Journal of Crohn's and Colitis, 2021, 222–227
doi:10.1093/ecco-jcc/jjaa177
Advance Access publication September 8, 2020
Original Article

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Effectiveness and Safety of Ustekinumab Intensification at 90 mg Every 4 Weeks in Crohn's Disease: A Multicentre Study

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Abstract

Background: The approved maintenance regimens for ustekinumab in Crohn's disease [CD] are 90 mg every 8 or 12 weeks. Some patients will respond partially to ustekinumab or will experience a secondary loss of response. It remains poorly known if these patients may benefit from shortening the interval between injections.

Methods: All patients with active CD, as defined by Harvey–Bradshaw score ≥ 4 and one objective sign of inflammation [C-reactive protein > 5 mg/L and/or faecal calprotectin > 250 µg/g and/or radiological and/or endoscopic evidence of disease activity] who required ustekinumab dose escalation to 90 mg every 4 weeks for loss of response or incomplete response to ustekinumab 90 mg every 8 weeks were included in this retrospective multicentre cohort study.

Results: One hundred patients, with a median age of 35 years [interquartile range, 28–49] and median disease duration of 12 [7–20] years were included. Dose intensification was performed after a median of 5.0 [2.8–9.0] months of ustekinumab treatment and was associated with

corticosteroids and immunosuppressants in respectively 29% and 27% of cases. Short-term clinical response and clinical remission were observed in respectively 61% and 31% after a median of 2.4 [1.3–3.0] months. After a median follow-up of 8.2 [5.6–12.4] months, 61% of patients were still treated with ustekinumab, and 26% were in steroid-free clinical remission. Among the 39 patients with colonoscopy during follow-up, 14 achieved endoscopic remission [no ulcers]. At the end of follow-up, 27% of patients were hospitalized, and 19% underwent intestinal resection surgery. Adverse events were reported in 12% of patients, including five serious adverse events.
Conclusion: In this multicentre study, two-thirds of patients recaptured response following treatment intensification with ustekinumab 90 mg every 4 weeks.

Key Words: Crohn's disease; ustekinumab; intensification

1. Introduction

Ustekinumab [Janssen Biotech, Inc.], a fully human IgG1 monoclonal antibody targeting the interleukin-12 [IL-12]/IL-23 shared p40 subunit, was recently approved for the treatment of Crohn's disease [CD]. The UNITI programme clearly demonstrated the efficacy of ustekinumab to induce and maintain clinical remission in moderate-to-severe CD, with continuous response for up to 4 years.[1] Patients receive a 6 mg/kg intravenous induction therapy, a 90 mg subcutaneous administration at 8 weeks and then ustekinumab 90 mg every 12 weeks [q12w], or ustekinumab 90 mg every 8 weeks [q8w], for maintenance therapy, according to the physician's judgement. As observed with anti-tumour necrosis factors [TNFs], about 20–35% of patients experienced loss of response to ustekinumab in clinical trials.[1–4] In patients treated with anti-TNFs, a dose–response relationship has been demonstrated. An increase in dose or dosing frequency is recommended in patients with loss of response.[5,6] In the UNITI programme, 20% of patients with loss of response during the 90 mg q12W regimen recaptured response after escalation to 90 mg q8W.[1]

Real-world effectiveness data provide valuable evidence to support the efficacy observed in randomized controlled trials. Real-world studies include patients representative of the real-world CD population and allow for a variable treatment regimen and optimization.[7] Some real-word studies have reported the experience with ustekinumab intensification from 90 mg q8W to q4W and even to q3W.[2–4,8] Recently, the University of Chicago group reported the effectiveness of ustekinumab dose interval shortening from 90 mg q8W to q4W in 51 patients with Harvey–Bradshaw score > 4.[9] They showed that dose escalation resulted in improvement in clinical indices of disease activity.

We aimed to evaluate the effectiveness and safety of intensification from 90 mg q8w to q4W in patients with incomplete or loss of response to ustekinumab in CD in a retrospective multicentre study.

