Comparative Efficacy of Inebilizumab Versus Rituximab for Attack Prevention in Aquaporin-4 Antibody-Positive Neuromyelitis Optica Spectrum Disorder: A Matching-Adjusted Indirect Comparison Analysis

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INTRODUCTION

- Neuromyelitis optica spectrum disorder (NMOSD) is a rare, autoimmune condition of the central nervous system, primarily affecting the optic nerves and spinal cord. It is characterized by severe attacks that can lead to significant pain, visual impairment, paralysis, and reduced quality of life.[1]
- Inebilizumab, a humanized anti-CD19 monoclonal antibody, is approved for use in patients with aquaporin-4 antibody-positive (AQP4+) NMOSD based on the pivotal phase 2/3 N-MOmentum trial,[2] while rituximab, a chimeric anti-CD20 monoclonal antibody, is commonly used off-label in this same patient group.
- Both inebilizumab and rituximab are recommended treatment options in international guidelines, including those from the Neuromyelitis Optica Study Group.[3] However, no head-to-head trial has directly compared their efficacy in preventing attacks in AQP4+ NMOSD.

OBJECTIVES

- To compare the efficacy of inebilizumab monotherapy with rituximab monotherapy in reducing the risk of an attack in adult patients with AQP4+ NMOSD.

METHODS

Data

- A systematic literature review was conducted in April 2023 and updated in March 2024 to identify relevant clinical studies evaluating inebilizumab and rituximab in patients with AQP4+ NMOSD. One study evaluating inebilizumab (N-MOmentum),[2] and eight studies evaluating rituximab were identified.[4–11] Most of the rituximab studies exhibited heterogeneity in patient populations (e.g., inclusion of non-exclusive AQP4+ populations) and treatment regimens (e.g., concomitant steroid use) that prevented their suitability for inclusion in an indirect treatment comparison.
- Kim et al,[6] a prospective single-arm trial, was the only rituximab monotherapy study with extractable individual patient data (IPD) for an AQP4+ population, enabling estimation of baseline and on-treatment time to first attack (TTFA), annualized attack rate (AAR), and disease duration. Of the 30 patients enrolled, 21 (70%) were AQP4+, and of these 17/21 (81%) had been previously treated with a maintenance immunosuppressive therapy (azathioprine, interferon beta, or prednisolone), all patients were biologic-naïve. Patients received rituximab induction therapy of 375 mg/m^2 weekly for 4 weeks or 1000 mg twice within a 2-week period, followed by a maintenance dose of 375 mg/m^2 whenever the frequency of memory B cells was ≥ 0.05% during the 24-month study period.
- Given the absence of a common comparator, an unanchored matching-adjusted indirect comparison (MAIC) was undertaken using data from Kim et al and N-MOmentum.
- In N-MOmentum, patients received 300 mg inebilizumab on days 1 and 15 during the 28-week randomized controlled period (RCP) and subsequently every 26 weeks as maintenance treatment in the open-label extension (OLE). Of patients randomized to inebilizumab, 161/174 were AQP4+, of whom 108/161 (67%) had previously been treated with a maintenance immunosuppressive therapy (primarily azathioprine or mycophenolate), including 23/161 (14%) with a prior biologic.

Statistical methods

- The MAIC was conducted in patients with AQP4+ NMOSD using IPD from N-MOmentum (n = 161)[2] and digitized IPD from Kim et al (n = 21).[6] This approach is consistent with NICE Decision Support Unit guidance and has previously been applied in rare diseases.[12,13]
- Baseline covariates considered for matching included age at baseline, sex, age at diagnosis (age at onset), disease duration, Expanded Disability Status Scale score, baseline AAR, and prior azathioprine use. Covariate selection was informed by analyses of the RCP of N-MOmentum and clinical expert input.
- The effective sample size (ESS) was calculated, and the distribution of patient weights was generated. Kaplan–Meier plots were generated for TTFA for both rituximab and inebilizumab in the unweighted and weighted N-MOmentum population.
- The primary outcome of the MAIC was TTFA, estimated as a hazard ratio (HR). The secondary outcome was AAR, estimated as a rate ratio (RR).
- Investigator-determined attacks were used to ensure consistency across studies, because adjudicated attacks were not reported in Kim et al.
- The base case analysis for TTFA used data from the RCP of the N-MOmentum study. Additional analyses included pooled data from the RCP and OLE of N-MOmentum.
- Propensity score weighting was implemented within the weighted proportional hazards Cox models (primary outcome) and the weighted negative binomial model (secondary outcome).

