Hepatitis B and hepatitis C virus and chronic kidney disease

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Abstract

The most common cause of liver disease in patients with chronic kidney disease (CKD) remains infection by hepatitis B virus (HBV) and/or hepatitis C virus (HCV). The adverse effects of HBV and/or HCV infections upon survival in patients with CKD have been repeatedly confirmed. An excess risk of death in HBsAg positive or anti-HCV antibody-positive patients may be at least partially attributed to chronic liver disease with its attendant complications. A negative impact of HCV infection on survival after renal transplantation has been linked to extrahepatic complications, including chronic glomerulonephritis, sepsis, chronic allograft nephropathy, post-transplantation diabetes mellitus, and abnormal metabolism of calcineurin-inhibitors. Transmission of HCV infection by grafts from HCV-infected donors has been unequivocally demonstrated. Registry analyses suggest that recipients of kidneys from anti-HCV antibody positive donors are at increased risk of mortality. Renal grafts from HCV-infected donors should be restricted to viremic anti-HCV positive recipients. Several drugs have been recently licensed for therapy of HBV infection but available data in patients with CKD is mostly limited to experience with lamivudine. The standard of care for hepatitis C infection in patients on regular dialysis is monotherapy with conventional interferon, according to recent guidelines. Only dire circumstances justify interferon use after renal transplantation. (Acta gastroenterol. belg., **2010**, 73, **465-471**).

Key words : hepatitis B virus, hepatitis C virus, dialysis, kidney transplantation, chronic kidney disease.

Introduction

The most common form of chronic liver disease among patients with chronic kidney disease (CKD), particularly patients on regular dialysis and renal transplant recipients, remains infection by hepatitis B virus (HBV) and/or hepatitis C virus (HCV). Patients on long-term haemodialysis are at high risk for acquisition of blood-borne pathogens, including HCV and HBV. This review will focus on the natural history, and management of liver disease associated with HBV and/or HCV infections among patients with CKD.

Natural history of HBV and HCV in patients with CKD

The natural history of HBV and/or HCV infection in patients with chronic kidney disease, particularly renal transplant recipients and patients on long-term dialysis, has not been thoroughly elucidated (1). Even in patients with intact kidney function, the course of HBV and/or HCV can be unpredictable as infection is frequently indolent, viral activity extends over decades rather than years, and timing of initial infection may be unclear. Numerous factors can accelerate progression of viral liver disease including alcohol abuse, co-infection with HIV, or HGV, and steatohepatitis. Because of antiviral therapy, implementation of studies on the natural history of HBV and/or HCV infection may soon be impossible.

Evaluation of the course of HBV and/or HCV infection in CKD population is even more complicated ; serum levels of aminotransferase are abnormally low in patients on long-term dialysis or with advanced chronic kidney disease hampering recognition of liver disease (2). Clinicians are commonly reluctant to perform liver biopsies in patients with CKD due to uraemic platelet dysfunction. Furthermore, long-term consequences of HBV and/or HCV infection are more difficult to appreciate in patients with CKD as they have lower life expectancy than non-uraemic patients. As recent guidelines encourage antiviral therapy for HBV (3) and/or HCV (1) in patients with CKD, natural history studies will become even more difficult in this population.

HBV and maintenance dialysis

The frequency of HBV infection remains low in dialysis units in the developed world with prevalence of chronic HBsAg seropositivity ranging from 0% to 10% in patients on long-term dialysis (4-5). Outbreaks of HBV infection, however, continue to be reported in dialysis units with cases of severe acute hepatitis and even death (4-5). The epidemiology of HBV among dialysis patients in the less-developed world is not well characterised ; there are scattered reports from typically single-center surveys with rates of chronic HBsAg seropositivity ranging between 2% and 20% (6-8). Detailed information on the incidence of HBV infection (i.e., seroconversion rate for HBsAg) among patients undergoing dialysis in developing countries has not been available.

Limited data exists on the natural history of HBV infection in patients with chronic kidney disease (CKD) including dialysis patients. Patients with advanced CKD

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have evidence of immune compromise at both B- and T-cell levels. Progression of HBV in patients on maintenance dialysis appears to be indolent with a relatively low viral load. We recently suggested (9) that haemodialysis *per se* can contribute to viral load reduction in such patients based on a prospective study on 40 HBsAg-positive patients on maintenance haemodialysis. We noted that HBV load decreased after haemodialysis in the majority of patients although the difference did not reach statistical significant significance (29,390 ± 48,820 *vs* 23,862.8 ± 4,350 copies/mL, NS). Possible mechanisms underlying this intradialytic decrease of HBV DNA in HBsAg positive patients may reflect the production of protective substances during the HD session and/or clearance of HBV viremia during hemodialysis, or peritoneal dialysis.

