


**Occult Hepatitis C Virus Infection in Hemodialysis**

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Nosocomial transmission in dialysis units maintains a higher prevalence of hepatitis C virus (HCV) infection than the general population.1,2 HCV infection has a detrimental effect on survival in patients on maintenance dialysis3 and after renal transplantation. In a recent meta-analysis of observational studies,4 incorporating 11,589 unique patients on maintenance dialysis, the summary estimate for adjusted relative risk for all-cause mortality was 1.34 (95% confidence interval 1.13 to 1.59). The excess risk for death in HCV-positive patients was partially attributed to chronic liver disease with its attendant complications, particularly hepatocellular carcinoma and liver cirrhosis.

Routine serologic testing for anti-HCV antibody (twice a year) and periodic testing for alanine aminotransferase and γ-glutamyl transpeptidase were suggested for detection of transmission of HCV within hemodialysis (HD) units.4 In the presence of elevated levels of liver enzymes, dialysis patients are usually tested for the major hepatitis viruses (hepatitis B virus [HBV] and HCV) with the differential diagnosis in this population including drugs hepatotoxicity, steatohepatitis, iron overload from repeated blood transfusions with ineffective erythropoiesis, and congestive heart failure. Three percent of patients on maintenance dialysis have elevated liver enzymes with unclear cause.5

A newly described entity that needs to be considered in this circumstance is so-called “occult HCV infection,” which refers to detection of HCV viremia (HCV RNA) in hepatocytes or peripheral blood mononuclear cells in the absence in serum of conventional serologic or virologic evidence of infection. Support for existence of this entity comes from the observation that HCV, although a hepatotropic virus, also can replicate at extrahepatic sites, including peripheral blood mononuclear cells.6 One report7 described occult HCV infection in patients with intact renal function and chronic liver disease of unknown cause, 57% of whom had HCV RNA in their liver.

Information about occult HCV infection in patients on maintenance dialysis is limited.8–10 Barril et al.9 in this issue of *JASN* detected genomic HCV RNA in the PBMC from 45% (49 of 109) of long-term HD patients who had unexplained abnormalities in liver chemistries and were repeatedly anti-HCV antibody and serum HCV RNA negative. Antigenomic HCV RNA was found in 26 (53%) of 49 patients detected by strand-specific real-time PCR. These patients were followed up for a mean of 23.8 ± 24.5 mo; mortality was significantly and independently associated with age and occult HCV infection (odds ratio 3.84; 95% confidence interval 1.29 to 11.43; *P* = 0.015), according to their logistic regression model.

This is the first description of the epidemiology and potential significance of occult HCV infection in patients on maintenance HD; however, there are some caveats, including the relatively small number of patients studied and the seemingly striking association between occult HCV and mortality in these dialysis patients. This link between occult HCV and mortality (odds ratio 3.84) was much stronger...
than that observed between “classic” hepatitis C and survival in dialysis populations (adjusted relative risk 1.34). It is difficult to explain these conflicting results, because a comparative study of nonuremic patients suggested occult HCV is a mild disease with less liver damage than “classic” chronic hepatitis C, and the percentage of HCV-infected hepatocytes seems significantly lower in patients with “occult” HCV. No liver biopsy information on occult HCV in dialysis patients was provided. Furthermore, occult HCV infection in dialysis patients has been studied only in patients with biochemical signs of liver disease of unknown cause, but it needs to be established in HD populations without biochemical dysfunction, which is often absent in HD populations. Typical HCV-related liver disease in patients with uremia is characterized by spuriously low aminotransferases even in the presence of active infection. Other authors have reported occult HCV infection after spontaneous or treatment-induced clearance of serum HCV RNA.

The clinical consequences of occult HCV infection include the risk for HCV transmission from patients with occult HCV within HD units. Although from a theoretical point of view we cannot exclude nosocomial spread of occult HCV among HD patients, the low incidence of de novo HCV in patients undergoing maintenance HD in the developed world is due to screening of blood donors for anti-HCV antibody and the implementation of infection control precautions. A Belgian multicenter study showed a seroconversion reduction from 1.4 to 0.0% in annual incidence of anti-HCV antibody by full implementation of infection control procedures to prevent transmission of blood-borne pathogens, including HCV. If occult HCV infection does transmit HCV within dialysis units, then it seems that current measures to control spread of HCV, although they do not incorporate routine PCR or nucleic acid technology, should be adequate; however, given previous experience with transmission of HBV infection in renal transplant recipients from donors with HBV serologies indicative of previous infection, more information is needed about occult HCV in this setting. HBV is transmitted from hepatitis B surface antigen–negative/anti–hepatitis B core antigen antibody–positive kidney donors with the incidence of de novo hepatitis B antigen seropositivity after renal transplantation ranging between 0.0 and 5.2%. Further information is needed to define the risk, if any, for HCV transmission from donors with occult HCV to uninfected recipients. Another theoretical concern is reactivation of HCV after renal transplantation in recipients with occult HCV because immunosuppressive therapy enhances HCV replication in organ transplant recipients.

