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Alimentary Tract

Real-life effectiveness of ustekinumab in inflammatory bowel disease patients with concomitant psoriasis or psoriatic arthritis: An IG-IBD study

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ABSTRACT

Background: Few data exist regarding the effectiveness of ustekinumab in inflammatory bowel disease (IBD) patients treated for concomitant psoriasis or psoriatic arthritis.
Aims: to describe the outcomes of IBD patients who received subcutaneous ustekinumab through a dermatological or rheumatological prescription.
Methods: This multicenter, retrospective study included all IBD patients who were started on ustekinumab for concomitant active psoriasis/ psoriatic arthritis, irrespective of IBD activity. The primary endpoint was overall ustekinumab persistence, defined as the maintenance of therapy because of sustained clinical benefit for IBD.
Results: Seventy patients (64 Crohn's disease / 6 ulcerative colitis) were enrolled. The median follow-up on ustekinumab therapy was 10.7 months (range, 1.4–67.3). Twelve patients (17.1%) withdrew the treatment after a median of 7.4 months (range, 0.9–23.8). The cumulative probability of maintaining ustekinumab treatment was 97.1% at 6 months and 77.1% at 12 months. Among the 56 patients with

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baseline active IBD, 34 (60.7%) were in clinical remission at the last follow-up visit. Their cumulative probability of achieving clinical remission was 84.7% and 63.9% at 6 and 12 months, respectively. Two patients stopped ustekinumab for an adverse event.
Conclusions: Subcutaneous ustekinumab had a good effectiveness profile for IBD patients treated for concomitant dermatological or rheumatological conditions.

1. Introduction

Ustekinumab is a fully human $IgG1_k$ monoclonal antibody that binds and blocks the p40 subunits of interleukin-12 and interleukin-23, two cytokines that are involved in the activation of Th1 and Th17-mediated immune responses [1].

Ustekinumab has been approved by the US Food and Drug Administration (https://www.accessdata.fda.gov/drugsatfda_docs/label/2016/761044lbl.pdf) and the European Medicines Agency (http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/human/medicines/000958/human_med_001065.jsp&mid=WC0b01ac058001d124) for the treatment of moderate-to-severe Crohn's disease (CD) in patients who failed or are intolerant to conventional therapy or tumor necrosis factor alpha (TNFα) antagonists [2]. Approval was based on results of the UNITI 1, UNITI 2 and IM-UNITI clinical trials, which found that intravenous treatment with ustekinumab (130 mg or 6 mg/Kg) was superior to placebo in inducing a clinical response at week 6 [3]. Furthermore, week-6 clinical responders, who received subcutaneous ustekinumab maintenance treatment (90 mg every 8 weeks or 12 weeks), had significantly higher rate of week-44 clinical remission than patients who received placebo [3]. Moreover, the IM-UNITI Long-Term Extension study showed that approximately 75% of patients in clinical remission at 1 year were still in remission at 2 years [4].

To date, several retrospective, observational studies on ustekinumab therapy for CD have shown that this drug is also effective when used through compassionate access programs for anti-TNFα-refractory patients [5–10]. In most of these studies, the induction and maintenance doses were highly variable among patients and often lower than those approved for CD. Patients with inflammatory bowel disease (IBD) have also been able to receive ustekinumab with a dermatological or rheumatological prescription if they had concomitant psoriasis or psoriatic arthritis [11–13]. Furthermore, ustekinumab has been used to resolve paradoxical anti-TNFα-induced psoriasis or arthritis in IBD patients, as reported in several case series [14–17]. These patients usually received the approved dosages of subcutaneous ustekinumab for these conditions, that is 45 mg at weeks 0 and 4, and then every 12 weeks for patients weighing less than 100 kg (for patients over 100 kg, the recommended dosage is 90 mg) [2].

