The Bruton tyrosine kinase inhibitor ibrutinib improves anti-MAG antibody polyneuropathy

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Abstract

Objective
To assess whether neuropathy with anti-myelin-associated glycoprotein (MAG) antibody may improve after treatment with ibrutinib, an oral inhibitor of Bruton tyrosine kinase, we prospectively treated with ibrutinib a cohort of 3 patients with anti-MAG neuropathy and Waldenström macroglobulinemia (WM).

Methods
All 3 patients underwent bone marrow biopsy showing WM, with MYD88^{L265P} mutated and CXCR4^{S338X} wild type, and were started on ibrutinib 420 mg/die. Patients were assessed at baseline, at 3-6-9 months, and at 12 months in 2 patients with a longer follow-up, using Inflammatory Neuropathy Cause and Treatment (INCAT) Disability Score, INCAT sensory sum score, and Medical Research Council sum score. The modified International Cooperative Ataxia Rating Scale was performed in 2 patients, whereas it was not used in the patient with Parkinson disease as a major comorbidity. Responders were considered the patients improving by at least one point in 2 clinical scales.

Results
All the patients reported an early and subjective benefit, consistent with the objective improvement, especially of the sensory symptoms as shown by clinical scales. Treatment was well tolerated.

Conclusion
These preliminary data point to a possible efficacy of ibrutinib in anti-MAG antibody neuropathy, which is the most common disabling paraproteinemic neuropathy, where active treatment is eagerly needed.

Classification of evidence
This study provides Class IV evidence that for patients with anti-MAG antibody neuropathy, ibrutinib improves neuropathy symptoms.

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Glossary

BMB = bone marrow biopsy; **BTK** = Bruton tyrosine kinase; **IgM** = immunoglobulin M; **INCAT** = Inflammatory Neuropathy Cause and Treatment; **MAG** = myelin-associated glycoprotein; **MGUS** = monoclonal gammopathy of undetermined significance; **WM** = Waldenström macroglobulinemia.

Anti-myelin-associated glycoprotein (MAG) antibody neuropathy is a chronic sensorimotor demyelinating polyneuropathy associated with immunoglobulin M (IgM) monoclonal gammopathy, manifestation of either a monoclonal gammopathy of undetermined significance (MGUS) or of a non-Hodgkin lymphoma, such as Waldenström macroglobulinemia (WM).[1,2] Anti-MAG antibodies are pathogenic,[3] and rituximab, a chimeric anti-CD20 monoclonal antibody, is currently the standard treatment. However, rituximab provides benefit in less than 50% of patients,[4] and repeated cycles are often necessary with progressive loss of benefit.

Recently, the discovery of the mutational profile of the MYD88 and CXCR4 genes has radically changed the diagnostic and prognostic evaluation of IgM monoclonal gammopathies. MYD88[L265P] has been found to be the most common mutation in WM and IgM-MGUS,[5] conferring prosurvival stimuli to tumor cells through constitutive activation of the Bruton tyrosine kinase (BTK) and nuclear factor kappa-light-chain-enhancer of activated B cells signaling. Conversely, the less common CXCR4 mutations are associated with adverse prognosis. Ibrutinib, the first-in-class inhibitor of BTK, has already been shown to be efficacious in B-cell non-Hodgkin lymphomas including WM, especially in those harboring MYD88[L265P] mutation and CXCR4 gene wild-type.[5,6]

In the study by Treon et al.,[5] 9 of 63 patients, 3 of whom had anti-MAG antibodies, received ibrutinib for progressive neuropathy. Subjective improvement occurred in 5 patients and 4 remained stable. In a subsequent study,[6] 4 of 31 patients with WM had been treated with ibrutinib for neuropathy, 2 remained stable and 2 had subjective improvement starting from week 9, with subsequent complete recovery in one patient. Despite the possibility of hematologic evaluation might have lacked specific scales to grade the response of neuropathy, still these preliminary data are promising and show that ibrutinib does not worsen rather may improve neuropathy.

We report on 3 patients with anti-MAG antibody neuropathy who had been successfully treated with ibrutinib. Demographic and hematologic data are summarized in table 1. All patients had neurophysiologic evidence of sensory-motor demyelinating polyneuropathy, with secondary axonal damage involving distal motor fibers in one patient (1).

The patients were assessed with Inflammatory Neuropathy Cause and Treatment (INCAT) Disability Score,[7] INCAT sensory sum score,[8] and Medical Research Council sum score. The modified International Cooperative Ataxia Rating Scale[9] was also performed in 2 patients (1 and 3) to evaluate tremor

and gait, whereas it was not used in patient 2, who had Parkinson disease as a major comorbidity. Responders were considered those patients who improved by at least one point in 2 clinical scales. Data regarding clinical scales are summarized in table 2.

