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Bevacizumab is safe in acute relapses of neuromyelitis optica

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Abstract

Objectives—Neuromyelitis optica (NMO) is a relapsing autoimmune disease targeting the spinal cord and optic nerve leading to paralysis and blindness. Current treatment for acute NMO attacks is immunosuppression with high-dose corticosteroids and/or plasmapheresis. Preclinical animal studies suggest that bevacizumab might be beneficial in limiting the extent of inflammation during a NMO relapse by reducing the disruption of the blood–brain barrier.

Methods—We carried out an open-label phase 1b safety and proof-of-concept trial in 10 participants with NMO immunoglobulin G seropositive NMO, NMO spectrum disease and those at high risk for developing NMO/NMO spectrum disease who presented with an acute attack of transverse myelitis, optic neuritis or brainstem inflammation. In addition to treating with 1 g of daily intravenous methylprednisolone, we infused 10 mg/kg of bevacizumab intravenously on day 1 of treatment. The primary outcome measure was safety and the secondary outcome measure was efficacy.

Results—Of the 10 participants enrolled, five presented with acute transverse myelitis, four with acute optic neuritis and one with a brainstem lesion. Bevacizumab was safe in all 10 participants, with only one serious adverse event within the 90-day follow up that was not attributed to the medication. Three patients recovered to pre-attack neurological function or better, and no patients required escalation to plasmapheresis.

Conclusions—Bevacizumab is a safe add-on therapy to high-dose corticosteroids for NMO/NMO spectrum disease patients presenting with an acute relapse.

Keywords

aquaporin-4; bevacizumab; neuromyelitis optica; vascular endothelial growth factor

Introduction

Neuromyelitis optica (NMO) is a recurrent neuroinflammatory disease that preferentially targets the optic nerves and spinal cord leading to blindness and paralysis.¹ Although historically considered a subtype of multiple sclerosis (MS) with overlapping symptoms,

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Conflict of interest

Dr Shin has no disclosures.

NMO is distinct radiologically and prognostically.^{2,3} NMO attacks typically produce moderate to severe inflammatory damage that leads to accumulation of disability with each attack.⁴ Therefore, it is crucial that optimal treatment for each relapse is provided to prevent permanent disability.

Bevacizumab is a recombinant humanized monoclonal immunoglobulin G1 antibody that binds to vascular endothelial growth factor (VEGF), and inhibits the interaction of VEGF to Flt1 and KDR receptors on the surface of endothelial cells. Bevacizumab is currently approved by the Food and Drug Administration for a variety of malignant indications, but has not been previously tested in neuroinflammatory diseases.⁵ The rationale for using bevacizumab in the acute treatment of NMO exacerbations is based on two observations. First, bevacizumab in patients with glioblastoma multiforme, a stage IV astrocyte brain cancer, is believed to restore the integrity of the blood–brain barrier (BBB) in areas of tumor disruption.⁶ This is best demonstrated by a study showing that bevacizumab delays the time to peak gadolinium enhancement by magnetic resonance imaging more than high-dose corticosteroids.⁶ The second observation is a study showing that VEGF exacerbates disruption of the BBB during central nervous system inflammatory disease in mice.⁷ This follows another study showing that NMO serum disrupts the BBB by upregulating VEGF.⁸ Disruption of the blood barrier during a NMO relapse could permit transfer of the pathogenic anti-aquaporin 4, granulocytes and leukocytes. Taken together, these studies suggest that BBB disruption in NMO attacks can be limited by targeting VEGF using bevacizumab.

The standard of care for management of acute relapses of NMO is 5 days of high-dose intravenous corticosteroids, but most patients are still left with residual disability after each attack despite early and aggressive immunosuppression.⁹ The present trial was designed to test the safety of adding bevacizumab to prevent central nervous system damage during acute NMO relapses. As a secondary outcome measure, disability scores were compared before the relapse, at the peak of the attack, at discharge from the hospital and on 90-day follow up in the clinic.