The effect of HBV infection on survival in long-term dialysis patients is controversial. Jha *et al*. (10) evaluated 424 patients maintained on regular dialysis for several years. The death rate was higher in HBsAg seropositive patients than HBsAg -seronegative individuals (72.7% (8/11) *versu*s 21.4% (9/42) ; $P < 0.01$). Liver failure was more frequent in HBsAg-seropositive than in HBsAg-seronegative individuals, 36.4% (4/11) *vs*. 0% (0/42), $P < 0.01$. Josselson and colleagues (11) in contrast retrospectively evaluated 101 patients on chronic hemodialysis over an 8-year period and did not detect a significant difference between HBsAg-seropositive ($n = 30$) and-seronegative ($n = 64$) patients in death rate (50% *versus* 34.4%), hospitalization rate (1.5/patient/year *versus* 1.2/patient/year) and days of hospitalization (18/patient/year *versus* 11.8 patient/year).

Chronic HBV in patients receiving long-term dialysis is usually asymptomatic and indolent, but it is associated with subtle hepatocellular dysfunction. A recent multicenter survey ($n = 727$) in northern Italy showed that serum aspartate aminotransferase (AST) and serum alanine aminotransferase (ALT) levels were higher in HBsAg seropositive compared to seronegative patients, AST, 29.6 ± 45.3 U/L *versus* 16.01 ± 15.82 U/L ($P < 0.0001$) and ALT 32.7 ± 54.6 *versus* 17.8 ± 20.9 IU/L ($P < 0.0001$). Multivariate analysis showed a significant and independent association between detectable HBsAg and HBV DNA in serum and raised AST and ALT activity (2). HBV infection also raises gamma-glutamyltranspeptidase (GGTP) activity in patients on dialysis. In a large cohort ($n = 757$) of patients on long-term dialysis in Italy, serum levels of gamma-glutamyltranspeptidase were significantly higher in HBsAg positive and/or anti-HCV positive patients compared to HBsAg negative/anti-HCV negative patients on dialysis ; 85.1 ± 184.1 *versus* 25.86 ± 23.9 U/L ($P = 0.0001$). The frequency of raised GGTP levels was 22.2% (41/184) among dialysis patients with chronic viral hepatitis. Multivariate analysis showed a significant and independent association between serum GGTP values and positive HBsAg ($P = 0.005$) or anti-HCV antibody ($P = 0.0001$) status (12).

HBV after renal transplantation

The significance of HBsAg seropositive status on patient survival after renal transplantation (RT) has also been a controversial issue. Early studies had short follow-up and failed to detect a difference in outcomes of renal transplantation between HBsAg-seropositive and HBsAg-seronegative renal transplant recipients. By contrast, subsequent studies with appropriate follow-up (5-20 years) and size found that HBsAg seropositive status had an adverse effect on transplantation outcomes. A meta-analysis of clinical, observational studies ($n =$ 6,050 RT recipients) found a link between HBsAg seropositive status and impaired patient/graft survival (13). The summary estimate of the adjusted relative risk (aRR) of death and graft dysfunction was 2.49 (95% Confidence Intervals, 1.64-3.78, $P = 0.0001$) and 1.44 (95% Confidence Intervals, 1.02-2.04, $P = 0.001$), respectively, in HBsAg positive renal transplant recipients compared to HBsAg negative counterparts. Antiviral therapy has improved the outcome of kidney transplant in recipients with chronic hepatitis B infection. Yaè *et al*. (14) recently reported that treatment of hepatitis B with nucleoside/nucleotide analogues has resulted in significantly improved patient survival at 20 years among HBsAg positive patients ($n = 38$) compared with HBsAg positive patients ($n = 25$) who did not receive antiviral treatment, 83% vs. 34%, $P = 0.006$. Lamivudine was the initial treatment but 62% of patients developed drug resistance after 4 years ; salvage treatment with adefovir or entecavir was well tolerated resulting in a three-log decrease in HBV DNA after six months and normalization of ALT in 75% of patients.

Immunosuppression after renal transplantation may stimulate HBV replication by a variety of mechanisms, for instance a glucocorticoid-responsive element that enhances replication has been detected in the HBV genome (15). The immunosuppressant azathioprine may stimulate intracellular HBV replication (16). Calcineurin inhibitors may directly enhance HBV replication and azathioprine may stimulate intracellular replication of HBV (17). Reactivation of HBV infection after renal transplantation has been observed in a renal transplant recipient who at the time of transplantation was HBsAg seronegative but displayed evidence of remote, resolved HBV infection (18).

