

Rituximab Treatment and Long-term Outcome of Patients With Autoimmune Encephalitis

Real-world Evidence From the GENERATE Registry

Franziska S. Thaler, MD, Luise Zimmermann, MD, Stefan Kammermeier, MD, Christine Strippel, MD, Marius Ringelstein, MD, Andrea Kraft, MD, Kurt-Wolfram Sühs, MD, Jonathan Wickel, MD, Christian Geis, MD, Robert Markewitz, MD, Christian Urbanek, MD, Claudia Sommer, MD, Kathrin Doppler, MD, Loana Penner, Jan Lewerenz, MD, Rosa Rößling, MD, Carsten Finke, MD, Harald Prüss, MD, Nico Melzer, MD, Klaus-Peter Wandinger, MD, Frank Leypoldt, MD, and Tania Kümpfel, MD, on behalf of the German Network for Research on Autoimmune Encephalitis (GENERATE)

Correspondence

Dr. Thaler
franziska.thaler@
med.uni-muenchen.de

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Abstract

Background and Objectives

To determine the real-world use of rituximab in autoimmune encephalitis (AE) and to correlate rituximab treatment with the long-term outcome.


Methods

Patients with NMDA receptor (NMDAR)-AE, leucine-rich glioma-inactivated-1 (LGII)-AE, contactin-associated protein-like-2 (CASPR2)-AE, or glutamic acid decarboxylase 65 (GAD65) disease from the German Network for Research on Autoimmune Encephalitis who had received at least 1 rituximab dose and a control cohort of non-rituximab-treated patients were analyzed retrospectively.

Results

Of the 358 patients, 163 (46%) received rituximab (NMDAR-AE: 57%, CASPR2-AE: 44%, LGII-AE: 43%, and GAD65 disease: 37%). Rituximab treatment was initiated significantly earlier in NMDAR- and LGII-AE (median: 54 and 155 days from disease onset) compared with CASPR2-AE or GAD65 disease (median: 632 and 1,209 days). Modified Rankin Scale (mRS) scores improved significantly in patients with NMDAR-AE, both with and without rituximab treatment. Although being more severely affected at baseline, rituximab-treated patients with NMDAR-AE more frequently reached independent living (mRS score ≤ 2) (94% vs 88%). In LGII-AE, rituximab-treated and nontreated patients improved, whereas in CASPR2-AE, only rituximab-treated patients improved significantly. No improvement was observed in patients with GAD65 disease. A significant reduction of the relapse rate was observed in rituximab-treated patients (5% vs 13%). Detection of NMDAR antibodies was significantly associated with mRS score improvement. A favorable outcome was also observed with early treatment initiation.

MORE ONLINE

 **Class of Evidence**
Criteria for rating
therapeutic and diagnostic
studies

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From the Institute of Clinical Neuroimmunology (F.S.T., T.K.), University Hospital and Biomedical Center, Ludwig-Maximilians-Universität, Munich; Section of Translational Neuroimmunology (L.Z., J.W., C.G.), Department of Neurology, Jena University Hospital, Jena; Department of Neurology (S.K.), University Hospital, Ludwig-Maximilians-University, Munich; Department of Neurology with Institute of Translational Neurology (Christine Strippel, N.M.), University of Muenster; Department of Neurology (M.R., N.M.), Medical Faculty, Heinrich Heine University Düsseldorf; Department of Neurology (M.R.), Center for Neurology and Neuropsychiatry, LVR-Klinikum, Heinrich Heine University Düsseldorf; Department of Neurology Martha-Maria Hospital (A.K.), Halle/Saale, Academic Hospital of University Halle-Wittenberg; Department of Neurology (K.-W.S.), Hannover Medical School; Department of Neurology (R.M., K.-P.W.), University Hospital Schleswig-Holstein, Lübeck; Department of Neurology (C.U.), Klinikum der Stadt Ludwigshafen a. Rh. gGmbH, Ludwigshafen; Department of Neurology (C. Sommer, K.D.), University Hospital Würzburg; Department of Neurology (L.P., J.L.), Ulm University; Department of Neurology and Experimental Neurology (R.R., C.F., H.P.), Charité - Universitätsmedizin Berlin; German Center for Neurodegenerative Diseases (DZNE) Berlin (R.R., H.P.); Neuroimmunology Section (K.-P.W., F.L.), Institute of Clinical Chemistry, University Hospital Schleswig-Holstein Kiel, Lübeck; and Department of Neurology (F.L.), Christian-Albrechts-Universität Kiel, Germany.

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F. Leypoldt and T. Kümpfel contributed equally to this work as co-senior authors.

German Network for Research on Autoimmune Encephalitis (GENERATE) coinvestigators are listed in Appendix 2 at the end of the article.

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Glossary

abs = antibodies; **AE** = autoimmune encephalitis; **CA** = cerebellar ataxia; **CASPR2** = contactin-associated protein-like-2; **CBA** = cell-based assay; **GAD65** = glutamic acid decarboxylase 65; **GENERATE** = GERman Network for Research on AuToimmune Encephalitis; **IHC** = immunohistochemistry; **IVIG** = IV immunoglobulin; **LE** = limbic/autoimmune encephalitis; **LGII** = leucine-rich glioma-inactivated-1; **mRS** = Modified Rankin Scale; **NMDAR** = NMDA receptor; **RIA** = radioimmunoassay; **SPS** = stiff-person syndrome.

Discussion

We provide real-world data on immunosuppressive treatments with a focus on rituximab treatment for patients with AE in Germany. We suggest that early and short-term rituximab therapy might be an effective and safe treatment option in most patients with NMDAR-, LGII-, and CASPR2-AE.

Class of Evidence

This study provides Class IV evidence that rituximab is an effective treatment for some types of AE.

Autoimmune encephalitis (AE) is an umbrella term for an emerging spectrum of immune-mediated neuropsychiatric disorders often associated with antibodies (abs) against neuronal cell surface, synaptic, or intracellular proteins.^{1,2} Anti-NMDA receptor (NMDAR)-AE, anti-leucine-rich glioma-inactivated-1 (LGII)-AE, anti-contactin-associated protein-like-2 (CASPR2)-AE, and anti-glutamic acid decarboxylase-65 (GAD65) disease together make up the majority of seropositive AE subtypes. NMDAR-AE affects young adults and children with female preponderance, is frequently associated with ovarian teratomas, and causes psychiatric symptoms, movement disorders, decreased consciousness, autonomic dysregulation, epileptic seizures, and central apnea.^{3,4} LGII-AE affects middle-aged or elderly patients, causes short-term memory deficits, confusion, and epileptic seizures,^{5,6} and is sometimes preceded by faciobrachial dystonic or tonic seizures.⁷ CASPR2-AE predominantly affects elderly men and causes encephalitis and neuromyotonia, neuropathic pain, ataxia, myoclonus, autonomic dysfunction, or a combination thereof (e.g., Morvan syndrome).^{8,9} GAD65 disease is considerably more heterogeneous, affects predominantly women of all ages, and may cause cerebellar ataxia (CA), limbic/AE (LE), stiff-person syndrome (SPS), isolated temporal lobe epilepsy, and overlap forms of the aforementioned manifestations.¹⁰⁻¹³

Early diagnosis and prompt initiation of immunotherapy is crucial and often leads to substantial or complete recovery from these severe disorders.⁸ However, treatment data from randomized trials are scarce.^{14,15} Empiric treatment of AE usually consists of a step-wise escalation of immunotherapy including first-line therapy with steroids, plasma exchange, IV immunoglobulin (IVIG), or combinations, followed by second-line therapy with cyclophosphamide, rituximab, or combinations.² Rituximab is a B cell-depleting monoclonal ab directed against CD20 with established efficacy in many neurologic autoimmune diseases including MS,¹⁶ and neuromyelitis optica spectrum disorders.¹⁷ Rituximab was shown to be effective in AE associated with different auto-abs.^{4,18,19}

By contrast, 1 randomized placebo-controlled trial with rituximab did not show efficacy in patients with SPS.¹⁵ Detailed and comparative evaluations of rituximab use and the long-term outcome between AE subtypes in a real-world setting are missing. In this study, we evaluated demographic and clinical characteristics, laboratory findings, and immunotherapies in patients with NMDAR-, LGII-, CASPR2-AE, or GAD65 disease in a cohort from the GERman NETwork for Research on AuToimmune Encephalitis (GENERATE) registry and compared patients who had received at least 1 rituximab dose with non-rituximab-treated patients. In the rituximab cohort, we specifically correlated early, high-dose, or prolonged rituximab treatment with the long-term outcome.

Methods

Standard Protocol Approvals, Registrations, and Patient Consents

All data were collected from the GENERATE registry, which is a noninterventional retrospective and prospective multicentric database for patients with AE in Germany, Austria, and Switzerland (generate-net.de). GENERATE was approved by the institutional review boards of all actively recruiting centers. Patients from participating centers entered into the registry until June 30, 2019, were analyzed. The study was performed according to the Declaration of Helsinki. All enrolled patients or their legal representatives gave written informed consent before enrollment in the registry.

Study Population

The following patients were included: (1) patients with detection of NMDAR-, LGII-, CASPR2-, or GAD65 abs according to the ab criteria below; (2) clinical diagnosis of AE based on the consensus criteria published in reference 2, or for patients with GAD abs, alternatively diagnosis of CA or SPS; (3) any documented treatment with rituximab; and (4) available information on the number, dosage, and timing of rituximab infusions. In addition, a control cohort with

consistent inclusion criteria except for rituximab treatment was included.

Analysis of Clinical, Laboratory, and Immunotherapy Profiles

Ab testing was performed in the respective GENERATE centers using cell-based assays (CBAs) and confirmation by immunofluorescence (commercial test kit panels Euroimmun, Lübeck) and/or immunohistochemistry (IHC) for NMDAR, LGI1, and CASPR2, and ELISA, radioimmunoassay (RIA), or CBA for GAD65. Patients fulfilling the following ab criteria in earliest available samples were included: NMDAR abs detected in serum by CBA confirmed by IHC (in the absence of confirmatory IHC in serum, only CBA serum titers of >1:500 were considered specific) and/or CSF positive; GAD abs >1:500 in CBA or >2000IE/mL in ELISA or RIA in serum and/or CSF positive; LGI1 abs at any titer in CSF and/or serum; CASPR2 abs >1:128 in serum and/or CSF positive.²⁰ Only IgG abs were considered relevant.