2. Methods

2.1. Study population

All consecutive adult patients between October 2015 and December 2018 with active CD, as defined by Harvey–Bradshaw score ≥ 4 and at least one objective sign of inflammation (C-reactive protein [CRP] ≥ 5 mg/L and/or faecal calprotectin ≥ 250 µg/g and/or radiologic and/or endoscopic evidence of disease activity) who required ustekinumab dose escalation to 90 mg q4W for loss of response [as defined by a loss of response after initial improvement of symptoms, according to the physician's judgement] or incomplete response [lack of improvement of clinical symptoms] to ustekinumab 90 mg q8W in 11 French university hospitals were included in a retrospective multicentre cohort study.

2.2. Data collection

The following data were recorded at baseline for each patient: sex, birth date, age at diagnosis, CD phenotype and behaviour according to Montreal classification, previous and concomitant medications, smoking status, previous intestinal resection, Harvey–Bradshaw score, CRP, ustekinumab induction regimen, and indication of intensification [loss of response or incomplete response, and luminal and/or perianal CD]. Harvey–Bradshaw score, CRP value, adverse events [AEs], concomitant medications, intervals of ustekinumab administration, ustekinumab discontinuation, CD-related hospitalization and intestinal resection data were collected at the first clinic visit after dose escalation, at 6 months, at the last visit under ustekinumab and at the date of the last follow-up. Endoscopic variables were also collected if available. This cohort was declared to the CNIL [Commission nationale de l'informatique et des libertés, declaration no. T196] as per national recommendations.

2.3. Outcome measures

Short-term clinical response response was defined by a decrease of Harvey–Bradshaw score ≥ 3 after dose intensification compared to baseline, with a decision to continue the same dose, and was evaluated at the first clinic visit after therapeutic escalation. Clinical remission was defined as a Harvey–Bradshaw score < 4. Endoscopic remission was defined by the absence of ulceration [exclusion of aphtae] and serious AEs as an AE-related hospitalization.

2.4. Statistical analysis

Quantitative variables are described as medians and interquartile range [IQR]. Categorical variables are presented as counts and percentages of the cohort. Change from baseline in quantitative variables was evaluated with a paired Student test or a Wilcoxon signed-rank test. The distribution of the delay until ustekinumab withdrawal and surgery were estimated with the non-parametric method of Kaplan–Meier. Risk factors for short-term response were assessed using a univariate logistic regression model with odds ratio and a 95% confidence interval; Firth's penalized likelihood was applied if necessary. Variables with a p-value < 10% were included in a multivariate logistic regression model. Statistical analyses were performed with SAS software version 9.4 [SAS Institute] and survival curves were built using RStudio software Version 1.0.143 [R.3.4.0 software].

3. Results

3.1. Characteristics of patients

A total of 100 were included. Demographic and baseline disease characteristics at ustekinumab intensification are listed in Table 1. Median duration of follow-up was 8.2 [IQR, 5.6–12.4] months. Fifty-two [52%] of the patients were female, the median age was 34.9 years [IQR, 28.1–46.3] and the median duration of CD was 11.6 years [IQR, 7.3–20.1]. According to Montreal classification, one-third [*n* = 31, 31%] had ileal disease, one-third [*n* = 29, 29%] had colonic disease and 40 [40%] had ileo-colonic disease. Most of the patients had complicated behaviours (B2—stricturing, 28 [28%] or B3—penetrating, 37 [37%]), 47 [47%] had perianal CD and 34 [34%] had extra-intestinal manifestations. All but one were previously exposed to anti-TNF and 55 [55%] to vedolizumab. Half of the patients had previous intestinal resection. The median duration of ustekinumab therapy before optimization was 5.0 [IQR, 2.8–9.0] months. At the time of therapeutic escalation, respectively 29 [29%] and 27 [27%] received co-treatment with steroids or immunosuppressants. Incomplete response [74, 74%] and luminal disease [77, 77%] were the main indications for ustekinumab intensification.

Table 1. Characteristics of the population at diagnosis.

