Review

How HCV has changed the approach to mixed cryoglobulinemia

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ABSTRACT

Mixed cryoglobulinemia is a systemic disease due to a small vessel immune-complex mediated vasculitis. The discovery of a viral origin of the disease has launched a great expectancy among researchers and the years after this finding have been characterized by the effort to reach viral eradication in the hope of obtaining disease remission. Moreover, the use of immunosuppressives has been discouraged for many years as they could favour viral replication, and HCV infection has represented a contraindication to the more recent biological drugs directed against cytokines. The trials with antiviral agents in this disorder, however, has not met the expectations, especially when challenged with some of the most severe complications of the disease; moreover, these medications were not devoid of unexpected side effects, such as the occurrence of peripheral neuropathies. Since lymphoproliferation is one of the features of the disease, this has focused the attention of investigators on the potential benefit of newly targeted therapies specifically directed against B-lymphocytes (such as rituximab). Preliminary results on the use of these medications are promising. Furthermore, the use of biological agents in small open trials in HCV positive arthritis patients has demonstrated an acceptable safety profile.

All these empirical observations should probably induce the scientific community to reconsider the therapeutical approach to HCV-related mixed cryoglobulinemia. Indeed, the use of aggressive chemotherapy treatments in the era preceding HCV discovery has not been associated with significant liver toxicities and standard chemotherapy during HCV-related lymphoma carried out a unexpected low rate of severe liver damage. Future efforts should probably focus on the potential benefit of a multi-step, combined anti-viral and cytotoxic therapy (both with standard regimens and new medications).

Introduction

Mixed cryoglobulinemia is a systemic disease due to a small vessel immune-complex mediated vasculitis. It is now clear that this clinical entity is a crossroads between autoimmune and lymphoproliferative disorders.

Hepatitis C virus plays a central role in the pathogenesis of this disorder, based on a number of empirical observations such as the high prevalence of HCV antibodies and genome in the serum of MC patients, the high concentration of viral particles in the cryoglobulins, the immuno-histochemical localization of HVC or its markers in peripheral blood mononuclear cells (PBMC) and in tissue samples (1-3).

The host immune response against HCV virus is not always protective against infection; indeed viral clearance is not associated with an immunization against re-infection. Immune response in chronic HCV carriers seems to exert a selective pressure on the virus, favouring the emergence of viral strains more prone to escape from it. In particular, a substantial divergence between humoral and cell mediated response to the virus has been unveiled; humoral response is responsible for extra-hepatic manifestations and seems to be of no effect in controlling the infection. Cell-mediated immune response has greater importance in the production of anti-viral cytokines but seems to have a role also in cytotoxic damage. Furthermore, lymphocytes, analogous to HIV infection, could represent a natural reservoir for the virus, favouring its persistence. Finally, the disease is generally associated with a lymphoproliferative disorder, often evolving into a frank lymphoma (4).

In this review we will critically discuss the risk/benefits of the management of

a virus triggered disorder such as mixed cryoglobulinemia.

Management of HCV before the discovery of HCV

In the era preceding the discovery of HCV, mixed cryoglobulinemia was viewed as a typical immune-complex mediated disorder and treated accordingly. In view of this model, the treatment was based on a more or less aggressive immunosuppressive regimen tailored to the severity of the disease and the type of organ involvement (Fig. 1). Aggressive therapies, such as plasma exchange, were used exclusively in cases of life-threatening or disabling conditions. Plasma exchange, with or without immunosuppressive drugs, has been successfully employed to treat rapidly progressive glomerulonephritis, motor neuropathy and hyperviscosity syndrome. Double filtration plasmapheresis was demonstrated to be as effective as conventional apheresis reducing the need for the substitution of proteins and fluids (5).

