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Human Autoantibodies Against MOG Isoforms

α3 Antibodies Suggest Relapsing Disease Course in Myelin Oligodendrocyte Glycoprotein Antibody–Associated Disease

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Abstract

Background and Objectives

A proportion of patients with myelin oligodendrocyte glycoprotein antibody-associated disease (MOGAD) experience relapses, but biomarkers predicting which patients are likely to relapse are not yet widely available. The MOGα1 isoform is the most commonly used in diagnostic MOG antibody assays, while the clinical relevance of antibodies against other MOG isoforms remains unclear.

Methods

This study used a stepwise approach using international multicenter serum samples collected prospectively. First, diagnostic accuracy of the MOGα1 and β1 isoforms was compared using 748 consecutive sera from Korean patients suspected of having demyelinating disease of the CNS. Next, the predictive values of antibodies against each of 7 MOG isoforms for relapses were assessed on sera from Korean patients with MOGAD (derivation cohort). Finally, the association between MOG isoform antibody with relapses was validated in 2 independent cohorts: a Korean validation cohort (n = 49) and a UK validation cohort (n = 56).

Results

Both MOGα1 antibody and MOGβ1 antibody assays had comparable diagnostic accuracy. Among patients with MOGAD, the presence of MOGα3 antibody was associated with a higher risk of relapse, with a hazard ratio of 4.3 in the derivation cohort (log-rank $p < 0.001$). This finding was also confirmed in an independent smaller Korean validation cohort (log-rank $p = 0.009$) and in a subgroup of UK validation cohort (log-rank $p = 0.048$).

Discussion

The presence of MOGα3-IgG in patients with MOGAD may be associated with an increased risk of relapse, indicating that early preventive treatment strategies may be appropriate in these individuals. MOGβ1-IgG demonstrated diagnostic accuracy similar to MOGα1-IgG.

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Glossary

ADEM = acute disseminated encephalomyelitis; **ARR** = annualized relapse ratio; **EDSS** = Expanded Disability Status Scale; **HR** = hazard ratio; **IDD** = inflammatory demyelinating disease; **IRB** = Institutional Review Board; **MFIr** = median fluorescence intensity ratio; **MOGAD** = myelin oligodendrocyte glycoprotein antibody-associated disease; **MOG-IgG** = myelin oligodendrocyte glycoprotein-immunoglobulin G; **MS** = multiple sclerosis; **NMOSD** = negative neuromyelitis optica spectrum disorder; **ON** = optic neuritis; **SNUH** = Seoul National University Hospital; **VFS** = visual function scale; **VIF** = variance inflation factor.

Classification of Evidence

This study provides Class II evidence that MOGα1 antibody and MOGβ1 antibody assays have comparable diagnostic accuracy for MOGAD.

Introduction

A proportion of patients with myelin oligodendrocyte glycoprotein-immunoglobulin G (MOG-IgG)–associated disease (MOGAD) experience relapses. Although early initiation of immune treatment at the first attack of disease has been proposed to reduce the risks of relapse,[1-5] biomarkers for the risk of future relapses are limited and have not yet been fully identified.[6-9] Although the "full length" α1-MOG isoform assay is currently used in MOG antibody assays, the role of 7 of the membrane-bound human isoforms, which share identical extracellular domains but differ in their cytosolic domains, in MOGAD diagnosis and prognosis is unclear.[10,11]

In this article, we evaluate the clinical utility of detecting antibodies to MOG isoforms as diagnostic and prognostic markers in MOGAD. Specifically, we address 2 questions: (1) whether MOGβ1-IgG has comparable diagnostic accuracy with the conventional MOGα1-IgG assay and (2) whether MOGα3-IgG positivity is associated with a higher risk of relapsing disease course in MOGAD.

Methods

Study Population Data Collection

We have conducted a stepwise international multicenter retrospective cohort study, including a derivation cohort and 2 validation cohorts. The sera of 748 patients who were suspected to having an inflammatory demyelinating disease (IDD) from 14 secondary or tertiary hospitals between November 2009 and April 2023 were screened for MOG-IgG against α1 and β1 MOG isoforms. Screening assay for 2 isoforms of MOG-IgG (α1 [NM_206809.3] and β1 [NM_002433.4]) were performed either by live cell-based flow cytometry assay with minor modifications of our previous methods using median fluorescence intensity ratio (MFIr)[12-14] or by live cell-based assay,[15] using full length of human MOG. The cutoff for seropositivity was defined as the mean MFIr of the negative control group plus 8 SDs, as previously described,[14] and was applied to all 7 MOG isoform assays. Among those, the derivation cohort consisted of adult patients who meet the international MOGAD panel proposed criteria[8,16] at Seoul National University Hospital (SNUH). Patients who were followed for more than 12 months or experienced a relapse (second attack) during the follow-up period were included in the study. All sera were sampled within 2 years of disease onset. Demographics, clinical features, clinical course, and long-term immunotherapy data were obtained by reviewing medical records. The medical records for relapse, Kurtzke Expanded Disability Status Scale (EDSS)[17] and visual function scale (VFS) at the last follow-up, and maintenance immunotherapy were also collected. The Korean validation cohort comprised a nationwide cohort in Korea across 8 secondary or tertiary hospitals, except SNUH. The same clinical information used in the derivation cohort was collected using the case report form for patients with MOGAD with adequate clinical information, from November 2012 to August 2023. The UK validation cohort included patients seen in the UK nationally commissioned negative neuromyelitis optica spectrum disorder (NMOSD)/MOGAD Oxford service up to November 2021. Relapse was defined as a new clinical episode that occurred at least 30 days after the onset date of last acute attack.[8]