Methods

This was a single-center, phase I, open label study of bevacizumab in 10 patients with NMO/NMO spectrum disease (NMOSD) by Wingerchuk criteria, or at high risk for developing NMO based on typical NMO presentations detailed in Table 1, who were admitted with acute relapses of transverse myelitis, optic neuritis or brainstem disease.^{10,11} Patients aged 18–70 years were eligible for enrolment if they presented to the Johns Hopkins Hospital, Baltimore, Maryland, USA, between February 2014 and August 2014 with new neurological symptoms with confirmed changes on physical examination and/or a supporting contrast-enhancing lesion on magnetic resonance imaging; all patients had changes on clinical examination except patient 2, who presented with lightheadedness and intractable nausea, and was found to have a new lesion in the area postrema. All patients had symptoms for 24 before administration of bevacizumab, and infectious and metabolic causes for pseudo-relapse were assessed and ruled out. On day 1 of admission, patients received 1000 mg of methylprednisolone plus 10 mg/kg of bevacizumab intravenously. All

patients received the dose of bevacizumab within 24 h after the initial dose of methylprednisolone. On days 2–5, patients received daily 1000-mg intravenous methylprednisolone only. The primary safety end-point was measured by the incidence of adverse events and side-effects; the secondary efficacy end-point was change in neurological disability measured by the Expanded Disability Status Score (EDSS) during hospitalization, at discharge and at 90-day follow up.

The study was registered at <http://www.clinicaltrials.gov> and was approved by the Johns Hopkins institutional review board. Informed consent was obtained before enrolment. Statistical analysis on EDSS scores was carried out using two-tailed Wilcoxon matched-pairs signed-rank test with significant *P*-values defined as <0.05 .

Results

A total of 10 patients were screened for eligibility, enrolled, received the intervention and followed up 90 days later for examination to complete the study (Fig. 1). The median time to enrolment from symptom onset was 7.5 days. Five of the 10 patients met the Wingerchuk 2006 clinical criteria for NMO, four of whom were positive for the NMO immunoglobulin G, while two patients carried a diagnosis of NMOSD and the remaining three patients were high-risk for development of NMO (Table 1). Five patients presented with acute transverse myelitis, four with acute optic neuritis and one with acute symptoms attributable to the brainstem (light-headedness and nausea with corresponding area postrema lesion; Table 1).

All adverse events were logged daily during hospitalization, as well as at 90-day follow up (Table 2). There was one serious adverse event in the present study: patient 1 developed a urinary tract infection 47 days after her single dose of bevacizumab for which she was hospitalized overnight for treatment. Given the temporal profile and mechanism of action of the medication, the urinary tract infection was not thought to be related to the medication. Based on previous studies and the use of bevacizumab in other conditions, the greatest serious adverse events of concern were hemorrhagic or thromboembolic events, none of which occurred in this 10-patient NMO study population.¹² Two patients developed disease recurrence after discharge during the 90-day patient follow up: patients 7 and 8 recurred 82 and 72 days after bevacizumab administration, respectively. Both patients received additional infusions of 1000-mg intravenous methylprednisolone daily for 5 days.

The efficacy of bevacizumab add-on to high-dose corticosteroids was measured by the impact on disability after an acute relapse. The EDSS was calculated for each patient at baseline before the relapse, at the peak of relapse, on discharge from the hospital and again 90 days later on follow up in the outpatient clinic. In six patients, the EDSS score at the peak of relapse was higher compared with baseline (Fig. 2). After a 5-day course of corticosteroids plus a single infusion of bevacizumab, three of the six EDSS scores declined back to baseline or better at 90 days. The other four patients showed no meaningful changes on EDSS from baseline to admission despite presentation of a clinical relapse. The median baseline EDSS was 1.5, which increased to a median of 3.5 at the peak of the attack ($P = 0.035$; Fig. 3), which declined to clinically meaningful 3.0 at 90-day follow up, but was not statistically significant ($P = 0.233$; Fig. 3).