Discovery of HCV: antiviral therapy

After the discovery of the viral aetiology of the disease, a therapeutic revolution took place. On the one hand, immunosuppression was viewed with caution or discouraged, based on the assumption that it could exacerbate viral replication. On the other hand, all the attention was concentrated on the possibility of eradicating the virus as a way to cure the disease (1-3, 6-11). Soon after the discovery of the association with HCV infection (12-13) in 1993, we undertook a randomized cross-over trial with interferon alpha in MC patients. Despite a beneficial effect on purpura and on a number of serological tests (such as transaminases, cryocrit, CD4/CD8 ratio) the result was transient and relapsed after the cessation of therapy (14). Subsequently, from 1993 until now, a number of clinical trials have been conducted to verify the effect of increasingly aggressive antiviral therapy to eradicate the virus. Table I resumes the main trials with interferon in MC patients (14-20). The eradication rate and the efficacy of the treatment were higher with the addition of ribavirin (Table II) and the use of differing doses and administration schedules (21-25). However, only selected manifestations could take advantage of antiviral treatment and a growing number of reports point out a worsening or the appearance of new manifestations after discontinuation of treatment or persistently active vasculitis despite complete viral eradication (26-27). Some disease manifestations (such as involvement of the peripheral nervous system) could also worsen during antiviral treatment (28).

Current management of HCV infection is scheduled according to the genotype and to the initial response after a period of treatment. The mainstay of treatment is usually the combination of interferon and ribavirin. In Genotype 1 and 4 usually antiviral treatment is decided on the basis of the presence of detectable HCV RNA and the severity of liver disease. The treatment is prolonged up

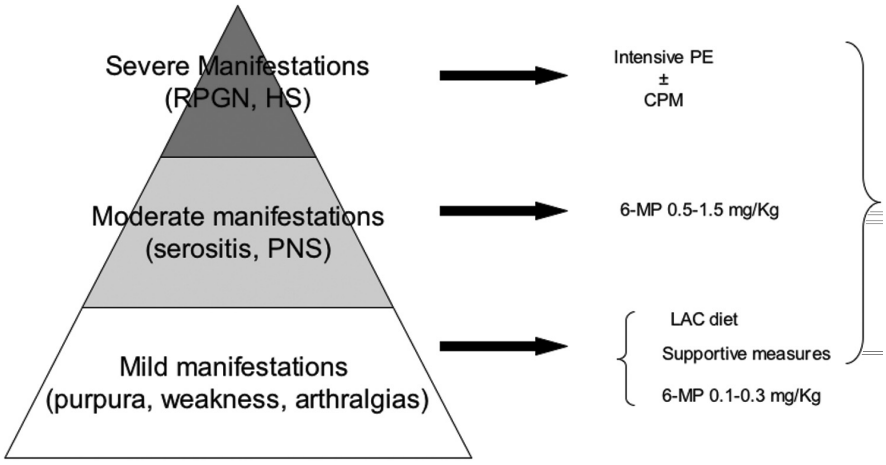

Fig. 1. Management of mixed cryoglobulinemia before HCV discovery.
Legend to the figure: RPGN: rapidly progressive glomerulonephritis; HS: hyperviscosity syndrome; PNS: peripheral nervous system involvement.

Table I. Trials with alpha interferon in mixed cryoglobulinemia.

Study	Type of study	N° pt	Response %	Follow-up
Ferri C *et al,* 1993 (14)	randomized	26	*PR 77	100% relapses after discontinuation
Misiani R *et al,* 1994 (15)	randomized	53	60	100% relapses after discontinuation
Dammacco F *et al,* 1994 (16)	randomized	65	CR + **PR 67-70	Relapse within 3 m: 100% PDN alone, 70% IFN alone
Cohen T *et al,* 1996 (17)	Prospective, open	20	CR + PR 60	92% clinical relapses after < 12 m
Casato M *et al,* 1997 (18)	Prospective, open	31	CR 61 MR 38	Relapse depending on IFN cumulative dose; response median duration: 35.9 m; CCR in 3 pts for > 5 years
Mazzaro C *et al,* 1997 (19)	Prospective, open	42	CR 31 PR 55 °MR 14	6 pt in remission after 12 m from discontinuation
Mazzaro C *et al,*2000 (20)	randomized	7	Complete or partial remission of GN	100% relapses after discontinuation

*CR: complete remission; **PR: partial remission; °MR: minor response.

Table II. Trials with alpha interferon-ribavirin in mixed cryoglobulinemia.