	Patients [*n* = 100]
Female [*n*, %]	52 [52%]
Age, years [median, IQR]	34.9 [28.1–49.3]
Disease duration, years [median, IQR]	11.6 [7.3–20.2]
Smoking [*n*, %]	25 [25%]
Localization [Montreal] [*n*, %]	
Ileal [L1]	31 [31%]
Colonic [L2]	29 [29%]
Ileo-colonic [L3]	40 [40%]
Behaviour [Montreal] [*n*, %]	
Inflammatory [B1]	35 [35%]
Stricturing [B2]	28 [28%]
Penetrating [B3]	37 [37%]
Perianal Crohn's disease [Montreal] [*n*, %]	47 [47%]
Extra-intestinal manifestation [*n*, %]	34 [34%]
Previous therapy [*n*, %]	
Thiopurines	91 [91%]
Methotrexate	51 [45%]
Anti-TNF	99 [99%]
1 Anti-TNF	14 [14%]
2 Anti-TNF	70 [70%]
3 Anti-TNF	14 [14%]
4 Anti-TNF	1 [1%]
Vedolizumab	55 [55%]
Previous intestinal resection [*n*, %]	49 [49%]
Induction regimen [*n*, %]	
6 mg/kg IV	84 [84%]
Others	16 [16%]
Duration of therapy before intensification, months [median, IQR]	5.0 [2.8–9.0]
Indication of intensification [*n*, %]	
Incomplete response	74 [74%]
Loss of response	26 [26%]
Luminal disease	77 [77%]
Perianal disease	16 [16%]
Both luminal and perianal disease	7 [7%]
Co-immunosuppressant [*n*, %]	27 [27%]
Steroids [*n*, %]	29 [29%]
Harvey–Bradshaw [median, IQR]	8 [5.0–11.2]
CRP, mg/L [median, IQR]	12.3 [5.0–30.5]

IQR, interquartile range.

3.2. Short-term response and remission

After a median of 2.4 [IQR, 1.3 –3.0] months following ustekinumab intensification, 61 patients [61%] experienced a clinical response. In addition, 31 [31%] and 27 [27%] of the patients achieved clinical remission and steroid-free clinical remission, respectively [Figure 1]. The median value of Harvey–Bradshaw index dropped significantly from 8.0 at baseline [IQR, 5.0–11.2] to 5.0 [IQR, 3.0–7.0] [$p = 0.001$]. Ten of 29 patients [35.5%] receiving steroids at inclusion were weaned before the first visit after ustekinumab escalation. In general, systemic steroid use was tapered according to ECCO guidelines. The median CRP level decreased from 12.3 mg/L [IQR, 5.0–30.5] to 9.6 mg/dL [IQR, 3.2–18.0] [$p = 0.2$]. Among the baseline factors evaluated in the univariate analysis [Table 2], loss of response to ustekinumab [vs incomplete response] was associated with short-term clinical response (odds ratio [OR], 3.03, 95% confidence interval [CI] [1.03; 8.91], $p = 0.044$) as well as duration of ustekinumab therapy before dose intensification [OR, 1.11, 95% CI [1.00; 1.22], $p = 0.051$]. However, no factors were independently associated with short-term clinical response in multivariate analysis probably due to multicollinearity.

3.3. Long-term outcomes

Follow-up information at 6 months was available for 69 of the 100 patients. Of those, 34 [49%] were in steroid-free clinical remission. The median Harvey–Bradshaw score was 4 [2.5–6.0] and the median CRP level was 8.5 [2.25–17.3] mg/L. Among the 35 non-responders to ustekinumab 90 mg q4W in the short term, six [17.1%] achieved clinical remission at 6 months.

The median Harvey–Bradshaw score of the 65 short-term responders decreased from 7 [IQR, 5–10] at baseline to 3.5 [IQR, 2–5] after 6 months [$p < 0.001$], and the CRP level dropped from 9.3 mg/L [IQR, 3.2–21.1] at baseline to 4 mg/L [IQR, 1.2–10.2] after 6 months [$p = 0.02$].

