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LETTER TO THE EDITORS

Rituximab in refractory chronic inflammatory demyelinating polyradiculoneuropathy: report of four cases

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Dear Sirs,

Chronic inflammatory demyelinating polyradiculoneuropathy (CIDP) is a rare disorder causing progressive or relapsing weakness and sensory disturbances [1]. CIDP is sustained by both humoral and cell-mediated immunity directed against myelin sheath antigens [2]. First-line treatments include corticosteroids, intravenous immunoglobulins (IVIg), and plasma exchange that are effective in about 80% of patients [3]. Unresponsive patients are treated with other immunosuppressive and immunomodulatory drugs. Four randomized trials and many observational studies of these drugs have been performed but are inconclusive [4]. We provide additional data supporting the efficacy of rituximab even in severely compromised patients who did not respond to first- or second-line treatments.

We treated with rituximab four severe CIDP patients, after proven ineffectiveness of first- or other second-line drugs, or wishing to spare steroid in a young severely affected patient, experiencing significant side effects. Diagnostic category was definite CIDP for all patients, following EFNS/PNS guidelines [5]. The study was approved by the ethics committee of San Raffaele Hospital and all patients gave written informed consent to off-label rituximab treatment. Table 1 summarizes demographic and clinical characteristics of our cohort.

A comparison of the standard nerve conduction parameters between the pre- and post-treatment follow-up examinations was performed. Moreover, a nerve conduction velocity (NCV) index was assessed, to allow an easier longitudinal evaluation. NCV index was calculated as previously reported [6]. Briefly, conduction velocities of four nerves were considered (i.e., motor conduction velocity of deep peroneal and ulnar nerve; sensory conduction velocity of sural nerve and wrist-finger segment of the median nerve) to obtain nerve NCV Z scores [(patient's NCV value − mean NCV value in control healthy subjects)/standard deviation (SD) of the same nerve in control healthy subjects]. The patient's NCV index was the mean of the NCV Z scores of all nerves considered.

Neurological assessment was performed on each treatment cycle. All patients showed marked amelioration in terms of limbs' strength, measured by MRC sum score, and disability, evaluated through INCAT score (Table 2). The interval between rituximab first cycle and the beginning of clinical recovery was very short for all patients; in the second patient, rituximab mainly acted as a steroid-sparing drug (patient could discontinue oral steroids 6 months after first rituximab infusion, maintaining stable disease). Table 2 also shows a consistent B-cell pool depletion.

The second patient was excluded from neurophysiological analysis, given the complete nerve unexcitability in all the assessments made. For the other patients, at least two examinations, one before (1 month) and one after starting therapy (6 months), were available. All patients had a neurophysiological improvement at the post-treatment studies (Table 3).

All three patients had an NCV index value <2 at each investigation, consistent with an NCV score exceeding

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Table 1 Demographic and clinical characteristics of the patients with CIDP

Patient (sex, age)	Neuropathy duration (years)	Pre-RTX therapy	Hematologic disease	RTX cycles[a]
1 (M, 39)	2.5	IVIg, Steroid, CYC	None	4
2 (M, 15)	12.5	IVIg, Steroid, CSA, CYC, AZA, MTX	None	4
3 (F, 65)	1.5	IVIg, Steroid	IgM k MGUS (anti-MAG negative)	3
4 (M, 79)	0.5	IVIg, Steroid	None	3

Patient (sex, age)	MRC ss pre-RTX	INCAT pre-RTX (arm + leg)	RTX cycles[a]
1 (M, 39)	51	6 (3 + 3)	4
2 (M, 15)	24	9 (4 + 5)	4
3 (F, 65)	22	9 (4 + 5)	3
4 (M, 79)	33	9 (4 + 5)	3

Age and neuropathy duration refer to the time of initiation of treatment with rituximab

AZA azathioprine, *CYC* cyclophosphamide, *CSA* cyclosporin, *MTX* methotrexate, *RTX* rituximab, *IVIg* intravenous immunoglobulin, *MGUS* monoclonal gammopathy of undetermined significance, *INCAT* Inflammatory Neuropathy Cause and Treatment arm and leg disability scores, *MRCss* Medical Research Council sum score

[a] 1st cycle: two 1000 mg IV infusions separated by 2 weeks from each other; from the 2nd cycle: single 1000 mg IV infusion every 6 months

[b] Patient suffered from significant steroid side effects (bilateral thigh bone fracture)

Table 2 Clinical assessment after last rituximab cycle and B-cell profile

Patient (sex, age)	Months before clinical improvement	FU (months)	MRC ss post-RTX	INCAT post-RTX (arm + leg)	CD19 + B cells% pre-RTX (n.v. 5–20)
1 (M, 39)	2	36	60	1 (1 + 0)	2.8_{L}
2 (M, 15)	–	24	30	8 (4 + 4)	5.4
3 (F, 65)	4	20	45	4 (3 + 1)	32.8_{H}
4 (M, 79)	2	18	51	6 (3 + 3)	4.8

