Clinical Trial/Experimental Study

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A pilot safety study of ublituximab, a monoclonal antibody against CD20, in acute relapses of neuromyelitis optica spectrum disorder

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Abstract

Objective: To test the safety of ublituximab, a B cell depleting agent, as add-on therapy in the acute treatment of relapses of neuromyelitis optica spectrum disorder.

Methods: We conducted an open-label phase 1b safety and proof-of-concept trial in 5 subjects with aquaporin-4 (AQP4)-immunoglobulin G (IgG) seropositive neuromyelitis optica spectrum disorder (NMOSD) who presented with acute transverse myelitis and/or optic neuritis. In addition to treating with 1 g of daily intravenous methylprednisolone, we infused a single dose of 450 mg of ublituximab within 5 days of relapse onset. The primary outcome measure was safety, and the secondary efficacy measures included change in Expanded Disability Status Scale (EDSS), durability of remission and B cell counts.

Results: Five NMOSD subjects were enrolled, 4 of whom presented with acute transverse myelitis and 1 with acute optic neuritis. Ublituximab proved to be safe in all 5 NMOSD subjects, with no serious adverse events recorded. There were no opportunistic infections in any of the subjects; however, 1 subject experienced a transient leukopenia. EDSS scores dropped from a median of 6.5 on admission to 4.0 on 90-day follow up. Two subjects did not achieve total B cell depletion and relapsed within 3 months.

Conclusions: Ublituximab is a safe add-on therapy for NMOSD patients presenting with acute transverse myelitis and optic neuritis. Preliminary evidence suggests a promising benefit on durability of remission when B cell depletion is achieved. A placebo-controlled trial is necessary to confirm these findings.

Classification of Evidence: This study provides Class IV evidence that for patients with NMOSD with acute transverse myelitis or optic neuritis, ublituximab is safe and may improve neurological outcome.

Abbreviations: AQP4 = aquaporin-4, EDSS = Expanded Disability Status Scale, MRI = magnetic resonance imaging, MS = multiple sclerosis, NMOSD = neuromyelitis optica spectrum disorder, SAE = serious adverse event.

Keywords: aquaporin-4, B cells, CD20, Devic's, neuromyelitis optica

1. Introduction

Neuromyelitis optica spectrum disorder (NMOSD) is a severe, demyelinating autoimmune disease of the central nervous system (CNS) that preferentially affects the optic nerves and spinal cord.[1] Although historically considered a subtype of multiple sclerosis (MS) with overlapping symptoms, NMOSD is distinct radiologically and prognostically and has a pathophysiology unresponsive to typical MS treatments.[2,3] In 2004, an antibody targeting the water channel protein, aquaporin-4, was found to be associated with NMOSD.[4] Compared with MS, NMOSD exhibits an older age at onset, a poorer prognosis, and a rarity of cerebrospinal fluid oligoclonal IgG bands.[5] NMOSD attacks typically produce moderate to severe disability that leads to accumulation of disability with each attack; between attacks, patients generally remain neurologically stable without evidence of progressive deterioration.[6] Therefore, it is crucial that aggressive treatment for each relapse is optimized to prevent disability.

NMOSD affects predominantly women, with a female to male ratio of 6.5:1.[5] The relative frequency of NMOSD among demyelinating disorders is quite variable, being higher in Asian, Hispanic, and African populations compared with whites. The few population-based prevalence studies of NMO conducted provide prevalence rates of 0.32 to 3.1 per 100,000.[5]

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The authors report no conflicts of interest

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The current standard of care for treatment of acute NMOSD attacks of both optic neuritis and transverse myelitis is a 5-day course of high dose methylprednisolone (1000 mg daily).[2] In some patients, this course of steroid treatment is sufficient to suppress CNS inflammation and reverse some neurologic dysfunction. In many patients, steroids are not sufficient to suppress CNS inflammation, and treatment escalation to plasma exchange is necessary. Plasma exchange is effective in improving neurological function back to baseline in up to 65% of relapses.[7] Additional therapies have been investigated to mitigate CNS damage from NMOSD relapses and improve outcomes, including C1-esterase inhibitor in which 8 of 10 subjects returned to their baseline within 30 days of their attack.[8]