After a median follow-up of 8.2 [5.6–12.4] months, 61 [61%] were still being treated with ustekinumab. The cumulative probabilities of ustekinumab persistence were 81% at 6 months and 51% at 12 months [Figure 2]. At the end of follow-up, 26 [26%] patients were in steroid-free clinical remission. Reasons for ustekinumab withdrawal were the absence of response to optimization, loss of response and pregnancy in 23 [38%], 13 [21%] and three [5%] patients, respectively. Nine patients de-escalated ustekinumab, seven to 90 mg q8W and two to 90 mg q6W after a median time of 7.4 [IQR, 5.5–13.2] months since optimization. Thirty-nine patients had colonoscopy after a median interval of 5.9 [2.4–7.8] months after ustekinumab intensification. Endoscopic remission was observed in 14 patients [35.9%].

Sixteen [16%] patients had ustekinumab intensification for perianal disease and 7 [7%] for both perianal and luminal CD. Among them, 14/23 [61%] experienced an immediate response according to physician judgment. Closure of perianal fistula was observed in 5/23 [22%] patients at final follow-up. Conversely, four patients experienced worsening perianal CD that needing perianal surgery during follow-up.

3.4. Surgery and hospitalization

After a median follow-up of 8.2 [IQR, 5.6–12.5] months, 27 [27%] patients needed CD-related hospitalization. Major abdominal surgery

was required for 19 [19%] patients. Of these, 11 did not respond to ustekinumab intensification, whereas eight had a secondary loss of response to ustekinumab 90 mg q4W. The cumulative risks of hospitalization and surgery are highlighted in Supplementary Figures 1 and 2.

3.5. Adverse events

During the follow-up period, there were no deaths or malignancy. Thirteen AEs were reported in 12 patients [12%], including eight infections [Table 3]. Five patients experienced severe AEs including two pyelonephritis, one nasopharyngitis with epiglottitis, one pneumonitis, and one infectious colitis. None of these AEs had led to definitive ustekinumab withdrawal.

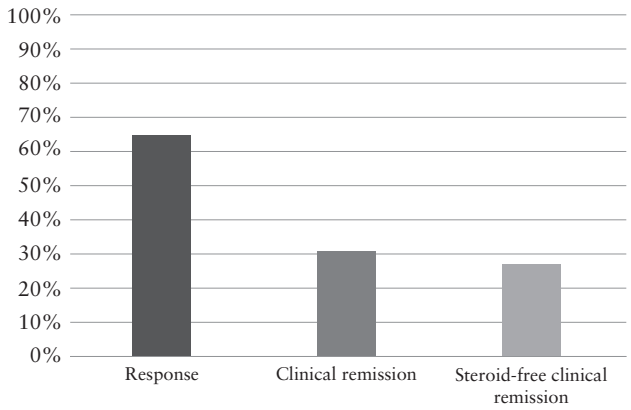

Figure 1. Short-term effectiveness of ustekinumab intensification from 90 mg q8W to q4W.

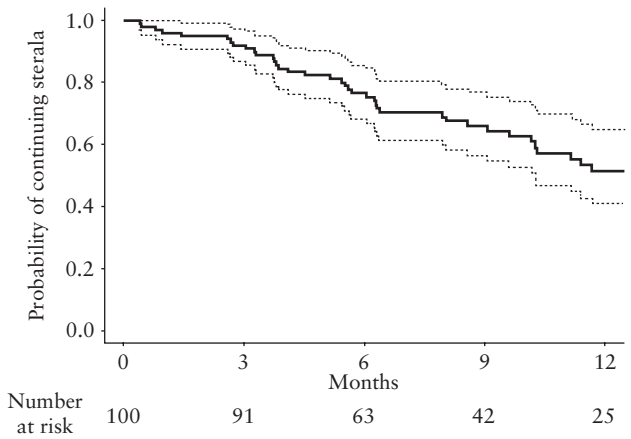

Figure 2. Kaplan–Meier analysis of persistence of ustekinumab after intensification.

4. Discussion

This national, retrospective, multicentre, observational cohort study assessed the effectiveness and safety of ustekinumab dose escalation in CD. Two-thirds of patients recaptured response and about half of them had steroid-free clinical remission at 6 months. Importantly, most patients were candidates for surgery or inclusion in a clinical trial, as many had previous exposure to anti-TNFs therapy and vedolizumab, with active disease as indicated by objective signs of inflammation despite ustekinumab therapy. In this refractory population, 20% of the patients needed major abdominal surgery at the end of follow-up.