Data on any immunotherapy were recorded. First-line immunotherapy was defined as treatment with corticosteroids, plasma exchange/immunoabsorption, and IVIG; second-line therapy included rituximab in the rituximab cohort and all other immunotherapies except reapplied corticosteroids, IVIG, and plasma exchange in both cohorts. The occurrence of relapses during follow-up was based on the overall clinical impression of the treating physician. Functional status was assessed using the modified Rankin Scale (mRS) at the peak of disease and then throughout disease course. Side effects of rituximab treatment were queried from all participating centers.

Primary Research Question

Do rituximab-treated patients with NMDAR-AE, LGI1-AE, CASPR2-AE, and GAD65 disease have a better outcome than non-rituximab-treated patients?

Classification of Evidence

This study provides Class IV evidence that rituximab is an effective treatment for some types of AE.

Statistics

Statistical tests were performed using Prism Software (GraphPad). Normality testing was performed using the D'Agostino-Pearson omnibus test. Continuous variables with >2 subgroups were compared using the Kruskal-Wallis test followed by the Dunn multiple comparisons test and with 2 subgroups using the Mann-Whitney test. Ordinal variables were compared using the χ^2 test or the Fisher exact test. The Benjamini-Hochberg procedure was performed to control for multiple testing. Multivariate analysis was performed by ordinal logistic fit using JMP software (Version 16, JMP, A Business Unit of SAS, Cary, NC).

Data Availability

No deidentified patient data will be shared. No study-related documents will be shared. Reasonable requests from any

qualified investigator for anonymized data will be considered by the corresponding author.

Results

Patient Characteristics

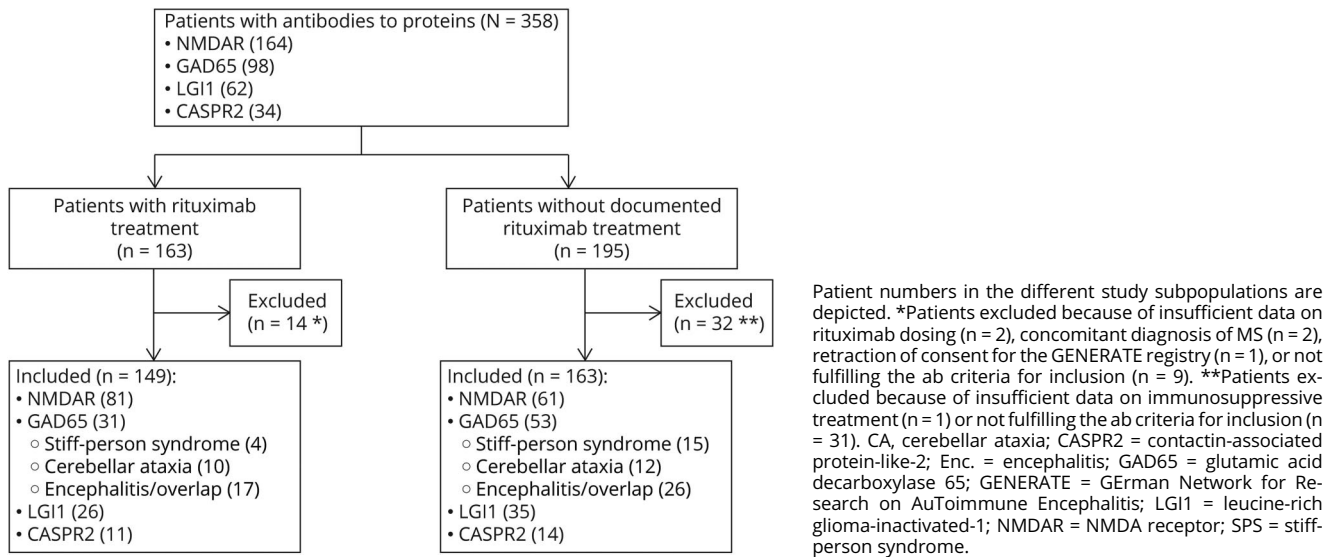
We identified 358 patients with NMDAR-AE, GAD65 disease, LGI1-AE, or CASPR2-AE. One hundred sixty-three patients (46%) were treated with rituximab. Based on the inclusion criteria, 14 patients in the rituximab cohort and 32 patients in the control cohort were excluded from further analysis (Figure 1, eFigure 1, links.lww.com/NXI/A595). Our final study cohort comprised 149 patients in the rituximab cohort (NMDAR-AE: n = 81, GAD65 disease: n = 31, LGI1-AE: n = 26, and CASPR2-AE: n = 11) and 163 patients in the control cohort (NMDAR-AE: n = 61, GAD65 disease: n = 53, LGI1-AE: n = 35, and CASPR2-AE: n = 14) (Figure 1). Overall, rituximab was administered most frequently in NMDAR-AE (57%), followed by CASPR2-AE (44%), LGI1-AE (43%), and GAD65 disease (37%). Clinical characteristics as well as CSF and MRI parameters, as expected, varied considerably between the ab subgroups (Table 1). Differences between the rituximab cohort and the control cohort indicating severity bias were observed for patients with NMDAR-AE and GAD65 disease: patients with NMDAR-AE treated with rituximab had a significantly higher mRS score at peak of disease (rituximab cohort: median: 4.0; control cohort: median: 3.0) and a significantly higher frequency of decreased consciousness (Table 1). In patients with GAD65 disease, the mRS score at the peak of disease was also higher in the rituximab cohort (median: 3.0) compared with the control cohort (median: 2.0) (Table 1).

First-Line and Second-Line Treatments

All patients with rituximab treatment received prior first-line immunotherapy. In the control cohort, 4 patients (7%) with NMDAR-AE, 5 patients (9%) with GAD65 disease, and 1 patient (7%) with CASPR2-AE had no prior first-line immunotherapy (Table 2). Time to initiation of first-line therapy was shortest in patients with NMDAR-AE, and the therapy was started significantly earlier in patients with NMDAR-AE treated with rituximab (median: 16 days) compared with patients with NMDAR-AE not receiving rituximab (median: 33 days) (Table 2). In all subgroups, the majority of patients received a combination of different first-line treatments with steroids and plasma exchange being the most frequent combination in the overall cohort (n = 103; 33%) (Figure 2, A–H). As expected, because of severity bias, patients in the rituximab cohort were treated significantly more often with combinations of first-line therapy (Figure 2, A–H). Physicians reported some improvement following first-line therapy in the majority of patients independent of the subgroup. Of interest, the frequency of this observation was similar between patients later receiving rituximab and patients who were treated differently (Table 2).

Forty patients (25%) in the control cohort and 38 patients (26%) in the rituximab cohort received a second-line immunotherapy

Figure 1 Study Population Profile



other than rituximab. The frequency of application of second-line immunotherapies other than rituximab did not differ between the rituximab cohort and the control cohort (Table 2). These second-line immunotherapies included cyclophosphamide, azathioprine, mycophenolate mofetil, methotrexate, bortezomib, daratumumab, tacrolimus, and basiliximab (Figure 2, I–P) and were applied before, parallel to, or after rituximab therapy. In patients with NMDAR-AE and GAD65 disease, more aggressive second-line therapies such as cyclophosphamide, bortezomib, or daratumumab were applied more frequently in the rituximab cohort compared with the control cohort (Figure 2, I–P). Other than this and the above-mentioned severity bias, we did not observe significant selection bias between patients treated with and without rituximab.

Description of Rituximab Treatments

A wide spectrum of rituximab treatment regimens was observed in our rituximab cohort. In detail, patients with GAD65 disease and CASPR2-AE received rituximab significantly later (GAD65: median 1,209 days, CASPR2: 632 days) than patients with NMDAR-AE (median: 54 days) and LGI1-AE (median: 155 days) (Figure 3A; Table 2). Time from initiation of first-line treatment to rituximab treatment was shortest in NMDAR-AE (median: 30 days) and longest in GAD65 disease (median: 141 days) (Figure 3B; Table 2). Sixteen (20%) patients with NMDAR-AE received rituximab very early within 2 weeks after first-line immunotherapy. The median number of infusions and total rituximab dose did not differ significantly among the subgroups (Figure 3C, D; Table 2). The duration of rituximab treatment, defined as the time from first to last infusion, was shortest in NMDAR-AE (median: 24 days) and longest in GAD65 disease (median: 454 days) (Figure 3E and Table 2). The percentage of patients who received only induction therapy defined as time between first to last rituximab treatment of less than 6 months

was highest in patients with NMDAR-AE (54%) and lowest in patients with GAD65 abs (27%); patients with LGI1- and CASPR2-AE were in between (35% and 46%, respectively) (Figure 3F; Table 2). Side effects after rituximab treatment were rare (n = 5, 3.4%); however, they were not systematically registered in this study. In detail, we observed n = 2 infusion-related reactions (n = 1: urticaria with, however, simultaneous IVIG application; n = 1: tremor, tachycardia, and fear); n = 1 lymphopenia leading to a reduction of the rituximab dose; n = 1 frequent infections; and n = 1 unknown side effect.

Follow-up and Treatment Response

Follow-up data were available for 282 patients (90%) with a median follow-up duration of 41 months with no significant differences between rituximab-treated patients and controls regarding follow-up data availability and duration (Table 2). The distribution of mRS scores at the peak of disease and at last follow-up improved significantly in patients with NMDAR-AE and in patients with LGI1-AE both in the rituximab cohort and in the control cohort. In patients with CASPR2-AE, a significant improvement was observed only in the rituximab cohort, but not in the control cohort. No significant improvement was observed in patients with GAD65 disease (Figure 3G). In addition, in patients with GAD65 disease, no significant improvement was observed when mRS scores were analyzed in the different disease subentities (encephalitis/overlap syndrome, CA, and SPS) (eFigure 2A, links.lww.com/NXI/A596).

