Journal of Crohn's and Colitis, 2018, 1249–1254
doi:10.1093/ecco-jcc/jjy087
Advance Access publication June 22, 2018
Short report

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Efficacy of Adalimumab for Treatment of Perianal Fistula in Children with Moderately to Severely Active Crohn's Disease: Results from IMAgINE 1 and IMAgINE 2

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Abstract

Background and Aims: Adalimumab has been shown to be more effective than placebo in healing fistulae in adults with moderately to severely active Crohn's disease. The efficacy and safety of adalimumab in healing fistulae in children/adolescents with Crohn's disease from the 52-week IMAgINE 1 clinical trial, and its open-label extension IMAgINE 2, are reported.

Methods: Children/adolescents with perianal fistulae at baseline of IMAgINE 1 were assessed for fistula closure and improvement during IMAgINE 1 [Weeks 0–52] and from Week 0 of IMAgINE 2 [Week 52 of IMAgINE 1] through to Week 240 of IMAgINE 2 using non-responder imputation.

Results: A total of 36 children/adolescents had fistulae at baseline of IMAgINE 1 and were included in the analysis. Fistula closure and improvement were observed in 44.4% and 52.8%, respectively, at Week 12. Rates of closure and improvement were maintained throughout the analysis period to Week 292. No new safety signals were identified.

Conclusions: In children/adolescents with moderately to severely active, fistulizing Crohn's disease, adalimumab induced perianal fistula closure and improvement within 12 weeks of treatment, with rates that were sustained for more than 5 years. The safety profile of adalimumab in patients with fistulae at baseline was similar to that of the overall population in IMAgINE 1/2. ClinicalTrials.gov identifiers: IMAgINE 1 (NCT00409682); IMAgINE 2 (NCT00686374).

Key Words: Anti-TNF; adalimumab; fistula

Abbreviations: AE, adverse event; anti-TNF, anti-tumour necrosis factor; CD, Crohn's disease; CRP, C-reactive protein; ECCO, European Crohn's and Colitis Organisation; ew, every week; HD, high dose; hNRI, hybrid non-responder imputation; LD, low dose; NRI, non-responder imputation; TEAE, treatment-emergent adverse event.

1. Introduction

Crohn's disease [CD] is a chronic inflammatory disorder, principally of the gastrointestinal tract, associated with characteristic mural and often transmural granulomatous inflammation.[1,2] Population-based studies have estimated that the cumulative incidence of perianal fistulae in patients with CD ranges from 23% to 38%.[3] In a defined paediatric cohort, the cumulative incidence of perianal fistula was 9.4% at 10 years after diagnosis of CD.[4] Severe perianal fistulizing disease is a potential predictor of poor disease outcome in paediatric CD patients.[5] Complex perianal CD, commonly featuring perianal fistula, has a considerable negative impact on quality of life.[6]

Anti-tumour necrosis factor [anti-TNF] biologic therapies infliximab[7,8] and adalimumab[9] have been reported to be effective treatments in healing fistulae in adult patients with CD, but data about fistulae healing with anti-TNF therapy in children/adolescents are limited.[5]

IMAgINE 1 was a 52-week, randomized, double-blind Phase III trial to evaluate the efficacy and safety of adalimumab in children/adolescents with moderately to severely active CD.[10] Patients who completed IMAgINE 1 and who had responded at any time were eligible to enter the open-label extension study, IMAgINE 2. The long-term efficacy and safety of adalimumab for treatment of IMAgINE 1/2 patients with CD have been reported recently.[11]

In the current analysis of IMAgINE 1/2, we examined the efficacy of adalimumab for fistula healing over time, covering a total period of 292 weeks of adalimumab exposure.

2. Methods

2.1. Study design and population

IMAgINE 1 [NCT00409682][10] and IMAgINE 2 [NCT00686374][11] methods have been described previously. Patients from the overall intention-to-treat population with fistulae at screening and baseline of IMAgINE 1 were assessed in the current analysis. Fistulae were defined by draining cutaneous fistulae upon gentle compression during physical examination, without use of pelvic magnetic resonance imaging. All fistulae were perianal. Further details are provided in the Supplementary Methods.