Study	Type of study	N° pt	Response %	Follow-up
Calleja JL *et al*. 1999 (21)	Prospective, open	36	*PR 100%	Relapse in 25%
Sabry AA, 2002 (22)	Prospective, open	20	**CR 89%	–
Mazzaro C *et al*. 2005 (23)	Prospective, open	18	CR + PR 100%	44% relapses after discontinuation
Cacoub P *et al*. 2005 (24)	Prospective, open	9	CR + PR 100%	1/9 relapse after discontinuation
Saadoun D *et al*. 2006 (25)	Retrospective single centre	72	CR 62	PEG IFN + ribavirin higher sustained response Early virological response, absence of renal failure = clinical response

**CR: complete remission; *PR: partial remission.

to 48 weeks. The rate of eradication reaches 45-52%. In genotype 2 and 3 the treatment period is generally of 24 weeks and is based on the HCV RNA independently of the severity of liver involvement, since the eradication rate is higher (75-90%) (29). Figure 2 shows the prevalence of HCV genotypes in a series of 90 MC patients of our unit. Despite previous reports showing a higher prevalence of 2a/2c, the most frequent genotype in our series is 1b, followed by 2a/2c and then by other genotypes. About 30% of our patients undergo antiviral treatment.

Although antiviral therapy has been increasingly employed in mixed cryoglobulinemia patients and a number of evidences suggested a favourable effect on viral load paralleling the outcome of some manifestations, such as skin and kidney involvement or lymphoproliferation, a number of shortcomings emerged with the extensive use of these medications. Furthermore, it should be reminded that particularly alpha interferon owns the potential of exacerbating vascular and autoimmune manifestations of the disease, given its antiangiogenetic and autoimmune "triggering" properties and therefore might be contraindicated in the presence of severe or life threatening manifestations (30-31).

So, the question arises whether and how an immunosuppression is still possible in a virus-induced autoimmune disease.

Immunosuppression in HCV

What we have learned from mixed cryoglobulinemia

After a careful review of aggressive chemotherapy treatments in the era preceding HCV discovery, we were surprised to realize that, in spite of the high prevalence of liver involvement in mixed cryoglobulinemia patients (32-33), a significant liver toxicity was rarely recorded. On the other hand, based on the presence of a smouldering lymphoproliferative process, newer therapeutic strategies with the employment of anti-CD20, rituximab, have been investigated and a number of data indicate that this medication could prove useful in the treatment of life threatening or disabling manifestations of the disease, without any significant harm (34-35). Recently, a protocol combining antiviral treatment and anti CD20 has been proposed (36).

But, more indirect evidence that an appropriate immunosuppression is not necessarily harmful in mixed cryoglobulinemia may be confirmed by the experience collected in other HCV-related conditions.

What we have learned from lymphoma

HCV infection carries an increased risk of developing a lymphoma. HCV-associated lymphomas represent a variety of histological sub-types, most frequently non-Hodgkin's B cell lymphomas (37). Some of these appear to be highly responsive to anti-viral therapy, providing clinical evidence for a pathogenetic association (38-39).

However, the overwhelming majority of MC patients bear a benign monoclonal component (IgMk) that only in a minority of cases could evolve into a frank lymphoma. The management of HCV positive lymphoma poses the problem of the possibility of favouring viral progression and eventually of affecting the overall outcome of the disease (40).

Data concerning liver toxicity during chemotherapy in HCV positive lymphoma have been controversial, largely for the small number of studies undertaken and for the shortcomings in the study design. Seven to thirty percent of patients with lymphoma, however, may experience HCV-related hepatotoxicity secondary to chemotherapy, which, in turn, can carry a mortality rate as high as 20-45%. Factors linked to liver toxicity might be the distribution of HCV genotypes (1b versus other genotypes),