Secondary loss of response is frequent in patients treated with ustekinumab, ranging from 20% of patients in IM-UNITI to 35% in real-world observational studies.[1–4] To date, no prospective study has evaluated the management of loss of response during ustekinumab therapy. Randomized prospective studies evaluating the efficacy and safety of ustekinumab therapy in CD have not specifically evaluated the response to ustekinumab dose escalation. In the IM-UNITI trial, among 29 patients randomized to the ustekinumab 90 mg q12w group who lost response with therapeutic escalation to 90 mg q8w, 41% achieved clinical remission and 55% clinical response.[1] Some real-world retrospective studies have reported optimization to ustekinumab 90 mg q4W. Dose escalation [90 mg q4W or q6W] effectively recaptured clinical response in 9/17 [53%] patients one Canadian study.[4] The GETAID trial reported on long-term outcome in 88 patients treated by ten various regimens of ustekinumab.[2] Thirty-two patients required a dose intensification of ustekinumab during follow-up, among whom 12 received 90 mg q4W. This strategy was effective in 18 [56%] including a dose increase in two patients, interval reduction in seven and both in nine. In a Dutch study including 221 patients treated with ustekinumab, 11 patients were on a q4w interval and 70% were in corticosteroid-free clinical remission.[10] Another Canadian cohort recruited 62 patients with CD treated with 90 mg ustekinumab subcutaneously at weeks 0, 1, and 2 during induction and 90 mg every 4 [n = 48] or 8 [n = 14] weeks during maintenance.[3] Clinical and endoscopic outcomes were not different between the two maintenance regimens. Some studies have reported outcomes after a combination of intravenous re-induction with a dose escalation strategy, with this being

Table 2. Outcome of adverse events [AEs].

	AE	Hospitalization	Treatment	Outcome of AE	Ustekinumab outcomes
Non-infectious	Urticaria	No	Anti-histaminic	Resolution	90 mg q4W continued
	Hair loss	No	—	Stabilization	90 mg q4W continued
	Asthenia	No	—	Resolution	90 mg q4W continued
	Headache	No	Paracetamol	Resolution	90 mg q4W continued
	Skin rash	No	—	Resolution	90 mg q4W continued
Infectious	Infectious colitis	Yes	Antibiotics	Resolution	90 mg q4W continued
	Otitis	No	Antibiotics	Resolution	90 mg q4W continued
	Pneumonitis	Yes	Antibiotics	Resolution	90 mg q4W continued
	Pharyngitis/epiglotitis	Yes	Antibiotics/steroids	Resolution	90 mg q4W continued
	Pyelonephritis	Yes	Antibiotics/double-J stent	Resolution	90 mg q4W continued
	Pyelonephritis	Yes	Antibiotics	Resolution	90 mg q4W continued
	Angina	No	Antibiotics	Resolution	90 mg q4W continued
	Sinusitis	No	Antibiotics/steroids	Resolution	90 mg q4W continued

effective in about half of patients.[3,10] More recently, the Chicago group has reported on the effectiveness of ustekinumab dose escalation to q4W in 110 patients with CD followed for a median time of 9 months.[9] Clinical response as defined by Harvey–Bradshaw score improvement was observed in 42% of the 78 patients with available data. During the follow-up period, clinical remission following interval shortening was achieved in 28% of the 51 patients with Harvey–Bradshaw score > 4 before interval shortening. In this single-centre study only a limited subset [$n = 11$] of patients had endoscopic evaluation following dose escalation. In the study reported here, we included only patients with clinically active CD, and at least one objective sign of inflammation, with a standardized follow-up in 11 different centres. Our results are in line with those from Chicago, reporting clinical remission in one-third of patients. In our cohort, endoscopic data were available for 39 patients and endoscopic remission was observed in 14 of them.

