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Rituximab in patients with CIDP: A report of 13 cases and review of the literature

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Abstract

Background: A few case reports have shown controversial results of rituximab efficacy in patients with CIDP.

Objective: To analyze the efficacy of rituximab in a large CIDP cohort.

Methods: A retrospective, observational and multicenter study on the use of rituximab in CIDP.

We treated 13 Italian CIDP patients with rituximab after the partial or complete lack of efficacy of conventional therapies. Eight patients had co-occurring haematological diseases. Patients who improved by at least two points in standard clinical scales, or who reduced or discontinued the pre-rituximab therapies, were considered as responders.

Results: Nine patients (7 with haematological diseases) responded to rituximab: six of them, who were non-responders to conventional therapies, improved clinically, and the other three maintained the improvement that they usually achieved with intravenous Ig or plasma exchange. Significantly associated with shorter disease duration, rituximab responses started after a median period of 2.0 months (range, 1-6), and lasted for a median period of 1 year (range, 1-5).

Conclusions: Rituximab seems to be a promising therapeutic choice when it targets both CIDP and co-occuring haematological diseases. Timely post-onset administration of rituximab seems to be associated with better responses.

Introduction

Chronic inflammatory demyelinating polyradiculoneuropathy (CIDP) is a relapsingremitting, or chronic-progressive disease of the peripheral nervous system (1). The etiology of CIDP is unknown, but immunologic mechanisms, which involve both B and T cellmediated responses, presumably play a central role in the pathogenesis of the damage to peripheral myelin. Said mechanisms offer a rationale for immunoactive therapies, such as intravenous immunoglobulins (IVIg), corticosteroids, and plasma exchange (PE), but inadequate responses to these treatments lead to the use of immunosuppressant drugs.(2) Rituximab, a monoclonal anti-CD20 antibody, has recently been used for the treatment of anti-MAG antibody-associated polyneuropathy (3,4), another demyelinating neuropathy with immune-mediated pathogenesis. In CIDP, the drug proved to be efficacious in single cases (5-10), whereas in a prospective pilot trial (2 cases) it afforded no reduction in IVIg dosage (11).

We present 13 CIDP patients who were treated with rituximab in eight Italian centres after unsatisfactory responses to standard therapies.

Methods

We reviewed nationally registered (12) CIDP patients diagnosed in accordance with the EFNS/PNS criteria (13). Two of these cases had been previously reported (9,10). Table 1 summarizes the demographic and clinical characteristics of the selected 13 patients (8 men, 5 women; age range, 30-72 years, mean age, 55 years; mean neuropathy duration, 7 years). Routine laboratory tests, including glycaemia, serum thyroid hormones, B_{12} vitamin, tumor markers, and hepatitis C serology excluded other causes of neuropathy. Anti-MAG and anti-sulfatide antibody tests were negative. Clinical impairment and disability prior to rituximab were highly variable: mean value of 48 (range, 36-56) on the Medical Research Council (MRC) sumscore (14), and of 5 (range, 3-8) on the Inflammatory Neuropathy Cause and Treatment (INCAT) disability score (15). Disease course was relapsing-remitting in 9

patients, and chronic-progressive in 4. In 8 cases, CIDP co-occurred with haematological diseases. Rituximab was proposed for the following reasons: 7 patients were refractory to conventional immunosuppressive therapies, and quality of life was compromised to 6 patients by frequent recourse to PE/IVIg cycles (mean between-cycle interval, 44 days; range, 14-120); additionally, haematological diseases worsened in 4 cases. All patients gave written informed consent to rituximab treatment.

Rituximab dosage was 375 mg/sqm IV, weekly for 4 consecutive weeks, for 12 patients; one patient, who had severe Waldenstrom macroglobulinemia, received 1000 mg IV every six months for 2 years (4 infusions).

Neurological assessments were performed at baseline and every month for the first 6 months, then every 3 months (MRC sumscore for muscle strength, and INCAT scales for arm and leg disability), with \geq 1 year follow-up. CD19+ B cells, serum immunoglobulin levels, and platelet counts were checked regularly.

Before- and after-treatment electrophysiological data were available for 6 patients. Our analysis was based on ulnar nerve motor conduction velocity (MCV), because peroneal nerve MCV was not recordable in 3 patients. We considered \geq 10% changes in MCV values as indicators of therapeutic efficacy.

Responders were defined as those patients who improved by at least 2 points on each of the two clinical scales, or who maintained the degrees of improvement obtained with IVIg/PE cycles, without further cycles of IVIg/PE over the follow-up.

Our review of the literature included patients with pure CIDP, and excluded CIDP associated with anti-MAG/-sulfatide antibodies.

