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Original research

Serum neurofilament light chain levels at attack predict post-attack disability worsening and are mitigated by inebilizumab: analysis of four potential biomarkers in neuromyelitis optica spectrum disorder

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ABSTRACT

Objective To investigate relationships between serum neurofilament light chain (sNfL), ubiquitin C-terminal hydrolase L1 (sUCHL1), tau (sTau) and glial fibrillary acidic protein (sGFAP) levels and disease activity/disability in neuromyelitis optica spectrum disorder (NMOSD), and the effects of inebilizumab on these biomarkers in N-MOMentum.

Methods N-MOMentum randomised participants to receive inebilizumab or placebo with a randomised controlled period (RCP) of 28 weeks and an open-label follow-up period of ≥ 2 years. The sNfL, sUCHL1, sTau and sGFAP were measured using single-molecule arrays in 1260 scheduled and attack-related samples from N-MOMentum participants (immunoglobulin G (IgG) autoantibodies to aquaporin-4-positive, myelin oligodendrocyte glycoprotein-IgG-positive or double autoantibody-negative) and two control groups (healthy donors and patients with relapsing–remitting multiple sclerosis).

Results The concentration of all four biomarkers increased during NMOSD attacks. At attack, sNfL had the strongest correlation with disability worsening during attacks (Spearman $R^2=0.40$; $p=0.01$) and prediction of disability worsening after attacks (sNfL cut-off 32 pg/mL; area under the curve 0.71 (95% CI 0.51 to 0.89); $p=0.02$), but only sGFAP predicted upcoming attacks. At RCP end, fewer inebilizumab-treated than placebo-treated participants had sNfL > 16 pg/mL (22% vs 45%; OR 0.36 (95% CI 0.17 to 0.76); $p=0.004$).

Conclusions Compared with sGFAP, sTau and sUCHL1, sNfL at attack was the strongest predictor of disability worsening at attack and follow-up, suggesting a role for identifying participants with NMOSD at risk of limited post-relapse recovery. Treatment with inebilizumab was associated with lower levels of sGFAP and sNfL than placebo.

Trial registration number NCT02200770.

INTRODUCTION

Neuromyelitis optica spectrum disorder (NMOSD) is a rare autoimmune inflammatory disease of the

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Neuromyelitis optica spectrum disorder (NMOSD) is characterised by incremental permanent disability; thus, availability of biomarkers as indicators of the presence and progression of NMOSD is highly desirable. The aim of this study was to investigate the potential relationship between four putative biomarkers and disease activity/disability in participants from the N-MOMentum study and to assess the impact of inebilizumab treatment on their observed concentrations.

WHAT THIS STUDY ADDS

⇒ Serum neurofilament light chain measured at attack was the best predictor among biomarkers studied for disability worsening during and after attacks but was inferior to serum glial fibrillary acidic protein in prediction of future attacks. Compared with placebo, treatment with inebilizumab attenuated the elevation of biomarkers during attacks and reduced levels of these biomarkers over time in the absence of adjudicated attacks.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ These findings may help to inform progress towards assessment of clinical status, prognosis and treatment decisions for patients with NMOSD by means of routine measurement of biomarkers.

central nervous system (CNS) characterised by attacks of optic neuritis, transverse myelitis and, less commonly, brain or brainstem inflammation.¹ Attacks are thought to be caused by astroglial injury resulting in secondary demyelination and substantial tissue injury.² Incremental damage occurs in the context of acute attacks, which can be severe and cause permanent disability due to incomplete recovery; in contrast to multiple sclerosis (MS),

progressive worsening of disability independent of attacks is rare.³

Immunoglobulin G (IgG) autoantibodies to aquaporin-4 (AQP4-IgG) are pathogenic; up to 90% of patients with NMOSD are AQP4-IgG seropositive (AQP4+).^{4,5} In the CNS, AQP4-IgG binds to the extracellular domain of AQP4 expressed in the astrocyte, resulting in astrocytic damage through complement-mediated and complement-independent mechanisms.^{6,7} Damaged astrocytes compromise trophic support for surrounding oligodendrocytes and neurons, presumably leading to secondary inflammation, demyelination and axonal loss.⁸ Experimental data also suggest that AQP4-IgG induces cytokine production, increasing blood–brain barrier permeability.⁹

Identifying biomarkers as indicators of the presence and course of disease promises to improve diagnosis and management of neurological conditions such as NMOSD.¹⁰ Soluble glial fibrillary acidic protein (GFAP), an abundant cytoskeletal intermediate filament in astrocytes, is released into cerebrospinal fluid (CSF) and serum following astroglial injury.¹¹ Serum GFAP (sGFAP) was previously found to correlate strongly with NMOSD attacks,^{12–14} including attack prediction.¹⁴ Neurofilaments are structural proteins, exclusively expressed in neurons, forming an essential part of the cytoskeletal scaffold.¹⁵ Axonal damage leads to elevated CSF and serum concentrations of neurofilament light chain (NfL) in the CSF and serum.¹⁶ NfL was validated as a highly sensitive biomarker of neuroaxonal damage, regardless of cause,¹⁷ and serum NfL (sNfL) is a biomarker of neuronal injury in various neurodegenerative diseases, as well as in NMOSD.^{12,13,15,18,19}

Ubiquitin C-terminal hydrolase L1 (UCHL1) is a highly abundant neuron-specific protein that forms part of the ubiquitin proteasome system of protein degradation.²⁰ Tau forms an important part of the microtubule structure in the axonal cytoskeleton.²¹ Neuronal damage causes release of UCHL1 and tau into CSF and plasma, and elevated serum levels have been observed in several neurological and neurodegenerative diseases, including Alzheimer's disease, epilepsy and MS.^{15,22} GFAP, NfL, tau and UCHL1 concentration detection was previously limited to CSF; however, development of highly sensitive, single-molecule array (SIMOA) technology (Quanterix; Lexington, Massachusetts, USA) has allowed for reliable serum measurement.

N-MOmentum was a randomised, placebo-controlled, double-blind, phase 2/3 trial assessing the efficacy and safety of inebilizumab, an anti-CD19, B-cell-depleting antibody, in participants with NMOSD.^{1,23} The aim of the current study was to investigate potential relationships between sGFAP, sNfL, serum tau (sTau) and serum UCHL1 (sUCHL1), and disease activity in N-MOmentum study participants and to assess the impact of inebilizumab on concentrations of these putative biomarkers.

METHODS

Study design and participants

sGFAP, sNfL, sUCHL1 and sTau concentrations were assessed in N-MOmentum participants,²³ a healthy donor reference cohort, and patients with relapsing–remitting MS (RRMS).²⁴

Full details of N-MOmentum have been published previously.²³ In brief, adults with AQP4+ or AQP4-IgG seronegative (AQP4–)²⁵ NMOSD, an Expanded Disability Status Scale (EDSS) score of 8.0 or less and a recent history of NMOSD attack were eligible (see online supplemental methods).²³

Participants were randomly assigned (3:1) to receive intravenous inebilizumab 300 mg or placebo (saline) administered on

days 1 and 15 of the randomised controlled period (RCP). The RCP lasted for 28 weeks or until adjudicated attack occurrence. Attacks, defined by protocol-defined criteria, were adjudicated based on neurological evaluations and MRI data (on a criteria-dependent basis) by an independent expert committee during the 17 days post-attack. Attack severity was graded according to a modified version of the Opticospinal Impairment Scale (OSIS) that characterises attacks as major or minor based on changes in domain-specific scores for neurological function.^{26–28} Attack recovery assessment was performed 28 days post-attack and graded according to change in the same domain-specific scores relative to the score at time of attack. Disability was assessed using the EDSS and modified Rankin Scale (mRS).²⁸ Depending on baseline EDSS score, participants were considered to have a worsening EDSS score if they had a worsening of ≥ 2 points (baseline=0 points), ≥ 1 points (baseline=1–5 points) or ≥ 0.5 points (baseline ≥ 5.5 points).

