

Hepatitis C in Renal Disease, Hemodialysis and Transplantation

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Immunosuppression in Hepatitis C Virus-Infected Patients after Kidney Transplantation

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Abstract

Hepatitis C virus (HCV) infection is an important health problem in kidney transplant recipients with a significantly higher prevalence than in the general population. Kidney transplantation remains the treatment of choice for most HCV-infected patients with end-stage kidney disease, in spite of lower patient and graft survival as compared to HCV-negative patients. Immunosuppression likely has significant consequences on HCV replication and/or disease after transplantation. However, determining the best immunosuppressive strategies after kidney transplantation in the presence of HCV infection remains challenging. The use of induction therapy is not contraindicated, and a short-course induction may actually be beneficial in HCV-infected kidney transplant recipients. Corticosteroid withdrawal may be an acceptable option in HCV-infected patients with specific comorbidities such as diabetes mellitus or osteoporosis. The best calcineurin inhibitor to be used in HCV-infected patients remains to be determined, as there is a lack of large controlled trials addressing this particular issue. Overall, immunosuppressive regimens need to be individualized according to clinical parameters other than HCV, such as the patient's immunological risk and other comorbidities. In conclusion, there is a need for prospective controlled studies to define the optimal immunosuppressive regimen in HCV-infected kidney transplant recipients.

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Chronic hepatitis C virus (HCV) infection is a major public health problem, with an estimated prevalence of 2% worldwide [1], the prevalence being significantly higher in kidney transplant recipients [2]. The natural history of chronic

HCV infection in kidney transplant recipients is not completely understood, and the medical management of these patients remains difficult. In 2011, determining the best immunosuppressive strategies after kidney transplantation in the presence of HCV infection remains challenging, as no definite given regimen has proven its clinical superiority. This article will focus on the management of chronic HCV infection in kidney transplant recipients, highlighting the potential impact of the different immunosuppressive drugs on the outcome of HCV infection in this population, as well as discussing some potential areas for future clinical research.

Patient and Graft Survival

In recent years, accumulating evidence has shown kidney transplantation to confer a long-term survival advantage over dialysis in HCV-infected patients and, therefore, it should be considered the treatment of choice for most end-stage renal disease patients with HCV infection [3, 4]. Despite some conflicting reports, however, HCV-infected patients appear to have an overall lower patient and graft survival as compared with HCV-negative transplant recipients. It is postulated that kidney transplantation, with its need for immunosuppression, increases the risk of posttransplant liver disease and new-onset diabetes among HCV-infected patients, which may adversely affect patient survival [2]. HCV infection may also affect graft survival by enhancing the risk of de novo or recurrent glomerulopathies [5, 6].

There have been several publications in the last two decades on the impact of HCV infection on outcomes after kidney transplantation. Studies with short follow-up (<10 years) failed to show significant differences in patient survival between HCV-positive and -negative recipients [7–9]. However, the majority of recent studies, with extended follow-up, show a detrimental effect of HCV infection on patient survival [10–15]. Therefore, the duration of follow-up seems to be crucial in the evaluation of outcomes, as liver disease can develop slowly (or late) after transplantation.

Regarding graft survival, while numerous studies have reported a deleterious effect of HCV [13, 15, 16], an equal number of studies have indicated outcomes that are comparable to those seen in HCV-negative recipients [10–12]. For example, in an observational cohort study, Forman et al. [11] showed that anti-HCV antibody positivity was not significantly associated with death-censored allograft loss, after adjusting for confounding pre- and posttransplant variables. Similarly, Bouthot et al. [10] found no difference in graft survival with 45 months of follow-up. However, in the larger United Network for Organ Sharing (UNOS) study by Meier-Kriesche et al. [13], a trend toward worse death-censored graft survival in HCV-positive patients as early as after 3 years was found. The Australian and New Zealand registry also found a markedly worse graft survival at both 5 and

10 years in HCV-positive recipients [15]. Most frequent causes of graft failure in this study were glomerulonephritis, chronic allograft nephropathy and death in HCV-infected patients. The outcome of HCV-infected kidney recipients is well summarized by a meta-analysis of eight clinical trials including 6,365 patients, which demonstrated a significantly lower patient and graft survival in HCV-infected recipients (adjusted RR 1.79, 95% CI 1.57–2.03, and 1.56, 95% CI 1.35–1.8, respectively) [17]. The increased mortality was partially related to an increase in liver-related mortality. Increased graft loss associated with HCV status has been associated in part with the occurrence of HCV-related renal disease [18].

Apart from differences in study design and follow-up period, severity and duration of HCV infection, liver histology and associated comorbidities at the time of transplantation, differences in immunosuppressive regimens may also be partly responsible for the discordant patient and graft survival outcomes observed in previous studies. The intensity and type of induction and maintenance immunosuppressive regimens may indeed have a significant impact on the course of HCV infection after transplantation.

