Prognostic Value of Serum NfL for Subclinical Disease Activity and Worsening in Patients with RMS: Results from the Phase 3 ASCLEPIOS I and II Trials

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Introduction

- Neurofilament light (NfL) is a biomarker of neuro-axonal injury and loss.[1] In RMS, high sNfL levels have been found to correlate with active T2 lesions, relapses,[2,3] brain volume loss,[4] and acute inflammatory neuronal damage[1]
- In the Phase 3 ASCLEPIOS I/II trials, ofatumumab significantly lowered sNfL levels from the first assessment at M3 to M24 vs teriflunomide, while brain volume change was not significantly different between the two treatment arms[5]

Objective

- To confirm the prognostic value of baseline sNfL for brain lesion formation and volume change on MRI in RMS patients, and investigate the relationship of sNfL with regional brain volume change

Methods

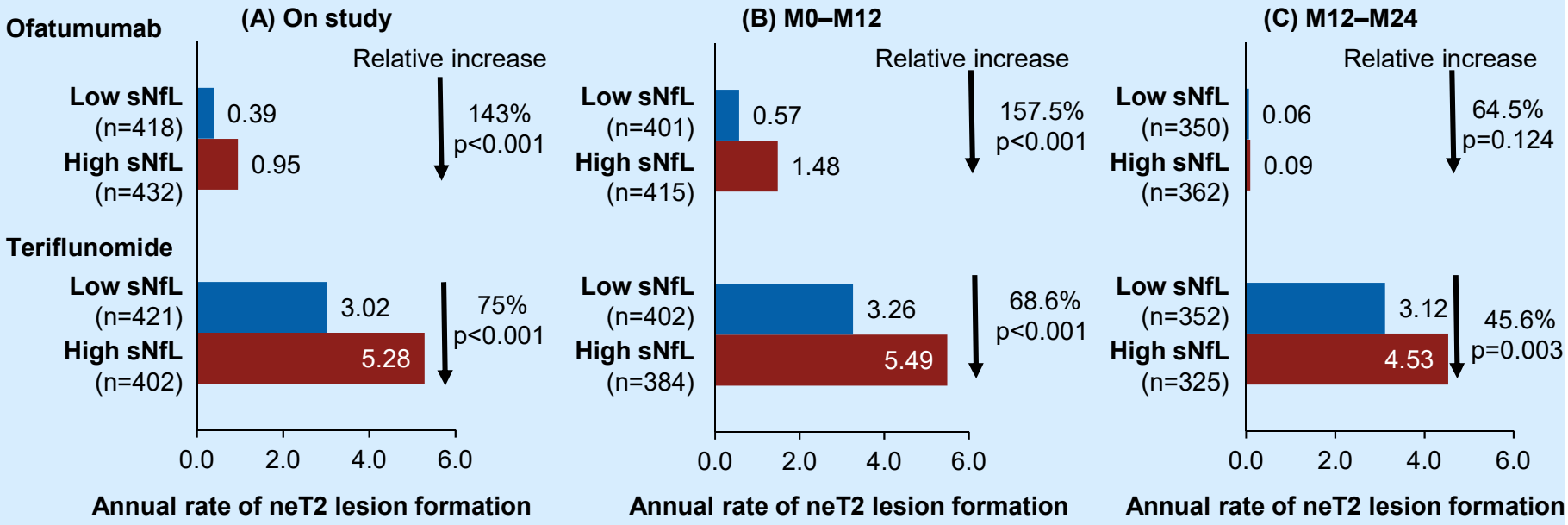
- In this preplanned pooled ASCLEPIOS I/II analysis (N=1882), patients were stratified by median baseline sNfL levels (9.3 pg/mL) into high (>median) and low (≤median) categories to assess the prognostic value of sNfL for the below parameters:
  - **Annual rate of new/enlarging T2 lesions in Year 1 and 2** *(data were estimated using a negative binomial model)*
  - **Annual rate of percentage volume change for whole brain, cortical gray matter, white matter and thalamus over 2 years** *(data were estimated using a random coefficients model*)*
  - **Correlations between sNfL and regional brain volume change at M24** *(data were estimated using a Person correlation coefficients)*
- NfL levels in serum were measured using Quanterix Simoa NF-light Assay Advantage Kit**

**The analytical sensitivity was confirmed to be 2.817 pg/mL, and the reportable range was 2.817 – 1546 pg/mL. Linearity of the assay was assessed across a range of below LLoQ to 1538 pg/mL in serum. Linear regression result was R2 = 0.9964. Intra-assay precision was demonstrated by testing 8 samples across assay reportable range independently for 6 times in a single run with highest observed CV of 10%. Inter-assay precision was demonstrated by testing 8 samples independently for 3 times per run for 6 runs (2 runs per day), with the highest observed CV of 11%.