Two reference cohorts of individuals without NMOSD were used as controls: one comprising age-matched and sex-matched healthy donors (n=85) and another comprising untreated patients with moderate-to-severe RRMS (baseline EDSS score >3.5; n=23) from the USA and Europe.²⁴

Standard protocol approvals, registrations and participant consent

Participants were screened at 99 outpatient specialty clinics or hospitals in 25 countries. Institutional review boards or ethics committees at study sites approved the protocol. The study is registered with ClinicalTrials.gov (NCT02200770), and was conducted in accordance with the provisions of the International Council for Harmonisation Guidelines for Good Clinical Practice and the principles of the Declaration of Helsinki in its currently applicable version.

Assessment of concentrations of biomarkers of CNS damage

Blood samples were collected from N-MOmentum participants during RCP study visits on days 1 (baseline), 15, 29, 57, 85, 113, 155 and 197, and during any assessment visit for new or worsening NMOSD symptoms. In the reference cohorts,²⁴ participants were untreated and blood was collected at the single baseline visit. Ten healthy donors underwent repeated longitudinal sampling for serial biomarker measurements. As validated in serum samples from patients with MS or traumatic brain injury,^{29,30} biomarker concentrations were determined using the SIMOA assay. Quantification of sNfL, sTau and sUCHL1 was performed using 'Neurology 4-plex B' kits run on the SIMOA HD-X Analyzer, and also included sGFAP. In-depth analysis of the N-MOmentum sGFAP data set was recently reported, focusing on attack severity and prediction.¹⁴ This data set is also included in the current study for comparison with the other biomarkers that focus on long-term disability. Assays for all four biomarkers were undertaken in parallel on the same SIMOA assay plate. Elevated serum biomarker concentrations were defined as being more than two SDs above the healthy donor mean (sGFAP: >170 pg/mL, sNfL: >16 pg/mL, sTau: >1.3 pg/mL and sUCHL1: >52 pg/mL) according to established laboratory procedures³¹; two healthy donors were outliers (according to the 95% trend/mean SD rule) and excluded from analyses for all biomarkers measured.

Statistical analyses

The current analyses are exploratory and are for hypothesis generation only (see online supplemental methods for full

details). In brief, the utility of biomarker concentrations at baseline and at time points during the RCP as a predictor of future attack risk was assessed using multivariate Cox proportional hazards regression. The Wilcoxon signed-rank test was used to evaluate statistical significance of increases of each biomarker from each time point to attack in paired samples.

A mixed-effects logistic regression model was used to evaluate statistical significance of elevated biomarker concentrations in attack samples versus samples drawn during scheduled visits; sensitivity analyses were conducted to assess the performance of the model across participants in different treatment arms and in those who did or did not experience attacks during the RCP.

Correlations between changes in EDSS scores, EDSS component scores and biomarker concentrations from baseline to attack were evaluated using Spearman's Rho. Multiple linear regression was used to assess independent correlation of each biomarker with EDSS score change at attack and preceding attack after controlling for baseline EDSS score and age. The Mann-Whitney U test was used to further evaluate statistical significance of biomarker changes and the occurrence/absence of protocol-defined EDSS score worsening.

The significance of changes in biomarker concentrations from baseline to attack was evaluated in both RCP treatment groups using the Wilcoxon signed-rank test. Fold changes from baseline between treatment groups and in participants who did or did not experience attacks were assessed using the Mann-Whitney U test. Significance of changes in sNfL concentrations between treatment groups was also assessed using a mixed linear model including baseline sNfL, EDSS score and age as covariates and a per-subject random intercept term. All statistical analysis was performed in R V.4.1.3.

Data availability

Study data will be made available to others (see online supplemental methods). For more information, or to submit a request, please email: medicalinformation@horizontherapeutics.com.

RESULTS

Study participants

The trial profile for N-MOmentum and full details of participant demographics who provided biomarker samples were reported.^{14,23} In total, 215 participants provided 1260 serial and NMOSD attack-related samples for biomarker concentration analysis. Most participants were women (194/215 (90.2%)) and approximately half were white (110/215 (51.2%)). At baseline, 198 participants (92.1%) were AQP4+, 7 (3.3%) were seropositive for myelin oligodendrocyte glycoprotein-immunoglobulin G (MOG+), and 10 (4.7%) had no detectable autoantibodies for AQP4 or myelin oligodendrocyte glycoprotein (MOG) (double-negative participants). Demographics were similar in the inebilizumab (n=164) and placebo (n=51) groups.¹⁴

CNS damage biomarker concentrations increase during NMOSD attacks

Significant increases in all four biomarkers were observed in serum samples taken from the whole cohort in the week before, on the day of and during the week following adjudicated attacks (figure 1); every participant had at least one EDSS assessment after an attack therefore guarding against bias introduced by informative censoring of participants who withdrew from the trial following attack. Mean sGFAP and sNfL concentrations increased above the defined elevated concentration (ie, >2 SDs from healthy donor means) during the week following clinical attack onset, while mean

sTau and sUCHL1 concentrations remained below elevated levels at all time points assessed. Mean sNfL levels remained elevated in samples taken after (>7 days) attack onset, in contrast to sGFAP, which returned to baseline levels (figure 1A–B). Locally estimated scatterplot smoothing regression lineplots of biomarker changes in relation to time of attack show similar results (online supplemental figure 1). These attack-related biomarker patterns were obvious for AQP4+ participants, but not for MOG+ or double-negative participants.

Among 198 AQP4+ participants with available biomarker data, there were 32 adjudicated attacks. Twelve participants had a more than twofold change in sNfL (3 had a more than twofold change in sNfL but not in sGFAP), 20 had a more than twofold increase in sGFAP (11 had a more than twofold increase in sGFAP but not in sNfL) and 9 did not have a corresponding increase of more than twofold in sGFAP or sNfL. Additionally, outside of attacks, 4 participants had a more than twofold change in sNfL alone, 15 in sGFAP alone and 3 in both sGFAP and sNfL. As a sensitivity analysis, a mixed-effects model for logistic regression was used to account for relevant variables and recurrent measurements in one model. The results were similar, with sGFAP, sNfL and sTau showing statistically significant associations with attacks (online supplemental eTable 1).

Biomarkers of CNS damage are elevated in patients with NMOSD and may be predictive of upcoming attacks

In participants with NMOSD, sGFAP concentrations were elevated at baseline versus healthy donors and patients with RRMS (30% of AQP4+ participants had sGFAP concentrations >2 SDs above healthy donor means vs 14% of MOG+ patients, 10% of double-negative patients, 9% of those with RRMS and 3.5% of healthy donors) (figure 2A). Similarly, elevated sNfL levels were observed in 37% of AQP4+ patients, 43% of MOG+ participants, 10% of double-negative patients, 26% of those with RRMS and 3.5% of healthy donors (figure 2B). The proportions of participants with elevated baseline sTau and sUCHL1 concentrations, or with increased serum GFAP:NfL ratios, were similar in the three N-MOmentum populations (figure 2C–E).

Regression analysis performed in the AQP4+ participants demonstrated that elevated biomarker concentrations in the day 1 RCP sample equated to HRs for an adjudicated NMOSD attack during the RCP of 0.78–2.56, although only the highest value, obtained for sGFAP, was significant (figure 2F); time between day 1 of the RCP and last attack ranged from 3 to 199 days. Similarly, the likelihood ratio test on nested Cox regression models (sGFAP vs all four biomarkers) lacked statistical significance ($\chi^2=5.22$; $p=0.16$), indicating that biomarkers other than sGFAP did not contribute added value as predictors of upcoming attack risk (online supplemental eTable 2).

