Association of serum neurofilament light chain levels and neuropsychiatric manifestations in systemic lupus erythematosus

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Abstract

Background: The aim was to evaluate the diagnostic potential of serum neurofilament light chain (sNfL) measurements in patients with neuropsychiatric systemic lupus erythematosus (NPSLE).

Methods: sNfL levels were determined by single molecule array assay in a retrospective cross-sectional cohort of 144 patients with systemic lupus erythematosus (SLE). After log-transformation of sNfL levels, mean sNfL levels were compared between NPSLE patients and SLE patients without neuropsychiatric disease using Student's t test. Furthermore, the association of different neuropsychiatric manifestations with sNfL levels was assessed using a one-way analysis of variance (ANOVA) with post hoc analysis. Associations of sNfL with clinical and laboratory parameters were assessed by correlation and multiple linear regression analysis.

Results: NPSLE patients ($n = 69$) had significantly higher sNfL levels than SLE patients without neuropsychiatric disease manifestations ($n = 75$; mean difference: 0.13, 95% CI: 0.04–0.22, $p = 0.006$). With regard to the category of NPSLE manifestation, mean sNfL levels were only increased in NPSLE patients with focal central nervous system (CNS) involvement ($n = 45$; mean difference: 0.16, 95% CI: 0.02–0.30, $p = 0.019$), whereas mean sNfL levels of NPSLE patients with diffuse CNS and peripheral nervous system involvement did not differ from those of SLE patients without neuropsychiatric manifestations. Age and serum creatinine concentrations were identified as relevant contributors to sNfL levels.

Conclusion: sNfL is a promising, easily accessible biomarker for neuropsychiatric involvement in SLE patients and might therefore complement the diagnostic workup of SLE patients with suspected involvement of the nervous system.

Keywords: biomarker, CNS, neurofilament light chain, neurolupus, NPSLE

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Introduction

Systemic lupus erythematosus (SLE) is a chronic autoimmune disease, which can affect multiple organ systems including the central nervous system (CNS) and peripheral nervous system (PNS). Approximately half of the SLE patients will develop neuropsychiatric SLE (NPLSE) during their disease course, mostly within 3–5 years from SLE onset.[1] This is of clinical importance as neuropsychiatric manifestations considerably impact quality of life and are associated with poor prognosis.[2]

To establish a consistent nomenclature for research and clinical practice, the American College of

Rheumatology (ACR) suggested a set of case definitions for 12 CNS and 7 PNS syndromes associated with SLE.[3] The CNS syndromes can be further categorized as either focal neurological or diffuse psychiatric/neuropsychological syndromes.[4] This heterogeneity of potential disease manifestations has been one of the main obstacles for the development of a diagnostic biomarker for NPSLE; currently, there is no gold standard approach.

The pathogenesis of NPSLE is particularly complex and the precise mechanisms remain elusive. As it is highly unlikely that a single pathogenic pathway accounts for the observed variety of neuropsychiatric symptoms, a multifactorial process of interrelated mechanisms is believed to be responsible for NPSLE development. Some of the proposed mechanisms include blood-brain barrier dysfunction, cytokine- and autoantibody-mediated neuroinflammation, and vascular processes, which ultimately result in neuronal damage.[4] Neurofilament light chains (NfL) are structural scaffolding proteins that are exclusively expressed in central and peripheral neurons. Following neuronal damage due to neurodegenerative, inflammatory, vascular, or traumatic processes, they are released into cerebrospinal fluid (CSF) and consecutively into the blood to a lesser extent.[5] Because the release of NfL is not restricted to specific pathophysiological processes, it could thus serve as a suitable biomarker to detect neuropsychiatric manifestations in SLE patients.

In 2003, Trysberg *et al.*[6] observed seven-fold higher NfL levels in the CSF of SLE patients with CNS manifestation in comparison to SLE patients without CNS symptoms and even 51-fold higher levels than in healthy controls. In addition, a recent study by Tjensvoll *et al.*[7] found an association of CSF NfL levels with intrathecal anti-NR2 antibodies and immunoglobulin G levels in SLE patients. However, because spinal taps to obtain CSF are invasive and cannot be performed on a regular basis, only the recent development of highly sensitive immunoassays to detect NfL in serum (sNfL) now promises a broad application of NfL level assessment in clinical routine.

Therefore, the aim of this study was to evaluate for the first time the potential of sNfL as an easily accessible blood biomarker of neuronal damage to identify SLE patients with neuropsychiatric manifestations. Furthermore, we investigated the impact of clinical and laboratory parameters on sNfL levels in lupus patients.