Although patients with NMDAR-AE treated with rituximab were affected more severely at baseline (Table 1), at final follow-up, 94% of rituximab-treated patients compared with 88% of nontreated patients had reached independent living (mRS score ≤ 2 , $p = 0.33$). Patients with LGI1-AE reached independent living in 83% of cases treated with rituximab and

Table 1 Characterization of the Patient Cohort

	NMDAR			GAD65			LGI1			CASPR2		
	Ritux (n = 81)	Ctrl (n = 61)	p Value	Ritux (n = 31)	Ctrl (n = 53)	p Value	Ritux (n = 26)	Ctrl (n = 35)	p Value	Ritux (n = 11)	Ctrl (n = 14)	p Value
Female; n (%)	62 (77)	46 (75)	>0.99	26 (84)	34 (64)	0.08	13 (50)	18 (51)	>0.99	1 (9)	0 (0)	0.44
Age at onset, y; mean (95% CI)	28 (25–31)	32 (28–36)	0.20	46 (40–53)	51 (47–55)	0.27	61 (55–66)	63 (59–67)	0.46	66 (60–72)	69 (63–75)	0.40
Symptoms; n (%)												
Seizures	57 (70)	34 (56)	0.08	14 (45)	24 (45)	>0.99	17 (65)	25 (71)	0.78	7 (64)	10 (71)	>0.99
Sensible deficits	14 (17)	8 (13)	0.64	4 (13)	6 (11)	>0.99	1 (4)	6 (17)	0.22	3 (27)	4 (29)	>0.99
Decreased consciousness	53 (65)	23 (38)	0.001	7 (23)	4 (8)	0.09	10 (39)	13 (37)	>0.99	3 (27)	5 (36)	>0.99
Psychiatric symptoms	76 (94)	55 (90)	0.53	8 (26)	14 (26)	>0.99	18 (69)	16 (46)	0.08	5 (45)	8 (57)	0.70
Autonomic dysfunction	35 (43)	20 (33)	0.23	2 (6)	3 (6)	>0.99	3 (12)	4 (11)	>0.99	0 (0)	2 (14)	0.49
Movement disorder	39 (48)	20 (33)	0.09	13 (42)	19 (36)	0.64	2 (8)	6 (17)	0.45	3 (27)	4 (29)	>0.99
Paresis	7 (9)	8 (13)	0.42	1 (3)	5 (9)	0.41	1 (4)	3 (9)	0.63	0 (0)	1 (7)	>0.99
Cerebellar symptoms	8 (10)	10 (16)	0.31	13 (42)	20 (38)	0.82	1 (4)	0 (0)	0.43	3 (27)	1 (7)	0.29
Brainstem symptoms	16 (20)	14 (23)	0.68	9 (29)	12 (23)	0.60	1 (4)	2 (6)	>0.99	1 (9)	0 (0)	0.44
Cognitive impairment	69 (85)	47 (77)	0.28	13 (42)	28 (53)	0.37	23 (88)	29 (83)	0.72	10 (91)	10 (71)	0.34
ICU admission; n (%)	38 (47)	24 (39)	0.40	2 (6)	0 (0)	0.13	0 (0)	3 (9)	0.25	1 (9)	1 (7)	>0.99
Tumor; n (%)	14 (17) ^a	12 (20) ^b	0.83	1 (3) ^c	1 (2) ^d	>0.99	2 (8) ^e	1 (3) ^f	0.57	0 (0)	3 (21) ^g	0.23
mRS score worst status; median (IQR)	4 (2)	3 (2)	0.005	3 (2)	2 (1)	0.003	3 (2)	3 (2)	0.77	3 (1)	3 (1.25)	0.95
CSF/MRI profiles												
CSF cc ≥ 5/μL; n (%)	61 (73)	41 (67)	0.35	7 (23)	6 (11)	0.22	4 (15)	3 (9)	0.45	7 (64)	3 (21)	0.05
CSF cc; median, (IQR)	41 (92)	34 (61)	0.22	8 (6)	8 (12)	0.86	6 (5)	8 (13)	0.34	9 (13)	8 (4)	0.61
CSF protein >0.45 mg/dL; n (%)	24 (30)	20 (33)	0.72	10 (32)	25 (47)	0.25	9 (35)	11 (31)	>0.99	8 (73)	10 (71)	>0.99
Elev. protein; median (IQR)	54 (12)	68 (39)	0.02	53 (14)	55 (18)	0.89	59 (18)	58 (12)	>0.99	63 (16)	57 (26)	0.83
CSF-specific OCBs; n (%)	48 (59)	25 (41)	0.04	15 (48)	23 (43)	0.82	2 (8)	1 (39)	0.57	2 (18)	2 (14)	>0.99
MRI abnormalities; n (%)	40 (49)	29 (48)	0.87	16 (52)	26 (49)	>0.99	21 (81)	30 (86)	0.73	7 (64)	9 (64)	>0.99

Abbreviations: CASPR2 = contactin-associated protein-like 2; cc = cell count; Ctrl = controls; Elev. = elevated; GAD65 = glutamic acid decarboxylase 65; ICU = intensive care unit; IQR = interquartile range; Lgi1 = leucine-rich glioma-inactivated protein 1; mRS = Modified Rankin Scale; NMDAR = NMDA receptor; OCB = oligoclonal band; Ritux = Rituximab-treated patients.

^a 14x teratoma, ^b 9x teratoma, 2x prostate cancer, 1x small-cell lung cancer, ^c 1x unknown tumor, ^d 1x small-cell lung cancer, ^e 1x neuroendocrine tumor small intestine, 1x oligoastrocytoma, ^f 1x mamma carcinoma, ^g 1x thymoma, 1x unclear pulmonary lesion and mediastinal lymphadenopathy, 1x prostate cancer. Continuous variables were compared using the Mann-Whitney test, and categorical values were compared using the Fisher exact test. Unadjusted *p*-values are indicated.

p Values reaching statistical significance after adjustment using the Benjamini-Hochberg procedure with a false discovery rate of 10% are indicated in bold.

in 78% of cases without rituximab treatment ($p = 0.74$). In CASPR2-AE, independent living was observed in 80% of cases treated with rituximab vs 57% of cases who did not receive B-cell depletion ($p = 0.60$). In contrast, patients with GAD65 disease treated with rituximab, who were more severely affected at baseline, continued to have a lower rate of independent living compared with the non-rituximab-treated control cohort at last follow-up (52% vs 75%, $p = 0.07$).

When we analyzed the mRS scores in the rituximab cohort throughout follow-up in more detail, we found patients with NMDAR-AE to improve significantly already before rituximab

initiation (Figure 3, G.a I-II), presumably because of first-line treatments. After initiation of rituximab treatment, patients continued to improve significantly (Figure 3G.a II-III). No significant difference in the mRS score was observed in patients with NMDAR-AE exhibiting a tumor compared with those without a tumor both regarding mRS score at worst status and mRS score at last follow-up (eFigure 2B, links.lww.com/NXI/A596). In LGI1 patients, a significant improvement was already observed before rituximab treatment was initiated (Figure 3G.c I-II). After initiation of rituximab treatment, the mRS scores continued to drop; however, this improvement did not reach statistical significance (Figure 3G.c II-IV). In patients

Table 2 Immunotherapy and Follow-up of Patients

	NMDAR			GAD65			LGI1			CASPR2		
	Ritux (n = 81)	Ctrl (n = 61)	p Value	Ritux (n = 31)	Ctrl (n = 53)	p Value	Ritux (n = 26)	Ctrl (n = 35)	p Value	Ritux (n = 11)	Ctrl (n = 14)	p Value
Prior 1st-line immunotherapy												
n (%)	81 (100)	57 (93)	0.03	31 (100)	48 (91)	0.15	26 (100)	35 (100)	>0.99	11 (100)	13 (93)	>0.99
Time to 1st line ^a , d; median (IQR)	16 (33)	33 (93)	0.0009	466 (1,306)	1,040 (1856)	0.31	52 (185)	43 (168)	0.38	149 (741)	157 (414)	0.87
Response to 1st line ^b ; n/n (%)	40/55 (73)	38/43 (88)	0.08	22/26 (85)	24/30 (80)	0.74	14/16 (88)	27/27 (100)	0.13	4/5 (80)	8/8 (100)	0.38
Rituximab treatment												
Time to therapy ^a , d; median (IQR)	54 (200)	/	/	1,209 (2,331)	/	/	155 (192)	/	/	632 (722)	/	/
Time from 1st line, d; median (IQR)	30 (105)	/	/	141 (544)	/	/	47 (127)	/	/	67 (190)	/	/
No. of infusions, n; median (IQR)	3 (1)	/	/	4 (6)	/	/	3.5 (1.5)	/	/	4 (3)	/	/
Cumulative dose, g; median (IQR)	2.6 (2.0)	/	/	3.5 (4.0)	/	/	3.0 (2.0)	/	/	3.0 (2.5)	/	/
Dose/infusion, g; median (IQR)	1.0 (0.3)	/	/	1.0 (0.3)	/	/	1.0 (0.02)	/	/	1.0 (0)	/	/
1st to last infusion, d; median (IQR)	24 (491)	/	/	454 (1,116)	/	/	227 (484)	/	/	203 (490)	/	/
Induction only (<6 mo); n (%)	44 (54)	/	/	8 (27)	/	/	9 (35)	/	/	5 (46)	/	/
Other 2nd-line immunotherapy^c												
n (%)	20 (25)	11 (18)	0.41	13 (42)	11 (21)	0.05	4 (15)	14 (40)	0.05	1 (9)	4 (29)	0.34
Follow-up (FU)												
FU data available, n (%)	68 (84)	56 (92)	0.21	30 (97)	48 (91)	0.41	25 (96)	32 (91)	0.63	9 (82)	14 (100)	0.18
Duration, mo; median (IQR)	35 (44)	26 (39)	0.26	72 (97)	72 (87)	0.68	40 (27)	31 (42)	0.17	39 (24)	34 (40)	0.87
mRS score ≤2 at last FU; n (%)	48 (94)	49 (88)	0.33	14 (52)	36 (75)	0.07	20 (83)	25 (78)	0.74	4 (80)	8 (57)	0.60
Relapse during FU; n (%)	13 (19) ^d	7 (13)	0.34	^e	/	/	5 (20)	10 (31) ^f	0.40	1 (11)	2 (14)	>0.99
Timing of relapse; n	<1 y: 4	<1 y: 1	/	/	/	/	<1 y: 1	<1 y: 5 ^f	/	<1 y: 0	<1 y: 0	/
	1–2 y: 4 ^d	1–2 y: 4	/	/	/	/	1–2 y: 1	1–2 y: 2 ^f	/	1–2 y: 1	1–2 y: 0	/
	2–5 y: 4	2–5 y: 2	/	/	/	/	2–5 y: 3	2–5 y: 3	/	2–5 y: 0	2–5 y: 2	/
	>5 y: 1day	>5 y: 0	/	/	/	/	>5 y: 0	>5 y: 0	/	>5 y: 0	>5 y: 0	/
Relapse after rituximab treatment, n (%)	3 (4) ^g	/	0.18 ^h	/	/	/	3 (12) ^g	/	0.12 ^h	0 (0)	/	0.50 ^h

Abbreviations: CASPR2 = contactin-associated protein-like 2; FU = follow-up; GAD65 = glutamic acid decarboxylase 65; IQR = interquartile range; Lgi1 = leucine-rich glioma-inactivated protein 1; mRS = modified Rankin Scale; NMDAR = NMDA receptor.