Testing Antibody Against MOG Isoforms

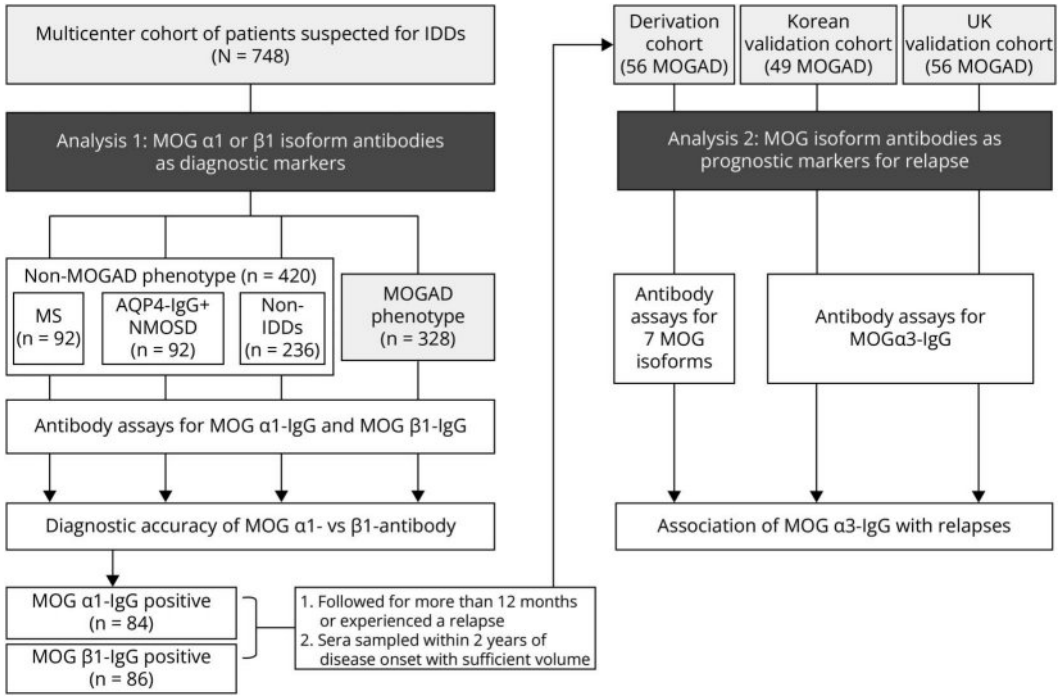
Five other human MOG isoforms (α2 [NM_206812.3], α3 [NM_001008228.2], β2 [NM_001008229.2], β3 [NM_206811.3], and β5 [NM_206810.3]) were cloned individually into the pIRES2-DsRed2 vector (Clontech) and used as substrates in flow cytometric assays with minor modifications from our previous protocol.[12-14] All patients in the derivation cohort were tested for MOG-IgG against 5 isoforms of MOG. Among these 5 MOG-IgG isoforms, the most valuable one was selected, and validation was performed in new cohorts. Laboratory personnel performing the assays were blinded to patients' clinical information and disease outcomes.

Statistical Methods

The comparisons between subgroups were performed using chi-square or Fisher- exact test for categorical variable and Student *t* test or Kruskal-Wallis test with post hoc analysis

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Figure 1 Study Flowchart



AQP4 = anti–aquaporin-4 immunoglobulin G, IDD = inflammatory demyelinating disease, MOG = myelin oligodendrocyte glycoprotein, MOGAD = myelin oligodendrocyte glycoprotein antibody-associated disease, MS = multiple sclerosis, NMOSD = neuromyelitis optica spectrum disorder.

(Mann-Whitney *U* test) for continuous variables. If the variables did not meet normality assumptions, the correlations between antibody test results were assessed using Spearman correlation analysis. A binary logistic regression analysis was performed to identify demographic/clinical factors or isoforms of MOG-IgG associated with a relapsing course. Variables with a p value < 0.2 in the univariable analyses were included in the multivariable model. The variance inflation factor (VIF) was calculated for each independent variable, and variables with VIF ≥10.0 were excluded from the multivariable analysis. In addition, an exploratory multivariable Cox proportional hazards regression analysis was performed by simultaneously entering all clinically relevant covariates regardless of their significance in univariable analyses. Kaplan-Meier (KM) curves were plotted for relapse-free survival, and subgroup comparisons were conducted using univariable Cox proportional hazards regression. Subgroups analysis was planned for variables that differed between cohorts. In addition, a sensitivity analysis was performed by restricting the analysis to participants with samples obtained within 3 months of clinical onset to assess the potential impact of sampling time on the prognostic association of MOGα3-IgG seropositivity with relapse risk. For all tests, p values were 2-sided, and the significance level was set at 0.05. Statistical analyses were performed using the SPSS software (version 23 for Windows; IBM, Chicago, IL), R software (version 3.6.3; The R Foundation for Statistical Computing, Vienna, Austria), or the GraphPad Prism software (version 5.0; GraphPad Software Inc., La Jolla, CA).

Standard Protocol Approvals, Registrations, and Patient Consent

This study was approved by the SNUH Institutional Review Board (IRB) (approval number: SNUH [H-1902-083-1010], Severance Hospital [IRB No.4-2023-0811]), and the IRB of Oxfordshire Research Ethics Committee Ref 10/H0606/56. All patients provided written informed consent before participating.

Data Availability

Individual participant data will not be made publicly available due to potential confidentiality concerns related to the rarity of the condition and the small study population. Further information about the data sets is available from the corresponding author on reasonable request from any qualified investigator.

