Rituximab as second-line therapy after new direct antiviral agents in peripheral neuropathy Hepatitis C Virus related : always correct therapeutic approach?

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To the Editor,

Nowadays, Hepatitis C virus (HCV) infection remains a major public health problem in many countries (1). The cryoglobulinemic vasculitis HCV-related may involve small vessels of skin, kidney and peripheral nervous system. The treatment of peripheral neuropathy (PN) HCV related is based on corticosteroids, plasmapheresis, rituximab and new direct antiviral agents therapy (DAAs) (2). In May 2015, a male of 54-years old was referred to our Department for recurrent palpable purpura on legs, asthenia, arthralgias, sicca syndrome (dry mouth and eyes), paresthesias, burning and pain in all limbs. The clinical and laboratory parameters are reported in table 1. In peripheral blood, the cytometry detected monoclonal kB cells lymphocytes (MBL), CD20+, CD10-, CD38, CD23-, CD5+, CD22+, CD79b+, FMC7+, CD81+, CD200-. Computed tomography scan showed slight hepatomegaly, normal spleen, no lymphoadenophaties.

The Electromyography (EMG) highlighted axonal motor-sensitive neuropathy to all limbs. From June to August 2015, therapy with sofosbuvir 400 mg/day, plus ribavirin 1000 mg/day started. After one month, HCV-RNA viremia was undetectable. At the end of therapy, clinical regression of purpura, asthenia and arthralgias were achieved. In August 2016 a complete immunological response has been reported (see table 2).

However, in the peripheral blood MBL was still detectable and the EMG reported no remission of neuropathy.

In September 2016, peripheral sensitive polyneuropathy of the 4 limbs worsened ; therefore treatment with 48 rituximab started (schedule 1000 mg at days 1 and 15). After treatment, in upper limbs hypoesthesias/paresthesias and pain were clinically improved, but not in lower limbs. After rituximab, cryocrit, HCV-RNA and MBL were undetectable (see table 2). Similar observations are ready reported in the interferon treatments (3). The pathogenesis of neuropathy HCV related remains largely speculative.

The cryoglobulinemic vasculitis or necrotizing arteritis seems to play a key role in the direct damage of the small vessels around the nerve (2). However others "cryoglobulinemia independent" pathogenesis have been advocated, such as a direct viral infection,

Table1. — **Clinical and laboratory data at baseline.**

Parameter	
Age (years)	54
HCV genotype	2
HCV-RNA	3.1 x 10^6 copies IU/ml
HBsAg	Negative
AntiHBs	Negative
Anti HBc	Positive
White blood cell count	7,15x10^3 /mcL
Hemoglobin	12,3 g/dl
Platelet count	209 x10^3 /mcL
AST	18 U/L
ALT	27 U/L
GGT	19 U/L
Creatinine	1.0 mg/dl
Rheumatoid factor	114 U/L
C4 (10-40 mg/dl)	3 mg/dl
Cryoglobulinemia Type II (IgM/k) Cryocrit	4%
Metavir liver fibrosis score	F1
Bone marrow	MBL
B-cell clonal	Monoclonal IgG/K
SSA/SSB	Pos/Pos

Legend : SSA/SSB (autoantibodies in Sjögren's syndrome, MBL (Monoclonal B cell Lymphocytes).

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Table 2. — **Clinical and laboratory data during treatment and follow-up**

	Start DAAs therapy Baseline (June 2015)	End of treatment (November 2015)	9th month follow-up (August 2016)	Start Rituximab (October 2016)	12th month follow-up (September 2017)	24th month follow-up (September 2018)	36th month follow-up (September 2019)
HCV-RNA	+	-	-	-	-	-	-
Purpura	+	-	-	-	-	-	-
Asthenia	+	-	-	-	-	-	-
Arthralgia	+	-	-	-	-	-	-
Neuropathy	+	+	+	+	+	+	+
Sicca syndrome	+	+	+	+	+	+	+
ALT (U/L)	28	18	n.r.	30	20	30	28
Cryocrit (%)	4	n.r	0	1	0	0	0
Rheumatoid Factor (IU/ml)	114	n.r	18	18	16	n.r.	<10
C4 mg/dl	3	n.r	17	16	21	21	24
Fibrosis	F1	n.r.	n.r.	n.r.	n.r.	n.r.	n.r.
Peripheral blood citometry	Monoclonal B cells IgG/k			Monoclonal B cells IgG/k			No clonality

Legend : DAAs (Direct Antiviral Agents), nr (not reported).

perivascular mononuclear inflammatory cells, or, more likely, virus triggered immune-mediated mechanisms. In particular, cases with neuropathy HCV related without cryoglobulinemia have been reported (4). More recently HCV particles have been detected in peripheral nerve and muscle biopsies without mixed cryoglobulinemia suggesting a virus triggered immune-mediated mechanisms (5). Low-medium dosages of steroids are considered a cornerstone in the treatment of cryoglobulinemic vasculitis (2). The rituximab played an increasing key role as second-line therapy in non-responders or relapsed patients (2). Several studies highlighted that vasculitis symptoms, purpura and arthralgias disappeared or improved after DAAs therapy (2). However, half of the patients with PN seems refractory to DAAs therapy or relapse after treatment. Also in this setting of patients, rituximab as second-line therapy is a cornerstone to improve sensory neuropathy (2). In our case, DAAs therapy was effective not only for HCV but also for purpura, asthenia and arthralgias ; however, we recorded no results about PN and sicca syndrome. Moreover, we observed immunological response with undetectable levels of cryoglobulins, normalization C4 level. Rituximab produced not only the B cell clone disappearance but also an improvement of hypoesthesia, paresthesias and pain in upper limbs, but no clinical response in legs. In conclusion, DAAs therapy induced a sustained virological and immunological complete response. After rituximab, the B cell clone disappeared without a complete remission of neuropathy. In PN-HCV related, considering the achievement of complete virological and immunological response, these events suggest alternative ways to cryoglobulinemic vasculitis and underlying monoclonal B lymphocytes as such as cellular immunity T helper mediated (6). In patients with a complete virological and immunological response, these alternative pathways could play a prominent role in PN cases refractory to DAAs or immunosuppressors generating an unmet clinical need.

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