The rationale for using ublituximab is based on the known roles of B cells as antigen-presenting cells and as precursors of plasmablasts and plasma cells that produce antibodies. NMOSD is characterized by the presence of an aquaporin-4 (AQP4) antibody, which are produced by differentiation of B cells to plasma cells. Because these AQP4 antibodies may be pathogenic, B cells recognizing AQP4 may be directly involved in the disease process as well.[9] B cells also play a role as potent antigen presenting cells in NMO which communicate with AQP4-reactive pathogenic T cells.[10,11] The strongest evidence of the importance of B cells in NMO comes from studies of B cell depletion, most commonly with anti-CD20 monoclonal antibody, rituximab. Rituximab has been shown in multiple retrospective and 2 prospective studies to be effective in reducing NMO relapses up to 90% and achieving remission in up to 80% of patients solely by its action on CD20+ B cells.[12] These human trials strongly suggest a critical role for B cells in the pathophysiology of human disease. While typically used in the prevention of disease, B-cell depletion may be beneficial in the treatment of an acute relapse as well. Emerging evidence indicates that peripheral B cells are activated during a relapse and plasmablast production of anti-AQP4 antibodies spikes.[13] B cells are also found within acute lesions of the spinal cord and optic nerve suggesting roles both in the blood and in the CNS during a relapse.[14] In addition, acute B cell depletion may lead to a more durable remission for NMOSD patients who have a high relapse rate.

2. Methods

This was a single center, phase I, class IV, open label study of ublituximab in NMOSD patients with acute relapses. Patients with NMO spectrum disorder who met the 2015 International Panel for NMO Diagnosis criteria[15] aged 18 to 65 and presented to the Johns Hopkins Hospital between January and September 2016 with new neurologic symptoms were eligible for enrollment if they demonstrated a new contrast-enhancing lesion on magnetic resonance imaging (MRI) of the spinal cord, brainstem, or optic nerves. On days 1–5 of admission, patients received 1000 mg of intravenous methylprednisolone. A dose of 450 mg of intravenous ublituximab was infused within the 5-day treatment course. Plasmapheresis was initiated after day 5 in patients who showed no or minimal improvement with corticosteroids alone. All patients were enrolled within 10 days of symptom onset.

The primary endpoint was safety and the secondary endpoints were efficacy on reducing disability, durability of remission, and B cell counts. Hospitalized patients were monitored daily for adverse events and examined on admission, discharge, and 90-day follow-up using the standardized Expanded Disability Status Scale (EDSS) and MRI. Statistical analysis where possible was descriptive only.

2.1. Standard protocol approvals, registrations, and patient consents

The study was approved by the Johns Hopkins Institutional Review Board and informed consent was obtained prior to enrollment. The identifier for the trial on the ClinicalTrials.gov website is NCT02276963.

3. Results

Six patients were screened for eligibility, and 5 were enrolled, received the intervention, and followed up 90 days later for examination to complete the study (Fig. 1). All 5 were seropositive for the AQP4-IgG. Four of the 5 presented with acute transverse myelitis and 1 presented with acute optic neuritis (Table 1). The median duration of disease of these 5 patients was 14 years (range, 6.4–16.5) and the median number of previous relapses was 5 (range, 3–6).

There were no serious adverse events (SAEs) in this study. Based on previous studies, the greatest SAEs of concern would be serious infections, infusion reactions, and liver disease. None of these were an issue with these participants. One subject experienced leukopenia approximately 24 hours after the infusion: total leukocytes dropped from a baseline of 7000 cells/μL

Table 1

Patient characteristics.

Subject	Age	Sex	Race	Diagnosis	Duration of disease, y	Number of previous relapses	Clinical presentation	Background immunotherapy
1	41	F	H	NMOSD (Ab +)	14.0	3	Cervical myelitis affecting bilateral lower limb strength	None
2	54	F	AA	NMOSD (Ab +)	6.4	6	Cervicothoracic myelitis affecting bilateral lower limb strength	Mycophenolate 2500 mg daily, dose last adjusted 11 months prior
3	48	F	AA	NMOSD (Ab +)	16.5	5	Thoaracic myelitis affecting bilateral lower limb strength	None
4	26	F	AA	NMOSD (Ab +)	8.6	4	Optic neuritis causing blindness	Mycophenolate 3000 mg daily, dose last adjusted 2 years prior
5	53	F	AA	NMOSD (Ab +)	15.6	6	Cervicothoracic myelitis affecting bilateral lower limb strength	RTX, 2 grams every 6 months, last infused 5 months prior

AA = African–American, Ab = antibody, F = female, H = Hispanic, NMOSD = neuromyelitis optica spectrum disorder, RTX = rituximab.

(absolute lymphocytes of 1870 cells/μL) to a nadir of 2980 cells/μL (absolute lymphocytes of 280 cells/μL) and then rebounded back to baseline within 72 hours. There was no adverse effect that resulted from the leukopenia, such as infection. This SAE was thought to be related to study drug.

Consistent with previous studies of ublituximab, 3 of 5 subjects experienced an acute sharp headache and body pain within 30 minutes of infusion start time, lasting approximately 30 minutes without changes to vital signs and resolving with acetaminophen administration. This side effect has been observed with ublituxumab in other studies which responds to acetaminophen or no intervention.

