Digestive and Liver Disease 57 (2025) 707–715

Contents lists available at ScienceDirect

Digestive and Liver Disease

journal homepage: www.elsevier.com/locate/dld

Alimentary Tract

Change in fatigue in patients with ulcerative colitis or Crohn's disease initiating biologic therapy

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ARTICLE INFO

Article history:
Received 3 July 2024
Accepted 12 December 2024
Available online 8 January 2025

Keywords:
Biologic treatment
Clinical remission
Fatigue
Inflammatory bowel disease

ABSTRACT

Background: Fatigue is common among patients with inflammatory bowel diseases (IBDs) and is associated with decreased quality of life (QoL).
Aims: Describe fatigue evolution and identify factors associated with fatigue outcomes in patients with ulcerative colitis (UC) or Crohn's disease (CD) initiating biologic treatment.
Methods: Data from adult Belgian patients with UC or CD enrolled in a prospective real-world study were utilized. Fatigue and QoL were assessed using the Functional Assessment of Chronic Illness Therapy-Fatigue (FACIT-F) and the Short Inflammatory Bowel Disease Questionnaire, respectively. Factors associated with fatigue outcomes were assessed using multivariate regression.
Results: 465 patients were included: 174 with UC and 291 with CD. Average FACIT-F scores indicated improvements in fatigue after 6 months, before stabilizing. A higher probability of fatigue disappearance was associated with clinical remission and was more likely in patients with UC than CD. Patients achieving clinical remission had lower probability of fatigue. Patients with fatigue improvements experienced greater QoL improvements than patients with fatigue persistence.

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https://doi.org/10.1016/j.dld.2024.12.011

Conclusions: Real-world findings suggest fatigue partly improves in the first 6 months of biologic treatment. Clinical remission was associated with greater probability of fatigue disappearance and lower likelihood of fatigue persistence. Further research into factors associated with fatigue in patients with IBD is warranted.

1. Introduction

Inflammatory bowel diseases (IBDs), such as ulcerative colitis (UC) or Crohn's disease (CD), are chronic conditions characterized by symptoms including diarrhea, fecal urgency, incontinence, and abdominal cramps [1,2]. IBDs affect approximately 6.8 million people globally, with the highest prevalence reported in Europe (505 and 322 cases per 100,000 for UC and CD, respectively) and North America (286 and 319 cases per 100,000 for UC and CD, respectively) [3,4].

Fatigue is a common symptom among patients with IBD, thought to be more frequent and severe than in the general population, and is associated with reduced quality of life (QoL) [5,6]. The prevalence of fatigue is estimated to be from 41 % to 48 % for patients with IBD in remission, and from 71 % to 86 % in patients with active IBD [5]. Additionally, the European Crohn's and Colitis Organisation survey of nurses lists fatigue as one of the top five research priorities in IBD, given its widespread nature and negative effect on QoL [7].

The efficacy and safety of biologic therapies for the treatment of IBDs have previously been demonstrated [8–11], and are recommended by both the American Gastroenterological Association and the European Crohn's and Colitis Organisation in patients with UC and CD [12–16]. However, the impact of biologic therapies on fatigue in patients with IBDs is less well understood.

This analysis of prospectively collected observational data aimed to assess factors associated with fatigue among patients with UC and CD initiating biologic therapy in Belgium. The specific objectives were to describe the evolution of fatigue and to identify factors associated with time to fatigue disappearance, time to fatigue improvement, and with fatigue persistence among patients with UC or CD initiating any biologic treatment. An additional objective was to assess changes in QoL among patients initiating biologic treatment who demonstrated fatigue persistence and those who demonstrated fatigue improvement.

2. Methods

2.1. Study design

The PASS study (NCT02674308) was a prospective, observational, international, multicenter cohort study, designed primarily to assess the long-term safety of initiating biologic treatments in patients with UC or CD.

Patients were treated with biologic therapies as part of routine standard of care as directed by their physician according to local prescribing information. Participation in this study did not alter the patient-physician relationship, nor did it influence physicians' therapeutic management of patients. As such, the study design allowed investigators to modify or change patients' treatment for UC or CD without having to withdraw the patient from the study.

2.2. Participants

This analysis was restricted to patients enrolled in PASS living in Belgium (MLN-0002_401 [Belgium local add-on study]) because only these patients completed fatigue assessments (see Methods, Assessments). Adult patients aged 18 years or older with a diagnosis of UC or CD who were initiating biologic treatment were included in the study. Patients with prior exposure to vedolizumab were excluded. All patients or legal representatives provided written informed consent and signed release forms permitting access to medical records at baseline and during their participation in the study.

2.3. Assessments

Data were collected at baseline and 6-month intervals and included treatment information; IBD activity assessment (partial or full Mayo score for patients with UC and Harvey-Bradshaw Index score for patients with CD); health care resource utilization; patient-reported QoL (including fatigue); and adverse events and additional safety information. The follow-up time for patients in this analysis was 4.5 years, and data were collected between October 19, 2016, and December 10, 2021.

To assess fatigue, patients completed the Functional Assessment of Chronic Illness Therapy-Fatigue (FACIT-F) questionnaire. The FACIT-F comprises 13 questions scored on a 5-point Likert scale (0–4), giving a total score ranging from 0 to 52, with lower scores indicating greater fatigue [17]. Mean FACIT-F scores at each 6-month assessment were used to examine the evolution of fatigue. Consistent with previous studies in IBD, fatigue was defined as a FACIT-F score of <40 [18,19]. Therefore, fatigue disappearance (in patients with baseline fatigue) was defined as a total FACIT-F score of >40, clinically meaningful fatigue improvement was defined as a 4-point increase in FACIT-F score from the previous assessment, and fatigue persistence within 1 year from baseline was defined as two consecutive FACIT-F scores of <40. Considering that some previous studies have compared FACIT-F scores to general population estimates [17,20,21], and although not currently available for Belgium, fatigue disappearance and persistence were additionally assessed using a cut-off of 43.5 as reported by Montan et al. among the general population in neighboring Germany [22].