Results

Both MOGα1 Antibody and MOGβ1 Antibody Assays Had Comparable Diagnostic Accuracy

From the derivation cohort, 748 patients suspected to have an IDD of CNS were initially screened (Figure 1). Four-hundred and 25 participants (56.8%) were female, and the median age was 42.9 years (IQR 32.0–56.5). Among those, 328 patients (43.9%) had phenotype compatible with MOGAD; 25 (7.6%) anti–aquaporin-4 immunoglobulin G (AQP4-IgG) NMOSD, 53 (16.2%) recurrent optic neuritis (ON), 70 (21.3%)

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Table 1 Comparison of Diagnostic Accuracy Between MOGα1-IgG Assay and MOGβ1-IgG Assay

	MOGα1-IgG	MOGβ1-IgG
Classification accuracy of assay[a]		
Sensitivity (95% CI)	25.6 (21.0–30.3)	26.2 (21.6–30.8)
Specificity (95% CI)	98.8 (98.1–99.5)	98.6 (97.8–99.4)
Positive predictive value (95% CI)	94.4 (89.6–99.2)	93.5 (88.4–98.6)
Assay positivity in each diagnostic group (n)		
IDD with phenotype compatible with MOGAD (328), n (%)	84 (25.6)	86 (26.2)
AQP4-IgG–negative NMOSD (25), n (%)	12 (48.0)	12 (48.0)
ON, recurrent (53), n (%)	34 (64.2)	33 (62.3)
ON, monophasic (70), n (%)	18 (25.7)	20 (28.6)
Other brain or brainstem syndrome (35), n (%)	11 (31.4)	11 (31.4)
ADEM (27), n (%)	6 (22.2)	7 (25.9)
Isolated myelitis (118), n (%)	3 (2.5)	3 (2.5)
Non-MOGAD phenotype (420), n (%)	5 (1.2)	6 (1.4)
AQP4-IgG–positive NMOSD (92), n (%)	0	0
MS[b] (92), n (%)	3 (3.3)	3 (3.3)
Non-IDD[c] (236), n (%)	2 (0.8)[d]	3 (1.3)[e]

Abbreviations: ADEM = acute disseminated encephalomyelitis; AQP4 = aquaporin 4; MS = multiple sclerosis; NMOSD = neuromyelitis optica; non-IDD = neurologic disease other than the inflammatory demyelinating disease; ON = optic neuritis.
[a] Calculated as follows: sensitivity = assay positivity among "IDD with phenotype compatible with MOGAD" group, specificity = assay positivity among "non-MOGAD phenotype" group, positive predictive value = positive results in "IDD with phenotype compatible with MOGAD"/positive results in all patients.
[b] A total of 4 (4.3%) patients with MS were positive for MOGα1-IgG or MOGβ1-IgG (2 positive both for MOGα1-IgG and MOGβ1-IgG, 1 MOGα1-IgG positive only, and 1 MOGβ1-IgG positive only).
[c] eAppendix 1 for the detailed diagnosis.
[d] One myasthenia gravis and 1 peripheral vertigo.
[e] MOGα1-IgG–positive patients and another CNS graft vs host disease.

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monophasic ON, 35 (10.7%) brain and/or brainstem/cerebellar lesions, 27 (8.2%) acute disseminated encephalomyelitis (ADEM), and 118 (36.0%) myelitis. The other 420 patients consisted of 92 AQP4-IgG–positive NMOSD (21.9%), 92 multiple sclerosis (MS) (21.9%), and 236 non-IDD (56.2%) (see eAppendix 1 for the detailed diagnosis).

In 328 patients with core features of MOGAD, 88 (26.8%) had antibodies against MOGα1 (84/328, 25.6, %) or MOGβ1 (86/328, 26.2%). The MOGα1-IgG and MOGβ1-IgG assay results were strongly correlated (ρ = 0.587, 95% CI 0.536–0.634, $p < 0.0001$), and most patients showed concordant positivity across both assays. A total of 6 patients with core features of MOGAD showed discordant result for 2 isoforms of MOG-IgG: 2 (recurrent ON) were positive only for MOGα1-IgG and 4 (1 recurrent ON, 2 monophasic ON, and 1 ADEM) were positive only for MOGβ1-IgG (Table 1).

Among patients with MOGAD, the presence of antibody against MOGα3 was associated with relapsing disease course.

Among 84 patients from the derivation cohort who met the international panel criteria for MOGAD,[8] 56 patients who were followed for more than 12 months or experienced a relapse and had sufficient sera sampled within 2 years of disease onset were included (Figure 1, Table 2, and eTable 1).

The fluorescence signal of antibodies bound to the α1 or β1 MOG isoforms was higher in most cases than for other isoforms (MOGα2, MOGα3, MOGβ2, MOGβ3, and MOGβ5; Figure 2). A subset of patients with MOGAD (17.9%, 10/56) and those with relapsing MOGAD (25.0%, 7/28) demonstrated reactivity to these other isoforms (Figure 2, eTable 1, and eFigure 1). Subsequently, we compared the predictive accuracy of those 5 isoforms (MOGα2, MOGα3, MOGβ2, MOGβ3, and MOGβ5) to identify individuals with a relapsing disease course. Among the MOG isoforms, positivity on the MOGα3-IgG assay showed high positive predictive value (87.5%) and specificity (96.4%), although differences compared with other isoforms were modest (eTable 1). In the MOGα3-IgG–positive group, the number of relapses (mean 1.0 vs 0.3, $p = 0.005$), the proportion of relapsing patients (87.5 vs 31.2%, $p = 0.004$) within the first year of disease, and the annualized relapse ratio (ARR) during total follow-up (median [IQR], 0.32 [0.22–0.41] vs 0.00 [0.00–0.29]; $p = 0.043$) were significantly higher than the MOGα3-