Despite reports on the use of ustekinumab in IBD patients who also have dermatological or rheumatological disease [11–13], data on the effectiveness of this therapy are lacking. Therefore, the aim of this report is to describe the real-life outcome of IBD patients who received subcutaneous ustekinumab for a dermatological or rheumatological prescription because of active psoriasis or psoriatic arthritis, according to the current SCP.

2. Materials and methods

2.1. Patient enrollment

We performed a retrospective, observational cohort study in 12 Italian centers affiliated to the Italian Group for the Study of Inflammatory Bowel Disease (IG-IBD). The study included all consecutive IBD patients who received subcutaneous ustekinumab through a dermatological or rheumatological prescription between July 2012 and December 2017. The diagnoses of psoriasis (including paradoxical anti-TNFα-induced psoriasis) and psoriatic arthritis had been made according to the EULAR and GRAPPA classification criteria [18,19].

For each patient, data were retrospectively extracted from the medical records and inserted into a study-specific case report form. The collected baseline data included: gender, age, weight, smoking habit, type of extra-intestinal disease (psoriasis or psoriatic arthritis), type and duration of IBD, location of IBD according to the Montreal classification [20], clinical activity and previous therapies. The date of the first ustekinumab dose, concomitant therapies, induction and maintenance doses and the date of last administration or follow-up visit were also recorded. Reasons for ustekinumab discontinuation were categorized as no benefit for IBD (including primary and secondary non-response), no benefit for joint or skin diseases, intolerance or adverse events. Baseline and follow-up clinical activity was measured using the Harvey Bradshaw Index (HBI) [21] for CD and the Partial Mayo Score (PMS) [22] for ulcerative colitis (UC). Follow-up endoscopic data were recorded when available. The study protocol was approved on 13th of July 2017 by the Ethics Committee of the coordinating center (Fondazione Policlinico Universitario A. Gemelli IRCCS, Università Cattolica del Sacro Cuore, Rome, Italy). Every patient provided written informed consent. The study protocol conforms to the ethical guidelines of the 1975 Declaration of Helsinki (6th revision, 2008) as reflected in a priori approval by the institution's human research committee.

2.2. Clinical outcomes of ustekinumab-treated patients

The primary objective of our study was to assess the overall ustekinumab persistence, defined as the maintenance of ustekinumab therapy through the last observation time because of sustained clinical benefit for IBD. Clinical benefit was defined as a significant improvement in IBD-related symptoms according to the judgment of each patient's physician, leading to continuing ustekinumab treatment, without steroids, immunosuppressants or surgery. Secondary outcomes were: (1) proportion of patients achieving IBD clinical remission at the last follow-up visit among patients with active disease at baseline; (2) the association between each variable and IBD clinical remission; (3) rate of clinical remission of psoriasis or psoriatic arthritis; (4) proportion of patients achieving endoscopic remission at any time, and (5) safety of ustekinumab therapy.

2.3. Outcome measures

Regarding CD patients, clinical remission was defined as an HBI $\leq$4 [21]. Considering UC patients, clinical remission was defined as a PMS $\leq$ 2 with no subscore >1 [22]. Endoscopic remission was defined as achievement of complete mucosal normalization, except for residual aphthous ulcers for CD [8], and as an endoscopic Mayo subscore $\leq$1 for UC [22]. The psoriasis and psoriatic arthritis clinical activities during follow-up were assessed by each centers' experi-

enced dermatologists and rheumatologists, respectively. Remission of psoriasis was defined by a Psoriasis Area and Severity Index (PASI) response of at least 75% from baseline [23]. For psoriatic arthritis, we determined if patients had minimal disease activity (MDA) by assessing psoriasis, enthesitis, tender and swollen joint counts, patient-reported domains including pain on a visual analogue score (VAS) and global disease activity VAS, and results of the Health Assessment Questionnaire (HAQ). A patient was classified as achieving MDA when five of the seven following criteria were met: tender joint count ≤1; swollen joint count ≤1; PASI ≤ 1 or body surface area ≤3; VAS ≤ 15; global disease activity VAS ≤ 20; HAQ score ≤ 0.5; and tender entheseal points ≤1 [24].

