

Impact of eculizumab on disability measures in patients with aquaporin-4 antibody-positive neuromyelitis optica spectrum disorder: phase 3 PREVENT study

P1343

Jacqueline Palace;¹ Sean J. Pittock;² Achim Berthele;³ Kazuo Fujihara;⁴⁻⁶ Ho Jin Kim;⁷ Michael Levy;^{8,9} Ichiro Nakashima;^{4,10} Murat Terzi;¹¹ Natalia Totolyan;¹² Shanthi Viswanathan;¹³ Kai-Chen Wang;^{14,15} Amy Pace;¹⁶ Marcus Yountz;¹⁶ Róisín Armstrong;¹⁶ Dean M. Wingerchuk¹⁷

¹John Radcliffe Hospital, Oxford, UK; ²Mayo Clinic, Rochester, MN, USA; ³Klinikum rechts der Isar, Technical University of Munich, Munich, Germany; ⁴Tohoku University, Sendai, Japan; ⁵Fukushima Medical University, Fukushima City, Japan; ⁶Southern TOHOKU Research Institute for Neuroscience (STRINS), Koriyama, Japan; ⁷Research Institute and Hospital, National Cancer Center, Goyang, South Korea; ⁸Johns Hopkins University, Baltimore, MD, USA; ⁹Massachusetts General Hospital and Harvard Medical School, Boston, MA, USA; ¹⁰Tohoku Medical and Pharmaceutical University, Sendai, Japan; ¹¹Ondokuz Mayıs University, Samsun, Turkey; ¹²First Pavlov State Medical University of St Petersburg, St Petersburg, Russia; ¹³Kuala Lumpur Hospital, Kuala Lumpur, Malaysia; ¹⁴Cheng-Hsin General Hospital, Taipei, Taiwan; ¹⁵School of Medicine, National Yang Ming University, Taipei, Taiwan; ¹⁶Alexion Pharmaceuticals, Boston, MA, USA; ¹⁷Mayo Clinic, Scottsdale, AZ, USA

INTRODUCTION AND PURPOSE

- Neuromyelitis optica spectrum disorder (NMOSD) is a rare, relapsing, autoimmune, inflammatory disorder resulting in central nervous system tissue destruction.^{1,2}
- Relapse-related tissue damage leads to the accumulation of significant, and mostly irreversible, disability.¹
- At least two-thirds of patients with NMOSD have aquaporin-4 immunoglobulin G (AQP4-IgG) antibodies;^{3,4} these antibodies are reported to trigger the complement cascade, which is implicated in astrocyte destruction and neuronal injury.⁵
- Eculizumab is a humanized monoclonal antibody that inhibits the terminal complement protein C5.⁶
- In the phase 3, randomized, double-blind PREVENT study (NCT01892345) in adults with AQP4-IgG-positive NMOSD,⁷ there was a 94% reduction in relapse risk with eculizumab versus placebo.⁸
 - Hazard ratio: 0.058; 95% confidence interval (CI): 0.017–0.197; $p < 0.0001$.⁸
- Here, we report changes in disability scores from baseline to study end in PREVENT using both pre-specified⁷ and *post hoc* analyses.

RESULTS

Patients and treatment

- 143 patients received blinded trial treatment (Table 1).⁷
- Median (range) duration of treatment was 89.43 (3.1–211.1) weeks for eculizumab and 41.29 (6.1–208.1) weeks for placebo.

Table 1. Baseline demographic and clinical characteristics

Characteristic	Eculizumab (n = 96)	Placebo (n = 47)
Female, n (%)	88 (91.7)	42 (89.4)
Mean (SD) age, years		
At first dose of trial medication	43.9 (13.32)	45.0 (13.29)
At initial clinical presentation	35.8 (14.03)	38.5 (14.98)
Diagnosis, n (%)		
Neuromyelitis optica	69 (71.9)	38 (80.9)
NMOSD	27 (28.1)	9 (19.1)
Mean (SD) ARR 24 months before screening	1.94 (0.896)	2.07 (1.037)
Median (range) EDSS score	4.00 (1.0–7.0)	4.00 (1.0–6.5)
Median (range) mRS score	2.0 (0–4)	2.0 (0–4)
Median (range) HAI score	2.0 (0–8)	2.0 (0–6)
ISTs at baseline, n (%)		
None	21 (21.9)	13 (27.7)
Corticosteroids alone	16 (16.7)	11 (23.4)
Azathioprine ± corticosteroids	37 (38.5)	13 (27.7)
Mycophenolate mofetil ± corticosteroids	17 (17.7)	8 (17.0)
Other drug ^a ± corticosteroids	5 (5.2)	2 (4.3)
Previous rituximab treatment, ^b n (%)	26 (27.1)	20 (42.6)