When AQP4+ participants in the two treatment arms of N-MOmentum were stratified according to respective cut-off values for sGFAP, sNfL, sTau and sUCHL1, those with elevated baseline values in the inebilizumab group had a significantly higher likelihood of experiencing an attack during the RCP than those without elevations. In the placebo group, a similar trend in AQP4+ participants was observed for sGFAP ($p=0.067$); however, differences in the Kaplan-Meier curves for all four biomarkers lacked statistical significance (online supplemental efigure 2). For all AQP4+ placebo- and inebilizumab-treated participants, broadly similar findings were observed for sNfL, sTau and sUCHL1 in heat maps of day 1 CNS biomarker concentrations in the subsets of participants who experienced attacks during the RCP (online supplemental efigure 3).

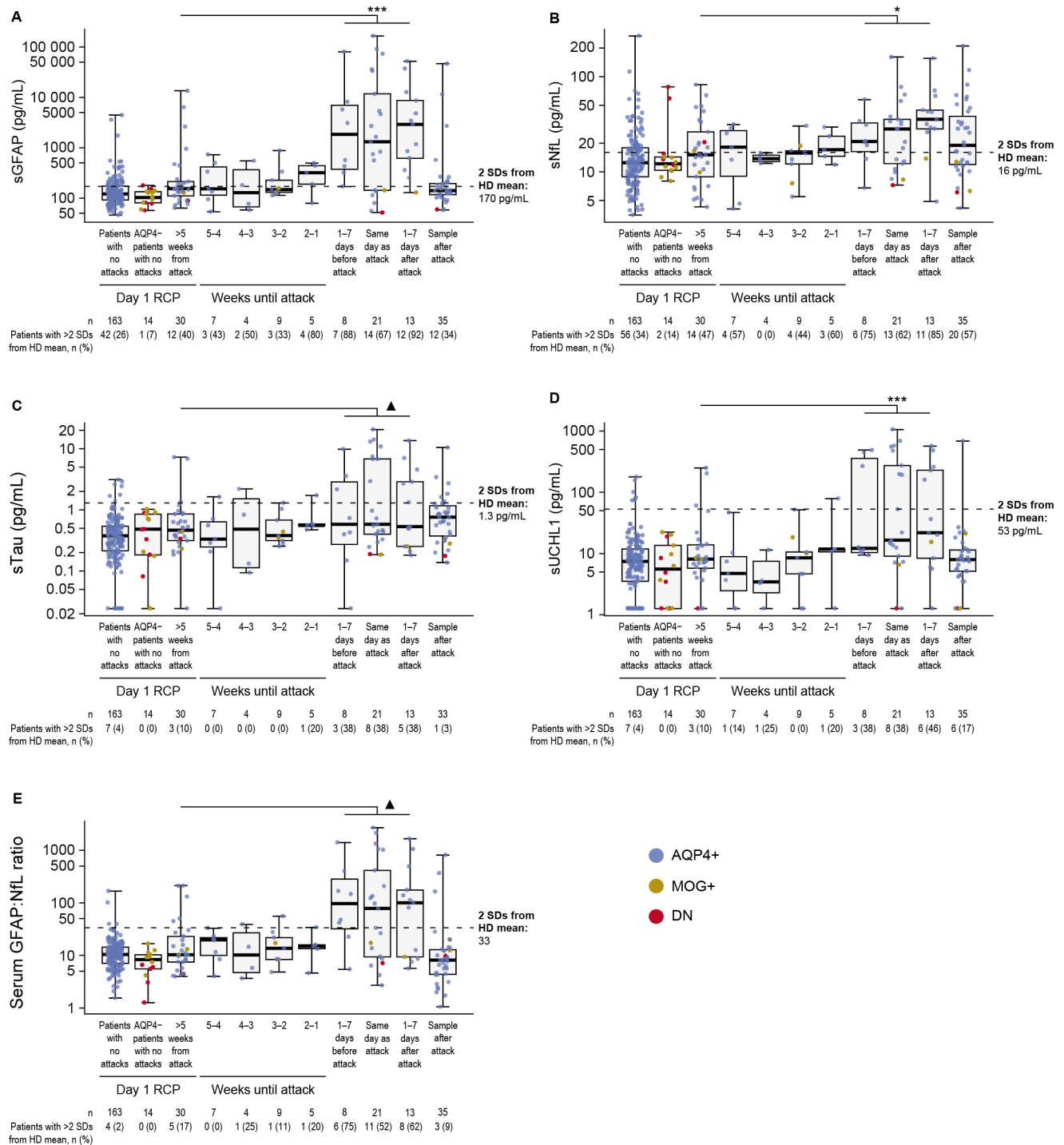


Figure 1 Boxplots displaying (A) sGFAP, (B) sNfL, (C) sTau, (D) sUCHL1 and (E) serum GFAP:NfL ratio in samples drawn during the lead-up to an NMOSD attack and in day1/RCP samples drawn >5 weeks from the attack in participants who experienced an NMOSD attack during the RCP. Horizontal dotted lines show 2 SDs from the mean of the HD control cohort; sGFAP, 170 pg/mL; sNfL, 16 pg/mL; sTau, 1.3 pg/mL; sUCHL1, 53 pg/mL; sGFAP:sNfL ratio, 33. Note the differing y-axis scales, particularly the logarithmic scale for sGFAP. Median (IQR) attack follow-up was at 108 (27–124) days. ▲*p*<0.10; **p*<0.05; ***p*<0.01; ****p*<0.001, Wilcoxon signed-rank test, samples drawn at baseline versus 1 week until attack. AQP4+, seropositive for immunoglobulin G autoantibodies to aquaporin-4; AQP4-, seronegative for immunoglobulin G autoantibodies to aquaporin-4; DN, double-negative; GFAP, glial fibrillary acidic protein; HD, healthy donor; MOG+, seropositive for myelin oligodendrocyte glycoprotein-immunoglobulin G; NfL, neurofilament light chain; NMOSD, neuromyelitis optica spectrum disorder; RCP, randomised controlled period; sGFAP, serum glial fibrillary acidic protein; sNfL, serum neurofilament light chain; sTau, serum tau; sUCHL1, serum ubiquitin C-terminal hydrolase L1.

Biomarkers other than sGFAP do not add value in identifying attacks

Assessment of biomarker concentrations in the context of attacks and attack severity demonstrated that sNfL, sTau and sUCHL1

were not as sensitive in predicting attacks or attack severity as was sGFAP. Notably, 37.5% of participants (3/8) without elevated sGFAP during an attack had elevated sNfL; sTau and sUCHL1 elevations did not occur in the absence of increased sGFAP