Because of concerns about progression of liver disease after renal transplantation, HBV infection had been regarded as a relative contraindication to renal transplantation. The decision on whether or not to perform kidney transplantation in HBsAg seropositive candidates should be based on both liver histology and evaluation of HBV replication using serum markers, that is, hepatitis B ‘e’ antigen (HBeAg) and HBV DNA. The absence of serum markers of replication before RT, however, does not preclude reactivation of HBV after transplantation. In renal transplant candidates with evidence of ongoing HBV replication (i.e., HBeAg seropositivity or detectable

HBV DNA in serum), antiviral therapy should be started before transplantation to prevent acceleration of liver disease after introduction of immunosuppression. Although renal transplantation is not precluded in patients with histologically mild HBV-related liver disease, all patients with HBV infection must be warned that even histologically mild disease can progress when immunosuppression is introduced (3).

Therapy of HBV in patients with CKD

Recent guidelines discuss antiviral treatment of HBV in patients with immune dysfunction (3). In HBsAg seropositive patients with detectable HBV DNA in serum, antiviral therapy of HBV is indicated both before and after renal transplantation. Patients with persistent HBsAg seropositivity, normal serum AST and ALT levels and no detectable HBV DNA in serum were previously defined as 'healthy carriers' but are now referred to as 'inactive carriers'. Only biochemical and virological monitoring before renal transplant and during dialysis is advised in inactive carriers with surveillance for hepatocellular carcinoma.

Several oral medications, nucleos(t)ide analogues, are currently approved for the treatment of chronic HBV infection- lamivudine, adefovir, entecavir, telbivudine, and tenofovir. No controlled clinical trials address antiviral treatment of HBV infection in patients on regular dialysis. Available information on antiviral treatment of hepatitis B in patients on dialysis mostly concerns lamivudine, an oral nucleoside analogue reverse transcriptase inhibitor. A few uncontrolled clinical trials (19-22) have studied the effect of antiviral therapy with lamivudine for HBV infection in patients on dialysis. Overall, the rate of HBV DNA clearance was 78.9% (30 of 38 patients reached the clearance of HBV DNA from serum). No information on histological improvement during therapy or sustained virological and biochemical rates in available.

More information exists on the antiviral therapy of HBV after renal transplantation. Very limited studies are available on interferon (IFN) therapy for HBV infection after transplantation. Indeed, a high rate of acute graft rejection induced by IFN had been observed. Most information on antiviral therapy of HBV after RT concerns lamivudine but no controlled clinical trials exist ; however, several trials with uncontrolled design and appropriate size have evaluated efficacy and safety of lamivudine in renal transplant recipients with HBV infection. A meta-analysis of 14 clinical trials including a total of 184 RT patients reported that mean overall clearance of HBV DNA and HBeAg from serum after lamivudine treatment were 91% and 27%, respectively (23). The high rate of HBV resistance to lamivudine now limits the use of this drug. To date, no clear consensus exists as to when lamivudine should be started or discontinued in renal transplant recipients with HBsAg but an apparent improvement in the survival rate of HBsAg seropositive renal transplant recipients receiving antiviral therapy has been noted (14, 24-25).

Fontaine and coworkers administered adefovir to 12 patients with lamivudine-resistant HBV infection (26). Duration of adefovir therapy ranged between 3 and 19 months, and 11 renal transplant recipients were included in the study group. The median serum levels of HBV DNA declined from 8.76 $\log_{10}$ Eq/mL at baseline to 2.97 $\log_{10}$ Eq/mL after 12 months. No relevant adverse effects were noted. Additional small studies have also been reported on adefovir use after RT.

Kamar and coworkers are the first authors to report on entecavir use for HBV (27) in ten RT recipients with lamivudine-resistant HBV infection. Nine patients received adefovir and one entecavir, respectively, in addition to lamivudine. The addition of entecavir was associated with a significant drop in HBV DNA viral load, from 3.86 $\log_{10}$ copies/mL at baseline, to 2.97 $\log_{10}$ copies/mL at 12 months after initiation of entecavir. No information currently exists on the use of tenofovir and/or telbivudine in patients with HBV infection and CKD.

HCV and maintenance dialysis

There is evidence of a relationship between anti-HCV seropositive status and greater death rate among patients on long-term dialysis (28-29). According to a meta-analysis of clinical, observational studies (seven studies including a total of 11,589 patients on long-term dialysis), the presence of anti-HCV antibody was an independent and significant risk factor for death in patients on maintenance dialysis. The summary estimate for adjusted relative risk of all-cause mortality was 1.34 (95% CI, 1.13-1.59) for anti-HCV positive in comparison with anti-HCV negative patients on regular dialysis (30). In a Japanese cohort ($n = 76,201$), a strong and independent link between positive anti-HCV positive status and higher mortality was found, the adjusted hazard ratio being 1.37 ($P < 0.0003$) (8). As a cause of death, hepatocellular carcinoma and liver cirrhosis were significantly more frequent among anti-HCV-positive than -negative dialysis patients.

