

The BCL2 Inhibitor Venetoclax Plus Rituximab Is Active in MYD88 Wild-Type Polyneuropathy With Anti-MAG Antibodies

Chiara Briani, MD,* Andrea Visentin, MD, PhD,* Francesca Castellani, MD, Mario Cacciavillani, MD, PhD, and Livio Trentin, MD

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Correspondence

Dr. Briani
chiara.briani@unipd.it

Abstract

Objectives

Ibrutinib is active in anti-myelin-associated glycoprotein (MAG) polyneuropathy with MYD88^{L265P} mutation; however, its efficacy is likely to be low in MYD88 wild-type patients. Venetoclax, an oral inhibitor of BCL2, in combination with rituximab is highly active in ibrutinib-resistant hematologic malignancies. We report on the first patient with anti-MAG polyneuropathy and MYD88 wild-type who responded to venetoclax-rituximab.

Methods

A 62-year-old woman with chronic lymphocytic leukemia had IgM/K anti-MAG neuropathy. She needed bilateral support to walk outdoors, despite therapy with rituximab/cyclophosphamide. Tremor and symptoms at arms prevented her capability of performing common tasks. Bone marrow genetic showed lack of MYD88 mutation. Venetoclax was given orally starting from 20 mg up to 400 mg for 24 months. Rituximab was administered IV, after the ramp-up phase, at 375 mg/m² for the second month and then monthly at 500 mg/m² for months 3–7.

Results

After 12 months of venetoclax IgM levels decreased from 1.16 to 0.52 g/L, the paraproteins became undetectable and anti-MAG antibody titer decreased. The patient regained the capability of walking independently. Tremor disappeared, she is back able to write and knitt.

Discussion

The first patient with anti-MAG neuropathy treated with venetoclax-rituximab shows encouraging results.

Classification of Evidence

This study provides Class IV evidence that for a patient with relapsed anti-MAG antibody polyneuropathy, MYD88 wild-type, venetoclax plus rituximab is effective.

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Class of Evidence

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*These authors contributed equally to this work.

From the Department of Neuroscience (C.B., F.C.), University of Padova; Hematology and Clinical Immunology Unit (A.V., L.T.), Department of Medicine, University of Padova; and CEMES (M.C.), Data Medica Group, Padova, Italy.

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Introduction

Neuropathy with antibodies to myelin-associated glycoprotein (MAG) is the most common IgM paraproteinemic neuropathy, characterized by sensory ataxic gait and upper limbs tremor, with motor involvement occurring late in the disease course.¹ Although the IgM paraprotein is commonly a monoclonal gammopathy of undetermined significance, the monoclonal IgM may also underscore a lymphoproliferative disorder, most commonly Waldenstrom macroglobulinemia, but also marginal zone lymphoma or chronic lymphocytic leukemia (CLL).² No adequate immunotherapy has so far been shown to be effective in anti-MAG antibody neuropathy,³ although rituximab seems to be active in almost half of the patients.

Recently, the discovery of the mutational profile of the *MYD88* and *CXCR4* genes has radically changed the diagnosis and prognostic evaluation of IgM monoclonal gammopathies. The genetic landscape of polyneuropathy with anti-MAG antibody reveals the recurrence of *MYD88*^{L256P} mutation in 60% of patients and the lack of *CXCR4*^{S338X} in almost all cases⁴ opening new therapeutic avenues. Ibrutinib, targeting Bruton tyrosine kinase, a downstream protein of the *MYD88* signaling pathway, is active in B-cell–driven diseases including anti-MAG antibody neuropathy.^{5,6} However, response to continuous

ibrutinib is likely to be low in *MYD88* wild-type patients. B-cell lymphoma 2 (*BCL2*) is a key antiapoptotic protein overexpressed in B-cell malignancies, including CLL. Venetoclax is an oral inhibitor of *BCL2* that in combination with rituximab is highly active in ibrutinib-resistant hematologic malignancies.⁷

We describe a patient with CLL and anti-MAG antibody polyneuropathy treated with venetoclax plus rituximab after poor and not durable response to rituximab and cyclophosphamide.

Methods

A 62-year-old woman, affected by CLL with IgM/K monoclonal protein, had anti-MAG antibody neuropathy since 2017. She complained of severe tremor and symptoms at arms preventing her capability of writing and performing common tasks, as well as gait instability that gradually progressed so that from January 2019, she needed bilateral support to walk outdoors. From March to July 2019, she was treated with rituximab-cyclophosphamide with only slight improvement.

She came to our attention in February 2020 for symptoms worsening at both lower (Inflammatory Neuropathy Cause and Treatment, INCAT, disability score 3) and upper (INCAT 3) limbs. The neurologic exam showed tremor at upper limbs, ataxic unstable gait, sensory loss at foot, and reduced vibration sense up to the knees. Bone marrow biopsy confirmed CLL, and genetic assessment showed the lack of *MYD88*, *CXCR4*, and *TP53* mutations.