RESULTS

Matching

- For the base case analysis, age at baseline, AAR, and sex were selected for the matching as these were considered to be the most important prognostic factors and potential treatment effect modifiers. Of note, female sex has previously been identified as having a higher risk of relapse than male sex.[14]
- Baseline characteristics for both studies are shown in **Table 1**. After aligning patient selection and matching, differences were eliminated or minimized.

Time to first attack

Base case analysis

- In the unmatched analysis using RCP data from N-MOmentum for inebilizumab, the estimated HR for TTFA was 0.59 (95% confidence interval [CI] 0.22–1.56) favoring inebilizumab versus rituximab (**Figure 1**). In the matched analysis, the HR was 0.54 (95% CI 0.20–1.44) suggesting a 46% risk reduction with inebilizumab versus rituximab (**Figure 1**).

Scenario analyses

- Results were consistent across scenario analyses (**Table 2**). In a scenario using pooled RCP and OLE data from N-MOmentum, the estimated HR for TTFA was 0.58 (95% CI 0.25–1.38) in the unmatched analysis and 0.55 (95% CI 0.22–1.34) in the matched analysis (**Figure 2**). This corresponds to a 45% reduction in risk for inebilizumab compared with rituximab.

Annualized attack rate

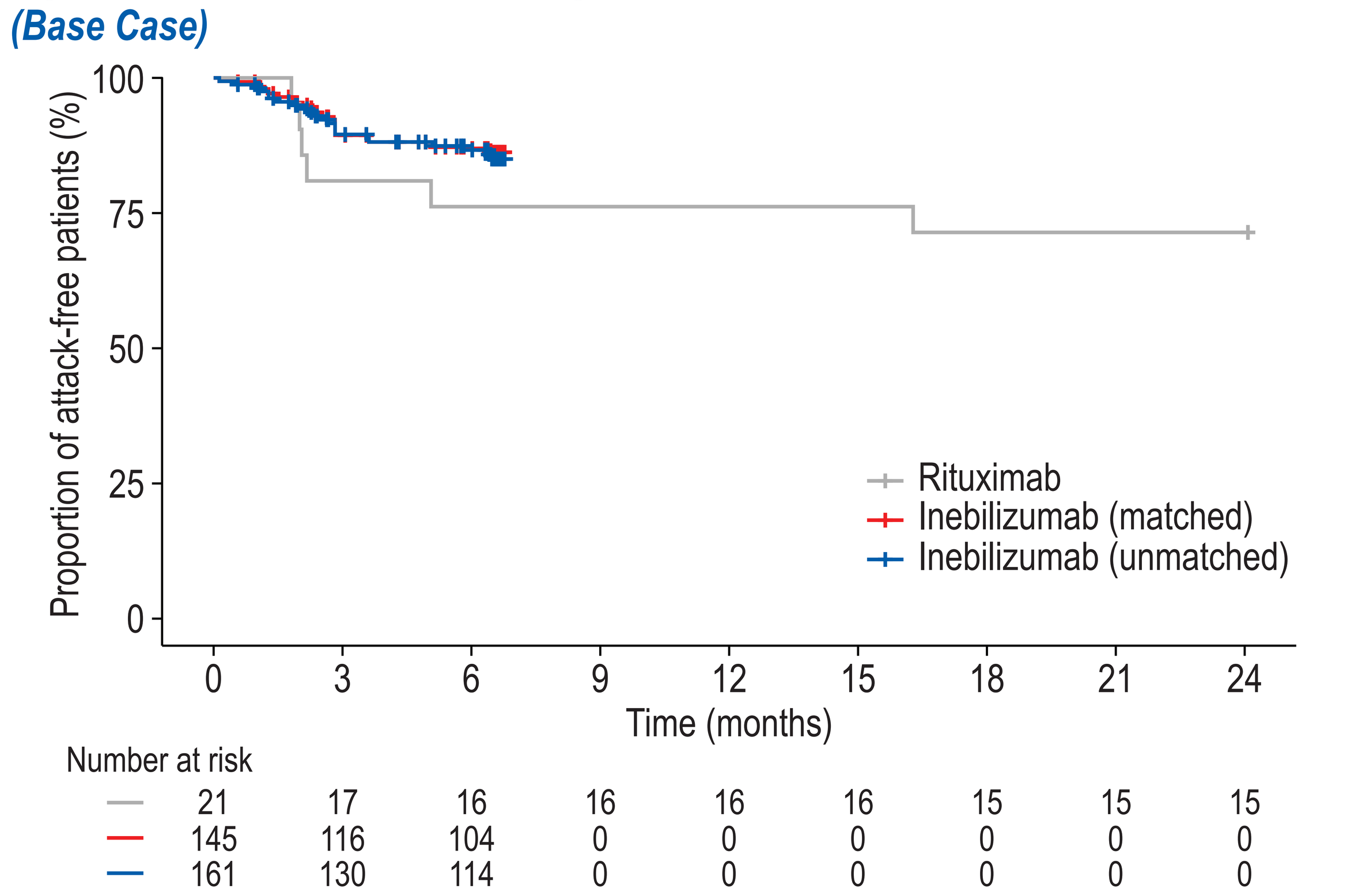
- Secondary analyses of AAR using pooled RCP and OLE data from N-MOmentum for inebilizumab demonstrated a RR of 0.37 (95% CI 0.14–0.97) in the unmatched analysis and 0.32 (95% CI 0.12–0.85) in the matched analysis, favoring inebilizumab versus rituximab (**Figure 3**).

Table 1. Baseline Characteristics in Kim et al and N-MOmentum

Covariate	Kim et al, 2011 (AQP4+ population)	N-MOmentum RCP		N-MOmentum OLE + RCP	
	Rituximab (n = 21)	Inebilizumab unmatched (n = 161)	Inebilizumab matched (ESS = 136.6)	Inebilizumab unmatched (n = 213)	Inebilizumab matched (ESS = 176.1)
Proportion with AQP4+ NMOSD, %	100	100	100	100	100
Age, years, mean (SD)	41 (10.3)	43.2 (11.6)	41.0 (10.3)	43.0 (12.3)	41.0 (10.3)
Proportion male, %	4.8	6.2	4.8	6.1	4.8
Age at diagnosis, years, mean (SD)	35.8 (10.9)	41.2 (12.1)	39.3 (10.9)	40.9 (12.8)	39.2 (11.0)
Log(disease duration), mean (SD)[a]	1.28 (0.96)	1.02 (1.23)	0.77 (1.14)	1.05 (1.22)	0.77 (1.17)
EDSS score, mean (SD)	4.8 (2.0)	3.8 (1.8)	3.76 (1.72)	4.0 (1.8)	3.88 (1.73)
Log(AAR) prior to treatment, mean (SD)[a]	0.44 (0.68)	0.19 (0.84)	0.44 (0.67)	0.17 (0.81)	0.44 (0.67)
Prior azathioprine treatment, %	23.8	39.1	36.6	39.4	36.7

