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Alimentary Tract

Dose de-escalation to adalimumab 40 mg every three weeks in patients with inflammatory bowel disease—A multicenter, retrospective, observational study

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ABSTRACT

Background: Data about the outcomes after adalimumab dose de-escalation in inflammatory bowel disease (IBD) are scarce.
Objectives: To assess the outcomes after adalimumab dose de-escalation, and to identify potential factors associated with failure.
Methods: Retrospective, observational study including all IBD patients who had undergone adalimumab dose de-escalation to 40 mg every three weeks across seven GETAID centers, between June 2011 and September 2017. Failure of adalimumab dose de-escalation was defined as the need for treatment re-escalation, discontinuation of adalimumab, or clinical, biochemical and/or morphologic disease relapse.
Results: Fifty-six patients were identified (n = 46 Crohn's disease, n = 10 ulcerative colitis). Median (IQR) duration of follow-up after adalimumab dose de-escalation was 15.9 (7.9–30.6) months. Adalimumab dose de-escalation was a failure in 21/56 (37.5%) patients and successful in 35/56 (62.5%) patients. Median (IQR) time until failure was 8.9 (4.6–15.6) months. At multivariate analysis, inactive disease at magnetic resonance imaging and/or endoscopy in the year before adalimumab dose de-escalation decreased the risk of failure with a factor five ($P = 0.02$).
Conclusions: Adalimumab dose de-escalation to 40 mg every three weeks is possible in almost two thirds of IBD patients. Objective morphologic signs of active disease should be ruled out before considering a de-escalation strategy with adalimumab.

1. Introduction

Inflammatory bowel disease (IBD) is a global disease with a high disease burden [1]. Both Crohn's disease (CD) and ulcerative colitis (UC) have a chronic, relapsing character [2,3]. Despite the rapidly growing therapeutic armamentarium, tumor necrosis factor antagonists (anti-TNFs) remain the cornerstone in the treatment of IBD [4]. Adalimumab, a subcutaneous administered, fully human anti-

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TNF agent, has shown to induce and maintain clinical response, clinical remission and mucosal healing in both CD [5–8] and UC [9–11]. The conventional adalimumab induction scheme is 160 mg at week zero, and 80 mg at week two, followed by a maintenance therapy with adalimumab 40 mg every other week [4].

Dose de-escalation of therapy is of interest because (i) it might reduce health care costs, which remain an important pharmacoeconomic issue even in the current era of biosimilars, and (ii) it could prevent adverse events linked to anti-TNF therapy, such as infections and malignancy [12]. Also, paradoxical immune-mediated inflammation can lead to arthralgia and dermatologic manifestations [13], the latter reported in up to one fifth of IBD patients treated with anti-TNF therapy [14,15].

While encouraging results coming from the field of rheumatology exist [16–19], data about the outcomes after dose de-escalation of adalimumab in patients with IBD are scarce. In the majority of IBD patients who previously had to dose-escalate adalimumab to 40 mg every week, dose de-escalation of therapy has been shown possible [20,21]. A recent, retrospective study with a median follow-up time of 24 months showed that 65% of CD patients who de-escalated to adalimumab 40 mg every three weeks remained in clinical remission [22]. This study was limited by a single-center design and did not include patients with UC. Further more, imaging and endoscopy data before adalimumab dose de-escalation were mainly lacking, however there is a strong dissociation between symptoms and intestinal inflammation in CD [23], and lessons from the STORI trial underlined the need for objective disease activity assessment before de-escalating therapy [24].

Hence, the objectives of our study were to assess the outcomes after adalimumab dose de-escalation in a multicenter cohort of IBD patients, and to identify potential predictors associated with failure of adalimumab dose de-escalation.

2. Methods

2.1. Design and patient selection

All GETAID (Groupe d'Etude Thérapeutique des Affections Inflammatoires du Tube Digestive) centers were invited to participate in this retrospective, observational study. Eventually, patients were selected in seven French referral IBD centers (Nancy, Besançon, Montpellier, Lille, Amiens, Créteil, Lyon). All adult patients with CD or UC who had undergone adalimumab dose de-escalation from 40 mg every other week to 40 mg every three weeks, between June 2011 and September 2017, were eligible for inclusion. Only patients during maintenance therapy, and in clinical remission as judged by the treating physician at the moment of adalimumab dose de-escalation, were selected. Patiens who had temporarily postponed adalimumab administration due to an infection or decreased compliance were excluded for analysis.

