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Ofatumumab Reduces Clinical and Radiological Activity in People With Recently Diagnosed Treatment-Naive Relapsing Multiple Sclerosis Irrespective of Baseline Serum Neurofilament Light Chain Levels

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KEY FINDINGS & CONCLUSIONS

- In the subgroup of RDTN participants with relapsing multiple sclerosis (MS) enrolled in the ASCLEPIOS I/II trials, ofatumumab was consistently associated with reductions in clinical and radiological activity versus teriflunomide regardless of baseline sNfL levels
- Ofatumumab also significantly increased the odds of maintaining NEDA-3 status compared with teriflunomide regardless of baseline sNfL levels
- The results support the benefit of using high-efficacy therapies, such as ofatumumab, at an early stage in the MS disease course irrespective of the sNfL levels at baseline

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INTRODUCTION

- In the phase 3 ASCLEPIOS I/II trials (NCT02792218/NCT02792231) in people with relapsing multiple sclerosis (pwRMS), ofatumumab was significantly more effective than teriflunomide at suppressing magnetic resonance imaging lesion and relapse activity and reducing 3-month confirmed disability worsening risk regardless of baseline levels of serum neurofilament light chain (sNfL)[1]
- Baseline sNfL levels were prognostic for on-study lesion formation in the overall ASCLEPIOS I/II population[1]
- The prognostic value of sNfL for lesion formation was also demonstrated in the subgroup of recently diagnosed (within 3 years) treatment-naive (RDTN) pwRMS, a population for whom disease prognosis is a challenge due to the considerable variability of disease course[1]

OBJECTIVE

- To compare the effects of ofatumumab versus teriflunomide on relapses, new or enlarging T2 (neT2) lesions, and the odds of maintaining no evidence of disease activity (NEDA-3) status in RDTN participants from ASCLEPIOS I/II based on their baseline sNfL levels

METHODS

Study design

- A total of 1882 pwRMS were randomized to ofatumumab or teriflunomide in ASCLEPIOS I/II
- The baseline sNfL cutoff was predefined in the clinical study protocol (i.e., before measuring sNfL or any clinical or radiological outcomes) as the median sNfL value for the overall population across ASCLEPIOS I/II (9.3 pg/mL)
- The subgroup of RDTN participants was stratified into high (>baseline median) and low (≤baseline median) sNfL groups
- Quantification of sNfL levels was performed centrally (Navigate BioPharma Services, Carlsbad, CA, USA), as a single batch at the end of the trials, using a validated Quanterix Simoa® NF-light advantage kit

Outcomes

- Within each sNfL subgroup, the following outcomes were compared for ofatumumab versus teriflunomide:
  - **Adjusted annualized relapse rates (ARR)** over the study duration (up to 30 months)
  - **Adjusted annualized rates of neT2 lesions** (last available scan compared to baseline)
  - **Proportion of RDTN participants achieving NEDA-3** at Months 12 and 24

Statistical analyses

- **Adjusted ARR**
  - Negative binomial regression model with log-link to the number of relapses, adjusted for treatment, baseline sNfL category, region, and study as factors; number of relapses in previous year, baseline Expanded Disability Status Scale (EDSS), baseline number of gadolinium-enhancing (Gd+) T1 lesions, and the patient's age at baseline as covariate; and treatment by baseline sNfL category interaction
- **Adjusted annualized rates of neT2 lesions** (compared to baseline)
  - Negative binomial model adjusted for treatment, baseline sNfL category, region, and study as factors; age and baseline volume of T2 lesions as continuous covariates; and treatment by baseline sNfL category interaction
- **Effect on NEDA-3**
  - Logistic regression for each time period adjusted for treatment and region as factors, and age, baseline EDSS, and number of Gd+ T1 lesions at baseline as continuous covariates

RESULTS

Participants

- Among 1882 pwRMS randomized, 576 were RDTN and had sNfL data at baseline (**Table 1**)

Table 1. Baseline demographics and disease characteristics of RDTN pwRMS

Parameters	Low sNfL category (≤9.3 pg/mL) N=274 (47.6%)	High sNfL category (>9.3 pg/mL) N=302 (52.4%)
Age (years)	36.7±8.8	35.9±9.7
Female sex, n (%)	180 (66)	209 (69)
MS duration since first symptom (years)	3.5±4.4	3.1±3.6
Number of relapses in the year before the study	1.3±0.7	1.3±0.7
Time since onset of most recent relapse (months)	5.8±4.8	5.8±5.7
EDSS score	2.2±1.2	2.3±1.2
Normalized brain volume (cm^3)	1478.4±64.9	1468.2±71.1
Number of Gd+ T1 lesions	0.4±1.0	2.6±4.8
Patients free of Gd+ T1 lesions, n (%)	206 (75)	116 (38)
T2 lesion volume (cm^3)	5.9±7.2	12.3±12.4
sNfL (pg/mL), median	6.77	15.29

Data are expressed as mean±SD unless specified otherwise.

EDSS, Expanded Disability Status Scale; Gd+, gadolinium-enhancing; MS, multiple sclerosis; pwRMS, people with relapsing multiple sclerosis; RDTN, recently diagnosed treatment-naive; SD, standard deviation; sNfL, serum neurofilament light chain.