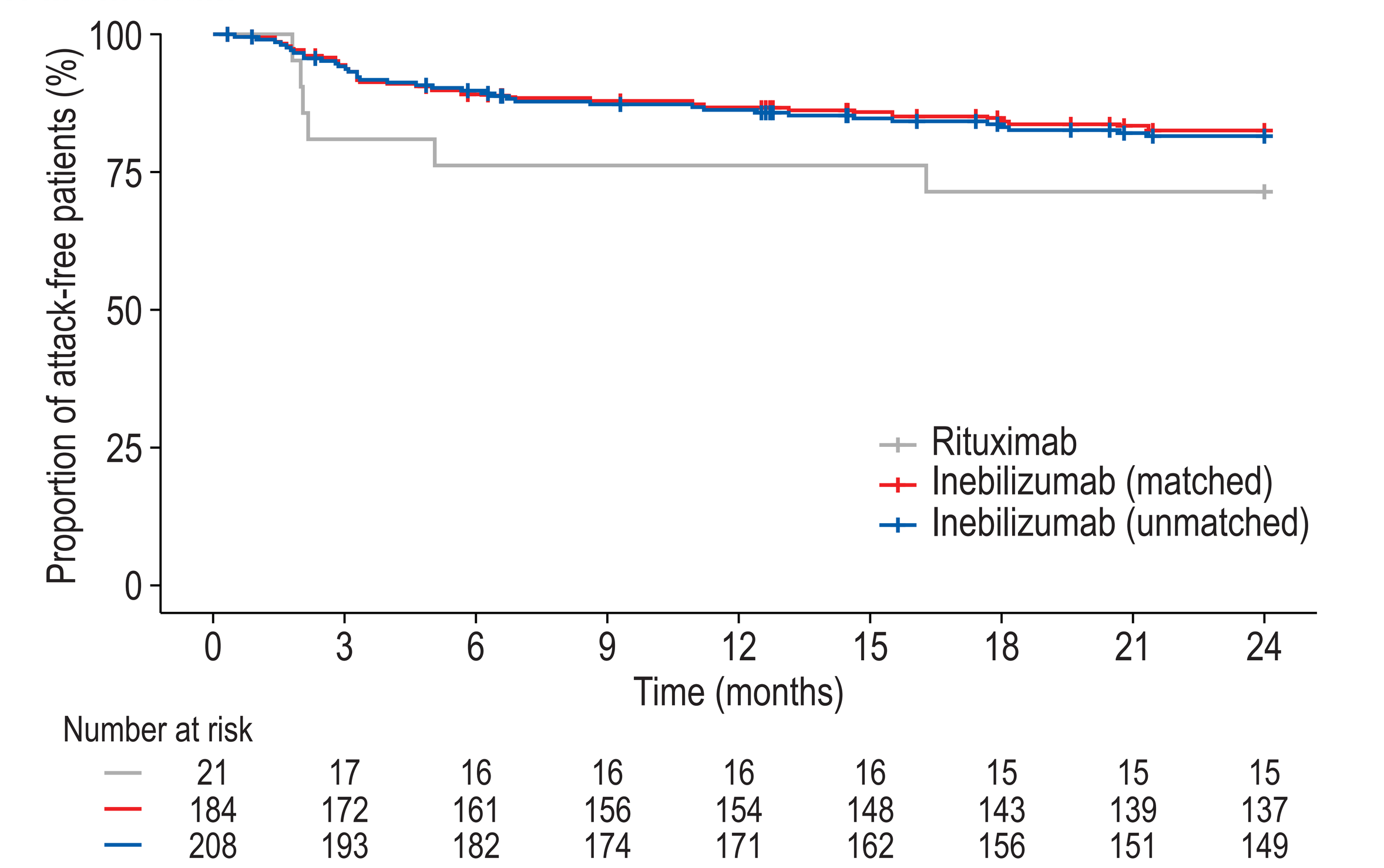
Matched variables are shaded in light orange.
[a]Log transformation was applied to reduce skewness in the empirical distributions of disease duration and baseline AAR.
AAR, annualized attack rate; AQP4, aquaporin-4; EDSS, Expanded Disability Status Scale; ESS, effective sample size; NMOSD, neuromyelitis optica spectrum disorder; OLE, open-label extension; RCP, randomized controlled period; SD, standard deviation.

