Prevalence of microalbuminuria in HCV Patients and Influence of Interferon Therapy

Thesis
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By

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HEPATITIS C AND KIDNEY DISEASE

1. Cryoglobulinemia

Cryoglobulinemia is defined as the presence of immunoglobulins in serum which reversibly precipitate in vitro at low temperatures. Hepatitis C is most commonly associated with mixed Cryoglobulinemia (MC), which can be classified as type II in which the precipitates contain polyclonal IgG and monoclonal IgM with antigammaglobulin (rheumatoid factor activity) or Type III MC in which precipitates are composed of polyclonal IgG and polyclonal IgM ***(Agnello, 2000).***

Up to 90% of patients with cryoglobulinemia have anti-HCV, indicating that the disease is not really essential, but rather related to HCV. Cryoglobulinemia is more common in women than men and typically occurs after decades of HCV infection; Cryoglobulins consist of complexes of rheumatoid factor (RF), IgG, anti-HCV, and HCV virions ***(Agnello et al., 1992).***

The cause of cryoglobulinemia is not well understood; it appears to be due to excessive proliferation of B cells

induced by the chronic antigenic stimulation of HCV infection. Frank symptomatic cryoglobulinemia occurs in 1% or less of patients and usually is associated with high levels of RF and cryoglobulins. In these patients, typical symptoms are fatigue and palpable purpura, which histologically consists of a leukocytoclastic vasculitis (with complexes of anti-HCV and HCV in injured tissue). Typical renal manifestations of cryoglobulinemia include proteinuria and microscopic hematuria with mild to-moderate renal insufficiency, and renal histology revealing membrane-oproliferative glomerulonephritis (MPGN) ***(Johnson et al., 1993).***

2. HCV-Related Glomerular Disease

The principal renal manifestation of HCV infection is MPGN, usually in the context of cryoglobulinemia. HCV is probably the major cause of idiopathic MPGN. The renal disease is rare in children and typically occurs in patients with long-standing infection, often in association with mild subclinical liver disease. Clinically, patients may have symptoms of cryoglobulinemia, including palpable purpura, arthralgias, neuropathy, and weakness. Renal manifestations

include nephrotic or nonnephrotic proteinuria and microscopic hematuria ***(Markowitz et al., 1998).***

Renal insufficiency is frequently mild. Most patients will have anti-HCV, as well as HCV RNA, in serum. Serum aminotransferase levels are elevated in 70% of patients, and the majorities have RF and low levels of complement. Cryoglobulins are detected in 50%–70% of patients. The pathogenesis of the glomerular injury in HCV infection is believed to result from deposition of circulating immune complexes of HCV, anti-HCV, and RF at the site of injury. Renal histology typically shows lobular accentuation of the glomerular tuft with increased mesangial cellularity and matrix, endothelial swelling, splitting of capillary basement membrane and intracapillary accumulations of eosinophilic material representing precipitated immune complexes or cryoglobulins ***(Johnson et al., 1993).***

On electron microscopy (EM), immune complexes are usually subendothelial and may have a finely fibrillar or tactoid pattern. Both subendothelial and mesangial immune complexes can be identified by EM, typically without distinctive substructure. In both forms of HCV associated MPGN, mesangial and capillary wall deposition of IgM, IgG,

and C3 is usually, but not invariably present. Other forms of glomerular injury reported in patients with HCV infection include membranous glomerulonephritis, IgA nephropathy, postinfectious glomerulonephritis, focal and segmental glomerulosclerosis, fibrillary glomerulonephritis, and immunotactoid glomerulopathy. Recurrence of MPGN in renal allografts has been suspected in a small number of patients ***(Baid et al., 2000).***

Treatment of hepatitis C virus-related glomerulonephritis

The mainstay management for HCV-related glomerulonephritis is immunosuppressive therapy (corticosteroids and cytotoxic agents), plasmapheresis and antiviral therapy. The proven beneficial measures for nephroprotection (blood pressure lowering, antiproteinuric and lipid-lowering agents) are applicable in the majority of cases, given that the predominant clinical manifestations of the disease are proteinuria, hypertension and progressive reduction of renal function. Owing to the relationship between HCV infection and the immune response targeting the glomeruli, there are two modern approaches for the therapy of HCV-related glomerulonephritis: (i) antiviral treatment with a combination of standard or pegylated interferon (IFN) with ribavirin

(RBV) without significant side effects in order to achieve sustained viral response (SVR) ***(Perico et al., 2009)*** and (ii) immunosuppressive therapy (including rituximab administration) followed by antiviral treatment, particularly in patients with acute nephritic or nephritic syndrome ***(Fabrizi et al., 2007).***

Generally, the combined therapy with IFN [either in its standard or pegylated (PEG-IFN) form] and RBV aims to reduce the viral load and rituximab aims to reduce B lymphocytes (through its adherence to the CD20 cell surface antigen). Rituximab seems to have better results than classic immunosuppressants, corticosteroids and cyclophosphamide, achieving complete or partial clinical remission in 80–90% of the cases, with skin and renal disease responding better compared with nerve or joint disease. Rituximab affects mainly monoclonal IgM production, cryoglobulin composition and renal immune complex deposition by improving the vasculitic symptoms ***(Cacoub et al., 2008).***

