Hepatitis C recurrence after liver transplantation

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Abstract

Hepatitis C-related cirrhosis is the major indication for liver transplantation (LT).

This disease recurs histologically in nearly all the HCV-infected patients during the first postoperative year. Chronic hepatitis C evolves to cirrhosis in 20% of the cases within 5 years after LT. However, the 5-year survival for a HCV-infected recipient is still comparable to that of a patient grafted for another indication ; it will become worse later.

High viremia after LT is associated with a more severe liver recurrent disease. The influence of viral genotype remains controversial.

The impact of the type of immunosuppression on HCV recurrence is unclear. Steroids, that increase viremia, might have a deleterious effect on the outcome of chronic HCV-disease after LT.

Antiviral combined therapy (Interferon + Ribavirin) soon after transplantation, before disease recurrence, is probably the best treatment at the present time ; this remains still unproven.

Retransplantation for HCV recurrent cirrhosis allows a 60% survival at 1 year. (Acta gastroenterol. belg., **1999**, 62, **428-431**).

Key words : liver, liver transplantation, retransplantation, hepatitis C, recurrent hepatitis C, immunosuppression, steroids, rejection, Interferon, Ribavirin.

Hepatitis C has emerged as the most common indication for liver transplantation (LT). Over 95% of patients undergoing LT for hepatitis C have HCV RNA detectable in their serum by PCR following LT (1). Allograft infection with host HCV is almost universal and represents the primary cause for chronic hepatitis after LT (2-8). HCV infection of the graft may lead to its failure, making retransplantation mandatory to avoid death.

1. Clinical features of HCV recurrence

Hepatitis C recurs histologically in 40 to 90% of HCV-infected recipients in the first postoperative year ; the mean time to the development of recurrence is reported to be 206 days (9). An episode of acute hepatitis is usually observed in more than 50% of the patients within 2 to 6 months after LT (7,10), characterized by high titers of serum HCV RNA and increased transaminases, at levels lower than those observed in the acute phase of the disease in immunocompetent patients (11,12,13). Liver biopsy reveals lobular hepatitis. Some degree of chronic hepatitis will develop in 50 to 90% of the patients transplanted for HCV infection at 12 months after LT (7,10,14).

Chronic hepatitis C on the graft evolves to cirrhosis more quickly than in native livers (15). Occurrence of cirrhosis soon after LT is observed in a small percentage of patients (1,5,10,16,17). Five years after transplantation, the proportion of HCV-related cirrhosis is estimated at 20% (7,17).

A severe form of cholestatic hepatitis is reported in less than 10% of the people transplanted for HCV disease, with a rapid progression to liver failure requiring re-LT (18,19).

A small proportion of the HCV liver recipients are "healthy carriers" : they have normal ALT, minimal histological changes but a persistent sometimes high viremia.

Despite HCV recurrence on the graft, 5-year survival in patients receiving a new liver because of HCV-related cirrhosis remains comparable to that of patients grafted for other liver diseases : 75% (7). In some series, even 10 years after LT, the survival rate is identical in HCV- or non HCV-related diseases (8). However, most authors agree with the fact that recurrent cirrhosis will make retransplantation necessary in 1/5 of the patients (20). In the United States, 10% of the transplanted HCV patients die secondary to recurrent disease.

2. Influence of HCV viremia on disease outcome

The prognostic implication of HCV RNA level prior to transplantation, concerning the severity of HCV reinfection after LT, remains controversial (10,11) ; in some series, high viremia at the time of transplantation seems to induce a quicker and more severe recurrence on the graft.

After transplantation, HCV RNA is detected by PCR within the first 2 weeks and its level increases thereafter, reaching values significantly higher than pre-LT in 1 to 2 months ; levels of viremia are then at least 10-fold increased (11,13,14,21,22). The initial decline in HCV RNA in serum could be due to an uptake by the new liver. A higher post-transplant viral load is associated with more severe liver disease (14).

The serum HCV RNA level correlates with the occurrence of acute hepatitis on the graft (10,13,22) ; the quantity of HCV RNA in the transplanted liver is also important during the acute hepatitis

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phase (23,24). The decrease in HCV RNA levels in the liver is associated with the occurrence of histological lesions of chronic hepatitis ; this suggests that an immunological response to the viral infection of the graft plays a role in the development of these lesions.

For some authors (21), HCV genotype 1 is associated with more agressive recurrent disease ; for others (25-29), it does not influence survival, recurrent disease or development of cirrhosis.

Coinfection with other viruses, such hepatitis G virus (30) or hepatitis B virus (31), does not influence the post-LT course of HCV-related disease.

3. Impact of immunosuppression on HCV recurrence

As a higher post-transplant viral load is associated with a more severe recurrent hepatitis on the graft, it may be postulated that factors able to promote a viremia increase are likely to aggravate the course of the disease. Intensity of immunosuppression might be a possible predictor of disease severity.

Steroids

In the non-transplant setting, steroids increase hepatitis C viremia (32). After LT, pulsed intravenous methylprednisolone therapy is associated with transient 4 to 100-fold increase in the HCV RNA level and with an increased frequency of subsequent development of acute hepatitis C (9,13,34). Higher serum HCV RNA concentrations 12 months post-transplant are associated with longer duration of steroid therapy (33). Unfortunately, results are conflicting, some authors being unable to demonstrate a correlation between cumulative doses of steroids and acceleration of recurrent hepatitis C (35).

