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BRIEF REPORT

Low Recruitment in a Double-Blind, Placebo-Controlled Trial of Ocrelizumab for Autoimmune Encephalitis: A Case Series and Review of Lessons Learned

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ABSTRACT

Introduction: Observational data suggest that B-cell-depleting therapies are effective for antibody-mediated autoimmune encephalitis. However, randomized controlled trials are needed. Here, we report challenges encountered in a randomized, placebo-controlled trial of ocrelizumab for autoimmune encephalitis that failed to meet recruitment goals.

Methods: This was a single-center, 12-month, randomized, double-blind, placebo-controlled trial. Patients with autoimmune encephalitis were randomized in 1:1 fashion to placebo or ocrelizumab infusion after receiving first-line immunotherapy. The primary endpoint of the study was clinical worsening, defined as a perceived decline by the patient or clinician or a decrease in the Lawton and Brody Instrumental Activities of Daily Living Scale (IADL), along with either worsening on the Texas Functional Living Scale (TFLS) or hospitalization for symptoms of encephalitis.

Results: Among 16 eligible patients, only three enrolled in the study, which closed due to poor recruitment. Two participants were randomized to the ocrelizumab arm and one to the placebo arm. The single patient in the placebo arm (NMDAR+) met the primary endpoint at 12 weeks and received open-label ocrelizumab with improvement. In the ocrelizumab arm, one participant (NMDAR+) demonstrated marked improvement, and the second (LGI1+) remained clinically stable. There were no serious adverse events associated with ocrelizumab.

Conclusion: Clinical trial recruitment for autoimmune encephalitis is challenging, and our trial did not meet recruitment goals. Large, multicenter clinical trials are still needed, and careful attention must be given to study design, endpoints, and patient selection. Instrumented functional rating scales will be valuable outcome measures for future studies.

Trial Registration: ClinicalTrials.gov identifier: NCT03835728.

Keywords: Autoimmune encephalitis; Clinical trial; Encephalitis; Neuroimmunology

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Key Summary Points

Why carry out this study?

Treatment of autoimmune encephalitis is largely guided by observational data, with few clinical trials published to date.

The aim of this trial was to determine the safety and efficacy of ocrelizumab in patients with antibody-mediated encephalitis.

What was learned from the study?

Out of 16 eligible participants, only three underwent randomization, and the study was closed due to poor recruitment.

The most common reason cited for deferring enrollment was concern about receiving placebo.

Future clinical trials for autoimmune encephalitis will require a multicenter design, creative recruitment strategies, and rescue therapy plans to meet recruitment goals.

INTRODUCTION

Autoimmune encephalitis (AIE) is an inflammatory disorder of the brain, commonly associated with autoantibodies against neuronal cell-surface proteins. The disorder is an important cause of acute neuropsychiatric symptoms, presenting with memory impairments, refractory seizures, psychosis, and hyperkinetic movements [1, 2]. Epidemiologic studies suggest that AIE is a common cause of encephalitis, with a similar prevalence to common causes of infectious encephalitis in younger populations [3–5].

Early recognition and treatment of AIE can result in marked clinical improvement and favorable long-term outcomes [6–8]. To date, there are few published clinical trials for disease-modifying therapy in AIE, with treatment recommendations largely based on retrospective series and expert opinion. Treatment of AIE typically involves immunotherapy, and commonly used agents include intravenous glucocorticoids, intravenous immunoglobulins (IVIG), and plasmapheresis. Immunosuppressive therapies are generally recommended in refractory cases or for relapses [1, 2, 9]. Rituximab is commonly used in cases of antibody-mediated AIE given its targeted depletion of CD20+ B lymphocytes. Observational studies suggest B-cell depletion via rituximab improves functional outcomes and reduces relapses in antibody-mediated AIE [6, 7].

Ocrelizumab is a humanized monoclonal antibody targeting CD20, which was designed to reduce immunogenicity seen with rituximab (a chimeric antibody). Ocrelizumab has approval in North America and Europe for treatment of multiple sclerosis (MS). In MS clinical trials, ocrelizumab demonstrated rapid and sustained B-cell depletion, making it a plausible therapy for antibody-mediated AIE [10]. Here, we report a series of patients enrolled in a randomized, double-blinded, placebo-controlled trial of ocrelizumab in patients with antibody-positive AIE.