Methods

Study design and patient cohort
Between 2004 and 2019, 159 patients who presented at the Division of Nephrology, Rheumatology and Clinical Immunology of the University Medical Center Mainz (Germany) were screened for eligibility for inclusion in this cross-sectional study based on available medical records. Inclusion criteria were a confirmed diagnosis of SLE defined as fulfillment of at least four of the ACR criteria for the classification of SLE,[8] and availability of complete clinical characterization at time point of serum collection. Patients with a documented concomitant neurological disease, which was likely responsible for the observed neurological symptoms, were excluded. Diseases that led to study exclusion included a diagnosis of Alzheimer's dementia, brain tumors, herniated vertebral disk, or traumatic brain injury in the past. All the remaining patients received a thorough diagnostic workup at the time of diagnosis to exclude differential diagnoses of neuropsychological symptoms. Examinations included brain imaging, laboratory examinations, lumbar puncture, and neuropsychological evaluation as deemed necessary by the treating physician, and were therefore not performed in a standardized form. Serum samples were collected prospectively and stored at −80°C in aliquots to avoid repeated freeze and thaw cycles. Creatinine and C-reactive protein (CRP) levels were assessed as part of the routine diagnostics.

Standard protocol approvals, registrations, and patient consents
This study was approved by the Standing Committee for Clinical Studies of the Johannes Gutenberg University (number 837.467.13); written informed consent was obtained from all patients.

Analysis of sNfL and anti-NR2 antibody levels
sNfL levels were determined using the highly sensitive single molecule array (SiMoA) technology. Samples were measured in duplicates in several rounds by SiMoA HD-1 (Quanterix, USA) using the NF-Light Advantage Kits (Quanterix)

according to manufacturer's instructions. Resorufin-β-D-galactopyranoside (RGP) was incubated at 33°C for 60 min prior to running the assay. The coefficient of variation (CV, as a percentage) of the two replicates was obtained by dividing the standard deviation of both replicates by the mean of both replicates multiplied by 100. CVs above 20% (or missing replicate result) were measured twice. Finally, the mean intra-assay CV of 5.9% was obtained by averaging all individual sample CVs. Two low and high controls, consisting of recombinant human NfL antigen, were included in each sample run to monitor plate-to-plate variation (low: mean 8.8 pg/ml, interassay CV 13.6%; high: mean 192.7 pg/ml, interassay CV 13.3%). sNfL measurements were performed in a blinded fashion without information about clinical data.

Statistical analyses

All statistical analyses were performed using SPSS version 23.0 (IBM Corp, Armonk, NY); figures were created using GraphPad Prism 7.0 for Windows (Microsoft, Redmond, WA). Continuous variables were tested for normal distribution using the Kolmogorov–Smirnov test. sNfL levels were log-transformed to achieve a normal distribution. Comparisons of the mean between baseline characteristics were tested by Student's t test in case of normal distribution and by Mann–Whitney U test in non-normally distributed variables. Categorical variables were compared with the chi-square test and Fisher exact test if appropriate. As a primary analysis, differences in mean log-sNfL levels between SLE patients with and without neuropsychiatric manifestation were tested by Student's t test. As secondary analyses, area under the curve (AUC) derived from receiver operating characteristic (ROC) analysis was calculated for sNfL levels. To assess the effects of different NPSLE manifestations on log-sNfL levels, we conducted a one-way analysis of variance (ANOVA) with Tukey post hoc analysis. Isolated associations of sNfL levels with clinical and laboratory parameters were assessed using Spearman correlation analyses with Bonferroni correction for multiple testing. Furthermore, the contribution of the variables sex, age, disease duration, presence of neuropsychiatric symptoms, creatinine and CRP concentrations, and presence of immunosuppressive treatment to the prediction of sNfL levels were evaluated in a multiple linear regression analysis. For linear regression analysis, categorical variables were dummy coded. If not stated otherwise, two-sided values of $p < 0.05$ were considered significant.

Data availability

The data underlying this article will be shared in anonymized format on request of a qualified investigator to the corresponding author for purposes of replicating procedures and results.

Results

In total, 144 patients were included in this study. Descriptive statistics and group comparisons of the cohort are presented in Table 1. Importantly, we observed no age differences at time point of serum collection between patients with and without neuropsychiatric disease manifestation. The proportion of patients with renal dysfunction was higher in patients with NPSLE than in patients without neuropsychiatric phenomena, whereas there was no difference in median serum creatinine levels.