2.2. Study outcomes and definitions

The objectives of our study were to assess the outcomes after adalimumab dose de-escalation in a multicenter cohort of IBD patients, and to identify potential predictors associated with failure of adalimumab dose de-escalation.

Failure of adalimumab dose de-escalation was defined as (i) the need for treatment re-escalation, by increasing adalimumab dosing frequency back to 40 mg every other week, and/or adding an immunomodulator to the treatment with adalimumab, (ii) discontinuation of adalimumab treatment because of insufficient response or inacceptable side effects of adalimumab, or (iii) clinical disease relapse (i.e. the presence of one or more of the following symptoms, if attributed to the IBD by the treating physician: abdominal pain, cramping, gastrointestinal bleeding, weight loss, and abnormal stool frequency), biochemical disease relapse (i.e. repeatedly elevated C-reactive protein (CRP) level $\geq$5 mg/L without other, non-IBD related explanation) and/or morphologic disease relapse (i.e. radiologic and/or endoscopic IBD activity as judged by an experienced radiologist or endoscopist, respectively).

Succesful adalimumab dose de-escalation was defined as the absence of failure of adalimumab dose de-escalation at the end of follow-up. Patients were followed up until (i) adalimumab treatment was stopped or (ii) last news.

2.3. Statistical analysis

Categorical variables were described as percentages, and continuous variables as mean with standard deviation (SD) or median with interquartile range (IQR), depending on their distribution. For the comparative analysis of variables between groups, Chi-2 or Fisher's exact test was used for categorical variables and Student's or Wilcoxon test for continuous variables.

To identify factors associated with failure of adalimumab dose de-escalation, bivariate and multivariate Cox models (selection of candidate variables at the $P < 0.1$ threshold) were used. The index date was the date of de-escalation of adalimumab. The association strength was estimated by hazard ratios (HRs) and their 95% confidence intervals (95% CIs).

The threshold for statistical significance was set at 5%. All statistical analyses were performed using SAS software (version 9.4, SAS Institute Inc., Cary, NC, USA).

3. Results

3.1. Baseline patient characteristics

A total of 56 patients (46 CD, 10 UC) were included. Median (IQR) duration of follow-up for the overall study population was 15.9 (7.9–30.6) months, accounting for 100 person-years of follow-up. Baseline patients' and disease characteristics at the moment of adalimumab dose de-escalation are shown in Table 1. The median (IQR) time of treatment with adalimumab at the moment of adalimumab dose de-escalation was 36 (19–51) months.

All patients were in clinical remission at the time of adalimumab dose de-escalation. Twenty-five of 28 (89.3%) patients with available CRP levels were in biochemical remission (i.e. CRP level <5 mg/L). There were 39/56 (69.6%) patients who had undergone morphologic assessment of disease activity in the year before adalimumab dose de-escalation: 14 patient had undergone magnetic resonance imaging (MRI), 18 patients had undergone endoscopy and 7 patients had undergone both. Six of 39 (15.4%) patients had active disease at this assessment. In 25/56 (44.6%) patients both biochemical and morphologic data at the moment of adalimumab dose de-escalation were available, and 18 (72%) of those patients were in deep remission (i.e. clinical remission according to the treating physician, and CRP <5 mg/L, and absence of active disease at MRI and/or endoscopy).

In 54/56 (96%) patients the final decision to de-escalate therapy was initiated by the treating physician, and in 2/56 (4%) patients the final decision to de-escalate therapy was initiated by the patient.

3.2. Retention rates

At the end of follow-up, 24 of 46 (52.2%) CD patients and 4 of 10 (40%) UC patients were no longer on adalimumab 40 mg every three weeks regimen. Hence, the crude retention rates were 47.8% for CD, and 60% for UC, respectively ($P = 0.49$).

Table 1
Baseline patients' and disease characteristics at the moment of adalimumab dose de-escalation.