Neurophysiology confirmed sensorimotor demyelinating polyneuropathy, with a severe decrease of motor conduction velocity, increased distal latencies (LD), and signs of temporal dispersion: left median nerve motor LD 9.0 ms, normal values (nv) <3.5 ms, conduction velocity (CV) 28 m/s in the tract elbow-wrist; left ulnar nerve motor LD 5.36 ms, nv <3.1 ms, CV 37 m/s in the tract below elbow-wrist; right peroneal nerve LD 8.7 ms, nv <5.5 ms, CV 19 m/s (nv >40 m/s); left tibial nerve LD 9.8 ms, nv <6 ms with CV 18 m/s (nv >40 m/s); left median nerve sensory CV at third finger 19 m/s (nv > 48 m/s); and the absence of the sensitive action potential of the left sural nerve.

Venetoclax was given orally after a lead-in weekly ramp-up starting from 20 mg to 50-100-200-400 mg and then at 400 mg/d till 24 months.⁷ Rituximab was administrated IV, after the ramp-up phase, at 375 mg/m² for the second month and then monthly at 500 mg/m² for months 3–7. The patient completed the ramp-up phase and received all the 6 doses of rituximab without serious adverse event. For dyspepsia and decreased appetite, venetoclax was reduced to 300 mg once daily. Neutropenia and infections did not occur.

Results

After 12 months of venetoclax, lymphocyte count remained stable (1,100/μL vs 1,040/μL) and IgM levels and anti-MAG

Table Clinical and Biochemical Data During Treatment

Variable (unit, range)	#1 (IgM/K)					
	-6 m	0	+3 m	+6 m	+9 m	+12 m
Age (y)	61	62				
eGFR (mL/min, 90–120)	98	99				
MYD88 L265P	—	Wild type				
CXCR4 S338X	—	Wild type				
WBC (n/L, 4.4–11.0)	4.21	4.28	3.68	3.63	3.74	3.33
Lymph (n/μL, 1.1–4.8)	1.12	1.11	1.06	1.10	1.53	1.04
Hb (g/L, 123–153)	130	128	128	124	134	127
PLT (n/L, 150–450)	227	229	226	217	227	240
Paraprotein (g/L, –)	0.86	0.85	0.41	0	0	0
IgM (g/L, 0.4–2.4)	1.15	1.16	1.06	0.8	0.58	0.52
FLC κ (mg/L, 4.5–22.3)	8.8	8.81	7.03	7.11	7.02	7.80
FLC λ (mg/L, 4.8–21.9)	11.6	11.70	9.43	9.86	9.69	9.40
Anti-MAG (BTU/L, –)	16.2	18.5	25.3	19.7	13.1	8.74
B. J. protein (–)	neg	neg	neg	neg	neg	neg

Abbreviations: anti-MAG = anti-myelin-associated antigen antibody; B. J. protein = Bence Jones protein; CXCR4 = C-X-C chemokine receptor type 4; eGFR = estimated glomerular filtration rate; FLC = free light chain; Hb = hemoglobin; Lymph = lymphocytes; MYD88 = myeloid differentiation primary response 88; neg = negative; PLT = platelets; WBC = white blood cell count.

Normal ranges have been reported in brackets.

antibody titer decreased from 1.16 to 0.52 g/L and 18,500 vs 8,764 BTU/mL, respectively. Remarkably, the 2 IgM/K monoclonal proteins (0.25 and 0.60 g/L before treatment) became undetectable from the sixth month (Table). The gait greatly improved, the patient now walks independently (INCAT lower limbs 1) and uses only unilateral support only to walk for long distances outdoors. Sensation of lower limbs and vibration sense also improved. She regained the capability of writing and knitting, tremor disappeared (INCAT upper limbs 1). Neurophysiology also dramatically improved at upper limbs (left median nerve motor LD 4.8 ms with CV 35 m/s in the tract elbow-wrist; left ulnar nerve motor LD 3.1 ms, CV 38 m/s under-elbow-wrist; and left median nerve sensory CV at the third finger [31 m/s, nv > 48 m/s]).

Discussion

We report the first patient with anti-MAG polyneuropathy successfully treated with venetoclax in combination with rituximab, showing encouraging results. Venetoclax acts by binding the antiapoptotic protein BCL2, which is overexpressed in CLL cells, thus leading to their programmed cell death. The decrease of the CLL-associated IgM paraprotein, the IgM levels, and anti-MAG antibody titer is likely related to the decrease of CLL burden.

Although we report benefit in a single case, the developing drugs targeting different IgM mutational profiles will hopefully allow neurologists to borrow hematologic treatments for IgM paraproteinemic neuropathies. Controlled studies are warranted.

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Disclosure

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Appendix Authors

Name	Location	Contribution
Chiara Briani, MD	Department of Neuroscience, University of Padova, Italy	Drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data; study concept or design; analysis or interpretation of data
Andrea Visentin, MD, PhD	Hematology and Clinical Immunology Unit, Department of Medicine, University of Padova, Italy	Drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data; study concept or design; analysis or interpretation of data
Francesca Castellani, MD	Department of Neuroscience, University of Padova, Italy	Major role in the acquisition of data
Mario Cacciavillani, MD, PhD	CEMES, Data Medica Group, Padova, Italy	Major role in the acquisition of data
Livio Trentin, MD	Hematology and Clinical Immunology Unit, Department of Medicine, University of Padova, Italy	Analysis or interpretation of data

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