UPLIZNA®
inebilizumab-cdon

Inebilizumab for treatment of neuromyelitis optica spectrum disorder in patients with prior rituximab use from the N-MOmentum study

Eoin P Flanagan, Michael Levy, Eliezer Katz, Daniel Cimbora, Jorn Drappa, Maureen A Mealy, Dewei She, Bruce AC Cree

UPLIZNA demonstrated efficacy in reducing the risk of attacks in patients with NMOSD regardless of prior rituximab use.[1]

UPLIZNA and rituximab have not been studied in a head-to-head clinical trial.

Analysis was not powered to detect differences within subgroups and results should be considered descriptive and exploratory.

Mult Scler Relat Disord. 2022;57:103352. doi:10.1016/j.msard.2021.103352
NMOSD, neuromyelitis optica spectrum disorder.

INDICATION

UPLIZNA (inebilizumab-cdon) is indicated for the treatment of neuromyelitis optica spectrum disorder (NMOSD) in adult patients who are anti-aquaporin-4 (AQP4) antibody positive.

IMPORTANT SAFETY INFORMATION

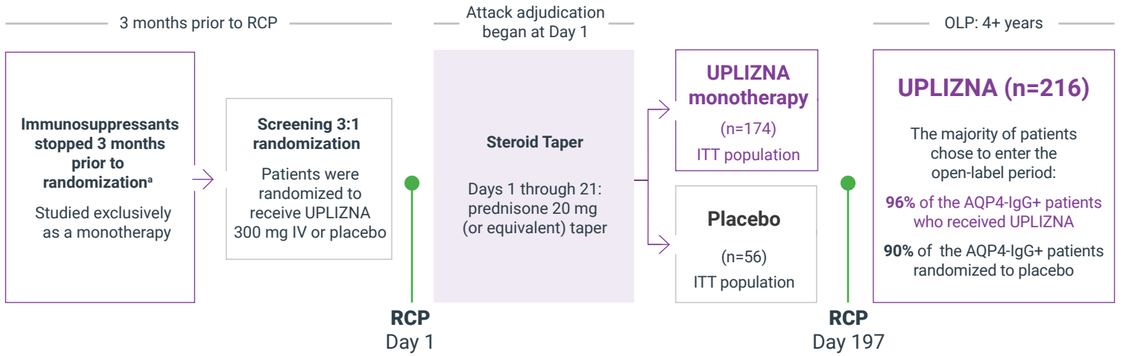
UPLIZNA is contraindicated in patients with:

- A history of life-threatening infusion reaction to UPLIZNA
- Active hepatitis B infection
- Active or untreated latent tuberculosis

Please see additional Important Safety Information throughout and accompanying Full Prescribing Information.

N-MOmentum was a **phase 2/3, multicenter, double-blind, randomized placebo-controlled trial** with an open-label period[2]

N-MOmentum was the largest NMOSD trial to date (n=230), recruiting diverse participants from 24 countries in the first randomized trial of a B-cell–depleting therapy[2-8]



- ***Inclusion criteria:*** Adults diagnosed with NMOSD, EDSS score ≤8.0, and a history of 1 attack requiring rescue therapy during the year before screening or ≥2 attacks requiring rescue therapy in the 2 years before screening[2]
- ***Primary endpoint:*** Time to onset of an NMOSD attack on or before day 197[2]
- ***Robust attack adjudication:*** All attacks were verified by an independent relapse-adjudication committee using 18 predefined attack criteria[2,9]
- UPLIZNA delivered significant reduction in attacks through the first 28 weeks of treatment, with a 77% relative risk reduction vs placebo; 11% of AQP4-IgG+ patients on UPLIZNA and 42% on placebo experienced an attack (HR=0.227 [95% CI: 0.121-0.423], *P*<0.0001 [primary endpoint])[3]

17 participants with prior rituximab use were studied in a post hoc analysis to see if UPLIZNA demonstrated efficacy in reducing the risk of attacks regardless of former treatment.[1]

[a]Due to a half-life of ≤24 hours, AZA and MMF were allowed up until Day 1. Rituximab was stopped 6 months prior to randomization, unless the patient had B-cell counts above the LLN.[8]

AQ4-IgG+, aquaporin-4-immunoglobulin G positive; AZA, azathioprine; CI, confidence interval; EDSS, Expanded Disability Status Scale; HR, hazard ratio; ITT, intention-to-treat; LLN, lower limit of normal; MMF, mycophenolate mofetil; OLP, open-label period; RCP, randomized controlled period.

IMPORTANT SAFETY INFORMATION (cont'd)

WARNINGS AND PRECAUTIONS

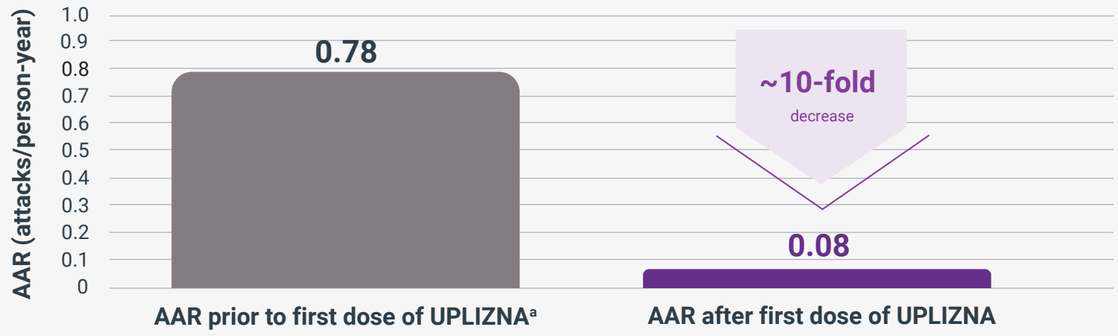
Infusion Reactions: UPLIZNA can cause infusion reactions, which can include headache, nausea, somnolence, dyspnea, fever, myalgia, rash, or other symptoms. Infusion reactions were most common with the first infusion but were also observed during subsequent infusions. Administer pre-medication with a corticosteroid, an antihistamine, and an anti-pyretic.

Infections: The most common infections reported by UPLIZNA-treated patients in the randomized and open-label periods included urinary tract infection (20%), nasopharyngitis (13%), upper respiratory tract infection (8%), and influenza (7%). Delay UPLIZNA administration in patients with an active infection until the infection is resolved.