METHODS

Standard Protocol Approvals, Registrations, and Patient Consent

This study (ClinicalTrials.gov identifier: NCT03835728) was approved by the institutional review board at the University of Texas Southwestern Medical Center (UTSW) (STU 2018-0185). The study was performed in accordance with the Helsinki Declaration of 1964 and its later amendments. All participants provided written consent to participate in the study, including consent to publication of de-identified data.

Study Design

This study was designed as a 12-month, single-center, randomized parallel-group, double-blind, placebo-controlled trial. Recruitment

occurred between February 2019 and July 2020. Due to poor enrollment, the study was closed, with the last patient completing study procedures in October 2020.

Participants

Participants were recruited from the inpatient and outpatient setting at UTSW. Adult patients (age 18 years or older) presenting with acute neuropsychiatric syndromes that met criteria for possible or definite AIE as defined by Graus et al. [11] were evaluated for eligibility. In addition to meeting AIE criteria, patients were required to have one of four cell-surface neuronal autoantibodies (*N*-methyl-D-aspartate receptor [NMDAR]), leucine-rich glioma-inactivated protein 1 [LGI1], contactin-associated protein-like 2 [CASPR2], dipeptidyl-peptidase-like protein 6 [DPPX]) present in serum or CSF, detected via cell-based assay. Participants were required to complete treatment with typical "first-line" immunotherapies, including intravenous glucocorticoids and plasma exchange within 4 weeks of enrollment. Participants were excluded if they did not have one of the four aforementioned antibodies, were pregnant, had a history of immunosuppression within the past year, had an active malignancy requiring treatment, had evidence of chronic hepatitis or tuberculosis infection, or otherwise had a medical condition that, in the opinion of the investigators, precluded the use of ocrelizumab. Prior use of intravenous immunoglobulin was allowed.

Study Treatment

Eligible and consenting participants were randomized in 1:1 allocation to receive ocrelizumab or matching placebo, provided by the drug manufacturer, Genentech. Ocrelizumab was administered as two 300-mg infusions approximately 14 days apart, followed by a 600-mg infusion 24 weeks later. Participants who met the clinical worsening endpoint within the first 6 months of the study were offered the option of receiving a single, open-label dose of ocrelizumab 600 mg. Antipyretics and antihistamines were administered prior to each infusion to minimize infusion reactions.

Randomization and Blinding

Randomization was performed using a block design stratified by NMDAR antibody or other antibody, and was performed by the research pharmacy at UTSW. All members of the study team and study participants were blinded to treatment assignment.

Endpoints

The primary endpoint of this study was failure to complete the 12-month study due to clinical worsening. Participants would exit the study upon meeting the primary endpoint, and a single dose of open-label ocrelizumab was offered if the endpoint was met within the first 6 months. Clinical worsening was defined as a perception of decline reported by the patient, caregiver, or clinician or a decrease in the Lawton and Brody Instrumental Activities of Daily Living Scale (IADL) by one or more points. Additionally, one of the following criteria was required to confirm worsening: (1) a documented worsening of the Texas Functional Living Scale (TFLS) by 0.5 standard deviations or greater or (2) clinical symptoms consistent with encephalitis requiring hospitalization. Secondary outcomes included the time to treatment failure and a change in the TFLS at 6 and 12 months compared to baseline.

Safety and tolerability were assessed via self-reported adverse events (AE), physical examination, clinical lab monitoring, and vital signs. During each infusion, participants were monitored for signs of infusion reactions and the rate of infusion was gradually increased if no signs of infusion reaction were present. For milder infusion reactions, the rate of infusion was decreased and symptoms clinically monitored. For severe infusion reactions, the infusion was held until symptoms resolved, then resumed at half the infusion rate. Where appropriate additional antipyretics or antihistamines were administered for infusion reactions. The study team asked about any additional adverse events during each study visit and assessed the severity and relationship of all reported adverse events to the study drug and procedures.

