Liver transplantation in viral hepatitis. New insights

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Abstract

Liver transplantation is the only therapeutic option for end- stage liver disease. When disease is due to hepatitis B, C or D viruses, transplantation is aggravated by important morbidity related to the recurrence of viral infections. The risk of reinfection has led to the identification of prognostic criteria and measures for preventing or diminishing the reinfection hazard. HBV recurrences can be diminished with the use after transplantation of immunoglobulins against the HBsAg (HBIg). With this prophylaxis the risk of reinfection is proportional to the viremic load before transplantation ; it is high (> 90%) in patients with elevated viremia, low in non-viremic HBsAg carriers (such as those with fulminant hepatitis or HDV coinfection), intermediate in the remaining cases. The recent availability of potent antivirals against the HBV has provided a tool to further reduce the reinfection risk. Antiviral therapy or immunoprophylaxis, however, may lead to the emergence of resistant mutants ; combination therapies appear in order to prevent this event.

There is at present no valid prognostic indicator to identify HCV transplants at risk of recurrent disease or prophylactic measure to prevent reinfection. Reinfection is virtually universal and the course of infection is apparently benign over the short term in the majority of cases ; the disease is rapidly progressive with cholestatic features mimicking chronic rejection in 10-20% of HCV reinfected transplants. Neither the HCV genotype nor coinfection with HGV appear to influence the clinical outcome. The long-term prognosis appears at present less favourable than previously perceived ; several studies indicate a progressive reduction of the survival curve due to insidious HCV cirrhosis developing over 5 to 7 years. Interferon or Ribavirin monotherapy are not effective for prevention or therapy of recurrences while their combined use yields promising results. (Acta gastroenterol. belg., **1999**, *62*, **342-347**).

Key words : viral hepatitis, liver transplantation, immunoprophylaxis, antivirals.

Liver transplantation (LT) in viral liver disorders is aggravated by a significant risk of recurrence of the original viral infection in the grafted liver (1,2). The risk of recurrent disease may abolish the surgical efforts and thus forces the transplantation team to identify patients who are less likely to become reinfected and have the best chance of long-term survival.

Hepatitis B

The rate of HBV reinfection in non-protected HBsAg carriers is over 80%. Reinfection is almost invariability accompanied by recurrence of hepatitis B (3).

A proportion of reinfected patients has developed a rapidly progressive disease characterized by the presence of high levels of HBV DNA and HBsAg in serum and massive amounts of HBcAg and HBsAg in liver. This syndrome, named "fibrosing cholestatic hepatitis" (4) almost invariably led to graft loss and death or retransplantation. Retransplantation was also immediately followed by recurrent disease and loss of the second graft (5).

The main factors influencing the risk of recurrence in HBsAg carriers treated with HBIg were identified in the replication level of HBV before LT and in the clinical type of the original disease leading to liver failure (6).

- *Viremia.* Different studies showed that the risk was almost absolute (96%) for highly viremic patients (HBeAg and/or HBV-DNA positive in serum by standard hybridization assays). The risk was consistent yet not prohibitive in patients without the HBV-DNA or with anti-HBe and decreased to acceptable levels in non-viremic subjects (3-4,7-8). More recent studies using Polymerase Chain Reaction (PCR) methods have confirmed the prognostic value of the viral load pre-transplantation. With sensitive assays the critical level defining a consistent versus low risk of reinfection appears to be around 0.1 pg/ml (10^4 virus/ml) ; of note, the risk remains consistent in patients with 0.1-1 pg/ml (HBV titer :10^4-10^5 virus/ml), a viral load that frequently cannot be detected by standard hybridization (9,10).
- *Clinical type of liver disease.* The rate of reinfection and associated disease is significantly lower in patients transplanted for fulminant hepatitis B than in those transplanted for cirrhosis (8). Probably in most patients presenting with fulminant hepatitis HBV has been cleared or viremia has much decreased by the time of transplantation serum (HBV DNA is most often negative, also by PCR) ; fulminant disease is thought to represent a hyperergic immunological reaction to simultaneously eliminate all infected hepatocytes.

Measures to prevent HBV reinfection

The administration of HBIg in the perioperative period (11,12) was not enough to contain the reinfection risk and reduced survival of HBV patients (in early series the two-year survival ranged from 36% to 72% with an average of 53%).