Patients with severe manifestations should be treated more aggressively, not only by immunosuppressive agents but also with plasma exchange therapy for the first 6 months and then after having achieved remission, should start

antiviral treatment ***(Pipitone and Salvarani, 2008).*** Plasmapheresis has a more direct and effective impact on rapidly progressive glomerunephritis involving the central nervous, gastro-intestinal and respiratory system, provided it is combined with immunosuppressive therapy to prevent cryoglobulin redeposition after the session ***(Saadoun et al., 2008).***

Depending on the degree of proteinuria and renal failure, the Kidney Disease: Improving Global Outcomes (KDIGO) ***(KDIGO et al., 2008)*** and the American Association for the Study of Liver Diseases (AASLD) ***(Ghany et al., 2009)*** guidelines are follows: all patients should be treated with angiotensin converting enzyme inhibitor and angiotensin receptor blockers. In patients with cryoglobulinaemia, mild proteinuria and slow progression of renal disease treatment is suggested with IFN (standard or PEG-IFN form) in low doses combined with RBV ***(Lo et al., 2009; Namba et al., 2010).***

In patients with a significant degree of proteinuria and an acute flare of cryoglobulinaemia, rituximab (although its exact dose has not been elucidated yet) or cyclophosphamide with methylprednisolone or plasmapheresis followed by the

appropriate antiviral therapy after remission should be prescribed. However, a number of issues need further clarification regarding the exact duration of the treatment, its efficacy and safety ***(Saadoun et al., 2008).***

The antiviral treatment is usually prescribed for 6–12 months (in patients who respond to IFN within the first 3 months of treatment) ***(Saadoun et al., 2008).*** Patient's response to antiviral therapy depends on the viral genotype. SVR is achieved in 65–90% of patients with genotypes 2 and 3, compared with only 30–50% of those with genotype 1 ***(Perico et al., 2009).***

Hepatitis C virus and haemodialysis

Hepatitis C virus-infected HD patients have lower survival rates compared with HCV patients without renal failure, because they also present comorbid diseases, including co-infections [for instance with hepatitis B virus (HBV) or human immunodeficiency virus (HIV)] ***(Perico et al., 2009).***

The prevalence of Chronic hepatitis C (CHC) among patients with ESRD on maintenance HD is higher than the general population, ranging from 1.9 to 84.6% ***(Rahnavardi***

et al., 2008), with the highest records in Brazil ***(Ahmetagic et al., 2006)*** and Perou ***(Sypsa et al., 2005).*** In Greece, the disease prevalence ranges from 9.9% in 1945 to 24% in 2005 ***(Rigopoulou et al., 2005).***

The high seropositivity rate reflects intensive viral exposure and hospital transmission in HD environment because of frequent subcutaneous vascular punctures, frequent transfusions (although they have been dramatically reduced since erythropoietin use and blood product control in recent years) and inadequate screening for CHC ***(Fabrizi et al., 2002).***

Predisposal factors for infection considered are time on HD ***(Kalantar-Zadeh et al., 2007)***, diabetes mellitus, young age, receiving HD treatment from multiple different centres and co-infection with HBV and HIV ***(El-Amin et al., 2007).***

It is noteworthy that the lack of a reliable method for early diagnosis of HCV seropositivity is partly responsible for the increased prevalence of CHC in this patient group. In particular, the diagnosis of CHC is based on the detection of antibodies against the virus by enzyme linked immunoassay (ELISA) and determination of HCV RNA by polymerase chain reaction (PCR). It is known that ELISA, first- and

second-generation tests, detects false negative results in 2.6% of immunocompromised patients (group to which HD patients belong); therefore, the ELISA third-generation test is suggested for anti-HCV evaluation in HD patients ***(Bukh et al., 1993).***

Moreover, samples for HCV RNA testing should be obtained at the initiation of HD session, before heparin administration and blood contact with the haemofilter, because part of the HCV RNA binds to the dialyser membrane, affecting the accurate determination of viral load and changing the reliability of the method ***(Okuda et al., 1999).***

More contemporary and sensitive methods for the qualitative detection of the virus, such as the HCV RNA qualitative assay based on transcription-mediated amplification (TMA), are considered a better option. The largest study evaluating TMA has been conducted in Greece, where in 366 HD patients the percent virus detection increased to 33.3% ***(Rigopoulou et al., 2005).***

Of particular interest is the capability to find the virus nuclear antigen even before the detection of its antibodies by ELISA. Therefore, HCV infection can be determined 1.5

months earlier than the virus antibodies by ELISA and only 2 days later by the detection of viral RNA ***(Fabrizi et al., 2009).***