Although this study was not powered for efficacy and there was no control arm, we looked for a signal of efficacy by measuring the impact of ublituximab on disability following an acute relapse. The EDSS was calculated for each patient at baseline before the relapse based on previous clinic notes, at the peak of relapse, upon discharge from the hospital and again 90 days later on follow up in the outpatient clinic. In 4 of 5 patients, the EDSS score at the peak of relapse was higher than their baseline, due to a combination of inflammation and tissue damage from the new MRI-confirmed NMO lesion (Fig. 2). Following a 5-day course of steroids plus a single dose of 450 mg of ublitiximab, EDSS scores declined in 3 of 5 subjects by 90 days. The median baseline EDSS was 4.0, which increased to a median of 6.5 at the peak of the attack. The median EDSS on discharge was still 6.5 which was 5 days after admission for 2 subjects and 19 days after admission for 3 subjects. At 90-day follow-up, the median EDSS score was back to a 4.0 among the 3 subjects who remained in remission and all 3 of those subjects were within 1.0 EDSS points of their baseline (Fig. 3).

Immediate B cell depletion with a single dose of 450 mg IV ublituximab was confirmed in 4 of 5 subjects and sustained at ≤0.2% for 2 months (Fig. 4). In 1 subject, the B cell count dropped from 29% to 0.9% measured 30 days after infusion but did not reach zero. In 2 subjects, relapses occurred 58 and 81 days

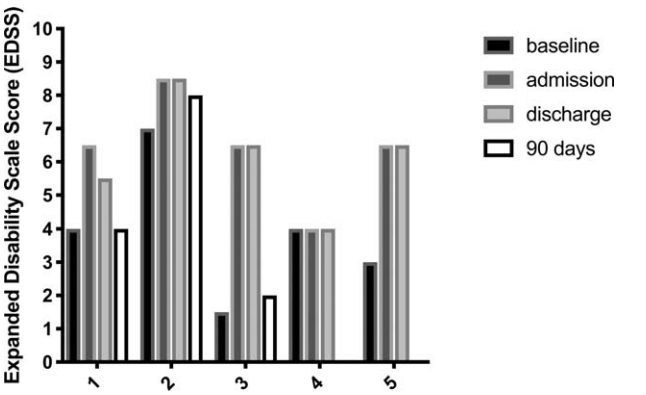

Figure 2. Individual Expanded Disability Status Scale (EDSS) scores. Expanded disability scale scores were recorded for each patient at baseline from previous clinic visit, at peak of relapse at admission, on discharge from the hospital, and at 90-day follow up in clinic. In 4 patients, the EDSS increased from baseline to the acute relapse, and in 3 subjects the EDSS declined back to within 1.0 points of baseline by 90 days. Patients 4 and 5 relapsed after discharge and the 90-day follow-up (scores not shown).

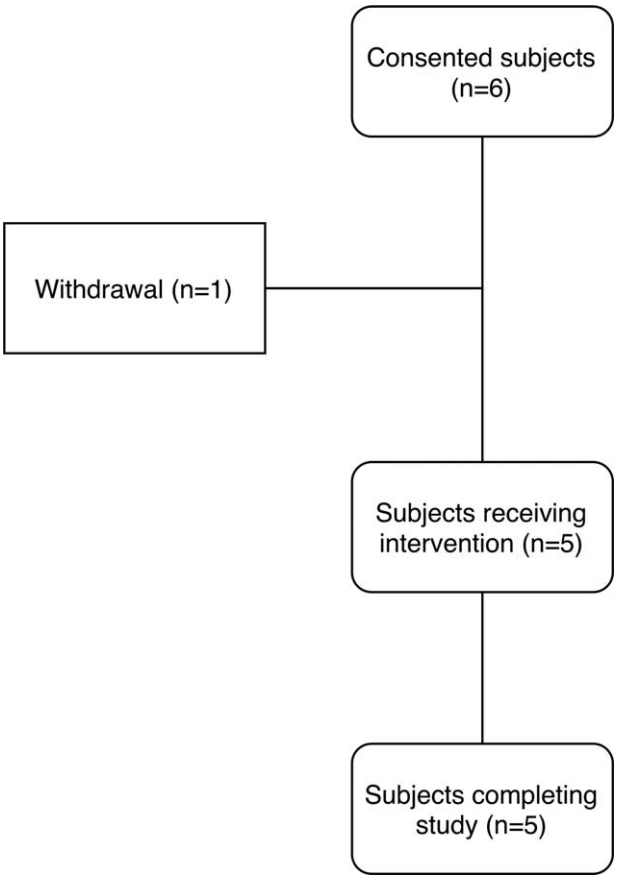

Figure 1. Flow diagram of single center trial. Six patients were screened, 5 consented, and enrolled in the trial, and 5 completed. All 5 patients received the full study intervention and completed the trial at 90-day follow-up.