Patient (sex, age)	CD19 + B cells% post-RTX (n.v. 5–20)	CD20 + B cells% pre-RTX	CD20 + B cells% post-RTX	CD19 + CD27 + B cells% pre-RTX	CD19 + CD27 + B cells% post-RTX
1 (M, 39)	0.0	4.9	0.0	–	0.0
2 (M, 15)	0.0	12.9	0.0	2	–
3 (F, 65)	0.0	32.9	0.0	–	0.0
4 (M, 79)	0.0	4.6	0.0	0.7	0.0

FU follow-up, *MRCss* Medical Research Council sum score, *RTX* rituximab, *INCAT* Inflammatory Neuropathy Cause and Treatment arm and leg disability scores, *CD19+/CD27+ B cells* total memory B cells, $_{L}$ below the lower reference limit, $_{H}$ above the upper reference limit

Table 3 Neurophysiological parameters

Patient (sex, age)	DML (%)	dAMP (%)	MCV (%)	CB (%)
1 (M, 39)	−25	117	71	
3 (F, 65)	−18	104	56	−92
4 (M, 79)	−63	−65	45	
Mean	−35	52	57	−92

Values reported in the table are percentage of variation between pre-treatment and post-treatment neurophysiological tests, in single patients and in the group

DML distal motor latency, *d AMP* distal CMAP amplitude, *MCV* motor conduction velocities, *CB* conduction block

negatively the mean normal value >2 SD. The longitudinal NCV index study showed worsening values during the pre-treatment period, and improvement at the post-treatment follow-up in comparison with pre-treatment values (Fig. 1).

Growing scientific data confirm the central role of B cells and autoantibodies in the pathogenesis of nerve demyelination [7]. Nevertheless, previous reports for the off-label use of rituximab, a chimeric monoclonal antibody that binds to CD20, showed conflicting results [8–16]. CIDP is a heterogeneous disease, supported by different arms of the immune response, and rituximab could be

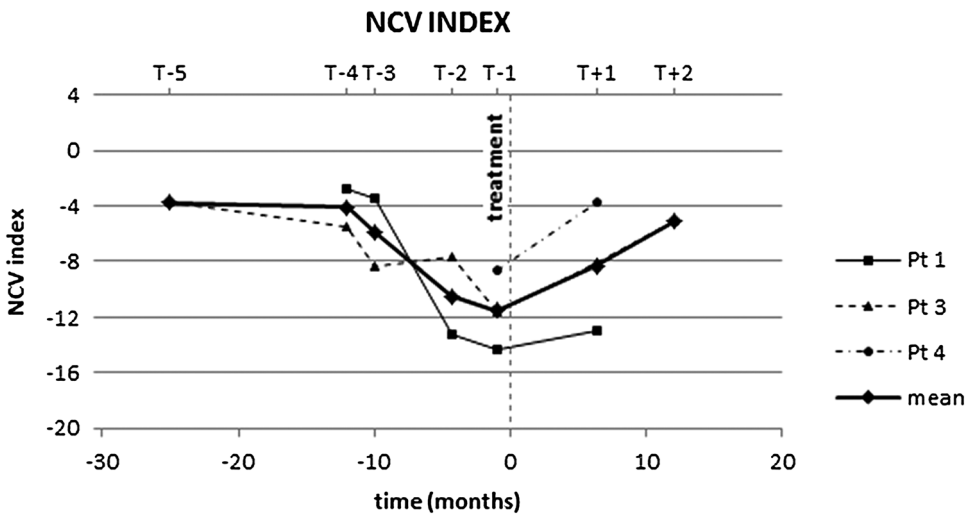

Fig. 1 NCV Index changes before and after treatment with rituximab. T, neurophysiological timepoint referred to the start of treatment (*vertical dashed line*)

effective in a subpopulation of patients harboring a specific B-cell response, as confirmed by previous observations [14]. Furthermore, of the three adult patients presenting with a short-lasting, aggressive CIDP form, the patient with MGUS responded more slowly to treatment than the other two patients, suggesting different pathogenic mechanisms and, probably, the involvement of less differentiated CD20-expressing B-cell subpopulations in CIDP not associated with hematologic conditions. This could explain the different response rate to rituximab in these patients.

Further controlled trials and identification of specific biomarkers are needed to improve patient selection criteria and to evaluate short- and long-term efficacy of the drug, but rituximab confirms to be a promising option in patients with refractory CIDP.

Compliance with ethical standards

Conflicts of interest None.

Ethical standard All procedures performed 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.

Informed consent Informed consent was obtained from all individual participants included in the study.

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