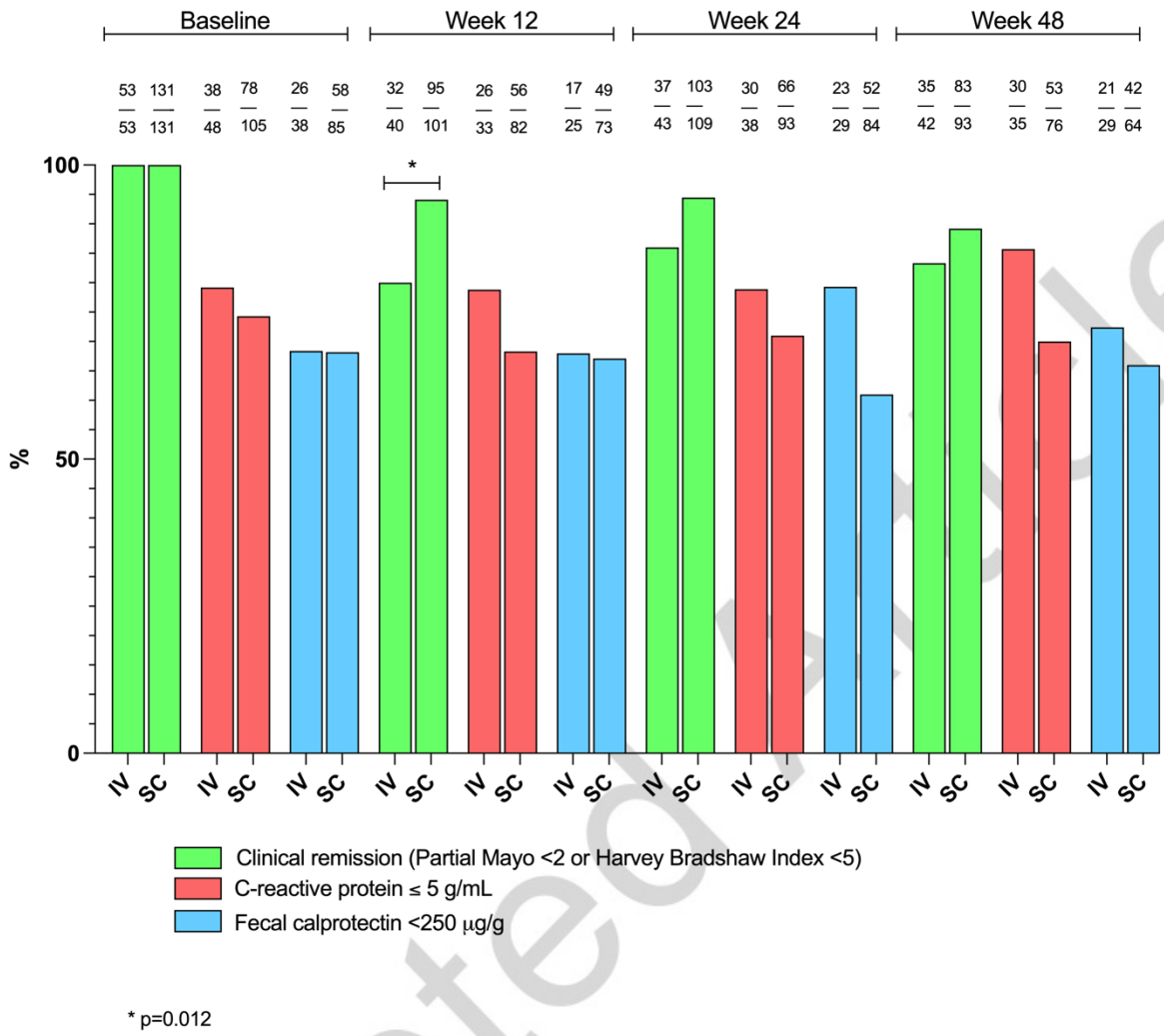

IV: Intravenous, SC: subcutaneous

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Figure 2. Clinical, biochemical and fecal calprotectin remission in UC and CD

