Letters

RESEARCH LETTER

Safety and Efficacy of Bortezomib in Patients With Highly Relapsing Neuromyelitis Optica Spectrum Disorder

In neuromyelitis optica spectrum disorder (NMOSD), enhanced plasma cell activity contributes to antiaquaporin-4 autoantibody (AQP4-ab) production.[1] Longitudinal data indicate that 25% to 66% of patients with NMOSD who are treated with azathioprine, rituximab, and other immune-modifying therapies still experience relapses.[2] Here we assess the safety and efficacy of bortezomib, a selective inhibitor of the 26S proteasome subunit, among patients with highly relapsing NMOSD.

Methods | This is a registered longitudinal study from the National Institutes of Health (NCT02893111) that was conducted from December 2015 to January 2017. Five Chinese female patients who satisfied the 2015 diagnostic criteria of NMOSD were enrolled.[3] The study protocol and supporting documentation were approved by the ethical committee of Tianjin Medical University General Hospital. Written informed consent was obtained from each patient or a legally acceptable surrogate. The characteristics of patients and their responsiveness to prior therapies were collected and illustrated in the **Table**. Study patients received 4 cycles of subcutaneous bortezomib at a dosage of 1 mg/m^2 of body surface area on days 1, 4, 8, and 11 per cycle followed by a 10-day treatment-free interval. This intervention was concurrent with an oral corticosteroid or azathioprine regimen.

Relapses, Expanded Disability Status Scale scores, and pain levels (visual analog scale) were assessed by 2 experienced neurologists who were blinded to the study. Serum AQP4-ab titers were tested by a green fluorescent protein–AQP4 fluorescence immunoprecipitation assay. Peripheral B cells and plasma cell counts were measured by flow cytometry with anticluster of differentiation (CD) 19 (allophycocyanin; Biolegend) and anti-CD138 (fluorescein isothiocyanate; Biolegend), respectively. Descriptive values are given as medians (interquartile range [IQR]) for continuous variables.

Results | Despite undergoing vigorous therapies (Table), all the patients experienced at least 2 relapses in the previous 6 months or 3 relapses throughout the years (**Figure**, A). After initiating bortezomib treatment, 4 of the 5 patients, including patient 2, were relapse-free during the 1-year follow-up. A myelitis relapse was only observed in patient 1 when the patient experienced slight paraplegia 10 months following the onset of bortezomib. Magnetic resonance imaging with gadolinium enhancement showed a new lesion in the 12th thoracic–first lumbar segment of the spinal cord. Prompt treatment with intravenous methylprednisolone (500 mg/d) for 5 days ameliorated her symptoms.

None of the 5 patients experienced further neurological deterioration at the conclusion of the study. The median Expanded Disability Status Scale scores reduced from a median (IQR) of 5.50 (3.75-6.25) at baseline to 3.50 (0.75-4.25) after 1-year follow-up (Figure, B). Their visual analog scale scores also declined from a median (IQR) of 6.0 (5.0-6.75) on study entry to 3.0 (2.25-3.75) after 12 months. Compared with the baseline, serum AQP4-ab titers reduced from a median (IQR) of 66.4nM (35.7-147.3) to 27.1nM (18.7-34.9) after 1 year (median reduction, 59.2%) (Figure, C). Peripheral CD19$^+$ B cell counts declined from a median (IQR) of 230/μL (175-390) to 41/μL (21-158) and CD138$^+$ plasma cell counts decreased from 7/μL (6-13) to 2/μL (1-3) after 1 year. Finally, the observed adverse effects related to bortezomib were mild and transient (Table).

Discussion | The reason that a proportion of patients with NMOSD treated with rituximab still experience attacks may be derived from resistance to CD20 devoid of long-lived plasma cells that are resistant to depletion.[4,5] Bortezomib can deplete long-lived plasma cells.[6] Our results support this notion and suggest that bortezomib could serve as a promising escalation therapy for highly active NMOSD that does not respond well to or does not tolerate current immunosuppressive treatments. In addition, clinical improvements among the 5 patients were closely associated with the reduction of autoimmune activity, reflected by a decrease in serum AQP4-ab titers, peripheral plasma cell count, and precursor B cells with proteasome inhibition. However, this study is limited by a small and heterogeneous sample size of Asian women. Large-scale randomized clinical trials are further required to generate definitive evidence.