*The annual change of brain volume refers to the slope in year 2 of treatment. CV, coefficient of variation; LLoQ, lower limit of quantification; M, month; MRI, magnetic resonance imaging; NfL, neurofilament light; RMS, relapsing multiple sclerosis; sNfL, serum NfL; 1. Siller N, et al. Multiple sclerosis 2019; 25(5): 678-86. 2. Kuhle J, et al. Neurology 2019; 92(10): e1007-15. 3. Kuhle J, et al. Multiple sclerosis 2016; 22(12): 1550-9. 4. Kuhle J, et al. Neurology 2017; 88(9): 826-31. 5. Hauser SL, et al. N Engl J Med 2020; 383: 546-57.

Results: T2 lesion formation

Annual rate of neT2 lesion formation by baseline NfL high-low subgroups, by treatment

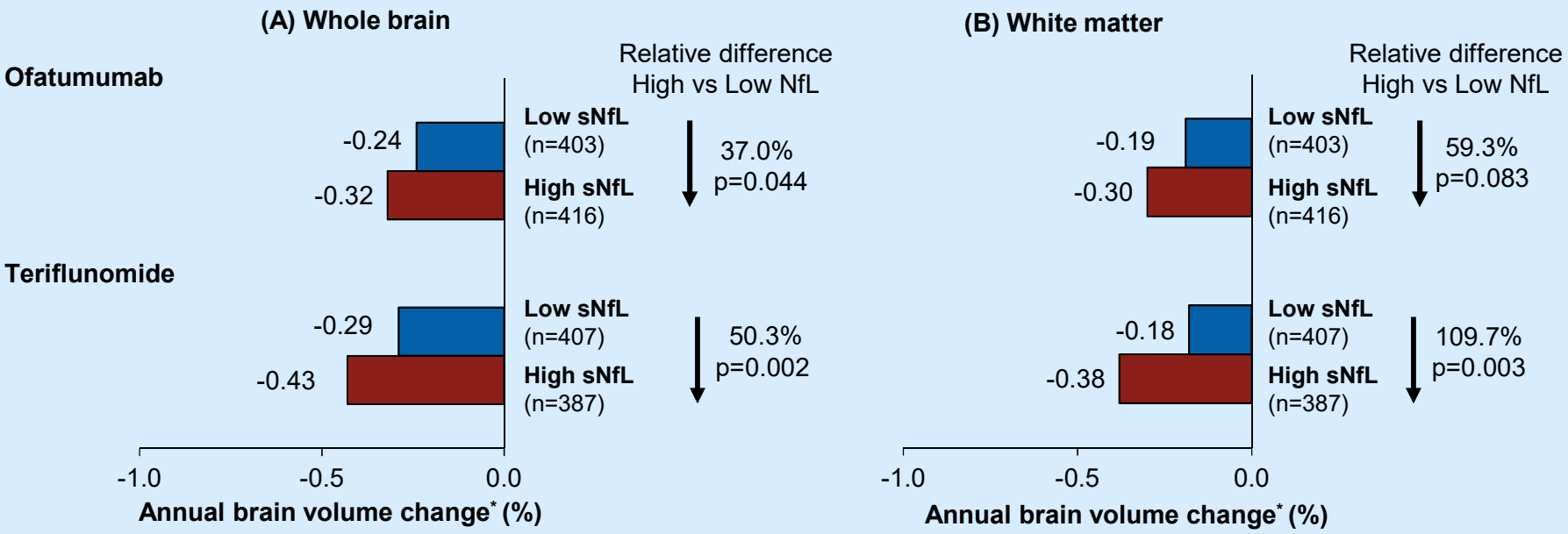


High (vs low) baseline sNfL was prognostic of increased on-study neT2 lesion formation in Year 1 and Year 2

M, month; neT2, new/enlarging T2; NfL, neurofilament light; sNfL, serum NfL

Results: Brain volume change

Annual rate of whole brain and white matter volume change by baseline NfL high-low subgroup, by treatment