In a first step, we aimed to assess whether sNfL levels differed between patients with and without neuropsychiatric disease manifestation. In our cohort, NPSLE patients ($n = 69$; mean: 1.19, SD: 0.28) had higher log-sNfL levels than SLE patients without neuropsychiatric symptoms ($n = 75$; mean: 1.06, SD: 0.28; mean difference: 0.13, 95% CI: 0.04–0.22, $p = 0.006$; Figure 1(a)). sNfL levels exhibited an ROC-AUC for prediction of the presence of neuropsychiatric symptoms (NPSLE) of 0.646 (95% CI: 0.554–0.738, $p = 0.003$; Figure 1(b)).

In a second step, patients were assigned to one of the following disease manifestation categories[4] (confirmed by appropriate additional diagnostics at a time point previous to serum collection):

1. No NPLSE
2. NPSLE with PNS manifestation including cranial neuropathy, polyneuropathy, mononeuropathy, acute inflammatory demyelinating polyradiculopathy, myasthenia gravis, plexopathy, and autonomic disorders
3. NPSLE with diffuse CNS manifestation including cognitive dysfunction, mood and anxiety disorders, psychosis, acute confusional state, and headache
4. NPSLE with focal CNS manifestation including cerebrovascular disease, seizures, myelopathy, aseptic meningitis, movement disorder, and demyelinating syndrome.

Table 1. Patient characteristics.

Measures	All patients (n = 144)	SLE without NP phenomena (n = 75)	NPSLE (n = 69)	p value
Age, median (IQR), y	40.5 (30.0–51.0)	37.0 (28.0–51.0)	43.0 (35.0–50.5)	0.208
Female sex, no. (%)	124 (86.1%)	67 (89.3%)	57 (82.6%)	0.244
Age at SLE diagnosis, median (IQR), y	28 (21.0–39.0)	27.0 (21.0–37.0)	29.0 (19.75–40.5)	0.567
Disease duration, median (IQR), y	7.5 (2.0–17.0)	7.0 (2.0–16.25)	9.0 (2.0–17.5)	0.638
Immunosuppressive treatment at time point of serum collection, no. (%)	122 (84.7%) (treatment status unknown in 8 cases)	61 (81.3%) (treatment status unknown in 3 cases)	61 (88.4%) (treatment status unknown in 5 cases)	0.043
Creatinine (mg/dl), median (IQR), n = 124	0.80 (0.72–0.93)	0.78 (0.71–0.92)	0.8 (0.7–1.1)	0.144
Renal dysfunction (creatinine > 1.2 mg/dl), n = 124	17 (13.7%)	4 (5.3%)	13 (18.8%)	0.023
CRP (mg/l), median (IQR)	2.1 (1.0–6.7)	1.8 (0.8–6.9)	2.4 (1.0–5.3)	0.745

CRP, C-reactive protein; IQR, interquartile range; no, number; NP, neuropsychiatric; NPSLE, neuropsychiatric systemic lupus erythematosus; SLE, systemic lupus erythematosus; y, years.
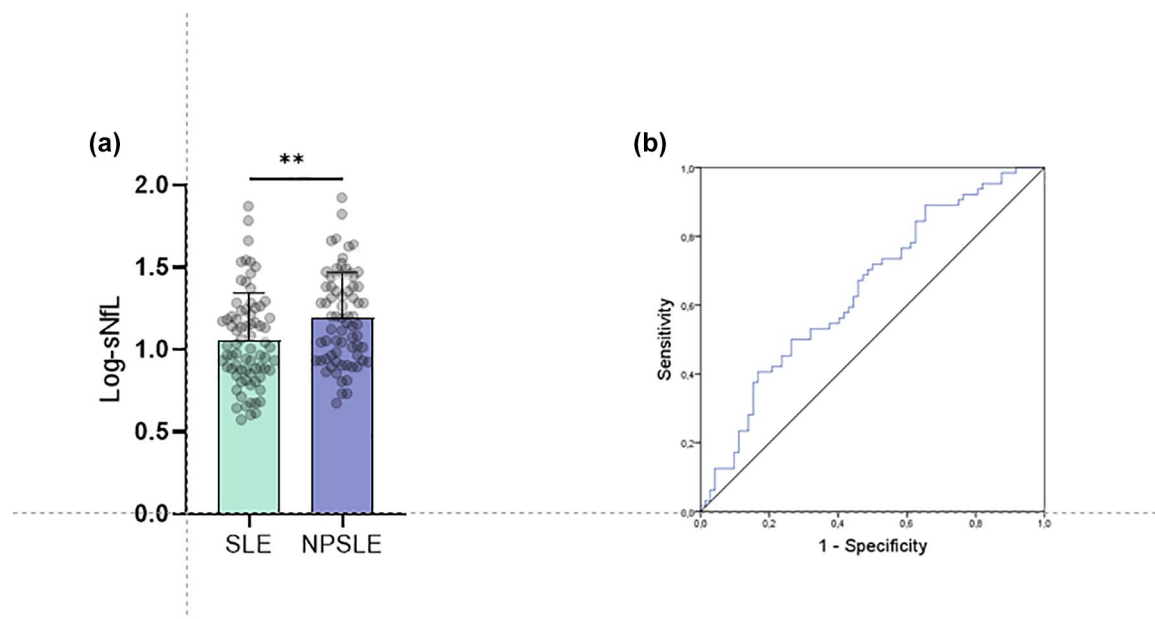