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Published Online: July 10, 2017. doi:10.1001/jamaneurol.2017.1336

Table. Characteristics of Patients With Neuromyelitis Optica Spectrum Disorder Receiving Bortezomib Therapy

Characteristic	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5
Before BTZ treatment					
Age at disease onset, y	41	27	43	36	43
Age at BTZ initiation, y	42	43	43	37	53
Anti-AQP4-ab	+	+	+	+	+
Duration of disease at BTZ initiation, y	1.7	16.5	0.4	1.8	10.9
Relapses, No.	5	14	2	4	15
Coexisting autoimmune disease	None	None	None	Myasthenia gravis	Sjögren syndrome
Coexisting autoantibodies	ANA, SSA	ANA, SSA, Ro-52, RF, and nRNP	ANA	ANA and AChR	ANA, SSA, Ro-52, and SSB
EDSS score at BTZ initiation	6.5	5.5	6.0	2.5	5.0
VAS score at BTZ initiation	6.0	6.0	6.5	4.0	7.0
Attacks in the year before BTZ treatment, No.	3 (1 attack of corpus callosum, 1 of ON, and 1 of LETM)	3 (1 attack of brain stem attack, 1 of ON, and 1 of LETM)	2 (1 attack of ON and 1 of LETM)	3 (2 attacks of LETM and1 of ON)	3 (2 Attacks of ON and 1 brain stem and subcortical attack)
Attack prevention 2 y before BTZ treatment	Prednisone,15-20 mg/d; rituximab to deplete B cell counts[a]	IV cyclophosphamide, 0.4 g/w, total 10.0 g; prednisone, 15 mg/d; AZA, 3 mg/kg/d	Prednisone, 15 mg/d; AZA, 3 mg/kg/d	Prednisone,15-20 mg/d; AZA, 3 mg/kg/d	Prednisone, 20-30 mg/d; AZA, 3 mg/kg/d; rituximab to deplete B cell counts[a]
Responses to prior therapies 2 y before BTZ treatment	Poor; 1 attack experienced while using rituximab	Poor; 1 attack experienced even while using a combination of prednisone and AZA	Poor; 1 attack experienced when using a combination of prednisone and AZA (unable to tolerate AZA)[b]	Poor; 2 attacks experienced when combination of prednisone and AZA, but unable to tolerate AZA[b]	Poor; 2 attacks experienced while using rituximab, or 2 relapses experienced while using a combination of prednisone and AZA
Peripheral $CD19^+$ B cells, counts/μL[c]	230	270	374	194	156
Peripheral $CD138^+$ plasma cells, counts/μL	6	11	6	7	14
1-Year follow-up after initial BTZ treatment					
Attacks, No.	1 (Myelitis)	0	0	0	0
EDSS score	3.5	4.0	1.0	0.5	3.5
VAS score	3.5	3.0	2.0	2.5	4.0
Peripheral $CD19^+$ B cells, counts/μL	41	25	211	105	16
Peripheral $CD138^+$ plasma cells, counts/μL	2	0	3	2	1
Attack prevention after discontinuation of BTZ	Prednisone, 15 mg/d	AZA, 3 mg/kg/d	Prednisone, 15 mg/d	Prednisone, 15 mg/d	Prednisone, 20 mg/d
BTZ-related adverse effects	Headache, common cold	Headache, enterocolitis	Macula-papular rash at the injection site	Common cold	Macula-papular rash at the injection site

Abbreviations: AChR+, antiacetylcholine receptor antibody; ANA, anti-nuclear antibody; AQP4-ab, antiaquaporin-4 autoantibody; AZA, azathioprine; BTZ, bortezomib; CD, cluster of differentiation; EDSS, Expanded Disability Status Scale; IV, intravenous; LETM, longitudinal extensive transverse myelitis; nRNP, antinuclear ribonucleoprotein antibody; ON, optica neuritis; RF, rheumatic factor; Ro-52, anti-Ro-52 antibody; SSA, anti–Sjögren syndrome A antibody; SSB, anti–Sjögren syndrome B antibody; VAS, visual analog scale.

[a] The patient had ever received rituximab treatment, total 400 mg/cycle, 2 cycles to ensure that $CD19^+$ and $CD27^+$ memory B cells were less than 0.05% of the peripheral blood mononuclear cell count.

[b] The reason for discontinuation of AZA treatment was hepatic dysfunction.