^aFrom symptom onset; ^bcalculated for the proportion of patients for whom information regarding response to 1st-line immunotherapy was available; ^cexcept rituximab, corticosteroids, and PLEX; ^d1 patient experienced relapses both after 1–2 y and >5 y from disease onset; ^ein patients with GAD abs, chronic worsening rather than clear relapses is observed; ^f1 patient experienced relapses both after <1 y and after 1–2 y; ^gNMDA-AE: 1 relapse occurred 3 mo after initiation of rituximab, 1 relapse occurred 1 y and 8 mo after last rituximab infusion, 1 relapse occurred during continued rituximab treatment with yearly infusions; LGI1-AE: 1 relapse occurred 6 mo after last rituximab infusion, 1 relapse occurred under low-dose rituximab treatment with application of 100 mg every 6 mo, 1 relapse occurred 2 y and 8 mo after last rituximab infusion. ^hComparison with the relapse rate in the control cohort.

Continuous variables were compared using the Mann-Whitney test, and categorical values were compared using the Fisher exact test.

Unadjusted *p* values are indicated. *p* Values reaching statistical significance after adjustment using the Benjamini-Hochberg procedure with a false discovery rate of 10% are indicated in bold.

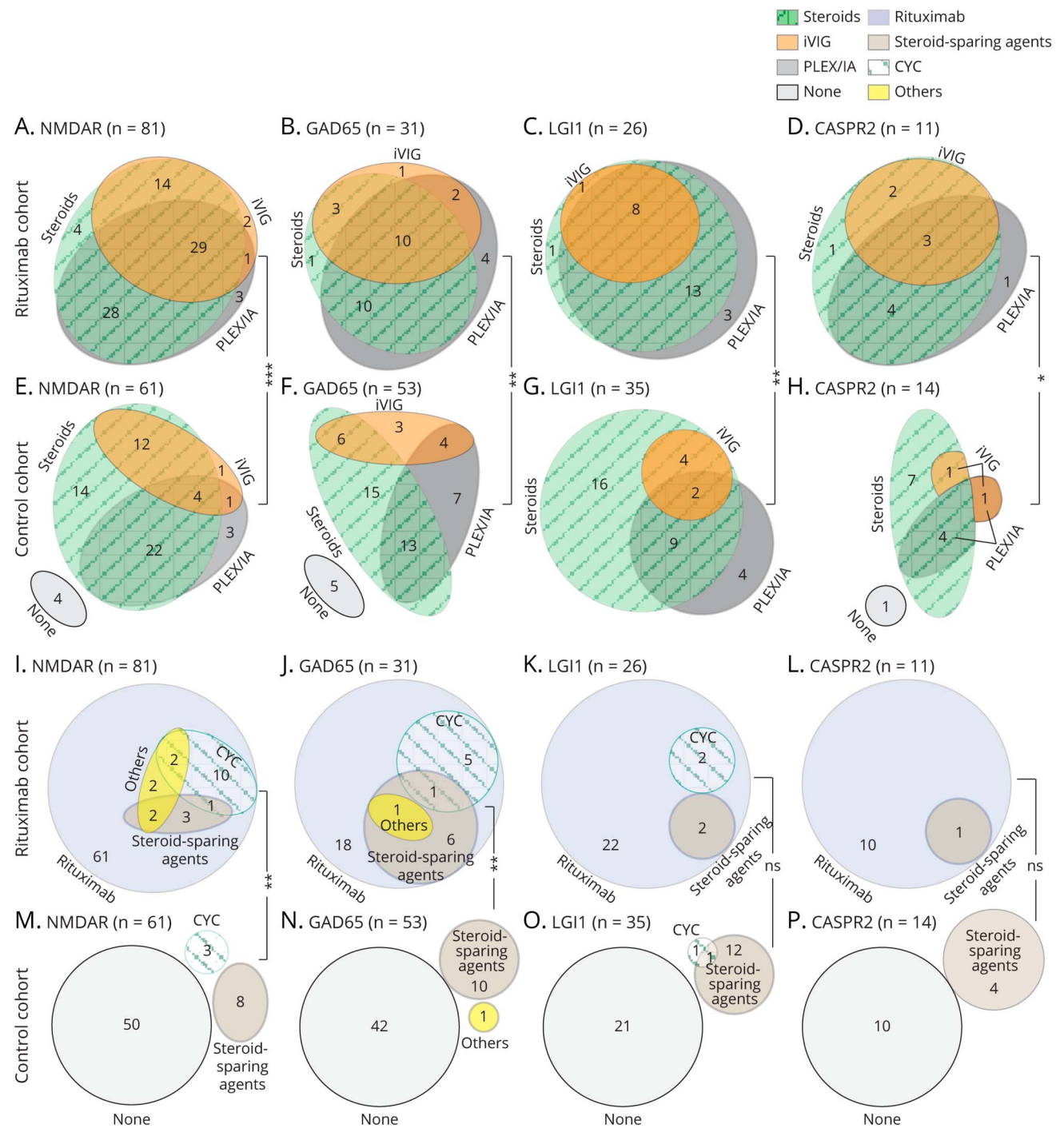
with CASPR2-AE, mRS scores decreased after initiation of rituximab treatment (Figure 3G.d II-IV) without reaching significance presumably because of small patient numbers.

Nineteen relapses (14%) were reported during follow-up in the rituximab cohort (NMDAR-AE: n = 13, 19%; LGI1-AE: n = 5, 20%; and CASPR2-AE: n = 1, 11%). Of note, only 6 relapses (5%) in the rituximab cohort occurred after rituximab treatment was started (NMDAR-AE: n = 3, 4%; LGI1-AE: n = 3;

12%) (Table 2). The other 13 relapses occurred before rituximab initiation. In the control cohort, 19 relapses (13%) occurred (NMDAR-AE: n = 7, 13%; LGI1-AE: n = 10, 31%; CASPR2-AE: n = 2, 14%), which was more frequent than those observed in the rituximab group after initiation of rituximab (*p* = 0.02) (Table 2).

Finally, we performed a multivariate analysis for the rituximab cohort to identify factors associated with the extent of

Figure 2 Venn/Euler Diagrams Showing Applied Mono- and Combination First-Line and Second-Line Immunotherapies