Adapted from *New England Journal of Medicine*, Pittock SJ *et al.* Eculizumab in aquaporin-4-positive neuromyelitis optica spectrum disorder, doi:10.1056/NEJMoa1900866. Copyright © 2019; Massachusetts Medical Society. ^aCyclosporine, cyclophosphamide, methotrexate, mizoribine or tacrolimus. ^bPatients previously receiving rituximab could be included in the trial if they had not received rituximab in the 3 months before screening. ARR, annualized relapse rate; EDSS, Expanded Disability Status Scale; HAI, Hauser Ambulation Index; IST, immunosuppressive therapy; mRS, modified Rankin Scale; NMOSD, neuromyelitis optica spectrum disorder; SD, standard deviation.

Pre-specified analyses of changes from baseline in disability scores

- Distributions of changes from baseline to study end are shown in Figures 1A, C and E.⁷
- Mean (standard deviation) changes from baseline to study end for measures of neurological disability favoured eculizumab over placebo, as follows.
 - EDSS: −0.18 (0.814) versus 0.12 (0.954); $p = 0.0597$.
 - mRS: −0.24 (0.72) versus 0.09 (0.75); $p = 0.0154$.
 - HAI: −0.39 (1.08) versus 0.51 (1.61); $p = 0.0002$.
- A fixed-sequence hierarchical testing procedure was used in PREVENT. Because the p value for change in EDSS score exceeded 0.05, p values for changes in mRS and HAI scores (lower in the hierarchy) were considered nominal.⁷
- Changes in EDSS, mRS and HAI scores from baseline to each scheduled visit up to 1 year (based on the sensitivity analyses) are provided in Figures 1B, D and F.⁷