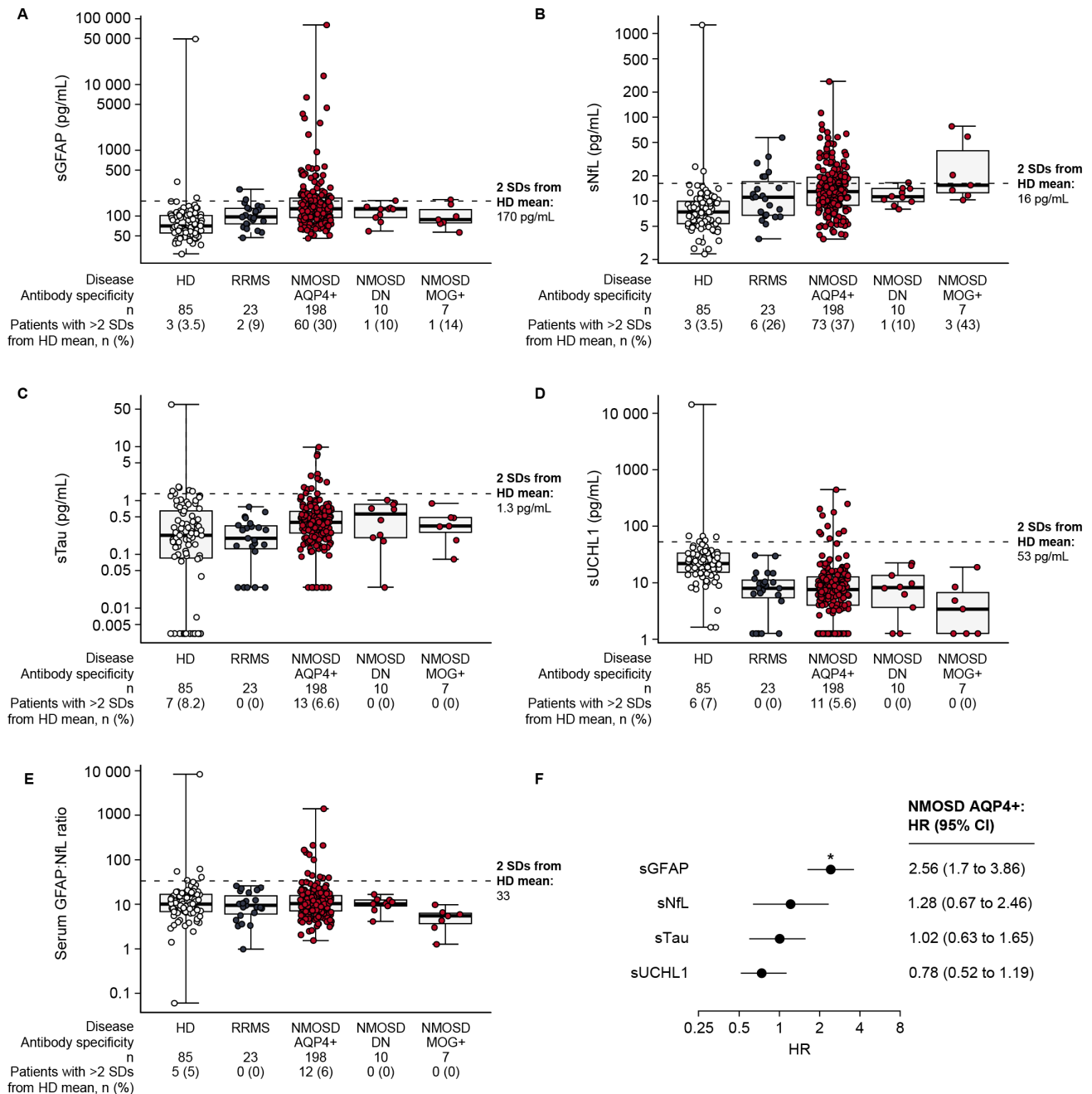


Figure 2 Boxplots of day 1/RCP serum CNS damage biomarkers relative to HDs. (A) sGFAP, (B) sNfL, (C) sTau, (D) sUCHL1 and (E) serum GFAP:NfL ratio. Patients were determined to be ‘high’ for each cut-off based on levels being higher than two SDs from the mean of the HD cohort. Horizontal dotted line in each case represents the threshold for 2 SDs from the HD mean; sGFAP, 170 pg/mL; sNfL, 16 pg/mL; sTau, 1.3 pg/mL; sUCHL1, 53 pg/mL; sGFAP:sNfL ratio, 33. (F) Forest plot of Cox regression coefficients from model fit using day 1/RCP CNS damage biomarker concentrations as predictors of RCP attack risk in AQP4+ participants. Note the differing logarithmic y-axis scales, particularly the scale for sGFAP. HR for sGFAP, * $p < 0.05$. AB, antibody; AQP4+, seropositive for immunoglobulin G autoantibodies to aquaporin-4; CNS, central nervous system; DN, double-negative; GFAP, glial fibrillary acidic protein; HD, healthy donor; MOG+, seropositive for myelin oligodendrocyte glycoprotein-immunoglobulin G; NfL, neurofilament light chain; NMOSD, neuromyelitis optica spectrum disorder; RCP, randomised controlled period; RRMS, relapsing–remitting multiple sclerosis; sGFAP, serum glial fibrillary acidic protein; sNfL, serum neurofilament light chain; sTau, serum tau; sUCHL1, serum ubiquitin C-terminal hydrolase L1.

(figure 3A). Logistic regression analysis demonstrated that the predictive capability of the biomarkers assessed was equal to or worse than the predictive capability of sGFAP alone in predicting attacks in AQP4+ participants (figure 3B and C). These findings were not observed in AQP4– participants (figure 3A).

sNfL is the strongest correlate of changes in disability

A correlation analysis between biomarker concentrations and three measures of disability in the N-MOMentum study (EDSS,

OSIS^{26 27} and mRS²⁸) was undertaken in AQP4+ participants. sNfL correlated significantly with changes in ambulation subscale scores (Spearman $R = 0.58$ (95% CI 0.24 to 0.92)) and pyramidal functional system scores (Spearman $R = 0.46$ (95% CI 0.12 to 0.80)) of the EDSS during attack assessments (figure 4A). Increased biomarker concentrations generally correlated with OSIS scores (figure 4B). Compared with the other biomarkers, sNfL was more sensitive for myelitis events but less sensitive for