Explanatory variables to identify factors associated with fatigue outcomes included type of biologics started at baseline, age, body mass index (BMI), sex, use of other medications, previous biologic therapy, UC or CD diagnosis, time since symptom onset, extraintestinal manifestations, history of or active fistula, and clinical remission (partial Mayo score of ≤ 2 for patients with UC and Harvey-Bradshaw Index score of ≤ 4 for patients with CD).

QoL was assessed at baseline, 6 months, and 12 months using the Short Inflammatory Bowel Disease Questionnaire (SIBDQ), which comprised 10 items scored on a 7-point Likert scale (1–7), yielding a total score of 7–70, with higher scores indicating better QoL [23]. Additionally, binary variables were created for each of the 10 SIBDQ items by grouping responses 6 and 7 on the Likert scale to indicate 'no impact' and items 1–5 to indicate 'some impact' of that item on patient QoL. The association between fatigue disappearance and the individual SIBDQ items was then assessed.

2.4. Statistical analysis

Time to fatigue disappearance and time to fatigue improvement were explored using Kaplan-Meier estimates. The association between explanatory variables and fatigue disappearance and fatigue

improvement was assessed using proportional hazard ratio models. Associated explanatory variables were identified using stepwise-effect selection, and added to or removed from the model at an alpha level of 0.05.

Factors associated with the fatigue persistence within 1 year from baseline were assessed using logistic regression models. Associated explanatory variables were also identified by stepwise-effect selection, with variables added or removed from the model at an alpha level of 0.05.

Models for fatigue persistence and fatigue disappearance were restricted to patients with fatigue at baseline, whereas models for fatigue improvement included all patients enrolled in the PASS study in Belgium. Multiple imputation was used for missing data.

3. Results

3.1. Patient characteristics

In total, 465 patients enrolled in the PASS study in Belgium were included in this analysis (see Table 1 for baseline demographic and disease characteristic). Of these, 174 patients had a diagnosis of UC and 291 had a diagnosis of UC. Among all initiated biologic treatments, vedolizumab was the most common (55.7 %), followed by adalimumab (16.8 %), infliximab (15.3 %), ustekinumab (10.8 %), and golimumab (1.5 %). At baseline, 26.2 % of patients were in clinical remission and 23.5 % of patients had extraintestinal manifestations. At baseline, 331 and 371 patients had fatigue at baseline when defined as a FACIT-F score of <40 and <43.5, respectively.

Table 1
Baseline demographics and disease characteristics in patients initiating biologic treatment.

	All patients (N = 465)
Age, years, mean (SD)	42.4 (16.0)
Female, *n* (%)	257 (55.3)
BMI, kg/m^2, mean (SD)	24.2 (4.8)
Type of IBD, *n* (%)	
UC	174 (37.4)
CD	291 (62.6)
Mayo score (UC), mean (SD)	5.1 (2.2)
HBI score (CD), mean (SD)	6.3 (4.9)
Type of biologic treatment, *n* (%)	
Vedolizumab	259 (55.7)
Adalimumab	78 (16.8)
Infliximab	71 (15.3)
Ustekinumab	50 (10.8)
Golimumab	7 (1.5)
Age at symptom onset, years, mean (SD)	30.3 (14.9)
Age at initial diagnosis, years, mean (SD)	31.5 (14.7)
Disease duration,[a] years, mean (SD)	10.8 (11.1)
FACIT-F total score, mean (SD)	28.9 (12.8)
History of prior biologic use, *n* (%)	
No	270 (58.1)
Yes	195 (41.9)
Clinical remission at baseline, *n* (%)	
No	267 (57.4)
Yes	122 (26.2)
Missing	76 (16.3)
Extraintestinal manifestations at baseline, *n* (%)	109 (23.5)
Calprotectin result, *n* (%)	
Negative (<50 µg/g)	9 (1.9)
Borderline (50–100 µg/g)	20 (4.3)
Positive (>100 µg/g)	126 (27.1)
Missing	310 (66.7)
C-reactive protein result, *n* (%)	
Normal (<3 mg/L)	150 (32.3)
Elevated (3–10 mg/L)	122 (26.2)
Severe (>10 mg/L)	125 (26.9)
Missing	68 (14.6)
Steroid use at baseline, *n* (%)	
Yes	203 (43.7)
No	262 (56.3)
Methotrexate or thiopurine use at baseline, *n* (%)	
Yes	123 (26.5)
No	342 (73.5)

BMI, body mass index; CD, Crohn's disease; FACIT-F, Functional Assessment of Chronic Illness Therapy-Fatigue; HBI, Harvey-Bradshaw Index; IBD, inflammatory bowel disease; UC, ulcerative colitis.

[a] Disease duration from initial IBD diagnosis to index date.

3.2. Evolution of fatigue

Overall, an improvement in fatigue was observed in the first 6 months following initiation of biologic treatment, with mean (95 % confidence interval [CI]) FACIT-F scores increasing from 28.9 (27.7–30.0) at baseline to 33.3 (32.0–34.7) at month 6 (P < 0.0001) (Fig. 1). FACIT-F scores remained stable from month 6 to 54, following initial improvements. Patients who achieved clinical remission post induction had greater improvements in fatigue than patients who did not (Fig. 2). Average FACIT-F scores among patients with UC and CD were similar at each 6-month assessment (Supplementary Fig. 1).