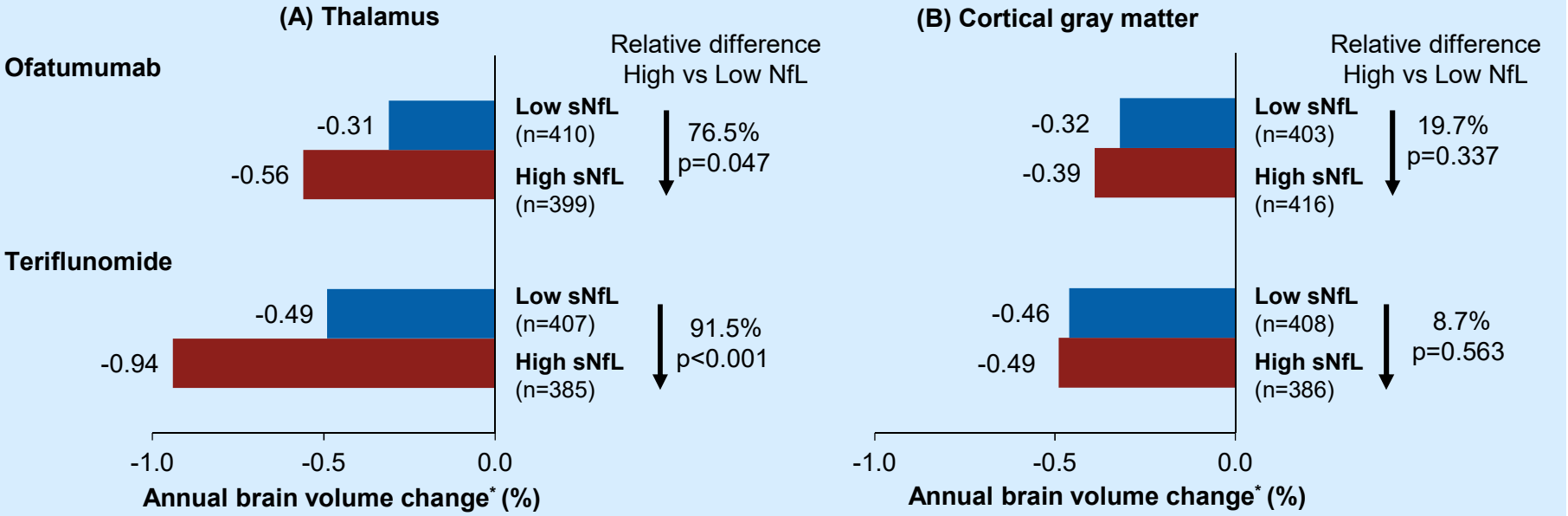
- Baseline sNfL was correlated with whole brain volume change (ofatumumab =−0.283, p<0.0001; teriflunomide r=−0.269, p<0.0001)
- Baseline sNfL was correlated with white matter volume change (ofatumumab r=−0.292, p<0.0001; teriflunomide r=−0.286, p<0.0001)

High (vs low) baseline sNfL was prognostic of a higher annual percentage volume change in whole brain and white matter

*The annual brain volume change is estimated based on a random coefficient model and represents the slope (percentage brain volume change) in the second year of treatment
BVC, brain volume change; NfL, neurofilament light; sNfL, serum NfL

Results: Brain volume change

Annual rate of thalamic and cortical gray matter volume change by baseline NfL high-low subgroups, by treatment



- Baseline sNfL was correlated with thalamic volume change (ofatumumab r=−0.416, p<0.0001 and teriflunomide r=−0.368, p<0.0001)
- Baseline sNfL was less correlated with cortical gray matter volume change (ofatumumab r=−0.080, p=0.0466; teriflunomide r=−0.068, p=0.0965)

High (vs low) baseline sNfL was prognostic of a higher annual percentage volume change in the thalamus but not in the cortical gray matter

*The annual brain volume change is estimated based on a random coefficient model and represents the slope (percentage brain volume change) in the second year of treatment
BVC brain volume change; NfL, neurofilament light; sNfL, serum NfL

Conclusions

- The prognostic value of baseline sNfL has been prospectively shown based on ASCLEPIOS I and II phase 3 trials for on-study:
  - lesion formation in both the first and second year of treatment
  - brain volume loss, and particularly thalamic volume loss
- Baseline sNfL has the strongest correlation with thalamic volume change
- These results corroborate findings from previous post hoc studies[1,2] that support the use of sNfL as a prognostic marker for ongoing and future disease activity and accelerated volume loss of brain structures mainly affected by white matter lesions in patients with RMS
- sNfL can help to assess the risk of further disease activity and worsening, and may assist in making treatment decisions

Disclosures

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MRI, magnetic resonance imaging; RMS, relapsing multiple sclerosis; sNfL, serum neurofilament light

1. Kuhle J, et al. Neurology 2019; 92(10): e1007-15. 2. Häring DA, et al. Neurol Neuroimmunol Neuroinflamm 2020; 7(5).