

Treatment of Chronic Hepatitis C Virus Infection Following Renal Transplantation

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Chronic hepatitis C virus (HCV) infection is a major issue in the general population. Its prevalence in renal patients is high, varying from country to country and from one center to another, albeit declining during the last decade since the implementation of the use of recombinant erythropoietin and the screening of blood products for HCV. It has been shown recently that chronic HCV infection has a negative impact upon both long-term patient and graft survivals following kidney transplantation. This is mainly related to i) HCV-related liver lesions, i.e. cirrhosis, and ii) the possible role of HCV in chronic allograft nephropathy. Therefore, the prevention of HCV-related pathologies is of major importance.

In immunocompetent patients it has been shown that it is possible to cure HCV infection in almost 40% of patients using a dual therapy based on recombinant alpha interferon (αIFN) and Ribavirin. In renal transplant patients no randomized study has been conducted so far that addresses anti-HCV therapy. We only have scattered data where the end points vary, ego biochemical response, i.e aminotransferase levels, liver histology, virological response, or side effects.

Alpha-Interferon

A few pilot studies have been conducted in the early or mid nineties: usually alpha-IFN was administered for 6 months, on a weekly basis of three injections of 3 to 6 million units each, with sometimes a loading dose during the first weeks (9 million units per injection). This resulted in a biochemical response in approximately 70% of cases, associated with a transient clearance of HCV RNA in approximately 50% of cases. However, the virological relapse usually occurred when αIFN was withdrawn. When assessed, the treatment was associated with an improvement in liver histology, particularly regarding the inflammatory score. However, the major concerns of this therapy were the side-effects: apart from flue-like symptoms and anemia, the rate of acute renal failure during therapy was abnormally high and ranged from 10 to 70% (mean 40%). The acute renal failure was a consequence of either acute (vascular) rejection or particular changes in the mesangium of glomeruli. Despite αIFN withdrawal with or without methylprednisolone pulses, up to 50 % of the acute renal failures resulted in graft loss. No predictive factors for acute renal failure while on αIFN therapy were found. Therefore, αIFN should not to be used in renal transplant patients except in those with HCV-related hepatic cholestatic fibrosis. The latter condition can rapidly lead to liver failure and, because αIFN can dramatically improve this condition, this justifies its use even if it leads to renal allograft failure.

Ribavirin

Ribavirin is a guanosine analogue. In combination with αIFN in HCV(+)ve immunocompetent patients it has a dramatic efficacy upon HCV infection. Earlier studies have evaluated Ribavirin monotherapy in liver allograft recipients : its use was associated with a significant improvement in liver enzymes although it did not affect HCV RNA or liver histology. In renal transplant patients only one limited study has been published so far. Amongst seven patients, five had a biochemical and a virological response. Very recently we conducted a pilot study where 16 RT patients were given a 12 months course of ribavirin monotherapy (1000 mg/d) for either HCV-related liver lesions and/or HCV-related de novo glomerulopathy. The treatment was completed in 13 patients. It was associated with a dramatic decrease in liver enzymes although there was no significant change in HCV RNA. When present at the beginning, proteinuria disappeared during therapy and renal function improved. Thirteen patients underwent liver biopsies before and at the end of ribavirin therapy: this showed no significant improvement in the activity score while the fibrosis score increased significantly from 1.5 to 2.5. The major side effect was hemolytic anemia since ribavirin accumulates in red blood cells in case of renal insufficiency. This requires huge amounts of recombinant erythropoietin in order to maintain the recommended daily dosage. Therefore, from these preliminary results we conclude that in HCV(+)ve RT patients ribavirin monotherapy might be used only in those with de-novo glomerulopathy in order to improve the renal parameters.

Amantadine

Amantadine is an antiviral agent that is effective against influenzae viruses and flaviviridae In HCV(+)ve immunocompetent

patients, when it is used in combination with aIFN and ribavirin it increases the rate of virological response when compared with a dual therapy based on aIFN with ribavirin. The daily dosage was 200 mg (adapted to renal function); it had few side effects. In RT patients no study has been published so far. We conducted a pilot study in 10 HCV(+ve) RT patients. Amantadine monotherapy for 6 months was associated with a significant decrease in liver enzymes, but without any change in HCV RNA levels. There were no significant side effects.

In summary we cannot use the current association of drugs active against HCV in HCV(+)ve RT patients that are used in the immunocompetent population. However, in case of HCV-related hepatic cholestatic fibrosis or in case of HCV-related de novo proteinuria aIFN and ribavirin can be used, respectively. When available in the general population, the new agents such as antiprotease and antihelicase might be tested in HCV(+)ve RT patient. Finally, we recommend the treatment of HCV(+) hemodialysis patients who are candidates for renal transplantation because, in this setting, we can achieve a HCV clearance in approximately 40% using aIFN therapy alone without it resulting in a relapse when the patient has a transplant.

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