2.2. Efficacy and safety assessments

Fistula closure and fistula improvement were defined as closure of all IMAgINE 1 baseline fistulae or a decrease in number by ≥50%, respectively, for at least two consecutive visits. These end points were assessed at pre-specified time points in IMAgINE 1/2 and data were pooled, thereby capturing efficacy data over 292 weeks of adalimumab treatment. In addition, maintenance of fistula closure was analysed to Week 240 of IMAgINE 2 in patients with fistula closure at Week 0 of IMAgINE 2. Serum samples were obtained at selected time points for measurement of adalimumab concentration.

In IMAgINE 1, subgroup analyses of fistula closure in patients were performed for key potential predictors of response: randomized dose of adalimumab (high dose [HD] or low dose [LD]), prior infliximab therapy [yes versus no], corticosteroid use at baseline [yes versus no], immunomodulator use at baseline [yes versus no] and C-reactive protein [CRP] levels [<1 vs ≥1 mg/dL at baseline].

Safety was monitored in the subgroup of patients with fistulae, as described in the Supplementary Methods.

2.3. Data analyses and statistical methods

IMAgINE 1 data were analysed using non-responder imputation [NRI] and as-observed methods. For NRI, patients with missing data and those who escalated to open-label every week [ew] adalimumab dosing were imputed as non-responders. Patients who moved to blinded weekly dosing were not imputed and were counted according to their observed response.

IMAgINE 2 data were analysed using a hybrid non-responder imputation [hNRI] method as used previously in IMAgINE 2 analysis,[11] and as-observed methods. For hNRI, missing data were treated as follows: patients who discontinued from the study owing to study-site closure due to approval of adalimumab in the respective country [n = 10] were analysed using the last observation carried forward from that time point onwards; patients with missing data, or who discontinued for other reasons, were imputed as non-responders using the NRI method. Fisher's exact test and one-way analysis of variance were used to compare fistula closure in subgroup analyses. See the Supplementary Methods for details.

3. Results

3.1. Patient disposition, demographics and baseline characteristics

IMAgINE 1 baseline characteristics for this analysis are shown in Table 1. Of the 188 patients randomized in IMAgINE 1,[10] 36 [19.1%] patients [mean age 14.4 years] had at least one fistula; 23 of the 36 patients had a single fistula. All fistulae were draining enterocutaneous perianal fistulae. Baseline characteristics were similar between randomized groups receiving LD or HD adalimumab in IMAgINE 1, except for antibiotic use [Table 1].

3.2. Fistula closure and improvement

In IMAgINE 1, fistula closure and improvement were achieved in 44.4% and 52.8% of patients, respectively, at Week 12 by NRI analysis, with similar results in as-observed analysis [Figure 1a and b]. Rates of fistula closure and improvement were sustained to Week 52 in both NRI [50.0% and 58.3%, respectively] and as-observed analyses [42.3% and 46.2%, respectively]. Serum concentration of adalimumab in patients with fistula closure trended slightly higher than those not achieving fistula closure [Supplementary Table 1]. In IMAgINE 2, fistula closure and improvement rates were generally maintained with long-term [in total 292 weeks] adalimumab treatment, although hNRI and as-observed rates diverged as expected due to patient discontinuation from the study [Figure 1a and b]. At Week 292, 36.1% of patients by hNRI analysis and 90.9% of patients by as-observed analysis had fistula closure, and the same proportions of patients had documented fistula improvement. The majority of patients [64% hNRI, 100% as observed] who entered IMAgINE 2 with healed fistulae maintained fistula closure up to Week 240 of IMAgINE 2 [Figure 2].

In subgroup analyses, patients who were randomized to HD [versus LD] adalimumab, those who were naïve to infliximab [versus experienced], and those taking systemic corticosteroids or immunomodulators at IMAgINE 1 baseline [versus not taking] experienced generally higher rates of fistula closure, although no statistical significance was demonstrated at measured time points [Supplementary Table 2]. Interestingly, patients with CRP ≥ 1 mg/dL at IMAgINE 1 baseline consistently showed higher fistula closure rates than patients with CRP < 1 mg/dL, with statistical significance demonstrated at two time points [Supplementary Table 2]. Other covariates explored, including gender, age, weight, baseline antibiotic use, CD disease duration, CD disease severity, CD location, and number of fistulae, were not associated with fistula closure or improvement [data not shown].