Table 2 Demographic and Clinical Factors

	Derivation cohort				Korean validation cohort				UK validation cohort			
	Total	MOGα3-IgG (+)	MOGα3-IgG (−)	*p* Value	Total	MOGα3-IgG (+)	MOGα3-IgG (−)	*p* Value	Total	MOGα3-IgG (+)	MOGα3-IgG (−)	*p* Value
Number, n	56	8	48		49	8	41		56	17	39	
Female, n (%)	24 (42.9)	2 (25.0)	22 (45.8)	0.444	26 (53.1)	5 (62.5)	21 (51.2)	0.706	34 (60.7)	12 (70.6)	22 (56.4)	0.383
Age at onset, med, y (IQR)	35.3 (23.4–51.9)	43.5 (36.0–56.9)	33.9 (23.1–51.5)	0.224	39.1 (26.4–47.2)	41.3 (38.3–47.0)	39.1 (23.7–49.9)	0.498	35.2 (28.0–43.1)	38.7 (31.8–52.8)	34.2 (27.4–41.6)	0.103
Pediatric onset, n (%)	2 (3.6)	0 (0.0)	2 (4.2)	>0.999	2 (4.1)	0 (0.0)	2 (4.9)	>0.999	5 (8.9)	0 (0.0)	5 (12.8)	0.309
Disease duration, med, y (IQR)	4.18 (3.49–6.96)	3.88 (2.80–7.68)	4.18 (3.55–6.96)	0.792	2.55 (2.08–4.58)	3.01 (2.30–5.32)	2.52 (2.08–4.50)	0.515	3.4 (2.0–4.3)	3.6 (2.8–4.8)	3.3 (1.9–4.2)	0.465
Oral corticosteroid at the first attack												
Duration, med, mo (IQR)	1.57 (0.77–6.47)	1.18 (0.84–1.68)	1.80 (0.72–7.35)	0.858	1.80 (0.59–5.14)	0.73 (0.14–1.44)	2.59 (0.68–5.51)	0.086	6.00 (0.98–12.5)	8.5 (1.03–13.00)	6.00 (0.98–11.75)	0.452
Over 6 mo, n (%)	12/45 (26.7)	0/6 (0.0)	12/39 (30.8)	0.171	11/47 (23.4)	1/7 (14.3)	10/40 (25.0)	>0.999	26/55 (47.3)	10/16 (62.5)	16/39 (41.0)	0.234
Presence of relapses, n (%)												
During f/u period	28 (50.0)	7 (87.5)	21 (43.8)	0.051	21 (42.9)	7 (87.5)	14 (34.1)	0.015	23 (41.1)	8 (47.1)	15 (38.5)	0.569
Within 1 y of onset	22 (39.3)	7 (87.5)	15 (31.2)	0.004	14 (28.6)	3 (37.5)	11 (26.8)	0.672	19 (33.9)	5 (29.4)	14 (35.9)	0.763

Abbreviations: f/u = follow-up; Ig-G = immunoglobulin G; IQR = interquartile range; med = median; mo = month; MOG = myelin oligodendrocyte glycoprotein.

IgG–negative group (Figure 3). The KM curve showed significantly higher risk of relapsing disease course in MOGα3-IgG–positive group (log-rank $p < 0.001$; Figure 3). Subgroup participants sampled within 3 months of clinical onset yielded consistent result (log-rank $p < 0.001$, eFigure 2). No significant differences were observed in sex, age, disease duration, time from attack onset to sampling, or clinical manifestations between the MOGα3-IgG–positive and MOGα3-IgG–negative groups. Cox proportional hazards regression analysis revealed that the risk of relapse was 4.3 times higher (hazard ratio (HR), 4.288; 95% CI 1.785–10.304; $p = 0.001$) in MOGα3-IgG–positive group (eTable 3).

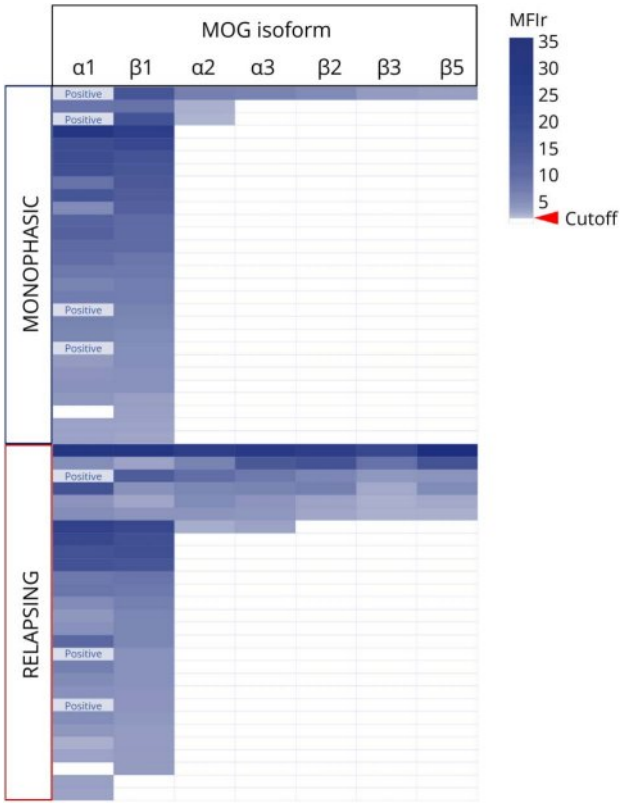
MOGα3 Antibody and MOGAD Relapse: Validation in 2 Independent Cohorts

To validate our findings, we examined the relationship between MOGα3 antibodies and disease relapse using serum samples obtained from 2 independent cohorts: Korean and the United Kingdom (Figure 1, Table 2, and eTable 1). Most of the participants (94.4%) in 2 validation cohort were adults, and 57.1% were female (eTable 4). The KM curve for this Korean validation cohort also showed a significantly higher risk (log-rank $p = 0.009$; Figure 4A) of relapse in MOGα3-IgG–positive group (eTable 5). Moreover, in the MOGα3-IgG–positive group, the number of relapses (median 1.0 vs 0.0. $p = 0.037$), ARR (median [IQR], 0.36 [0.20–0.80] vs 0.00 [0.00–0.46]; $p = 0.049$; Figure 4A), and the proportion of relapsing patients (87.5 vs 34.1%, $p = 0.015$) were significantly higher than the MOGα3-IgG–negative group. The results remained consistent when restricted to patients sampled within 3 months of clinical onset (log-rank $p = 0.033$; eFigure 3). EDSS and VFS at the last follow-up and maintenance immunotherapy did not differ between groups. There was no significant differences in sex, age, disease duration, time from attack onset to sampling, or clinical manifestations at onset between the MOGα3-IgG–positive and MOGα3-IgG–negative groups (eTable 1).

