

Treatment of Hepatitis C Virus-Related Systemic Vasculitis

Although the cause of most systemic vasculitides was unknown at the beginning of the 1950s, the prognosis for patients with systemic vasculitis improved dramatically with the introduction of corticosteroids¹. Later, other studies showed that immunosuppressive treatment, usually with cyclophosphamide, improved the prognosis of severe forms of systemic necrotizing vasculitis even further^{2,3}. Although more efficacious, combination therapy with corticosteroids plus cyclophosphamide also increased the frequency of adverse events³. A more rational therapeutic strategy in patients with systemic vasculitis related to underlying infection^{4,5} is aimed at the associated infection in combination with short term, low dose corticosteroids^{6,7}. Such an approach has been used successfully in patients with vasculitis related to hepatitis B virus (HBV) and the human immunodeficiency virus (HIV)⁶.

Numerous extrahepatic manifestations have been associated with hepatitis C virus (HCV) infection, including mixed cryoglobulinemia (MC), glomerulonephritis, porphyria cutanea tarda, and sicca syndrome⁸⁻¹⁴. Cryoglobulins are classified as either type II MC, which includes a monoclonal component, or type III MC, defined by the association of polyclonal immunoglobulins¹⁵. MC is a systemic vasculitis characterized by proliferation of B cell clones producing pathogenic IgM with rheumatoid factor activity¹⁶. MC leads to clinical manifestations ranging from the so-called MC syndrome (purpura, arthralgia, asthenia) to more serious lesions with neurologic and renal involvement¹⁷. HCV infection is associated with most cases of MC. Sixty percent to 80% of patients with MC are infected with HCV¹⁴. The primary role of HCV in the mechanism of cryoprecipitation is mainly suggested by its selective concentration in cryoglobulins¹⁸. Molecular evidence of antigen-driven B cell proliferation is definitively provided in HCV-associated type II MC, and HCV appears as the key trigger¹⁹.

Limited data are available regarding the treatment of patients with HCV-related systemic vasculitis. Interferon- α (IFN- α), corticosteroids, immunosuppressive agents, and plasmapheresis have been proposed as treatments, but the optimal therapeutic regimen remains controversial. Treatment of HCV-associated MC with severe organ involvement may target either the viral trigger (HCV) or downstream pathogenic events by means of less specific approaches such as corticosteroids, immunosuppressives, or plasmapheresis. Current treatments directed to the B cell arm of autoimmunity in type II MC (i.e., corticosteroids, cyclophosphamide, and plasmapheresis) may lead to life-

threatening complications, are difficult to manage in the long term, and finally, do not improve HCV-MC vasculitic manifestations²⁰⁻²². On the other hand, present data do not support that antiviral therapy alone may completely suppress the B cell response in type II MC, at least in the short term, and additional therapeutic options are required.

TREATMENT OF HCV-RELATED VASCULITIS WITH IFN- α

Treatment of HCV-related cryoglobulinemic vasculitis with IFN- α is associated with a relatively poor response and a high relapse rate, especially in severe cases²⁰⁻²³. IFN- α monotherapy was effective in 50% to 100% of patients with purpuric skin lesions, but did not clearly show efficacy on neural or renal involvement. Clinical improvement of HCV-related vasculitis correlated with virological response, i.e., negative or significant decrease in serum HCV RNA level. A viral response at the end of treatment has been reported in 15%–60% of patients receiving IFN- α monotherapy, 2 to 3 million IU 3 times weekly for 6 to 12 months. However, when followup was sufficient, most responders developed viral and clinical relapses following IFN- α withdrawal (Table 1). Such results are quite similar to those reported in patients without extrahepatic manifestations, where a 12-month course of IFN- α monotherapy led to a sustained viral response in only 15%–20% of patients. These results were probably due to the mechanisms of action of IFN- α on viral turnover²⁴. In patients infected with HCV without extrahepatic manifestations, combination therapy with IFN- α plus ribavirin was much more efficacious, with sustained viral response in 35%–80% of cases depending on their pretreatment characteristics^{25,26}.