Figure 1. Comparison of sNfL levels between SLE and NPLSE patients. (a) Mean log-transformed sNfL levels are higher in NPSLE patients than in SLE patients without neuropsychiatric disease manifestation. The height of the columns marks the mean, whiskers depict the standard deviation. **A significance level of $p < 0.01$. (b) ROC analysis for the prediction of the presence of NPSLE manifestation exhibited an AUC of 0.646 (95% CI: 0.554–0.738, $p = 0.003$) for sNfL levels.
AUC, area under the curve; NPSLE, neuropsychiatric systemic lupus erythematosus; ROC, receiver operating characteristic; SLE, systemic lupus erythematosus; sNfL, serum neurofilament light chain.

The group of NPLSE with PNS manifestation included 10 patients [cranial neuropathy ($n = 1$), polyneuropathy ($n = 6$), mononeuropathy ($n = 1$), myasthenia gravis ($n = 2$)], the group of NPSLE with diffuse CNS manifestations included 14 patients [cognitive dysfunction ($n = 1$), mood and
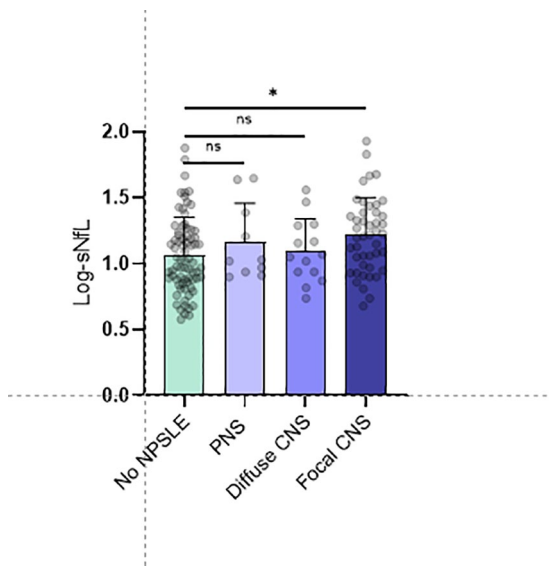
Figure 2. Comparison of sNfL levels between SLE patients and different neuropsychiatric SLE manifestations. Mean log-transformed sNfL levels are higher in NPSLE patients with focal CNS manifestation than in SLE patients without neuropsychiatric disease manifestation. The height of the columns marks the mean, whiskers depict the standard deviation. *A significance level of $p < 0.05$.
CNS, central nervous system; NPSLE, neuropsychiatric systemic lupus erythematosus; PNS, peripheral nervous system; SLE, systemic lupus erythematosus; sNfL, serum neurofilament light chain.

anxiety disorder ($n = 10$), headache ($n = 3$)], and the group of focal CNS manifestation included 45 patients (Supplemental Table). We then conducted a one-way ANOVA to assess the effects of different neuropsychiatric manifestations on log-sNfL levels [no neuropsychiatric manifestation (mean: 1.06, SD: 0.28), PNS manifestation ($n = 10$, mean: 1.19, SD: 0.29), diffuse CNS manifestation ($n = 14$, mean: 1.10, SD: 0.24), and focal CNS manifestation ($n = 45$, mean: 1.22, SD: 0.28)]. Log-sNfL levels differed significantly for the different categories of neuropsychiatric manifestations [$F_{(3,140)} = 3.20$, $p = 0.025$]. Tukey post hoc analysis revealed a significant difference between log-sNfL levels of the groups with no neuropsychiatric manifestation and patients with focal CNS manifestation (0.16, 95% CI: 0.02–0.30, $p = 0.019$; Figure 2).