Discussion

The present single-center, phase I, open-label study of bevacizumab add-on therapy in 10 patients with acute relapses consistent with NMO met its objective to test the safety of bevacizumab in this patient population. There was one SAE in the course of this trial unrelated to bevacizumab, no evidence of hemorrhage or thromboembolic events and no significant metabolic or hematologic abnormalities as a result of using a single dose (10 mg/kg) of bevacizumab in this study population. Although not designed for efficacy, five patients showed improved EDSS disability scores on follow up compared with admission. A placebo-controlled trial is necessary to determine if combination therapy is better than high-dose corticosteroids alone.

This is among the first prospective interventional trials of a therapy to treat acute relapses of NMO, and the first to utilize the mechanism of action against VEGF. The rationale for blocking VEGF and thereby limiting the spread of BBB disruption would portend a better long-term outcome and reduced neurological disability after a NMO attack. While not designed to assess efficacy, there are indications from the present study that bevacizumab might be beneficial in this patient population. First, no patients required escalation to plasma exchange after high-dose corticosteroids and bevacizumab. All 10 patients showed clinical improvement by discharge, although the EDSS score might not have reflected some of those improvements. Second, three of the six patients whose EDSS initially worsened on admission recovered back to baseline EDSS by follow up. Weighing the potential benefits on reducing the permeability of the BBB during an inflammatory attack against the excellent safety profile observed in the present study, bevacizumab might be considered for future study as an add-on to currently available therapy.

The present small study was limited by several factors. The size of the study population might not have been sufficient to show less common adverse events seen in larger cancer populations, such as thromboembolic disease or gastrointestinal hemorrhage. A larger NMO study population with a placebo group is necessary to survey for a complete adverse event profile. There also exists the possibility that patients with non-NMO/non-MS neuroimmunological disorders were included, as patients considered to be high-risk for NMO/NMOSD did not meet the diagnostic criteria, including those who might be positive for anti-MOG (for which testing is not currently available in the USA). The present study was further limited by two additional relapses that occurred after bevacizumab administration shortly before the 90-day follow up, confounding the final EDSS score. Finally, the EDSS disability scale used in the present study was limited in the accuracy and granularity to detect acute changes in four out of 10 acute relapses. As an example, patients 4 and 9 were admitted to the hospital with clinically evident deterioration in vision, but their total EDSS score was unchanged from baseline. Refer to Table 3 for visual acuities of patients presenting with ON. A scale specific for NMO attacks might be more sensitive to neurological changes observed in this study population.

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Figure 1.

Flow diagram of single-center trial. A total of 10 patients were screened, consented and enrolled in the trial. All 10 patients received the full study intervention and completed the trial at 90-day follow up.

Figure 2.

Individual Expanded Disability Status Scores. Expanded Disability Scale Scores were recorded for each patient at baseline, at peak of relapse on admission, on discharge and at 90-day follow up in the clinic. In six patients, the Expanded Disability Status Score increased from baseline to the acute relapse, of which three returned to baseline on follow up. Five patients showed a decline in Expanded Disability Status Score from admission to follow up.

Figure 3.

Box-plot of Expanded Disability Status Scores. The median Expanded Disability Status Score at baseline was 1.5, which increased to 3.5 at peak of relapse ($P = 0.035$). The median Expanded Disability Status Score at 90-day follow up was 3.0, but was not statistically different from admission ($P = 0.233$). Differences were calculated using Wilcoxon matched-pairs signed-rank test for paired, non-parametric comparisons. Error bars represent the minimum and maximum data points, box plots represent 25th and 75th interquartiles.