TREATMENT OF HCV-RELATED VASCULITIS WITH IFN- α PLUS RIBAVIRIN

Combination therapy with IFN- α plus ribavirin seems to provide much better short and longterm results in patients with HCV-related vasculitis than historically reported with IFN- α . In 3 recent uncontrolled studies²⁷⁻²⁹, combination therapy with IFN- α and ribavirin showed enhanced efficacy on the main HCV-related vasculitic manifestations (cutaneous: 100%, renal: 50%, and neural: 25%–75%). In a small series, Zuckerman, *et al*²⁷ reported after a short duration of treatment and followup that only 2/9 patients had a viral response. A clinical response was noted in all patients with skin involvement, but in only half the patients with nerve or renal involvement. In the largest published study of 27

Table 1. Overview of treatments in HCV-related systemic vasculitis.

Study	No. of Patients	Visceral Involvement			Treatments	Duration of Treatment (followup)	Reponse				
		Skin	Kidney	Nerve			Skin	Kidney	Nerve	Deaths	Negative Viremia
Ferri, randomized cross-over ²¹	20	20	1	20	IFN 2M IU/day for 1 mo, then IFN 2M IU every other day for 5 mo	6 mo (6 mo)	20/20	0/1	0/20	0	2/13
Misiani, prospective, randomized, controlled ²⁰	53	31	40	15	IFN 3M IU × 3/wk for 6 mo; steroids < 0.2 mg/kg/day	6 mos (6–12 mos)	IFN 56% vs steroids 0%		4/53	IFN 15/25 vs controls 0/24	
Dammaco, prospective, randomized, controlled ²³	52	52	28	20	IFN 3M IU × 3/wk + prednisone 16 mg/day Prednisone 16 mg/day No treatment	12 mos (8–17 mos)		8/15 9/17	0/52	5/12 7/14	
Casato, retrospective ²²	31	31	11	24	IFN 3M IU/day for 3 mo, then IFN 3M IU every other day for 9 mo	16 mos (33 mos)	17/31	ND	ND	5/31	11/24
Durand, open uncontrolled ³⁷	5	4	1	1	Ribavirin 100–1200 mg/day	10–36 mos (ND)	4/4	1/1	0/1	0/5	3/5 (viremia decrease)
Zuckerman open, uncontrolled ²⁷	9	7	2	4	IFN 3M IU × 3/wk + ribavirin 400 to 1000 mg/day	6 mos (8 mos)	7/7	1/2	1/4	0/9	2/9
Naarendorp, open uncontrolled ²⁸	11	8	4	7	IFN 3M IU × 3/wk + ribavirin (in 4 pts)	(5 to 60 mos) (ND)	3/8	1/4	3/7	1/11	2/9
Cacoub Retrospective ²⁹	27	23	8	19	IFN 3M IU × 3/wk + ribavirin 400–1000 mg/day	20 and 14 mos for IFN & ribavirin (57 mos)	20/23	4/8	11/19	2/27	16/27
Sansonno, open uncontrolled ³⁹	20	16	1	7	Rituximab IV 375 mg/m ² /wk	4 wks (12 mos)	14/16	0/1	6/7	0/20	0/20 (increased viremia)
Zaja, open uncontrolled ⁴⁰	15	12	2	8	Rituximab IV 375 mg/m ² /wk	4 wks (6 mos)	10/12	1/2	7/7	0/15	0/15
Cacoub, open uncontrolled ³⁰	9	7	3	6	PEG-IFN 1.5 μg/kg/wk + ribavirin 800–1200 mg/day	14 mos (18 mos)	6/7	3/3	6/6	0/9	7/9

IFN: interferon alpha; ND: not done.