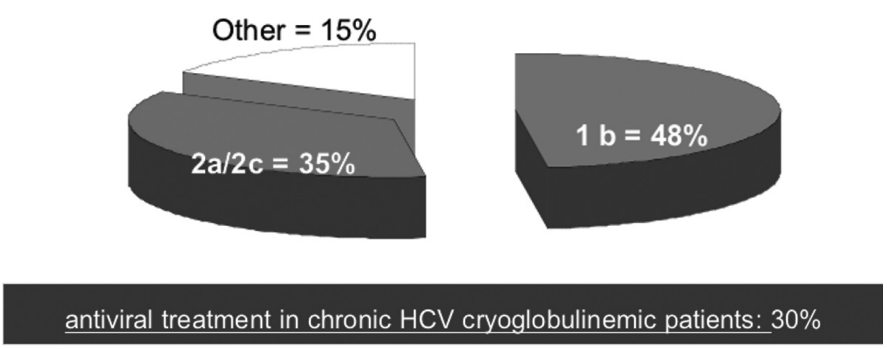

Fig. 2. Viral genotypes in our series of 90 MC patients.

baseline HCV loads, HBV co-infection, patients characteristics (presence of active hepatitis) and chemotherapy regimens (in particular, use of corticosteroids and combination with rituximab). In addition, the use of chemotherapy may generate long term risk of progressive liver damage, favouring the appearance of liver cirrhosis (41).

The largest experiences regarding the treatment of HCV positive lymphoma patients in recent years concern 2 multicentre studies that carry opposing conclusions (42-43).

In the first one, employing intensive regimens, the occurrence of liver toxicity was high (65% of the patients, of which 46 % of the cases were severe), although liver damage was not related to liver impairment prior to chemotherapy, nor to the type of regimen employed (42).

In the second study, standard regimens were employed and the frequency of liver toxicity was low as compared to the former, being comparable to the frequency of liver damage in patients without HCV infection (43).

In conclusion, standard regimens with cyclic chemotherapy including cyclophosphamide do not seem to worsen liver function, even in the absence of antiviral therapy. However, although less frequent than in HBV infection, these complications occur in a subset of patients with mortality rates up to 45%. Therefore, baseline screening for HBV and HCV before initiation of chemotherapy is crucial. High-risk patients having chronic active hepatitis, high baseline HCV viral load, HBV co-infection and receiving cytotoxic drugs, corticosteroids and rituximab (particularly if combined) should be closely monitored for serum transaminases, bilirubin and HCV RNA levels (41).

What we have learned from rheumatoid arthritis

The prevalence of HCV among rheumatoid arthritis is as high as in the general population (up to 20% in areas of higher prevalence such as in southern Italy) (44). Since the prevalence of this disease is relatively high (0.5-1%), it can be estimated that a significant proportion of RA patients have a concomitant HCV infection (45). Moreover, a number of HCV positive patients may develop a chronic polyarticular disease that can be difficult to distinguish from rheumatoid arthritis. Recently, anti cyclic citrullinated peptide antibodies have emerged as a valid aid in the differential diagnosis between HCV-related arthritis and true rheumatoid arthritis with concomitant HCV infection (46).

The treatment of rheumatoid arthritis, particularly in more severe cases, embraces the use of immunosuppressive drugs, including the more recent biologics and corticosteroids. While the use of some medications have proven safe and effective in HCV positive patients in small open trials, such as cyclosporine-A (47), other medications are contraindicated for the potential risk of liver toxicity. However, therapy of up to one year with methotrexate does not necessarily result in liver cirrhosis and this drug is currently used in clinical practice (48-49).

The use of corticosteroids has been for a long time refrained in HCV (50), for the risk of progression of liver damage. However, recent data on liver transplant have contradicted earlier reports (51-53). The safer approach would be to use the minimal dose effective to control the symptoms and to rapidly taper this medication as soon as the clinical goal is obtained.

Data regarding anti-TNF show that these medications can be used safely in chronic HCV positive rheumatoid patients (54).

As regards antimalarials, no definitive conclusion can be drawn, as conflicting results have been reported on the effect of these medications on liver toxicity in HCV positive patients (48).

