Monthly intravenous maintenance treatment with ustekinumab regains clinical response in patients with Crohn's disease who no longer respond to the drug when administered subcutaneously

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Abstract

Background: Several studies have assessed the efficacy of re-induction and subcutaneous intensification of ustekinumab (UST) to regain clinical remission of inflammatory bowel disease (IBD). However, very few have evaluated the effectiveness of intravenous UST for this purpose.

Objectives: The aims of the study were to evaluate the efficacy of high-dose intravenous UST (USTiv) for regaining remission in Crohn's Disease (CD) and to assess the safety of the drug.

Design: Observational, retrospective, single-center study.

Methods: All patients who had received intravenous UST to regain remission until June 2023 were included. Clinical response was evaluated using the Harvey-Bradshaw Index. Drug survival was calculated using Kaplan–Meier curves.

Results: Twenty-three patients (52% female, mean age 40.5 ± 13.9) with CD were included. Seven (30%) patients had an incomplete primary response to UST, while 16 (70%) presented a secondary loss of response. Clinical response rates for USTiv administered monthly were 17/23 (73.9%) at week 8, 14/23 (60.9%) at week 16, and 10/12 (83.3%) at 1 year. Clinical remission rates were 11/23 (47.8%), 9/23 (39.1%), and 8/12 (66.7%), respectively. Median drug survival was 15.3 ± 7.7 months. Two patients (8%) experienced recurrent mild respiratory infections. No patients discontinued USTiv due to adverse events.

Conclusion: More than half of the patients with CD who underwent maintenance treatment with USTiv regained clinical response after failing with subcutaneous UST treatment. No significant adverse events were observed.

Plain language summary

An alternative way to use ustekinumab for Crohn's disease patients who lose response

Ustekinumab (UST) is a drug widely used to treat Crohn's Disease (CD), and it's commonly administered subcutaneously. However, some patients do not respond well enough or lose the benefits of the treatment over time. In this study, we evaluated whether switching to intravenous UST could help patients regain control of their symptoms. We reviewed data from 23 patients with CD who received this treatment at our hospital. Most had

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previously responded to subcutaneous UST but later experienced a loss of effectiveness. After switching to intravenous UST, more than half of the patients showed improvement at 8 and 16 weeks, and this response was maintained in many patients after one year. The treatment was generally well tolerated, and no one had to stop it because of side effects. These results suggest that intravenous UST may be a helpful option for patients with CD who no longer respond to the standard treatment.

Keywords: Crohn's disease, inflammatory bowel disease, ustekinumab

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Introduction

Inflammatory bowel disease (IBD), which includes Crohn's disease (CD) and ulcerative colitis (UC), is a chronic condition of the gastrointestinal tract that affects millions of people worldwide.[1]

The introduction of biological drugs has transformed the management of IBD and has significantly improved clinical remission rates. Ustekinumab (UST) is a monoclonal antibody targeting the p40 subunit of interleukins 12 and 23 and is widely used due to its effectiveness and safety profile. Current guidelines recommend UST in patients who failed or did not tolerate a first-line anti-tumor necrosis factor (TNF) treatment.[2,3]

According to the current recommendations, treatment entails an induction dose of 6 mg/kg of intravenous UST (USTiv) at week 0, followed by a subcutaneous (USTsc) dose of 90 mg at week 8 and maintenance treatment with 90 mg USTsc, generally every 8 weeks.[4–6] In patients with a suboptimal response or secondary loss of response to the USTsc standard dose, various dose adjustment strategies are used off-label to regain response to the drug, generally by administering an additional USTiv dose of 6 mg/kg or shortening the interval of administration of the USTsc maintenance dose from every 8 to every 4 or 6 weeks.[7,8]

Recently, maintenance treatment with USTiv has been increasingly used in routine clinical practice. However, to date, only three studies have evaluated the efficacy and safety of this approach, all with small series. One study reported six cases that underwent rescue treatment by changing maintenance treatment to weight-adjusted intravenous UST, resulting in clinical improvement.[9] Two retrospective studies showed rates of clinical response of 82.6% at week 12 and 60% at week 16, respectively.[10,11]

This study aims to evaluate the effectiveness and safety of USTiv as a maintenance treatment strategy at our center.