patients with chronic hepatitis C complicated by systemic vasculitis, patients received IFN- α for 20 \pm 14 months and ribavirin for 14 \pm 12 months²⁹. After a mean followup of 57 months, 25/27 patients (93%) were alive and followed as outpatients and 2 had died secondary to cirrhosis. Most patients (75%) with negative viremia at the end of followup were complete clinical responders for vasculitis. On the other hand, in complete clinical responders, decrease in HCV RNA was significant. Age, sex, clinical vasculitic involvement, mean duration or total cumulative dose of IFN- α or ribavirin, and use of steroids or plasmapheresis did not differ significantly according to clinical response. A more recent study showed that treatment with polyethylene glycol-conjugated (pegylated) IFN- α -2b (PEG-IFN- α -2b) and ribavirin can achieve complete clinical response in most patients with HCV-MC vasculitis. Complete clinical response correlated with the eradication of HCV and required a shorter period (14 months) than previously reported with IFN- α and ribavirin³⁰. After a first-line treat-

ment with prednisone, furosemide, or plasmapheresis, antiviral therapy with standard or pegylated IFN- α associated with ribavirin has also proved its efficacy on cryoglobulinemic glomerulonephritis³¹. A sustained viral response was achieved in 70% of patients, leading to significant decrease in daily proteinuria, cryoglobulin level, and stabilization of serum creatinine level.

In rare cases of HCV-related vasculitis, complete clinical responders had viral clearance long after clinical remission. Some patients (3 patients reported by Casato, *et al*²² and one in our series²⁹) remained in clinical remission despite persistent viremia. On the other hand, discordance between viral response and cryoglobulinemia vasculitis, as well as between vasculitis and cryoglobulinemia, has been reported^{32,33}. The possibility that cryoglobulinemia may be treatment-related needs further confirmation³⁴.

Although these recent studies were retrospective and uncontrolled, they strongly suggest that treatment with IFN plus ribavirin can achieve a complete clinical response in

most patients with HCV-related systemic vasculitis. Complete clinical response usually but not always correlates with viral response.

IS THERE A PLACE FOR TREATMENT STRATEGIES OTHER THAN IFN PLUS RIBAVIRIN IN HCV-RELATED SYSTEMIC VASCULITIS?

In comparison with IFN plus ribavirin, other treatment strategies have not shown superior efficacy. Corticosteroids, used alone or in addition to IFN, did not improve response of HCV-related vasculitic manifestations in 2 controlled studies^{20,23}. However, in personal observations, use of high-dose intravenous corticosteroids has been initially useful for control of life-threatening organ involvement while awaiting the generally slow response to antiviral treatments. Low-dose corticosteroids may also help to control minor intermittent inflammatory signs such as arthralgia, but do not succeed in cases of major organ involvement (i.e., neurologic, renal) or in longterm control of vasculitis. One potential concern regarding the use of corticosteroids and immunosuppressives is their propensity to worsen HCV viremia, as observed in the posttransplantation setting. This phenomenon, however, has not been reported in patients with HCV-related vasculitis. Use of plasma exchange may permit rapid control of life-threatening symptoms of vasculitis without using high-dose intravenous corticosteroids or immunosuppressive treatments²⁹. When used in combination with anti-HCV treatment, plasma exchange did not modify viral response if IFN was given after each plasma exchange session³⁵.

Monotherapy with ribavirin, although ineffective in eradicating HCV when used in isolation³⁶, may be effective in patients with HCV-cryoglobulinemic vasculitis, as suggested by Durand, *et al*³⁷. IFN and ribavirin may have both antiviral and immunomodulatory effects. For example, IFN may exert its effects via inhibition of viral replication rather than by complete eradication of the virus, or by an anti-inflammatory (Th2-like) cytokines³⁸.