CONCLUSIONS

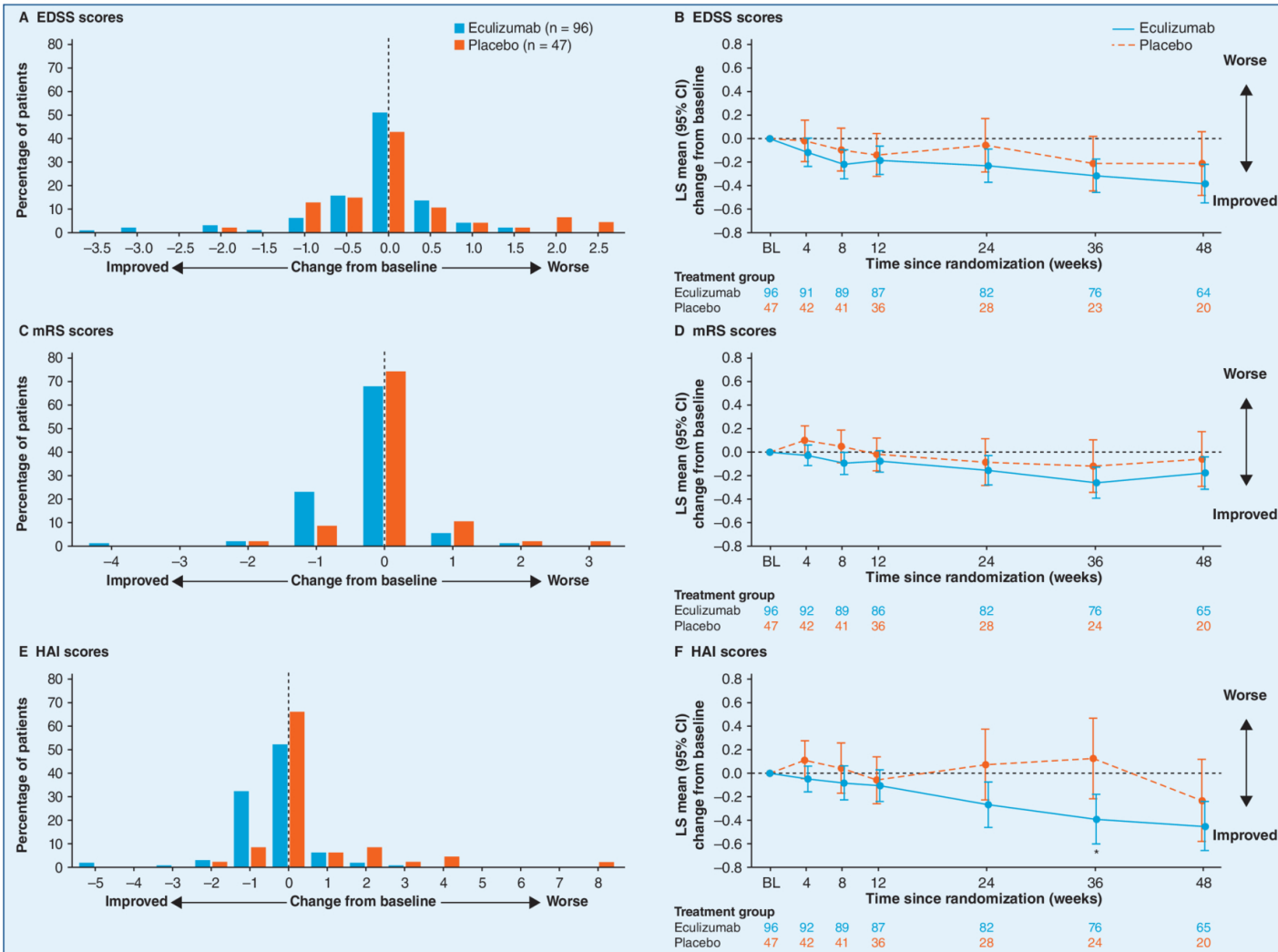
- In patients with AQP4-IgG-positive NMOSD, eculizumab demonstrated a positive impact on neurological and functional disability compared with placebo, as measured by the EDSS, mRS and HAI.
- These outcomes continue to be assessed in the ongoing open-label extension study in order to characterize the long-term impact of eculizumab on disability.

METHODS

- Design.⁷
 - International, phase 3, randomized, double-blind, parallel-group, placebo-controlled, time-to-event trial.
- Patients.⁷
 - Main inclusion criteria: age ≥ 18 years; AQP4-IgG-seropositive status; ≥ 2 relapses in previous 12 months or ≥ 3 in previous 24 months (with ≥ 1 in previous 12 months); Expanded Disability Status Scale (EDSS) score ≤ 7.0 .
 - Main exclusion criteria: rituximab or mitoxantrone treatment in previous 3 months, intravenous immunoglobulin in previous 3 weeks, or prednisone dosages > 20 mg/day (or equivalent for other corticosteroids) at screening.
- Treatment.⁷
 - Vaccinated against *Neisseria meningitidis* before trial treatment.
 - Patients randomly allocated (2:1) to intravenous eculizumab or matching placebo, with eculizumab administered at 900 mg weekly for first four doses, then 1200 mg every 2 weeks from following week.
 - Permitted immunosuppressive therapy continued if stable dose at baseline.
 - Treatment continued until patient experienced a physician-determined relapse, patient discontinued or trial ended.
- Disability assessments.⁷
 - EDSS, modified Rankin Scale (mRS) and Hauser Ambulation Index (HAI)