Materials and methods

Design and data collection

This was a single-center retrospective study. Data were retrospectively collected from the electronic clinical reports of each patient in a de-identified Excel Database. All data were compiled in an Excel database with no patient identifiers. A restricted access list with the patients' history numbers was available to the researchers.

Population

All patients with CD who received maintenance USTiv treatment after an incomplete response or secondary loss of response to USTsc until June 2023 were included.

Exclusion criteria were as follows: patients under 18 years of age at the beginning of the treatment, patients not using UST in monotherapy, patients who had not received maintenance treatment with USTiv for at least 16 weeks, and those who received USTiv maintenance without a previous attempt at treatment with USTsc.

Variables

Personal and demographic variables, including age, sex, and smoking habits, were collected. Baseline disease variables such as type, age at

diagnosis, extension, behavior (according to the Montreal classification), disease severity and duration, extraintestinal manifestations, IBD-related surgeries, and past treatments were included. Data related to USTiv treatment, including the timing of initiation of the drug and the induction and maintenance USTiv doses, were recorded. Side effects were collected from medical reports.

Disease activity was evaluated with the Harvey-Bradshaw Index (HBI) for CD. Response to the maintenance treatment with USTiv was evaluated at baseline, 8 weeks, 16 weeks, and 12 months after treatment initiation.

The following definitions were used:

- HBI scores of <5 points were taken to indicate remission, scores of 5–7 points mild disease, 8–16 points moderate disease, and >16 points severe disease.
- Clinical response was defined as a reduction of $\geqslant 3$ points on the HBI from baseline alongside criteria of clinical remission. Clinical remission was defined as an HBI < 5.
- Intensification was defined as any increase in the UST dose, either due to a shortening of the time between USTsc 90 mg doses (from every 8 weeks to every 4 or 6 weeks) or to a change in the route of administration (UST 130 mg iv every 4 weeks instead of USTsc). Re-induction was defined as receiving an intravenous dose of UST adjusted by weight before intensification.

Statistical analysis

For quantitative variables, the mean and standard deviation were calculated. Qualitative variables were expressed as percentages with their 95% confidence intervals. The Mann–Whitney "*U*" test was used to compare quantitative variables, while the Chi-Square test or Fisher's exact test was used to compare proportions. The level of statistical significance was set at 0.05. Kaplan–Meier survival analysis was used to evaluate survival treatment. To evaluate potential predictors of intensification response, a univariate analysis was performed. Qualitative variables were analyzed using Kaplan–Meier curves and evaluated using the log-rank test. Quantitative variables were subdivided by the median, and Kaplan–Meyer curves were drawn to compare the groups. A Cox logistic regression was planned, contingent upon a sufficient sample size to allow a multivariate analysis.

Sub-analyses were also planned to determine whether there were differences in response between patients who experienced a primary failure with UST compared to those who presented with a secondary failure. In addition, the presence of differences between patients who were intensified to USTiv starting from a dose of USTsc every 8 weeks and those starting from a dose of USTsc every 4 weeks was determined.

The reporting of this study conforms to the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement.[12] The corresponding checklist is added as Supplemental File 1.

Results

Until June 2023, 111 patients with IBD had been treated with UST in our hospital. Four of them started USTiv maintenance after induction, usually due to severe disease, while 107 received USTsc maintenance. Of these, 25 patients switched to USTiv maintenance therapy. Two had UC and were excluded from the analysis, while 23 had CD and were included. A detailed flowchart is provided in Figure 1.

Of the 23 patients, 12 were female (52%) and 10 were active smokers (43%). The mean age was 40.5 ± 13.9 years. The mean duration of IBD follow-up prior to starting UST treatment was 8.9 ± 7.3 years. See detailed characteristics of patients in Table 1.

Except for one patient who received UST as first line, all patients had received other IBD treatments prior to the introduction of UST (96%, $n = 22$). Most of the patients (96%) had received previous anti-TNF treatment; five (22%) had received two anti-TNF treatments. Data are shown in Table 2.

All patients started UST treatment with a standard intravenous induction dose adjusted according to weight, followed by standard USTsc maintenance with 90 mg every 8 weeks. No patients received concomitant treatment with thiopurines or other biological treatments.