Evaluations

Participants were evaluated in person at weeks 0, 2, 4, 8, and 12, and then every 3 months, with additional safety visits as necessary. An approximately 1-hour battery of neuropsychological tests designed to efficiently assess broad neurocognitive domains was performed at baseline and at weeks 0, 4, 12, 24, 36, and 48 by an Association of Postdoctoral Programs in Clinical Neuropsychology (APPCN) fellowship-trained neuropsychologist (D.D.). Neuropsychological measures included the TFLS, Lawton and Brody IADL, Test of Premorbid Functioning, Montreal Cognitive Assessment (MoCA), Trail Making Test parts A and B, Symbol Digit Modalities Test, Controlled Oral Word Association test (letters F-A-S), animal fluency, and the Hopkins Verbal learning Test–Revised. In addition, telephone contact that included the IADL assessment was carried out in weeks 6 and 10, and occurred monthly between in-person assessments thereafter. Safety and adverse events were assessed at all visits, with laboratory monitoring occurring at all in-person assessments. Final study visits occurred at month 12 for all participants.

Laboratory Assessments

Blood samples were obtained during all in-person assessments for safety assessment, antibody testing, and quantification of CD19+ lymphocytes. Testing for the four neuronal cell-surface antibodies of interest were performed on serum samples using a fixed-cell based assay (Euroimmun). Study investigators were blinded to the results of follow-up antibody and CD19 testing to maintain blinding during the study period.

RESULTS

Participants

Twenty-one patients meeting criteria for possible AIE were prescreened for eligibility, of which 16 had a neuronal cell-surface antibody in the serum or CSF. All 16 were invited to participate, but only four consented for the study, with three participating in study procedures. The fourth patient had evidence of latent tuberculosis infection during screening laboratory testing. Among the 12 eligible individuals that did not proceed with consent and screening, reasons included patient/family concern about placebo-controlled design (n = 7), immunosuppressive treatment prior to presentation (n = 3), and medical conditions precluding study enrollment (n = 2) (Fig. 1). Due to poor enrollment, the trial was closed to recruitment in July 2020, and the last study visit was completed in October 2020.

Participant 1 (LGI1-Positive)

A 70-year-old Caucasian man with a history of type 2 diabetes mellitus, atrial fibrillation, and hypothyroidism presented to our center with 6 months of seizures and cognitive decline. His first symptoms were brief episodes of dystonic posturing in the arm and face consistent with faciobrachial dystonic seizures (FBDS). These episodes increased in frequency, and were followed by generalized seizures. Approximately 30 days later, he began to experience significant short-term memory impairment and agitation, and eventually stopped working. His memory continued to worsen, and he presented to our center 6 months into his course. Neurocognitive assessment with the MoCA was 21, and he demonstrated frequent paraphasic error and FBDS. An MRI of the brain demonstrated T2 hyperintensity within the left hippocampal formation. Cerebrospinal fluid (CSF) analysis demonstrated a normal white cell count and protein level. Oligoclonal bands and IgG index were not tested. Electroencephalography (EEG) demonstrated left temporoparietal sharp waves and polymorphic delta slowing. He was managed with intravenous glucocorticoids and plasmapheresis during hospitalization and demonstrated some mild improvement in cognition, but still had severe memory impairment and occasional FBDS.

Antibodies to LGI1 subsequently returned positive in serum and CSF (Mayo Clinic Lab), and he was enrolled in our trial. He was randomized to the treatment arm, receiving