Impact of Immunosuppression in HCV-Infected Kidney Transplant Recipients

The immunosuppression which needs to be administered after organ transplantation likely has significant consequences on HCV replication and its associated morbidity. The effect of immunosuppression is highlighted by the case of a transplant recipient who had spontaneous resolution of his HCV infection after complete withdrawal of immunosuppression [19]. However, it remains challenging to assess the impact of a specific immunosuppressive drug on the outcome of HCV infection in kidney transplant recipients. First, immunosuppressive drugs are generally given in combination and, frequently, novel strategies of immunosuppression are utilized in clinical studies (e.g. induction with anti-T cell antibodies followed by immunosuppression minimization, etc.). Second, there is a lack of large studies specifically performed in kidney transplant recipients addressing this particular issue. As a result, most of the inference regarding immunosuppression and HCV infection is drawn from studies or reports in liver transplant recipients. Finally, in attempting to determine the most appropriate immunosuppressive regimen after kidney transplantation, the overall risk of other adverse outcomes with each medication, such as the development of acute rejection or posttransplant diabetes mellitus, must be taken into consideration.

Calcineurin Inhibitors

The calcineurin inhibitors (CNI) cyclosporine and tacrolimus remain arguably the most important immunosuppressive drugs used nowadays in the prevention

of acute rejection after kidney transplantation. Although the two agents are somewhat similar, there are some differences among them which may be relevant regarding their influence on HCV infection. Tacrolimus is a slightly more potent immunosuppressant than cyclosporine (for a given degree of nephrotoxicity), and it has been associated with lower rates of acute rejection after kidney transplantation [20]. Tacrolimus is currently the preferred CNI in the majority of transplant centers in the US and in many European centers as well. However, in HCV-infected kidney transplant recipients, the use of tacrolimus has been shown to carry a higher risk for posttransplant diabetes mellitus [21]. Interestingly, *in vitro* studies suggest that cyclosporine may have an inherent anti-HCV activity, inhibiting viral replication, but it is not known whether this may have beneficial clinical implications and possibly protect from the adverse effects of HCV infection after transplantation [22], especially if lower acute rejection rates are observed in patients receiving tacrolimus as compared to cyclosporine. In addition, no significant differences with respect to viral replication and development of liver fibrosis after kidney transplantation have been found in a recent study [23]. In a large study by Luan et al. [24] using data from the Scientific Registry of Transplant Recipients (SRTR) involving more than 75,000 kidney transplant recipients (including 3,708 HCV-infected patients), the use of tacrolimus or cyclosporine was not associated with any survival benefit in HCV-infected patients, i.e. it could not be determined whether one specific CNI has a clear advantage over the other.

Recent literature in liver transplantation by Berenguer et al. [25] and other groups also suggests that overall there are no significant differences between cyclosporine or tacrolimus in posttransplant outcomes in HCV-infected patients. For example, in a meta-analysis of five studies involving 366 patients, patients receiving tacrolimus had similar incidence of graft loss and acute rejection as compared to patients receiving cyclosporine. In a recent study of HCV-positive liver transplant recipients included in the UNOS database, patients receiving cyclosporine were at slightly higher risk for patient death, graft loss and acute rejection as compared to patients receiving tacrolimus [26]. In contrast, in another recent multi-center Spanish cohort study of 410 liver transplant recipients with recurrent hepatitis C treated with pegylated interferon plus ribavirin therapy, cyclosporine was found to be protective against viral relapse, as compared to tacrolimus [27]. Therefore, both after kidney or liver transplantation, the best CNI to be used in HCV-infected patients remains to be determined. However, it appears unlikely that clear differences between the two CNIs will emerge from future clinical studies.

Steroids

Steroids are still widely used in kidney transplantation, at least during the first year after transplant. The possible detrimental relationship between the use of steroids in HCV-infected patients and the outcome of HCV infection has not

been clearly established. On the one hand, it has been known for some time that the administration of high-dose or intravenous boluses of steroids for the treatment of rejection is associated with an increased level of replication of HCV [28]. On the other hand, rapid weaning of steroids has been associated with inferior outcomes in HCV-infected liver transplant recipients [29], so that some moderate steroid use might have beneficial effects after transplantation. However, in another study in liver transplant recipients by Humar et al. [30], rapid steroid discontinuation was associated with lower rates of histopathologic hepatitis C recurrence and posttransplant diabetes mellitus. There are scarce data on the influence of steroid use or their withdrawal in kidney transplant recipients with HCV infection. In the study by Luan et al. [24], mortality was not significantly different between patients who received steroids and those who did not (hazard ratio 1.16, $p = 0.44$). In a small clinical study involving 12 HCV-infected kidney transplant recipients, it was found that rapid steroid withdrawal was not associated with a worse outcome [31].