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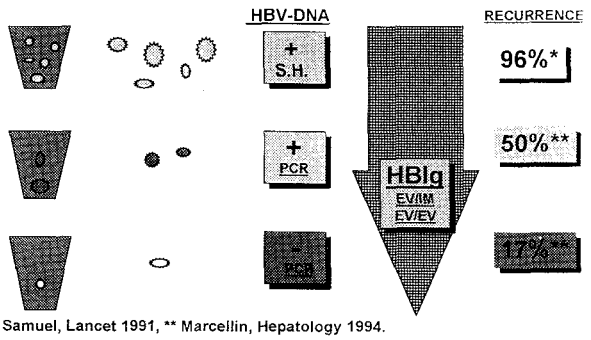

S.H. : standard hybridization
PCR : polimerase chain reaction

Fig. 1. — Pre-transplant viremia and risk of HBV recurrence in patiens treated with passive immunoprophylaxis.

This prompted the use of HBIg over the long term. Various regimens were developed, all including the use of high dosage of HBIg in the perioperative period (13-17). Usually 10000 IU are given iv during the anhepatic phase and another 10000 IU are given iv each day for the first week post-surgery. Then a HBIg load is given periodically based on the blood level of anti.HBs ; 1000 to 10000 IU are given iv or im when the titer of anti-HBs in serum diminishes below 100 IU/l. In a multivariate analysis of 372 patients with acute and chronic hepatitis B (5), HBIg prophylaxis was effective in increasing survival and controlling HBV reinfection with a reduction of the overall reinfection risk to 17% and 29% at 1 and 2 years, respectively, but was not able to diminish the reinfection rate in patients who were HBV DNA positive before LT ; in these patients the rate of reinfection remained high (96%) as opposed to a 29% reinfection rate in HBV DNA negative transplants. Discontinuation of HBIg resulted, even years after surgery, in the recurrence of HBV in the graft, in indication that HBIg prophylaxis needs to be maintained indefinitely (18,19).

Recently high dosage (10000 IU/monthly), fixed time regimens of HBIg have been proposed. Although preliminary results suggest that these regimens can consistently reduce the recurrence rate (20), the mercurial additives used in the preparation of HBIg may induce serious toxic effects and careful monitoring of mercury blood levels is mandatory. With more aggressive protocols of HBIg prophylaxis, which sustain anti-HBs to 500 IU/l during the first week after LT and tailor the dose and frequency of administration to the kinetics of anti-HBs clearance, HBV infection was prevented in 26 of 28 HBV patients (93%) ; 63% of these patients were originally HBV DNA positive (21). These data would indicate that highly viremic patients require higher dosages of HBIg and previous failures to prevent reinfection may be accounted for by inadequate HBIg regimens. A major problem of HBIg prophylaxis is the cost (20,22). Commercial HBIg preparations are obtained from limited human sources and are therefore very expensive ; their use over two years virtually doubles the cost of LT. Alternatively, the use of monoclonal anti-HBs has been proposed (23,24). This would overcome the limit posed by human sources of anti-HBs and provide standardised preparations available in short volumes.

Inherent problems to this type of prophylaxis are the technical difficulties in developing human sources of monoclonal antibodies and the possibility that envelope mutants of HBV arise due to the narrow immune pressure exerted by the limited specificities of the monoclonal antibody. Of six transplants with chronic hepatitis B given monoclonal anti-HBs , three became reinfected while circulating high titers of anti-HBs ; in each several mutations were found in the HBV-envelope gene (23).

HBV envelope escape mutants causing reinfection have also been reported after conventional polyclonal HBIg prophylaxis ; the HBIg affinity of these variants was reduced and their selection was more frequent in patients who remained viremic after surgery (25). Amino acid (aa) changes in the first loop (aa 124 to 137), and in the second loop (aa 138 to 147) of the a determinant of the HBsAg were identified and associated with a worse clinical outcome after transplantation (44% vs. 23% graft failure caused by HBV infection) (26).

Some of these variants might also result in potential aa changes in the HBV polymerase protein, which in turn might be responsible for resistance to antivirals like lamivudine or famciclovir ; in view of the overlapping between the two regions of HBV genome mutations in the s-gene can affect mutations in the polymerase-gene, and vice versa (27).

Attempts in recent years were aimed at preventing reinfection by clearing or reducing HBV viremia before LT. Early attempts with IFN given pre- and immediately post-LT were unsuccessful. The cytokine not only failed to prevent reinfection (42% of HBIg treated became reinfected compared to 58% of untreated controls) but induced also severe side effects (28) ; poor tolerance is a major limitation to the use of IFN in patients with decompensated liver disease.

The development of nucleosides analogues with strong activity against HBV has provided a valid therapeutic arsenal. Ganciclovir and arabinoside-monophosphate (ara-AMP) conjugated with lactosaminated human albumin were first used ; the latter is distinctly less toxic than free ara-AMP as it is targeted to the liver through specific receptors (29-31).