3.3. Fatigue disappearance

At baseline, 331 of 465 (71.2 %) patients had fatigue (defined as a FACIT-F score of <40), which was estimated to have disappeared on at least one occasion (at least one FACIT-F score of >40) in 6.8 % of patients by 6 months, 23.9 % by 12 months, and 31.3 % by 24 months (Fig. 3a). The proportion of patients with fatigue disappearance at each assessment remained relatively stable for the duration of the study (Fig. 3b).

The probability of fatigue disappearance defined as a FACIT-F score of >40 (Fig. 4a) was estimated to be higher in patients with UC than those with CD and in patients achieving versus not achieving clinical remission, and lower in patients who had extraintestinal manifestations at baseline versus those who did not. Type of biologic treatment started at baseline, age, BMI, sex, previous biologic treatment, time since IBD symptom onset, history of or active fistula, and history of IBD surgery were not associated with fatigue disappearance in the multivariate analyses.

Fatigue disappearance defined by a FACIT-F score of >43.5 was estimated to have occurred on at least one occasion in 5.5 %, 18.2 %, and 27.4 % of patients after 6, 12, and 24 months, respectively (Supplementary Fig. 2). The probability of fatigue disappearance (defined by a FACIT-F score of >43.5) was estimated to be higher in patients with UC than with CD and higher in patients who had achieved clinical remission versus those who did not (Supplementary Fig. 3a). Fatigue disappearance was also estimated to have been higher among the six patients with treatment-emergent serious infections than those without (Supplementary Fig. 3a).

Time to fatigue disappearance was estimated to have occurred at a faster rate and in greater proportions of patients with clinical remission than those without, with fatigue disappearance defined as both a FACIT-F score of >40 (Supplementary Fig. 4a) and >43.5 (Supplementary Fig. 4b).

3.4. Fatigue improvement

In the overall treatment group, the first episode of fatigue improvement (defined as a 4-point increase in FACIT-F score from the previous measure) was estimated to have occurred in 14.5 % of patients at 6 months, 42.5 % at 12 months, and 65.7 % at 24 months (Fig. 5a). The highest proportion of patients with fatigue improvement was observed at 6 months (44.9 %), before reducing to 32.9 % at 12 months and remaining relatively stable (24.2 %–30.7 %) up to 48 months (Fig. 5b).

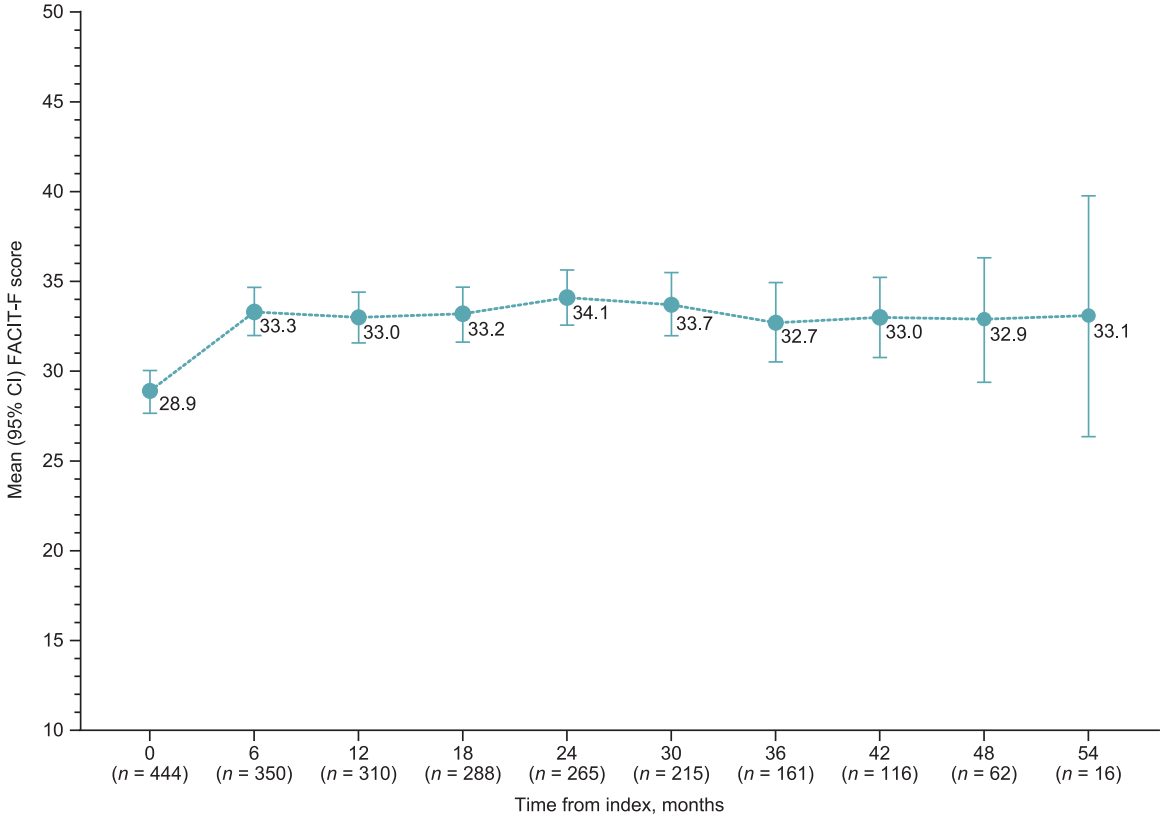

Fig. 1. Change in FACIT-F score over study duration in all patients.