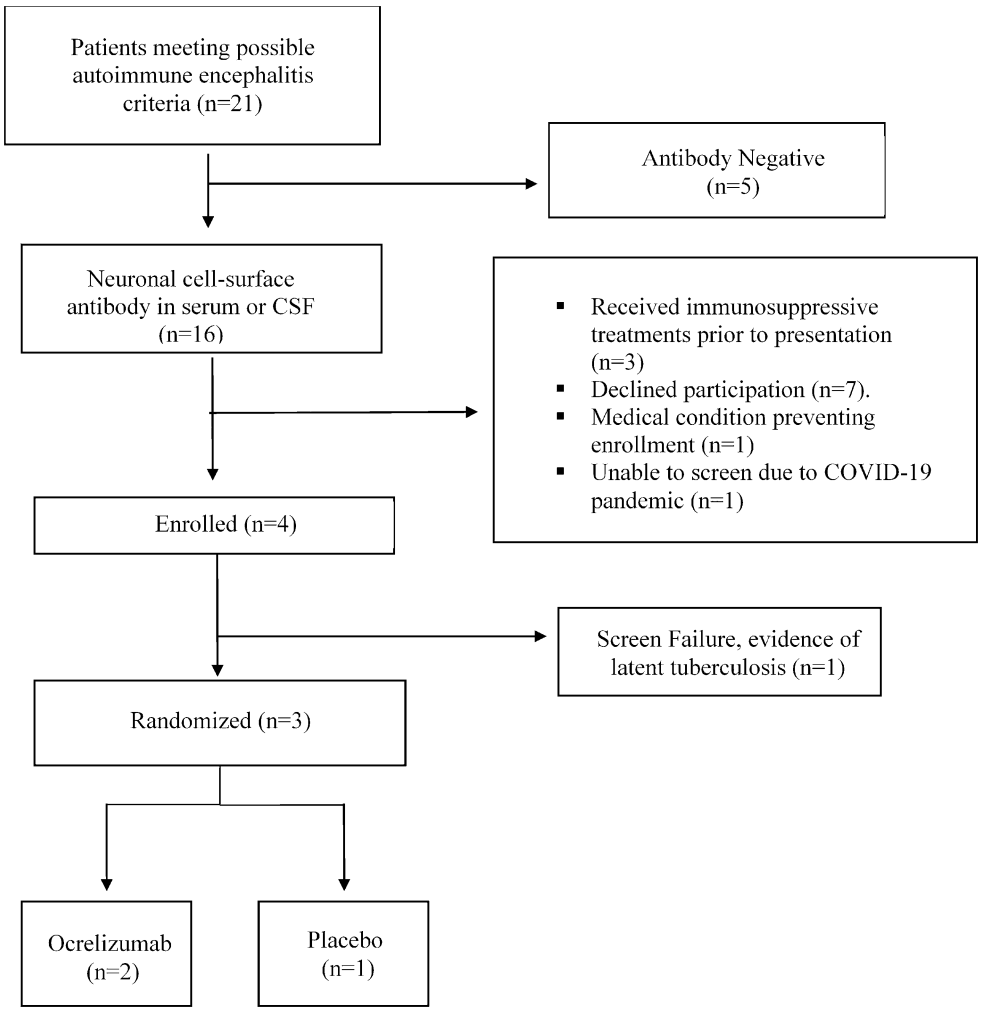


Fig. 1 CONSORT [Consolidated Standards of Reporting Trials] flow diagram

ocrelizumab during initial visits and at the 6-month visit. He experienced no serious adverse events related to ocrelizumab, but developed a mild rash and experienced a humeral fracture following a fall during the study. Neuropsychological assessments demonstrated consistent performance on the TFLS, with all performances within normal limits (Fig. 2), but prominent memory deficits and variable difficulty on measures of processing speed, verbal fluency, and executive functioning. Upon completing the study, he was transitioned to rituximab monotherapy, with plans to complete another 12 months of therapy. At last follow-up, he remained clinically stable, but still experienced severe memory impairment.

Participant 2 (NMDAR-Positive)

A 44-year-old Caucasian woman, previously healthy, presented to our center with 2 months of progressive neurological symptoms. Her first symptoms included prominent deficits in language fluency. She subsequently developed auditory hallucinations of music and worsening confusion. She was admitted to an outside hospital, where an MRI of the brain was normal. An EEG demonstrated generalized slowing, and CSF analysis was remarkable for 38 white blood cells and 11 oligoclonal bands. She was treated with a single course of IVIG and IV steroids, followed by a course of plasmapheresis, with improvement in her symptoms, but mild

residual language dysfunction. She was found to have NMDAR antibodies in the CSF (Mayo Clinic Lab) and was referred to our center for further management. She enrolled in our study, and was randomized to the placebo arm. Twelve weeks after the first visit, she experienced worsening language function and confusion. Neurological assessment demonstrated a decrease in TFLS T-score by more than one standard deviation, meeting the clinical worsening endpoint (Fig. 2). For her worsening, she was treated with a second course of plasmapheresis and IV steroids, followed by open-label ocrelizumab. She demonstrated steady improvement in her language function, and at last clinical follow-up reported rare word finding difficulty. Six months after ocrelizumab, she was initiated on rituximab with plans to continue therapy for another 12 months.