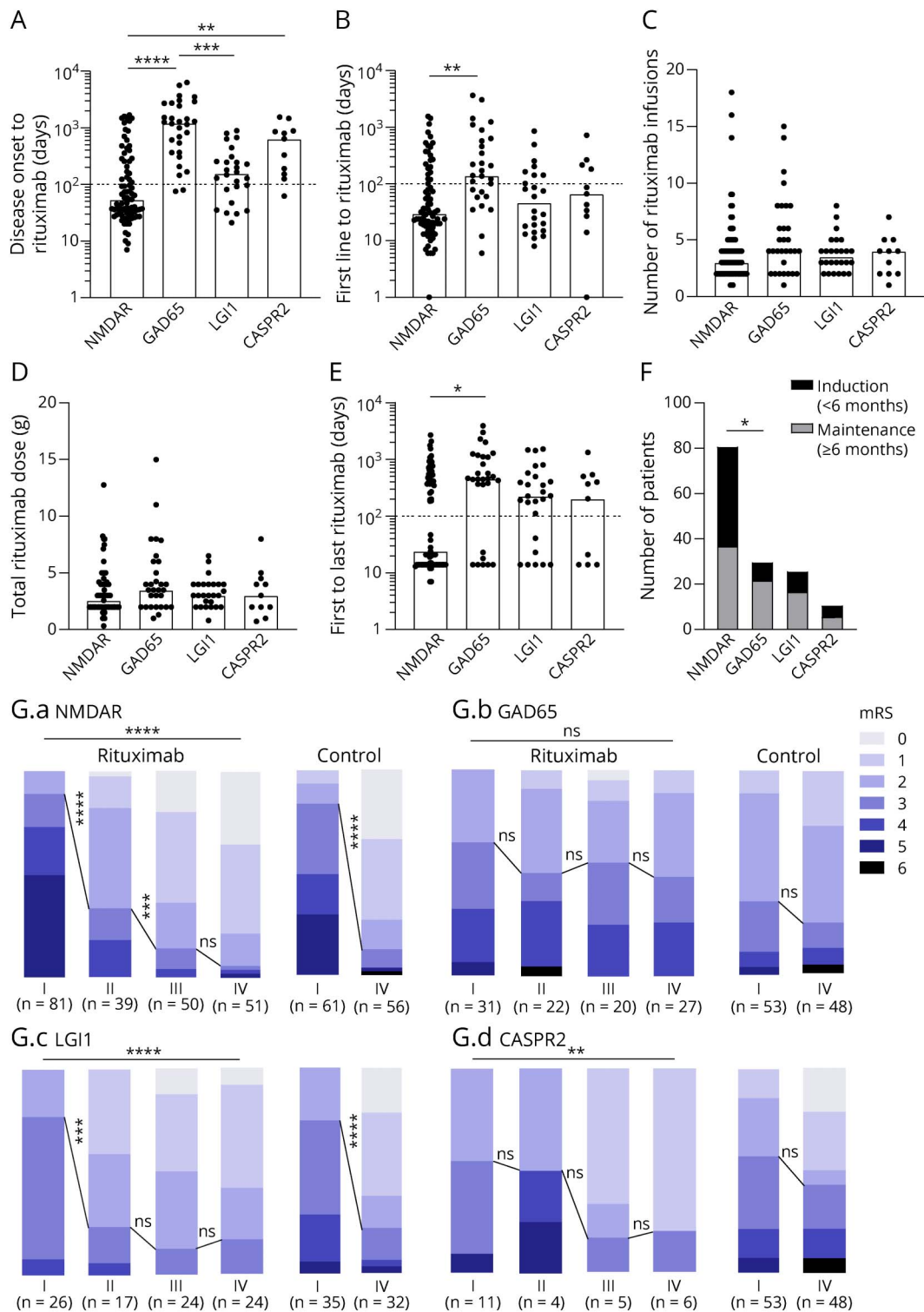


The numbers of patients treated with the respective prior first-line immunotherapies (A–H) and second-line immunotherapies (I–P) in the rituximab cohort (A–D) and in the control cohort (E–H) are depicted for the different ab subgroups (A, E, I, and M: NMDAR-AE; B, F, J, and N: GAD65 disease; C, G, K, and O: LGI1-AE; and D, H, L, and P: CASPR2-AE). Other second-line therapies included bortezomib (n = 6 in patients with NMDAR-AE treated with rituximab), daratumumab (n = 1 in patients with NMDAR-AE treated with rituximab), tacrolimus (n = 1 in patients with GAD65 disease treated with rituximab and n = 1 in patients with GAD65 disease not treated with rituximab), and basiliximab (n = 1 in patients with GAD65 disease treated with rituximab). Areas of Venn diagrams are proportional to the case numbers relative to the respective subgroup. (A–H) Proportions of combination first-line therapy relative to none/monotherapy were compared using the Fisher exact test. ****p* < 0.001, ***p* < 0.01, and **p* < 0.05. (I–P) Proportions of treatment with cyclophosphamide or other therapies relative to steroid-sparing therapies and no treatment were compared using the Fisher exact test. ****p* < 0.001, ***p* < 0.01, and **p* < 0.05. AZA = azathioprine; CASPR2 = contactin-associated protein-like-2; cyc = cyclophosphamide; GAD65 = glutamic acid decarboxylase 65; iVIG = IV immunoglobulin; MMF = mycophenolate mofetil; MTX = methotrexate; NMDAR = NMDA receptor; LGI1 = leucine-rich glioma-inactivated-1; PLEX = plasma exchange.

improvement as measured by the change in the mRS score from baseline to last follow-up. Most significantly, the AE subtype (NMDAR-AE) was associated with mRS score

improvement, whereas rituximab dosage and duration were not significantly associated with an improved mRS score (Table 3). mRS score improvement was also observed for early initiation

Figure 3 Rituximab Regimens Used in Patients With AE and the Outcome According to Subtypes of AE



(A–F) In different subgroups (NMDAR-AE, GAD65 disease, LGI1-AE, and CASPR2-AE), the duration in days from disease onset to initiation of rituximab treatment (A), the duration in days from initiation of first-line therapy to initiation of rituximab treatment (B), the number of rituximab infusions (C), the total cumulative rituximab dose (D), the duration in days from the first to the last rituximab infusion (E), and the number of patients receiving induction therapy (rituximab treatment <6 months) or induction + maintenance therapy (rituximab treatment ≥6 months) (F) are depicted. Bars indicate the median. Normality testing was performed using the D’Agostino-Pearson omnibus test. Continuous variables were compared using the Kruskal-Wallis test followed by the Dunn multiple comparisons test, and ordinal variables were compared using the Fisher exact test. **** $p < 0.0001$ *** $p < 0.001$, ** $p < 0.01$, and * $p < 0.05$. (G) mRS scores in the different ab subgroups were compared in the rituximab cohort and in the control cohort. The distribution of mRS scores is depicted at 4 time points: I, maximal mRS at symptom onset; II, mRS at initiation of rituximab treatment (from –2 months to +4 months from rituximab onset); III, mRS 4–12 months after initiation of rituximab treatment; IV, mRS at last follow-up with at least >12 months after rituximab treatment. The line represents the change in mRS scores dividing favorable mRS scores (0–2) and nonfavorable mRS scores (≥3). The ordinal χ^2 test was applied to compare the distribution of mRS scores. **** $p < 0.0001$ *** $p < 0.001$, ** $p < 0.01$, and * $p < 0.05$. CASPR2, contactin-associated protein-like-2; GAD65 = glutamic acid decarboxylase 65; mRS = modified Rankin Scale; NMDAR = NMDA receptor; LGI1 = leucine-rich glioma-inactivated-1.

Table 3 Multivariate Analysis of the Outcome

Parameters analyzed for an effect on outcome improvement (Δ mRS)				
Parameter	<i>p</i> Value	DF	RR	95% CI
Antibody type	<0.0001*	3		
GAD65 vs NMDAR			0.46	0.28–0.75
LGI1 vs NMDAR			0.84	0.34–1.46
CASPR2 vs NMDAR			0.70	0.52–1.39
Time from 1st-line therapy to rituximab initiation (d)	0.02	1		
≤ 60 vs > 60			1.45	1.05–1.97
Time to 1st-line therapy after symptom onset (d)	0.04	1		
≤ 30 vs > 30			1.35	1.01–1.80
No. of rituximab infusions (n)	0.05	2		
3–5 vs 0–2			2.2	0.99–5.00
≥ 6 vs 3–5			0.43	0.17–1.08
Time to rituximab initiation after symptom onset (d)	0.12	1		
≤ 90 vs > 90			0.73	0.48–1.09
Age (y)	0.44	3		
> 20 – 40 vs 0 – 20			0.86	0.45–1.67
> 40 – 60 vs > 20 – 40			0.69	0.35–1.35
> 60 vs > 40 – 60			0.89	0.45–1.73
Total rituximab dosage (g)	0.464	2		
> 2 – 5 vs 0 – 2			0.63	0.27–1.43
> 5 vs > 2 – 5			1.51	0.55–4.48
Duration of rituximab treatment (mo):	0.48	1		
< 6 vs ≥ 6			0.88	0.61–1.30
Sex	0.7086	1		
F vs M			0.95	0.73–1.24

Abbreviations: CASPR2 = contactin-associated protein-like 2; DF = degrees of freedom; GAD65 = glutamic acid decarboxylase 65; Lgi1 = leucine-rich glioma-inactivated protein 1; NMDAR = NMDA receptor; RR = relative risk. Unadjusted *p* values are indicated. *p* Values reaching statistical significance after adjustment using the Benjamini-Hochberg procedure with a false discovery rate of 10% are indicated in bold.

of rituximab treatment (≤ 60 days after initiation of first-line treatment), and a trend was observed for early initiation of first-line treatment (≤ 30 days after symptom onset).

Discussion

This study describes real-world data on rituximab usage in a large German cohort of patients with the most common AE

subtypes. We confirm the following: (1) Rituximab is the most frequent second-line immunotherapy that is used in nearly half of all patients with AE in Germany. (2) Rituximab usage differs within AE subtypes with patients with NMDAR-AE most frequently and patients with GAD65 disease least frequently receiving rituximab. Treatment was in all cases initiated following prior first-line immunotherapy. Patients with NMDAR-AE and GAD65 disease were more likely to be treated with rituximab if they presented with more severe disease (decreased levels of consciousness and higher mRS). (3) Patients with NMDAR-AE were treated earlier and more often (54%) received a short-term rituximab treatment (< 6 months) without repeated maintenance reinfusion than other AE subgroups. (4) The long-term outcome in patients with NMDAR-, LGI1-, and CASPR2-AE in the overall cohort was favorable with 91%, 80%, and 63% of the patients being able to function independently at last follow-up, respectively. (5) Although comparison of patients with and without rituximab treatment is prone to severity bias, we found some hints of a better outcome and fewer relapses in the former group: patients with NMDAR-AE treated with rituximab more often reached independent living at last follow-up although being affected more severely at baseline; patients with CASPR2-AE improved significantly better under rituximab treatment; patients with NMDAR-E and LGI1-AE experienced fewer relapses if treated with rituximab. (6) No significant improvement during follow-up of patients with GAD65 disease was observed both in the rituximab cohort and in the control cohort. However, although we did not observe a group effect in GAD65 disease, some individuals showed a remarkable response associated with B cell-depleting treatment.

In NMDAR-AE, treatment with rituximab is widely accepted. It has been used empirically since the first description of NMDAR-AE, and a large prospective case series⁴ and a systematic review²¹ could add further evidence that early second-line immunotherapy in patients not responding sufficiently to first-line immunotherapy was associated with better outcomes and fewer relapses. Recently, a meta-analysis of 14 retrospective and prospective case series summarizing 277 patients with AE (88.8% NMDAR-AE) concluded that rituximab is an effective second-line agent with an acceptable toxicity profile.¹⁹ Our data confirm and extend these observations. We found patients with NMDAR-AE treated with rituximab to have a favorable outcome. As patients treated with induction or maintenance therapy did not significantly differ in the outcome, our data support the notion that in many patients with NMDAR-AE, short-term rituximab treatment might be sufficient to control the disease. In a recent position paper by the Autoimmune Encephalitis Alliance Clinicians Network,²² this is reflected by the recommendation to consider long-term rituximab treatment mainly in relapsing disease.

Compared with NMDAR-AE, considerably less information on long-term immunosuppression and especially rituximab is available in other AE subtypes. For LGI1-AE, early initiation of any immune therapy was associated with better outcomes in studies with 29⁷ and 13 patients,²³ respectively. Only few patients were treated with rituximab in retrospective case

series^{19,24,25} and a small open-label trial.²⁶ In our cohort, we observed a surprisingly favorable outcome in patients with LGII-AE, with 80% reaching independent living (mRS score ≤ 2) (83% in the rituximab cohort and 78% in the control cohort). A systematic review²¹ showed full recovery or an mRS score of 0 in 27.8% of patients, with 8% of patients treated with rituximab and 18% of patients receiving second-line treatment. In light of these findings, we believe that rituximab treatment can be considered early in patients with LGII-AE as 1 possible immunosuppressive treatment, although the duration of therapy is unclear.

Relapses occurred in 16% of patients with NMDAR-AE and 26% with LGII-AE in our overall cohort. Previously, relapses were reported in 11.2% (85/758) of patients with NMDAR-AE and 18.8% (16/85) with LGII-AE.²¹ However, we did observe a reduced rate of relapses in patients with NMDAR-AE and LGII-AE treated with rituximab compared with patients without (independent of other second-line immunotherapies) suggesting better efficacy of rituximab in preventing relapses compared with other regimens. Nevertheless, this should be interpreted with caution because absolute patient numbers are small and controlled studies missing.

For the treatment of CASPR2-AE, even less evidence exists. In our series, 44% of patients with CASPR2-AE ($n = 11$) were treated with rituximab albeit considerably later than patients with NMDAR-AE. We could show significant improvement in patients with CASPR2-AE treated with rituximab, which was not observed in the control group. Although patient numbers were small, our results suggest an effect of rituximab treatment in CASPR2-AE but also indicate the need for larger numbers.