All adverse events that occurred from the start of ustekinumab treatment to the date of withdrawal or last follow-up had been recorded and were categorized as leading to drug withdrawal or not.

2.4. Statistical analyses

Data are described using means with standard deviation (SD) and medians with range for continuous data and using percentages for discrete data. Cumulative probabilities of persistence of ustekinumab therapy and IBD clinical remission over time were estimated using the Kaplan–Meier method. The chi-square test was performed to assess IBD remission at last follow-up according to baseline clinical activity and to compare rates of remission among patients with psoriasis and those with articular involvement.

Binary logistics regression was used to estimate the association between each predictor and IBD clinical remission at last follow-up visit and psoriasis or psoriatic arthritis remission. We included in the model all variables that were found, by descriptive statistics, to influence remission. Time-dependent predictors were updated at each available time point, and odds ratios (ORs) were calculated with 95% confidence intervals (CIs).

A $p < 0.05$ indicated statistical significance. Statistical analyses were performed using SPSS 24.0 for Windows.

3. Results

A total of 70 IBD patients (64 CD and 6 UC) at 12 participating centers received ustekinumab for a dermatological or rheumatological indication (active psoriasis or psoriatic arthritis). Baseline characteristics of the study patients are summarized in Table 1.

Table 1
Clinical characteristics of 70 patients with IBD and either psoriasis or psoriatic arthritis.

Characteristic	Value
Female, n (%)	45 (64.3)
Age, years, median (range)	41.75 (20.3–72.3)
Weight, kg, mean (SD)	62.32 (12.76)
Smokers, n (%)	20 (28.6)
Type of extra-intestinal disease, n (%)	
Psoriasis	45 (64.3)
Anti TNF-α induced psoriasis[a]	26 (57.7)
Psoriatic arthritis	25 (35.7)
Type of IBD, n (%)	
Crohn's disease	64 (91.4)
Ulcerative colitis	6 (8.6)
Duration of IBD, years, median (range)	10 (0.50–33.8)
CD disease location, n (%)[b]	
L1	15 (23.4)
L2	16 (25.0)
L3	27 (42.2)
L4	6 (9.4)
UC disease location, n (%)[c]	
E1	1 (16.7)
E2	2 (33.3)
E3	3 (50.0)
CD clinical activity (HBI), n (%)[b]	
≤ 5	12 (18.8)
5–7	7 (10.9)
8–16	30 (46.9)
≥ 16	15 (23.4)
UC clinical activity (PMS), n (%)[c]	
≤2	2 (33.3)
3–5	1 (16.7)
6–10	3 (50.0)
Previous exposure to anti-TNFα, n (%)	67 (95.7)
1 drug	26 (37.1)
2 drugs	37 (52.9)
3 drugs	4 (5.7)
Previous exposure to vedolizumab, n (%)	5 (7.1)
Previous therapies, n (%)	
Steroids	62 (88.6)
Thiopurine	38 (54.3)
Cyclosporine	9 (12.9)
Concomitant therapies, n (%)	
None	42 (60.0)
Steroids	23 (32.9)
Thiopurine	6 (8.6)
Methotrexate	5 (7.1)
Ustekinumab induction dosing, n (%)	
45 mg at week 0 and 4	46 (65.7)
90 mg at week 0 and 4	24 (34.3)
Ustekinumab maintenance dosing, n (%)	
45 mg every 12 weeks	42 (60.0)
90 mg every 12 weeks	28 (40.0)

[a] Out of 45 psoriatic patients.
[b] Out of 64 CD patients.
[c] Out of 6 UC patients.

3.1. Ustekinumab persistence

The median time on ustekinumab therapy was 10.7 months (range, 1.4–67.3 months). Twelve patients (17.1%), all with CD, withdrew from treatment after a median of 7.4 months (range, 0.9–23.8 months). Ustekinumab therapy was discontinued because it offered no benefit for skin or joint disease (in 6 of 12 patients, 50%), no benefit for IBD (primary non-response to induction in 1 patient and secondary loss of response in 3 patients), and adverse events (2 patients).