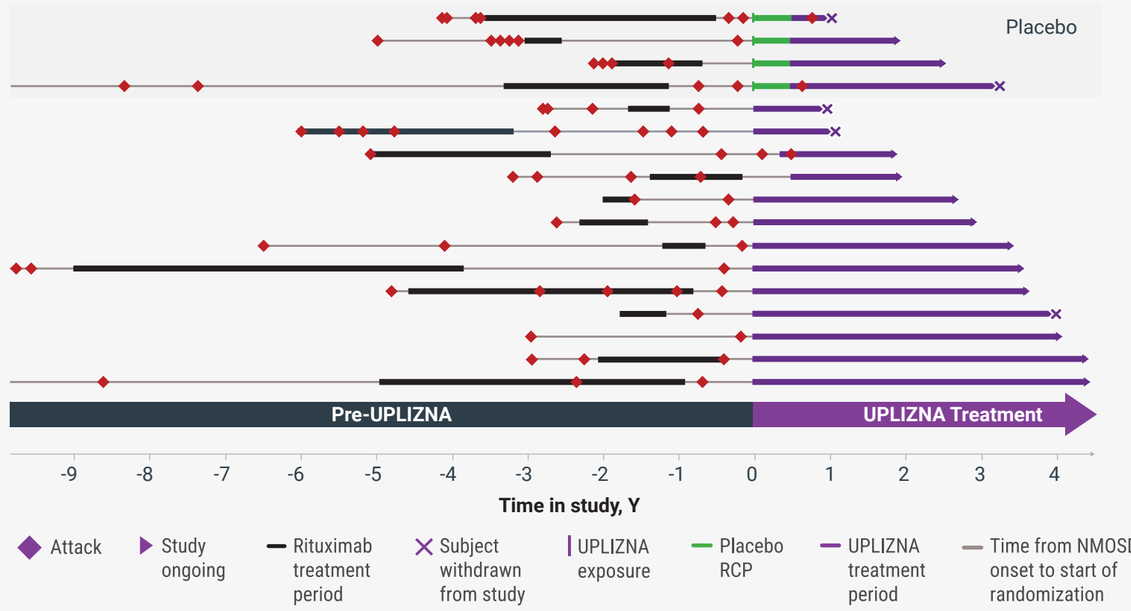
Please see additional Important Safety Information throughout and accompanying Full Prescribing Information.

In a post hoc analysis, **UPLIZNA decreased the rate of attacks in patients with prior rituximab use[1]**

AAR of patients with prior rituximab use (n=17)[1]



Summary of attack data in 17 N-MOmentum participants with prior rituximab use[1]



The data above are from a post hoc subgroup analysis of N-MOmentum in patients previously treated with rituximab (n=17).[1] Analyses were not powered to detect differences within subgroups and results should be considered descriptive and exploratory. UPLIZNA has not been studied head-to-head with rituximab.

- No attacks occurred in the 7 participants who previously experienced an attack while being treated with rituximab before entering the N-MOmentum study[1]

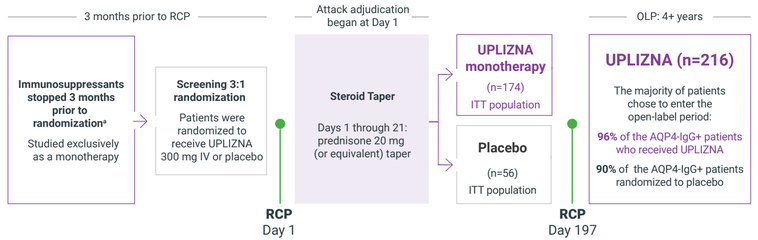
[a]Median time between last rituximab dose and first dose of UPLIZNA was 1.5 years (range: 0.8-4.4).[1]

AAR, annualized attack rate.

UPLIZNA™ inebilizumab-cdon

N-MOmentum was a **phase 2/3, multicenter, double-blind, randomized placebo-controlled trial** with an open-label period[2]

N-MOmentum was the largest NMOSD trial to date (n=230), recruiting diverse participants from 24 countries in the first randomized trial of a B-cell–depleting therapy[2-8]



- ***Inclusion criteria:*** Adults diagnosed with NMOSD, EDSS score ≤8.0, and a history of 1 attack requiring rescue therapy during the year before screening or ≥2 attacks requiring rescue therapy in the 2 years before screening[2]
- ***Primary endpoint:*** Time to onset of an NMOSD attack on or before day 197[2]
- ***Robust attack adjudication:*** All attacks were verified by an independent relapse-adjudication committee using 18 predefined attack criteria[2,9]
- UPLIZNA delivered significant reduction in attacks through the first 28 weeks of treatment, with a 77% relative risk reduction vs placebo; 11% of AQP4-IgG+ patients on UPLIZNA and 42% on placebo experienced an attack (HR=0.227 [95% CI: 0.121-0.423], *P*<0.0001 [primary endpoint])[3]

17 participants with prior rituximab use were studied in a post hoc analysis to see if UPLIZNA demonstrated efficacy in reducing the risk of attacks regardless of former treatment.[1]

[a]Due to a half-life of ≤24 hours, AZA and MMF were allowed up until Day 1. Rituximab was stopped 6 months prior to randomization, unless the patient had B-cell counts above the LLN.[6]

AQ4-IgG+, aquaporin-4-immunoglobulin G positive; AZA, azathioprine; CI, confidence interval; EDSS, Expanded Disability Status Scale; HR, hazard ratio; ITT, intention-to-treat; LLN, lower limit of normal; MMF, mycophenolate mofetil; OLP, open-label period; RCP, randomized controlled period.

IMPORTANT SAFETY INFORMATION (cont'd)

WARNINGS AND PRECAUTIONS

Infusion Reactions: UPLIZNA can cause infusion reactions, which can include headache, nausea, somnolence, dyspnea, fever, myalgia, rash, or other symptoms. Infusion reactions were most common with the first infusion but were also observed during subsequent infusions. Administer pre-medication with a corticosteroid, an antihistamine, and an anti-pyretic.

Infections: The most common infections reported by UPLIZNA-treated patients in the randomized and open-label periods included urinary tract infection (20%), nasopharyngitis (13%), upper respiratory tract infection (8%), and influenza (7%). Delay UPLIZNA administration in patients with an active infection until the infection is resolved.

Please see additional Important Safety Information throughout and accompanying Full Prescribing Information.

TEAEs were generally consistent among patients with and without prior rituximab use[1]

TEAEs and serious TEAEs after receiving UPLIZNA by prior rituximab use[1]

Event, n (%)	Prior rituximab use (n=17)	No prior use of rituximab (n=208)
TEAE		
Any	17 (100)	190 (91)
Related to UPLIZNA	9 (53)	79 (38)
Leading to treatment discontinuation	1 (6)	6 (3)
Grade ≥3	5 (29)	46 (22)
Serious	6 (35)	38 (18)
Serious and related to UPLIZNA	2 (12)	9 (4)
Death	0	2 (1)

- Serious TEAEs related to UPLIZNA were reported in 2 (12%) participants with prior rituximab use and included urinary tract infection and cellulitis[1]
- The most common AEs in participants with prior rituximab use were urinary tract infection and influenza[1]

AEs, adverse events; TEAEs, treatment-emergent adverse events.

IMPORTANT SAFETY INFORMATION (cont'd)

WARNINGS AND PRECAUTIONS (cont'd)

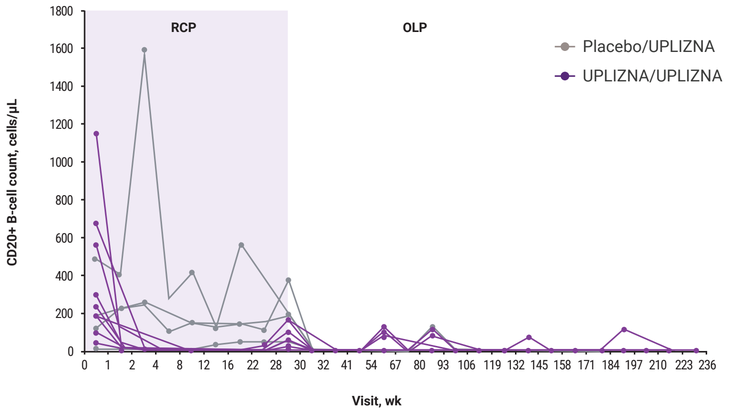
Infections (cont'd): Increased immunosuppressive effects are possible if combining UPLIZNA with another immunosuppressive therapy.