Patient 1 is a 73-year-old man, with a long history (from 2008) of anti-MAG antibody neuropathy. He had undergone therapy with plasma exchange, IV immunoglobulins, and rituximab with only partial benefit. After worsening, in December 2018, bone marrow biopsy (BMB) showed WM, with MYD88[L265P] mutation and a lack of CXCR4[S338X]. Ibrutinib 420 mg/die was started in January 2019. At baseline, he presented with distal weakness and hypoesthesia at the lower limbs, loss of vibration sense up to the knee, lower limbs areflexia, and upper limbs tremor (table 2). After 1 and 3 months of treatment, there was a slight improvement in touch sensation at the feet and in motor deficit at the toes (table 2). After 6 months, further improvement in touch sensation and distal motor deficit occurred, whereas tremor persisted. The clinical benefit was stable at 12 months (table 2). Monoclonal protein and IgM levels decreased. Anti-MAG antibodies decreased at 3 months but gradually increased thereafter (table 1).

Patient 2 is a 80-year-old man, affected with anti-MAG antibody neuropathy and Parkinson disease. BMB showed WM harboring MYD88[L265P] and unmutated CXCR4 gene. He started ibrutinib 420 mg/die in February 2019. At baseline, there was a severe sensory-motor impairment at 4 limbs (distal lower limbs and grip strength deficit, hypoesthesia and loss of vibration sense up to the knee, lower limbs areflexia, postural tremor at upper limbs, table 2). After 1 and 3 months of treatment, a slight improvement in sensory signs and symptoms occurred, with vibration sense and reflexes reappearing at the knees (table 2). The improvement was maintained 12 months later. Monoclonal protein and IgM levels steadily decreased, whereas the antibody titers decreased at 3 months and then increased thereafter (table 1).

Patient 3 is a 74-year-old woman with WM and anti-MAG neuropathy since 2015. She was treated in 2016 with cyclophosphamide and rituximab, with clinical stability. In 2018, for progressive worsening of gait instability (frequent falls) and lower limbs dysesthesias (table 2), she underwent BMB that confirmed WM with MYD88[L265P] mutation and unmutated CXCR4 gene. The patient started ibrutinib 420 mg/die in May 2019, and at the 1- and 3-month follow-ups, she already reported subjective improvement of touch sensation at the lower limbs (table 2). At the 6-month evaluation, she reported dramatic improvement in gait stability that further

Table 1 Clinical and biological characteristics of ibrutinib-treated patients

	#1 (IgM/κ)					#2 (IgM/λ)					#3 (IgM/κ)			
	0	+3 mo	+6 mo	+9 mo	+12 mo	0	+3 mo	+6 mo	+9 mo	+12 mo	0	+3 mo	+6 mo	+9 mo
Age (y)	73					81					74			
eGFR (mL/min)	87					90					52			
IPSSWM	1 intermediate risk					2 intermediate risk					1 intermediate risk			
Bone marrow LPL	10%					15%					15%			
MYD88 L265P	Mutated					Mutated					Mutated			
CXCR4 S338X	Wild type					Wild type					Wild type			
WBC (n/L)	8.4	8.7	8.7	7.9	7.9	4.4	5.7	5.6	5.3	5.6	6.7	7.1	7.1	8.6
Lymph. (n/μL)	3.2	3.1	2.6	2.3	2.4	1.1	1.0	1.7	0.9	0.5	1.4	1.8	1.6	1.78
Hb (g/L)	163	161	175	160	159	100	93	89	110	90	141	136	139	142
PLT (n/L)	214	168	193	198	210	124	77	99	112	168	240	216	200	203
Paraprotein (g/L)	6.5	5.0	5.4	4.0	4.28	7.2	3.5	3.3	3.4	3.7	10.6	5.9	5.6	5.4
IgM (g/L)	7.2	3.5	4.3	3.6	3.5	13.7	5.2	6.6	6.3	6.4	15.9	10.2	8.8	8.3
FLC κ (mg/L)	69.8	59.2	57.2	46.6	40.3	15.3	24.5	20.6	23.0	37.7	35.3	29.6	27.5	27.8
FLC λ (mg/L)	18.3	14.3	13.5	15.1	15.0	28.9	22.7	18.9	22.5	27.0	14.2	11.2	11.8	13
Anti-MAG (BTU/L)	52.9	35.1	67.9	60.4	51.7	>70.0	50.6	>70.0	70.0	64.6	51.5	37.8	>70.0	>70.0
B. J. protein	Neg	Neg	Neg	Neg	Neg	Neg	Neg	Neg	Neg	Neg	Neg	Neg	Neg	Neg

Abbreviations: 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; IgM = immunoglobulin M; IPSSWM = international prognostic scoring system on Waldenstrom macroglobulinemia; LPL = lymphoplasmocytic lymphoma infiltration; Lymph. = lymphocytes; MAG = myelin-associated glycoprotein; MYD88 = myeloid differentiation primary response 88; neg = negative; PLT = platelets; WBC = white blood cell count.