Patient 3 (NMDAR-Positive)

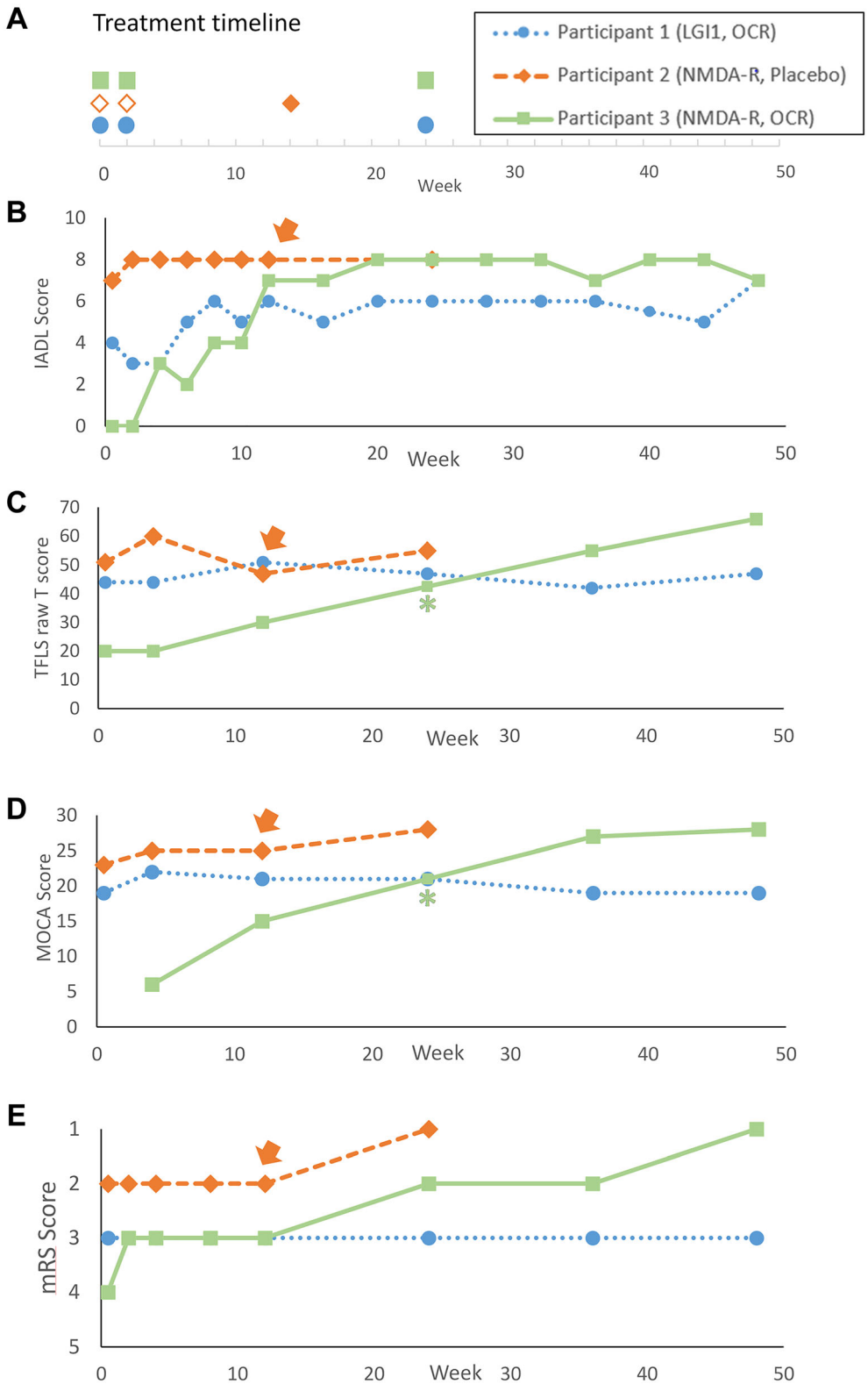
A 25-year-old African American woman was transferred to our facility for evaluation of anti-NMDAR encephalitis. She initially presented to an outside emergency department with seizures, described as a left gaze deviation followed by generalized tonic–clonic activity. She was started on levetiracetam, but continued to have seizures and returned to the emergency department. At her second presentation she was noted to have behavioral changes, including pressured speech and insomnia. While in the emergency room she had two further seizures, and was intubated. She quickly self-extubated the following day, and was able to protect her airway. Her symptoms continued to progress, and she developed dystonia in her jaw and limbs, along with agitation, which required intravenous dexmedetomidine to control. An EEG was performed that demonstrated left temporal intermittent rhythmic delta activity. MRI of the brain showed atrophy out of proportion to age, but no other abnormalities, and CSF showed normal cell count and protein level. Oligoclonal bands and IgG index were not sent. She was treated with plasmapheresis for presumed AIE approximately 3 weeks from symptom onset, and did not show significant improvement. She was transferred to our center for advanced therapies when her NMDAR antibodies returned positive in the CSF (Mayo Clinic Lab).

