Clinical and immunological worsening in a patient affected with waldestrom macroglobulinemia and anti-mag neuropathy after treatment with rituximab

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Current immune-modulating therapies for IgM paraproteinemic neuropathies (IgM-N) are often associated with severe complications and have not provided reliable evidences of long term efficacy.[1] Neuropathy associated with antibodies to myelin-associated-glycoprotein (anti-MAG) is a chronic-demyelinating sensorimotor neuropathy that counts for 50% of these diseases. Titre reduction of these antibodies has shown to be associated to an amelioration of the neuropathy.[2] Therefore a selective drug address to reduce these antibodies is the target of current pharmacological researches.

Rituximab is a mouse-human chimeric antibody directed against CD20 protein, eliminating the most of circulating Bcells.[3] It has shown positive effects in the treatment of Bcell lymphoma, rheumatoid arthritis and preliminary studies suggested also a promising role in IgM-N.[2,3] However, more recently several cases of clinical inefficacy or lack of effect on anti-MAG titre have been reported[4,5] in patients treated with Rituximab, leading to unclear conclusions about the usefulness of this therapy.

We reported the case of a 64-year-old-woman affected by Waldestrom macroglobulinemia and a neuropathy associated with anti-MAG IgM/k antibodies.

The haematological disease was diagnosed by bone marrow biopsy, when the patient was 56-year-old. Neither multiorgan involvement, nor iperviscosity syndrome were associated and IgM-paraprotein level was stable for 8 years (from 4 to 5 gr/lt at periodical evaluations). At the age of 64, a severe tremor and unsteadiness of gait appeared.

On neurological examination patient showed a mild increase of superficial, and a severe increase of propioceptive sensory threshold at lower limbs, apallestesia (loss of vibratory perception) from the knees, ataxic gait, positive Romberg sign, a 8 Hz-postural-kinetic tremor at all four limbs, areflexia, without any motor involvement.

Neurophysiolgical studies included motor and sensory conduction velocities in two arm nerves and one leg nerve, F responses of the ulnar nerve and peroneal nerve, H reflex of the soleus muscle, and EMG of distal arm and leg muscles examinations disclosed a sensory-demyelinating polyneuropathy. Stimulated PBMCs were analyzed by flow-cytometry (Beckman-Coulter Inc.) to asses IL1β, IL2, IFNγ, TNFα, IL6, IL10, IL12 producing CD4+, CD8+ and CD14+ cell percentage (Caltag Lab). Quantitative immunoglobulins IgM in serum was determinated by rate nephelometry (Beckman Instruments) and anti MAG antibody titre was determined by electrophoresis(SEBIA ITALY) in serum.

Serum anti-MAG IgM/k antibody titre and IgM level were 144.000 BTU and 5 gr/dL respectively; other antibodies to neuropathy-related-antigens as well as other toxic, metabolic, neoplastic, hereditary and infective causes of neuropathy were excluded. According to treatment recommendations in Waldestrom macroglobulinemia[6] and previous reports, treatment with Rituximab was decide to be tempted. Rituximab was injected at a dosage of 375 mg/m^2 once weekly for 4 weeks. As long as 3 months after theraphy, a severe worsening of all neurological signs and specifically of the tremor occured.

Immunological-parameters assessed at pre-treatment (T0) and 3 months after therapy(T3) showed an increase of IgM levels and anti MAG titre, as reported in table 1

Rituximab treatment was stopped and after other six months, IgM levels went back to pre-treatment value (4,580 gr/lt) and anti-MAG antibodies decreased to 132.000 BTU, but the patient went on worsening. Flow-cytometry was not re-assessed at that time.

Rituximab is a monoclonal antibody that specifically binds CD20 antigen. Encouraging results about the usefulness of this drug in IgM-N come from open pilot

Table 1A. The table shows (A) lymphocyte subsets (values are expressed as percentages % and as absolute cell number/ul); (B) cytokines production by SEB + anti CD28 stimulated CD4, CD8, CD14 cells percentage; (C) IgM levels (gr/dl) measured by electrophoretic pattern and anti-MAG antibody titers measured by ELISA test. All immunological parameters have been analyzed before treatment (T0) and 3 months after therapy (T3). Statistically significant values are signed.