Immunotherapeutic strategies for GAD65-AE remain highly controversial.²⁷ Most patients are considered to require immunotherapy, and early immunotherapy has been found to be associated with a better outcome.^{10,28} However, the different neurologic manifestations of SPS, CA, and LE appear to respond differently to treatments.²⁷ Treatment of SPS with IVIG has been examined in a small crossover placebo-controlled trial in 16 patients with SPS¹¹ and showed efficacy in approximately 80% of patients. The use of plasma exchange and corticosteroids was linked to ambiguous clinical responses,^{29,30} and immunosuppressive agents such as azathioprine, methotrexate, cyclophosphamide, and mycophenolate mofetil are currently used in clinical practice, however, with insufficient evidence from larger clinical trials.^{30,31} Rituximab was examined in a randomized, placebo-controlled trial in 24 patients with GAD65-SPS yet surprisingly did not show significant effects, possibly because of the long disease duration at the time of treatment initiation (8.0 years).¹⁵ The long-term outcome in SPS in general was poor, with 40% of patients not responding to immunotherapy.³² Although small case series show a benefit from immunotherapy including rituximab in GAD65-CA in 41%–48% of cases,^{33,34} the long-term outcome is poor in approximately 65% of patients.¹⁰ Similarly, most patients with GAD65-LE continue to have seizures with or without immunotherapy.^{35,36} Our data are

in line with these observations. Rituximab treatment was initiated very late after onset of symptoms in our patients, and we did not find a significant association with a better outcome in these patients. Yet, the functional level was better than expected with 67% of patients being able to live independently (mRS score ≤ 2) (52% in the rituximab group and 75% in the control group). In summary, our data support the notion that long-standing GAD65 disease does not respond to rituximab therapy. However, patients in early disease stages might be more likely to respond to rituximab treatment; however, response is difficult to predict, and a lack of response should trigger benefit-risk reevaluation of rituximab therapy.

We analyzed data acquired by the GENERATE network, a multicenter registry for AE in Germany. Of note, all participating centers had experience in treatment of AE, and thus, our study is not necessarily representative for nonexpert centers or centers outside Germany. Further limitations of our study are the observational character going along with a severity bias when patients with and without rituximab treatment are compared and the difficulty to differentiate rituximab treatment effects from spontaneous improvements or improvements due to concomitant treatments, the incomplete follow-up data with potential selection bias, and the lack of clinical criteria defining response to first-line therapies. Nevertheless, because randomized trials are difficult to conduct in rare diseases such as AE, real-world data from registries add important information on treatment profiles and sequences and may lead to standardized treatment protocols. In addition, single-center bias is unlikely due to the multicenter approach. Analysis of auto-ab levels, B-cell counts, and biomarkers like serum neurofilament light chain concentration throughout treatment course could add to future studies investigating the response to rituximab treatment in AE. In addition, safety data should be captured systematically.

Our results support the efficacy of early rituximab treatment in NMDAR-, LGII-, and CASPR2-AE and suggest that short-term therapy could be a treatment option. They also suggest that patients with long-standing GAD65 disease are less likely to benefit from B-cell depletion than the other AE subgroups. Nevertheless, future controlled, randomized, and prospective studies in addition to national and supranational registries with collaborative research efforts are in dire need in the field of AE. As an example of such collaborative research, the multicentric, double-blinded, and placebo-controlled phase II study GENERATE-BOOST is currently investigating the response to bortezomib in patients with severe AE.

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Appendix 1 Authors

Name	Location	Contribution
Franziska S. Thaler, MD	Institute of Clinical Neuroimmunology, University Hospital and Biomedical Center, Ludwig-Maximilians-University, Munich, Germany	Patient care, design of the study, data analysis, statistical analysis, and paper writing
Luise Zimmermann, MD	Section of Translational Neuroimmunology, Department of Neurology, Jena University Hospital, Germany	Patient care, data analysis, and revised the manuscript for intellectual content
Stefan Kammermeier, MD	Department of Neurology, University Hospital, Ludwig-Maximilians-University, Munich, Germany	Statistical analysis and revised the manuscript for intellectual content
Christine Strippel, MD	Department of Neurology with Institute of Translational Neurology, University of Muenster, Germany	Patient care, data analysis, and revised the manuscript for intellectual content
Marius Ringelstein, MD	Department of Neurology, Medical Faculty, Heinrich Heine University Düsseldorf, Germany; Department of Neurology, Center for Neurology and Neuropsychiatry, LVR-Klinikum, Heinrich Heine University Düsseldorf, Germany	Patient care, data analysis, and revised the manuscript for intellectual content
Andrea Kraft, MD	Department of Neurology, Martha-Maria Hospital, Halle/Saale, Academic Hospital of University Halle-Wittenberg, Germany	Patient care, data analysis, and revised the manuscript for intellectual content
Kurt-Wolfram Sühs, MD	Department of Neurology, Hannover Medical School, Hannover, Germany	Patient care, data analysis, and revised the manuscript for intellectual content
Jonathan Wickel, MD	Section of Translational Neuroimmunology, Department of Neurology, Jena University Hospital, Germany	Patient care, data analysis, and revised the manuscript for intellectual content
Christian Geis, MD	Section of Translational Neuroimmunology, Department of Neurology, Jena University Hospital, Germany	Patient care, data analysis, and revised the manuscript for intellectual content

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Name	Location	Contribution
Robert Markewitz, MD	Department of Neurology, University Hospital Schleswig-Holstein, Lübeck, Germany	Patient care, data analysis, and revised the manuscript for intellectual content
Christian Urbaneck, MD	Department of Neurology, Klinikum der Stadt Ludwigshafen a. Rh. gGmbH, Germany	Patient care, data analysis, and revised the manuscript for intellectual content
Claudia Sommer, MD	Department of Neurology, University Hospital Würzburg, Germany	Patient care, data analysis, and revised the manuscript for intellectual content
Kathrin Doppler, MD	Department of Neurology, University Hospital Würzburg, Germany	Patient care, data analysis, and revised the manuscript for intellectual content
Loana Penner	Department of Neurology, Ulm University, Germany	Data analysis and revised the manuscript for intellectual content
Jan Lewerenz, MD	Department of Neurology, Ulm University, Germany	Patient care, data analysis, and revised the manuscript for intellectual content
Rosa Rößling, MD	Department of Neurology and Experimental Neurology, Charité - Universitätsmedizin Berlin, Germany; German Center for Neurodegenerative Diseases (DZNE) Berlin, Germany	Patient care, data analysis, and revised the manuscript for intellectual content
Carsten Finke, MD	Department of Neurology and Experimental Neurology, Charité - Universitätsmedizin Berlin, Germany	Patient care, data analysis, and revised the manuscript for intellectual content
Harald Prüss, MD	Department of Neurology and Experimental Neurology, Charité - Universitätsmedizin Berlin, Germany; German Center for Neurodegenerative Diseases (DZNE) Berlin, Germany	Patient care, data analysis, and revised the manuscript for intellectual content
Nico Melzer, MD	Department of Neurology with Institute of Translational Neurology, University of Muenster, Germany; Department of Neurology, Medical Faculty, Heinrich Heine University Düsseldorf, Germany	Patient care, data analysis, and revised the manuscript for intellectual content
Klaus-Peter Wandinger, MD	Department of Neurology, University Hospital Schleswig-Holstein, Lübeck, Germany; Neuroimmunology section, Institute of Clinical Chemistry, University Hospital Schleswig-Holstein Kiel, Lübeck, Germany	Patient care, data analysis, and revised the manuscript for intellectual content

Continued

Appendix 1 (continued)

Name	Location	Contribution
Frank Leypoldt, MD	Neuroimmunology Section, Institute of Clinical Chemistry, University Hospital Schleswig-Holstein Kiel/Lübeck, Germany; Department of Neurology, Christian-Albrechts-Universität Kiel, Germany	Patient care, design of the study, data analysis, and paper writing
Tania Kümpfel, MD	Institute of Clinical Neuroimmunology, University Hospital and Biomedical Center, Ludwig-Maximilians-University, Munich, Germany	Patient care, design of the study, data analysis, and paper writing

Appendix 2 Coinvestigators

Name	Location	Role	Contribution
Michael Adelmann, MD	Vitos Weil-Lahn, Clinic for Neurology, Weilmünster, Germany	Site investigator	Contributor to the GENERATE registry
Luise Appeltshauser, MD	Department of Neurology, University Hospital Würzburg, Würzburg, Germany	Site investigator	Contributor to the GENERATE registry
Ilya Ayzenberg, MD	Department of Neurology, St. Josef Hospital, Ruhr University Bochum, Bochum, Germany	Site investigator	Contributor to the GENERATE registry
Carolin Baade-Büttner, MD	Department of Neurology, Jena University Hospital, Germany	Site investigator	Contributor to the GENERATE registry
Andreas van Baalen, MD	Clinic for Child and Adolescent Medicine II, University Hospital Schleswig-Holstein, Kiel, Germany	Site investigator	Contributor to the GENERATE registry
Sebastian Baatz, MD	Department of Neurology, Klinikum Altenburger Land GmbH, Altenburg, Germany	Site investigator	Contributor to the GENERATE registry
Bettina Balint, MD	Department of Neurology, University Hospital, Heidelberg, Germany	Site investigator	Contributor to the GENERATE registry
Sebastian Bauer, MD	Epilepsy Center Frankfurt Rhine-Main and Department of Neurology, Goethe University Frankfurt, Frankfurt am Main, Germany	Site investigator	Contributor to the GENERATE registry
Annette Baumgartner, MD	Department of Neurology, Medical Center, University of Freiburg, Faculty of Medicine, University of Freiburg, Freiburg, Germany	Site investigator	Contributor to the GENERATE registry

Appendix 2 (continued)