A total of 56 patients were included in the UK validation cohort from Oxford (Figure 1). There was no significant difference for risk of relapsing disease course between MOGα3-IgG–positive and MOGα3-IgG–negative groups using KM analysis (log-rank $p = 0.568$; Figure 4B; eFigure 4) and Cox proportional hazards regression analysis (HR, 1.318; 95% CI 0.509–3.414; $p = 0.569$; eTable 6) between the MOGα3-IgG–positive and MOGα3-IgG–negative groups in this cohort. Given that the median duration of oral corticosteroid use was shorter in both the derivation cohort (1.57 months, IQR 0.77–6.47) and the Korean validation cohort (1.80 months, IQR 0.59–5.14) compared with the UK validation cohort (8.00 months, IQR 1.42–13.0, $p = 0.001$; eTable 4) and that longer corticosteroid duration at the first MOGAD attack was significantly associated with a the lower risk of relapse in the UK cohort (HR, 0.839; 95%CI, 0.761–0.925, $p < 0.001$), we conducted a subgroup KM analysis on the UK validation cohort of patients who received oral corticosteroid or immunosuppressant for less than 6 months. In this subgroup analysis, MOGα3-IgG–positive group showed higher risk of relapse compared with their counter group (log-rank $p = 0.048$), and the ARR was higher

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Figure 2 Results of MOG-IgG Antibody Assays Using Different MOG Isoforms as the Test Substrate in the Derivation Cohort (n = 56)



The presence of antibodies to the α3 isoform is the most sensitive to identify relapsing MOGAD. All negative results are shown in white. Results labeled as "positive" indicate samples that were confirmed as positive by a cell-based fluorescence microscopic assay, for which MFIr values were not available. MFIr = median fluorescence intensity ratio, MOG = myelin oligodendrocyte glycoprotein.

(median [IQR], 0.36 [0.29–0.61] vs 0.00 [0.00–0.35]; p = 0.037) in the MOGα3-IgG–positive group (Figure 4C).

When all 3 cohorts were combined, the MOGα3-IgG–positive group exhibited a significantly higher risk of relapse (log-rank p = 0.005; Figure 5A; aHR, 2.678; 95% CI 1.485–4.831; p = 0.001; eTable 7). Furthermore, in a pooled subgroup of all 3 cohorts who had received oral corticosteroid or immunosuppressant for less than 6 months, positivity for MOGα3-IgG was significantly associated with higher risk of relapse (log-rank p = 0.001; Figure 5B; aHR, 3.578; 95% CI 1.686–7.594; p = 0.001; eTable 8). Finally, in a Cox proportional hazards regression analysis, the risk of relapse was 2.8 times higher (HR 2.812; 95% CI 1.445–5.473, p = 0.002), and the number of relapses within the first year (mean 1.13 vs 0.56; p = 0.024) and ARR (median [IQR], 0.36 [0.22–0.63] vs 0.00 [0.00–0.46]; p = 0.012) were higher in MOGα3-IgG–positive group than their MOGα3-IgG–negative counterparts in this subgroup (Figure 5B). Sensitivity analyses restricted to participants sampled within 3 months of clinical onset also showed consistent results (eFigure 5).

Classification of Evidence

This study provides Class II evidence that MOGα1 antibody and MOGβ1 antibody assays have comparable diagnostic accuracy for MOGAD.

Discussion

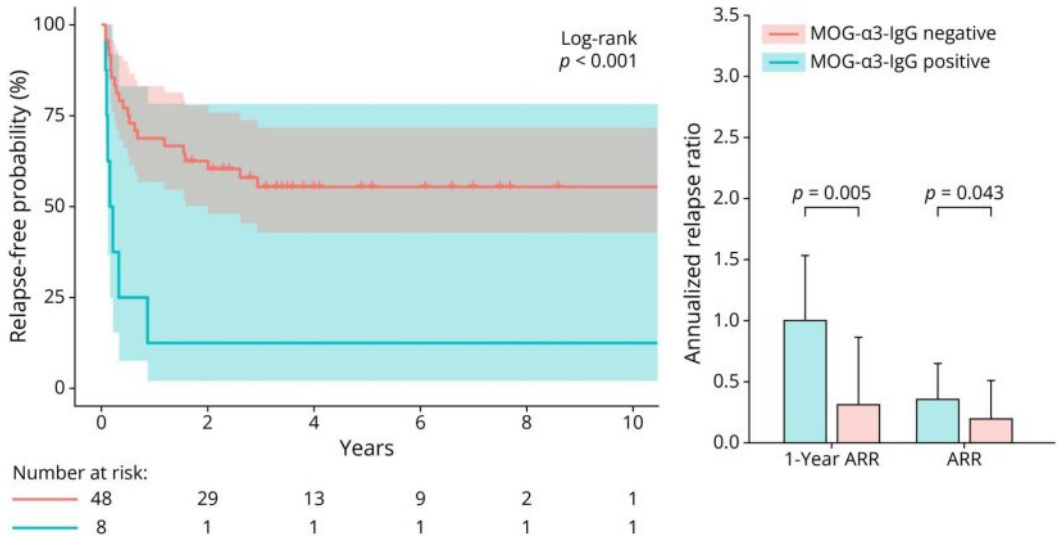
In this study, we assessed clinical utility of antibodies against different MOG isoforms and showed that (1) the MOGα1 and β1 isoforms are comparable as test substrates for the diagnosis of MOGAD and (2) patients with MOGAD (with antibodies to either the MOGα1 or β1 isoform) who also have MOGα3 antibodies have a higher likelihood to have a relapsing disease course, often with early relapses (within the first year). The relapse-predictive value of antibodies to the α3 isoform was confirmed through a stepwise approach in the derivation cohort, the Korean validation cohort, and the subgroup of the UK validation cohort who were treated for less than 6 months with corticosteroids. In the combined subgroup of all 3 cohorts that used oral corticosteroids or immunosuppressants for less than 6 months, MOGα3-IgG positivity was associated with 2.8-fold higher risk of relapsing disease course. However, it should be noted that most patients with relapsing MOGAD were MOGα3-IgG negative, which warrants careful interpretation of the present findings. Despite the limited sensitivity of MOG-α3-IgG positivity for predicting relapsing MOGAD, its very high specificity and positive predictive value indicate that it may still be of substantial clinical utility.