		T0	*T3*	*p*
Natural Killers CD16+	%	7.2	3.2	
	Cell/μL	100	48	
B Lymphocyte CD20+	%	3	0.1	< 0.05
	Cell/μL	43	1	
T Lymphocyte CD3+	%	88.4	95.1	
	Cell/μL	1227	1425	
T Lymphocyte CD4+	%	68.6	76.3	
	Cell/μL	952	1144	
T Lymphocyte CD8+	%	20.3	19.1	
	Cell/μL	282	287	

Table 1B.

	T0	*T3*	*p*
CD4 %			
IL2 producing cells	0	0	
IFNγ producing cells	0.4	0.3	
TNFα producing cells	0	0.7	
IL6 producing cells	0.2	0.3	
IL10 producing cells	0.1	0.2	
IL12 producing cells	0.1	0.1	
IL1b producing cells	0	0	
CD8 %			
IL2 producing cells	0.3	0.1	
IFNγ producing cells	0.3	0.2	
TNFα producing cells	1.1	0.9	
IL6 producing cells	0.1	0.2	
IL10 producing cells	0	0.1	
IL12 producing cells	0.2	0.1	
IL1b producing cells	0	0	
CD14%			
IL1b producing cells	2	1.9	
IL12 producing cells	1.5	1.8	
TNFα producing cells	4.5	5.1	
IL6 producing cells	3.5	27	<0.05
IL10 producing cells	2	2.1	

Table 1C.

	T0	*T3*	*p*
Anti-MAG (BTU)	144.000	174.000	
IgM (gr/dl)	5	7.9	

studies.[2]

Rituximab is active in up to 40 % of patients with Waldestrom macroglobulinemia, more likely if patients show low levels of IgM.[7] Consequently it's conceivable that the efficacy of this drug on IgM-N due to Waldestrom macroglobulinemia, could be related to decrease of this paraproteinemia as occurs in patients with IgM levels less than 40 g/L.

However the counteracting mechanisms induced on immune system by Bcell depletion are still elusive We studied clinical and immunological changes of a 64-year-old-woman affected by Waldestrom macroglobulinemia who showed a worsening of anti-MAG neuropathy after Rituximab treatment. The clinical worsening we observed was mirrored by immunological findings. Despite CD20 cells depletion, IgM levels, anti-MAG antibodies as well as percentage of IL6-producing CD14+cells raised.

This data are in accordance with previous studies reporting that IgM flare occurs in up to 40 % of patient treated with Rituximab, but such an increase doesn't herald a treatment failure.[8]

As far as concern cellular component, an hematologic response was evident in the peripheral depletion of CD20 (bone marrow biopsy was non performed for unwillingness of the patient).

However an IgM and anti-MAG increase, associated with worsening of symptomatology were documented

Similar clinical results were reported in other subjects treated with Rituximab: 5 patients affected with neuropathy associated with anti-MAG antibodies and 2 patients with multifocal motor neuropathy positive for antiganglioside antibodies,[4,5] but no details were given about cytokine network

All together these data can suggest that these autoantibodies are secreted by a cell population clearly insensitive to Rituximab. An explanation for the clinical and immunological worsening could be the disruption of idiotype-antiidiotype network. Bcell depletion can infact even involve those cells counteracting auto-antibodies secretion, depriving immune system of a natural resource against autoimmunity.

The increase in IL6-producing CD14+cells we detected, might be a further factor enhancing this auto-antibodies secretion. Its well known that this cytokine stimulates antibody-producers B lymphocytes and act as grow-factor for some neoplastic plasma-cells.[9] IL6 overproduction can therefore became an enhancer of the mechanisms of disease.

Considering our experience and previous cases, we think that identification of immunological and clinical features of potential responders to Rituximab treatment is mandatory before suggesting the use of this treatment for B-cell-mediated autoimmune diseases.

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