Figure 1. Time to First Attack Using RCP Data From N-MOmentum for Inebilizumab (Base Case)



RCP, randomized controlled period.

Figure 2. Time to First Attack Using Pooled RCP and OLE Data From N-MOmentum



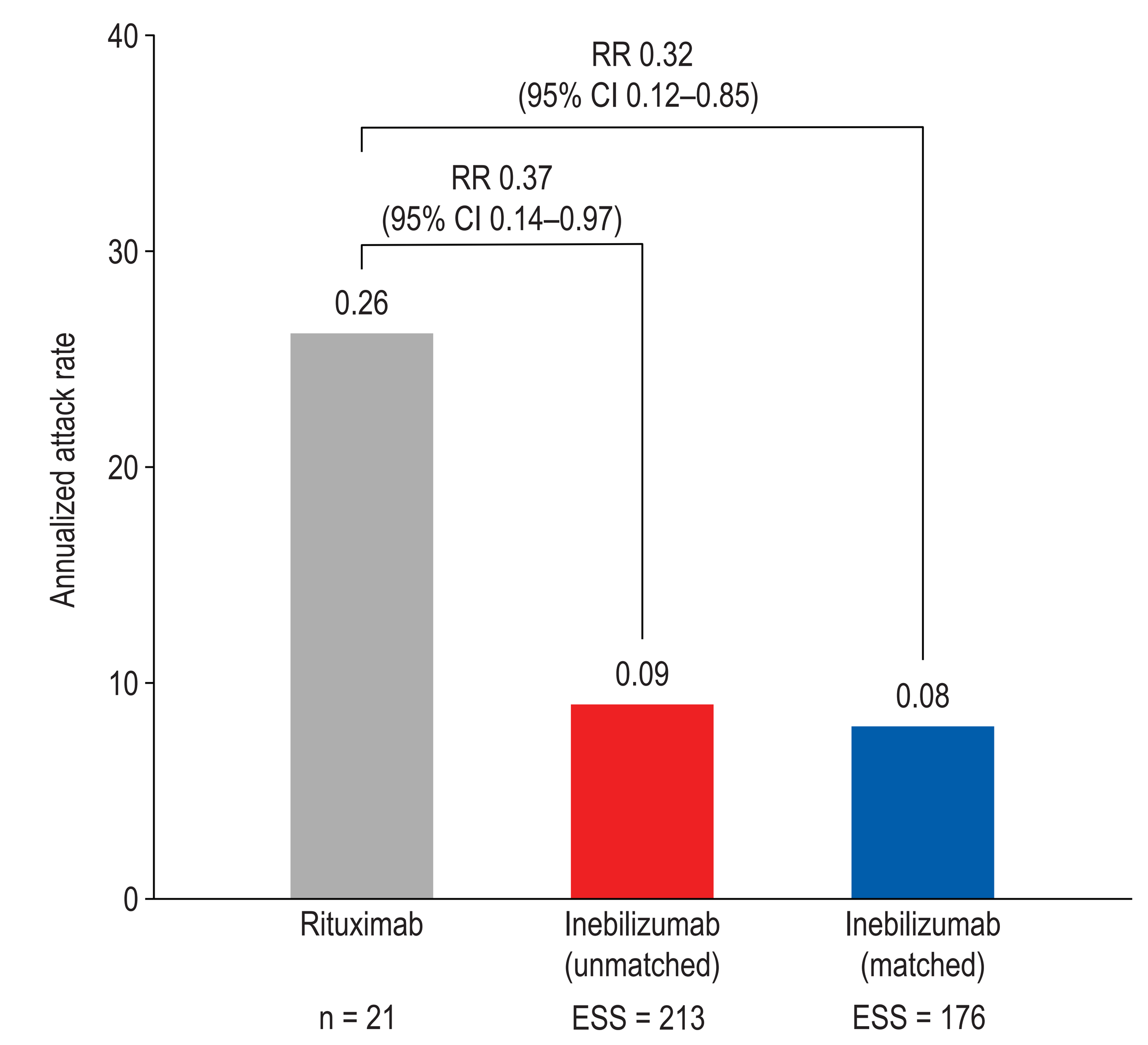
Note: n = 208 rather than 213 as shown in Table 1 because 5 patients had missing data on matching covariates.
OLE, open-label extension; RCP, randomized controlled period.