Name	Location	Role	Contribution
Sonka Benesch, MD	Department of Neurology, Klinikum Aschaffenburg-Alzenau, Germany	Site investigator	Contributor to the GENERATE registry
Robert Berger, MD	Department of Neurology, ASKLEPIOS Klinik Hamburg Altona, Hamburg, Germany	Site investigator	Contributor to the GENERATE registry
Sascha Berning, MD	Department of Neurology, Klinikum Osnabrück, Osnabrück, Germany	Site investigator	Contributor to the GENERATE registry
Sarah Bernsen, MD	Department of Neurodegenerative Disorders, University of Bonn, Germany	Site investigator	Contributor to the GENERATE registry
Christian Bien, MD	Bethel Epilepsy Center, Mara Hospital, Bielefeld, Germany	Site investigator	Contributor to the GENERATE registry
Corinna Bien, MD	Laboratory Krone, Bad Salzuflen, Germany	Site investigator	Contributor to the GENERATE registry
Andreas Binder, MD	Division of Neurological Pain Research and Therapy, Department of Neurology, University Hospital of Schleswig-Holstein, Kiel, Germany	Site investigator	Contributor to the GENERATE registry
Stefan Bittner, MD	Department of Neurology, University of Mainz, Mainz, Germany	Site investigator	Contributor to the GENERATE registry
Daniel Bittner, MD	Department of Neurology, Südlinikum Nordhausen, Nordhausen, Germany	Site investigator	Contributor to the GENERATE registry
Franz Blaes, MD	Department of Neurology, KKH Gummersbach, Gummersbach, Germany	Site investigator	Contributor to the GENERATE registry
Astrid Blaschek, MD	Department of Pediatric Neurology and Developmental Medicine and LMU Center for Children with Medical Complexity, Dr von Hauner Children's Hospital, LMU Hospital, Ludwig-Maximilians-Universität, Germany	Site investigator	Contributor to the GENERATE registry
Justina Dargvaiene, MD	Institute of Clinical Chemistry, University Hospital Schleswig-Holstein, Kiel, Schleswig-Holstein, Germany	Site investigator	Contributor to the GENERATE registry
Andre Dik, MD	Department of Neurology with Institute of Translational Neurology, University of Münster, Münster, Germany	Site investigator	Contributor to the GENERATE registry

Appendix 2 (continued)

Name	Location	Role	Contribution
Mona Dreesmann, MD	Department of Pediatrics, Ernst von Bergmann Klinikum, Potsdam, Germany	Site investigator	Contributor to the GENERATE registry
Friedrich Ebinger, MD	Pediatric Clinic, St. Vincenz Hospital, Paderborn, Germany	Site investigator	Contributor to the GENERATE registry
Lena Edelhoff, MD	Department of Neurology, Katholisches Marienkrankenhaus gGmbH, Hamburg, Germany	Site investigator	Contributor to the GENERATE registry
Sven Ehrlich, MD	Clinic for Neurology and Neurological Intensive Care Medicine, Hubertusburg Hospital, Wermsdorf, Germany	Site investigator	Contributor to the GENERATE registry
Katharina Eisenhut, MD	Institute of Clinical Neuroimmunology, University Hospital and Biomedical Center, Ludwig-Maximilians-University, Munich, Germany	Site investigator	Contributor to the GENERATE registry
Dominique Andres, MD	Section for Experimental Neuropsychiatry, Department of Psychiatry and Psychotherapy, Medical Center - University of Freiburg, Faculty of Medicine, University of Freiburg, Germany; Department of Psychiatry and Psychotherapy, Medical Center - University of Freiburg, Faculty of Medicine, University of Freiburg, Germany	Site investigator	Contributor to the GENERATE registry
Marina Entscheva, MD	Department of Neurology, ASKLEPIOS Fachklinikum Lübben, Lübben, Germany	Site investigator	Contributor to the GENERATE registry
Jürgen Hartmut Faiss, MD	Department of Neurology, Asklepios Fachklinikum Teupitz, Teupitz, Germany	Site investigator	Contributor to the GENERATE registry
Walid Fazeli, MD	Pediatric Neurology, Department of Pediatrics, Faculty of Medicine and University Hospital Cologne, University of Cologne, Cologne, Germany	Site investigator	Contributor to the GENERATE registry
Alexander Finke, MD	Department of Neurology, Städtisches Klinikum Lüneburg, Lüneburg, Germany	Site investigator	Contributor to the GENERATE registry
Dirk Fitzner, MD	Department of Neurology, University of Göttingen, Göttingen, Germany	Site investigator	Contributor to the GENERATE registry
Marina Flotats-Bastardas, MD	Department of Pediatric Neurology, Saarland University Hospital, Homburg, Germany	Site investigator	Contributor to the GENERATE registry

Appendix 2 (continued)

Name	Location	Role	Contribution
Friedemann Paul, MD	Department of Neurology, Charité Universitätsmedizin Berlin, Corporate Member of Freie Universität Berlin, Humboldt-Universität zu Berlin, Berlin Institute of Health, Berlin, Germany	Site investigator	Contributor to the GENERATE registry
Manuel Friese, MD	Institute of Neuroimmunology and Multiple Sclerosis, University Medical Centre Hamburg-Eppendorf, Hamburg, Germany	Site investigator	Contributor to the GENERATE registry
Marco Gallus, MD	Department of Neurology with Institute of Translational Neurology, University of Münster, Münster, Germany	Site investigator	Contributor to the GENERATE registry
Marcel Gebhard, MD	Department of Neurology, Martha-Maria Hospital, Halle/Saale, Academic Hospital of University Halle-Wittenberg, Germany	Site investigator	Contributor to the GENERATE registry
Christian Geis, MD	Section Translational Neuroimmunology, Department of Neurology, Jena University Hospital, Jena, Germany	Site investigator	Contributor to the GENERATE registry
Anna Gorsler, MD	Kliniken Beelitz GmbH, Neurologische Rehabilitationsklinik, Beelitz-Heilstätten, Germany	Site investigator	Contributor to the GENERATE registry
Armin Grau, MD	Department of Neurology, Klinikum der Stadt Ludwigshafen am Rhein, Germany	Site investigator	Contributor to the GENERATE registry
Oliver Grauer, MD	Neuro-Oncology Department, University Hospital Muenster, Muenster, Germany	Site investigator	Contributor to the GENERATE registry
Catharina Groß, MD	Department of Neurology with Institute of Translational Neurology, University of Münster, Münster, Germany	Site investigator	Contributor to the GENERATE registry
Halime Gül	Department of Neurology, University Hospital Ulm, Ulm, Germany	Site investigator	Contributor to the GENERATE registry
Robert Handreka, MD	Department of Neurology, University of Mainz, Mainz, Germany	Site investigator	Contributor to the GENERATE registry
Niels Hansen, MD	Department of Psychiatry and Psychotherapy, Göttingen, Germany	Site investigator	Contributor to the GENERATE registry
Martin Häusler, MD	Division of Neuropediatrics and Social Pediatrics, Department of Pediatrics, University Hospital RWTH Aachen, Aachen, Germany	Site investigator	Contributor to the GENERATE registry

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Appendix 2 (continued)

Name	Location	Role	Contribution
Joachim Havla, MD	Institute of Clinical Neuroimmunology, University Hospital and Biomedical Center, Ludwig-Maximilians-University, Munich, Germany	Site investigator	Contributor to the GENERATE registry
Chung Ha-Yeun, MD	Section of Translational Neuroimmunology, Hans Berger Department of Neurology, Jena University Hospital, Jena, Germany	Site investigator	Contributor to the GENERATE registry
Wolfgang Heide, MD	Department of Neurology, General Hospital Celle, Celle, Germany	Site investigator	Contributor to the GENERATE registry
Valentin Held, MD	Department of Neurology, Universitätsmedizin Mannheim, Heidelberg University, Mannheim, Germany	Site investigator	Contributor to the GENERATE registry
Kerstin Hellwig, MD	Department of Neurology, St. Josef Hospital, Ruhr University Bochum, Bochum, Germany	Site investigator	Contributor to the GENERATE registry
Philip Hillebrand, MD	Division of Pediatric Nephrology, Department of Pediatrics, University Children's Hospital Bonn, Bonn, Germany	Site investigator	Contributor to the GENERATE registry
Frank Hoffmann, MD	Department of Neurology, Krankenhaus Martha-Maria Halle-Doelau, Germany	Site investigator	Contributor to the GENERATE registry
Ulrich Hofstadt-van Oy, MD	Klinik für Neurologie, Knappschaftskrankenhaus Dortmund, Klinikum Westfalen, Dortmund, Germany	Site investigator	Contributor to the GENERATE registry
Fatme Seval Ismail, MD	Department of Neurology, University Hospital Knappschaftskrankenhaus Bochum, Ruhr University Bochum, Bochum, Germany	Site investigator	Contributor to the GENERATE registry
Martina Jansen	Neuroimmunology section, Institute of Clinical Chemistry, University Hospital Schleswig-Holstein Kiel/Lübeck, Germany	Site investigator	Contributor to the GENERATE registry
Max Kaufmann, MD	Institute of Neuroimmunology and Multiple Sclerosis, University Medical Center Hamburg-Eppendorf, Hamburg, Germany	Site investigator	Contributor to the GENERATE registry
Christoph Kellinghaus, MD	Department of Neurology, Klinikum Osnabrück, Osnabrück, Germany	Site investigator	Contributor to the GENERATE registry
Susanne Knake, MD	Epilepsy Center Hessen, Department of Neurology, Philipps University Marburg, Marburg, Germany	Site investigator	Contributor to the GENERATE registry

Appendix 2 (continued)

Name	Location	Role	Contribution
Peter Körtvelyessy, MD	German Center for Neurodegenerative Diseases (DZNE) Magdeburg, Magdeburg, Germany; Institute for Cognitive Neurology and Dementia Research, Magdeburg, Germany; Charité Universitätsmedizin Berlin, Department of Neurology and Experimental Neurology, Berlin, Germany	Site investigator	Contributor to the GENERATE registry
Stjepana Kovac, MD	Department of Neurology with Institute of Translational Neurology, University Hospital Münster, Münster, Germany	Site investigator	Contributor to the GENERATE registry
Markus Krämer, MD	Department of Neurology, Alfried Krupp Hospital, Essen, Germany	Site investigator	Contributor to the GENERATE registry
Christos Krogias, MD	Department of Neurology, St. Josef Hospital Bochum, Ruhr University Bochum, Germany; Medical Faculty, Ruhr University Bochum, Germany	Site investigator	Contributor to the GENERATE registry
Christoph Lehrich, MD	Clinic of Neurology with Institute of Translational Neurology, University of Münster, Münster, Germany	Site investigator	Contributor to the GENERATE registry
Andreas Linsa, MD	Klinik für Neurologie, Carl-Thiem Klinikum Cottbus gGmbH, Cottbus, Germany	Site investigator	Contributor to the GENERATE registry
Jan Lünemann, MD	Department of Neurology with Institute of Translational Neurology, University Hospital Münster, Münster, Germany	Site investigator	Contributor to the GENERATE registry
Michael Malter, MD	University of Cologne, Faculty of Medicine, University Hospital Cologne, Department of Neurology, Cologne, Germany	Site investigator	Contributor to the GENERATE registry
Kristin Stefanie Melzer, MD	Department of Neurology with Institute of Translational Neurology, University Hospital Münster, Münster, Germany	Site investigator	Contributor to the GENERATE registry
Til Menge, MD	Centre for Neurology and Neuropsychiatry, LVR-Klinikum Düsseldorf, Medical Faculty, Heinrich Heine University Düsseldorf, Düsseldorf, Germany	Site investigator	Contributor to the GENERATE registry

