

Therapy of HCV-Related Renal Disease

Giuseppe D'Amico, MD, FRCP



[Print this page](#)

Even though the association between HCV infection and membrano-proliferative GN, in the absence of complicating cryoglobulinemia, has been described some years ago in the USA, the majority of investigators throughout the world agree that the most frequent renal complication in patients with this infection is cryoglobulinemic GN, that occurs when a symptomatic mixed cryoglobulinemia (MC) has been induced by the virus. This glomerulonephritis, usually a membrano-proliferative GN with characterizing morphological features, complicates HCV-related mixed cryoglobulinemia almost exclusively when a monoclonal IgM rheumatoid factor is produced by the abnormal proliferation of a clone of B cells (type II mixed cryoglobulinemia): it is hypothesized that this monoclonal component of circulating cryoglobulins, usually an Ig Mk, deposits in the glomerulus due to a particular affinity for the glomerular matrix, and is the major cause of the glomerular damage, even more than the immunocomplexes which form from circulating immunoglobulins and viral antigens. It has been also hypothesized that the abnormal proliferation of B lymphocytes that leads to type II MC is due to replication of the virus in these cells. Therefore, an effective antiviral therapy in patients with HCV infection, type II MC, and glomerulonephritis, which blocks viral replication in the circulation and in the tissues, could block also the production of cryoglobulins and their intrarenal deposition.

Unfortunately, however, the available antiviral therapy is not effective in all patients. Interferon alfa (IFNa) gives a sustained virological response (defined as undetectable serum HCV-RNA levels 6 months after completion of treatment) in no more than 15-20% of patients after an initial 6-12 months course at the standard dose of 3 million units 3 times a week, and only marginally more favorable results after more intensive treatment courses (6-10 million units 3 times a week, or each day for the first 4-6 weeks). The combined treatment of IFNa at the standard dose with another antiviral agent, ribavirin, (1000-1200 mg orally/day) for at least 6 months, increases the sustained virologic response, but this occurs still in no more than 40-45% of patients. A very recent randomized trial using the combination of ribavirin with a new biologically active molecule obtained by addition of polyethylene glycol to interferon (peginterferon alfa-2b), demonstrated a further increase in the sustained virologic response to > 50% of patients. All antiviral agents can produce adverse effects that in at least 10% of patients necessitate discontinuation.

The majority of these studies demonstrated that eradication of virus with any antiviral agent is associated with an improvement or disappearance of the clinical manifestations of mixed cryoglobulinemia, including the renal syndrome, when they are mild and/or in a chronic stage. However, they revealed that antiviral therapy was not always able to prevent the progression of the renal damage in the presence of acute cryoglobulinemic GN and/or renal and systemic vasculitis, and that in this clinical conditions a combination therapy with anti-inflammatory and cytotoxic drugs, and sometimes also plasma exchange, can be necessary.

We, and others, continue to use the association of steroids and cyclophosphamide that had been extensively used before the 1990s, when the tests to detect HCV infection were not yet available and the mixed cryoglobulemia was called "essential". A detrimental effect of these two drugs in increasing viral titers and aggravating hepatic damage is obviously possible, even though we found no consistent retrospective evidence of acute hepatic damage with this combination of drugs in almost 100 treatment courses up to the beginning of 90s, with a few exceptions of reversible, moderately increased ALT levels.

Our current policy, in these acute flare-ups of cryoglobulinemic GN and vasculitis, is to associate to the standard antiviral therapy (IFNa 3 million units a week s.c. for 1 year + Ribavirin 1.0-1.2 g/day orally), steroids (0.75-1.0 g/day of methylprednisolone intravenously for 3 consecutive days, followed by prednisone for 6 months, at the initial dose of 0.5 mg/kg of body weight daily, tapered over a few weeks until small maintenance doses are achieved) and cyclophosphamide (2 mg/kg body weight, for 3-4 months). In the most severe cases, we add also plasmapheresis (exchanges of 3 liters of plasma 3-4 times per week, for 2-3 weeks) to remove acutely the circulating cryoglobulins.

References

1. Johnson RJ, Gretch DR, Couser WG, et al: Hepatitis C virus-associated glomerulonephritis. Effect of α -interferon therapy. *Kidney Int* 1994;46:1700-1704.
2. D'Amico G: Renal involvement in hepatitis C infection: cryoglobulinemic glomerulonephritis. *Kidney Int* 1998;54:650-671.
3. Zuckerman E, Keren D, Slobodin G, et al: Treatment of refractory, symptomatic, hepatitis C virus related mixed cryoglobulinemia with ribavirin and interferon-alpha. *J Rheumatol* 2000;27:2172-2178.
4. D'Amico G, Fornasieri A: Cryoglobulinemia. In: Brady HR and Wilcox CS (eds): *Therapy in Nephrology and Hypertension* (2nd Edition). Sanders Co., Philadelphia (in press).