Results

Table 1 shows the clinical data. Nine out of 13 (69%) patients responded to rituximab. Clinical improvements occurred at a median time of 2.0 months after the end of rituximab cycles, and lasted for up to one year. Among the 7 patients who were refractory to conventional therapies, one worsened under rituximab, whereas the other 6 improved by at least 4 points in the MRC score, and by 2 points in the INCAT scales, with a reduction of disability in quality-of-life-related daily activities, such as deambulation, handling knife and fork, washing hair, and doing-undoing zips. Of the 6 patients for whom rituximab replaced IVIg/PE cycles, 3 were responders: two patients ceased IVIg/PE and maintained the improvement achieved with these treatments prior to rituximab (benefits started at a median time of 2.0 months after rituximab, and lasted for ≥ 1 year); one patient stopped IVIg, and clinically improved (10). The 3 non-responders recorded worsened clinical symptoms after a 25% reduction in IVIg dosage (Table 1). No responders required any re-treatment throughout the follow-up period. We tried to correlate the response to rituximab with clinical variables, namely disease duration, course of disease, and association with haematological diseases. Mean disease durations in responders (4.3 years) were significantly shorter than in nonresponders (12.7 years; p=0.025, Mann-Whitney U test). Clinical improvement and course of the disease did not correlate. Seven of the 9 responders, and one of the 4 non-responders had haematological diseases, but the between-group difference was not significant (p=0.12, Fisher exact test).

Blood CD19+ B cells were undetectable in all 13 patients at month 1 post-rituximab cycles; they reappeared at month 6, and returned to pre-treatment values at months 9-12. Serum IgM levels were about 50% lower at 1-3 months post-treatment, and were still lower at month 12 than at baseline in patients with IgM monoclonal gammopathy of undetermined significance (MGUS) or with Waldenstrom macroglobulinemia. In contrast, serum IgA levels

were unchanged in the IgA MGUS patient. Platelet counts improved in the patient with idiopathic thrombocytopenic purpura (ITP) (10). Rituximab therapy respectively circumvented autologous peripheral blood stem cell transplantation and splenectomy in Waldenstrom macroglobulinemia and ITP patients.

Electrophysiological data showed $\geq 10\%$ ulnar nerve MCV improvement in 5 responders, and worsening in one non-responder (data not shown).

No major adverse effects were recorded. During the first rituximab infusion, one patient complained of flu-like symptoms, and another showed a mild skin allergy, which responded to corticosteroids.

Discussion

B cell-depleting antibody rituximab has current FDA approval for the treatment of non-Hodgkin lymphoma and rheumatoid arthritis, but its off-label use extends to several autoimmune diseases. Since rituximab could target the immunological mechanisms deemed to be involved in CIDP pathogenesis, the drug qualifies for CIDP patients who do not respond to standard therapies. The few relevant reports show controversial results in terms of drug efficacy. One study on 2 CIDP cases reports no benefit in the primary endpoint, namely a 25% reduction in IVIg dosage 1 year after rituximab therapy vs IVIg dosage in the year prior to rituximab (11). In contrast, four case reports describe clinical improvement in four rituximab-treated CIDP patients (Table 2) (5-8). Specifically, rituximab induced: the complete disappearance of a gastric lymphoma, and long-lasting improvements in neurological symptoms in a CIDP case (5); the remission of both neurological symptoms and haematological abnormalities for 17 months in a patient with CIDP and Evans syndrome (6); the stabilization of CIDP course for 11 months in a patient with diabetes mellitus (7). Combined with chemotherapy, rituximab proved successful in a case of CIDP associated with non-Hodgkin lymphoma (8).

To date, our cohort is the largest to be used to evaluate rituximab in CIDP. Our data show that rituximab induced a sustained remission of neurological symptoms in about 70% of CIDP patients. Although we do not advocate a syncretic approach, we note that this percentage is similar to that obtainable by pooling the 6 CIDP cases previously reported in the literature. Comparably with what was reported for anti-MAG neuropathy (16), rituximab efficacy lasted one year, or longer, both in our series and in those previously reported in the literature. As a result, patients either improved clinically, or were spared periodic IVIg/PE cycles. Regarding the responders, 3 of the 6 previously reported cases, and 7 of our 13 patients, had associated haematological diseases, and rituximab was effective for both pathologies. In all the given series, the drug was less effective for idiopathic CIDP than for CIDP and haematological diseases. These findings suggest that, when associated with haematological diseases, CIDP may have different pathogenic mechanisms from those underlying isolated CIDP. Although CIDP is considered an autoimmune disease, the target antigen and the precise roles of humoral and cell-mediated immunity remain unknown (17). Rituximab greater efficacy in CIDP associated with haematological diseases could imply that B cells, whether as antibody, or cytokine-producing cells, play a predominant role in the pathogenesis of these CIDP types. Responses to rituximab in demyelinating lymphomaassociated neuropathies (18) could support this view.

As a whole, the percentages of responders reported in the literature and in our series are similar to those reported for anti-MAG polyneuropathy (3,4), but the intervals between rituximab cessation and clinical improvement differed: 2-3 months in CIDP versus 6-8 months in anti-MAG polyneuropathy (3,4). It is likely that the longer intervals in anti-MAG polyneuropathy depend on the fact that rituximab does not target plasma cells, namely the cells directly involved in disease pathogenesis, and that benefits thus occur only after a sustained depletion of their precursors, the CD20+ B cells.