Characteristic	Total (n = 56)	CD (n = 46)	UC (n = 10)	*P*-value
Male, n (%)	25 (44.6)	21 (45.7)	4 (40)	1
Age at diagnosis, y, median (IQR)	25 (19–33)	24.5 (19–29)	40 (21–46)	0.21
Disease location (CD), n (%)[a]				
Ileal (L1)	–	8 (18.2)	–	–
Colonic (L2)	–	35 (79.5)	–	–
Ileocolonic (L3)	–	1 (2.3)	–	–
Upper Gastrointestinal (L4)	–	3 (6.7)	–	–
Disease behavior (CD), n (%)[a]				
Non structuring, non penetrating (B1)	–	30 (68.2)	–	–
Stricturing (B2)	–	9 (20.5)	–	–
Penetrating (B3)	–	5 (11.4)	–	–
Disease location (UC), n (%)[a]				
Rectitis (E1)	–	–	1 (10)	–
Left-sided colitis (E2)	–	–	5 (50)	–
Pancolitis (E3)	–	–	4 (40)	–
Smoking ever, n (%)	18/44 (40.9)	18/37 (48.6)	0/7 (0)	0.03
Disease duration, median, y, median (IQR)	9 (5–14)	9 (4.5–17)	8 (5–10)	0.64
Previous IBD-related surgery	15 (26.8)	13 (28.3)	3 (20)	0.71
Previous 5-ASA use, n (%)	28/45 (62.2)	20/36 (55.6)	8/9 (88.9)	0.12
Previous steroid use, n (%)	40/45 (88.9)	31/36 (86.1)	9/9 (100)	0.57
Previous IMM, n (%)	33 (58.9)	26 (56.5)	7 (70)	0.5
Previous anti-TNF use, n (%)	12 (21.4)	6 (13)	6 (60)	0.004
Concomitant steroid use, n (%)	0 (0)	0 (0)	0 (0)	–
Concomitant IMM use, n (%)	3 (5.4)	2 (4.3)	1 (10)	0.45
CRP level <5 mg/L, n (%)	25/28 (89.3)	19/22 (86.4)	6/6 (100)	1
Adalimumab TL (μg/mL), mean (SD)	12.5 (3.1) (n = 8)	11.9 (2.8) (n = 7)	17 (n = 1)	0.13

Legend: ASA: aminosalicylate; CD: Crohn's disease; IBD: inflammatory bowel disease; IMM: immunomodulator; IQR: interquartile range; SD: standard deviation; TNF: tumor necrosis factor; UC: ulcerative colitis.
[a] According to the Montréal classification.

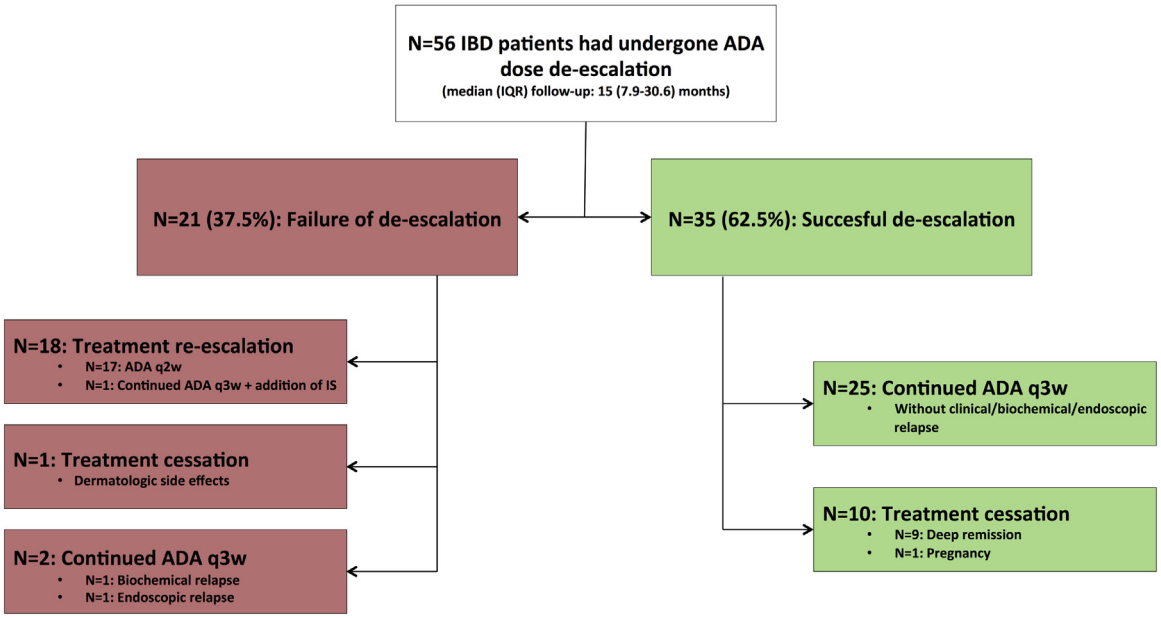

Fig. 1. Flow chart of outcomes after adalimumab dose de-escalation.
Legend: ADA: adalimumab; IS: immunosuppressant; q2w: 40 mg every other week; q3w: 40 mg every three weeks.