Table 2. Time to First Attack Scenario Analyses

	ESS	HR	95% CI
Base case (RCP)			
Matched – age, AAR, sex	**136.6**	**0.54**	**0.20–1.44**
No adjustment (naïve)	161	0.59	0.22–1.56
Scenario analyses			
Using pooled N-MOmentum RCP and OLE data for inebilizumab (including placebo crossover)			
Matched – age, AAR, sex	176.1	0.55	0.22–1.34
No adjustment (naïve)	213	0.58	0.25–1.38
Using pooled N-MOmentum RCP and OLE data for inebilizumab (excluding placebo crossover)			
Matched – age, AAR, sex	131.9	0.55	0.22–1.37
No adjustment (naïve)	154	0.60	0.25–1.46
Including disease severity for matching			
Matched – age, AAR, EDSS (RCP)	85.6	0.61	0.22–1.70
Matched – age, AAR, EDSS (pooled RCP + OLE)	118.6	0.63	0.25–1.60
Including disease duration for matching			
Matched – age, duration, AAR (RCP)	80.9	0.80	0.28–2.32
Matched – age, duration, AAR (pooled RCP + OLE)	103.8	0.73	0.28–1.88
Including all patients from both trials (AQP4+ and AQP4-)			
Matched – age, AAR, sex	87.7	0.61	0.27–1.37
No adjustment (naïve)	230	0.57	0.28–1.18

Note: Age at baseline and age at onset were identified as key prognostic variables in N-MOmentum; however, due to their correlation, simultaneous adjustment resulted in extreme weights, low ESS, and suboptimal covariate balance. Because adjustment for either variable alone yielded comparable results, age at baseline was selected for adjustment.
AAR, annualized attack rate; AQP4, aquaporin-4; CI, confidence interval; EDSS, Expanded Disability Status Scale; ESS, effective sample size; HR, hazard ratio; OLE, open-label extension; RCP, randomized controlled period.

Figure 3. Annualized Attack Rate Using Pooled RCP and OLE Data From N-MOmentum



CI, confidence interval; ESS, effective sample size; OLE, open-label extension; RCP, randomized controlled period; RR, rate ratio.

LIMITATIONS

- As with all unanchored MAICs, residual confounding cannot be excluded, because all prognostic factors and effect modifiers must be adequately captured to support valid inference.
- Additional limitations include reduced ESS after reweighting and reliance on digitized IPD.
- The small rituximab sample size, older AQP4-seropositive assay methodology (ELISA rather than cell-based assay), and single center, single-arm design of Kim et al warrant cautious interpretation.
- Differences in attack determination over time may represent an additional source of confounding.

CONCLUSIONS

- Although the MAIC analyses suggested a reduced risk of attack with inebilizumab versus rituximab, the small rituximab sample size resulted in wide confidence intervals precluding definitive conclusions.
- These findings are consistent with emerging real-world evidence suggesting improved outcomes with licensed therapies compared with rituximab in NMOSD (US: long-term relapse risk HR 0.12–0.24; rest of world: AAR HR 0.27–0.59).[15–19]

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DISCLOSURES

BACC, JP, KF, and HJK declare that this research was conducted in the absence of any commercial or financial relationship that could be construed as a potential conflict of interest.
MS, TAdM, JS, DC, and IMM are employees of Amgen.
KR is a director of Maths in Health.
SH is an employee of Oxford PharmaGenesis.

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