What we have learned from liver transplantation

HCV-related liver cirrhosis is the most common indication for orthotopic liver transplantation (OLT) in the United States and most European countries (55). Post-transplantation recurrence of hepatitis C virus infection is almost universal phenomenon, with a heterogeneous clinical course. Factors associated more consistently with recurrence are donor and recipient age, viral genotype 1, levels of viraemia before and after transplantation, graft ischemia, the use of anti thymocyte globulin and higher doses of corticosteroids (50-53, 56-61). Therapeutic strategies to minimize HCV recurrence can be utilized in the pre-, peri- or post-transplantation setting (61). Antiviral therapy using interferon and ribavirin and modifying immunosuppression are the main strategies to prevent progressive disease. The efficacy of interferon/ribavirin is blunted by frequent side effects and poor tolerance; current sustained virological response rate range from 20 to 30% (60-61). Furthermore, up to 87.5% of patients require reduction in dosage and up to 42.9% of patients require cessation of treatment because of adverse effects or because of the patient's choice to stop treatment. Considering the lack of clinical benefit and the frequent adverse effects, there is currently no evidence to recommend antiviral treatment for recurrent liver graft infection with HCV (62). Although immunosuppression has been thought to play an important role in the HCV recurrence after OLT, no definitive conclusion can be drawn. For example, initial reports have recommended an early withdrawal of steroids in order to improve prognosis (50), while more recent results on steroid withdrawal have contradicted earlier results (51-53). Published reports on the effect of mycophenolate have also been conflicting, with some suggesting a favourable impact (63-64), and others suggesting no impact or adverse effect (65-66). Among calcineurin inhibitors, there is no clear-cut difference between cyclosporine and tacrolimus in their effect on HCV (63).

A very large multicentre prospective controlled study of tacrolimus, mycophenolate mofetil and daclizumab used in combination to prevent or minimize the use of corticosteroids has recently been published. No noticeable differences in HCV recurrence were observed in the different immunosuppressive regimens. Multivariate analysis identified acute rejection and donor age as significant risk factors for HCV recurrence (67).

HCV and selected medications

HCV and corticosteroids

Most of the studies regarding the use of corticosteroids in HCV carriers come from experience in liver transplants (50-53, 68-71). Corticosteroids have a number of actions on the immune/inflammatory system and also a wide array of untoward effects on mineral metabolism and endocrine system. Early reports on the use of corticosteroids on HCV replication *in vivo* and *in vitro* have claimed an increased replication of the virus as a direct effect of these medications (68), whereas more recent reports have contradicted this hypothesis and more likely point to a downregulation of the immune system with subsequent increase of viral load (69). These findings indicated that the avoidance of high cumulative dosage of corticosteroids could be beneficial, although the experience with completely steroid-free immunosuppression is still limited (70). A number of data indicate that the rapidity of tapering, in addition to steroid duration, may have an impact on outcome (51, 71).

Overall, these data suggest making a parsimonious use of steroids, using the lower dosage tailored at controlling the target symptom, and to slowly taper these medications as soon as clinical remission is gained (to avoid a rapid restoration of the immune system).

HCV and immunosuppressives

Table III shows the rational basis, the potential benefits and contraindication to the use of some immunosuppressive medications in chronic HCV carriers.

Leflunomide acts mainly through the inhibition of T lymphocytes clonal expansion. Moreover, it also has anti-inflammatory properties, mainly those of inhibiting selected tyrosine kinases. Leflunomide analogue FK 778 has shown vasculoprotective effect in animal models (72-73). Moreover, active metabolites of leflunomide attenuate inflammatory hepatocyte injury by inhibiting Kupfer cells (74). This medication has been used to maintain remission in WG and as a steroid sparing steroid agent in moderately active SLE (75-76). On the contrary, this drug might be contraindicated for GI adverse events (in particular liver function tests) and for the description of cases of leflunomide induced necrotizing vasculitis (77-78).

As regards cyclosporine-A, numerous studies have shown an *in vitro* and *in vivo* inhibition of HCV replication (47, 79-80).

This medication exerts its immunosuppressive effect mainly through calcineurin mediated inhibition of IL-2, while the antiviral effect seems to be mediated by cyclophilin B (47, 80). However, during treatment with Cy-A, vasospastic effect on macro and microcirculation, increased blood viscosity, impairment of red blood cell deformability and increased platelet aggregation have been described, all potentially detrimental to vascular manifestations (81).