Both for our CIDP patients and for those previously reported, mean disease duration in responders was shorter than in non-responders. The phenomenon might derive from cumulative axonal damage in patients with greater disease durations, and from the possible down-regulation of CD20 molecule as a result of aggressive and prolonged pre-rituximab immunosuppressive therapies; such down-regulation could deny targets, and hence efficacy to rituximab.

In conclusion, although obtained in a relatively small number of patients, our data suggest that rituximab therapy for refractory CIDP may be promising and free from major adverse events, particularly if the disease has short duration, and is associated to haematological diseases that are potentially responsive to the drug.

Competing interests: None

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Patient (sex, age)	Disease course	Neuropathy duration*	Hematological Disease	Pre-rituximab therapy	Rationale for	MRC [§] INCAT [§]		Months before	Duration of follow-up ^
(,8-)		(years)		F.)	rituximab			improvement	(years)
1 (M, 72) ⁹	RR	3	Low-grade small B cell lymphoma	Ster, IVIG, AZA, Cyclosp	Refractory CIDP	36- <u>48</u>	5- <u>3</u>	6	5
2 (F, 56)	RR	2	Ig M MGUS	Ster, IVIg, PE	To spare PE	47- <u>53</u> †	6- <u>3</u>	6	4
3 (M, 35)	RR	10	-	Ster, PE, IVIg, AZA, MM	To spare IVIg	55-55	5-5	-	1
4 (M, 63)	RR	0	-	Ster, PE, IVIg, AZA	Refractory CIDP	50- <u>56</u>	5- <u>2</u>	2	4
5 (F, 65)	СР	4	Ig A MGUS	Ster, PE, IVIg, AZA	Refractory CIDP	56-47	3-4	-	1
6 (F, 67)	СР	1	Non-Hodgkin Lynphoma	Ster, PE, IVIg	Refractory CIDP	46- <u>54</u>	5- <u>3</u>	1	2
7 (M, 59) ¹⁰	RR	1	ITP	Ster, IVIg	To spare IVIg, Ster	47- <u>60</u>	5- <u>0</u>	1	2
8 (M, 50)	RR	7	Waldenstrom Macroglobulinemia	Ster, IVIg	To spare IVIg	47- <u>51</u> †	5- <u>3</u>	1	2
9 (F, 30)	RR	5	-	Ster, IVIg, AZA	Refractory CIDP	52- <u>56</u>	3- <u>1</u>	1	1
10 (M, 65)	RR	4	Ig M MGUS	Ster, IVIg, PE	Refractory CIDP	48- <u>52</u>	6- <u>4</u>	2	1
11 (F, 59)	СР	6	Ig M MGUS	Ster, IVIg, AZA	Refractory CIDP	40- <u>50</u>	8- <u>4</u>	4	1
12 (M, 53)	RR	18	-	Ster, IVIg, AZA, Cyclopho	To spare IVIg	50-50	5-5	-	1
13 (M, 45)	СР	19	-	Ster, IVIg, AZA, MM, Cyclosp	To spare IVIg, Ster	51-51	4-4	-	1

Table 1: Demographic and clinical characteristics of the CIDP patients

Superscript numbers in Patient column: references; RR: relapsing-remitting; CP: chronic-progressive; MGUS: monoclonal gammopathy of undetermine significance; ITP: idiopathic thrombocytopenic purpura; IVIg: intravenous immunoglobulin; AZA: azathioprine; Cyclopho: cyclophosphamide; Ster: steroids; PI plasma exchange; MM: mycophenolate mofetil; Cyclosp: cyclosporin; MRC: Medical Research Council sumscore; INCAT: Immune Neuropathy Cause an Treatment arm and leg disability scores; * from the onset of neurological symptoms; [§]the first number refers to values at baseline, and the second number to value at improvement; [†]the degree of improvement obtained after PE and IVIg cycles and maintained after rituximab; ^ which corresponded to duration of improvement in the responders

Author	N° of	Neuropathy	Pre-rituximab	Comorbidity	Clinical	Months	Duration of
	patients	duration	therapy		response	before	improvement
		(months)				improvement	(years)^
Gorson et al.		60	IVIg, AZA, MM,				
2007	2	(mean)	Ster, PE, Cyclopho	No	No	-	-
Kilidireas et al.				Gastric			
2006	1	10	No	lymphoma	Yes	2	> 5
Knecht et al.			Ster, PE, AZA,	Evans			
2004	1	17	Cyclopho	Syndrome	Yes	6	1.5
Kasamon et al.				Non-Hodgkin			
2002	1	< 12	Ster	lymphoma	Yes	2	n.a.
Műnch et al.	1	20	11.71	DM	N	1	1
2007		20	IVIg	DM	Yes		1

Table 2: Results of published studies on rituximab therapy in patients with CIDP

IVIg: intravenous immunoglobulin; AZA: azathioprine; Cyclopho: Cyclophosphamide; Ster: steroids; PE: plasma exchange; MM: Mycophenolate mofetil; DM diabetes mellitus; n.a.: not available; ^ which corresponded to duration of follow-up