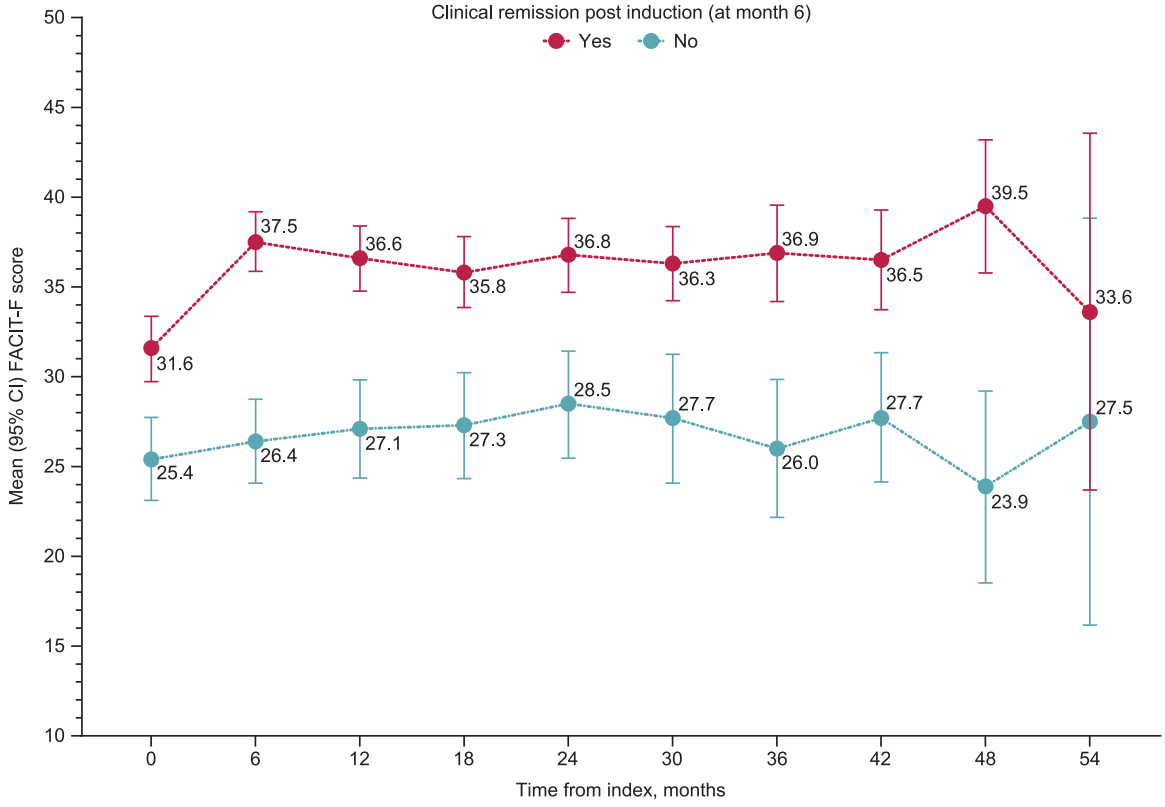

Fig. 2. Average FACIT-F scores stratified by clinical remission post induction (month 6).