To identify additional factors that contribute to sNfL levels in lupus patients, we first conducted bivariate correlation analyses. In these, sNfL levels demonstrated a moderate positive association with age ($r = 0.344$, $p < 0.001$) and renal function assessed by serum creatinine concentration ($r = 0.368$, $p < 0.001$). Furthermore, disease duration ($r = 0.243$, $p = 0.014$) and CRP levels ($r = 0.288$, $p = 0.004$) demonstrated a weak association with sNfL levels.

In a multiple linear regression model including sex, age, disease duration, presence of neuropsychiatric symptoms, creatinine and CRP levels, and presence of immunosuppressive treatment as independent variables, age (standardized coefficient $\beta = 0.246$) and creatinine concentration (standardized coefficient $\beta = 0.337$) were found to be significant predictors of sNfL levels (Table 2). The R^2 of the overall model was 0.223 [adjusted $R^2 = 0.171$; $F_{(7,104)} = 4.27$, $p < 0.001$].

Discussion

Owing to its heterogeneous character and lack of reliable biomarkers, diagnosing NPSLE is extremely challenging. In this study, sNfL levels were increased in SLE patients with neuropsychiatric manifestations in comparison to patients without such symptoms and could discriminate SLE from NPSLE patients moderately well. In addition, our data suggest that focal CNS manifestations particularly contribute to this sNfL level increase in NPSLE patients. However, age and renal function were identified as strong predictors of sNfL levels in multivariable analysis, and should, thus, be considered potential confounders.

The detection of antibodies against circulating neurofilaments in patients with NPSLE in the 1980s already led to the assumption that neuronal damage might have significance in the pathogenesis of neurological complications of SLE.[9,10] In line with this, CSF NfL levels were later found to be increased in SLE patients with CNS manifestations compared with SLE patients without CNS symptoms.[6] In this study, we were now able to demonstrate for the first time that NfL levels in serum can distinguish SLE patients with neuropsychiatric symptoms from those without.

In contrast to earlier detection methods, the measurement of sNfL offers the advantages of an easily accessible blood biomarker, which is currently being validated in a multitude of diseases with potential involvement of neuronal structures.[5] In multiple sclerosis, an autoimmune disease associated with

Table 2. Linear regression analysis for the prediction of log-sNfL levels.

Variable	b	SE(b)	β	t	95% lower CI	95% upper CI	p value
Intercept	0.751	0.189		3.977	0.377	1.126	<0.001
Sex	−0.006	0.075	−0.008	−0.086	−0.154	0.142	0.931
Age	0.005	0.002	0.246	2.539	0.001	0.009	0.013
Disease duration	0.004	0.003	0.141	1.491	−0.001	0.010	0.139
Neuropsychiatric phenomena	0.064	0.051	0.113	1.260	−0.037	0.165	0.211
Creatinine	0.090	0.023	0.337	3.838	0.044	0.137	<0.001
CRP	−0.001	0.003	−0.039	−0.445	−0.007	0.004	0.658
Immunosuppressive treatment	0.015	0.064	0.021	0.228	−0.112	0.141	0.820

CI, confidence interval; CRP, C-reactive protein; sNfL, serum neurofilament light chain.

demyelination and neurodegeneration, sNfL has been found to be useful in detecting and monitoring disease activity as well as treatment response.[11] Furthermore, sNfL levels were found to be increased up to 6 months after ischemic stroke,[12] and in cerebral vasculitis, marked increases of NfL levels even preceded the onset of arterial vessel abnormalities in magnetic resonance imaging (MRI).[13] As cerebrovascular disease, including CNS vasculitis, and demyelinating syndromes are among the potential manifestations of NPSLE,[3,14] these observations suggest that regular sNfL monitoring could be used to detect neuropsychiatric involvement early on, thereby promoting the initiation of adequate treatment before irretrievable neuronal loss leads to lasting functional impairment. In addition, the finding that successful therapy with cyclophosphamide was associated with corresponding NfL level decreases in a small group of NPSLE patients[6] warrants further investigations on sNfL as a potential treatment response biomarker.

