RITUXIMAB IN PATIENTS WITH REFRACTORY CHRONIC INFLAMMATORY DEMYELINATING POLYRADICULONEUROPATHY NOT ASSOCIATED WITH HAEMATOLOGICAL DISEASE

Medici D.* *, Ferrante T.* ***, Manneschi* *** L., Pedà G.* ***, Montanari E.* ***, Pavesi G.** ***, Gemignani F.** *****

Neurology Unit - Vaio Hospital – AUSL Parma
****** AOU Parma***
******* Polo Neurologico Interaziendale, Neuromuscolar Disease Section***

Introduction

Previous reports of small series or single cases tend to show that about half of patients with refractory CIDP can be responsive to Rituximab, but this is mainly seen in patients with associated haematological disease. Immunopathogenetic mechanism in CIDP seem to involve both B- and T-cell-mediated responses, it can be supposed that B cells play a predominant role in the pathogenesis of a CIDP subtype responder to Rituximab, as this is a monoclonal antibody against CD20+ B lymphocytes. However, it is also possible than Rituximab may have additional disease-modifying effects, such as reduced complement-dependent cytotoxicity, that are independent of antibody production

In occasional reports, Rituximab proved to be efficacious in chronic inflammatory demyelinating polyradiculoneuropathy (CIDP) refractory to first-line conventional immunosuppressive therapies, especially in presence of co-occurring autoimmune and haematological diseases. We report our experience in the treatment with Rituximab of patients with CIDP not associated with systemic diseases.

Materials and methods

We used a validated protocol, already implemented for patients oncohematology. This protocol provides the intravenous use of an antihistamine drug, methylprednisolone, an antiemetic, a gastric protector and Rituximab, so as to avoid the occurrence of any side effects due to the administration.

During the period 2010-2014, four patients with "pure" CIDP (3 women, 1 man, age 43-74 years) were treated with Rituximab after unsatisfactory responses or intolerance to first-line therapies. Rituximab dosage was 375 mg per sqm e.v, weekly for four consecutive weeks. Disease course was relapsing-remitting in 3 patients and chronic progressive in 1, with a disease duration of 5-10 years pre-Rituximab. Patients who improved by at least one point in lower limb score of Overall Neuropathy Limitation Scales (ONLS) were considered as responders. Patients treated with rituximab for neuropathy associated with anti-MAG antibodies were not included.

Results

Three of four patients responded to Rituximab, with discontinuation of previous therapies, whereas a 74-year-old woman with a 7 year history of chronic progressive CIDP continued to worsen, but in the last period the patient referred a subjective improvement. In the other patients improvement occurred 4-6 months after Rituximab was started. Responders maintained the best results during the follow-up period (22-50 months).

Pt., gender, age	Age at onset CIDP	Course	CIDP duration pre-Rituximab	Previous treatments	Latency treatment benefits with Rituximab	ONLS pre-Rituximab	ONLS 6 month	ONLS current	Duration Follow-up
1, F, 43	35	R-R	2	IVIg, Ster, PE	6 month	7 (2+5)	5 (1+4)	2 (0+2)	6 years
2, F, 77	66	R-R	10	IVIg, Ster, PE	4 month	8 (4+4)	6 (3+3)	4 (2+2)	2 years
3, M, 58	51	CP	4	IVIg, Ster, PE	6 month	9 (3+6)	7 (2+5)	6 (1+5)	2 years
4, F, 74	66	R-R	7	IVIg, Ster, PE, AZA, MM	-	9 (3+6)	9 (3+6)	9 (3+6)	1 years

Legend:
Pt: Patient, IVIg : Intravenous Immunoglobulin, Ster: Steroids, PE: Plasma Exchange, AZA: Azathioprine, MM: Micophenolate Mofetil, CP: chronic-progressive, RR: relapsing-remmitting

Pt	Nerve	Pre-RTX		6 months		Current	
		Latency (ms)	VCM (m/sec)	Latency (ms)	VCM (m/sec)	Latency (ms)	VCM (m/sec)
1	MEDIAN LEFT	11 - 19 - 23	30.1 - 41.6	7 - 13	39	9 - 14	44
	SPE RIGHT	11 - 25 - 30	26.3 - 27.7	11 - 22	27	10 - 26	21
	SPE LEFT	14 - 25 - 30	26.4 - 25.6	10 - 21	27	10 - 25	23
2	MEDIAN LEFT	11 - 31	12	10 - 28	13	7 - 17	22
	SPE RIGHT	inexcitable		inexcitable		6 (m.TA)	22
	SPE LEFT	inexcitable		inexcitable		5 (m.TA)	18
3	ULNAR LEFT	5 - 14- 18	25 - 30	4 - 12 - 15	27 - 34	4 - 13	28
	SPE RIGHT	inexcitable		inexcitable		inexcitable	
	SPE LEFT	inexcitable		9 (m.TA)	13	8 (m.TA)	15
4	ULNAR LEFT	6 - 15 - 21	23 - 18	6 - 15 - 20	23 - 19	5 - 15 - 20	24 - 21
	SPE RIGHT	inexcitable		inexcitable		inexcitable	
	SPE LEFT	inexcitable		inexcitable		inexcitable	

Conclusions

Our data show an initial and significant clinical improvement in the short term (4-6 months), a progressive improvement over time when treatment is carried out in chronic and when the cycles of therapy are modulated depending on the clinical response, electrophysiological and flow cytometry. We have also noticed a drug's effectiveness even in patients without hematologic diseases associated.

Our patients did not have related side effects of the drug and even later, while drugs that are used in patients non-responders, as azathioprine, methotrexate, cyclophosphamide, cyclosporine A have major side effects (bone marrow aplasia, myelosuppression, teratogenicity, infertility) and long latency times.

While there is a potential risk of progressive multifocal leukoencephalopathy (PML), in the literature are reported several cases of PML in patients treated with monoclonal antibodies almost always, however, in combination with chemotherapy or immunosuppressive agents. Despite Rituximab belong to this class of drugs the risk of PML is still low.

In conclusion, our data, although anecdotal, confirm that Rituximab may represent a treatment option in a subset of refractory CIDP patients, and controlled trials may be warranted. Predictors of response to Rituximab have not been identified, and our cases show that the treatment can be effective also in patients with longstanding disease.

Bibliography

Rituximab in patients with chronic inflammatory demyelinating polyradiculoneuropathy: a report of 13 cases and review of the literature.
Benedetti L, Briani C, Franciotta D, Fazio R, Paolasso I, Comi C, Luigetti M, Sabatelli M, Giannini F, Mancardi GL, Schenone A, Nobile-Orazio E, Cocito D.
J Neurol Neurosurg Psychiatry. 2011 Mar;82(3):306-8. doi: 10.1136/jnnp.2009.188912. Epub 2010 Jul 16.

Immunosuppressive treatment in refractory chronic inflammatory demyelinating polyradiculoneuropathy. A nationwide retrospective analysis.
Cocito D, Grimaldi S, Paolasso I, Falcone Y, Antonini G, Benedetti L, Briani C, Fazio R, Jann S, Matà S, Sabatelli M, Nobile-Orazio E; Italian Network for CIDP Register. Eur J Neurol. 2011 Dec;18(12):1417-21. doi: 10.1111/j.1468-1331.2011.03495.x. Epub 2011 Aug 5.

Treatment of IgM antibody associated polyneuropathies using rituximab.
Pestronk A, Florence J, Miller T, Choksi R, Al-Lozi MT, Levine TD. J Neurol Neurosurg Psychiatry. 2003 Apr;74(4):485-9.