Appendix 2 (continued)

Name	Location	Role	Contribution
Sven Meuth, MD	Department of Neurology with Institute of Translational Neurology, University Hospital Münster, Münster, Germany/Department of Neurology, Heinrich Heine University Düsseldorf, Düsseldorf, Germany	Site investigator	Contributor to the GENERATE registry
Gerd Meyer zu Hörste, MD	Department of Neurology with Institute of Translational Neurology, University and University Hospital Münster, Münster, Germany	Site investigator	Contributor to the GENERATE registry
Constanze Mönig, MD	Department of Neurology, University of Münster, Münster, Germany	Site investigator	Contributor to the GENERATE registry
Marie-Luise Mono, MD	Stadtspital Waid und Triemli, Zurich, Switzerland	Site investigator	Contributor to the GENERATE registry
Michael Nagel, MD	Department of Neurology, Klinikum Osnabrück, Osnabrück, Germany	Site investigator	Contributor to the GENERATE registry
Tobias Neumann-Haefelin, MD	Department of Neurology, Klinikum Fulda, Fulda, Germany	Site investigator	Contributor to the GENERATE registry
Jost Obrocki, MD	Clinic for Psychiatry and Psychotherapy, Sana Regio Kliniken-Klinikum Elmshorn, Germany	Site investigator	Contributor to the GENERATE registry
Thomas Pfefferkorn, MD	Department of Neurology, Klinikum Ingolstadt, Ingolstadt, Germany	Site investigator	Contributor to the GENERATE registry
Alexandra Philipsen, MD	Department of Psychiatry and Psychotherapy, University of Bonn, Germany	Site investigator	Contributor to the GENERATE registry
Johannes Piepgras, MD	Department of Neurology, Focus Program Translational Neuroscience and Immunotherapy, Rhine-Main Neuroscience Network, University Medical Center of the Johannes Gutenberg University Mainz, Mainz, Germany	Site investigator	Contributor to the GENERATE registry
Felix von Podewils, MD	Department of Neurology, Epilepsy Center, University Medicine Greifswald, Greifswald, Germany	Site investigator	Contributor to the GENERATE registry
Josef Priller, MD	Department of Neuropsychiatry, Charité, Universitätsmedizin, Berlin, Germany	Site investigator	Contributor to the GENERATE registry

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Name	Location	Role	Contribution
Anne-Katrin Pröbstel, MD	Neurologic Clinic and Policlinic, Departments of Medicine and Biomedicine, University Hospital of Basel, University of Basel, Basel, Switzerland	Site investigator	Contributor to the GENERATE registry
Johanna Maria Helena Rau, MD	Department of Neurology with Institute of Translational Neurology, University of Münster, Münster, Germany	Site investigator	Contributor to the GENERATE registry
Saskia Jania Räuber, MD	Department of Neurology with Institute of Translational Neurology, University of Münster, Münster, Germany	Site investigator	Contributor to the GENERATE registry
Gernot Reimann, MD	Department of Neurology, Klinikum Dortmund, Dortmund, Germany	Site investigator	Contributor to the GENERATE registry
Raphael Reinecke, MD	Epilepsy Center Frankfurt Rhine-Main and Department of Neurology, University Hospital and Goethe University Frankfurt, Frankfurt am Main, Germany	Site investigator	Contributor to the GENERATE registry
Marius Ringelstein, MD	Department of Neurology, Medical Faculty, Heinrich Heine University Düsseldorf, Düsseldorf, Germany	Site investigator	Contributor to the GENERATE registry
Hendrik Rohner, MD	Department of Psychiatry and Psychotherapy, University of Bonn, Bonn, Germany	Site investigator	Contributor to the GENERATE registry
Felix Rosenow, MD	Epilepsy Center Frankfurt Rhine-Main and Department of Neurology, Goethe University Frankfurt, Frankfurt am Main, Germany	Site investigator	Contributor to the GENERATE registry
Kevin Rostásy, MD	Pediatric Neurology, University of Witten/Herdecke, Children's Hospital Datteln, Datteln, Germany	Site investigator	Contributor to the GENERATE registry
Stephan Rüegg, MD	Department of Neurology, University Hospital Basel and University of Basel, Basel, Switzerland	Site investigator	Contributor to the GENERATE registry
Jens Schaumberg, MD	Department of Neurology, Community Hospital Helios Klinikum Uelzen, Uelzen, Germany	Site investigator	Contributor to the GENERATE registry
Jens Schmidt, MD	Department of Neurology, Neuromuscular Centre, Göttingen, Germany	Site investigator	Contributor to the GENERATE registry
Ina-Isabelle Schmütz	Neuroimmunology section, Institute of Clinical Chemistry, University Hospital Schleswig-Holstein Kiel/Lübeck, Germany	Site investigator	Contributor to the GENERATE registry

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Appendix 2 (continued)

Name	Location	Role	Contribution
Stephan Schreiber, MD	Department of Neurology, Asklepios Fachklinikum, Brandenburg, Germany	Site investigator	Contributor to the GENERATE registry
Gesa Schreyer	Neuroimmunology section, Institute of Clinical Chemistry, University Hospital Schleswig-Holstein Kiel/Lübeck, Germany	Site investigator	Contributor to the GENERATE registry
Ina Schröder	Neuroimmunology section, Institute of Clinical Chemistry, University Hospital Schleswig-Holstein Kiel/Lübeck, Germany	Site investigator	Contributor to the GENERATE registry
Simon Schuster, MD	Center for Integrative Psychiatry, University Hospital Schleswig-Holstein, Lübeck, Germany	Site investigator	Contributor to the GENERATE registry
Günter Seidel, MD	Department of Neurology, Asklepios Klinik Nord, Hamburg, Germany	Site investigator	Contributor to the GENERATE registry
Makbule Senel, MD	Department of Neurology, University Hospital Ulm, Ulm, Germany	Site investigator	Contributor to the GENERATE registry
Kai Siebenbrodt, MD	Epilepsy Center Frankfurt Rhine-Main and Department of Neurology, University Hospital and Goethe University Frankfurt, Frankfurt am Main, Germany; LOEWE Center for Personalized Translational Epilepsy Research (CePTER), Goethe University Frankfurt, Frankfurt am Main, Germany	Site investigator	Contributor to the GENERATE registry
Oliver Stammel, MD	Department of Neurology, ASKLEPIOS Klinik Hamburg Barmbek, Hamburg, Germany	Site investigator	Contributor to the GENERATE registry
Martin Stangel, MD	Department of Neurology, Hannover Medical School, Hannover, Germany	Site investigator	Contributor to the GENERATE registry
Henning Stolze, MD	Department of Neurology, Diako Flensburg, Germany	Site investigator	Contributor to the GENERATE registry
Muriel Stoppe, MD	Department of Neurology, University of Leipzig, Leipzig, Germany	Site investigator	Contributor to the GENERATE registry
Karin Storm van's Gravesande, MD	Department of Pediatrics, University Hospital Klinikum rechts der Isar, Technical University of Munich, School of Medicine, Munich, Germany	Site investigator	Contributor to the GENERATE registry

Appendix 2 (continued)

Name	Location	Role	Contribution
Steffen Sybre, MD	Clinic for Pediatric and Adolescent Medicine, Heidelberg University, Heidelberg, Germany	Site investigator	Contributor to the GENERATE registry
Simone Tauber, MD	Department of Neurology, RWTH University Hospital, Aachen, Germany	Site investigator	Contributor to the GENERATE registry
Florian Then Bergh, MD	Department of Neurology, Universität Leipzig, Germany	Site investigator	Contributor to the GENERATE registry
Corinna Trebst, MD	Department of Neurology, Hannover Medical School, Hannover, Germany	Site investigator	Contributor to the GENERATE registry
George Trendelenburg, MD	Department of Neurology, University of Göttingen Medical Center, Göttingen, Germany	Site investigator	Contributor to the GENERATE registry
Regina Trollmann, MD	Department of Pediatrics and Pediatric Neurology, Friedrich-Alexander-Universität Erlangen-Nürnberg, Erlangen, Germany	Site investigator	Contributor to the GENERATE registry
Hayrettin Tumani, MD	Department of Neurology, University Hospital Ulm, Ulm, Germany	Site investigator	Contributor to the GENERATE registry
Methab Türedi	Department of Neurology, University Hospital Ulm, Ulm, Germany	Site investigator	Contributor to the GENERATE registry
Matthias von Mering, MD	Department of Neurology, University of Göttingen, Göttingen, Germany	Site investigator	Contributor to the GENERATE registry
Judith Wagner, MD	Department of Neurology, Kepler University Hospital, Johannes Kepler University, Linz, Austria	Site investigator	Contributor to the GENERATE registry
Robert Weissert, MD	Department of Neurology, University of Regensburg, Regensburg, Germany	Site investigator	Contributor to the GENERATE registry
Heinz Wiendl, MD	Department of Neurology with Institute of Translational Neurology, University of Münster, Münster, Germany	Site investigator	Contributor to the GENERATE registry
Brigitte Wildemann, MD	Molecular Neuroimmunology Group, Department of Neurology, University of Heidelberg, Heidelberg, Germany	Site investigator	Contributor to the GENERATE registry
Karsten Witt, MD	Department of Neurology, School of Medicine and Health Sciences, University of Oldenburg, Oldenburg, Germany	Site investigator	Contributor to the GENERATE registry

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Name	Location	Role	Contribution
Sigrid Wöpking, MD	Department of Neurology, University Hospital, Technische Universität Dresden, Dresden, Germany	Site investigator	Contributor to the GENERATE registry
Benjamin Wunderlich, MD	Charité - Universitätsmedizin Berlin, Department of Neurology, Berlin, Germany	Site investigator	Contributor to the GENERATE registry
Lara Zieger, MD	Department of Neurology, Philipp University, Marburg, Germany	Site investigator	Contributor to the GENERATE registry

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