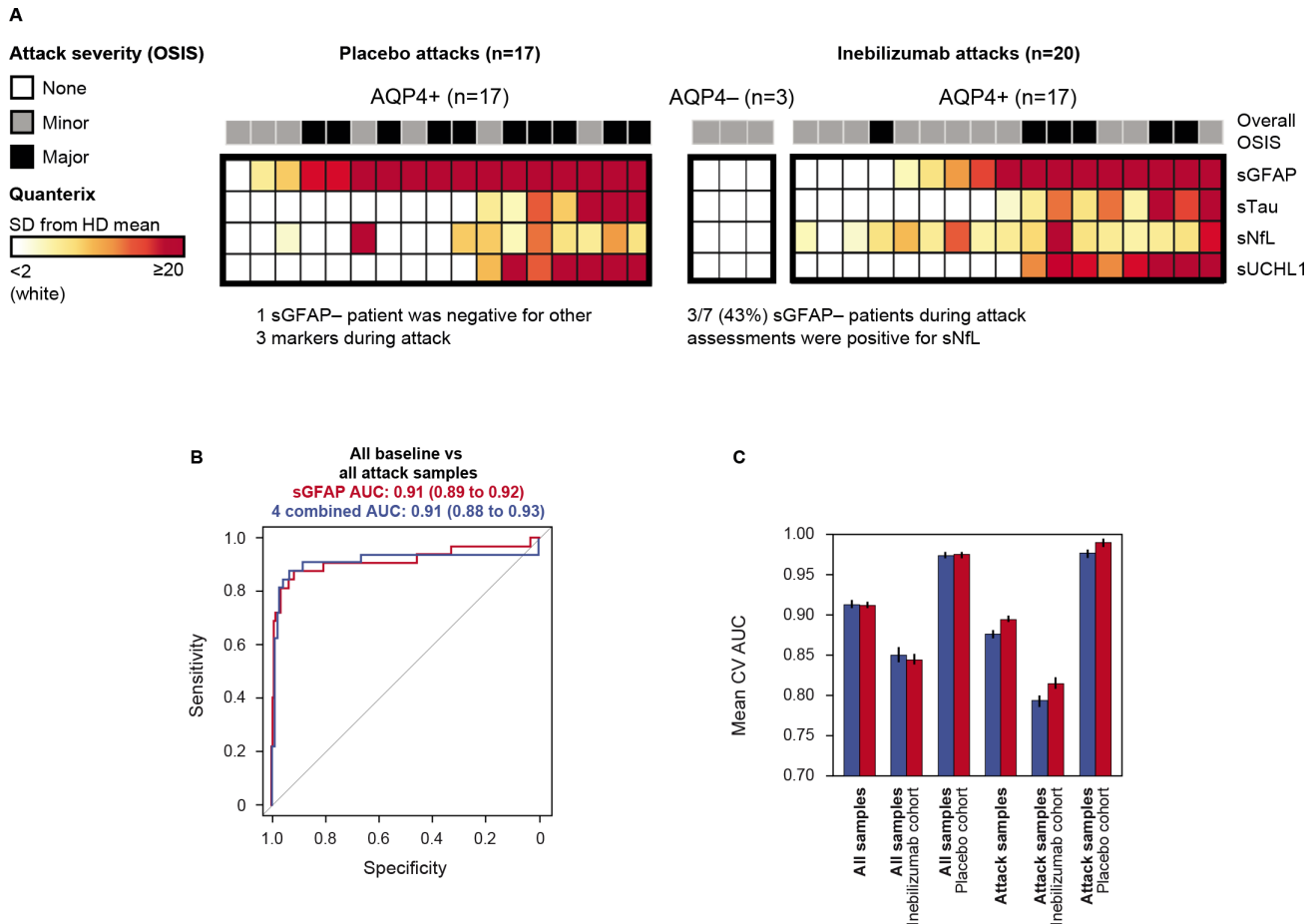


Figure 3 (A) Heatmap displaying concentration of CNS damage markers relative to HD reference cohort in samples drawn most proximal (+/- 7 days) to NMOSD attack in placebo-treated participants (left) and inebilizumab-treated participants (right). Heatmaps ordered by sGFAP concentration. (B) Mean ROC curves for out-of-fold predictions from 10 iterations of fivefold cross validation for mixed-effect logistic regression model fit to identify 37 attack samples versus remaining samples drawn during the study using sGFAP alone (red) versus all four CNS markers (blue) as predictors. (C) Sensitivity analysis displaying mean (+/- SEM) AUC from out-of-fold predictions for both models for all samples, samples drawn from the inebilizumab cohort and placebo cohort separately, then for those samples drawn from participants who experienced attacks during the RCP. One participant had a missing attack sample. AQP4+, seropositive for immunoglobulin G autoantibodies to aquaporin-4; AQP4-, seronegative for immunoglobulin G autoantibodies to aquaporin-4; AUC, area under the curve; CNS, central nervous system; CV, coefficient of variation; HD, healthy donor; NMOSD, neuromyelitis optica spectrum disorder; OSIS, Opticospinal Impairment Scale; RCP, randomised controlled period; ROC, receiver operator curve; sGFAP, serum glial fibrillary acidic protein; sNfL, serum neurofilament light chain; sTau, serum tau; sUCHL1, serum ubiquitin C-terminal hydrolase L1.

optic neuritis events. sNfL was the only biomarker to correlate with changes in mRS scores (figure 4C). Correlation analysis revealed that, of the four biomarkers, sNfL was the strongest correlate of EDSS scores (Spearman R=0.40 (95% CI 0.06 to 0.74)) (figure 4D, online supplemental eTable 3).

We explored whether elevated sNfL at attack predicted EDSS score worsening at follow-up assessments in AQP4+ participants, because elevated sNfL during attacks correlated with EDSS score changes during attack assessments. All participants were followed up at week 26 of the open-label period (OLP) (median (±IQR): 108 (27–124) days). Participants who displayed EDSS score worsening at follow-up had elevated sNfL (area under the curve: 0.71 (95% CI 0.51 to 0.89)). A cut-off of sNfL 32 pg/mL at attack optimally distinguished those with EDSS score worsening from those without at follow-up (figure 4E). We then assessed whether sNfL concentrations at attack were indicative of EDSS score worsening in the longer term. Median (IQR) sNfL concentration was higher in placebo-treated participants with EDSS score worsening at attack follow-up and confirmed at 3 months (3-month confirmed disability progression (CDP);

n=5, 55.3 (34.1–62.7) pg/mL) compared with the one participant with EDSS score worsening at attack follow-up but not confirmed at 3 months (35.6 pg/mL) or those with no EDSS score worsening at attack follow-up (n=11, 13.50 (10.31–26.10) pg/mL). In inebilizumab-treated participants, only one had EDSS score worsening with 3-month CDP. No statistical analysis was possible owing to the low sample size. Other CNS biomarkers were not significantly associated with EDSS score changes during attack or follow-up after controlling for sNfL changes in a multiple regression model. A mixed linear model of sNfL concentration versus EDSS score at attack and at attack follow-up was run as a sensitivity analysis and confirmed the correlation between these two variables after controlling for age and baseline disability score (online supplemental eTable 4).

Inebilizumab-treated participants had lower CNS damage biomarker levels than placebo-treated participants

sNfL levels were significantly lower in inebilizumab-treated than in placebo-treated AQP4+ participants (figure 5A). At the end of