More recently, Italian groups reported on the efficacy of anti-CD20 monoclonal antibody (rituximab) in patients with HCV-cryoglobulinemic vasculitis^{39,40}. Such an approach involves the use of monoclonal antibodies directed against CD20 antigen, a transmembrane protein expressed on pre-B lymphocytes and mature lymphocytes. Rituximab, a humanized murine monoclonal antibody, is highly effective for *in vivo* B cell depletion. Rituximab is an approved drug for the treatment of B-non-Hodgkin's lymphoma (B-NHL). In 2 recent small uncontrolled studies, 32 patients with HCV-cryoglobulinemic vasculitis resistant or intolerant to IFN- α monotherapy received intravenous infusion of 375 mg/m² rituximab weekly for 4 weeks. Patients were receiving no or low-dose steroids, and no anti-HCV therapy. After a mean followup of 12 months, a complete clinical response of cryoglobulinemic vasculitis (i.e., skin vasculitis, peripheral

neuropathy, arthralgias, fever) was observed in 80% of patients. Most clinical responders also had decrease in serum cryoglobulin levels, increase in C4 serum levels, and disappearance/deletion of peripheral B cell clones. Rituximab was well tolerated without severe side effects. At the end of the 12-month followup period, most (75%–87%) responders remained in remission. However, rituximab had a significant impact on HCV viremia. HCV RNA increased to about twice the baseline levels in responders, whereas it remained much the same in the nonresponders. It appears that rituximab has great efficacy on cryoglobulin production and its clinical consequences, i.e., inflammatory vascular lesions⁴¹. However, the absence of efficacy on HCV viral clearance, and even more, the increase in HCV viral load, may lead patients to develop more severe HCV-induced liver lesions and/or cryoglobulinemic relapses subsequently⁴².

TREATMENT OF HCV-RELATED VASCULITIS RELAPSES

Clinical relapses of HCV-related vasculitis are usually associated with relapsing HCV viremia. Higher efficacy of IFN plus ribavirin therapy seems associated with a prolonged duration of 18 to 24 months' treatment, particularly in cases with peripheral nerve or renal involvement, to avoid such relapses^{28,29}. However, the more recent use of PEG-IFN associated with ribavirin for a shorter duration (14 months) gave similarly good results³⁰. Although there is still controversy, the occurrence of B-NHL remains higher in patients with MC compared with the general population, even in patients who cleared HCV RNA following antiviral therapy^{43,44}.

We recently reported 2 patients who presented with cryoglobulinemic vasculitis due to chronic active HCV infection with no evidence of underlying malignant disease⁴³. After successful treatment of HCV infection, patients were sustained viral responders as they remained persistently HCV RNA-negative. Later on, cryoglobulinemia-related symptoms reappeared, with no HCV infection relapse (as shown by negative HCV viremia), but a malignant B-NHL was found in both cases. Others have reported on 4 cases of cryoglobulinemic vasculitis relapses without HCV infection relapse or underlying B-NHL, suggesting occult HCV infection⁴⁵. Clinicians should be aware of the possibility of malignant lymphoma when patients develop a relapse of cryoglobulinemia vasculitis without HCV viral relapse.

Recurrence of vasculitis-related symptoms after withdrawal of antiviral therapies with viral relapse (HCV RNA reactivation) can be successfully treated with another course of combination antiviral therapy with good response^{27,29}. Vasculitis relapses usually present the same vasculitis manifestations as were noted at presentation. Despite successes with combination antiviral treatment, HCV-related vasculitis remains a severe disease. Most series report a mortality rate of 8%–15%^{20-23,27-29}. Usually, death occurs in nonresponders after a prolonged course of vasculitis, and it is

often attributed to sepsis that may be due to underlying disease (i.e., cirrhosis) or to therapy (i.e., corticosteroids, immunosuppressive agents). Careful monitoring for adverse effects is mandatory since some manifestations of HCV-related vasculitis such as peripheral neuropathy^{29,46-48} or skin ulcers⁴⁹ may worsen with IFN therapy. In most cases, however, IFN treatment can be reinitiated without further problems. Tolerance to ribavirin is also reasonable, with the exception of hemolytic anemia requiring dosage reduction in some patients.