Upon transfer to our center she was lethargic and did not follow commands. She demonstrated severe global aphasia, only intermittently repeating nonsensical phrases, but showing no signs of comprehension. There were frequent episodes of dystonic posturing that did not have an EEG correlate. She developed symptoms of autonomic instability, including prolonged episodes of tachycardia and urinary retention without alternative explanation. She was given a course of intravenous methylprednisolone and IVIG at our center without immediate improvement.

Family consented to enroll in our study, and she was randomized to the ocrelizumab arm, receiving her first treatment approximately 8 weeks after symptom onset. She began to show gradual clinical improvement, with autonomic symptoms and agitation improving first. Her seizures were well controlled with valproic acid, clobazam, and lacosamide. Two weeks after admission, she was transferred to our rehabilitation unit with severe nonfluent aphasia, which gradually improved prior to discharge.

Approximately 1 week after discharge, she returned for a study visit, and reported multiple seizures. Family noted that she did not have access to her seizure medications, as her pharmacy did not have them on inventory. She was admitted to the neurology service and her seizure medications re-initiated, at which point her seizures were under control after 48 h of observation (Table 1). She remained seizure-free throughout the rest of the study.

For the remainder of the study, she demonstrated gradual clinical improvement, with only mild issues with language fluency at last follow-up. Likewise, she demonstrated dramatic and generally linear improvements on all neuropsychological assessments across the study, including the TFLS (Fig. 2).


A
Treatment timeline
Participant 1 (LGI1, OCR)
Participant 2 (NMDA-R, Placebo)
Participant 3 (NMDA-R, OCR)
0 10 20 30 40 50
Week
B
IADL Score
0 2 4 6 8 10
0 10 20 30 40 50
Week
C
TFLS raw T score
0 10 20 30 40 50 60 70
0 10 20 30 40 50
Week
D
MOCA Score
0 5 10 15 20 25 30
0 10 20 30 40 50
Week
E
mRS Score
1 2 3 4 5
0 10 20 30 40 50
Week

◀**Fig. 2** Functional and neuropsychological assessments. Data for study participants were derived from direct assessments (TFLS and MoCA), telephone survey (IADL) or chart review (modified Rankin scale [mRS]) over the course of the study. Treatment infusions were given at weeks 0, 2, and 24. Data at week 0 were collected prior to treatment. The arrow for participant 2 indicates the point of worsening that met criteria for study endpoint. Participant 2 received an open-label infusion of ocrelizumab at week 14. The asterisk (*) indicates missing data at week 24 for participant 3 due to COVID-19 restrictions. **a** Treatment timeline. Filled symbols = ocrelizumab; open symbols = placebo. **b** Instrumental Activities of Daily Living (IADL, full score = 8) scores. **c** Texas Functional Living Scale (TFLS). **d** Montreal Cognitive Assessment (MoCA, full score = 30). **e** Modified Rankin scale (mRS). LGI1 = leucine-rich glioma-inactivated protein 1; NMDAR = *N*-methyl-D-aspartate receptor; OCR = ocrelizumab

DISCUSSION

While our study failed to meet its primary objectives due to the small sample size, there are a number of important lessons from our experience that can be applied to future AIE trials. AIE is a relatively uncommon condition, and even at our tertiary care center with a high volume of AIE patients, we were unable to meet our recruitment goals. Likewise, recruitment has been challenging in other published single-center trials for AIE [9]. Future clinical trials for AIE will require a multicenter design to account for low enrollment at individual sites. Measures to promote awareness regarding the trial amongst clinicians and patient advocacy organizations will further support study sites in achieving recruitment goals.

Only 25% of eligible subjects enrolled in our study, and the most common concern was the possibility of being randomized to placebo. While controlled trials are lacking, large observational studies support the use of immunosuppressive therapies in AIE. Although there are limitations to retrospective studies, these data have led some clinicians to question the ethics of placebo-controlled trials in AIE. Accordingly, patients with AIE and their physicians perceive that therapies like rituximab are effective and readily available outside of clinical trials. To address these concerns, future AIE trials will require robust rescue therapy plans and close follow-up to identify non-responders early in their course. Three potential participants were excluded as they had already received immunosuppression (rituximab or cyclophosphamide) prior to transfer to our center, which presented another barrier to recruitment.