The experience in our center has confirmed that both are efficacious : in 12 patients treated with these drugs the HBV recurrence rate was reduced to 16.6%. The two antivirals were more effective in patients with moderate viremic levels before LT ; only one patient with viremia reduced to below 0.1 pg/ml of HBV (10^4 virus/ml) became reinfected (10).

Famciclovir and Lamivudine are the most promising of the new antivirals. They are given orally and are

well tolerated. Famciclovir given at a dose of 500 mg thrice daily was found to decrease by 90% HBV DNA levels in 30 candidates to LT ; 10 of the 30 treated patients became negative before transplantation ; however four of the five followed up patients had a recurrence although this was clinically mild in each patients (32). In another study, in nine of twelve treated patients post-LT levels of HBV-DNA decreased by 55-100% during Famciclovir therapy (500 mg three times daily for a mean of 13.5 months) (33).

Lamivudine appears even more successful. Each of 13 transplants given this drug at a dose of 100 mg daily before, during and after transplantation became HBV DNA negative after LT. Many lost also the HBsAg ; reinfection relapsed in one patient (34). In another study (35) serum HBV DNA was cleared in each of five HBsAg carriers given lamivudine 100 mg daily. Two patients, however, have developed recurrent hepatitis B sustained by the emergence of lamivudine resistant mutants..

In a recent study Lamivudine used before LT to reduce the viral load and after surgery in association with i.v. high dose of HBIg was effective in reducing the recurrence after LT in 10 patients. None of the treated patients had a HBV recurrence after 1.1 years of follow up (36).

Our experience confirms the efficacy of lamivudine in association with long term, intramuscolar low dose of HBIg ; viremia decreased in each of 42 treated patients and the drug was efficacious also in patients with high virus titers before treatment (37). None of the 31 patients who underwent transplantation and were followed up for a mean of 13.8 months has experienced a recurrence of HBV.

Mutations in the YMDD locus of the polymerase gene of HBV have been reported repeatedly both in HIV and HBV patients (38) ; they occur with frequency in transplanted patients and seem be less pathogenic to the graft than the mature virus (39-41). Mutations in the polymerase gene have been reported also in transplants given long term Famciclovir therapy (39).

A treated patient of ours who developed the YMDD mutations was successfully retreated with lamivudine after discontinuing the drug for some months ; HBV responsive to lamivudine re-emerged as the predominant viral population upon lamivudine discontinuation (42).

At present there is no clinical report documenting successful treatment of lamivudine-resitant mutants ; in an in vitro study these mutants were sensitive to adefovir dipivoxil (43).

In summary, the indications to LT in patients with terminal HBV liver diseases are based on a correct selection of patients, appropriate immunoprophylaxis and pre-emptive anti-viral therapy. The aim of the latter is to diminish viral replication to levels that are unlikely to transmit infection to the graft ; pre-emptive therapy must be started before surgery and should be continued for some time after surgery. The ideal HBsAg candidate to liver transplantation has undetectable HBV-DNA by PCR techniques, either spontaneously or after antiviral therapy. Of the many nucleosides analogue used in the attempt to reduce the viral load before transplantation, lamivudine seems to be the most efficacious.

A prolonged use of lamivudine as well as famciclovir can be complicated by the emergence of viral mutants.

Hepatitis C

Although hepatitis C has become the most important indication to LT, our knowledge of the pathogenesis of the infection and of the immunological factors protective from hepatitis C or conducive to recovery from the disease are largely unknown. Different from hepatitis B and D, no protocol of prophylaxis has so far been developed. Preparations with high levels of anti-E1 and anti-E2 antibody to the putative envelope of HCV were given to chimpanzees challenged with HCV but did not prevent infection and the claim that the administration of polyclonal human immunoglobulins reduced the incidence of recurrent HCV infection in LT has not led to a generalized use of this prophylaxis (44). Thus in the absence of any active intervention to control reinfection, the indications to transplant HCV patients have been based on the natural history post-LT and are liable to change as our knowledge of the course of HCV reinfection in grafted livers changes over the follow up time.

The data available from short term (less than 5 years) follow-ups indicate that recurrence of HCV infection is virtually universal but only about 50% of reinfected patients have clear clinical or histological signs of liver disease one to two years after surgery ; however even patients with normal ALT may exhibit mild histological abnormalities. In San Francisco 41 of 95 HCV-reinfected patients had a recurrence of hepatitis over a 3 years follow up period ; only 12 progressed to CAH (44). In Paris an acute lobular hepatitis developed within a mean of 4 months after transplantation in 52 of 79 patients who had anti-HCV before LT and in 22 of these patients the disease progressed to CAH ; the overall survival rates at 1 and 2 years were 95 and 90% (45). In Milano, 48 of 94 (51%) anti-HCV positive patients followed up for a mean of 28 months developed post-transplantation hepatitis and seven patients (7%) progressed to overt cirrhosis (46). In the first 17 patients transplanted in Torino HCV infection recurred in 16 (94%) ; nine of the 16 (56%) reinfected patients progressed to CAH (47). In 77 HCV patients transplanted so far in Torino 67% had a relapse of hepatitis C ; the course over a 6 months to 5 years follow-up was benign in 75%, rapidly progressive in 25% ; in the latter, the disease exhibited cholestatic features evolving rapidly to cirrhosis or ductopenia (48).