Cumulative ustekinumab persistence is shown in Fig. 1. The cumulative probability of maintaining ustekinumab treatment was 97.1% at 6 months and 77.1% at 12 months (Fig. 1a). For the 27 patients (38.5%) with a follow-up longer than 12 months, the cumulative probability of persistent clinical benefit of ustekinumab therapy was 93.3% (Fig. 1b).

3.2. IBD clinical remission

At baseline, 56 patients (52 CD, 4 UC) had active disease. Of these 56 patients, 34 (60.7%) were in clinical remission with ustekinumab treatment at the last follow-up visit (range, 1.4–67.3 months). The cumulative probability of achieving remission was 84.7% at 6 months and 63.9% at 12 months (Fig. 2). Only 2 patients who started ustekinumab in clinical IBD remission experienced a clinical relapse of IBD during the follow-up.

At logistic regression, no significant associations were found between IBD clinical remission and age, type of IBD, duration of IBD or concomitant immunosuppressant at baseline (data not shown).

3.3. Psoriasis and psoriatic arthritis remission

Ustekinumab induced clinical remission in 37 (82.2%) of 45 patients with psoriasis and in 15 (60%) of 25 patients with psoriatic arthritis. No significant differences in terms of clinical remission were found between patients with wild psoriasis and anti TNF-α induced forms (84% vs 78%, $p = 0.623$, chi-square test). However, patients with psoriasis had a significantly higher rate of remission

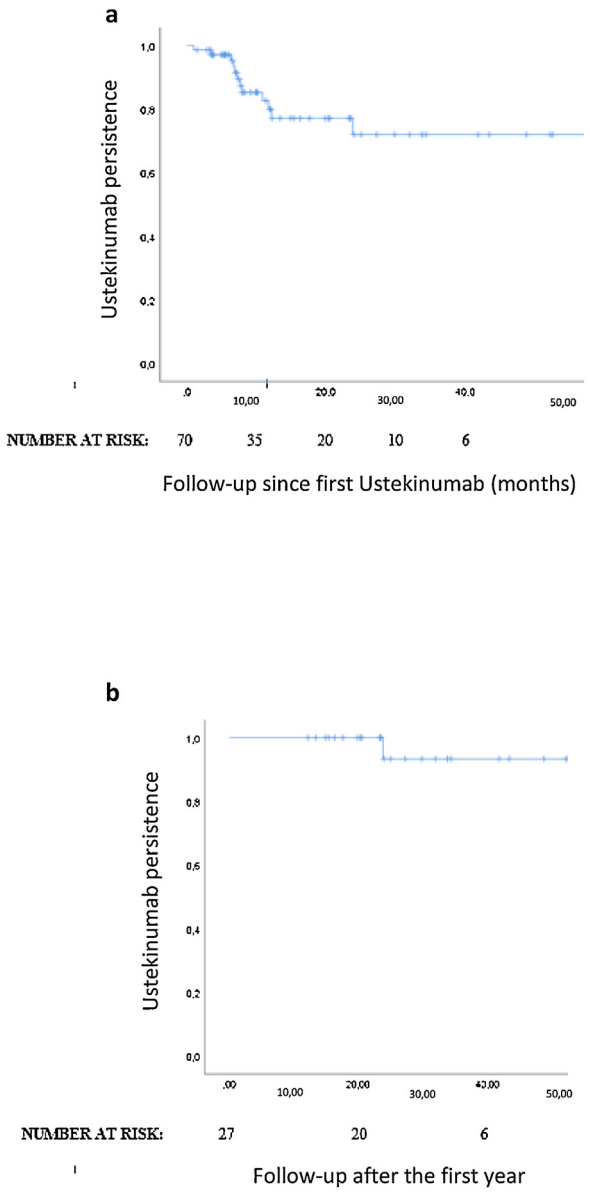

Fig. 1. (a, b) Kaplan–Meier survival curves for ustekinumab persistence. (a) For 70 IBD patients. (b) For the subgroup of 27 patients with long-term remission.