Antimetabolites

Mycophenolate mofetil (MMF) and mycophenolic acid are inhibitors of the metabolism of pyrimidines and have replaced azathioprine in most transplant centers as a standard immunosuppressive drug, in combination with CNI and steroids. Despite being a more potent immunosuppressive drug than azathioprine (as indicated by lower rates of acute rejection in most published studies after organ transplantation), MMF appears to be safe in kidney transplant recipients with chronic HCV infection. In the study by Luan et al. [24], the use of MMF among HCV-infected patients was associated with a 33% lower risk of mortality, suggesting possible beneficial effects of MMF. It should be mentioned that Rostaing et al. [32] found a significant increase of HCV viremia in 14 kidney transplant recipients who received MMF in place of azathioprine (or in addition to a CNI), but it is not clear if this effect had any deleterious consequences because the long-term outcome of these patients was not reported. In a recent study in liver transplant recipients, monotherapy with MMF was associated with better liver fibrosis scores compared to the use of CNI [33], although some reports have described a more severe hepatitis C recurrence in patients receiving MMF [34, 35]. Thus, these conflicting data highlight the difficulty to draw firm conclusions or precise guidelines currently regarding the use of MMF. However, most centers use MMF, in combination with a CNI, for maintenance immunosuppression after transplantation.

mTOR Inhibitors

Because of their potential broad antiviral activity and antiproliferative effects, mTOR inhibitors (sirolimus and everolimus) are two potentially attractive drugs to be included in immunosuppressive protocols for HCV-infected kidney transplant recipients. In an in vitro model of liver fibrosis, sirolimus was

associated with reduced fibrogenesis and cell proliferation [36]. There are scarce data, however, on a possible influence of mTOR inhibitors on outcomes of HCV-infected kidney transplant recipients in clinical practice. In the study by Luan et al. [24], the use of mTOR inhibitors in HCV-infected patients was associated with a non-significant 13% higher risk for mortality as compared to patients not receiving mTOR inhibitors. Switch from CNI to sirolimus in a small series of kidney transplant recipients was considered to be safe, but did not result in a significant decrease in HCV viral loads [37]. In liver transplantation, the use of sirolimus was assessed by Asthana et al. [38] in a retrospective study involving 141 liver transplant recipients with HCV-associated cirrhosis. Patients who received sirolimus had lower HCV-associated activity and fibrosis scores on serial liver biopsies. However, there was no difference in the incidence of recurrence of hepatitis or patient survival. Recently, it has been reported that the use of sirolimus was also associated with lower HCV viral load as compared to CNI in liver transplant recipients [39]. One of the problems with the use of mTOR inhibitors is their relatively inferior tolerability as compared to CNI-based regimens, so that at the present time it cannot be recommended to systematically use this class of drugs in HCV-infected kidney transplant recipients.

Induction Therapy

It is still debated whether all induction therapies have a deleterious impact on the outcome of HCV infection after kidney transplantation. The use of OKT3 (a monoclonal depleting antibody against CD3+ cells) has been clearly associated with a higher rate of severe recurrent hepatitis C in liver transplant recipients and, therefore, OKT3 does not appear to be a good choice for induction (or treatment of rejection) in HCV-infected transplant recipients [40]. The relationship between polyclonal T cell-depleting antibodies and HCV infection is more complex. In a retrospective review of 104 HCV-infected kidney transplant recipients, patients who received induction with antithymocyte globulin had similar HCV viral load as compared to patients without induction [41]. Other outcomes were also similar regardless of the induction therapy received. In the study by Luan et al. [24], induction with either depleting or non-depleting antibodies was associated with a 25% lower risk for mortality as compared to patients not receiving induction therapy, possibly due to a lower rejection rate with less anti-rejection therapy needed. In a recent single-center study that evaluated long-term outcome of 110 HCV-infected patients after kidney transplantation utilizing pre- and posttransplant liver biopsies, a subset analysis of 31 recipients showed that patients who received daclizumab had a worse progression of liver fibrosis score than patients receiving antilymphocyte globulins [4].

As for other immunosuppressants, most of the information on the impact of induction therapy on HCV infection comes from studies in liver transplantation. In a randomized controlled clinical trial (n = 64) performed in HCV-infected liver transplant recipients, there were no differences in transaminase

levels, HCV viral load, liver fibrosis and inflammation scores in patients receiving either antithymocyte globulin or steroids as induction therapy, suggesting that a short course of antithymocyte globulin induction may not be deleterious [42]. Another randomized controlled trial showed a similar rate of HCV recurrence in recipients receiving daclizumab compared to those receiving thymoglobulin [43]. However, a recent study based on the UNOS database showed that HCV-infected liver transplant recipients who received induction with antithymocyte globulin and steroids had an inferior graft survival than patients receiving daclizumab [44]. This finding, however, was not confirmed in another UNOS analysis, where induction therapy was actually associated with a better patient and graft survival, both in patients receiving either antithymocyte globulin or daclizumab [45]. Overall, although more prospective studies are needed, it may be reasonable to suggest that if induction therapy is administered, a short course would be preferable for HCV-infected patients.