IFN- α and ribavirin are effective in the treatment of many patients presenting with HCV-related vasculitis. Clinical response mirrors viral response. Tolerance of such treatment is not different in patients infected with HCV without vasculitis. Use of high-dose intravenous corticosteroids and/or plasmapheresis may be initially useful for control of life-threatening organ involvement while awaiting the generally slow response to antiviral treatments. Further large, prospective, multicenter studies are warranted in patients with HCV-related vasculitis followed for prolonged periods to assess efficacy and tolerance of the simultaneous blockade of both the infectious trigger HCV (using optimal antiviral therapy with PEG-IFN plus ribavirin) and the activated rheumatoid factor-positive B cells (using rituximab).

PATRICE CACOUB, MD,

Professor;

DAVID SAADOUN, MD;

DAMIEN SENE, MD;

NICOLAS LIMAL, MD;

JEAN-CHARLES PIETTE, MD,

Professor,

Department of Internal Medicine,

Hôpital de la Pitié-Salpêtrière, Paris, France.

Address reprint requests to Dr. P. Cacoub, Department of Internal Medicine, Hôpital La Pitié-Salpêtrière, 83 boulevard de l'Hôpital, 75651 Paris Cedex 13, France. E-mail: patrice.cacoub@psl.ap-hop-paris.fr

REFERENCES

- Frohnert PP, Sheps SG. Long-term follow-up of periarteritis nodosa. *Am J Med* 1967;43:8-14.
- Fauci AS, Doppman JL, Wolff SM. Cyclophosphamide-induced remissions in advanced polyarteritis nodosa. *Am J Med* 1978;64:890-4.
- Gayraud M, Guillevin L, Le Thoumelin P, et al. French Vasculitis Study Group. Long-term follow-up of polyarteritis nodosa, microscopic polyangiitis, and Churg-Strauss syndrome: analysis of four prospective trials including 278 patients. *Arthritis Rheum* 2001;44:666-75.
- Lie JT. Nomenclature and classification of vasculitis: plus ça change, plus c'est la même chose. *Arthritis Rheum* 1994;37:181-6.
- Somer T, Finegold SM. Vasculitides associated with infections, immunization and antimicrobial drugs. *Clin Infect Dis* 1995;20:1010-36.
- Guillevin L, Lhote F, Cohen P, et al. Polyarteritis nodosa related to hepatitis B virus. A prospective study with long-term observation of 41 patients. *Medicine (Baltimore)* 1995;74:238-53.
- Lhote F, Guillevin L. Polyarteritis nodosa, microscopic polyangiitis, and Churg-Strauss syndrome. Clinical aspects and treatment. *Rheum Dis Clin North Am* 1995;21:911-47.
- Lauer GM, Walker BD. Hepatitis C virus infection. *N Engl J Med* 2001;345:41-53.
- Ferri C, Greco F, Longobardo G, et al. Antibodies to hepatitis C virus in patients with mixed cryoglobulinemia. *Arthritis Rheum* 1991;34:1606-10.
- Misiani R, Bellavita P, Fenili D, et al. Hepatitis C virus infection in patients with essential mixed cryoglobulinemia. *Ann Intern Med* 1992;117:574-7.
- Cacoub P, Lunel-Fabiani F, Musset L, et al. Mixed cryoglobulinemia and hepatitis C virus. *Am J Med* 1994;96:124-32.