Mycophenolate mofetil and, more importantly, azatioprine, can show ribavirin-like effects on HCV replication *in vitro* (82). Moreover, mycophenolate

Table III. Rationale, potential benefit and contraindication to the use of immune-suppressives in chronic HCV infection.

Medication	PROS.	CONS.
Corticosteroids	*Rationale:* Inhibition of the inflammatory cascade through NF KB Effect on mineral metabolism and endocrine system	Direct or indirect ↑ of HCV viral replication *in vivo* and *in vitro*
Leflunomide	*Rationale:* Injibition of T lymphocytes clonal expansion Antiinflammatory properties Inhibition of selected tyrosine kinases Leflunomide analogue FK 778 vasculoprotective in animal models	Leflunomide induced necrotizing vasculitis GI adverse events (liver toxicity)
Cyclosporine-A	*Rationale:* Inhibition of IL2 and other proinflammatory cytokines Inhibition of HCV replication *in vitro* and *in vivo*	Vasospastic effect on macro and microcirculation, ↑ blood viscosity, ↓ red blood cell deformability, ↑ PLT aggregation → worsening of vascular manifestations Nephrotoxicity, hyprertension, neurotoxicity
Mycophenolate mofetil/Azathiopine	*Rationale:* Inhibition of T and B lymphocyte clonal expansion Ribavirin like action *in vitro* Prevention of arterial smooth muscle cell proliferation and proliferative arteriopathy in animal models	GI adverse events (liver toxicity)
Anti-TNF	*Rationale:* Inhibition of TNF-α Antiinflammatory activity TNFα implicated in refractoriness to IFN Failure of Etanercept in WG	↑ B cell (CD 19, CD20+) number and activity in the peripheral blood Autoantibodies (ANA, anti-DNA) SLE like syndromes
Anti-CD20	*Rationale:* Inhibition of B cells Effective targeting of autoreactive clones	↑ HCV RNA Possible progression of HCV infection

has shown a preventive effect on arterial smooth muscle cell proliferation and proliferative arteriopathy in animal models (83).
The former have been used as an alternative to cyclophosphamide in vasculitis either primary or secondary to autoimmune disorders, such as SLE (84). The latter is widely used to treat milder manifestations in connective tissue diseases and primary systemic vasculitides (such as arthritis, cutaneous involvement, cytopenias, serositis) and as maintenance treatment after induction regimens with cyclophosphamide (85-86).

HCV hepatitis and anti-TNF
Hepatitis C virus is widespread and it is estimated that it infects about 200 million people worldwide (87). There is a growing body of evidence supporting the hypothesis that TNF may be involved in the pathogenesis of hepatocyte destruction in chronic hepatitis C. HCV subjects have high TNF levels as compared to controls and there is a correlation between elevated levels of anti-TNF and serum alanine aminotransferase (ALT). Moreover, TNF has been implicated to refractoriness to antiviral treatment in HCV subjects and persistence of this cytokine despite viral eradication has been linked to relapse (47, 88). There have been several reports of HCV positive subjects who were treated with etanercept or infliximab for a variety of disease states such as rheumatoid arthritis, Crohn's disease and psoriatic arthritis. The dosage of etanercept used was 25 mg subcutaneously twice weekly in all cases, except for several case reports with psoriatic arthritis where the dose was titrated up to 50 mg subcutaneously twice weekly. The dosage of infliximab used varied from 3 to 5 mg/kg, either given once or given at weeks 0, 2 and 6 and then at 8-week intervals. In summary, there were no flares of chronic HCV after the start of treatment with infliximab or etanercept, as documented by stable liver function tests and/or stable HCV viral load (54). A published prospective analysis evaluated eight patients with RA and chronic HCV who were treated with etanercept 25 mg subcutaneously twice weekly. The patients were followed for 4 months, and there were no statistically significant changes in serum aminotransferases or mean viral load. Interestingly, the viral load decreased in seven of the eight patients while taking etanercept, but the difference did not achieve statistical significance (89).
A phase II randomized, double-blind, placebo controlled study evaluated etanercept for the treatment of chronic HCV. Fifty patients with chronic HCV were randomized to receive interferon, ribavirin and placebo or interferon, ribavirin and etanercept (25 mg subcutaneously twice weekly). The author found a higher frequency of disappearance of HCV RNA at 24 weeks in the etanercept group (63%) compared with the placebo group (32%) ($p<0.04$). In addition, more patients in the etanercept arm had ALT normalization and no detectable HCV RNA at 24 weeks when compared to placebo (58% with etanercept vs 28% with placebo, $p<0.04$) (90).
Since TNF alpha have been implicated in chronicization of HCV infection (see above), it might be indicated for the treatment of systemic manifestations of mixed cryoglobulinemia (49, 65-66). Anti TNF medications have been used for the treatment of refractory ANCA-associated vasculitides, Behçet's disease, Takayasu arteritis and systemic lupus erythematosus (91-92). On the other hand, in patients undergoing treatment with these medications, an increase in the number and activity of B cells (CD19 and CD20) (93) has been claimed and a number of vasculitides and SLE-like syndromes have been reported (Table III) (94).