The adverse effects of HCV infection on mortality in patients on regular dialysis have been recently linked to the detrimental effect of HCV on health-related quality of life. Health-related quality of life is associated with diminshed survival in patients with intact kidney function. Afsar and coworkers (31) evaluated 165 patients, 83 of whom being anti-HCV positive- the mental component summary score was independently associated with anti-HCV seropositive status ($P = 0.016$). The exact mechanisms underlying this relationship remain unclear. The presence of symptoms of depression might be one explanation as HCV infection and hemodialysis are both independently associated with an increased prevalence of depression, which in turn negatively affects health-related quality of life.

HCV after renal transplantation

Early studies were not able to detect a decrease in survival in anti-HCV positive renal transplant recipients. Subsequent studies provided with appropriate follow-up and size unequivocally showed a link between anti-HCV positive status and patient or graft survival after RT. A meta-analysis of clinical, observational studies investigating the effect of HCV antibody status on survival of renal transplant recipients identified eight clinical trials with 6,365 patients (32). Pooling of study results demonstrated that presence of anti-HCV antibody was an independent and significant risk factor for death and graft failure after RT ; the summary estimate for RR was 1.79 (95% CI, 1.57-2.03 ; homogeneity test, $P = 0.0427$) and 1.56 (95% CI, 1.35-1.80 ; homogeneity test, $P = 0.0192$), respectively. Progressive liver disease after renal transplantation has been implicated in the increased mortality rate among anti-HCV positive renal transplant recipients. Furthermore, the persistence of detectable HCV viremia after transplantation in anti-HCV positive recipients has been linked with the development of extra-hepatic complications such as *de novo* or recurrent glomerulonephritis, increased frequency of sepsis, new-onset diabetes mellitus after transplant (NODAT), and chronic allograft nephropahy (CAN) (1). Altered ciclosporine pharmacokinetics has been noticed in anti-HCV positive patients after renal transplantation (33)

Current status of renal transplantation from HCV-positive donors

Transmission of HCV infection via solid organ transplantation has been unequivocally demonstrated (1). This observation led organ procurement organizations (OPOs) to discard all HCV-infected kidneys, thus aggravating the current shortage of renal grafts. Some OPOs have introduced a policy of accepting kidneys from HCV-positive donors for HCV-positive recipients, but efficacy and safety of this approach remains controversial. Single-center experience has not reported deleterious effects on the short-term patient or graft survival ; in addition, time on the waiting list for recipients receiving kidneys from HCV positive donors was shortened and dialysis mortality decreased (34-35). However, information from large databases has suggested that HCV positive recipients who receive kidneys from HCV positive donors have slightly worse outcomes than HCV positive recipients who receive kidneys from HCV negative donors, even in the modern era of immunosuppression (36-37). Abbott and coworkers analyzed data from the 2002 United States Renal Data System and found an independent and significant association between donor anti-HCV seropositive status and an increased mortality risk among recipients, adjusted hazard ratio 2.12 (95% Confidence Interval, 1.72-2.87, $P < 0.001$) (37). Whether transplantation of deceased donor kidney allografts from donors with antibodies against HCV confers a survival advantage compared with remaining on the waiting list is a controversial issue. In their Cox regression model, Abbott and coworkers showed that receipt of a kidney from a deceased HCV positive donor was associated with increased survival rates in all patients, compared with remaining on the transplantation waiting list (adjusted hazard ratio for death, 0.76, $P < 0.025$). But the benefit associated with receipt of any deceased donor kidney compared with staying on the renal transplantation waiting list was much greater (adjusted hazard ratio for death, 0.46, $P < 0.001$) (38). The question whether HCV positive candidates derive a survival benefit from being transplanted with HCV positive kidneys (*versus* waiting for the next HCV negative kidney offer) is a difficult question to study at multicenter level as no national registry captures HCV status at the time of listing but only at the time of transplant. In their multivariate analysis, Kucirka *et al*. (39) found that, among 6,830 HCV positive recipients, death rate associated with transplantation of kidneys from HCV positive donors, compared with transplantation of kidneys from HCV negative donors, was significantly increased (HR, 1.29, 95% CI, 1.15-1.45, $P < 0.001$). According to ther calculation, this HR only translates to a difference of 1% in 1-year survival (94% for HCV negative kidneys vs. 93% for HCV positive kidneys) and a difference of 2% in 3-year survival (85% for HCV negative recipients vs. 83% for HCV positive kidneys). The conclusion of the authors was that opting for the currently available HCV positive kidney rather than waiting for the next available HCV negative kidney might be justified for many patients. In order to avoid transmission of HCV infection via transplantation, 'Kidney Disease : Improving Global Outcomes' (KDIGO) guidelines have recommended that kidneys from HCV-infected donors should not be used in recipients who are anti-HCV antibody positive without detectable HCV RNA in serum (1). In fact, transplantation of kidneys from viremic anti-HCV positive donors into recipients who are anti-HCV antibody positive but HCV RNA negative could have the effect of reintroducing HCV infection.