- Agnello V. The etiology and pathophysiology of mixed cryoglobulinemia secondary to hepatitis C virus infection. *Springer Semin Immunopathol* 1997;19:111-29.
- Cacoub P, Renou C, Rosenthal E, et al. Extrahepatic manifestations associated with hepatitis C virus infection: a prospective multicenter study of 321 patients. The GERMIVIC. Groupe d'Etude et de Recherche en Médecine Interne et Maladies Infectieuses sur le Virus de l'Hépatite C. *Medicine (Baltimore)* 2000;79:47-56.
- Cacoub P, Poynard T, Ghillani P, et al. Extrahepatic manifestations of chronic hepatitis C. MULTIVIRC Group. *Multidepartment Virus C. Arthritis Rheum* 1999;42:2204-12.
- Brouet JC, Clauvel JP, Danon F, Klein M, Seligmann M. Biologic and clinical significance of cryoglobulins. A report of 86 cases. *Am J Med* 1974;57:775-88.
- De Vita S, De Re V, Gasparotto D, et al. Oligoclonal non-neoplastic B cell expansion is the key feature of type II mixed cryoglobulinemia: clinical and molecular findings do not support a bone marrow pathologic diagnosis of indolent B cell lymphoma. *Arthritis Rheum* 2000;43:94-102.
- Gorevic PD, Kassab HJ, Levo Y, et al. Mixed cryoglobulinemia: clinical aspects and long-term follow-up of 40 patients. *Am J Med* 1980;69:287-308.
- Agnello V, Chung RT, Kaplan LM. A role for hepatitis C virus infection in type II cryoglobulinemia. *N Engl J Med* 1992;327:1490-5.
- De Re V, De Vita S, Marzotto A, et al. Sequence analysis of the immunoglobulin antigen receptor of hepatitis C virus-associated non-Hodgkin lymphomas suggests that the malignant cells are derived from the rheumatoid factor-producing cells that occur mainly in type II cryoglobulinemia. *Blood* 2000;96:3578-84.
- Misiani R, Bellavita P, Fenili D, et al. Interferon alpha-2a therapy in cryoglobulinemia associated with hepatitis C virus. *N Engl J Med* 1994;330:751-6.
- Ferri C, Marzo E, Longobardo G, et al. Interferon-alpha in mixed cryoglobulinemia patients: a randomized, crossover-controlled trial. *Blood* 1993;81:1132-6.
- Casato M, Agnello V, Pucillo LP, et al. Predictors of long-term response to high-dose interferon therapy in type II cryoglobulinemia associated with hepatitis C virus. *Blood* 1997;90:3865-73.
- Dammaco F, Sansonno D, Han JH, et al. Natural interferon-alpha versus its combination with 6-methyl-prednisolone in the therapy of type II mixed cryoglobulinemia: a long-term, randomized, controlled study. *Blood* 1994;84:3336-43.
- Neuman AU, Lam NP, Dahari H, et al. Hepatitis C viral dynamics in vivo and the antiviral efficacy of interferon alpha therapy. *Science* 1998;282:103-7.
- Poynard T, Marcellin P, Lee SS, et al. Randomised trial of interferon alpha 2b plus ribavirin for 48 weeks or for 24 weeks versus interferon alpha 2b plus placebo for 48 weeks for treatment of chronic hepatitis C. *Lancet* 1998;352:1426-32.