The risk of Hepatitis B Virus (HBV) reactivation has been observed with other B-cell-depleting antibodies. Perform HBV screening in all patients before initiation of treatment with UPLIZNA. Do not administer to patients with active hepatitis.

Although no confirmed cases of Progressive Multifocal Leukoencephalopathy (PML) were identified in UPLIZNA clinical trials, JC virus infection resulting in PML has been observed in patients treated with other B-cell-depleting antibodies and other therapies that affect immune competence. At the first sign or symptom suggestive of PML, withhold UPLIZNA and perform an appropriate diagnostic evaluation.

CD20+ B-cell counts decreased with UPLIZNA treatment in all participants with prior rituximab use[1]

Absolute CD20+ B-cell counts of individual participants with prior rituximab use during the RCP (weeks 0-28) and OLP (>week 28)[1a]



- No correlation between IgG level and infections was observed in a previous analysis of the N-MOmentum study[1]

[a]For CD19+ B-cell counts, assays for CD20+ B cells are used because the presence of UPLIZNA interferes with CD19+ B-cell assay.[8]

IMPORTANT SAFETY INFORMATION (cont'd)

WARNINGS AND PRECAUTIONS (cont'd)

Infections (cont'd): Patients should be evaluated for tuberculosis risk factors and tested for latent infection prior to initiating UPLIZNA.

Vaccination with live-attenuated or live vaccines is not recommended during treatment and after discontinuation, until B-cell repletion.

Reduction in Immunoglobulins: There may be a progressive and prolonged hypogammaglobulinemia or decline in the levels of total and individual immunoglobulins such as immunoglobulins G and M (IgG and IgM) with continued UPLIZNA treatment. Monitor the level of immunoglobulins at the beginning, during, and after discontinuation of treatment with UPLIZNA until B-cell repletion especially in patients with opportunistic or recurrent infections.

Please see additional Important Safety Information throughout and accompanying Full Prescribing Information.

UPLIZNA® inebilizumab-cdon

UPLIZNA reduced the risk of attacks in participants with NMOSD regardless of prior rituximab use[1]

- During the N-MOmentum trial, UPLIZNA delivered significant reduction in attacks through the first 28 weeks of treatment, with a 77% relative risk reduction vs placebo; 11% of AQP4-IgG+ patients on UPLIZNA and 42% on placebo experienced an attack (HR=0.227 [95% CI: 0.121-0.423], *P*<0.0001 [primary endpoint])[3a]

UPLIZNA delivered a ~10-fold reduction in AAR (AAR prior to UPLIZNA=0.78; AAR after first dose of UPLIZNA=0.08)[1]

Patients who experienced an attack while previously on rituximab were attack free on UPLIZNA[1]

Rates of adverse events and infusion-related reactions were generally consistent among patients with and without prior rituximab use[1]

"…None of the 7 participants in the study who experienced breakthrough attacks while previously being treated with rituximab went on to experience an attack while taking [UPLIZNA], suggesting that [UPLIZNA] might be effective in participants who experience treatment failure with rituximab."[1] –Eoin P Flanagan et al.

[a]In the AQP4-IgG+ patient population.[3]

IMPORTANT SAFETY INFORMATION (cont'd)

WARNINGS AND PRECAUTIONS (cont'd)

Fetal Risk: May cause fetal harm based on animal data. Advise females of reproductive potential of the potential risk to a fetus and to use an effective method of contraception during treatment and for 6 months after stopping UPLIZNA.

Adverse Reactions: The most common adverse reactions (at least 10% of patients treated with UPLIZNA and greater than placebo) were urinary tract infection and arthralgia.

Please see accompanying Full Prescribing Information.

References: 1. Flanagan EP, Levy M, Katz E, et al. Inebilizumab for treatment of neuromyelitis optica spectrum disorder in patients with prior rituximab use from the N-MOmentum Study. *Mult Scler Relat Disord*. 2022;57:103352. doi:10.1016/j.msard.2021.103352 **2.** 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;394:1352-1363. doi:10.1016/S0140-6736(19)31817-3 **3.** UPLIZNA (inebilizumab) [prescribing information] Horizon; 2021. **4.** ENSPRYNG® (satralizumab-mgwe) [prescribing information]. Genentech, Inc; 2022. **5**. SOLIRIS® (eculizumab) [prescribing information]. Alexion Pharmaceuticals, Inc; 2024. **6.** ULTOMIRIS® (ravulizumab-cwvz) [prescribing information]. Alexion Pharmaceuticals, Inc; 2024. **7.** Cree BAC, Kim HJ, Weinshener BG, et al. Safety and efficacy of inebilizumab for the treatment of neuromyelitis optica spectrum disorder: end-of-study results from the open-label period of the N-MOmentum trial. *Lancet Neurol*. 2024;23:588-602. doi: 10.1016/S1474-4422(24)00077-2 **8.** Data on File. Horizon; June 2021. **9.** Cree BAC, Bennett JL, Kim HJ, et al. Sensitivity analysis of the primary endpoint from the N-MOmentum study of inebilizumab in NMOSD. *Mult Scler*. 2021;27(13):2052-2061. doi:10.1177/1352458521988926

AMGEN Rare Disease

© 2024 Amgen Inc. All rights reserved. P-UPZ-US-00081-2 11/24

UPLIZNA® inebilizumab-cdon

January 2022

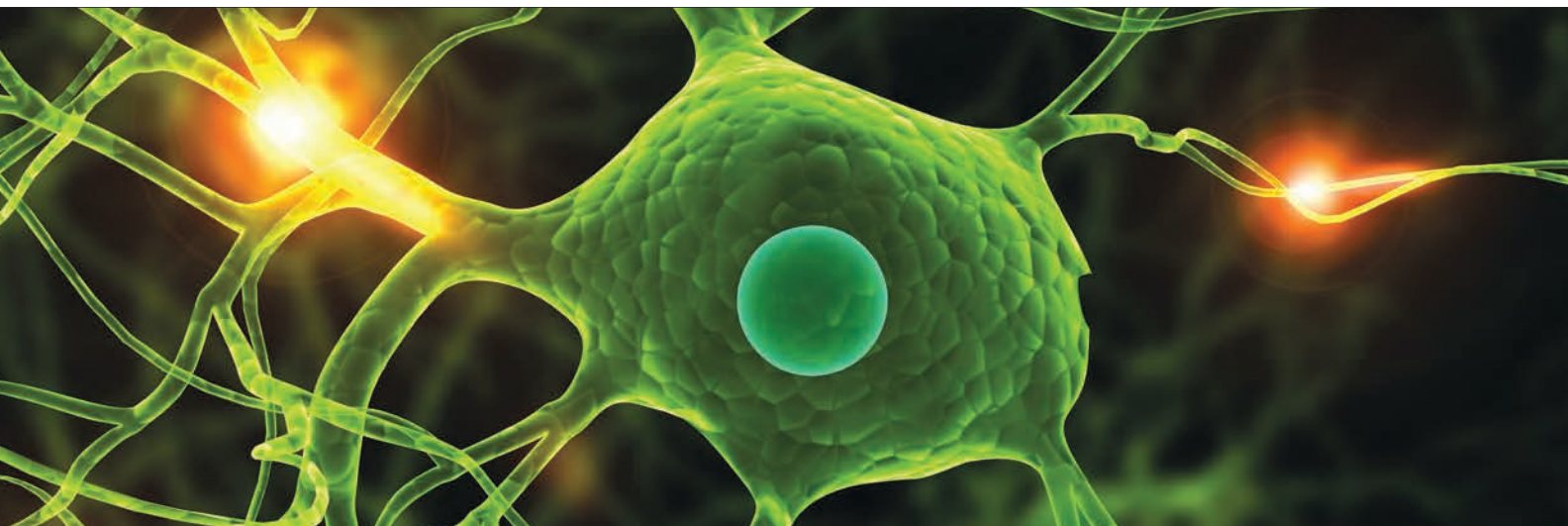
ELSEVIER

MULTIPLE SCLEROSIS
AND RELATED DISORDERS

Inebilizumab for treatment of neuromyelitis optica spectrum disorder in patients with prior rituximab use from the N-MOmentum Study