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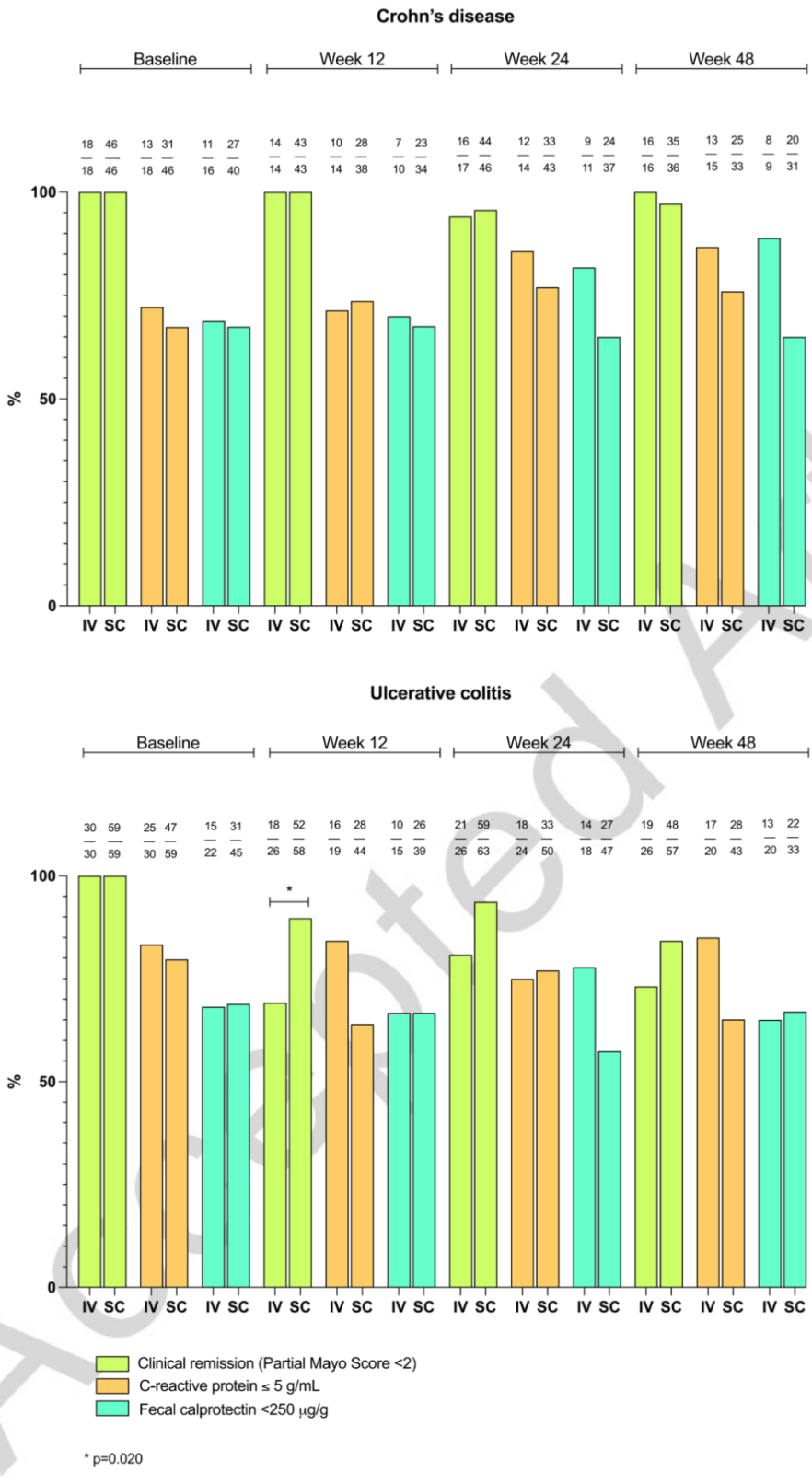

IV: Intravenous, SC: subcutaneous

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Figure 3. Drug formulation persistence