3.3. Outcomes after adalimumab dose de-escalation

As shown in Fig. 1, adalimumab dose de-escalation was a failure in 21 of 56 (37.5%) patients and successful in 35 of 56 (62.5%) patients. Median (IQR) time until failure of adalimumab dose de-escalation was 8.9 (4.6–15.6) months (Fig. 2).

In the subgroup of 21 patients with failure of adalimumab dose de-escalation, 18 (85.7%) patients had undergone treatment re-escalation, because of insufficient clinical, biochemical and/or morphologic disease control. In 17 patients adalimumab dosing frequency was increased back to 40 mg every other week, and in one patient an immunomodulator was added to adalimumab therapy. Only one of 18 patients eventually had to stop adalimumab three months later, while 17 of 18 patients were still under adalimumab therapy at the end of follow-up.

One of 21 (4.8%) patients with failure of adalimumab dose de-escalation stopped adalimumab because of inacceptable dermatologic side effects. Two of 21 (9.5%) patients continued adalimumab 40 mg every three weeks regimen until the end of follow-up, but suffered from a markedly biochemical (n = 1) or endoscopic disease relapse (n = 1), and were therefore considered as a failure of adalimumab dose de-escalation as well.

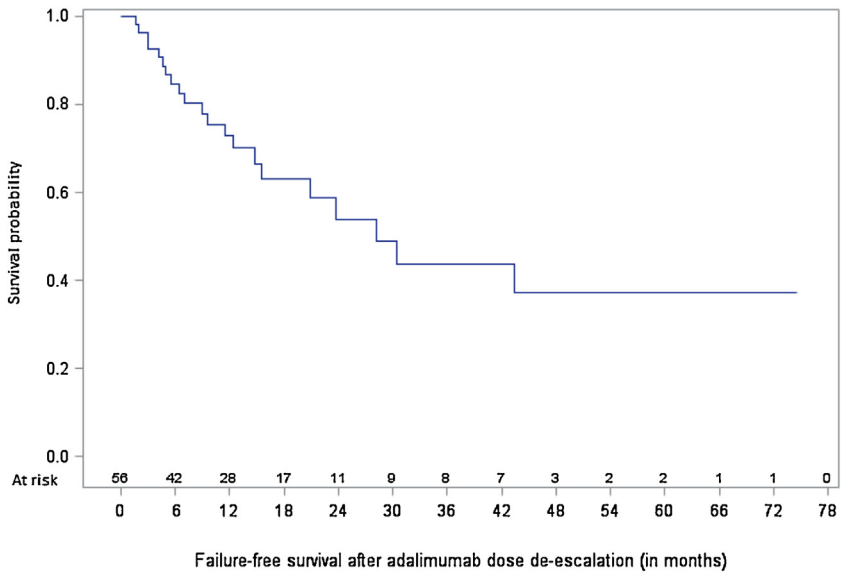

Fig. 2. Kaplan–Meier curve of the failure-free survival after adalimumab dose de-escalation.

Table 2
Variables associated with failure of adalimumab dose de-escalation.

Prognostic marker	Univariate analysis			Multivariate analysis		
	P-value	HR	95% CI	*P*-value	HR	95% CI
Gender	0.55	1.3	0.5–3.1	–	–	–
Age at diagnosis[a]	0.05	1	0.9–1	0.27	1	0.9–1
UC vs. CD	0.88	0.9	0.3–3.1	–	–	–
Previous or active smoking	0.73	1.2	0.4–3.5	–	–	–
Previous IBD surgery	0.83	0.83	0.4–2.7	–	–	–
Previous 5-ASA use	0.73	1.2	0.4–3.6	–	–	–
Previous IMM use	0.74	0.9	0.4–2.1	–	–	–
Previous anti-TNF use	0.72	0.8	0.3–2.4	–	–	–
Concomitant IMM use at baseline	0.82	1.2	0.3–5.2	–	–	–
CRP level at baseline[a]	0.10	1.1	1–1.1	–	–	–
Adalimumab TL before dose de-escalation[a]	0.13	0.6	0.3–1.2	–	–	–
Inactive disease at MRI and/or endoscopy at baseline[b]	0.03	0.3	0.1-0.9	0.02	0.2	0.1-0.8

Legend: ASA: aminosalicylate; CD: Crohn's disease; CI: confidence interval; HR: hazard ratio; IBD: inflammatory bowel disease; IMM: immunomodulator; MRI: magnetic resonance imaging; TNF: tumor necrosis factor; UC: ulcerative colitis.