The choice of an appropriate primary endpoint has been a significant challenge in AIE trial development. In our study, we chose clinical worsening as the primary endpoint. However, NMDAR encephalitis, the most common type of AIE, is largely a monophasic illness, with a relapse rate of approximately 12% [7]. A much larger sample size would be required to demonstrate a clinical effect of immunosuppression on relapses in this population. Positive outcome measures, such as clinical improvement in severe cases, may be a more appropriate endpoint in AIE trials, particularly those including NMDAR-positive subjects. Since participants with longer disease durations may not have appreciable improvement, future studies may consider limiting enrollment to subjects earlier in their disease course, or stratifying outcomes by disease duration. Clinical worsening may be a valid endpoint for LGI1-positive patients, given its relatively high relapse rate in the absence of prolonged immunotherapy.

The number of known autoantibodies associated with AIE has increased dramatically in recent years. The different AIE antibodies present with unique clinical features, malignancy associations, relapse rates, and clinical outcomes. We included four different antibodies with a low malignancy association in our study, including NMDAR and LGI1, the two most commonly encountered AIE antibodies. While this approach may improve trial enrollment, future AIE trials should consider restricting enrollment to a single antibody, or at least a single phenotype (such as limbic encephalitis), given differences in presentation and outcome.

The lack of a validated outcome measure has presented a significant barrier to clinical trials for AIE. The mRS has previously been utilized as a primary outcome measure for several important retrospective series of AIE treatment

Table 1 Endpoints and adverse events

	Ocrelizumab (n = 2)		Placebo (n = 1)
Antibody	**LGI1**	**NMDAR**	**NMDAR**
Confirmed clinical worsening (primary endpoint)	No	No	Yes
Time to clinical worsening (secondary endpoint)	–	–	12 weeks
mRS at first visit	3	4	2
mRS at last visit	3	1	1
Continued seizures during study	Yes	Yes	No
Adverse events			
Any adverse event	Rash	Rash	Rash
		Liver enzyme increase	
Infusion reactions	No	No	No
Serious adverse events (SAE)	Arm fracture	Hospitalization for seizures (due to medication nonadherence)	None
Serious infections	No	No	No

LGI1 = leucine-rich glioma-inactivated protein 1; NMDAR = *N*-methyl-D-aspartate receptor

outcomes due to its ease of use and general familiarity to neurologists [6–8]. The scale is heavily dependent on overall motor function and gait, making it an imperfect measure for assessment of AIE, which is associated with significant cognitive impairment and relative sparing of limb function. Our study included neuropsychological measures designed to assess multiple cognitive domains, with the TFLS utilized as an outcome measure to quantify ability in instrumental activities of daily living [12]. Although our findings are limited by the small number of subjects, we did observe an episode of clinical worsening in the study. In that instance, there was a relative worsening in the TFLS score, while the mRS remained unchanged. Correspondingly, there was significant, generalized improvement on neuropsychological measures, including the TFLS, in a study participant who showed marked clinical improvement across the 12-month study period. These findings suggest that measures such as the TFLS, which are more weighted toward cognitive functioning, have greater sensitivity for detecting worsening in AIE patients. Further study is needed to validate the role of the TFLS as an outcome measure for AIE.

CONCLUSIONS

Our study failed to meet recruitment goals, and future trials of AIE are needed to determine the efficacy and safety of immunosuppressive therapies. Our experience should inform future AIE trials, which will require a multicenter design and robust therapy plan to achieve adequate enrollment. Consideration should be given to cognitively weighted outcomes measures such as the TFLS.

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Disclosures. Kyle Blackburn has served on an advisory board for Genentech. David Denney reports no disclosures. Steven Hopkins reports no disclosures. Steven Vernino has served as a consultant for Alterity, Catalyst, Genentech, LabCorp, Argenx, and Sage Therapeutics. He has received research support from Dysautonomia International, Biohaven, Grifols, and Quest Diagnostics (through a licensing contract).

Compliance with Ethics Guidelines. This study was approved by the institutional review board of the University of Texas Southwestern Medical Center (STU 2018-0185). The study was performed in accordance with the Helsinki Declaration of 1964 and its later amendments. All participants provided written consent to participate in the study, including consent to publication of de-identified data.

Data Availability. De-identified data generated from this study are available upon request.

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