The previous study by Schanda et al.[18] did not identify MOGα3-IgG as a predictor of relapsing disease course in MOGAD. Several factors may account for this discrepancy. First, differences in treatment exposure, such as the duration of oral corticosteroid use, may have obscured the prognostic signal, as was similarly observed in our UK validation cohort before treatment-stratified analysis. Second, Schanda et al. included a substantially higher proportion of pediatric patients (47.5%), compared with our cohort (5.6%); given that pediatric MOGAD more frequently follows a monophasic course, this difference may have diluted the prognostic contribution of MOGα3-IgG. Finally, the previous study compared relapse rates without time-to-event analyses, whereas this study analyzed KM curve and Cox proportional hazards regression to explicitly account for the temporal dynamics of relapse.

Relapse susceptibility in MOGAD can be affected by a combination of intrinsic patient immune characteristics and extrinsic factors, including the timing and duration of immunotherapeutic intervention.[4,5] Our finding that MOGa3-IgG may be associated with increased relapse risk in MOGAD is in line with recent study suggesting that reactivity to non-P42 MOG epitopes is associated with the higher risk of MOGAD relapse[9] because both studies highlight that the MOG and antibody binding pattern may contribute to

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Figure 3 Time to Relapse Based on MOGα3-IgG Serostatus in the Derivation Cohort



Kaplan-Meier survival curves are shown for the MOGα3-IgG–positive (orange) and MOGα3-IgG–negative (blue) groups, with shaded areas denoting the 95% CIs. ARR = annualized relapse ratio, MOG = myelin oligodendrocyte glycoprotein.

a relapsing disease course. Conversely, because not all known relapse-associated factors were accounted for in this analysis, residual confounding remains possible.

Although the biological mechanisms underlying these phenomena remain unclear, together with our recent observation that showed early, short-term high-dose steroids can reduce the risk of relapses,[4] we speculate that severe initial inflammation may promote epitope spreading to activate the different B-cell clones and can develop more mature B-cell autoimmune network, ultimately increasing the risk of relapse. Moreover, it is conceivable that antibodies recognizing the MOGα3 isoform represent a higher-affinity population capable of monovalent binding. Unlike MOGα1 and MOGβ1, which possess a second hydrophobic domain that maintains MOG monomers at a distance permissive for bivalent antibody binding, MOGα3 lacks this domain, potentially leading to closer MOG clustering at the cell surface and favoring monovalent antibody binding, thereby enabling more efficient downstream effector mechanisms and contributing to a higher relapse risk.[19]

Another possible explanation may be complement-mediated mechanisms. Although complement activation is less prominent compared with AQP4-IgG–positive NMOSD, the strongest MOG-IgG–induced complement-dependent cytotoxicity levels were observed with MOGα1, MOGα3, and MOGβ1.[20,21] Furthermore, the MOGα3 structure can form a hexamer, which may increase its likelihood of engaging C1 interaction and relapses.[22,23] Supporting this hypothesis, patient-derived monoclonal MOG autoantibodies have recently been shown to mediate cytotoxicity through complement-dependent mechanisms, with variable cytotoxic capacity observed across different antibody clones.[24] Finally, complement factors are found to be associated with relapsing MOGAD in a very recent study.[25]