HCV and anti CD-20
The most important pathogenetic aspects of HCV-related mixed cryoglobulinemia are related to the deposition of HCV-containing immune-complexed in the target organs, the chronic stimulation of the immune system by HCV infection, sustaining the production of IgM rheumatoid factors and, eventually, a smouldering low grade lymphoproliferative process (1-3). Based on these observations a strong rationale for the use of anti CD-20 monoclonal antibodies has been advocated beginning in 2002 (95). A number of uncontrolled series or case reports have been published to date (34-35, 96-99). The main indications for rituximab therapy were non-responsiveness or intolerance to previous treatments, associated lymphoma or first line therapy for cryoglobulinemic vasculitis. Most of the patients received four weekly intravenous infusions of 375 mg/m^2 (100).
A number of clinical variables showed a favourable outcome after this therapy, such as cutaneous involvement (purpura, skin ulcers), weakness, arthralgias, fever, peripheral neuropathy, kidney involvement. This phenomenon was mirrored by a reduction of ESR, cryocrit, IgM rheumatoid factor and an increase of complement levels as well as restoration of many of the disturbances in B and T-lymphocyte homeostasis (34, 36, 95, 99). Moreover, in a number of subjects, the bone marrow smouldering lymphoproliferative process typical of the disease reverted to normal (95).
Of notice, the use of this medication appeared safe and well tolerated also in patients with decompensated liver cirrhosis. In these cases improvement of liver protidosynthetic activity, increased prothrombin time, impressive reduction or disappearance of ascites and encephalopathy were also observed, in spite of some increase in HCV viral titers or in ALT values (101).
Even if rituximab is well-tolerated, without significant liver toxicity, a number of reports claimed an inconstant increase of HCV RNA after its administration (34, 95-98). Enhancing viremia after this treatment is a potential harmful outcome, although no significant variation of liver transaminases or deterioration of liver disease were noticed in any of the series so far published (95-98, 100). To reduce the potential harm of these increases in HCV RNA titers, a combined approach with Peg-Interferon-ribavirin in refractory HCV positive MC cases has been suggested (36).

HCV and mixed cryoglobulinemia: conclusive remarks
All of the data discussed so far have clearly shown that viral eradication has

not necessarily represented the final answer for all of the manifestations of mixed cryoglobulinemia. Effective immunosuppression is still necessary to control potentially life threatening or disabling manifestations of the disease (such as widespread vasculitis, rapidly progressive glomerulonephritis, hyperviscosity syndrome, motor neuropathy). On the other hand, the experience before the discovery of HCV, the use of a variety of immunosuppressive regimens in other HCV-associated diseases and a more precise knowledge of the biology of the virus and of the mechanism of action of drugs, clearly demonstrated that an effective immunosuppression can be administered without potentially noxious adverse events. The growing knowledge of HCV and its interactions with the host may help to design clinical trials that combine viral eradication with modulation of the immune system and the inflammatory cascade. Mixed cryoglobulinemia in that respect may represent an ideal model for the study of an effective immunosuppression in a virus induced autoimmune disease.

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