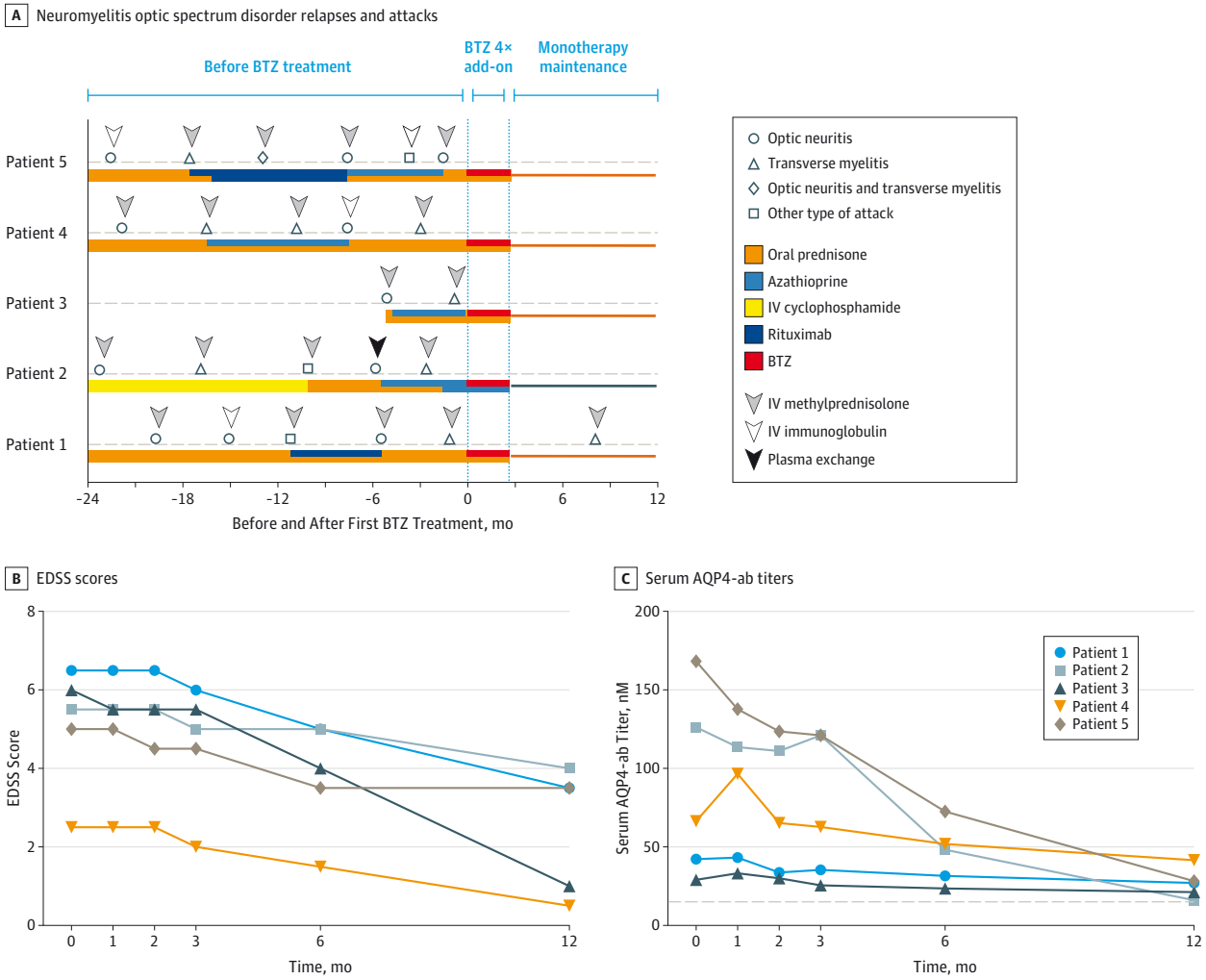
[c] Before receiving a bortezomib infusion, the peripheral blood $CD19^+$ B cells counts of all the 5 patients were in the normal range.

Author Contributions: Dr Shi had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.
Concept and design: Zhang, Shi.
Acquisition, analysis, or interpretation of data: All authors.
Drafting of the manuscript: Zhang, Shi.
Critical revision of the manuscript for important intellectual content: All authors.
Statistical analysis: Zhang, Tian, Han, Shi.
Obtained funding: Zhang, C. Yang, L. Yang, Shi.
Administrative, technical, or material support: Zhang, Tian, Han, Wang, Shi.
Supervision: Shi.

Conflict of Interest Disclosures: None reported.

Funding/Support: This study was supported by grant 2013CB966900 from the National Basic Research Program of China; grants 91642205, 81230028, 81601019, 81571172, and 81471221 from the Nature Science Foundation of China; grant 16SDG27250236 from the American Heart Association; grant

Figure. Clinical Course of Patients Before and After Starting Bortezomib (BTZ) as an Escalation Therapy



A, Neuromyelitis optica spectrum disorder relapses and attacks among patients before, during, and after receiving BTZ treatment. The zero on the x-axis represents the first subcutaneous injection of BTZ. On the line of dashes, different clinical courses or relapses are shown. The colored thread under the dashes represents different medications used throughout patient therapy. The arrowheads indicate the treatment option in acute relapse. After receiving 4 cycles of BTZ treatment, all patients continued to receive the treatment of oral prednisone or azathioprine. IV indicates intravenous. Alteration of Expanded Disability Status Scale (EDSS) scores (B) and serum antiaquaporin-4 autoantibody (AQP4-ab) titers (C) among patients with neuromyelitis optica spectrum disorder receiving BTZ treatment during 1-year follow up. The 0 month represents baseline before BTZ was administered. The cutoff of the negative value of the AQP4-antibody, shown by the dotted line, was set at 15.0nM in serum.

RO1NS092713 from the National Institutes of Health; and grant RG-1507-05318 from the National Multiple Sclerosis Society.

Role of the Funder/Sponsor: The funding organizations had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication.

Additional Contributions: We thank the patients who participated in this study, the neuroimmulogy team at Tianjin Medical University General Hospital for their uncompensated assistance, and Phyllis Minick, BA, PM Publications, for her editorial assistance. Ms Minick was compensated for her contribution.

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