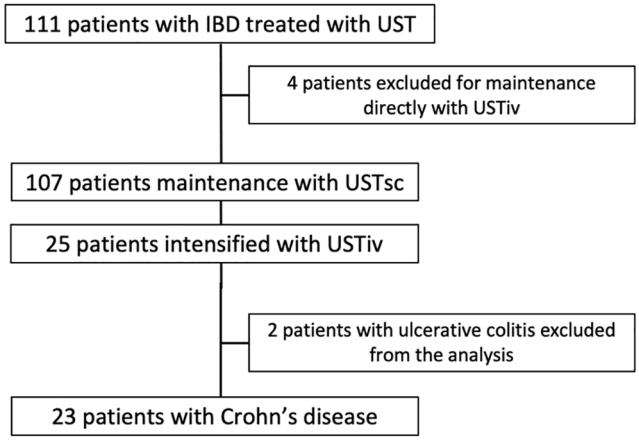

Figure 1. Flowchart of the study.

Intensification with USTiv maintenance was initiated after an intravenous re-induction dose (adjusted to weight). Nine patients (39%) were re-induced and intensified with USTiv directly from USTsc every 8 weeks, while 14 (61%) had previously received subcutaneous intensification with USTsc every 4 weeks.

Re-induction and intensification with USTiv were performed in seven patients (30%) due to primary failure to UST and in 16 patients (70%) due to secondary failure. The mean time between the start of UST and the switch to USTiv maintenance was 1.4 ± 1.3 years.

After starting USTiv, 17 patients (73.9%) showed clinical response, of whom 11 (47.8%) achieved clinical remission at week 8. Corresponding figures at week 16 were 14 patients (60.9%) with clinical response and 9 patients (39.1%) with clinical remission. Ten of the 12 patients who had currently achieved 12 months' follow-up (83.3%) maintained clinical response, and eight of them (66.7%) were also in clinical remission. All except one patient were corticosteroid-free. The mean survival time of USTiv treatment was 15.3 ± 7.7 months, see Figure 2.

Adverse events were recorded in two patients (9%), both of whom experienced recurrent respiratory infections. See detailed data in Table 3.

A univariate analysis was conducted to evaluate independent variables associated with a sustained response. The variables were sex, smoking status, age, age at diagnosis, disease extent and location, disease behavior, presence of perianal disease, disease severity, extraintestinal manifestations, previous surgeries, and prior IBD treatments. No associations were found.

Table 1. Demographic characteristics of the cohort.

Patients characteristics	CD (*n* = 23)
Gender (% women)	12 (52.2%)
Active smokers (%)	10 (43.5%)
Age (years)	40.5 ± 13.9
Age at diagnosis (A)	
A1—Less than 16 years	4 (17.4%)
A2—16–40 years	12 (52.4%)
A3—>40 years	7 (30.4%)
Extension of the disease (L)	
L1—Ileal	6 (26.1%)
L2—Colonic	3 (13%)
L3—Ileo-colonic	13 (56.5%)
L4—Isolated upper disease	1 (4.3%)
Behavior of CD (B)	
B1—Inflammatory	6 (26.1%)
B2—Stenotic	7 (30.4%)
B3—Penetrating	3 (13%)
B2 + B3	7 (30.4%)
Perianal disease	8 (32%)
Disease severity at diagnosis	
Mild-moderate	14 (60.9%)
Moderate-severe	9 (39.1%)
Previous IBD-related surgery (%)	10 (43.5%)
Ileal resection	2 (8.7%)
Right hemicolectomy + ileal resection	5 (21.4%)
Other procedures	3 (13%)
Extraintestinal manifestations (%)	7 (30.4%)

CD, Crohn's disease; IBD, inflammatory bowel disease.

Table 2. Previous IBD-related treatments used.

IBD- related treatments	CD (*n* = 23)
Previous treatments (%)	
Naïve	1 (4.3%)
Mesalazine	4 (17.4%)
Thiopurines	20 (87%)
Biological	22 (95.7%)
Anti-TNF	22 (95.7%)
Previous treatment with anti-TNF (%)	
Number of anti-TNF	
One	17 (73.9%)
Two	5 (21.7%)
Types of failure	
Primary	1 (4.3%)
Secondary	21 (91.3%)

CD, Crohn's disease; IBD, inflammatory bowel disease.

Specifically, previous treatment with USTsc dose and reason for intensification (incomplete primary response vs secondary loss of response) were analyzed separately. No associations were observed, see Figure 3. Extension of the disease (L1, L2, L3, and L4) and behavior of CD were also analyzed separately. No associations were observed, see Figure 3. As stated above, no significant differences were observed in either preplanned subanalysis.