*Eoin P. Flanagan [a], Michael Levy [b], Eliezer Katz [c], Daniel Cimbora [c], Jorn Drappa [c], Maureen A. Mealy [c], Dewei She [c], Bruce A.C. Cree [d],**

[a] *Departments of Neurology and Laboratory Medicine and Pathology, Mayo Clinic, Rochester, MN, USA*
[b] *Department of Neurology, Massachusetts General Hospital and Harvard Medical School, Boston, MA, USA*
[c] *Horizon Therapeutics (formerly Viela Bio) plc, Deerfield, IL, USA*
[d] *Department of Neurology, UCSF Weill Institute for Neurosciences, University of California San Francisco, 675 Nelson Rising Lane, Box 3206, San Francisco, CA, USA*



No responsibility is assumed by Elsevier for any injury and/or damage to persons or property as a matter of products liability, negligence or otherwise, or from any use or operation of any methods, products, instructions, or ideas contained in the material herein. Because of rapid advances in the medical sciences, in particular, independent verification of diagnoses and drug dosages should be made.

Multiple Sclerosis and Related Disorders 57 (2022) 103352

Contents lists available at ScienceDirect

Multiple Sclerosis and Related Disorders

journal homepage: www.elsevier.com/locate/msard

Inebilizumab for treatment of neuromyelitis optica spectrum disorder in patients with prior rituximab use from the N-MOmentum Study

Eoin P. Flanagan [a], Michael Levy [b], Eliezer Katz [c], Daniel Cimbora [c], Jorn Drappa [c], Maureen A. Mealy [c], Dewei She [c], Bruce A.C. Cree [d,*]

[a] Departments of Neurology and Laboratory Medicine and Pathology, Mayo Clinic, Rochester, MN, USA
[b] Department of Neurology, Massachusetts General Hospital and Harvard Medical School, Boston, MA, USA
[c] Horizon Therapeutics (formerly Viela Bio) plc, Deerfield, IL, USA
[d] Department of Neurology, UCSF Weill Institute for Neurosciences, University of California San Francisco, 675 Nelson Rising Lane, Box 3206, San Francisco, CA, USA

ARTICLE INFO

Keywords:
B-cell depletion
Inebilizumab
Neuromyelitis optica spectrum disorder
Rituximab

ABSTRACT

Background: The B-cell–depleting agent rituximab (anti-CD20) was historically used to prevent attacks in neuromyelitis optica spectrum disorder (NMOSD). Inebilizumab, which targets and depletes CD19-expressing B cells, plasmablasts, and some plasma cells, received approval from the US Food and Drug Administration for treatment of NMOSD based on results from the randomized, placebo-controlled, phase 2/3 N-MOmentum trial. Because of their closely related mechanisms of action, consideration as to whether inebilizumab may be a suitable treatment option for patients with prior rituximab experience is important. This post hoc analysis of data from N-MOmentum assessed inebilizumab efficacy and tolerability in participants previously treated with rituximab.

Methods: Adjudicated attacks, secondary efficacy outcomes, and treatment-emergent adverse events were assessed by prior rituximab use during a 6-month randomized control period and open-label period.

Results: Seventeen participants in N-MOmentum had prior rituximab use, of whom 13 were randomly assigned to the inebilizumab treatment group. Seven of these participants had breakthrough attacks prior to enrollment (annualized attack rate, 0.78 attacks/person-year) despite rituximab use. While they were receiving inebilizumab in the randomized control period, 1 of 13 participants with prior rituximab use had an attack (hazard ratio vs all placebo, 0.16; 95% confidence interval: 0.02 1.20; $p = 0.07$). Two additional participants with prior rituximab use experienced attacks on inebilizumab during the open-label period, with an overall annualized attack rate of 0.08 (95% confidence interval: 0.02 0.34) attacks/person-year. This annualized attack rate was similar to that of participants without prior rituximab use (0.10 [95% confidence interval: 0.07 0.15]). None of the 7 participants who experienced attacks while taking rituximab experienced an attack while receiving inebilizumab. Two (12%) participants with prior rituximab use experienced serious treatment-emergent adverse events related to inebilizumab, with serious or grade ≥3 infections occurring in 3 (18%) participants each. No deaths or opportunistic infections were reported in this cohort.

Conclusions: These findings support the efficacy of inebilizumab in participants with NMOSD who had previously been treated with rituximab. Infections occurred in nearly all study participants with prior rituximab exposure, highlighting a need for clinical vigilance in such individuals. Further studies are necessary to determine potential safety concerns of inebilizumab, including risk of infection, in rituximab-experienced patients.

ClinicalTrials.gov identifier: NCT02200770

1. Introduction

Neuromyelitis optica spectrum disorder (NMOSD) is a rare, chronic, autoimmune inflammatory disorder of the central nervous system characterized by recurrent attacks of optic neuritis and transverse myelitis and, less commonly, by brain involvement. (Pandit et al., 2015; Wingerchuk et al., 2015) Aquaporin-4 (AQP4)–immunoglobulin (Ig)G antibodies are a sensitive (>75% by cell-based assay) and highly specific (>99% by cell-based assay) diagnostic biomarker of NMOSD that appear to be pathogenic. (Wingerchuk et al., 2015; Jasiak-Zatonska et al., 2016; Lennon et al., 2005; Lennon et al., 2004; Waters et al., 2014) The role of pathogenic antibodies in NMOSD provided rationale for use of the

* Corresponding author.

https://doi.org/10.1016/j.msard.2021.103352
Received 31 March 2021; Received in revised form 24 September 2021; Accepted 24 October 2021
Available online 26 October 2021
2211-0348/© 2021 The Authors. Published by Elsevier B.V. This is an open access article under the CC BY license (http://creativecommons.org/licenses/by/4.0/).