Currently, no data exist to identify which patients are more likely to benefit from dose escalation, and management of attenuated response is based on clinical judgment. As for anti-TNF therapy, therapeutic drug monitoring with incorporation of pharmacokinetic data in developing a management algorithm for primary and secondary failure will probably become a mainstay of therapy, identifying appropriate patients needing a rescue dose.[11–13] In the UNITI programme, serum concentrations of ustekinumab were proportional to dose, and associated with clinical efficacy.[1,14] Also limited real-life data suggested better outcomes with higher exposure. Verstockt *et al*. demonstrated that a clear exposure–response relationship exists, both during induction as during maintenance therapy, with different thresholds depending on the targeted outcome.[15] Ustekinumab serum concentrations were higher in endoscopic responders at every time point. At week 8, a ustekinumab trough level lower than 5.0 µg/mL at week 8 almost ruled out endoscopic response later. During maintenance, thresholds of 2.3 µg/mL at week 16 and 1.9 µg/m at week 24 were identified as the minimal exposures needed to achieve endoscopic response after 6 months. In a retrospective study, Battat *et al*. reported that maintenance trough concentrations of ustekinumab above 4.5 µg/mL were associated with biomarker reduction and endoscopic response.[16] However, 42 of their 56 included patients had been dose-escalated to q4w maintenance in order to achieve these high maintenance levels. Three ongoing randomized clinical trials [Rescue trial, EudraCT number 2018-004269-14, The Power trial NCT03782376 and STARDUST trial NCT03107793] will address this issue and assess whether ustekinumab dose-optimization may improve endoscopic remission rates by rescuing patients who quickly lost response after subcutaneous maintenance and if a treat-to-target approach on endoscopic remission and ustekinumab trough level may improve long-term outcomes.

Regarding safety, no death was observed. Five patients required hospitalization for infectious AEs. Interpretation of these results is limited by the relatively small sample and short follow-up period of the cohort. The ongoing I-CARE study (European prospective cohort study assessing long-term safety of inflammatory bowel diseases therapies [NCT02377258]) should answer this question.

Our study has some limitations. The pharmacokinetics of ustekinumab could not be assessed, because this is not routinely performed in France. However, we used objective measures of effectiveness such as steroid-free clinical remission and mucosal healing. The strengths of the study include its multicentre national design including all consecutive CD patients treated with ustekinumab 90 mg q4W in 11 academic centres. Only patients with objective signs of inflammation and with a standardized follow-up, including Harvey–Bradshaw index and measurements of CRP levels, were included.

In conclusion, ustekinumab 90 mg q4W was effective in recapturing response and inducing clinical remission in a subset of patients with CD with loss of response or incomplete response under 90 mg q8W therapy. Our findings suggest that ustekinumab intensification may be considered in routine practice in CD patients who experience loss of response or insufficient response. Large prospective studies with ustekinumab serum monitoring are warranted to elucidate the best approach for optimizing drug therapy and to confirm the long-term safety and efficacy of this strategy.

Table 3. Factors associated with short-term clinical response.

	Univariate analysis		Multivariate analysis	
	OR [95% CI]	*p* value	OR [95% CI]	*p* value
Age	0.92 [0.96; 1.02]	0.642	—	
Disease duration	0.99 [0.94; 1.04]	0.649	—	
Localization[a]			—	
Ileal [L1]	1			
Colonic [L2]	2.19 [0.73; 6.66]	0.332		
Ileo-colonic [L3]	1.08 [0.42; 2.77]	0.135		
Montreal behaviour[a]			—	
Inflammatory [B1]	1			
Stricturing [B2]	0.71 [0.25; 2.00]	0.496		
Penetrating [B3]	0.76 [0.29; 2.00]	0.668		
Duration of therapy before intensification	1.11 [0.99; 1.22]	0.051	—	
Indication intensification [loss response vs incomplete response]	**3.03 [1.03; 8.91]**	**0.044**	—	
Indication intensification 2 [luminal vs perianal]	0.59 [0.24; 1.43]	0.242	—	
Immunosuppressant combination			—	
Azathioprine	1.95 [0.40; 9.57]	0.102		
Methotrexate	0.72 [0.14; 3.86]	0.239		
Steroids combination	0.59 [0.24; 1.43]	0.242	—	
Anti-TNF exposure ≥ 2	1.47 [0.50; 4.37]	0.482	—	
Vedolizumab exposure	1.15 [0.51; 2.61]	0.737	—	

[a]Firth's penalized likelihood was applied because of sparse data.