Discussion

Despite the recent introduction of new molecules such as JAK and IL23, gastroenterologists tend to intensify treatments before changing therapeutic targets, due to their greater experience with anti-TNF agents.

The results of our study show that intravenous maintenance of UST is an effective option for patients with CD who lose response with standard subcutaneous UST maintenance treatment. The study highlights the potential benefits of intravenous UST maintenance and its safety profile in a real-practice clinical setting.

The clinical response to USTiv was notable, with 73.9% of patients regaining clinical response at week 8, 60.9% at week 16, and 83.3% at month 12. These findings are consistent with previous studies on USTiv maintenance. In the study by Argüelles-Arias et al., which included 23 patients with IBD (19 with CD and 4 with UC), 43.5% achieved clinical remission while 82.6% patients achieved clinical response at week 12.[10] Similar

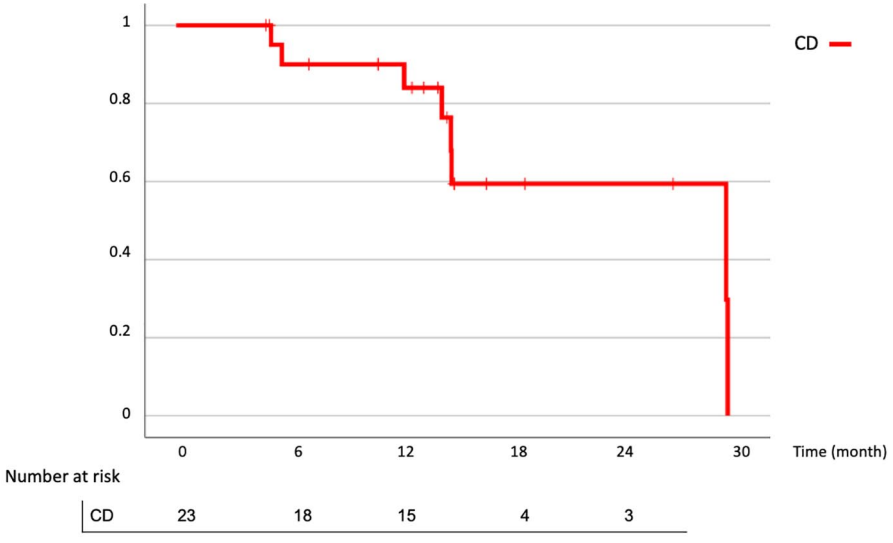

Figure 2. Kaplan–Meier USTiv treatment survival over time.
USTiv, intravenous ustekinumab.

Table 3. Data on intravenous maintenance with UST.

Patients characteristics	CD (*n* = 23)
Previous treatment with UST	
90 mg sc/8w	9 (39.1%)
90 mg sc/4w	14 (60.9%)
Reason for intravenous intensification	
Primary failure UST	7 (30.4%)
Secondary failure UST	16 (69.6%)
Harvey-Bradshaw score pre (mean)	9 ± 2
Harvey-Bradshaw score post (mean)	6 ± 3
Protein C Reactive pre mg/dL (mean)	1.8 ± 3.2
C-reactive protein post mg/dL (mean)	1.1 ± 3.3
Fecal calprotectin pre µg/g (mean)	
Available in 14 patients	507.1 ± 449
Fecal calprotectin pre µg/g (mean)	
Available in 6 patients	462.2 ± 351
8 weeks (*n* = 23)	
Clinical response	17 (73.9%)
Clinical remission	11 (47.8%)
No response	6 (26.1%)
16 weeks (*n* = 23)	
Clinical response	14 (60.9%)
Clinical remission	9 (39.1%)
No response	9 (39.1%)
12 months (*n* = 12)	
Clinical response	10 (83.3%)
Clinical remission	8 (66.7%)
No response	2 (16.7%)
Side effects (%)	
Recurrent respiratory infections	2 (8.7%)

CD, Crohn's disease; UST, ustekinumab.

data were described by Hermida et al., whose study included 12 patients with CD; they recorded clinical remission in 50% of patients at week 16 and in 64% at week 52, and clinical response in 60% of patients at week 16 and in 91% at week 52.[11] Neither in our study nor in those just described was it possible to identify risk factors or baseline characteristics associated with response. Smoking is known to negatively affect treatment response in CD, which may explain the relatively high proportion (40%) of active tobacco users in our series.[13] No significant differences were observed in response rates or treatment persistence between smokers and non-smokers. However, these results should be interpreted with caution, as the limited sample size reduces the statistical power to detect any potential associations.