- at baseline, at weeks 4, 8 and 12, and every 12 weeks thereafter (and at discontinuation/study end).
- After possible relapse – EDSS and HAI within 48 hours of possible relapse and intervals of 1, 4 and 6 (end of study) weeks later; mRS at week 6/end of study only.
- Statistical analyses of disability scores.⁷
 - Secondary endpoints (changes from baseline) – randomization-based nonparametric analysis of covariance adjusted for baseline scores and stratified by randomization strata.
 - Pre-specified sensitivity analysis (changes from baseline to each scheduled visit up to year 1) – mixed models for repeated measures with terms for treatment, visit, treatment-by-visit interaction, baseline score and observed randomization strata.
- Additional analyses performed *post hoc* for worsening of EDSS or HAI scores between baseline and study end.
 - EDSS worsening – increase of ≥ 2.0 from a baseline score of 0, ≥ 1.0 from a baseline score of 1.0–5.0, or ≥ 0.5 from a baseline score of ≥ 5.5 .
 - HAI worsening – increase of ≥ 2 from a baseline score of 0 or ≥ 1 from a baseline score of ≥ 1 .
 - Analyses used a logistic regression model, adjusting for baseline score and stratified by observed randomization strata.

Figure 1. Changes from baseline in disability scores⁷

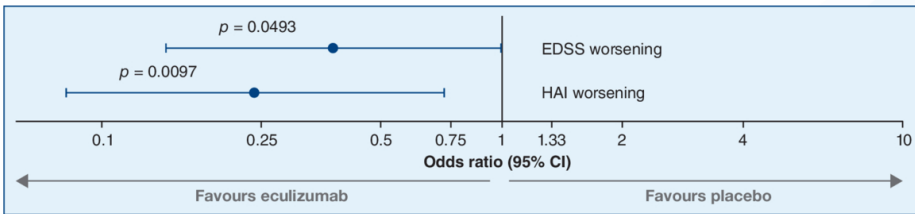


From *New England Journal of Medicine*, Pittock SJ *et al.* Eculizumab in aquaporin-4-positive neuromyelitis optica spectrum disorder, doi:10.1056/NEJMoa1900866 (supplementary appendix). Copyright © 2019; Massachusetts Medical Society. Reprinted with permission. Figures on the left-hand side show distributions of changes from baseline to the end of the trial. Figures on the right-hand side show changes from baseline to each scheduled visit during the first year for scores on the EDSS, mRS and HAI. *A priori* sensitivity analyses were conducted for the changes from baseline to each scheduled visit up to year 1 (figures on the right-hand side) using mixed models for repeated measures with terms for treatment, visit, treatment-by-visit interaction, baseline score and observed randomization strata. *Denotes two-sided nominal p value of 0.05. BL, baseline; CI, confidence interval; EDSS, Expanded Disability Status Scale; HAI, Hauser Ambulation Index; LS, least squares; mRS, modified Rankin scale.

Post hoc analyses of disability worsening

- Proportions of patients with worsening scores were significantly lower for eculizumab than for placebo.
 - EDSS: 11.5% versus 23.4%, respectively; odds ratio: 0.381; 95% CI: 0.146–0.997; $p = 0.0493$ (Figure 2).
 - HAI: 8.3% versus 23.4%, respectively; odds ratio: 0.240; 95% CI: 0.081–0.707; $p = 0.0097$ (Figure 2).

Figure 2. EDSS and HAI disability worsening



Worsening of EDSS score was defined as an increase of ≥ 2 from a baseline score of 0, ≥ 1 from a baseline score of 1.0–5.0, or ≥ 0.5 from a baseline score of ≥ 5.5 . Worsening of HAI score was defined as an increase of ≥ 2 from a baseline score of 0, or ≥ 1 from a baseline score of ≥ 1 . Each score was analysed using a logistic regression model, adjusting for baseline score and stratified by observed randomization strata (*post hoc* analysis). CI, confidence interval; EDSS, Expanded Disability Status Scale; HAI, Hauser Ambulation Index.

REFERENCES, ACKNOWLEDGEMENTS AND DISCLOSURES

References

- Wingerchuk DM *et al.* *Neurology* 1999;53:1107–14.
- Wingerchuk DM *et al.* *Lancet Neurol* 2007;6:805–15.
- Waters P *et al.* *J Neurol Neurosurg Psychiatry* 2016;87:1005–15.
- Jiao Y *et al.* *J Neuroinflammation* 2018;15:294.
- Davis J. *Am J Health Syst Pharm* 2008;65:1609–15.
- Pittock SJ *et al.* *New Engl J Med* 2019; doi:10.1056/NEJMoa1900866.
- Alexion Pharmaceuticals, Inc. Prescribing information, SOLIRIS. US Food and Drug Administration, 2019. Available from: https://www.accessdata.fda.gov/drugsatfda_docs/label/2019/125166s431blbct.pdf (Accessed August 2019).