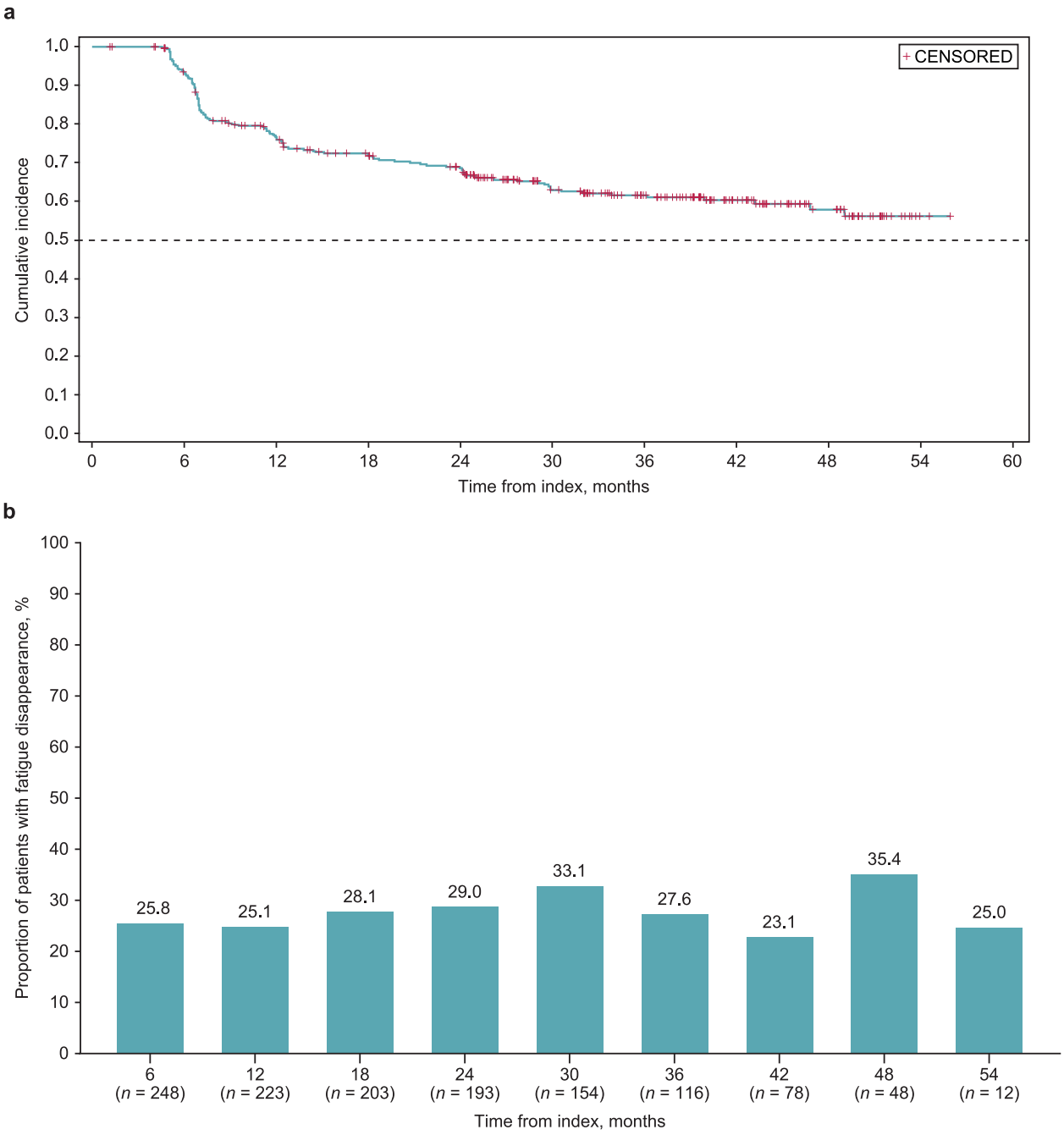

Fig. 3. (a) Kaplan-Meier curve estimate for time to first occurrence of fatigue disappearance in patients with fatigue at baseline. (b) Proportion of patients with fatigue disappearance at each assessment. Fatigue disappearance is defined as a FACIT-F score of >40 at each assessment in patients with fatigue at baseline.

Patients with fatigue at baseline (FACIT-F score of <40) were more likely to experience improvements in fatigue from their previous FACIT-F score following initiation of biologic treatment (Fig. 4b). Type of biologic treatment started at baseline, age, BMI, sex, previous biologic treatment, IBD diagnosis, time since IBD symptom onset, history of IBD surgery, extra-clinical manifestations, history of or active fistula, and clinical remission were not associated with fatigue improvement in the multivariate analyses.

3.5. Fatigue persistence

Among patients with fatigue at baseline, patients achieving clinical remission had a lower probability of fatigue persistence within 1 year from baseline, as defined by two consecutive FACIT-F scores of <40, than patients not achieving clinical remission (Fig. 4c). Patients achieving clinical remission also had a lower probability of fatigue persistence, as defined by two consecutive FACIT-F scores of <43.5, than patients not achieving clinical remission (Supplementary Fig. 3b).

Type of biologic treatment started at baseline, age, BMI, sex, previous biologic treatment, IBD diagnosis, time since IBD symptom onset, history of IBD surgery, extra-clinical manifestations, and history of or active fistula were not associated with fatigue persistence within 1 year.

3.6. Quality of life

Patients with fatigue improvement had an increase in average SIBDQ score from 42.3 at baseline to 50.4 at 6 months and 50.7