Acute cellular rejection episodes in HCV-recipients occur at a frequency similar to those reported in patients undergoing LT for other indications, but is associated with an increased mortality, compared to non HCV-infected subjects undergoing also acute rejection (20). It is the allograft rejection by itself, and not the increased immunosuppression, that is related to a more severe liver disease ; indeed, rejection may trigger immune-mediated hepatocellular damage (9). It is also possible that HCV recurrence either mimics or causes allograft rejection, resulting in a greater exposure to immunosuppressive agents. The association observed between rejection episodes, their treatment and severe recurrence are possibly in relation with an initial overtreatment of rejection due to misdiagnosis between rejection and hepatitis ; indeed, histological findings may be confusing (34).

Azathioprin

The independant effect of azathioprin on HCV recurrence has never been separately studied. In patients transplanted for HCV-related cirrhosis, transaminases are similar in people receiving or not that drug (8).

OKT3

Its administration seems to be a significant risk factor for both the time to development and the severity of histological recurrence of hepatitis C (36). However, it is difficult to differentiate effects of OKT3 to those related to the severity of rejection and of cumulative steroid exposure.

Calcineurin inhibitors

No difference in the severity of histological recurrence of hepatitis C is observed among recipients receiving Tacrolimus when compared to those on Ciclosporine (7,20). In one study, treatment with Tacrolimus was related to a worse HCV recurrence ; however, in that particular study, the drug was used a rescue therapy in corticoresistant acute rejection (37,38).

More intense initial therapy (calcineurin inhibitors + azathioprin + steroids) is associated with more frequent development of fibrosis (39). Fibrosis might also be a consequence of the action of Tacrolimus or Ciclosporine, which may induce fibrogenesis by increasing levels of transforming growth factor beta (40,41).

4. Management of HCV recurrence

Treatment with immunosuppressive drugs accelerates progression of chronic hepatitis. Liver damage in HCV infection involves host mediate immune responses (42). Thus, it seems a paradox that immunosuppressed patients may have a more agressive course of HCV infection than immunocompetent patients. When the immunosuppression is the most intense (in the first weeks after LT), HCV RNA rises in liver and serum and is associated with an increase in hepatic expression of HCV antigens. Later, reduction of immunosuppression may enhance immune response of the host and is likely to be associated with strong immunological attack against a highly infected liver, resulting in an increased lysis of hepatocytes harboring HCV. Indeed, a decrease in immunossupression a few months after LT may provoke activation of HCV, leading to severe, even fulminant, hepatitis (43).

In order to decrease the pathogenicity of HCV after LT, it is maybe of importance to administer an initial immunosuppressive treatment that limits viral replication (less steroids ?) followed by a relatively strong immunosuppression when viremia declines.

Modification in the immunosuppression

As viremia is high soon after LT, the management during this early phase of infection is important. Less immunosuppression in the weeks following LT may decrease viremia, and possibly lower the intensity of liver injury ; initial therapy without steroids appears to

be associated with a higher viremia at 3 months after LT than a treatment with steroids, but with a low viremia at 12 months (33).

Immunosuppression with Tacrolimus or Ciclosporine without steroids as early as 2 weeks after LT (44) or with mycophenolate mofetil (45) are reported safe. However, one study has examined the effect of early steroid withdrawal on the activity of post-transplant hepatitis C, without effect on HCV disease severity (46).

In the late post-transplant period, it is probably better in the setting of HCV disease to go on with a relatively high dose of a selective immunosuppressant, or even to increase it, in order to diminish the immune attack against the infected liver cells.

Antiviral therapy before transplantation

As high pretransplant HCV RNA levels has been reported to be associated with worse 5 year survival (20), antiviral therapy prior to LT might be a good choice. However, it is poorly tolerated in decompensated cirrhotic patients with neutropenia and low platelets count. There are no studies supporting any effect of Interferon with Ribavirin before LT on post-transplant outcome (47).

Antiviral therapy after transplantation

Interferon alone for 6 months normalizes the transaminases in 1 patient out of 5, lowers the viremia but has no influence on the histological picture (48,49). It may induce chronic rejetion leading to graft loss and retransplantation ; low maintenance ciclosporine levels may have contribute to rejection (50).

Ribavirin alone for half a year reduces the transaminases to a normal level but without any drop in the HCV RNA level (49,51).

Taken together in one study, these two drugs clear the HCV RNA in half of the patients, normalize the transaminases and improve the histology in all, at least at the end of the 1-year treatment (52). In another study, long-term results are disappointing after Interferon-Ribavirin combination treatment : among 8 patients having completed 1 year treatment, only 1 remains PCR negative for HCV RNA 3 months after cessation of therapy (53).

As reinfection of the graft occurs in all the recipients, it seem reasonable to try to prevent it. This preemptive approach combines the use of Interferon and Ribavirin as soon as 3 weeks after LT, when the condition of the patient has stabilized. This therapy eradicates HCV in serum in 40% of the cases (54) ; it seems to be at present the best choice. However, it remains unclear if this early treatment starting soon after LT will alter the natural history of the disease.

We are still unable to determine the prognostic indicators of survival that will identify the HCV patients who would do poorly after LT. Therapy should maybe be restricted only to patients with a bad prognosis, with demonstrable histologic disease progression, before the development of bridging fibrosis (55).

Retransplantation for hepatitis C recurrence

Series reviewing patients retransplanted for HCV recurrent infection on the liver graft report only a small number of cases. Acceptable results (50-60% 1-year survival) can be obtained if livers are transplanted before the onset of renal failure (56). Prognosis is better if retransplantation is performed for allograft failure unrelated to HCV infection (57-59).

Five-year survival rate of a recipient with HCV-related disease is not affected by a pre-existing HCV infection in the donor. If donor and recipient are HCV-unmatched, only 1 strain will prevail (60-62).

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