In general, NfL level increases are unspecific as they may arise from any process resulting in neural damage, which is often viewed as an obstacle for the implementation of sNfL level assessment into clinical routine. However, in SLE, this presumed shortcoming might actually be beneficial because it enables the detection of a wide range of potential neuropsychiatric manifestations. Of note, our additional comparison of sNfL levels between different categories of neuropsychiatric involvement suggests that focal CNS involvement, including cerebrovascular disease, seizures, myelopathy, aseptic meningitis, movement disorders,

and demyelinating syndromes contribute most to the observed sNfL level elevation in NPSLE patients. This is not surprising as these manifestations, which are usually associated with structural changes in brain imaging, are accompanied by a more pronounced release of neurofilaments.[15,16] Therefore, sNfL level assessment might be most useful to detect early focal neuronal damage, whereas it might be less suitable to diagnose diffuse neuropsychiatric manifestations. However, this observation could have resulted partly from a potential selection bias, as only patients with confirmed neuropsychiatric involvement, which was identified by retrospective inspection of medical reports, were included in the NPLSE cohort. As focal CNS involvement can be more easily detected and is more likely attributable to SLE than diffuse neuropsychiatric syndromes like headaches and mood disorders, the latter population might have been underrepresented in this study.

For the interpretation of sNfL values on the individual patient's level, it is important to account for parameters that will likely impact sNfL concentrations. In line with findings of a large population-based cohort study,[17] we found a moderate association of increasing sNfL levels with older age. Interestingly, sNfL levels were also dependent on renal function assessed by serum creatinine concentrations. An association of renal function and sNfL has been demonstrated in a recent study in older adults and patients with diabetes. As potential explanations for this observation, it was hypothesized that

NfL might be cleared from the blood by the kidneys or that neuronal damage might be linked to decreased renal synthesis of erythropoietin and vitamin D, which are believed to exert neuroprotective effects.[18] Because nephritis is a common manifestation in lupus patients, our findings underline the importance of interpreting sNfL only in the context of renal function. Indeed, in our multivariable regression analysis, creatinine concentrations showed a significant association with sNfL levels, whereas the presence of neuropsychiatric symptoms was not able to predict sNfL levels in this model. The proportion of patients with renal dysfunction was higher in NPLSE patients, whereas the median serum creatinine concentrations did not differ between the groups. Therefore, the possibility of renal dysfunction as a potential confounder must be acknowledged.

The retrospective and observational character of this study leads to several major limitations. First, patient inclusion and classification into NPSLE groups were solely based on data obtained from available medical records. Although the diagnostic workup was thorough and patient classification was performed with great care, we cannot fully rule out the possibility that some patients with neuropsychiatric manifestations attributable to conditions other than SLE were included into the analyses. Second, the lack of standardized brain imaging and CSF assessment at the time point of serum sample collection prevented us from controlling sNfL levels for other potential confounders including lesion volume or presence of intrathecal inflammation. Furthermore, we were not able to evaluate the prognostic value of sNfL levels because standardized follow-up data were also unavailable. An additional prospective study, which addresses these limitations is planned to confirm the results of this exploratory study.

Conclusion

We believe that our current pilot findings underline the potential of sNfL as a promising candidate biomarker to complement the diagnostic workup of SLE patients with suspected involvement of the nervous system. However, additional prospective and longitudinal studies are needed to evaluate its significance in the clinical setting and to further address the question of renal function as a potential confounder.

Author contributions

The authors confirm contribution to the article as follows: study conception and design were by SE and FL; data collection was by SE, SB, PM, FS, AW, AS, JW-M, and FL; analysis and interpretation of results were by SE, SB, FZ, JW-M, and FL; draft article preparation was by SE, SB, and FL. Equal contributions are by senior authors JW-M and FL. All authors reviewed the results and approved the final version of the article.

Conflict of interest statement

The authors declared the following potential conflicts of interest with respect to the research, authorship, and/or publication of this article: SE, SB, PM, FS, and AW report no disclosures. SB has received honoraria and compensation for travel from Biogen Idec, Merck Serono, Novartis, Sanofi-Genzyme, and Roche. AS has received speaker fees and grant/research support by AbbVie, Novartis, Roche, and GSK. FZ has recently received research grants and/or consultation funds from DFG, BMBF, PMSA, MPG, Genzyme, Merck Serono, Roche, Novartis, Sanofi-Aventis, Celgene, ONO, and Octapharma. JW-M has acted as consultant to Genfit, Gilead Sciences, Intercept Pharmaceuticals, IQVIA, Madrigal, Pfizer, Novartis, Roche, and Siemens Healthineers and has received research funding from Gilead Sciences. FL received consultancy fees from Roche and support with travel cost from Teva Pharma.

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Supplemental material

Supplemental material for this article is available online.

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