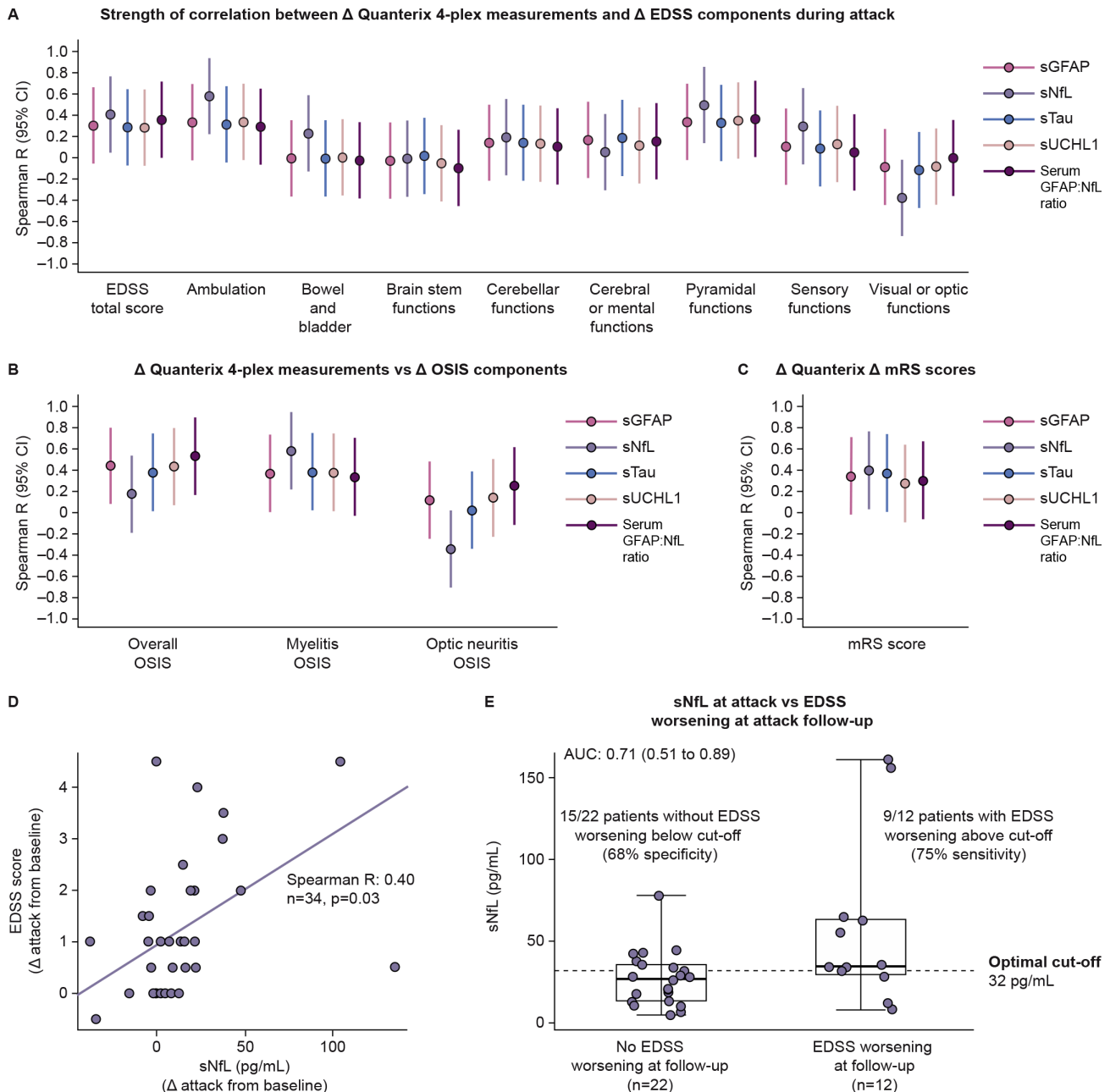


Figure 4 (A–C) Forest plots displaying strength of correlation between change from baseline in concentration of CNS damage biomarkers and change from baseline in (A) EDSS component scores, (B) the OSIS components scores and (C) mRS scores in AQP4+ participants. (D) Scatterplot displaying correlation between changes from baseline to attack in sNfL and EDSS scores during attack assessments. (E) Box and whisker plot displaying distribution of sNfL changes from baseline in participants who displayed EDSS score worsening at attack follow-up versus those who did not experience EDSS score change at follow-up. Optimal cut-off point determined using Youden's index. Attack follow-up was (median (\pm IQR)) 108 (27–124) days. AUC, area under the curve; CNS, central nervous system; EDSS, Expanded Disability Status Scale; GFAP, glial fibrillary acidic protein; mRS, modified Rankin Scale; OSIS, Opticospinal Impairment Scale; sGFAP, serum glial fibrillary acidic protein; sNfL, serum neurofilament light chain; sTau, serum tau; sUCHL1, serum ubiquitin C-terminal hydrolase L1.

the RCP, fewer participants receiving inebilizumab than placebo (22% vs 45%; OR 0.36 (95% CI 0.17 to 0.76), $p=0.004$, Fisher's exact test) had sNfL values above 16 pg/mL.

At the end of the RCP, inebilizumab-treated attack-free participants had significantly lower sNfL levels than attack-free participants receiving placebo (figure 5B, online supplemental file 2 eTable 5). Levels of the other three biomarkers in attack-free participants were also numerically lower after inebilizumab (online supplemental figure 4).

Finally, in participants who experienced an attack during the RCP (figure 5C), sNfL levels were lower in inebilizumab-treated than in placebo-treated patients after the end of the RCP (week 26 OLP, $p=0.03$ for median fold change from baseline between the two treatment groups). Elevated levels of the other three biomarkers were observed at the time of attack, with sGFAP reaching statistical significance ($p=0.037$ for median fold change from baseline between the two treatment groups) (online supplemental figure 5).

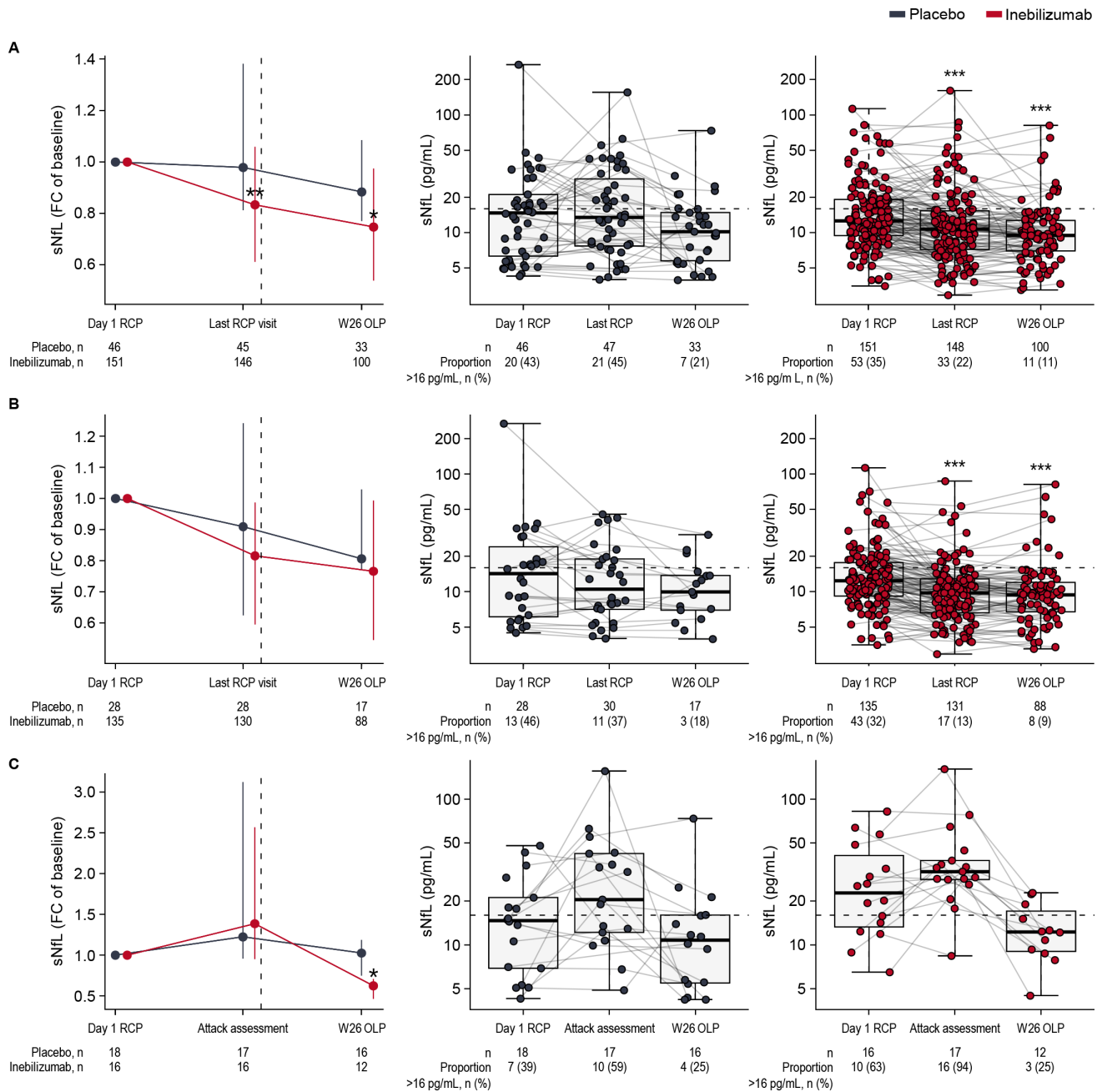


Figure 5 (A) Median (+/– IQR) fold change from baseline of sNfL in inebilizumab-treated and placebo-treated participants. Significance of changes between treatment groups assessed using Mann-Whitney U test. Boxplots of sNfL concentrations in (B) participants who did not experience RCP attacks and (C) those who did experience RCP attacks. Dashed vertical lines show when all participants received inebilizumab therapy at the end of the RCP and start of the OLP. Dashed horizontal lines show the threshold for elevated sNfL concentrations. Significance of changes from baseline in each treatment group was assessed using the Wilcoxon-signed rank test; *p<0.05; **p<0.01; ***p<0.001. FC, fold change; OLP, open-label period; RCP, randomised controlled period; sNfL, serum neurofilament light chain; W, week.