In conclusion, preliminary data suggest a high frequency of occult HCV infection in dialysis patients with elevated liver enzymes who are anti-HCV antibody and HCV RNA negative. Further studies are needed to assess the clinical consequences of occult HCV infection in dialysis patients and renal transplant recipients.

ACKNOWLEDGMENTS

This work was supported in part by the grant “Project Glomerulonephritis” in memory of Pippo Neglia.

DISCLOSURES

None.

REFERENCES

Should Complement Activation Be a Target for Therapy in Renal Transplantation?

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doi: 10.1681/ASN.2008101064

In the past two decades, there has been a significant expansion in the number of immunosuppressive drugs available to prevent acute transplant rejection. These primarily target lymphocyte function, which is a critical mediator of allograft injury; however, because of this progress, each new agent potentially offers a smaller incremental benefit in terms of preventing rejection and prolonging graft survival. It may therefore be timely to consider therapeutic agents that inhibit other components of the immune system.

The complement system is part of the innate immune system but is also intrinsically linked to adaptive responses. It consists of more than 30 soluble and membrane-bound proteins and is activated by three pathways. The Fc region of multimeric IgG and IgM complexes with antigen activates the classical pathway. In contrast, the alternative and mannose-binding lectin pathways do not require antigen but instead are triggered by activating surfaces such as bacterial cell walls or damaged endothelium. The pathways converge with the assembly of C3 and C5 convertases that cleave and activate multiple copies of the pivotal complement components C3 and C5, initiating the effector functions of complement. The membrane attack complex, C5b-9, is assembled by the terminal pathway and forms a membrane-spanning pore that either is cytolytic or, in lower concentrations, can have profound effects on cell phenotype.

The opsonins C3b, iC3b, and C3d are recognized by receptors on leukocytes promoting cell activation. As complement proteins are cleaved, the anaphylotoxins C3a and C5a are also generated. These small proteins signal through specific G protein–coupled receptors expressed primarily on myeloid but also nonmyeloid cells, including epithelial cells of the kidney. They have a multitude of actions, inducing chemotaxis and cell activation, and have significant effects on adaptive immune responses.

Whether the pleiotropic effects of complement activation influence renal transplant outcome has been extensively studied. There are certain situations when complement is involved in graft rejection, for example in hyperacute rejection in a presensitized patient or in xenotransplantation, when the classical pathway of complement is activated by preformed antibody. Another circumstance in which complement activation damages a transplant kidney is during ischemia and reperfusion. Damage to the endothelium impairs its capacity to control complement activation allowing the alternative pathway to proceed uninhibited.1 There is evidence that the membrane attack complex,2 C3a,3 and C5a all may contribute to this phase of injury; however, it has proved more difficult to demonstrate a role for complement activation during acute rejection.

Interest in this area has increased recently with the introduction of C4d staining of transplant biopsies as an indicator of humoral rejection. Complement component C4 is part of the classical pathway and is activated by antibody binding to the surface of endothelial cells. It is degraded to the relatively stable, biologically inert fragment C4d the detection of which serves as a marker of previous antidonor antibody binding. Although C4d staining is embedded in the Banff scoring system of transplant rejection, its presence does not prove that complement activation is an important mediator of acute humoral rejection.

So is now the time to consider complement activation as a target for therapeutic intervention in clinical renal transplantation? There are two reasons that this may be the case. First, there is an increasing amount of experimental evidence, primarily from animal models, that complement activation is an important cause of transplant injury. Second, interventions that can effectively inhibit complement activation or block the action of complement activation products are now available.

In this issue of the JASN, Gueler et al.4 use human biopsy tissue and a mouse model to assess the role of C5a in renal transplantation. The receptor for C5a is expressed on macrophages and neutrophils infiltrating the graft as well as some tubular and glomerular cells. The in vitro data in the article suggest that expression on both native and infiltrating cells is important. In a fully mismatched transplant model, treatment with a C5a receptor antagonist significantly improved survival. The timing of treatment was critical and was most effective when started before transplantation. This suggests an important role for C5a in the injury that occurs as a result of ischemia reperfusion. This notion is consistent with other reports demonstrating a role for C5a in renal ischemia reperfusion injury induced by cross-clamping of the renal artery. Both C5a antagonists5,6 and C5a receptor gene silencing7 reduce damage in this model. Also, in a syngeneic mouse transplant model, when the kidney was perfused ex vivo with a C5a receptor antagonist, there was a reduction in the level of injury.8

The situation is more complex than this. Starting treatment after reperfusion improves renal function and prolongs graft

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