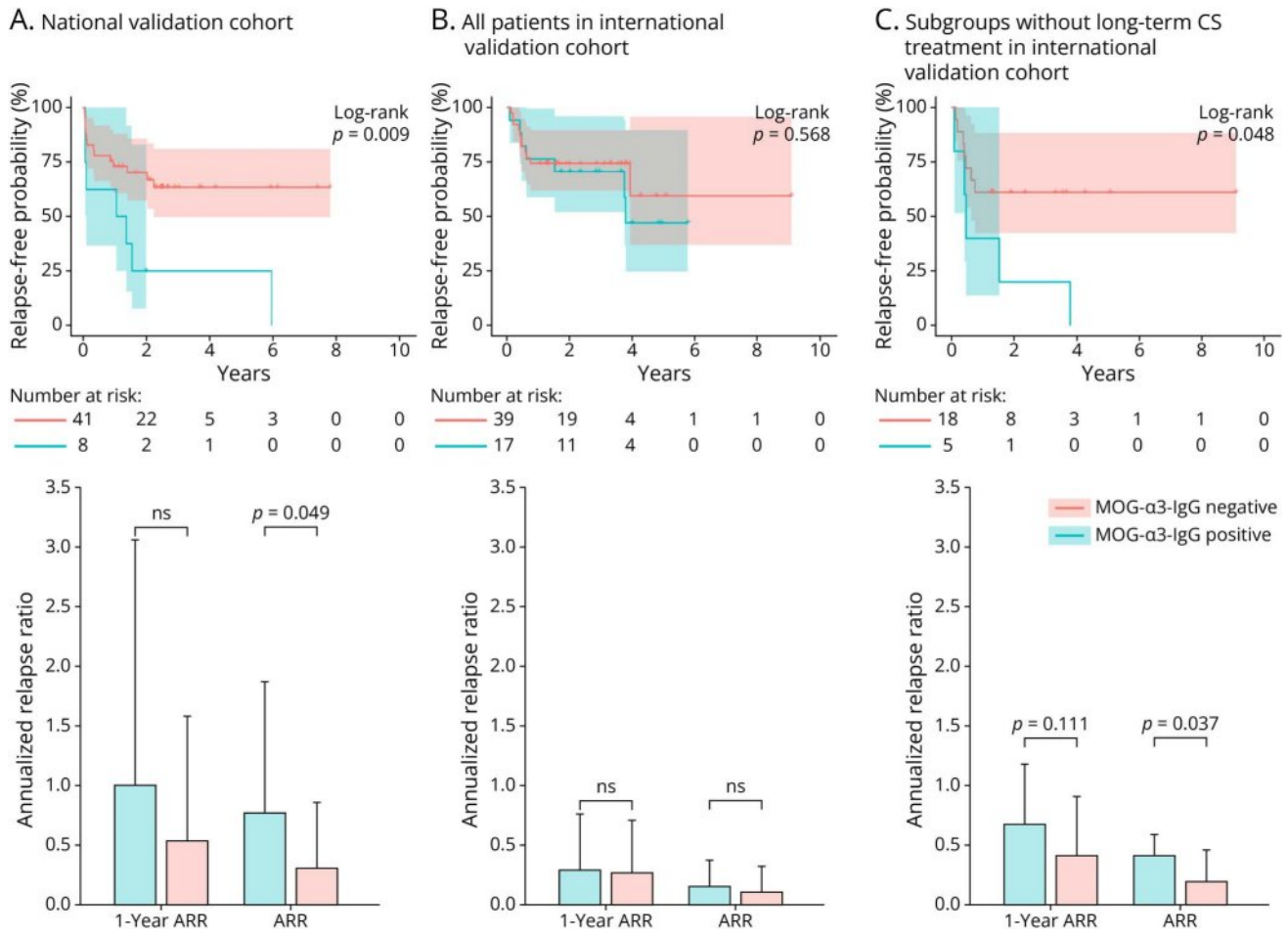
Longer-term oral corticosteroid treatment may have confounded the prognostic association of MOGα3-IgG, particularly given that relapses were predominantly concentrated within the first year of follow-up, during which corticosteroids may have exerted their suppressive effect on relapse activity. This is supported by the low overall relapse rate and the independent association between prolonged oral corticosteroid use and reduced relapse risk observed in the UK validation cohort (eTable 6), potentially obscuring the prognostic difference between MOGα3-IgG–positive and MOGα3-IgG–negative patients.

Currently, the MOGα1 isoform is widely used in the diagnostic antibody test for MOGAD. However, these assays are not fully accurate because of the risk of false positive and their titer-dependent positive predictive value.[26] To overcome this limitation, we explored alternative isoform-based assays. The MOGβ1 isoform did not demonstrate superior diagnostic accuracy compared with the conventional antibody assay. Therefore, clinical criteria[8] are required to complement a diagnostic test result, and the development of a test with better metrics to identify antibodies specifically in patients with MOGAD remains an elusive unmet need.

This study has limitations. It was a retrospective cohort study. We made efforts to minimize bias by strictly applying inclusion criteria and using only relatively early disease samples for testing. MOG-IgG titers are known to gradually decline after clinical onset, with approximately half of patients

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Figure 4 Time to Relapse Based on MOGα3-IgG Serostatus in the 2 Validation Cohorts



Kaplan-Meier survival curves are shown for the MOGα3-IgG–positive (orange) and MOGα3-IgG–negative (blue) groups, with shaded areas denoting the 95% CIs. ARR = annualized relapse ratio, CS = corticosteroid, MOG = myelin oligodendrocyte glycoprotein, n.s = not significant.

becoming low positive by around 12 months.[27] Therefore, the timing of sampling is an important factor when interpreting MOG-IgG results. In this study, however, 77.6% (125/161) of patients were sampled within 6 months of clinical onset, reducing the potential impact of this variable. Moreover, because only MOGα3 reactivity was assessed in the validation cohorts, we could not evaluate other isoforms. Evaluation of additional isoforms in future studies would help clarify the contribution of broader MOG-Ig reactivity. Finally, as a cross-sectional study, longitudinal changes in MOG isoform antibody titers and potential isoform spreading could not be evaluated.

In addition, combining 3 cohorts in the subgroup analysis raises the possibility that the results could have been confounded by a few cohorts with strong directional effects. However, we believe that this risk was minimized because we first confirmed the same trend through subgroup analyses within each cohort before combining them. We also did not include pediatric patients, and the results should be replicated and validated in that group of patients. Furthermore, across all 3 cohorts, the numbers of patients and relapse events were relatively modest, which underscores the need for future large, prospective studies including randomized controlled trials. Nevertheless, this is the first study to evaluate the clinical utility of human MOG isoforms, and by applying a stepwise approach across 2 independent validation cohorts, we successfully reproduced and verified the findings initially observed in the derivation cohort.