Analysis using a mixed-effects linear model to assess the impact of inebilizumab on sNfL concentrations similarly showed significant decreases at week 28 of the RCP and during attack assessments in inebilizumab-treated participants (online supplemental eTable 5).

DISCUSSION

Serum levels of CNS tissue injury biomarkers (GFAP, NfL, tau and UCHL1) increased during NMOSD attacks, reflecting CNS damage associated with the clinical event. Concentrations of the biomarkers (especially sGFAP, sNfL and sUCHL1)

increased during the days before the attack, which is consistent with the hypothesis that attacks are caused by accumulation of underlying tissue damage, ultimately culminating in clinical manifestations.

The correlation between sNfL levels and EDSS scores at attack support a direct link between neuroaxonal loss and disability worsening in NMOSD attacks. Assessment of sNfL during an attack could help to inform clinicians about attack severity and the likelihood of post-attack residual disability, and therefore may have the potential to guide therapeutic interventions at the time of attack.^{32–35}

Follow-up studies could assess potential clinical benefits of triaging patients with high sNfL at attack onset for immediate plasmapheresis rather than awaiting the outcome of standard treatment with corticosteroids alone. Determining the clinical utility of sNfL for NMOSD attack management requires further investigation.

sGFAP levels have been linked to attack severity, inflammatory damage and disability worsening in NMOSD.¹⁴ The results presented here, however, indicate that sNfL is a stronger biomarker of NMOSD-related disability than sGFAP. Additionally, the correlation between sNfL levels at attack and disability worsening at follow-up may reflect attack severity, with more severe attacks associated with higher sNfL levels and increased risk of residual disability. Another interpretation is that neuronal damage may not be limited solely to acute attacks but may also occur during apparent clinical remission. Limited data are available from the literature to support or refute this hypothesis. Studies longitudinally assessing the visual pathway in patients with NMOSD observed attack-independent deterioration, suggesting neurodegeneration.^{36 37} Cross-sectional sample collection studies have demonstrated a lack of significant reduction in sNfL levels between relapse and remission phases,¹² and a slower reduction in sNfL levels during remission phases in NMOSD versus MS.¹³ In a recent small longitudinal Korean study (n=20), however, inter-attack sNfL elevations were not observed in 14 patients whose disease was clinically stable for at least 24 months following rituximab treatment.³⁸

The N-MOmentum data and those of other groups^{12 13} contrast with other recent study results of sGFAP and sNfL in patients with AQP4+ NMOSD. In a prospective cohort of 33 patients, median baseline sGFAP was not elevated compared with MOG+ patients and healthy donors, and baseline sNfL levels did not differ substantially between groups. In contrast to N-MOmentum findings, only elevated sGFAP, and not elevated sNfL, predicted a future attack and was significantly associated with worse clinical disability scores, including EDSS scores.³⁹ These discordant findings may be explained by the time period between the most recent clinical attack and blood sampling (median: 26³⁹ vs 4 months¹³), patients with quiescent versus active disease, and different immunotherapies included in each study.^{13 14 39}

Compared with placebo, participants treated with inebilizumab had smaller biomarker elevations during attacks, likely reflecting overall less severe attacks, as previously described for inebilizumab.²³ At the end of the RCP, sNfL levels were significantly lower with inebilizumab than with placebo. Furthermore, in the absence of attack, sGFAP levels were significantly lower with treatment. This evidence for a putative effect of inebilizumab on disease severity is reinforced by previous results that showed more favourable disability outcomes with inebilizumab than with placebo.²⁸

In approximately one-third of adjudicated attacks in AQP4+ inebilizumab-treated participants, no sNfL or sGFAP elevations were reported, which may be because of inebilizumab decreasing NMOSD attack severity and therefore lowering levels of these biomarkers. Conversely, some participants did not experience attacks but had elevated sNfL or sGFAP levels, which could potentially reflect subclinical disease activity previously described with other paraclinical modalities.³⁶ Further investigations are underway to determine whether these findings have clinical significance.

Several strengths and limitations deserve mention. N-MOmentum was a large, randomised, placebo-controlled trial in which attacks were confirmed by independent expert

committees using prespecified criteria.¹ Availability of data from inebilizumab-treated and placebo-treated participants provided the potential to reveal effects of therapy on CNS damage biomarkers. Reference cohorts of healthy donors and patients with RRMS were also included to assess the specific utility of biomarker elevation in participants with NMOSD, but sampling serum and CSF from healthy controls can be challenging. Then again, the biomarker assessment was exploratory, and N-MOmentum was not specifically designed to have adequate statistical power for biomarker analysis. Moreover, although an analysis on the relationship between sNfL concentrations at attack and 3-month CDP was performed, there was no definitive confirmation that sNfL concentrations predict the durability of the EDSS score worsening, probably owing to the small sample size. Further study focusing on EDSS scores over longer intervals in a larger population is needed to improve understanding of the implications of the data presented here.⁴⁰

In conclusion, sNfL, a biomarker of axonal damage, measured at attack, is the best predictor among the CNS damage biomarkers studied here for disability worsening during and after attacks. However, sNfL is inferior to sGFAP in predicting future attacks, consistent with the current concept of NMOSD being a primary astrocytopathy. Compared with placebo, inebilizumab appears to attenuate biomarker elevation during attacks and to reduce biomarker levels over time in the absence of adjudicated attacks. These findings may help to inform progress towards assessment of clinical status, prognosis and treatment decisions for patients with NMOSD by routinely measuring easily accessible serum biomarkers.

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REFERENCES

- 1 Cree BA, Bennett JL, Sheehan M, *et al*. Placebo-controlled study in neuromyelitis optica—ethical and design considerations. *Mult Scler* 2016;22:862–72.
- 2 Fujihara K, Mitsu T, Nakashima I, *et al*. Neuromyelitis optica should be classified as an astrocytopathic disease rather than a demyelinating disease. *Clin Exp Neuroimmunol* 2012;3:58–73. 10.1111/j.1759-1961.2012.00030.x Available: <http://doi.wiley.com/10.1111/cen3.2012.3.issue-2>
- 3 Wingerchuk DM, Pittock SJ, Lucchinetti CF, *et al*. A secondary progressive clinical course is uncommon in neuromyelitis optica. *Neurology* 2007;68:603–5.
- 4 Jarius S, Paul F, Weinschenker BG, *et al*. Neuromyelitis optica. *Nat Rev Dis Primers* 2020;6:85.
- 5 Li J, Bazzi SA, Schmitz F, *et al*. Molecular level characterization of circulating aquaporin-4 antibodies in neuromyelitis optica spectrum disorder. *Neurol Neuroimmunol Neuroinflamm* 2021;8:e1034.
- 6 Duan T, Smith AJ, Verkman AS. Complement-independent bystander injury in AQP4-igG seropositive neuromyelitis optica produced by antibody-dependent cellular cytotoxicity. *Acta Neuropathol Commun* 2019;7:112.
- 7 Herwerth M, Kenet S, Schifferer M, *et al*. A new form of axonal pathology in a spinal model of neuromyelitis optica. *Brain* 2022;145:1726–42.
- 8 Yick L-W, Ma OK-F, Ng RC-L, *et al*. Aquaporin-4 autoantibodies from neuromyelitis optica spectrum disorder patients induce complement-independent immunopathologies in mice. *Front Immunol* 2018;9:1438. .
- 9 Takeshita Y, Fujikawa S, Serizawa K, *et al*. New BBB model reveals that IL-6 blockade suppressed the BBB disorder, preventing onset of NMOSD. *Neurol Neuroimmunol Neuroinflamm* 2021;8:e1076.
- 10 Polivka J, Polivka J Jr, Krakorova K, *et al*. Current status of biomarker research in neurology. *EPMA J* 2016;7:14.
- 11 Mitsu T, Takano R, Fujihara K, *et al*. Marked increase in cerebrospinal fluid glial fibrillar acidic protein in neuromyelitis optica: an astrocytic damage marker. *J Neurol Neurosurg Psychiatry* 2009;80:575–7.
- 12 Chang X, Huang W, Wang L, *et al*. Serum neurofilament light and GFAP are associated with disease severity in inflammatory disorders with aquaporin-4 or myelin oligodendrocyte glycoprotein antibodies. *Front Immunol* 2021;12:647618.