Table 1. Baseline demographics and clinical characteristics of patients with fistulae at IMAgINE 1 baseline.

	LD adalimumab 20/10 mg [*n* = 21]	HD adalimumab 40/20 mg [*n* = 15]	All patients [*n* = 36]
Male, *n* [%]	17 [81.0]	7 [46.7]	24 [66.7]
Mean age ± SD, years	14.3 ± 2.1	14.5 ± 2.3	14.4 ± 2.2
≥13 years, *n* [%]	14 [66.7]	11 [73.3]	25 [69.4]
Caucasian, *n* [%]	18 [85.7]	14 [93.3]	32 [88.9]
Mean weight ± SD, kg	46.1 ± 9.8	45.7 ± 12.1	45.9 ± 10.6
≥40 kg, *n* [%]	15 [71.4]	11 [73.3]	26 [72.2]
Fistulae per patient [all perianal], *n*			
1	14	9	23
2	3	5	8
3	2	0	2
≥4	2	1	3
Baseline median CRP [range], mg/dL[a]	2.04 [0–7.8]	1.33 [0.2–6.8]	1.95 [0–7.8]
≥1 mg/dL, *n* [%]	11 [55.0]	9 [60.0]	20 [57.1]
Baseline median PCDAI [range]	42.5 [30.0–60.0]	45.0 [32.5–62.5]	42.5 [30.0–62.5]
Median disease duration [range], years	2.1 [0.3–9.2]	2.8 [0.3–7.0]	2.5 [0.3–9.2]
Baseline medication use, *n* [%]			
Systemic corticosteroids	10 [47.6]	3 [20.0]	13 [36.1]
IMMs	13 [61.9]	12 [80.0]	25 [69.4]
Thiopurines[b]	10 [47.6]	9 [60.0]	19 [52.8]
Methotrexate	3 [14.3]	3 [20.0]	6 [16.7]
Antibiotics[c]	6 [28.6]	0	6 [16.7]
Metronidazole	4 [19.1]	0	4 [11.1]
Ciprofloxacin	2 [9.5]	0	2 [5.6]
Prior infliximab use, *n* [%]	7 [33.3]	6 [40.0]	13 [36.1]

CRP, C-reactive protein; HD, high dose; IMM, immunomodulator; LD, low dose; PCDAI, Paediatric Crohn's Disease Activity Index; SD, standard deviation.
[a]One CRP measurement missing from the LD adalimumab group. [b]Azathioprine, 6-mercaptopurine.
Comparisons between LD and HD subgroups were calculated by using Fisher's exact test. [c]More patients in the HD group were receiving antibiotics compared with the LD group [$P = 0.03$], otherwise $P > 0.05$.

3.3. Safety and tolerability

The safety profile of adalimumab in children/adolescents enrolled in the IMAgINE 1 and IMAgINE 2 clinical trials has been reported previously.[10,11] Treatment-emergent adverse events [TEAEs] during IMAgINE 1 and IMAgINE 2 for patients with fistulae are presented in Supplementary Table 3. The safety profile and rates of TEAEs were consistent with those of the overall IMAgINE 1/2 study population.

4. Discussion

In IMAgINE 1/2, adalimumab treatment of children/adolescents with moderately to severely active CD complicated by perianal fistulae was efficacious in achieving fistula closure as early as Week 12 in approximately half of the patients, and rates of closure were sustained for more than 5 years. Furthermore, the majority of patients who entered IMAgINE 2 with healed fistulae maintained fistula closure up to Week 240 of IMAgINE 2. Fistula improvement rates were generally slightly higher than closure rates across both studies, indicating that patients who do not achieve complete fistula closure may still derive clinically meaningful benefit from treatment. Our results complement a previous evaluation of the efficacy of adalimumab in inducing and maintaining fistula closure in 117 adults with fistulizing CD.[9]