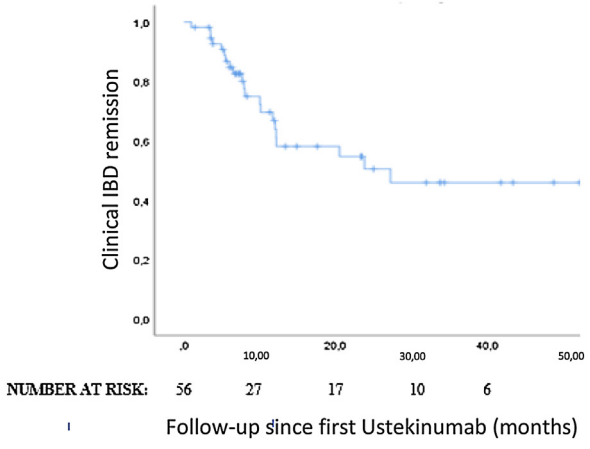

Fig. 2. Kaplan–Meier survival curve for clinical IBD remission among 56 (80%) of 70 patients with clinically active disease at baseline.

Table 2
Results of binary logistics regression for clinical remission in 70 patients with IBD and psoriasis or psoriatic arthritis.

Variable	OR (95% CI)	P
Gender (male vs. female)	4.53 (1.01–20.2)	0.047
Age (<45 vs. >45 years)	0.27 (0.06–1.08)	0.065
Smoking habit (yes vs. no)	0.31 (0.08–1.19)	0.089
Extra-intestinal disease (psoriasis vs. psoriatic arthritis)	5.26 (1.39–19.9)	0.014
Type of IBD (Crohn vs Ulcerative colitis)	2.23 (0.16–31.0)	0.548
Concomitant immunosuppressants	0.40 (0.08–1.92)	0.255

Table 3
Adverse events attributed to ustekinumab, in 70 patients with IBD and psoriasis or psoriatic arthritis.

Adverse event	Events, n	Patients, n
Any adverse event	10	9
Infections	5	5
Postoperative sepsis[a]	2	2
Intra-abdominal abscess[a]	1	1
Pneumonia	1	1
Acute gastroenteritis[b]	1	1
Worsening of IBD requiring proctectomy	1	1
Thyroid cancer	1	1
Acute renal colic	1	1
Intestinal obstruction[c]	1	1[c]
Worsening of arthralgia[c]	1	1[c]

[a] Led to discontinuation of ustekinumab.
[b] Required emergency department care.
[c] In the same patient.

than did patients with articular involvement (p = 0.042, chi-square test).

Logistic regression showed that male gender (OR = 4.53; 95% CI, 1.01–20.2; p = 0.047) and a diagnosis of psoriasis (OR = 5.26; 95% CI, 1.39–19.93; p = 0.014) were significantly associated with clinical remission (Table 2).

3.4. Endoscopic outcome

Follow-up endoscopy had been done for 27 ustekinumab-treated patients (22 CD and 5 UC, 38.5%) after a median time of 12 months (range, 0.3–60 months). Of these, 24 patients (88.9%) had baseline disease activity that was moderate to severe while the remaining three patients (2 CD and 1 UC) started ustekinumab when they were in clinical remission. Endoscopic remission was reported in 10 of the 22 CD patients (45%) and in 3 of the 5 UC patients (60%).

3.5. Safety

In the entire study group, 10 adverse events were experienced by 9 patients (Table 3), causing two patients to withdraw from ustekinumab treatment. One of these patients had undergone planned stoma closure surgery 11 months after starting ustekinumab therapy and experienced postoperative sepsis, while the other patient had an intra-abdominal abscess 2 months after the first ustekinumab dose and was treated surgically. Three adverse events required emergency department care, including one case each of acute intestinal obstruction (treated conservatively), dehydration due to acute gastroenteritis, and acute renal colic.