- 13 Watanabe M, Nakamura Y, Michalak Z, *et al.* Serum GFAP and neurofilament light as biomarkers of disease activity and disability in NMOSD. *Neurology* 2019;93:e1299–311.
- 14 Aktas O, Smith MA, Rees WA, *et al.* Serum glial fibrillary acidic protein: a neuromyelitis optica spectrum disorder biomarker. *Ann Neurol* 2021;89:895–910.
- 15 Lycke JN, Karlsson JE, Andersen O, *et al.* Neurofilament protein in cerebrospinal fluid: a potential marker of activity in multiple sclerosis. *J Neurol Neurosurg Psychiatry* 1998;64:402–4.
- 16 Forgrave LM, Ma M, Best JR, *et al.* The diagnostic performance of neurofilament light chain in CSF and blood for alzheimer's disease, frontotemporal dementia, and amyotrophic lateral sclerosis: a systematic review and meta-analysis. *Alzheimers Dement (Amst)* 2019;11:730–43.
- 17 Bäckström D, Linder J, Jakobson Mo S, *et al.* Nfl as a biomarker for neurodegeneration and survival in Parkinson disease. *Neurology* 2020;95:e827–38.
- 18 Gaetani L, Blennow K, Calabresi P, *et al.* Neurofilament light chain as a biomarker in neurological disorders. *J Neurol Neurosurg Psychiatry* 2019;90:870–81.
- 19 Lin T-Y, Vitkova V, Asseyer S, *et al.* Increased serum neurofilament light and thin ganglion cell-inner plexiform layer are additive risk factors for disease activity in early multiple sclerosis. *Neurol Neuroimmunol Neuroinflamm* 2021;8:e1051.
- 20 Hallengren J, Chen PC, Wilson SM. Neuronal ubiquitin homeostasis. *Cell Biochem Biophys* 2013;67:67–73.
- 21 Barbier P, Zejneli O, Martinho M, *et al.* Role of tau as a microtubule-associated protein: structural and functional aspects. *Front Aging Neurosci* 2019;11:204.
- 22 Mondello S, Palmio J, Streeter J, *et al.* Ubiquitin carboxy-terminal hydrolase L1 (uch-l1) is increased in cerebrospinal fluid and plasma of patients after epileptic seizure. *BMC Neurol* 2012;12:85.
- 23 Cree BAC, Bennett JL, Kim HJ, *et al.* Inebilizumab for the treatment of neuromyelitis optica spectrum disorder (N-MOMentum): a double-blind, randomised placebo-controlled phase 2/3 trial. *Lancet* 2019;394:1352–63.
- 24 Agius MA, Klodowska-Duda G, Maciejowski M, *et al.* Safety and tolerability of inebilizumab (MEDI-551), an anti-CD19 monoclonal antibody, in patients with relapsing forms of multiple sclerosis: results from a phase 1 randomised, placebo-controlled, escalating intravenous and subcutaneous dose study. *Mult Scler* 2019;25:235–45.
- 25 Sechi E, Buciu M, Pittock SJ, *et al.* Positive predictive value of myelin oligodendrocyte glycoprotein autoantibody testing. *JAMA Neurol* 2021;78:741–6.
- 26 Wingerchuk DM, Hogancamp WF, O'Brien PC, *et al.* The clinical course of neuromyelitis optica (Devic's syndrome). *Neurology* 1999;53:1107–14.
- 27 Pittock SJ, Lennon VA, McKeon A, *et al.* Eculizumab in AQP4-IgG-positive relapsing neuromyelitis optica spectrum disorders: an open-label pilot study. *Lancet Neurol* 2013;12:554–62.
- 28 Marignier R, Bennett JL, Kim HJ, *et al.* Disability outcomes in the N-MOMentum trial of inebilizumab in neuromyelitis optica spectrum disorder. *Neurol Neuroimmunol Neuroinflamm* 2021;8:e978.
- 29 Abdelhak A, Huss A, Kassubek J, *et al.* Serum GFAP as a biomarker for disease severity in multiple sclerosis. *Sci Rep* 2018;8:14798.
- 30 Czeiter E, Amrein K, Gravestijn BY, *et al.* Blood biomarkers on admission in acute traumatic brain injury: relations to severity, CT findings and care path in the CENTER-TBI study. *EBioMedicine* 2020;56:102785.
- 31 Marshall WJ, Bangert SK. *Clinical biochemistry: metabolic and clinical aspects*. 2nd edition. Churchill Livingstone, 2008.
- 32 Kimbrough DJ, Fujihara K, Jacob A, *et al.* Treatment of neuromyelitis optica: review and recommendations. *Mult Scler Relat Disord* 2012;1:180–7.
- 33 Kleiter I, Gahlen A, Borisow N, *et al.* Neuromyelitis optica: evaluation of 871 attacks and 1,153 treatment courses. *Ann Neurol* 2016;79:206–16.
- 34 Trebst C, Jarius S, Berthele A, *et al.* Update on the diagnosis and treatment of Neuromyelitis Optica: recommendations of the neuromyelitis optica Study Group (NEMOS). *J Neurol* 2014;261:1–16.
- 35 Kleiter I, Gahlen A, Borisow N, *et al.* Apheresis therapies for NMOSD attacks: a retrospective study of 207 therapeutic interventions. *Neurol Neuroimmunol Neuroinflamm* 2018;5:e504.
- 36 Oertel FC, Havla J, Roca-Fernández A, *et al.* Retinal ganglion cell loss in neuromyelitis optica: a longitudinal study. *J Neurol Neurosurg Psychiatry* 2018;89:1259–65.
- 37 Ringelstein M, Harmel J, Zimmermann H, *et al.* Longitudinal optic neuritis-unrelated visual evoked potential changes in NMO spectrum disorders. *Neurology* 2020;94:e407–18.
- 38 Hyun J-W, Kim Y, Kim SY, *et al.* Investigating the presence of interattack astrocyte damage in neuromyelitis optica spectrum disorder: longitudinal analysis of serum glial fibrillary acidic protein. *Neurol Neuroimmunol Neuroinflamm* 2021;8:e965.
- 39 Schindler P, Grittner U, Oechtering J, *et al.* Serum GFAP and NFL as disease severity and prognostic biomarkers in patients with aquaporin-4 antibody-positive neuromyelitis optica spectrum disorder. *J Neuroinflammation* 2021;18:105.
- 40 Barro C, Healy BC, Liu Y, *et al.* Serum GFAP and NFL levels differentiate subsequent progression and disease activity in patients with progressive multiple sclerosis. *Neurol Neuroimmunol Neuroinflamm* 2023;10:e200052.