Therapy of HCV in patients with CKD

The benefits and side-effects of antiviral therapy in patients receiving long-term dialysis with HCV infection have been evaluated in several trials. In a recent meta-analysis conducted on 24 clinical trials including 529 patients treated with standard IFN monotherapy, the overall estimate of sustained virological response (SVR) and drop-out rate were 39% and 19%, respectively (40). Drop-outs were mostly related to flu-like symptoms and to gastrointestinal or haematological changes.

The preliminary information on monotherapy with pegylated IFN does not suggest any additional benefit in terms of virologic response to monotherapy with standard or conventional IFN. As listed in Table 1, SVR rate obtained with peg-IFN monotherapy ranged between

Table 1. — **Outcomes of Peg-IFN monotherapy in patients with chronic HCV infection on maintenance dialysis**

Study (reference)	Antiviral regimen	Patients attaining an SVR*
Sporea I. *et al*. (2006) (41)	Peg-IFN α-2a	30% (3/10)
Chan T.M. *et al*. (2007) (51)	Peg-IFN α-2a	33% (2/6)
Amarapurkar D. *et al*. (2007) (52)	Peg-IFN α-2b	50% (3/6)
Ayaz C. *et al*. (2008) (53)	Peg-IFN α-2a	50% (11/22)
Ucmak H. *et al*. (2008) (54)	Peg-IFN α-2a	50% (6/12)
Akhan S.C. *et al*. (2008) (55)	Peg-IFN α-2a	50% (6/12)
Dzekova P. *et al*. (2009) (42)	Peg-IFN α-2a	36% (5/14)

* SVR calculated according to an intention-to-treatment analysis.

30% and 50%, as shown by most recent trials (41-43). Tolerance to pegylated IFN monotherapy was unsatisfactory. We performed a meta-analysis of 16 clinical trials (254 patients) on monotherapy with pegylated IFN, the summary estimates of SVR and drop-out rate were 33% and 23%, respectively (43). The most common cause of drop-outs were the haematological adverse effects.

Little information exists on combined antiviral therapy (ribavirin plus conventional or pegylated IFN) for HCV infection in patients on long-term dialysis (44-46). Only one controlled clinical trial exists- Rendina *et al*. in 70 HCV-infected patients on regular dialysis found that SVR rate was 97% in patients treated with pegylated IFN plus ribavirin *versus* 0% in untreated controls (45). These encouraging results have not been confirmed in subsequent studies where the rates of SVR ranged between 7% and 71%. The American Association for the Study of Liver Disease does not recommend the use of ribavirin in patients with glomerular filtration rate under 50 mL/min/1.73 m^2. A low clearance of ribavirin has been reported in patients with renal failure ; also, clearance of ribavirin during haemodialysis does not occur. Ribavirin accumulation can give haemolytic anemia, a condition which can be dangerous in patients with CKD, who often have baseline anaemia as well as other comorbidities, such as cardiac ischemia at baseline. The KDIGO workgroup suggested ribavirin use in patients on maintenance haemodialysis, only after taking some safety procedures- 1) very low ribavirin dose (200-300 mg thrice weekly), 2) weekly monitoring of haemoglobin levels, and 3) high dose of erythropoietin for anaemia. According to KDIGO guidelines, the standard of care in HCV-infected patients receiving long-term dialysis is monotherapy with conventional IFN, the quality of evidence being moderate for SVR on this point (1).

Acute or subacute rejection, which is frequently not sensitive to steroids, is frequently (up to 50%) observed in renal transplant recipients receiving IFN (47-50). The immunomodulatory activity of IFN is probably responsible of such a phenomenon. The KDIGO guidelines recommended IFN use after RT only in patients with fibrosing cholestatic hepatitis or life-threatening vasculitis where the risk of not implementing treatment justifies the possible loss of the allograft (1).

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