[a] Continuous variables have no reference level; odds ratio's express the variation of risk for an increase of one unit of the variable.

[b] As assessed in the year before adalimumab dose de-escalation.

In the subgroup of 35 patients in which adalimumab dose de-escalation was successful, nine eventually stopped adalimumab treatment in the setting of deep remission, as judged by the treating physician, and based on clinical, biochemical and/or morphologic data. One patient stopped adalimumab treatment because of pregnancy.

3.4. Factors associated with failure of adalimumab dose de-escalation

At univariate analysis, a higher age at diagnosis ($P = 0.05$) and inactive disease on MRI and/or endoscopy in the year before adalimumab dose de-escalation ($P = 0.03$) were associated with a lower risk of failure of adalimumab dose de-escalation, the latter being the only one withheld after multivariate analysis (HR 0.2, 95% CI 0.1–0.8, $P = 0.02$; Table 2).

4. Discussion

Dose de-escalation of therapy is a potential strategy to reduce health care costs and minimize the risk of adverse events due to a treatment. In rheumatoid arthritis, The Dose Reduction Strategy of Subcutaneous TNF inhibitors (DRESS) trial has shown that dose-reduction or stopping adalimumab or etanercept was possible in two thirds of patients with a low disease activity [16]. The DRESS trial was a non-inferiority study comparing a disease-activity guided dose optimization with tight control monitoring without tapering, and had major disease flaring as primary outcome. Disease-activity guided dose optimization led to considerable cost savings, while no relevant loss of quality of life was observed [17].

Our study adds to the scarce existing data on adalimumab dose de-escalation to 40 mg every three weeks in IBD. To the best of our knowledge, we are the first to report outcomes after adalimumab dose de-escalation in a real-life IBD cohort comprising also UC patients, and this in a study with a multicenter design. In contrast to a previous study [22], data about objective disease activity (MRI and/or endoscopy) before adalimumab dose de-escalation were available in the majority of patients.

After a median follow-up time of 16 months, adalimumab dose de-escalation had failed in little more than one third of patients, meaning that around two thirds did not perceive any disadvantage of reduced adalimumab dosing. The median time to failure of adalimumab dose de-escalation was nine months. IBD type did not influence outcomes (*data not shown*). Our results are in line

with previous data reported by the Leuven group [22]. In their cohort of 40 CD patients, 12 (30%) patients developed a clinical relapse after a median (IQR) time of 6.9 (2.8–14.5) months. During a median follow-up of two years, 14 of 40 (35%) patients needed dose escalation back to 40 mg every other week [22].

The annual risk of treatment failure in adalimumab-treated IBD patients is approximately 20% [25]. We could not compare outcomes of patients on a de-intensified adalimumab dosing regimen with patients on continued standard dosing of adalimumab, due to the lack of a control group. The previous cited work of Van Steenbergen et al. did include a sex- and age-matched control cohort, but this approach has several limitations [22]. More data are available in the field of rheumatology [18,19]. No difference in disease control was noted in a retrospective trial comparing outcomes between patients (n = 117) with ankylosing spondylitis on a standard regimen of anti-TNF treatment vs. patients on a tapering strategy [18]. These findings were confirmed in a large Czech study [19]. On the contrary, a French trial comprising 136 patients with rheumatoid arthritis showed more disease relapse in patients on a de-intensified anti-TNF dosing regimen, compared with patients on a standard dosing scheme [26]. Only a prospective, randomized-controlled trial can truly assess differences in outcomes between different adalimumab treatment regimens in IBD patients.