Acknowledgements

PREVENT was sponsored by Alexion Pharmaceuticals. The authors would like to thank the patients for participating in the trial, as well as their families, and the PREVENT trial investigators and coordinators. Writing assistance for this poster was provided by Oxford PharmaGenesis, Oxford, UK, with funding from Alexion Pharmaceuticals.

Disclosures

BA, AP and MY – employees of and hold stock in Alexion. AB – compensation for clinical trials received by his institution from Alexion Pharmaceuticals, Biogen, Novartis Pharmaceuticals, Roche, Sanofi Genzyme and Teva Pharmaceuticals; personal fees and non-financial support from Bayer Healthcare, Biogen, Merck Serono, Mylan, Novartis Pharmaceuticals, Roche and Sanofi Genzyme. KF – consultancy/speaker fees from Alexion Pharmaceuticals, Asahi Kasei Medical, Biogen, Chugai, Eisai, Mitsubishi-Tanabe Pharma, Nitro, Novartis Pharmaceuticals, ONO Pharmaceutical, Takeda and Teijin. HJK – research support from Merck Serono, the Ministry of Science and ICT, Sanofi Genzyme, Teva-Handok and UCB; consultancy/speaker fees from Celtrion, Eisai, HanAll BioPharma, MedImmune, Merck Serono, Novartis, Sanofi Genzyme, Teva-Handok and UCB; serves on a steering committee for MedImmune/Viola Bio; is co-editor for the *Multiple Sclerosis Journal – Experimental, Translational and Clinical*, and associate editor for the *Journal of Clinical Neurology*. ML – research support from Alexion Pharmaceuticals, Amaryn, Apopharma, Sanofi Genzyme, Shire, Viola Bio (formerly MedImmune) and Viropharma; serves as a consultant for Alexion Pharmaceuticals, Apopharma, Chugai, MedImmune, Quest Diagnostics, Sanofi Genzyme and Shire. IN – personal fees from Biogen Japan, Mitsubishi Tanabe Pharma, Novartis Pharmaceuticals and Takeda Pharmaceuticals; grants from LSI Medicine, the Ministry of Education, Science and Technology of Japan, and the Ministry of Health, Welfare and Labor of Japan. JP – partly funded

by highly specialized services to run a national congenital myasthenia service and a neuromyelitis service; support for scientific meetings and fees for advisory work from Abide, Alexion, ARGENX, Bayer Schering, Biogen Idec, Chugai Pharma, EuroImmun, MedDay, MedImmune, Merck Serono, Novartis, Roche, Sanofi Genzyme and Teva; grants from Abide, Bayer Schering, Biogen Idec, Merck Serono, Novartis and Teva; grants from EDEN, GMSI, the Guthy-Jackson Charitable Foundation, the John Fell Fund, the Medical Research Council, the MS Society, National Institute for Health Research and the Oxford Health Services Research Committee for research studies. SUP – grants, personal fees and non-financial support from Alexion Pharmaceuticals; grants from the Autoimmune Encephalitis Alliance and Grifols; grants, personal fees, non-financial support and other from MedImmune, Inc; patent # 9,891,219 (application # 12-573942) *Methods for treating neuromyelitis optica (NMO) by administration of eculizumab to an individual that is aquaporin-4 (AQP4)-IgG antibody positive*. MT, SV and K-CW have nothing to disclose. NT – personal fees from Bayer, Janssen, Merck, Recceptos, Inc., Roche, Sanofi Genzyme and Teva; grants and personal fees from Actelion, BIOCAD (Russia) and Novartis; grants from GeNeuro. DMW – grants from Alexion Pharmaceuticals during the conduct of the study; personal fees from Biogen, BrainStorm Therapeutics, Caladrius, Celgene, MedImmune, Novartis and ONO Pharmaceutical.