B-cell–depleting antibody rituximab, which targets the B-cell antigen CD20, to prevent NMOSD attacks. (Cree et al., 2005; Damato et al., 2016; Trebst et al., 2014) Although evidence for use of rituximab in NMOSD largely comes from retrospective studies, (Cree et al., 2005; Damato et al., 2016; Trebst et al., 2014) its efficacy was supported by recent results from the randomized, placebo-controlled RIN-1 study conducted in Japan. (Tahara et al., 2020)

Inebilizumab is an afucosylated humanized immunoglobulin (Ig) G1κ monoclonal antibody that binds to the B-cell surface antigen CD19 and depletes a wide range of B cells, including plasmablasts and plasma cells. (Cree et al., 2019; Forsthuber et al., 2018) The efficacy and safety of inebilizumab in individuals with NMOSD were demonstrated in the randomized, double-blind, phase 2/3 placebo-controlled N-MOmentum study (ClinicalTrials.gov identifier: NCT02200770). (Cree et al., 2019) Because of their closely related mechanisms of action, it is possible that inebilizumab may not be a suitable treatment option for patients previously treated with rituximab who experienced ongoing disease activity or adverse events with rituximab treatment. Inebilizumab targets a broader range of B cells, including antibody-producing cells unrecognized by anti-CD20 agents (Forsthuber et al., 2018); therefore, it is also possible that inebilizumab may have a greater therapeutic impact than rituximab. This post hoc analysis assessed efficacy and safety outcomes in participants with prior rituximab use who received inebilizumab in N-MOmentum to evaluate whether prior rituximab exposure was associated with attack activity or unexpected safety signals during inebilizumab treatment. Both of these concerns are of pragmatic interest to neurologists who may be considering the merits of initiating inebilizumab in patients with NMOSD previously treated with rituximab.

2. Materials and methods

Detailed methods of N-MOmentum were previously published. (Cree et al., 2019) Briefly, adults with NMOSD were randomized 3:1 to receive intravenous inebilizumab or placebo during a 6-month randomized control period. At the end of that period, participants could choose to receive inebilizumab during an open-label period. Patients who were previously treated with rituximab were permitted to enroll in the study, provided that their most recent rituximab treatment was >6 months before the baseline visit or that their B-cell counts had reconstituted above the lower level of normal (Cree et al., 2019) due to the similarity of mechanisms of action between rituximab and inebilizumab and also to characterize the B-cell depletion following inebilizumab treatment. Exclusion criteria, including a list of concomitant medications that precluded study enrollment, have been previously published. (Cree et al., 2019) No patients received intravenous Ig or subcutaneous Ig during the study.

Post hoc analysis of efficacy and safety outcomes were performed in the subgroups of participants with and without prior rituximab use. Attacks during the randomized control period were analyzed using a Cox proportional hazards regression, (Cree et al., 2019) with all participants who received placebo (regardless of rituximab use) as the reference group. Annualized attack rates (AARs) after the first dose of inebilizumab (randomized control period and open-label period) were calculated using total exposure in person-years. Secondary endpoints assessed included change from baseline in Expanded Disability Status Scale scores, number of active lesions on magnetic resonance imaging (MRI), and number of NMOSD-related hospital stays. (Cree et al., 2019) Safety outcomes included the number of treatment-emergent adverse events (TEAEs) and laboratory parameters (B-cell count, IgG level, and lymphocyte and neutrophil counts). Secondary endpoints and safety outcomes were summarized with descriptive statistics.

3. Results

Of 230 participants who were randomized and received ≥1 dose of inebilizumab or placebo, 17 were treated with rituximab before entering the study; of these, 13 received inebilizumab and 4 received placebo (Table 1). Reported reasons for discontinuation of rituximab were available for 10 of 17 participants and included ongoing disease activity during rituximab treatment (n = 4), changes in insurance coverage (n = 4), change in health care professional (n = 1), and participation in the N-MOmentum trial (n = 1). Most participants with prior rituximab use were women (94%) and seropositive for AQP4-IgG (94%), with a median age of 46 (interquartile range, 31 49) years. Prior to the first dose of inebilizumab, the AAR of this cohort was 0.78 attacks/person-year. Seven participants in this cohort experienced attacks within 6 months of after a rituximab infusion. Baseline characteristics of participants with prior use of rituximab were similar to those without prior experience with rituximab (n = 208), including prior use of azathioprine and mycophenolate mofetil (Supplemental Table 1).

The individual attack timelines of the 17 participants with prior rituximab use are presented in Fig. 1A. During the randomized control period, 1 of 13 (8%) participants with prior rituximab use who received inebilizumab experienced an attack compared with 22 of 56 (39%) participants assigned to placebo (regardless of rituximab use; hazard ratio [HR] 0.16; 95% confidence interval [CI]: 0.02 1.20; $p = 0.07$). Two additional participants with prior rituximab use experienced attacks while receiving inebilizumab during the open-label period, both of whom were originally randomized to placebo. The 3 rituximab-experienced participants who had attacks while taking inebilizumab had 1 attack each during their time in the study (1.54 years for the participant randomized to inebilizumab; 0.51 and 2.74 years for the

Table 1
Demographics and Baseline Characteristics of Participants in N-MOmentum With Prior Rituximab Use

Parameter	Randomized control group		
	Inebilizumab (n=13)	Placebo (n=4)	Overall (N=17)
Age, median (IQR), y	47 (32-50)	38 (29-46)	46 (31-49)
Women, n (%)	13 (100)	3 (75)	16 (94)
White or Asian, n (%)	4 (31)	1 (25)	5 (29)
AQP4-IgG seropositive	12 (92)	4 (100)	16 (94)
B-cell count, median (IQR), cells/μL			
CD19+	239.8 (181.2-319.3)	150.3 (67.8-330.1)	239.7 (171.8-319.3)
CD20+	235.7 (181.2-300.9)	150.7 (66.4-333.1)	219.5 (173.1-300.9)
Time between last rituximab dose and first dose of inebilizumab, median (range), y	1.5 (0.8-4.4)	1.3 (0.9-3.1)	1.5 (0.8-4.4)
Rituximab doses, median (range), n	1 (1-11)	1 (1-2)	1 (1-11)
Attack while on rituximab, n (%)	5 (38)	2 (50)	7 (41)
AAR before first dose of inebilizumab (range)	0.73 (0.34-1.89)	0.92 (0.40-1.88)	0.78 (0.34-1.89)

AQP4, aquaporin-4; AAR, annualized attack rate; IgG, immunoglobulin; IQR, interquartile range. Statistical comparisons between the two groups were not performed because the sample size of the prior rituximab group was too small for meaningful analysis.