The safety profile of UST observed was favorable: only two patients (8%) presented adverse events, in both cases mild recurrent respiratory infections. No opportunistic or severe infections were observed. This low incidence of adverse events is encouraging, especially in a population with extensive prior exposure to immunosuppressants and biologics, which can increase the risk of infections and other complications.

The majority of patients had experienced moderate to severe disease at diagnosis and had a substantial history of prior treatments, and so they comprised a population with complex and refractory disease. These results are consistent with those previously reported elsewhere.

Despite the promising outcomes, our study has several limitations. The sample size was small, and the retrospective design limits the ability to generalize findings and reduces the power of the subanalyses. Also, the retrospective design may have favored selection bias by detecting only patients with prolonged response. However, because of the cost of these drugs, the biological treatments registry in our Health System is extremely accurate. We carefully checked the registries for any patient receiving additional 130 mg IV doses after subcutaneous treatment, thus making selection bias very unlikely. Disease activity was evaluated with clinical scores, and limited data were available regarding biochemical parameters (given the retrospective nature of the study, few patients were evaluated with fecal calprotectin) and/or endoscopic mucosal healing. This lack of standardized objective measures reflects real-world clinical practice, where patients are not prone to frequent repeated endoscopic or

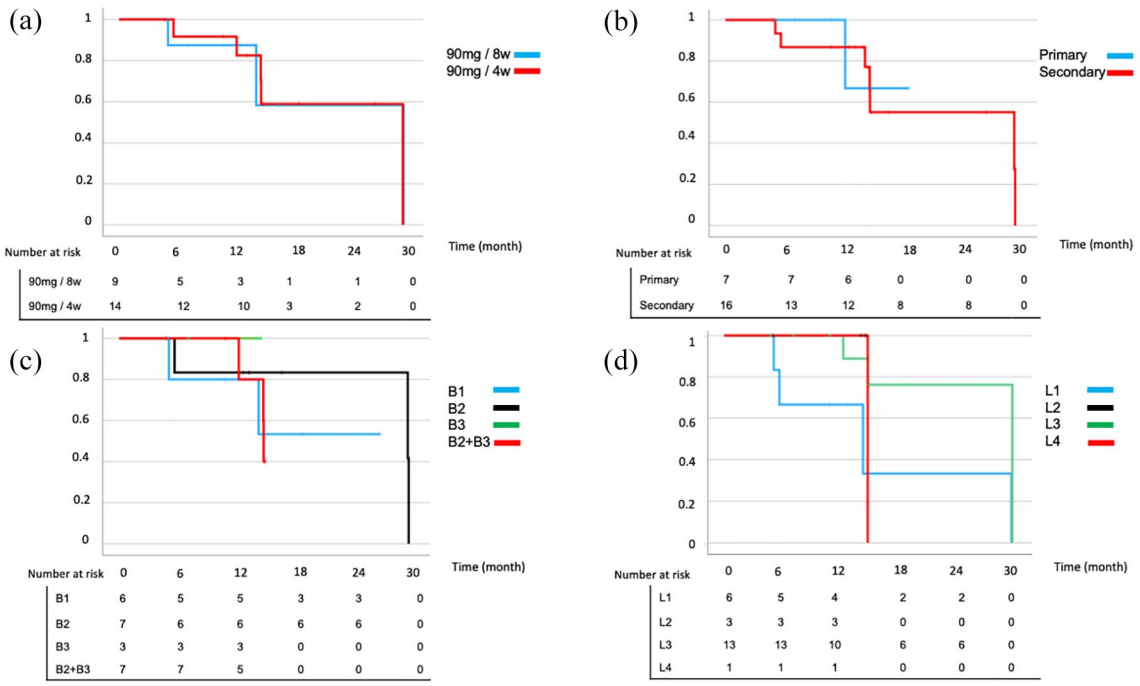

Figure 3. (a) USTiv treatment survival curves over time according to USTsc dose, (b) USTiv treatment survival curves over time according to the reason for intensification, (c) USTiv treatment survival curves over time according to behavior of disease, and (d) USTiv treatment survival curves over time according to the extension of the disease.
USTiv, intravenous ustekinumab; USTsc, subcutaneous ustekinumab.

laboratory examinations, and the generalized practice in our environment of performing exhaustive activity evaluation before changing a biological treatment, but not before dose adjustments. In addition, the heterogeneity of the medical histories and the differences in the criteria applied by the physicians to establish the indication of intensification made it difficult to standardize the results. Finally, as the determination of UST levels is not widely available in routine clinical practice, data on UST levels were not available in our series.