In subgroup analyses of fistulae closure during IMAgINE 1 evaluating possible associations with randomized dose of adalimumab [HD or LD] or prior [infliximab] or concomitant [corticosteroids or immunomodulators] medication covariates, no statistically significant differences were demonstrated between these subgroups. However, higher fistula closure rates in patients with higher baseline serum CRP levels [≥1 mg/dL] were observed. Indeed, CRP has been recognized as a marker for detection and follow-up of disease activity in patients with CD,[12] and trials with anti-TNFs have shown that an elevated CRP level predicts better response in patients with CD.[12]

Despite the increasing number of treatment options, medical management of perianal fistula in patients with CD remains challenging.[13,14] Antibiotics provide a first-line management option, but are not feasible for long-term use.[13] Immunomodulators such as thiopurines may offer long-term improvements, but achievement of clinical efficacy may require >3 months of treatment[13] and may increase lymphoma risk.[15,16] Anti-α4 integrin-targeting agents natalizumab and vedolizumab are approved for use in the treatment of CD in adults,[17] although evidence of efficacy in fistula healing is currently modest.[18,19] ECCO guidelines recommended anti-TNF therapy for induction and maintenance therapy in treatment of fistulae in paediatric patients following appropriate antibiotic and surgical management of lesions.[5] Our findings add to previous evidence with infliximab, supporting the use of anti-TNFs in the treatment of children/adolescents with fistulae.[20–26]

Our analysis has several limitations. Patients were not randomly assigned to treatment according to the presence of a fistula at baseline, the study was not powered to detect statistical differences between treatment groups, the study was not placebo controlled, and an imbalance in baseline antibiotic therapy between dosing groups was present. Fistula assessment was based on physical examination only and did not include imaging. Furthermore, recruitment into IMAgINE 2 may have constituted a selection for responders, as is typical for extension studies. Finally, the analysis population was relatively small, although to our knowledge the present analysis