Furthermore, significant difficulties for early diagnosis of HCV infection are pointed out when the course of infection is indolent and liver biochemistry increase is mild ***(Furusyo et al., 2000).*** Generally, HD patients without chronic liver disease have lower aminotransferase values compared with the non-uremic population. This feature complicates the diagnosis of HCV infection in HD patients, because liver enzyme values do not increase significantly above or they may be within the normal range. By using a lower cut-off value of serum alanine aminotransferase (ALT), e.g. reduced by half ***(Lopes et al., 2006)*** or ALT ≥ 27 IU/l ***(Espinosa et al., 2000)***, HD patients with HCV infection could be identified. Consequently, it is recommended monitoring ALT monthly, screening for HCV antibodies every 6 months ***(Centers for Disease Control and Prevention, 2001)*** and hepatitis A and B vaccination, as co-infection with other hepatotropic viruses aggravates the prognosis ***(Zylberberg et al., 1998).***

Basically, the exact extent of liver damage can only be established by liver biopsy ***(Fabrizi et al., 2009).*** Transjugular liver biopsy is preferable over the percutaneous owing to the abnormalities of platelet function that characterize these patients ***(Baid-Agrawal et al., 2008).*** Regarding the non-invasive tests ***(Shaheen et al., 2007)***, although at first Fibrotest was considered a reliable marker of liver fibrosis on HD patients (thus great portion of liver biopsies could have been avoided) ***(Varaut et al., 2005)***, recent data queried its diagnostic value ***(Canbakan et al., 2010)***; thus, more research is necessary in this field.

It has been suggested that the degree of liver damage was milder in HCV-HD patients compared with HCV patients without renal failure or chronic renal disease without been on HD ***(Lemos et al., 2007).*** This fact could be attributed to different immunological status, lower viral load, prolonged hepatocellular growth factor secretion and increase in endogenous IFN after each HD session ***(Badalamenti et al., 2003).*** Similar findings have been found in patients with recurrent CHC after liver transplantation, where the progression rate of liver fibrosis was lower in HCV patients with renal insufficiency compared with HCV

patients with normal renal function ***(Cholongitas et al., 2009).***

Nevertheless, HCV-HD patients have poorer prognosis compared with HD patients without HCV infection. In a recent meta-analysis, which included seven trials with 11589 patients, it was found that HCV-HD patients presented 1.3 times greater risk of death (mainly because of the development of cirrhosis and hepatocellular carcinoma) with regard to HCV-HD patients ***(Fabrizi et al., 2007).***

Treatment of hepatitis C virus in haemodialysis patient

Treatment of HCV in HD patients is complex and difficult. Joint action of nephrologists and hepatologists for close monitoring of these patients is necessary, as still an optimal antiviral treatment regimen has not been determined ***(Liu et al., 2009; Alsaran et al., 2011).*** The value of HCV genotype as a predictor of response to IFN therapy is debatable. Patients with CHC on HD may receive standard IFN (2a or 2b) in a dose of 3mU three times weekly or a reduced dose of PEG-IFN, 2a or 2b, 135 mg and 1 mg/kg/week, respectively, with or without the addition of low-dose RBV ***(Ghany et al., 2009).***

PEG-IFN alone does not seem to overweigh standard IFN in achieving SVR, because around one-third of CHC patients on HD were successfully treated by standard or PEG-IFN monotherapy. Moreover, the combination of IFN with RBV in a markedly reduced dose might be tested, providing that the levels of haemoglobin are under close monitoring ***(Fabrizi et al., 2010).***

Finally, in terms of acute HCV infection, the early introduction of PEG-IFN in patients who did not have spontaneous clearance of HCV by 16 weeks has been associated with high SVR rates ***(Liu et al., 2010).*** In addition, taking into account the possible mild course of HCV infection, it seems reasonable that antiviral therapy is not an optimal option for patients with a diminished likelihood of survival or with complications such as diabetes mellitus or congestive heart failure ***(Nicot et al., 2010).***

Based on KDIGO recommendations, candidates for antiviral treatment are patients who meet the criteria for inclusion in the list for kidney transplantation because they are considered to have higher survival advantage ***(Fabrizi et al., 2002).*** Successful pretransplant treatment reduces post-transplant virological relapse, incidence of diabetes mellitus

and de novo glomerulonephritis in HCV recipients ***(Nicot et al., 2010).***

Hepatitis C virus and renal transplantation (RT)

The CHC is a point of great concern in the renal transplantation (RT), as 5–40% of kidney transplant recipients suffer from CHC ***(Pereira et al., 1997).*** The HCV-recipients present increased morbidity not only because of liver pathology but also because of other comorbidities. They are at a high risk of developing post-transplant diabetes mellitus, sepsis ***(Perico et al., 2009)***, glomerulonephritis ***(Ozdemir et al., 2006)***, renal graft nephropathy (acute and chronic) and renal thrombotic microangiopathy ***(Fontaine et al., 2004).***

- **Prospective hepatitis C virus renal transplant donors**

Several studies have shown that the use of kidney grafts from anti-HCV-positive donors in HCV recipients is associated with superior patient survival compared with those remaining on dialysis ***(Abbott et al., 2004).*** Hence, as the list of candidate recipients is constantly increasing without the concomitant augment of available donor organs, the KDIGO