4. Discussion

This study focused on the clinical effectiveness and safety of subcutaneous ustekinumab therapy in 70 IBD patients who started treatment through a dermatological or rheumatological prescrip-

tion for concomitant psoriasis or psoriatic arthritis, respectively. The patients had a median duration of IBD of 10 years, and 95.7% of them had a previous exposure to at least one TNFα inhibitor. No patient received intravenous ustekinumab treatment, as approved for CD [2], but all received subcutaneous doses for psoriasis or psoriatic arthritis. The fact that all patients were similarly treated is a particular strength of this study, compared to other real-world studies in which multiple ustekinumab induction and maintenance regimens were used [5–10].

In our cohort, the median follow-up on ustekinumab therapy was 10.7 months, and the cumulative probability of maintaining ustekinumab treatment, because of sustained IBD clinical benefit, was 97.1% at 6 months and 77.1% at 12 months. These figures are in line with other real-life studies that reported an ustekinumab failure-free persistence over 70% at 1 year [8,10]. This long duration of efficacy of ustekinumab, also found in the IM-UNITI Long-Term Extension study [4], can be considered more stable as a maintenance therapy over anti-TNF agents, which have an estimated risk of response loss of 15%–20% per patient-year of follow-up [25,26].

In our study, 56 of the 70 patients started ustekinumab with clinically active IBD, and 34 of them (60.7%) achieved clinical remission at their last follow-up. The cumulative probability of achieving remission in this subgroup was 84.7% at 6 months and 63.9% at 12 months. Logistic regression did not reveal any association between clinical remission and baseline clinical variables, although the statistical power was limited by the small numbers of UC patients (n = 6) and of patients treated concomitantly with immunosuppressants (n = 11).

Recently, data on the efficacy of ustekinumab in UC have been reported [27,28]. In particular, a single infusion of ustekinumab (both at the dosage of 130 mg and of 6 mg/kg) seemed to be effective in inducing clinical remission at week 8 in patients with moderate-severe UC who had previously failed conventional or biologic therapy [27]. Moreover, week-8 clinical responders, who received subcutaneous ustekinumab maintenance treatment (90 mg every 8 weeks or 12 weeks), were more likely to achieve clinical remission at week 44 than patients who received placebo [28]

The advantage of combination therapy with an immunomodulator versus monotherapy with ustekinumab is still under debate. A post-hoc analysis of the IM-UNITI trial did not reveal differences in clinical remission at week 52 between patients who also received immunodulators and those who did not [3]. These results were attributed to the low rate of immunogenicity of ustekinumab and the not significant impact of immunomodulators on serum ustekinumab concentration and immunogenicity [3,29,30]. Conversely, concomitant immunosuppression therapy seemed to be associated with better outcomes in real-life studies [7,9]. According to the Group d'Etude Therapeutique des Affections Inflammatoires du Tube Digestif (GETAID), anti-TNFα-refractory CD patients treated with ustekinumab benefited from concomitant immunosuppression therapy at inclusion (OR = 5.43 vs. patients who did not receive immunosuppressants, assessed at 3 months) [7]. Moreover, Ma et al. [9] showed that combination therapy had a lower risk of response loss to ustekinumab during maintenance than monotherapy did (hazard ratio, 0.39).

Clinical remission of psoriasis or psoriatic arthritis was achieved by 52 patients in our study (74%), with a significantly higher rate of remission among patients with psoriasis. These results are in line with primary studies of these two pathologies. Ustekinumab had a good efficacy profile for plaque psoriasis, with a therapeutic gain over placebo (in terms of a PASI 75 response at week 12 over 60%) in two clinical trials [31,32]. In contrast, results in psoriatic arthritis patients, despite being significant, are not as impressive. In the PSUMMIT 1 and 2 trials, an American College of Rheumatology 20 (ACR20) response at week 24 (primary endpoint) was achieved by 42%–44% of patients who received ustekinumab 45 mg dosing and by 43%–49.5% of those who received 90 mg, compared with only 20%–23% of patients on placebo [33,34]. Differently from these trials, in our study we did not use predefined time points, and we defined clinical remission of psoriatic arthritis according to MDA.