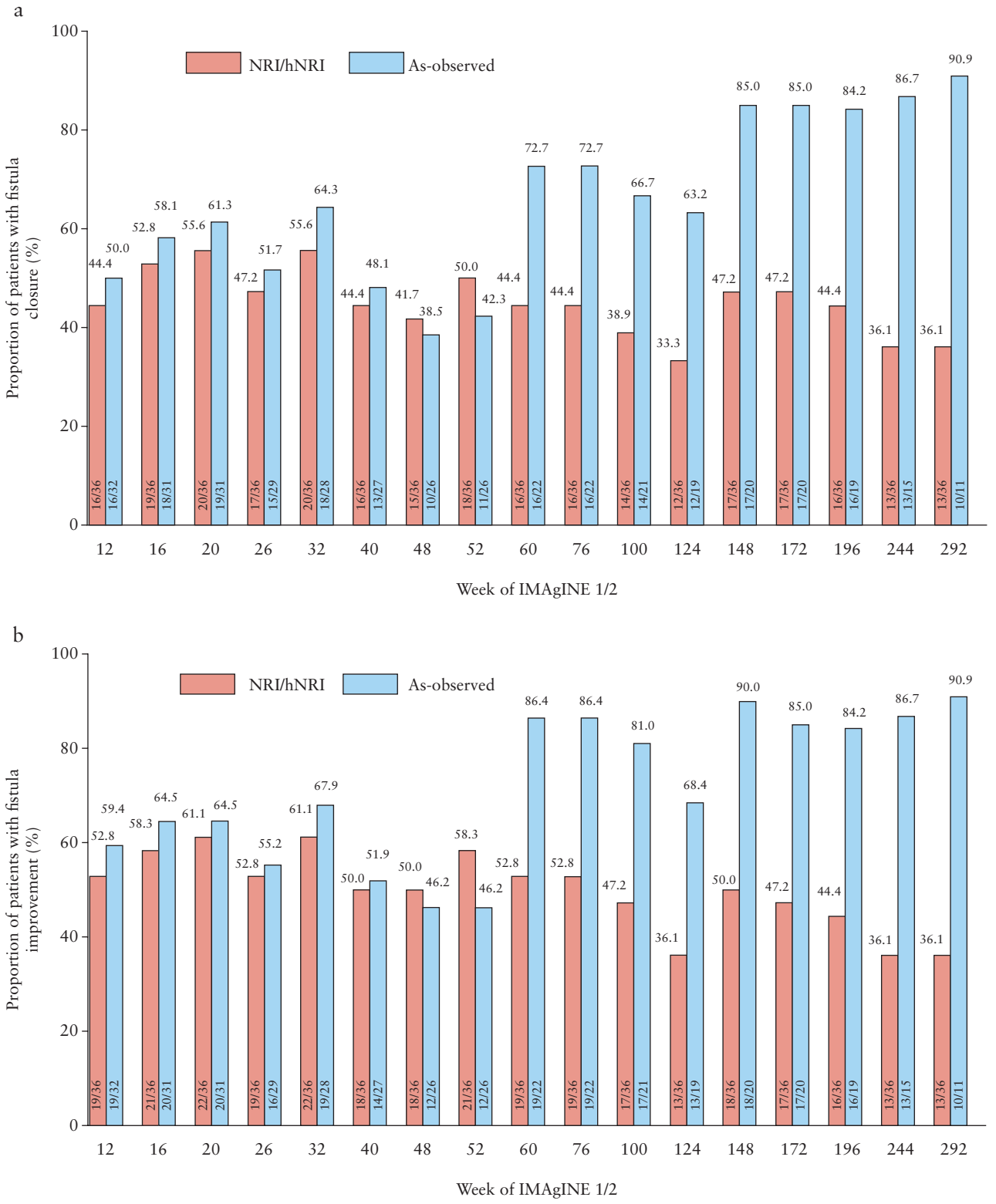

Figure 1. Fistula closure rates [a] and fistula improvement rates [b] with adalimumab treatment from Week 12 to Week 292 in IMAgINE 1 and IMAgINE 2 in patients with fistulae at baseline (non-responder imputation [NRI] in IMAgINE1, hybrid non-responder imputation [hNRI] in IMAgINE2 and as-observed analyses).

included the largest number of paediatric CD patients with fistulae from a clinical trial as well as the longest follow-up yet reported.

In conclusion, adalimumab treatment led to clinically meaningful rates of fistula closure and improvement within 12 weeks in children/adolescents with moderately to severely active fistulizing CD. Fistula closure and improvement rates were stable over time and sustained for more than 5 years. The safety profile was similar to that previously reported for the overall IMAgINE 1/2 study population.