Whether higher dosing of adalimumab leads to more adalimumab-related side effects, remains unclear. In a single-centre study comprising 583 patients, we previously reported an association between cutaneous infections and higher anti-TNF dosing [14]. In contrast, cross-sectional findings showed similar serum levels in patients with and without anti-TNF associated skin lesions [15,27,28]. In the propensity score-matched cohort study of Zavada et al., the incidence of adverse events and infections did not significantly differ between patients on a standard versus those on a tapered anti-TNF dosing regimen [19]. In our cohort, dermatologic adverse events linked to adalimumab therapy disappeared in 4 out of 7 (57.1%) patients after dose de-escalation to 40 mg every three weeks (*data not shown*). We could not explore the link with adalimumab drug levels since these were only available in 8 of 56 (14.2%) patients at baseline. In the Leuven cohort, adalimumab dose de-escalation was associated with a complete disappearance of adverse events in 17 of 32 (53%) patients; skin manifestations disappeared in 8 of 16 (50%) patients [22]. Serum levels at baseline were not predictive of disappearance of adverse events [22]. Data from an ongoing trial comparing two drug regimens of adalimumab in patients with moderately-to-severe UC [29], and from the prospective iCARE study [30], might further elucidate the relationship between dosing and tolerability and safety of adalimumab.

At multivariate analysis, inactive disease on MRI and/or endoscopy in the year before adalimumab dose de-escalation decreased the risk of failure of adalimumab dose de-escalation with a factor five. This result adds to the accumulating evidence for objective assessment of disease activity prior to therapy de-escalation or therapy cessation in IBD. Van Steenbergen et al. reported a CRP level <3.5 mg/L at dose de-escalation as the only independent factor associated with dose-escalation-free survival, but did not have enough imaging or endoscopy markers available for analysis [22]. In a prospective trial evaluating IBD course after anti-TNF withdrawal in patients receiving combination therapy with an immunomodulator, CRP levels ≥5 mg/L and fecal calprotectine levels ≥300 μg/L were associated with an increased risk of disease relapse [24]. A meta-analysis found that relapse rates after cessation of an anti-TNF agent in CD decreased by half in patients with endoscopic remission before anti-TNF discontinuation, compared with those without endoscopic remission [31].

Our study had several limitations. It was retrospective, and the sample size was relatively small. We used a clear definition for failure of adalimumab dose de-escalation, based on clinical, biochemical and morphologic criteria, however no validated scores were utilized. There was no systematic assessment of objective disease parameters (e.g. fecal calprotectine levels, CRP levels, endoscopy or MRI) at a fixed moment during follow-up. Also, MRIs and/or endoscopies before adalimumab dose de-escalation were not centrally-read. Further more, data about adalimumab drug levels before dose de-escalation were only available in a minority (<15%) of patients, however therapeutic drug monitoring could probably help us in daily clinical practice to identify possible candidates for dose de-escalation. For example, one could assume that in patients in remission despite low (or even absent) trough levels, dose de-escalation or treatment cessation is unlikely to provoke disease relapse. Nevertheless, in the Leuven cohort, no minimal adalimumab serum level to consider or maintain dose de-escalation could be withheld [22].

In conclusion, this retrospective, multicenter trial showed that adalimumab dose de-escalation from 40 mg every other week to 40 mg every three weeks was possible in almost two thirds of IBD patients. Inactive disease on MRI and/or endoscopy in the year before adalimumab dose de-escalation was associated with significant lower failure rates of adalimumab dose de-escalation, and this supports the need for objective assessment of disease remission before tapering treatment with anti-TNF agents in IBD. Prospective trials are needed to further elaborate the relationship between different adalimumab dosing regimens, and effectiveness, tolerability, and safety outcomes of therapy.

Conflicts of interest

LP received travel fees from Ferring, Takeda. GPDC received lecture fees from Pfizer, MSD, Abbvie, Takeda, Ferring and consulting fees from Takeda, Tillots Pharma, Janssen. LV received fees from Abbvie, Takeda, Ferring, MSD, Pfizer, Janssen. MF received consulting and lecture fees from Abbvie, MSD, Takeda, Boehringer, Janssen, Ferring, Pfizer. SN received consulting and lecture fees from MSD, Abbvie, Takeda, Janssen, Pfizer, Norgine, Tillots. LPB received consulting fees from Merck, Abbvie, Janssen, Genentech, Mitsubishi, Ferring, Norgine, Tillots, Vifor, Pharmacosmos, BMS, UCB-pharma, Hospira, Celltrion, Takeda, Biogaran, Boerhinger-Ingelheim, Lilly, Pfizer, HAC-Pharma, Index Pharmaceuticals, Amgen, Sandoz, Forward Pharma GmbH, Celgene, Biogen, Lycera, Samsung Bioepis, and lecture fees from Merck, Abbvie, Takeda, Janssen, Ferring, Norgine, Tillots, Vifor, Mitsubishi, HAC-pharma. None declared.

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