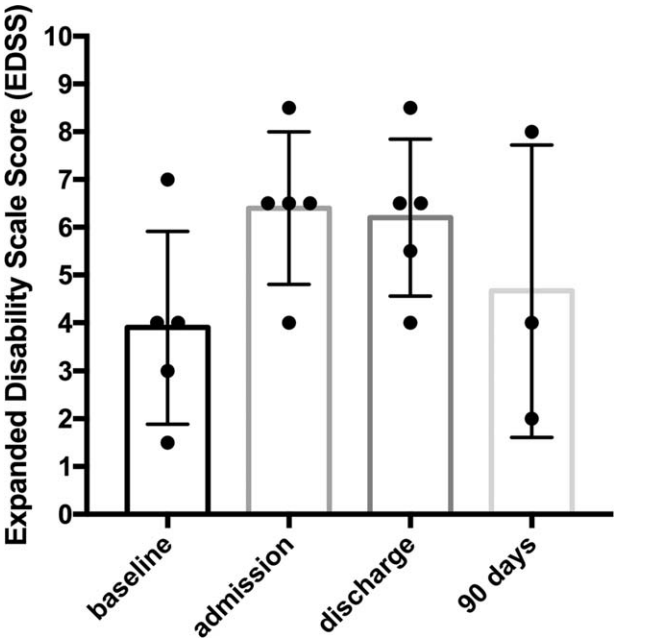

Figure 3. Box-plot of EDSS scores. The median EDSS score at baseline was 4.0, which increased to 6.5 at admission. The median EDSS score at discharge was still 6.5 and at 90-day follow up for those who remained in remission was 4.0. Scores for the 2 patients who relapsed were not included in the 90-day follow up. Error bars represent the 25th and 75th percentiles. EDSS = Expanded Disability Status Scale.

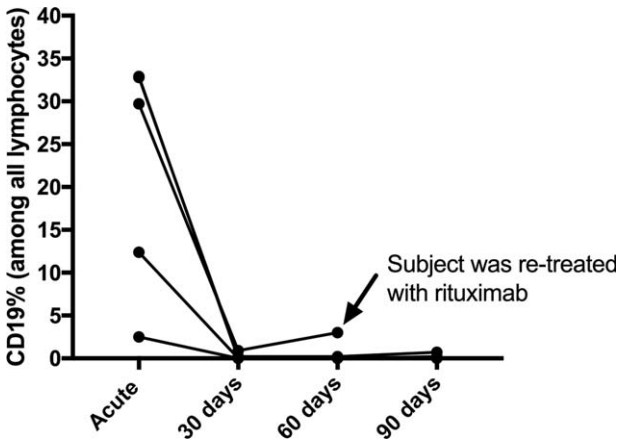

Figure 4. B cell counts. With a single dose of 450 mg of ublituximab, B cells were depleted in 4 of 5 subjects. One subject who did not deplete by 30 days showed continued repletion to 3% by 60 days and was subsequently retreated with rituximab. Two subjects who relapsed before 90 days showed counts of zero at 60 days and 0.2% to 0.7% at 90 days.

after initial B cell depletion and both of these events were associated with B cell populations of <0.2% at day 60, and repopulation to 0.2% to 0.7% by day 90. Both of these relapses required escalated treatment with plasma exchange due to poor response with corticosteroids alone.

4. Discussion

This single center, phase I open-label study of ublituximab add-on therapy in 5 patients with acute NMO relapses met its objective to test the safety of acute B cell depletion with ublituximab in this patient population. There were no SAEs in the course of this trial, except for a transient leukopenia in 1 subject with no clinical manifestation. With a single 450 mg intravenous dose, 4 of 5 subjects achieved an acute B cell depletion with at least 2 months of durability. Although not designed for efficacy, this trial demonstrated that neurologic disability improved in the 3 subjects who achieved immunological remission.

There are obvious limitations in making efficacy conclusions based on this study. This phase I trial was not controlled with a group that received standard of care only or placebo. In addition, the open-label design is subject to performance and detection biases. A blinded, randomized, placebo-controlled prospective trial is needed to determine the accurate impact of ublituximab on neurologic disability. In addition, the single 450 mg dose of ublituximab which only led to B cell depletion for 2 months needs to be adjusted for longer durability. Acute B cell depletion in NMO may have benefits to both the active attack and to the durable preventive effect protecting against future relapses that add to the disability. Larger studies are needed to distinguish between these potential mechanisms.

Ethical approval: All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Author contributions

Conceptualization: Maureen A. Mealy, Michael Levy.
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