In the series from Hannover, 62% of the HCV transplants are surviving 10 years after LT (49) ; this rate is no different from that of HCV-negative liver transplants. Also in this series recurrent disease run a

rapidly progressive course in 20% of the 71 patients examined.

It has been concluded that the almost universal recurrence of HCV infection is acceptable in view of the limited impact of hepatitis C on health and survival ; however in all large series a minority of patients runs a rapidly progressive disease. No specific factor increasing the virulence of infection in this subset has been identified with the possible exception of the genotype of HCV ; genotype 1b appeared a major determinant of increased pathogenicity in European but not in US series (50).

Recent reports based on more extended periods of follow -up have shown that the survival courve of HCV transplants is not stable but steadily declines even after 5 years of follow-up. In analogy with the French data, in the King's College series from London, the cumulative survival of 149 HCV-positive transplants was 79% at one year, 74% at 3 years and 70% at five years. In analyses from the US UNOS registry, graft and patient survival after liver transplantation for terminal HCV liver disorders were distinctly lower than after transplantation for alcoholic liver disease. In our series the 2 years mortality was 29.6% in HCV transplants without associated hepatocellular carcinoma, higher then in patients trasplanted for other indications.

While the current data indicate that patients with HCV infections have excellent short-term results after LT, as the follow-up progresses one can expect to see an increasing number of patients with recurrent hepatitis C leading to liver failure ; although more insidious than recurrence of hepatitis B, the course of recurrent hepatitis C may nevertheless be more accelerated than the ordinary disease.

Prophylactic protocols of treatment post-transplantation are promising but need the confirmation of controlled studies (51).

Therapy of the recurrent hepatitis with interferon failed and was complicated by a 25% rate of chronic rejection (52).

Monotherapy with Ribavirin at dose of 800-1200 mg/day orally was efficacious in normalising aminotransferases but did not induce the clearance of HCV-RNA ; in contrast interferon abated viremia in a higher proportion of patients (53-54). The two drugs had a synergistic effect on the treatment of HCV recurrence in the study of Bizollon *et al.* (55). Optimal combination protocols need yet to be defined ; the adverse events of Ribavirin (emolitic anemia and iron overload) and interferon (rejection) remain problematic.

Table I. — **Cumulative results of therapy with interferon of HCV recurrence after LT**

		ALT normalization
Wright, Transplantation 1994		0%
Feray, Hepatology 1995	➡	9%
Vargas, Transplant.Proc. 1995		14%
Gane, Transplant.Int 1995		28%
1/50 treated pts. cleared HCV-RNA 20% graft rejection		

In summary, in contrast with the good prognosis after LT in the short time, long time recurrence of HCV can be complicated by cirrhosis, chronic rejection and graft loss. In 10-20% of patients an aggressive cholestatic disease recurs with high mortality and needs retransplantation.

There is at present no valid prognostic indicator of HCV recurrence. The most efficacious prophylactic or therapeutic option appears to be the association of ribavirin and interferon.

Hepatitis D

As HDV infection can recur only if HBV infection also recurs (56), and the original HBV infection of many HDV transplant candidates is low grade (such as to make transmission of this virus to the liver graft unlikely) recurrence of hepatitis D is infrequent and easily controlled by HBIg prophylaxis. In France, the 5 years survival rate was 88% without deaths due to recurrent hepatitis D or B (57) ; in Italy it was 75% (58). In the minority (< 10%) of the patients who become reinfected the clinical course of recurrent disease is usually relatively benign ; in the French series a few patients recovered completely over the medium term. Of 29 HDV patients transplanted in Turin the survival rate was 90% and only 1 patient (4%) developed a recurrence after a 3-82 months follow-up (average 25.2 months).

In summary, in view of the low risk of HBsAg reapparence after LT in HBV-HDV patients and of the good control obtained with the HBIg prophylaxis, HDV disease appears at present the best indication to LT among viral hepatitides.

HDV transplant candidates with productive HBV infections (HBV-DNA positive) should be treated with antivirals in order to abate HBV viremia ; further action depends on the efficacy of antiviral therapy.

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