However, the study also has many strengths: it is one of the largest to date reporting the—reasonable—efficacy of this particular intensification approach. Previous studies had evaluated the utility of other dose adjustment strategies: the study STARDUST study assessed the efficacy of a treat-to-target strategy with early endoscopy, the POWER trial evaluated the utility of a single IV re-induction and, most recently, the REScUE study investigated the effect of a single IV re-induction followed by USTsc maintenance every 4 weeks.[14–16] Although statistically significant differences were not observed in any of these studies, none of them evaluated the possibility of maintenance treatment with USTiv, as implemented in our cohort.

The role of UST serum levels is controversial. Some studies support their use[17] while others did not show a clear association with clinical or endoscopic outcomes.[18] It can be hypothesized that increasing the total monthly dose and using intravenous administration may lead to higher serum concentrations or increased bioavailability compared to subcutaneous administration. However, further investigation is needed to clarify the potential mechanisms underlying the usefulness of intravenous UST intensification

Our study supports the use of USTiv in patients who lose response to standard USTsc maintenance treatment. Future prospective studies with larger cohorts are needed to validate these findings, identify risk factors for response, and optimize UST dosing strategies.

Conclusion

In conclusion, USTiv maintenance treatment appears to be effective and safe in patients with CD who have lost response to subcutaneous treatment. Nearly 60% of our patients achieved a clinical response. Therefore, USTiv maintenance treatment could be considered as a rescue option before changing therapeutic targets in patients who have lost response to USTsc.

Declarations

Ethics approval and consent to participate

The study was reviewed and approved by the local ethics committee (CEIM2022/5045). Given the study's retrospective nature and its lack of any impact on the patient's evolution or treatment, it was not considered necessary to obtain informed consent. The study was conducted in compliance with the requirements of the 1975 Declaration of Helsinki.

Consent for publication

Not applicable.

Author contributions

Berta López-Sáez: Conceptualization; Data curation; Formal analysis; Investigation; Methodology; Writing – original draft.

Ariadna Altadill: Conceptualization; Data curation; Formal analysis; Investigation; Methodology; Writing – original draft.

Eduard Brunet-Mas: Conceptualization; Data curation; Formal analysis; Funding acquisition; Investigation; Methodology; Project administration; Writing – original draft.

Belen Garcia-Sagué: Investigation; Writing – review & editing.

Luigi Melcarne: Investigation; Writing – review & editing.

Laura Patricia Llovet: Investigation; Writing – review & editing.

Luis Enrique Frisancho: Investigation; Writing – review & editing.

Anna Puy: Investigation; Writing – review & editing.

Sergio Lario: Investigation; Methodology; Writing – review & editing.

Maria Jose Ramirez-Lazaro: Investigation; Methodology; Writing – review & editing.

Jorge Del Estal: Data curation; Investigation; Writing – review & editing.

Albert Villoria: Investigation; Writing – review & editing.

Xavier Calvet Calvo: Conceptualization; Data curation; Formal analysis; Investigation; Methodology; Project administration; Supervision; Validation; Writing – review & editing.

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Competing interests

EB-M has served as a speaker and consultant for Janssen, Chiesi, Kern, Takeda, and Galapagos. LM has served as a speaker and consultant for Abbvie, Janssen, Tillots, Pfizer, Lilly, and Takeda. AV has served as a speaker and consultant for Janssen, Abbvie, Pfizer, and Tillots. XC has received grants for research from Abbott, MSD, and Vifor, and fees for advisory board services from Abbott, MSD, Takeda, and Vifor. He has also given lectures for Abbott, MSD, Takeda, Shire, and Allergan. BL-S, AA, BG-S, LPL, LEF, AP, SL, MJR-L, and JDE have no conflicts of interest to report. No artificial intelligence was used in this work.

Availability of data and materials

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

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Supplemental material

Supplemental material for this article is available online.

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