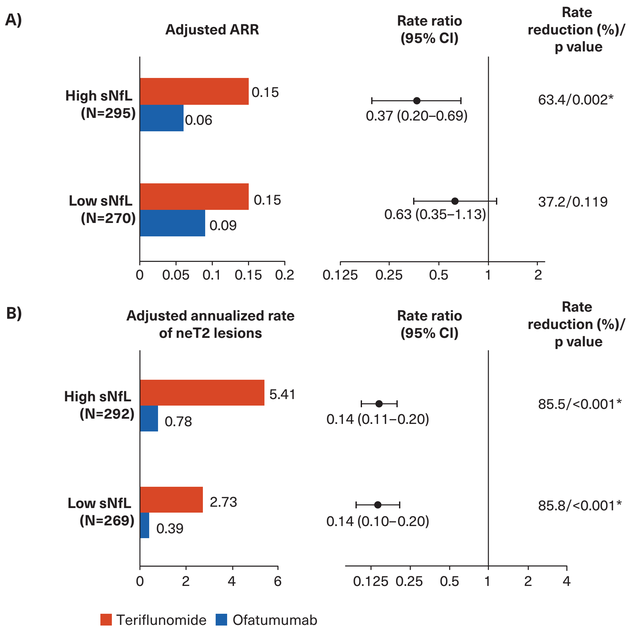
Relapses

- Ofatumumab reduced the adjusted ARR by 63.4% (p=0.002) and 37.2% (p=0.119) versus teriflunomide in the high and low sNfL categories, respectively (**Figure 1A**)

neT2 lesions

- Ofatumumab reduced the annualized rate of neT2 lesions by 85.5% and 85.8% versus teriflunomide (both p<0.001) in the high and low sNfL categories, respectively (**Figure 1B**)

Figure 1. Treatment effect on (A) ARR and (B) neT2 lesions per baseline sNfL

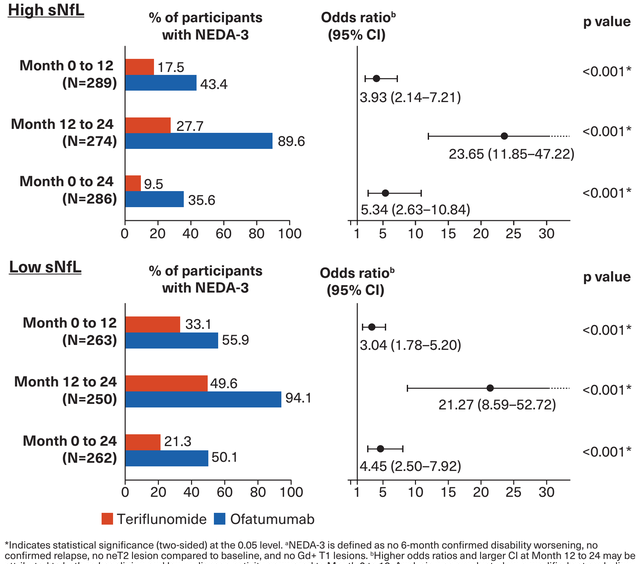


*Indicates statistical significance (two-sided) at the 0.05 level. ARR, annualized relapse rate; CI, confidence interval; N, number of participants in the related sNfL category; neT2, new or enlarging T2; sNfL, serum neurofilament light chain.

NEDA-3

- A significantly higher proportion of RDTN participants achieved NEDA-3 status with ofatumumab versus teriflunomide, regardless of baseline sNfL levels (**Figure 2**)

Figure 2. Treatment effect on NEDA-3 status[a] per baseline sNfL



*Indicates statistical significance (two-sided) at the 0.05 level. [a]NEDA-3 is defined as no 6-month confirmed disability worsening, no confirmed relapse, no neT2 lesion compared to baseline, and no Gd+ T1 lesions. [b]Higher odds ratios and larger CI at Month 12 to 24 may be attributed to both re-baselining and lower disease activity compared to Month 0 to 12. Analysis was conducted on a modified set excluding RDTN participants who discontinued from study drug prematurely for reasons other than "lack of efficacy" or "death" and had NEDA-3 before discontinuations. CI, confidence interval; Gd+, gadolinium-enhancing; N, number of participants in the related sNfL category with data available over the corresponding period; NEDA-3, three-parameter no evidence of disease activity; neT2, new or enlarging T2; RDTN, recently diagnosed treatment-naive; sNfL, serum neurofilament light chain.

Reference

1. Ziemssen T, et al. *Front Immunol*. 2022;13:852563.

Abbreviations

ARR, annualized relapse rate; **CI,** confidence interval; **EDSS,** Expanded Disability Status Scale; **Gd+,** gadolinium-enhancing; **MS,** multiple sclerosis; **NEDA-3,** three-parameter no evidence of disease activity; **neT2,** new or enlarging T2; **pwRMS,** people with relapsing multiple sclerosis; **RDTN,** recently diagnosed treatment-naive; **SD,** standard deviation; **sNfL,** serum neurofilament light chain.

Disclosures

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