Table 1

Patient characteristics

Patient	Age	Sex	Race	NMO diagnosis	Duration of disease (years)	No. previous relapses	Clinical presentation	Background immunotherapy
1	60	F	C	NMO (Ab+)	28.4	12	Thoracic myelitis affecting bilateral lower limb strength	Mycophenolate
2	54	F	C	NMOSD (Ab+)	30.1	2	Area postrema lesion causing light-headedness and intractable nausea	Rituximab
3	53	F	C	High-risk (Ab-neg)	0.8	2	Focal thoracic myelitis affecting bilateral lower limb strength + previous history of optic neuritis	None
4	68	F	AA	NMO (Ab+)	30.6	2	Bilateral optic neuritis causing vision loss	None
5	20	F	C	NMO (Ab-neg)	3.7	10	Cervical myelitis affecting unilateral upper limb strength	Rituximab
6	51	F	C	High-risk (Ab-neg)	0.3	2	Multifocal optic neuritis causing unilateral vision loss + previous history of optic neuritis	None
7	37	M	C	NMOSD (Ab+)	0.7	2	Thoracic myelitis affecting bilateral lower limb strength	Rituximab
8	37	F	C	NMO (Ab+)	12.0	2	Cervical myelitis affecting unilateral upper limb strength	None
9	51	F	AA	NMO (Ab+)	9.6	4	Unilateral optic neuritis causing vision loss	Rituximab
10	24	F	A	High-risk (Ab-neg)	0.0	0	Chiasmal and bilateral optic tract neuritis causing bilateral vision loss	None

A, Asian; AA, African American; Ab, antibody; C, Caucasian; neg, negative; NMO, neuromyelitis optica; NMOSD, neuromyelitis optica spectrum disease.

Table 2

Adverse events

Subject	Date of bevacizumab	Date of follow up	Event	Start date	End date	Severity	Action taken
1	2/11/2014	5/9/2014	UTI*	3/27/2014	3/31/2014	Moderate	Overnight admission; Macrobid
			LE pitting edema	4/11/2014	4/18/2014	Moderate	LE elevation
			LE edema	5/2/2014	Ongoing	Mild	None
2	2/22/2014	5/30/2014	None	NA	NA	NA	NA
3	3/14/2014	6/16/2014	Diarrhea	3/19/2014	4/7/2014	Moderate	Discontinued citalopram
			Intermittent eye pain	4/10/2014	Ongoing	Mild	None
			Facial rash	4/24/2014	5/12/2014	Moderate	Oral abx by PCP
4	4/14/2014	7/14/2014	None	NA	NA	NA	NA
5	4/15/2014	7/28/2014	Intermittent headache	4/15/2014	6/28/2014	Mild	Started amitriptyline
			Bruising	7/7/2014	7/28/2014	Moderate	Referral to Rheumatology
			Rash	7/25/2014	7/27/2014	Mild	Referral to Rheumatology
6	7/7/2014	10/17/2014	None	NA	NA	NA	NA
7	7/9/2014	10/17/2014	Numbness and foot drop	9/29/2014	Ongoing	Moderate	IV methylprednisolone for new inflammation
8	7/10/2014	10/17/2014	Intermittent headache	7/13/2014	Ongoing	Moderate	Ketorolac
			Constipation	7/13/2014	7/14/2014	Moderate	Senna, docusate, Miralax
			Rash (arm)	7/24/2014	7/27/2014	Mild	None
			Neck pain	7/29/2014	7/31/2014	Moderate	None
			Groin pain	7/29/2014	7/31/2014	Moderate	None
			Back pain and intermittent numbness in right leg	9/20/2014	Ongoing	Moderate	IV methylprednisolone for new inflammation
9	7/25/2014	10/27/2014	Tongue, throat and mouth pain	7/27/2014	7/29/2014	Mild	None
10	8/6/2014	11/10/2014	None	N/A	N/A	N/A	N/A

abx, antibiotics; IV, intravenous; LE, lower extremity; NA, not applicable; PCP, primary care provider; UTI, urinary tract infection.

* Serious adverse event for overnight hospitalization, assessed as unrelated to study medication.

Table 3

Visual acuities in patients presenting with optic neuritis

	Patient 4		Patient 6		Patient 9		Patient 10	
	Right	Left	Right	Left	Right	Left	Right	Left
Baseline	20/200	20/800	20/25	20/25	20/80	LP	20/20	20/20
Peak	CF	HM	20/25	20/25*	CF	NLP	20/50	20/60
Discharge	CF	HM	20/25	20/25*	20/200	LP	20/50	20/40
90-day follow up	20/400	20/800	20/25	20/25	20/80	LP	20/20	20/20

CF, counting fingers; HM, hand motion; LP, light perception only; NLP, no light perception.

* With left lower visual field cut.