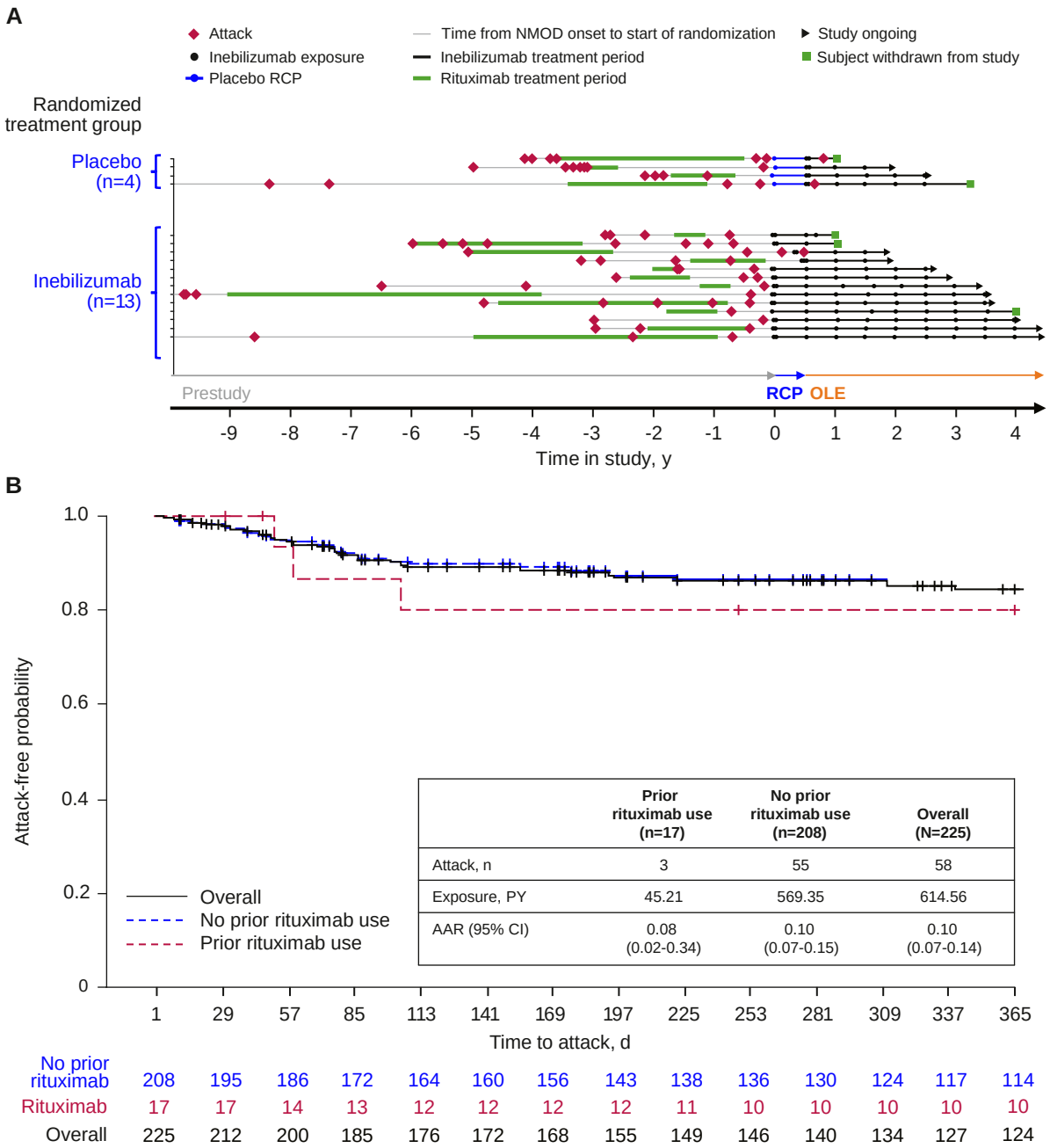


Fig. 1. Summary of attack data in participants with prior rituximab use. (A) Timeline of treatment history and adjudicated attacks by treatment assignment in the randomized control period. (B) Kaplan–Meier plot of attack-free probability after the first dose of inebilizumab by prior rituximab use. AAR, annualized attack rate; CI, confidence interval; NMOSD, neuromyelitis optica spectrum disorder; OLE, open-label period; P-Y, participant year; RCP, randomized control period.

participants randomized to placebo). All 3 attacks were myelitis, one of which was graded as mild by the opticospinal impairment scale. (Wingerchuk et al., 1999) After the first inebilizumab administration, the AAR of rituximab-experienced participants was similar to those without prior rituximab use (0.08 and 0.10 attacks/person-year, respectively; Fig. 1B).

Secondary endpoints assessed during the randomized control period are summarized in Supplemental Table 2. Among 13 participants with prior use of rituximab who received inebilizumab during the randomized control period, 2 (15%) experienced worsening of Expanded Disability Status Scale scores, 6 (46%) had active lesions on MRI, and 1 (8%) had a hospital stay related to NMOSD. One of the 2 cases of Expanded Disability Status Scale score worsening and hospitalization were related to the attack that occurred during the randomized controlled period. Secondary outcomes in the inebilizumab groups were generally similar regardless of prior rituximab use.

Nine of 17 (53%) participants with prior rituximab use and 79 of 208 (38%) without prior rituximab use experienced a TEAE associated with inebilizumab (Table 2). Low rates were observed of serious TEAEs related to inebilizumab in both groups. Serious TEAEs related to inebilizumab were reported in 2 (12%) participants with prior rituximab use and included urinary tract infection and cellulitis. The proportions of participants who experienced infusion-related reactions while receiving inebilizumab were similar regardless of prior rituximab use. Most participants, with or without prior rituximab experience (94% and 70%, respectively), had ≥1 infection while receiving inebilizumab. Serious and grade ≥3 infections each occurred in 3 (18%) participants with prior rituximab experience and 20 (10%) and 22 (11%) participants,

Table 2
TEAEs, Serious TEAEs, and TEAEs of Special Interest After Receiving Inebilizumab by Prior Rituximab Use

Event, n (%)	Prior rituximab use (n=17)	No prior use of rituximab (n=208)
TEAE		
Any	17 (100)	190 (91)
Related to inebilizumab	9 (53)	79 (38)
Leading to treatment discontinuation	1 (6)	6 (3)
Grade ≥3	5 (29)	46 (22)
Serious	6 (35)	38 (18)
Serious and related to inebilizumab	2 (12)	9 (4)
Death	0	2 (1)
TEAE of special interest		
Any	16 (94)	157 (76)
Infusion-related reaction	2 (12)	25 (12)
Anaphylactic reaction	0	0
Hypersensitivity	1 (6)	2 (1)
Infections	16 (94)	146 (70)
Serious	3 (18)	20 (10)
Grade		
1	9 (53)	115 (55)
2	12 (71)	75 (36)
3	2 (12)	17 (8)
4	1 (6)	4 (2)
5	0	1 (<1)
Hepatic function abnormality	1 (6)	14 (7)
Cytopenia	1 (6)	12 (6)
Opportunistic infections	0	2 (1)
Unconfirmed PML	0	1 (1)[a]

PML, progressive multifocal leukoencephalopathy; TEAE, treatment-emergent adverse event. [a]Magnetic resonance imaging and JCV results were inconclusive.[11] Statistical comparisons between the two groups were not performed because the sample size of the prior rituximab group was too small for meaningful analysis.

respectively, without prior rituximab experience. In participants with prior rituximab use, serious and/or grade ≥3 infections included nasopharyngitis (grade 3), urinary tract infection (serious and grade 3), cellulitis (serious and grade 3), and perforated appendicitis (serious and grade 4), all occurring in 1 participant each. No deaths, opportunistic infections, or cases of progressive multifocal leukoencephalopathy, a recognized complication of B–cell-depleting therapies, (Focosi et al., 2019) were reported among the 17 rituximab-experienced participants. The most common AEs in participants with prior rituximab use were urinary tract infection and influenza (Supplemental Table 3).

CD20+ B-cell counts decreased with inebilizumab treatment in all participants with prior rituximab use (Fig. 2). After inebilizumab treatment, participants with and without prior rituximab use experienced annual reductions from baseline in IgG levels of 42.3 mg/dL/year and 49.5 mg/dL/year, respectively ($p = 0.67$). While they were receiving inebilizumab, 6 (35%) participants with prior rituximab use and 30 (15%) participants without prior rituximab use experienced IgG levels <500 mg/dL (Fig. 3). No correlation between IgG level and infections was observed in a previous analysis of the N-MOmentum study.(15) IgM levels were similarly reduced following inebilizumab treatment regardless of prior rituximab use (Supplemental Fig. 1). Generally similar lymphocyte and neutrophil counts by toxicity grade were observed with the inebilizumab treatment group regardless of prior rituximab experience, with most reported as grade 0/1 in both groups (Supplemental Table 4).