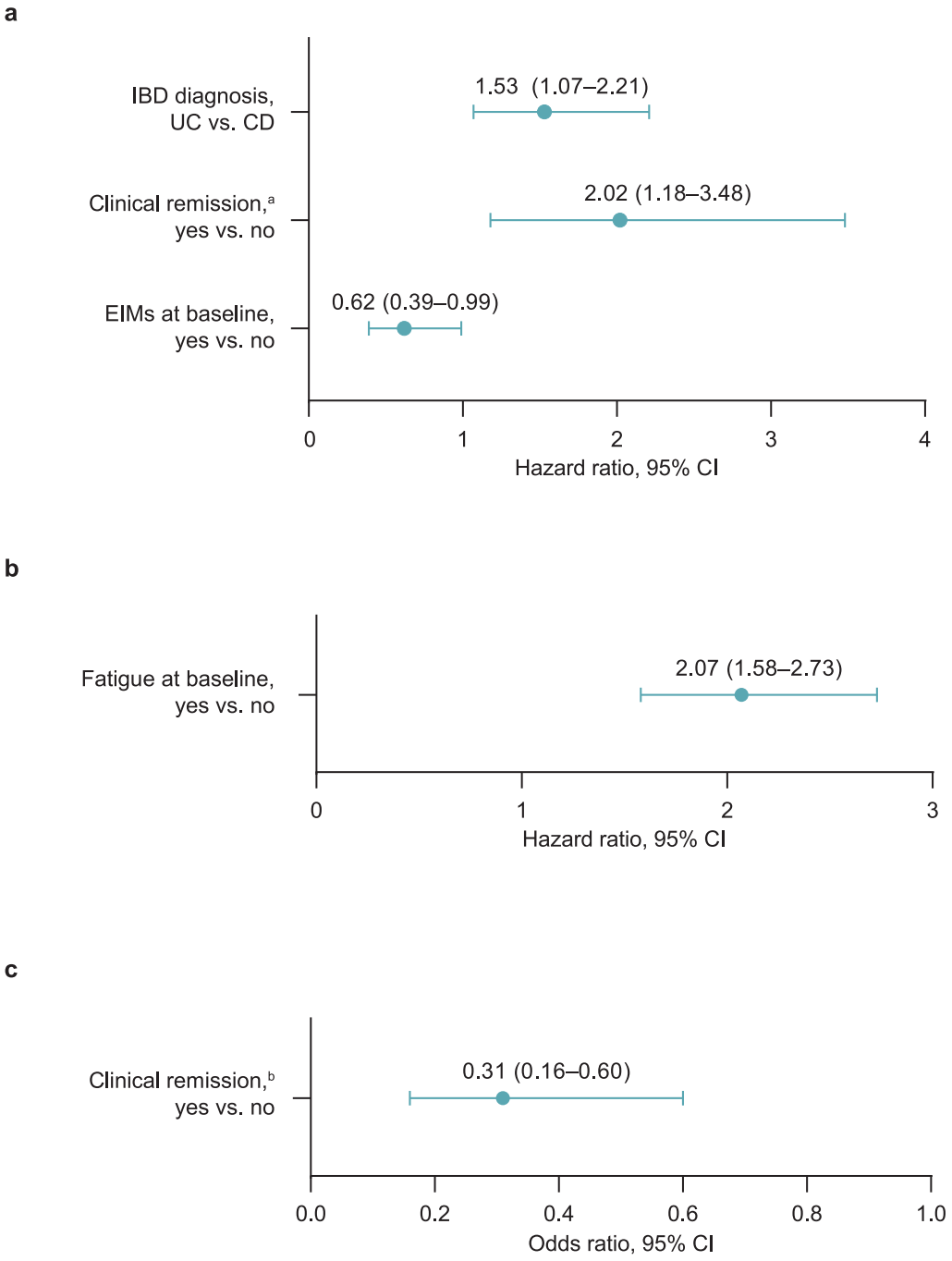

Fig. 4. Factors associated with (a) fatigue disappearance; (b) fatigue improvement; and (c) fatigue persistence within 1 year. Fatigue disappearance was defined as a FACIT-F score of >40. Fatigue improvement was defined as a 4-point increase in FACIT-F score from the previous measure. Therefore, patients with no fatigue at baseline could experience fatigue (FACIT-F score >40) that subsequently improved during follow-up. Fatigue persistence within 1 year was defined as two consecutive FACIT-F scores of <40. [a]Clinical remission at fatigue disappearance. [b]Clinical remission at fatigue persistence. EIM, extraintestinal manifestation.

at 12 months (Supplementary Fig. 5). Patients with fatigue persistence within 1 year also had an increase in average SIBDQ score; however, these increases were smaller in magnitude, increasing from 39.1 at baseline to 43.6 and 43.9 at 6 and 12 months, respectively.

Of the seven individual SIBDQ items, only two were associated with fatigue disappearance, both when defined as a FACIT-F score of >40 and >43.5 (Supplementary Fig. 6a and b). Fatigue disappearance was estimated to be lower in patients who indicated that they were not impacted by abdominal pain, but higher in patients not impacted by depression or discouragement.

4. Discussion

Initial improvements in fatigue measured by mean FACIT-F scores were observed in patients after 6 months of initiating biologic treatment. The increase in mean (95 % CI) FACIT-F score from 28.9 (27.7–30.0) at baseline to 33.3 (32.0–34.7) at 6 months is above the threshold of a 4-point increase that is considered to be a minimal clinically important difference [17]. Importantly, improvements in FACIT-F scores were maintained during the study period, with a mean (95 % CI) of 34.1 (32.6–35.6) at 2 years and 33.1 (26.4–39.8) at the final 4.5-year assessment.