Rituximab

The anti-CD20 monoclonal antibody rituximab is increasingly used in kidney transplantation for the prevention or treatment of humoral rejection and in the treatment of posttransplant lymphoproliferative disorder. Rituximab has also been administered for the treatment of severe HCV-associated mixed cryoglobulinemia in non-transplant patients. Hepatitis flares have been described in HCV-infected patients receiving rituximab for non-Hodgkin lymphoma, indicating that rituximab should be considered with caution in the presence of HCV infection. For example, in a study including 131 HCV-infected patients with diffuse large B-cell lymphoma treated with rituximab, incidence of severe liver toxicity was significantly higher (27%) as compared to non-HCV-infected patients (3%) [46]. In addition, in the subgroup of 34 patients in whom HCV viral load was measured, a significant increase in HCV RNA levels during rituximab therapy compared to baseline was found. After kidney transplantation, some reports have also associated the use of rituximab with a higher incidence of opportunistic infections (mostly bacterial and fungal infections). On the other hand, in a series of 7 HCV-infected kidney transplant recipients, therapy with rituximab was not associated with a flare of chronic hepatitis C, and HCV viral loads remained stable after a 12-month follow-up period [47].

New Compounds

To our knowledge, there is no reported clinical experience regarding the use of the costimulation blocker belatacept in HCV-infected kidney transplant recipients. A related drug, abatacept, was safely used in the non-transplant setting in 2 HCV-infected patients treated for rheumatoid arthritis [48]. Alemtuzumab (Campath) induction was associated with high HCV replication rates in liver transplant recipients in the Pittsburgh experience [49], but data in kidney transplant recipients are lacking, and caution is recommended because this agent can

be associated with intense immunosuppression when administered to transplant recipients.

Optimal Immunosuppressive Regimen in HCV-Infected Kidney Transplant Recipients

Determining the most appropriate immunosuppressive regimen for kidney transplant recipients with chronic HCV infection is challenging. The current literature is still somewhat controversial regarding the deleterious (or beneficial) effects of one specific drug on the outcome of HCV infection after transplantation, and therefore, evidence-based guidelines cannot be proposed in 2011. Immunosuppressive regimens need to be individualized according to clinical parameters other than HCV solely, such as the patient's immunological risk and other comorbidities (for example, risk for diabetes mellitus). The use of induction therapy is not contraindicated in these patients and a short-course induction may actually be beneficial in HCV-positive patients via a reduction in the occurrence of acute rejection, thereby avoiding high-dose steroid boluses. No clear advantage appears to exist for the use of anti-IL-2 receptor monoclonal antibodies as compared to antithymocyte globulins. Again, the choice between these drugs should be made taking into account the overall immunological risk of the patient. However, from past experience it can be stated that the OKT3 monoclonal antibody should not be administered in these patients, as it has been associated with severe hepatitis C. Withdrawal of steroids may be an acceptable option in HCV-infected kidney transplant recipients with specific comorbidities such as diabetes mellitus or osteoporosis. However, it is not clear if a low-dose maintenance steroid therapy might have some beneficial effects in the long-term regarding liver disease. MMF and mycophenolic acid appear to be safe in these patients, and should probably be favored over azathioprine. To date, there are insufficient data to recommend the systematic use of mTOR inhibitors in HCV-infected transplant recipients. More debatable is the type of CNI to be used. On the one hand, tacrolimus is associated with a higher risk for the development of posttransplant diabetes mellitus than cyclosporine, whereas, on the other hand, it appears to be associated with better outcomes in terms of acute rejection and possibly allograft survival, even in HCV-infected patients. Clear differences between the two CNIs remain difficult to demonstrate in this patient population.

Conclusions

The immunosuppressive regimen required after organ transplantation is associated with increased HCV replication and, in general, an accelerated and more

severe course of HCV-associated liver disease. However, there are no prospective studies directly comparing different immunosuppressive regimens in HCV-infected kidney transplant recipients. Therefore, there is a need to perform prospective controlled studies with long-term follow-up in order to compare different immunosuppressive protocols (e.g. induction vs. no induction, cyclosporine vs. tacrolimus, steroids vs. no steroids, etc.) to more precisely define the optimal immunosuppressive therapy and the consequences of HCV infection after kidney transplantation. The potential beneficial effects of cyclosporine shown *in vitro* still need to be confirmed in properly designed randomized controlled trials. Given the increasing number of HCV-infected transplant candidates, delineating the optimal immunosuppressive drugs or regimens should be a research priority in kidney transplantation in the upcoming years.

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