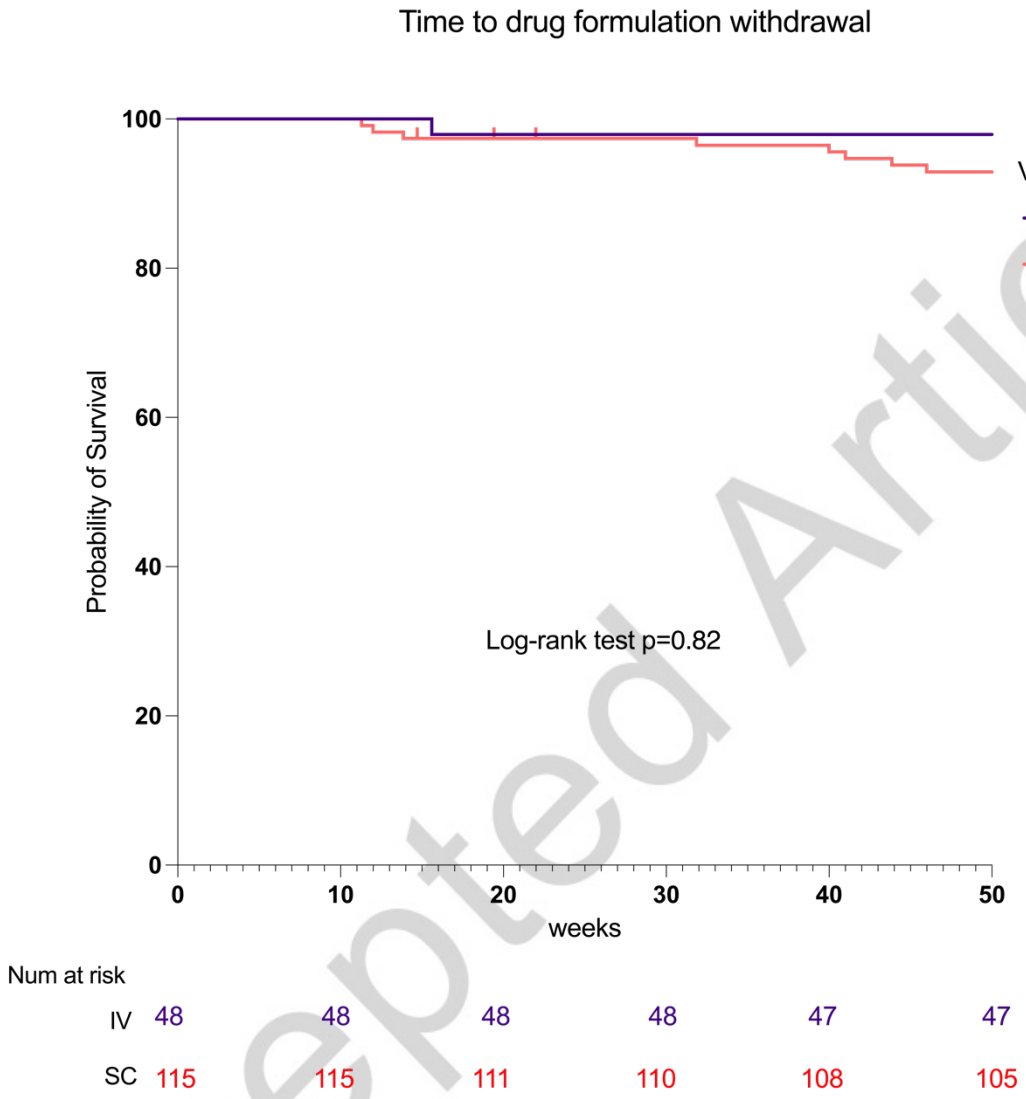

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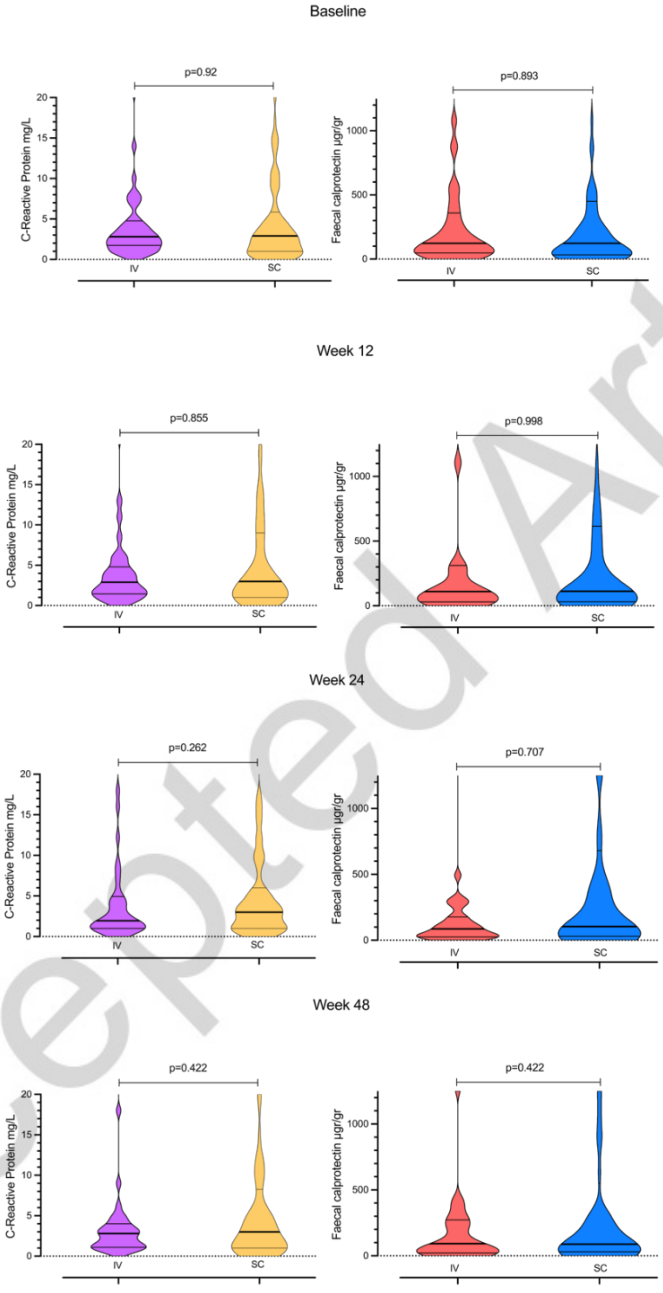
Figure 4. Violin plots showing C-Reactive Protein and Fecal calprotectin distribution at the different time-points



Violin plots show median (solid line), IQR (dotted line), maximum and minimum. Outliers were removed for graph representation but accounted for statistical comparison. Mann–Whitney U test was used to compare medians at baseline, week 12, 24 and 48.

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