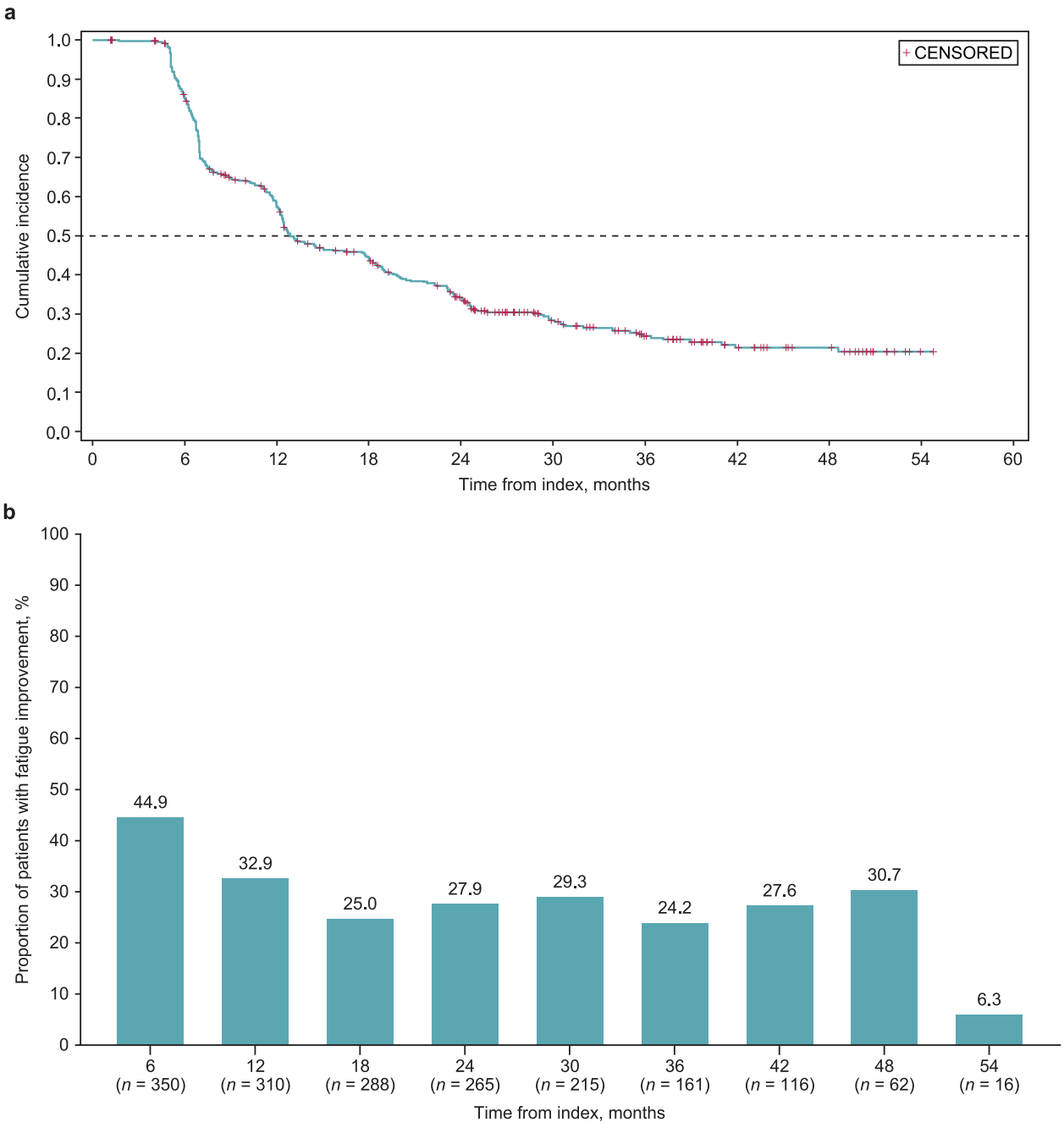

Fig. 5. (a) Kaplan-Meier curve estimate for time to first occurrence of fatigue improvement. (b) Proportion of patients with fatigue improvement at each assessment. Fatigue improvement was defined as a 4-point increase in FACIT-F score from the previous measure. Therefore, patients with no fatigue at baseline could experience fatigue (FACIT-F score >40) that subsequently improved during follow-up.

The Kaplan-Meier curve estimate showed that fatigue disappearance occurred on at least one occasion in 23.9 % of patients by 12 months. Interestingly, however, the proportion of patients with fatigue disappearance remained relatively stable (23.1 %–35.4 %) for the duration of the study. Similarly, although the Kaplan-Meier estimate showed that 65.7 % of patients experienced fatigue improvement on at least one occasion by 24 months, the proportion of patients with fatigue improvement was highest at 6 months, before reducing and stabilizing for the majority of the study, in line with initial improvements in mean FACIT-F score. This suggests that, although notable proportions of patients are likely to experience fatigue disappearance and improvement following the initiation of biologic therapies, fatigue is not stable and is likely to fluctuate over time. This shows that fatigue is multifactorial and highlights the importance of regular routine assessments of fatigue in patients with UC or CD.

Achieving clinical remission after induction, a diagnosis of UC compared with CD, and the absence of extraintestinal manifestations were factors associated with fatigue disappearance. Fatigue disappearance was also estimated to have occurred at a faster rate and in more patients with clinical remission than those without. Clinical remission was also associated with a lower likelihood of fatigue persistence within 1 year, whereas only fatigue at baseline was associated with fatigue improvement, as might be expected. The finding that achieving clinical remission was associated with an increased likelihood of fatigue disappearance over time and a

lower likelihood of fatigue persistence within 1 year using both a FACIT-F score of <40 and <43.5 to define fatigue is consistent with previous studies that have found higher levels of fatigue in patients with greater disease activity [24–26]. Future research might benefit from extending these findings to examine the relationship between steroid-free clinical remission and the evolution of fatigue. However, high levels of fatigue have also been reported in patients with IBD with very low disease activity [26,27], suggesting that additional factors beyond achieving clinical remission should be considered for improving fatigue.

Furthermore, very few of the explanatory variables included in this analysis were associated with fatigue outcomes. As such, the association between fatigue and factors not measured in these analyses warrants further investigation. Among potential factors for consideration are stress and psychological wellbeing because patients classified as having more severe courses of fatigue have previously been found to be more likely to have lower wellbeing [26]. An additional potential factor is physical exercise, although evidence of its association with fatigue in patients with IBD is limited. One pilot study found that advice to increase physical exercise was associated with reductions in fatigue as measured by the Inflammatory Bowel Disease-Fatigue questionnaire but not by the FACIT-F [28]. A longitudinal study of clinical attendees diagnosed with CD also found that establishing a regular exercise regimen was independently associated with improvements in levels of physical fatigue [29]. Additional research to examine the associations between physical exercise and fatigue outcomes, such as those reported in this analysis, is therefore warranted.

In this study, patients with fatigue improvement had greater improvements in QoL, as measured by the SIBDQ, than patients with fatigue persistence within 1 year. This is consistent with findings that patients reporting higher levels of fatigue also report reduced wellbeing [26]. Interestingly, a systematic review by Radford et al. found some evidence that patients with IBD who are more physically active report better QoL [5], highlighting the importance of considering physical exercise in future research of fatigue in patients with IBD. Additionally, depression has been found to be a factor that contributes to fatigue in patients with IBD [30], although this was not assessed in this study using a validated index of depression. However, the SIBDQ item relating to depression or discouragement was associated with fatigue disappearance, with patients who indicated they were not impacted by depression or discouragement at baseline having a higher probability of fatigue disappearance. Future research should therefore consider assessing comorbid depression when investigating IBD related fatigue.