4. Discussion

This post hoc analysis of N-MOmentum assessed the efficacy and safety of inebilizumab in participants with NMOSD who were previously treated with rituximab. Because inebilizumab and rituximab target and deplete B cells, (Damato et al., 2016; Cree et al., 2019) this analysis aimed to provide insight as to whether prior experience with rituximab may predict the efficacy of inebilizumab in this cohort. Overall, efficacy of inebilizumab was comparable for participants with or without prior rituximab exposure. The AAR of the cohort of participants with prior rituximab use decreased from 0.78 at baseline to 0.08 with inebilizumab treatment and was similar to the AAR of participants without prior rituximab use (0.10). Furthermore, none of the 7 participants in the study who experienced breakthrough attacks while previously being treated with rituximab went on to experience an attack while taking

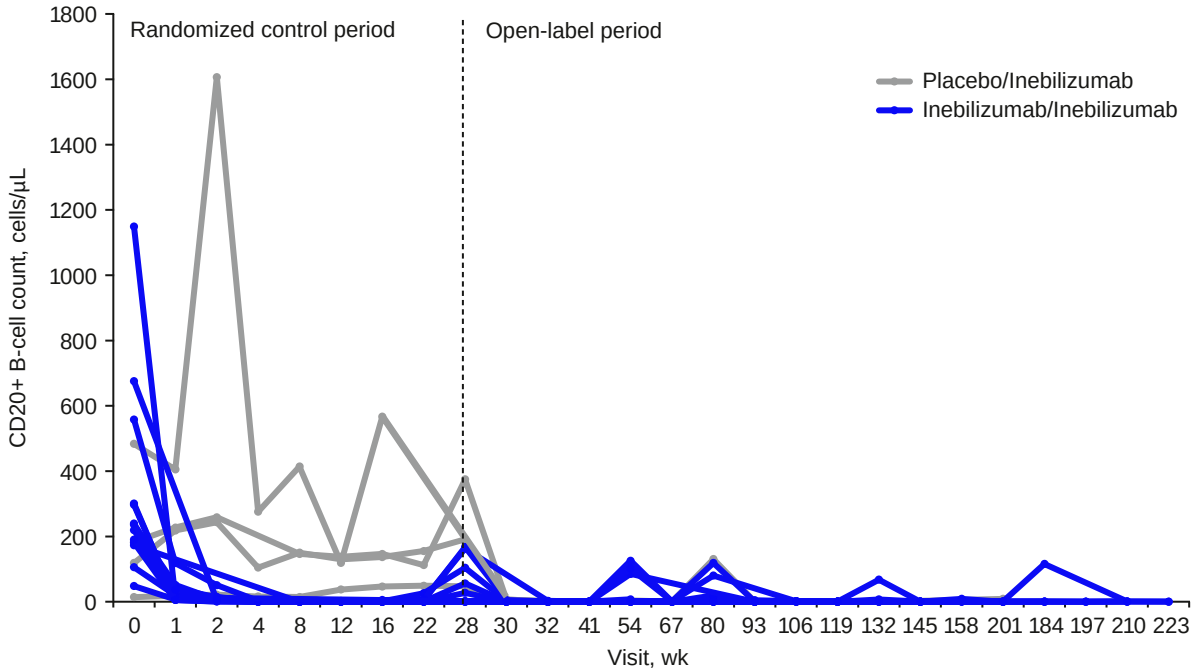


Fig. 2. Absolute CD20+ B-cell counts of individual participants with prior rituximab use during the randomized control period (weeks 0-28) and open-label period (>week 28). All participants received inebilizumab during the open-label period.

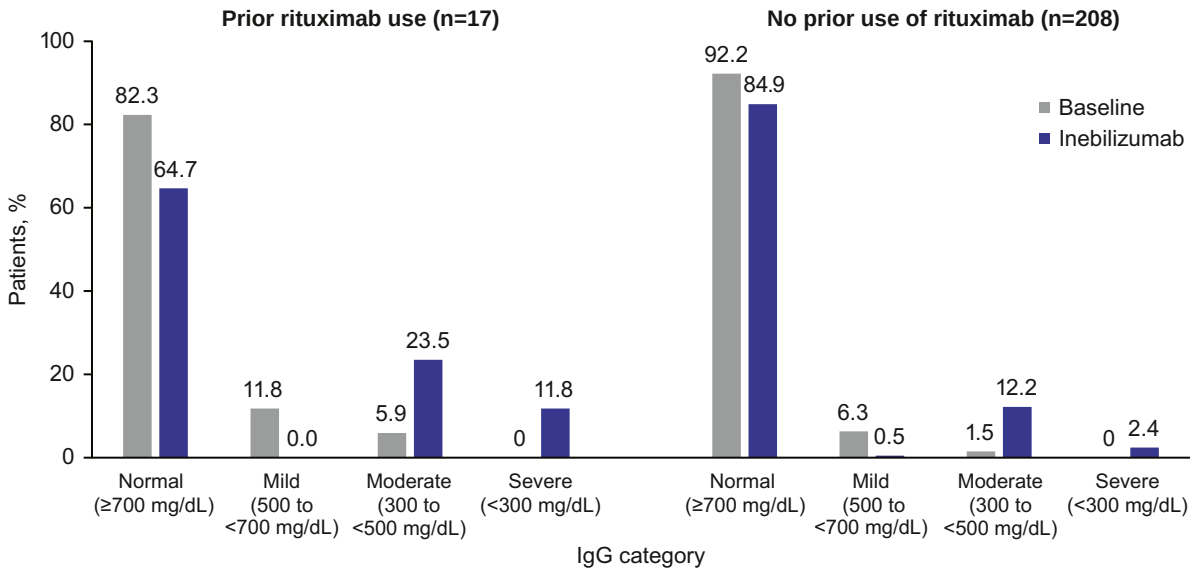


Fig. 3. IgG concentrations at baseline and with inebilizumab treatment in participants with and without prior use of rituximab. IgG, immunoglobulin G.

inebilizumab, suggesting that inebilizumab might be effective in participants who experience treatment failure with rituximab.

A similar analysis was performed to assess eculizumab, (Pittock et al., 2019) a terminal complement inhibitor, in 46 participants with prior rituximab experience in the PREVENT study. (Levy et al., 2020) This study found a significantly lower risk of adjudicated relapse with eculizumab compared with placebo (HR 0.09; 95% CI: 0.01 0.77; $p<0.01$) in the rituximab-experienced cohort. Eculizumab targets the terminal complement pathway (a critical component of the innate immune system); therefore, the potential risks of eculizumab might be different than the risks of inebilizumab, which targets B cells involved in adaptive immune responses, in patients with prior rituximab use. Rituximab is commonly used for treatment of NMOSD; therefore, continuing to investigate the efficacy and safety of newer therapies in the NMOSD treatment landscape will be crucial in patients previously treated with rituximab.