Personal non-commercial use only. The Journal of Rheumatology Copyright © 2005. All rights reserved.

26. Manns MP, McHutchison JG, Gordon SC, et al. Peginterferon alfa-2b plus ribavirin compared with interferon alfa-2b plus ribavirin for initial treatment of chronic hepatitis C: a randomised trial. *Lancet* 2001;358:958-65.
27. Zuckerman E, Keren D, Slobodin G, et al. Treatment of refractory, symptomatic, hepatitis C virus related mixed cryoglobulinemia with ribavirin and interferon- α . *J Rheumatol* 2000;27:2172-8.
28. Naarendorp M, Kalleymuchikkal U, Nuovo GJ, Gorevic PD. Longterm efficacy of interferon- α for extrahepatic disease associated with hepatitis C virus infection. *J Rheumatol* 2001;28:2466-73.
29. Cacoub P, Lidove O, Maisonnobe T, et al. Interferon alpha and ribavirin treatment in patients with hepatitis C virus-related systemic vasculitis. *Arthritis Rheum* 2002;46:3317-26.
30. Cacoub P, Saadoun D, Limal N, Sene D, Lidove O, Piette JC. PEGylated interferon alfa-2b and ribavirin treatment in patients with hepatitis C virus-related systemic vasculitis. *Arthritis Rheum* 2005;52:911-5.
31. Alric L, Plaisier E, Thebault S, et al. Influence of antiviral therapy in hepatitis C virus-associated cryoglobulinemic MPGN. *Am J Kidney Dis* 2004;43:617-23.
32. Martins Junior EV, Gaburri AK, Gaburri PD, Chebli JM. Cutaneous vasculitis with undetectable cryoglobulinemia in chronic hepatitis C. *J Gastroenterol Hepatol* 2004;19:1220-1.
33. Levine JW, Gota C, Fessler B, Cooper SM, Calabrese L. Persistent cryoglobulinemic vasculitis following successful HCV eradication [abstract]. *Arthritis Rheum* 2004;50:S125.
34. Kimyai-Asadi A, Gohar K, Kang P, Usman A, Zenenberg R, Jih MH. Mixed cryoglobulinemia secondary to interferon therapy for hepatitis C: case report & review of the literature. *J Drugs Dermatol* 2002;1:72-5.
35. Hausfater P, Cacoub P, Assogba U, Lebon P, Piette JC. Plasma exchange and interferon-alpha pharmacokinetics in patients with hepatitis C virus-associated systemic vasculitis. *Nephron* 2002;91:627-30.
36. Zoulim F, Haem J, Ahmed SS, et al. Ribavirin monotherapy in patients with chronic hepatitis C: a retrospective study of 95 patients. *J Viral Hepat* 1998;5:193-8.
37. Durand JM, Cacoub P, Lunel-Fabiani F, et al. Ribavirin in hepatitis C related cryoglobulinemia. *J Rheumatol* 1998;25:1115-7.
38. Kaplanski G, Marin A, Maisonnobe T, et al. Increased soluble p55 and p75 tumour necrosis factor- α receptors in patients with hepatitis C associated mixed cryoglobulinaemia. *Clin Exp Immunol* 2002;127:123-30.
39. Sansonno D, De Re V, Lauletta G, Tucci AF, Boiocchi M, Dammacco F. Monoclonal antibody treatment of mixed cryoglobulinemia resistant to interferon-alpha with an anti-CD20. *Blood* 2003;101:3818-26.
40. Zaja F, De Vita S, Mazzaro C, et al. Efficacy and safety of rituximab in type II mixed cryoglobulinemia. *Blood* 2003;101:3827-34.
41. Dammacco F, Sansonno D, Piccoli C, Tucci FA, Racanelli V. The cryoglobulins: an overview. *Eur J Clin Invest* 2001;31:628-38.
42. Roccatello D, Baldovino S, Rossi D, et al. Long-term effects of anti-CD20 monoclonal antibody treatment of cryoglobulinaemic glomerulonephritis. *Nephrol Dial Transplant* 2004;19:3054-61.
43. Fois E, Guimard Y, Sene D, et al. Rechute des vascularites systémiques liées au virus de l'hépatite C, sans rechute virologique: se méfier du lymphome. *Rev Med Interne* 2003;24:93s.
44. Saadoun D, Suarez F, Lefrere F, et al. Splenic lymphoma with villous lymphocytes, associated with type II cryoglobulinemia and HCV infection: a new entity? *Blood* 2005;105:74-6.
45. Lerat H, Hollinger FB. Hepatitis C virus (HCV) occult infection or occult HCV RNA detection? *J Infect Dis* 2004;189:3-6.
46. Cacoub P, Maisonnobe T, Thibault V, et al. Systemic vasculitis in patients with hepatitis C. *J Rheumatol* 2001;28:109-18.
47. Lidove O, Cacoub P, Hausfater P, et al. Cryoglobulinémie et hépatite C: aggravation de la neuropathie périphérique après prise d'interféron alpha. *Gastroentérol Clin Biol* 1999;23:403-6.
48. Rutkove SB. An unusual axonal polyneuropathy induced by low-dose interferon alfa-2a. *Arch Neurol* 1997;54:907-8.
49. Cid MC, Hernandez-Rodriguez J, Robert J, et al. Interferon-alpha may exacerbate cryoglobulinemia-related ischemic manifestations: an adverse effect potentially related to its anti-angiogenic activity. *Arthritis Rheum* 1999;42:1051-5.