The key strengths of this study are the large sample size and assessment of the course of fatigue over a long 4.5-year follow-up period. However, limitations inherent to observational studies should be considered when interpreting the findings presented in this analysis. Such studies are prone to selection bias in that patients who were willing to participate might have different clinical characteristics to those who were not, and the lack of randomization introduces the potential for confounding by unmeasured variables. There was also notable loss to follow-up: of the initial 465 patients enrolled, 265, 161, and 62 remained in the study at months 24, 36, and 48, respectively. This highlights the difficulty of collecting long-term data in real-world conditions. Data collection also relied on patients self-reporting over the previous 6 months, which may have been subject to recall bias, and this analysis did not include more objective measures such as endoscopic healing. As data were collected as part of routine clinical practice, some data may be missing, such as baseline clinical remission for some patients. There may also be factors that might be associated with fatigue that were not collected, such as hemoglobin, c-reactive protein and fecal calprotectin levels. Additionally, the objective of this study was to look at the impact of any biologic treatment on fatigue and was not powered to ascertain differences between specific therapies. Future studies might consider investigating differences in specific biologic treatments, which may be informative for patients and clinicians. Finally, fatigue was assessed using the FACIT-F, which has no unanimously accepted threshold for defining fatigue. To mitigate this, thresholds of both <40 and <43.5 that have been previously reported in the literature were utilized in this study, with little impact on results.

In conclusion, clinically meaningful improvements in fatigue were observed in patients with UC and CD in the first 6 months following initiation of biologic therapy, which then fluctuated on an individual basis over 4.5 years of follow-up. A higher probability of fatigue disappearance was associated with achieving clinical remission, and was more likely in patients with UC than CD and in those without extraintestinal manifestations at baseline. Clinical remission was also associated with a lower likelihood of fatigue persistence within 1 year. Further research into factors associated with fatigue outcomes and fatigue persistence in patients with IBD despite clinical remission, such as psychological status or physical exercise, is warranted.

Ethical considerations

All patients or legal representatives provided written informed consent and signed release forms permitting access to medical records at baseline and during their participation in the study.

Funding

This study was sponsored by Takeda. The trial sponsor (Takeda) designed the trial in conjunction with the principal academic investigators.

Writing assistance

Medical writing support was provided by Jon Waldron, PhD, of Excel Scientific Solutions, Inc., a member of Envision Pharma Group, and funded by Takeda.

Data availability

The datasets, including the redacted study protocol, redacted statistical analysis plan, and individual participants' data supporting the results reported in this article, will be made available within 3 months from initial request, to researchers who provide a methodologically sound proposal. The data will be provided after its deidentification, in compliance with applicable privacy laws, data protection, and requirements for consent and anonymization. Data are available upon request via application at https://search.vivli.org.

Conflict of interest

E.L. reports educational and research grants from AbbVie, Fresenius Kabi, Janssen, Pfizer, and Takeda; speaker fees from AbbVie, Bristol Myers Squibb, Celgene, Dr Falk, Ferring, Galapagos, Janssen, Pfizer, and Takeda; serving on advisory boards for AbbVie, Arena, Bristol Myers Squibb, Celgene, Eli Lilly, Ferring, Gilead-Galapagos, Janssen, Pfizer, and Takeda; and being a consultant for AbbVie. P.B. reports research grants from AbbVie, Amgen, Celltrion, Mylan, Pfizer, and Takeda; lecture fees from AbbVie, Celltrion, Eli Lilly, Janssen, and Takeda; and consulting fees from AbbVie, Arena, Bristol Myers Squibb, Celltrion, Dr Falk, Eli Lilly, Galapagos, Janssen, Pentax, PSI-CRO, Roche, Takeda, and Tetrameros. A.C. reports consultancy fees from AbbVie, Galapagos, Janssen, and Takeda; and speaker fees from AbbVie, Celltrion, Galapagos,

Janssen, and Pfizer. S.V. reports grants from AbbVie, Galapagos, Johnson & Johnson, Pfizer, and Takeda; and consulting and/or speaker fees from AbbVie, AbolerIS, AgomAb, Alimentiv, Arena, AstraZeneca, Avaxia, Boehringer Ingelheim, Bristol Myers Squibb, Celgene, CVasThera, Cytoki, Dr Falk, Eli Lilly, Ferring, Galapagos, Genentech-Roche, Gilead, GSK, Hospira, Imidomics, Janssen, Johnson & Johnson, Materia Prima, Merck Sharp & Dohme, MiroBio, Morphic, MrMHealth, Mundipharma, Pfizer, Prodigest, Progenity, Prometheus, Robarts Clinical Trials, Second Genome, Shire, Surrozen, Takeda, Theravance, Tillots, and Zealand. V.S. reports receiving a research grant from Takeda. F.B. reports grant/research support from AbbVie, Amgen, Janssen, and Takeda; being a speaker for AbbVie, Celltrion, Ferring Holding SA, Janssen, Merck Sharp & Dohme, Pfizer, and Takeda; honoraria from AbbVie, Amgen, Arena, Celltrion, Ferring Holding SA, Fresenius Kabi AG, Galapagos, Janssen, Merck Sharp & Dohme, Pfizer, and Takeda. F.F. reports research grants from Takeda. A.H. and G.V.G. are employees of Takeda. J.Z. is an employee of and holds stock/stock options in Takeda. The other authors declare no conflicts of interest.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.dld.2024.12.011.

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