Findings of the current analysis provide important insight into whether previous experience with a B-cell–depleting agent may introduce unique safety concerns for inebilizumab in patients with NMOSD. Inebilizumab had a generally similar safety profile in participants with and without prior rituximab use, with similar rates of TEAEs and infusion-related reactions. Sixteen (94%) participants with prior use of rituximab experienced infections, resulting in an infection rate numerically higher than the group with no prior use of rituximab (70%); however, most of these infections were grade 1/2. Furthermore, the low number of participants greatly limits the assessment of infection risk in this cohort. The same is true of the numerically greater proportion of participants with prior rituximab use who experienced IgG levels <500 mg/dL than those with no prior use of rituximab. Additional data from more patients being converted from rituximab to inebilizumab are needed to better characterize the infection risk and correlation to IgG level in this group.

A key limitation of the current analysis is the limited number of participants with prior rituximab experience relative to the number of study participants in N-MOmentum. The low enrollment of rituximab-experienced participants is likely attributable to the related mechanisms of the two agents and the exclusion of patients with rituximab use in the 6 months before screening. Another limitation to this study is the inclusion criteria that required patients with prior rituximab exposure to either reconstitute B cells to the lower limit of normal or to not have been treated with rituximab for ≥6 months. These inclusion requirements were employed to limit the potentially confounding effects of prior rituximab use during the relatively short duration of the randomized control period (limited to a maximum of 6.5 months of potential placebo). These concerns are not relevant to clinical practice in which efficacy is evaluated on an individual basis. Patients could potentially be switched from rituximab to inebilizumab without evidence of B cell reconstitution, or sooner than 6 months after the last rituximab infusion, and the inebilizumab prescribing information does not include such limitations.

5. Conclusions

Overall, the findings of this analysis may support the efficacy of inebilizumab in preventing attacks in participants with NMOSD regardless of prior rituximab experience. Further studies are necessary to determine potential safety concerns of inebilizumab, including risk of infection and hypogammaglobulinemia, in patients with prior rituximab use.

Competing Interests

Eoin P. Flanagan is a site principal investigator of a trial funded by MedImmune/Horizon Therapeutics (formerly Viela Bio) and received funding to support the trial. Michael Levy has received research support from Genentech, Horizon Therapeutics (formerly Viela Bio), and Alexion and has received consulting fees from Genentech, Horizon Therapeutics, Alexion, Mitsubishi Pharma, and UCB Pharmaceuticals. Bruce A.C. Cree has received consulting fees from Alexion, Atara, Autobahn, Biogen, EMD Serono, Novartis, Sanofi, TG Therapeutics, and Therini and has received research support from Genentech. Daniel Cimbora, Jorn Drappa, Eliezer Katz, Maureen A. Mealy, and Dewei She are employees of and own stock in Horizon Therapeutics (formerly Viela Bio).

Acknowledgments

This study was supported by Horizon Therapeutics (formerly Viela Bio). Medical writing and editorial assistance were provided under the direction of the authors by Sara Gibson, PhD, of MedThink SciCom and Sherri Damlo, ELS, with support from Horizon Therapeutics.

Source of funding

The sponsor, Horizon Therapeutics (formerly Viela Bio), played a

role in the design and conduct of the study, as well as the analysis and interpretation of the data, in collaboration with the study's investigators.

Data statement

Data that are nonproprietary in nature can be shared on request.

Author statement

All listed authors meet the criteria for authorship set forth by the International Committee of Medical Journal Editors.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.msard.2021.103352.

References

Pandit, L, Asgari, N, Apiwattanakul, M, et al., 2015. Demographic and clinical features of neuromyelitis optica: a review. Mult. Scler. 21 (7), 845–853.

Wingerchuk, DM, Banwell, B, Bennett, JL, et al., 2015. International consensus diagnostic criteria for neuromyelitis optica spectrum disorders. Neurology 85 (2), 177–189.

Jasiak-Zatonska, M, Kalinowska-Lyszczarz, A, Michalak, S, Kozubski, W., 2016. The immunology of neuromyelitis optica-current knowledge, clinical implications, controversies and future perspectives. Int. J. Mol. Sci. 17 (3), 273.

Lennon, VA, Kryzer, TJ, Pittock, SJ, Verkman, AS, Hinson, SR., 2005. IgG marker of optic-spinal multiple sclerosis binds to the aquaporin-4 water channel. J. Exp. Med. 202 (4), 473–477.

Lennon, VA, Wingerchuk, DM, Kryzer, TJ, et al., 2004. A serum autoantibody marker of neuromyelitis optica: distinction from multiple sclerosis. Lancet 364 (9451), 2106–2112.

Waters, PJ, Pittock, SJ, Bennett, JL, Jarius, S, Weinshenker, BG, Wingerchuk, DM., 2014. Evaluation of aquaporin-4 antibody assays. Clin. Exp. Neuroimmunol. 5 (3), 290–303.

Cree, BA, Lamb, S, Morgan, K, Chen, A, Waubant, E, Genain, C., 2005. An open label study of the effects of rituximab in neuromyelitis optica. Neurology 64 (7), 1270–1272.

Damato, V, Evoli, A, Iorio, R., 2016. Efficacy and safety of rituximab therapy in neuromyelitis optica spectrum disorders: a systematic review and meta-analysis. JAMA Neurol. 73 (11), 1342–1348.

Trebst, C, Jarius, S, Berthele, A, et al., 2014. Update on the diagnosis and treatment of neuromyelitis optica: recommendations of the Neuromyelitis Optica Study Group (NEMOS). J Neurol 261 (1), 1–16.

Tahara, M, Oeda, T, Okada, K, et al., 2020. Safety and efficacy of rituximab in neuromyelitis optica spectrum disorders (RIN-1 study): a multicentre, randomised, double-blind, placebo-controlled trial. Lancet Neurol. 19 (4), 298–306.

Cree, BAC, Bennett, JL, Kim, HJ, et al., 2019. Inebilizumab for the treatment of neuromyelitis optica spectrum disorder (N-MOmentum): a double-blind, randomised placebo-controlled phase 2/3 trial. The Lancet 394 (10206), 1352–1363.

Forsthuber, TG, Cimbora, DM, Ratchford, JN, Katz, E, Stuve, O., 2018. B cell-based therapies in CNS autoimmunity: differentiating CD19 and CD20 as therapeutic targets. Ther. Adv. Neurol. Disord. 11, 1756286418761697.

Wingerchuk, DM, Hogancamp, WF, O'Brien, PC, Weinshenker, BG., 1999. The clinical course of neuromyelitis optica (Devic's syndrome). Neurology 53 (5), 1107–1114.

Focosi, D, Tuccori, M, Maggi, F., 2019. Progressive multifocal leukoencephalopathy and anti-CD20 monoclonal antibodies: What do we know after 20 years of rituximab. Rev. Med. Virol. 29 (6), e2077.

Greenburg, B, She, D, Ratchford, J, et al., 2021. Immunoglobulin kinetics and infection risk after long-term inebilizumab treatment for NMOSD. Poster presented at: ACTRIMS Forum. February 25-27.

Pittock, SJ, Berthele, A, Fujihara, K, et al., 2019. Eculizumab in aquaporin-4-positive neuromyelitis optica spectrum disorder. N Engl. J. Med. 381 (7), 614–625.

Levy, M, et al., 2020. Efficacy and safety of eculizumab in patients with neuromyelitis optica spectrum disorder previously treated with rituximab: findings from the phase 3 PREVENT study. Neurology 94, 15 supplement. Abstract 1788.

This reprint is provided with the support of Horizon Therapeutics.

89334

ELSEVIER

email: reprints@elsevier.com

P-UPZ-US-00106-2 06/22