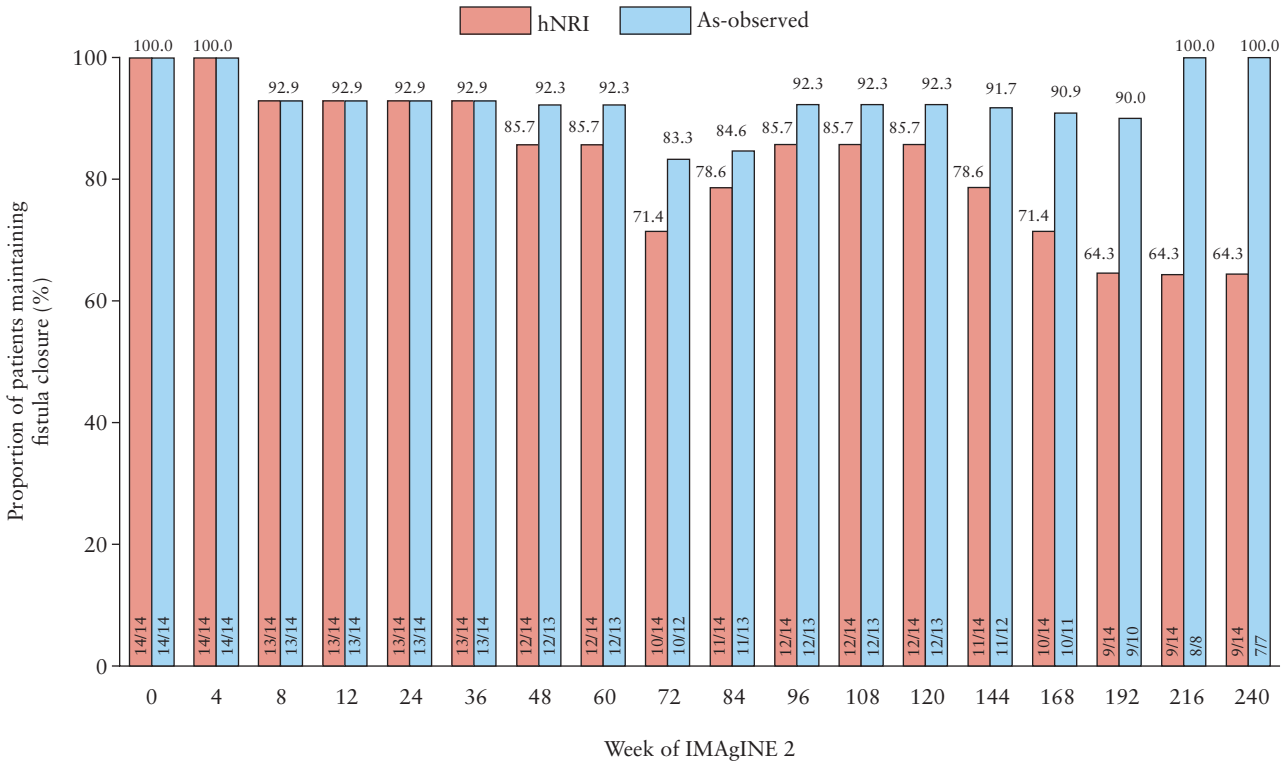

Figure 2. Long-term maintenance of fistula closure through to Week 240 of IMAgINE 2 in patients with fistula closure at IMAgINE 2 baseline (hybrid non-responder imputation [hNRI] and as-observed analyses). IMAgINE 2 baseline [Week 0 data] was derived from the IMAgINE 1 study Week 52 dataset.

Funding

AbbVie Inc. funded the study and the analysis, provided financial support for medical writing, and reviewed and approved the final draft.

Conflict of Interest

FR has received speaker fees from Shering-Plough, Nestlé, MeadJohnson, Ferring, MSD, Johnson & Johnson, Centocor and AbbVie; serves as a board member for: SAC:DEVELOP (Johnson & Johnson), CAPE (AbbVie) and LEA (AbbVie), and has been invited to MSD France, Nestlé Nutrition Institute, Nestlé Health Science, Danone, MeadJohnson, Takeda, Celgene, Biogen, Shire, Pfizer and Therakos.

JR has received consultancy fees from AbbVie, Janssen, Luitpold and Pfizer; is a board member for GI Health Foundation; and has received financial support for research from AbbVie and Janssen.

WAF has received consultancy fees from Connecticut Children's Medical Center—Safety Office as part of a subcontracted NIH clinical trial award; serves as a board member [no personal compensation] for AbbVie and UCB; and serves as a consultant [no personal compensation] for AbbVie, Boehringer Ingelheim Pharma, Janssen Research & Development, Celgene Corporation, Genentech and Shire Development.

MCD has received consultancy fees from AbbVie, Janssen, Takeda, Pfizer, Celgene, Boehringer Ingelheim, Prometheus Labs and UCB; and has received research support from Janssen.

DT has received consultation fees, research grants, royalties or honoraria from Janssen, Pfizer, Toronto Hospital for Sick Children, Ferring, MegaPharm, AstraZeneca, AbbVie, Takeda, Rafa, Boehringer Ingelheim, Biogen, Atlantic Health and Shire, during the last 3 years.

JSH has received consultancy fees from Janssen Ortho Biotech, AbbVie, Celgene, Entera Health, Pfizer, Soligenix, Takeda, Lilly, Genentech, Boehringer Ingelheim and AstraZeneca; has provided expert testimony on behalf of Janssen Ortho Biotech; has received speaker fees from Janssen Ortho Biotech; and has received payment for development of educational presentations from Janssen Ortho Biotech.

AL, SE, J-FM, GA and AMR are employees of AbbVie, and may own AbbVie stock and/or options.

Acknowledgments

Medical writing support was provided by Kevin Hudson, 2 the Nth, funded by AbbVie Inc.

Author Contributions

All authors were involved in the conception and design of the study, analysed and interpreted the study data, critically reviewed the content of this manuscript, and approved the final version for submission.

Supplementary Data

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

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