Considering safety, 10 patients (12.8%) experienced an adverse event in our study, and two patients requiring ustekinumab withdrawal. These data confirm the large experience in the psoriasis and psoriatic arthritis populations, where ustekinumab treatment did not increase the risk of death, cardiovascular events, malignancy or serious infections [35,36].

Our study has several limitations: primarily this is a retrospective study, including patients with different lengths of follow-up and different time intervals between each clinical evaluation. Second, we included a mixed cohort of IBD patients who were not stratified for disease (54 CD and 6 UC). Third, we reported endoscopic outcome data only for a minority of patients (38.5%), and did not use an endoscopic score to assess Crohn's disease as Ma et al. did in their study [8]. Finally, we did not have data on the effectiveness of dose adjustment in cases of partial loss of response, since our patients were treated with fixed dosages of ustekinumab according to prescribing indications for psoriasis and psoriatic arthritis.

5. Conclusion

Our study shows that ustekinumab is safe and effective in patients with IBD and concomitant psoriasis or psoriatic arthritis, even at lower induction dose and different regimens compared to those approved for CD. Future studies are required to evaluate the effectiveness of ustekinumab administered at the higher IBD dosages on concomitant extra-intestinal disease manifestations and to position ustekinumab within the therapeutic algorithm, in relation to other biological therapies, for patients with multiple, concomitant, immune-mediated inflammatory diseases.

Conflict of interest

Daniela Pugliese received speaker fees from AbbVie, MSD, Takeda and Janssen. Marco Daperno has served as a speaker, consultant, advisory board member and/or was sponsored for participation at medical congresses by the following organizations: AbbVie, Biogen, Chiesi, Ferring, Hospira, Janssen, MSD, Mundipharma, Pfizer, Sofar, Takeda. Gionata Fiorino has served as a consultant and advisory board member for MSD, Takeda, AbbVie, and Janssen. WF received speaker fees form Mundipharma, and Zambon, served on the advisory board for Abbvie, and received an unconditioned grant from MS&D. Livia Biancone has served as a speaker or advisory board member for the following organizations: MSD, Takeda, Abbvie, Zambon. Mundipharma, Wasserman, Ferring, and Sofar Flavio Caprioli: served as consultant to Mundipharma, Abbvie, MSD, Takeda, Janssen, Roche, and Celgene. He received lecture fees from Abbvie, Ferring, Takeda, Allergy Therapeutics, and Janssen, and unrestricted research grants from Giuliani, Sofar, MS&D, Takeda, and Abbvie. Maria Cappello: lecture fees from Abbvie, MSD, Takeda, Shire, Vifor, Pharmanutra. Stefano Alivernini: has received fees for consultancy and/or lectures from: Bristol-Myers Squibb, Eli Lilly, Janssen, Novartis and Sanofi. Elisa Gremese: has received fees for consultancy and/or lectures from: Abbvie, BristolMyers Squibb, Celgene, Eli Lilly, Janssen, MSD, Mundipharma, Novartis, Pfizer, Roche, Sandoz, Sanofi and UCB. Alessandro Armuzzi: consulting and/or advisory board fees from AbbVie, Allergan, Amgen, Biogen, Celgene, Celltrion, Ferring, Hospira, Janssen, Lilly, MSD, Mundipharma, Pfizer, Samsung Bioepis, Sofar and Takeda; lecture and/or speaker bureau fees from AbbVie, AstraZeneca, Chiesi, Ferring, Hospira, Janssen, MSD, Mitsubishi-Tanabe, Medtronic, Mundipharma, Nikkiso, Pfizer, Otsuka, Samsung Bioepis, Takeda, Tigenix and Zambon; and research grants from MSD and Takeda. All the other authors have no conflict of interest to declare.

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