Table 2 Clinical scales at the baseline and the follow-up of ibrutinib-treated patients

	INCAT disability score (upper limbs + lower limbs)	ISS	MRC sum score	mICARS
1				
Baseline	2 + 2	8	53	27
3 mo	2 + 2	6	55	27
6 mo	2 + 1	5	55	25
9 mo	2 + 1	5	55	25
12 mo	2 + 1	5	55	23
2				
Baseline	4 + 4	9	51	—
3 mo	3 + 3	6	53	—
6 mo	3 + 3	6	53	—
9 mo	3 + 3	6	53	—
12 mo	3 + 3	6	53	—
3				
Baseline	0 + 1	5	60	15
3 mo	0 + 1	4	60	15
6 mo	0 + 1	3	60	13
9 mo	0 + 0	3	60	10

Abbreviations: INCAT = Inflammatory Neuropathy Cause and Treatment Disability Score; ISS = INCAT sensory sum score; MRC = Medical Research Council sum score; mICARS = modified International Cooperative Ataxia Rating Scale.

improved at month 9 (table 2). Monoclonal protein and IgM levels steadily decreased, whereas the antibody titers decreased at 3 months and then increased thereafter (table 1).

Therapy was well tolerated, and none developed atrial fibrillation or infections. All patients are currently still receiving treatment.

Discussion

Anti-MAG antibody neuropathy is a slowly progressive neuropathy that may become disabling when sensory ataxia worsens or motor impairment occurs. Efficacy after treatment with rituximab is reported only in approximately half of the patients, highlighting the unmet need for effective therapeutic options. The discovery of the mutational profile of the *MYD88* and *CXCR4* genes[10] have opened new potential therapeutic avenues. Data from previous hematologic studies[5,6] were also encouraging regarding neuropathies, including those associated with anti-MAG antibodies.

We have reported on the first 3 patients treated with ibrutinib, 2 after the loss of response to rituximab. All the patients reported an early and subjective benefit, especially of the sensory symptoms, which has also been supported by the objective improvement of at least one point in 2 neurologic scales. Less perception of benefit after therapy was reported by the oldest patient, who had a concomitant disabling Parkinson disease. To note, an early improvement was also recorded in patient 1, who had a long history of anti-MAG antibody neuropathy with poor response to previous treatments. The biological effect of ibrutinib was demonstrated by the steady decrease of the IgM levels and of the monoclonal component. Surprisingly (but consistently), the anti-MAG antibody titer decreased at the 3 months follow-up but at subsequent evaluation, increased regardless of the IgM level and of clinical improvement.

It is well known that the severity of the neuropathy does not correlate with the anti-MAG antibody titer, which also does not correlate with the paraprotein entity. Furthermore, if despite the halving of the monoclonal paraprotein, the antibody titer persists elevating, it is likely that the quantity of the antibody-producing cells is low compared with the whole paraprotein. Another possibility is that ibrutinib may succeed in eliminating the WM malignant cells, but it is less active in the lymphoplasmocytes producing anti-MAG antibodies. The possibility of serum factors that influence the in vitro antibody binding or the assays' variability because of the differences in the ELISA plates or their handling, or standard curves generated by positive controls, should also be considered. Finally, the lymphoplasmocytes that produce the anti-MAG antibodies may have a survival advantage, explaining why only less than 50% of anti-MAG neuropathy patients respond to rituximab or eventually relapse.

Our preliminary data in 3 patients point to a possible efficacy of ibrutinib in anti-MAG antibody neuropathy, which is the most common disabling paraproteinemic neuropathy.

Study funding

Disclosure

Publication history

Appendix Authors

Name	Location	Contribution
Francesca Castellani, MD	Department of Neurosciences, University of Padova	Major role in the acquisition of data; analyzed the data; interpreted the data; drafted the manuscript for intellectual content

Appendix *(continued)*

Name	Location	Contribution
Andrea Visentin, MD, PhD	Hematology and Clinical Immunology Unit, Department of Medicine, University of Padova	Major role in the acquisition of data; interpreted the data; drafted the manuscript for intellectual content
Marta Campagnolo, MD	Department of Neurosciences, University of Padova	Major role in the acquisition of data; interpreted the data
Alessandro Salvalaggio, MD	Department of Neurosciences, University of Padova	Major role in the acquisition of data; interpreted the data
Mario Cacciavillani, MD, PhD	CEMES, Data Medica Group, Padova	Major role in the acquisition of data; interpreted the data
Cinzia Candiotto, PhD	Immunology and Molecular Oncology, Veneto Institute of Oncology IOV, IRCCS	Major role in the acquisition of the genetic data; interpreted the data
Roberta Bertorelle, MD	Immunology and Molecular Oncology, Veneto Institute of Oncology IOV, IRCCS	Major role in the acquisition of the genetic data; interpreted the data
Livio Trentin, MD	Hematology and Clinical Immunology Unit, Department of Medicine, University of Padova	Major role in the acquisition of data; interpreted the data

Appendix *(continued)*

Name	Location	Contribution
Chiara Briani, MD	Department of Neurosciences, University of Padova	Designed and conceptualized the study; coordinated the study; interpreted the data; drafted the manuscript for intellectual content

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