Funding

None.

Conflict of Interest

M.F. has received consultant/lecture fees from Abbvie, MSD, Takeda, Celgene, Gilead, Boehringer, Amgen, Biogen, Tillots, Pfizer, Janssen, Celltrion and Ferring. L.P.B.has received consulting fees from Merck, Abbvie, Janssen, Genentech, Ferring, Norgine, Tillots, Vifor, Shire, Therakos, Pharmacosmos, Pilège, BMS, UCB-Pharma, Hospira, Celltrion, Takeda, Biogaran, Boerhinger-Ingelheim, Lilly, Pfizer, and HAC-Pharma. This author has also received lecture fees from Merck, Abbvie, Takeda, Janssen Cilag, Ferring, Norgine, Tillots, Vifor, Therakos, HAC-Pharma, and Mitsubishi. S.N. has received consulting fees from Merck, Abbvie, Takeda, Ferring, Norgine, Vifor Pharma, Novartis, Janssen Cilag, Hospira, Takeda and HAC-Pharma. R.A. has received consultant/lecture fees from Abbvie, MSD, Takeda, Amgen, Biogen, Tillots, Pfizer, Janssen and Ferring. C.G. has received lecture/consulting fees from Abbvie, Takeda, Pfizer, Celltrion and Janssen. P.V., AnneB., F.B., L.B., M.D.: none. G.B. received lecture fees from Abbvie, Ferring, MSD, Takeda and Pfizer and consultant fees from Takeda, Janssen. S.V. has received consulting fees from Abbvie, MSD, Takeda, Vifor Pharma and Ferring. F.P. has received lecture fees from Abbvie, MSD, Takeda, Janssen, Ferring, Pfizer; consulting fees from Abbvie and Ferring. J.F. has received consulting fees from Abbvie, Astellas Pharma, Covidien, Ferring, Jansen Cilag, MSD, Pfizer, and Takeda. Anthony.B. has received consulting fees from Abbvie, Amgen, Biogen, Janssen, MSD, Pfizer, Roche, Takeda and Tillots; lecture fees from Abbvie, Amgen, Biogen, Janssen, Mayoly-Spindler, MSD, Norgine Pfizer, Roche, Takeda and Tillots. L.P. has received personal fees from Abbvie, Ferring, Norgine, Takeda; advisory board fees from Janssen, Takeda; and presentation fees from Ferring. B.F. has received consulting fees from Abbvie, MSD, Norgine and Ferring. L.S. received lecture fees from Abbvie, Amgen, Ferring, Janssen, MSD, Takeda and consultant fees from Takeda. D.L. declares counseling, boards, transports or fees from Abbvie, Biogaran, Biogen, Ferring, HAC-pharma, Janssen, MSD, Novartis, Pfizer, Prometheus, Roche, Takeda, Theradiag, Tillots. X.R. reports a relationship with Abbvie, MSD, Janssen Cilag, and Takeda. X.T. has received consulting fees from Janssen, Pfizer and Abbvie. This author has also received lecture fees from MSD, Abbvie, Takeda, Janssen, Norgine and Ferring.

Author Contributions

Study concept and design: MF, LPB, MD, XT. Acquisition of data: MF. Analysis and interpretation of data: MF, LPB, MD, XT. Drafting of the manuscript: MF, LPB, MD, XT. Critical revision of the manuscript for important intellectual content: SN, RA, CG, PV, GB, SV, FP, JF, AB, AB, FB, LP, BF, LB, LS, DL, XR. Approval of the final manuscript: MF, LPB, MD, XT, SN, RA, CG, PV, GB, SV, FP, JF, AB, AB, FB, LP, BF, LB, LS, DL, XR. Guarantor of the article: MF.

Supplementary Data

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

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