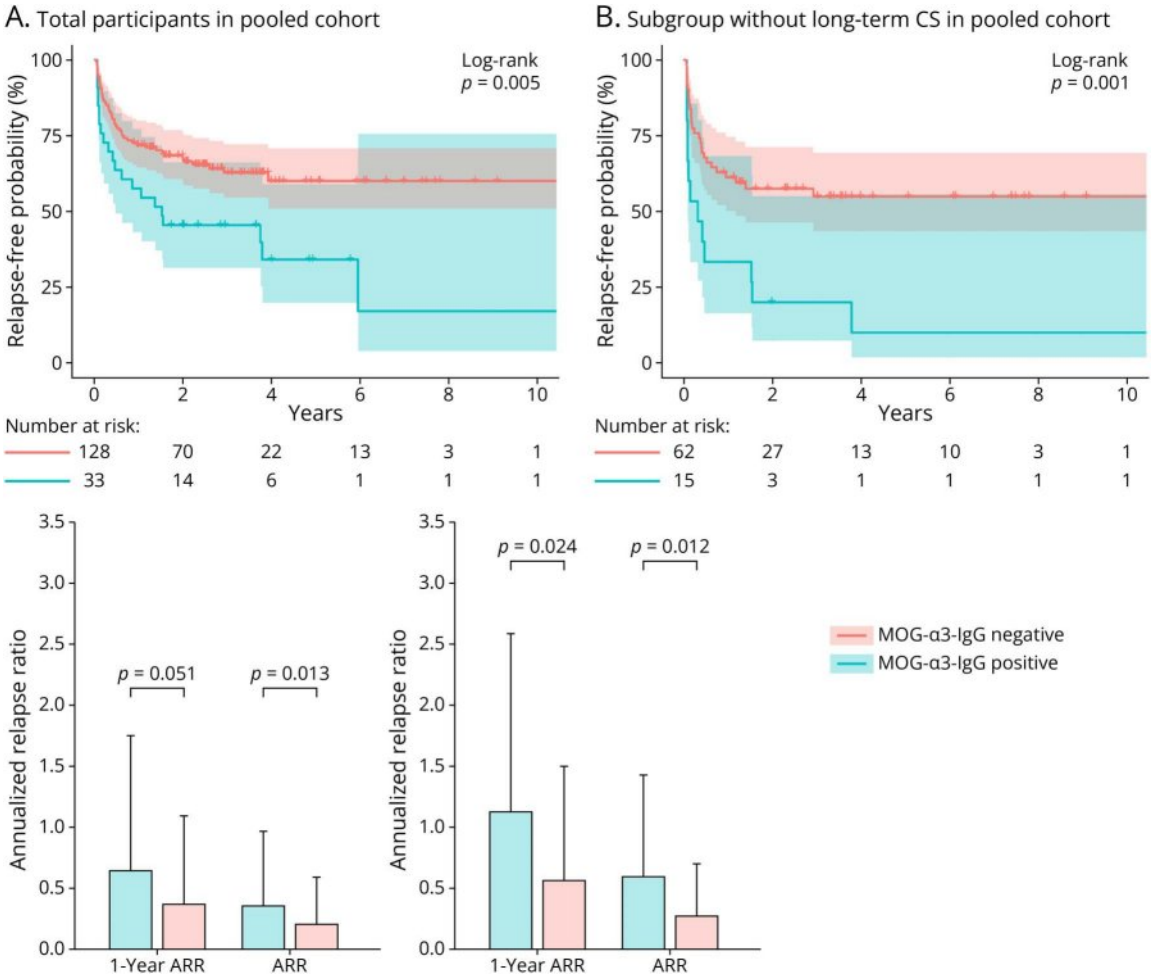
In conclusion, we identified that MOGβ1-IgG detection demonstrated similar diagnostic accuracy to MOGα1-IgG, and MOGα3-IgG was found to be associated with a higher risk of relapse. Therefore, the data suggest that early longer-term immunosuppressant might be considered in those who are positive for MOGα3-IgG. The biological mechanisms underlying the association between MOGα3 binding and relapse rates require further investigation.

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Figure 5 Comparing a Collated Cohort of MOGα3-IgG Positive vs MOGα3-IgG Negative From 3 Independent Cohorts Without Nonsteroidal Immunosuppressant and CS Over 6 Months



Kaplan-Meier survival curves are shown for the MOGα3-IgG–positive (orange) and MOGα3-IgG–negative (blue) groups, with shaded areas denoting the 95% CIs. ARR = annualized relapse ratio, CS = corticosteroid, MOG = myelin oligodendrocyte glycoprotein.

Ministry of Health and Welfare. All samples derived from the National Biobank of Korea were obtained with informed consent under institutional review board–approved protocols.

Author Contributions

Y.N. Kwon: drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data; study concept or design; Analysis or interpretation of data. M. Leal Rato: drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data; study concept or design; analysis or interpretation of data. J-S. Kim: major role in the acquisition of data. Kyung Seok Park: major role in the acquisition of data. H-S. Lee: major role in the acquisition of data. S-H. Baek: major role in the acquisition of data. B-J. Kim: major role in the acquisition of data. Y.H. Chung: major role in the acquisition of data. J-H. Min: major role in the acquisition of data. S. Kim: major role in the acquisition of data. E. Sohn: major role in the acquisition of data. S-i. Oh: major role in the acquisition of data. S.B. Kim: major role in the acquisition of data. S.W. Kim: major role in the acquisition of data. H.Y. Shin: major role in the acquisition of data. K.H. Kim: major role in the acquisition of data. H.J. Kim: major role in the acquisition of data. B. Kim: major role in the acquisition of data. J-J. Sung: major role in the acquisition of data. S. Messina: major role in the acquisition of data. M.R. Woodhall: major role in the acquisition of data. H. Bayuangga: major role in the acquisition of data. M.I. Leite: major role in the acquisition of data. R. Geraldes: drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data; analysis or interpretation of data. J. Palace: major role in the acquisition of data. P.J. Waters: drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data; Study concept or design; analysis or interpretation of data. S-M. Kim: drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data; study concept or design; analysis or interpretation of data.

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