Recurrent allograft disease : viral hepatitis

Marina Berenguer

Hospital Universitario La FE, Servicio de Gastroenterología y Hepatología, Valencia, Spain.

Abstract

Viral hepatitis is the leading indication for liver transplantation (LT) in the majority of transplant centers. Post-transplantation outcome in these patients largely depends on the prevention of allograft reinfection. In contrast to hepatitis B where excellent results have been achieved following the implementation of effective measures to prevent HBV (1,2), recurrent hepatitis C is an increasing problem facing liver transplant hepatologists and surgeons (3-5). HBV recurrence is effectively contained by the use of hepatitis B inmunoglobulins with antivirals (6,7). Unfortunately, no effective prophylactic therapy is available for hepatitis C so that recurrent hepatitis C occurs almost invariably. Progression to severe allograft fibrosis is often rapid. Current antivirals, including peg-interferons, are limited by substantial toxicities that compromise their efficacy (3,8). Hence, it is not surprising that although some improvements have been made in the treatment of recurrent hepatitis C, a substantial proportion of HCV-infected patients develop recurrent allograft end-stage liver disease leading to a decrease in graft survival, an increase in the need for re-transplantation, and ultimately, a decrease in patient survival (4,5). (Acta gastroenterol. belg., **2005**, 68, **337-346**).

Key words : Hepatitis B, hepatitis C, liver transplantation, live-donor liver transplantation, donor, lamivudine, adefovir, interferon, ribavirin, fibrosis, cirrhosis.

1. Recurrent hepatitis B virus infection

HBV-related liver disease represents 5 to 10% of LT in most series. Indications for transplantation in these patients do not differ from other groups, and include complications from portal hypertension or hepatic insufficiency and/or the development of a hepatocellular carcinoma (HCC). In the absence of effective prophylactic therapies, HBV recurs in 75-90% of cases, causing in a substantial proportion of these patients severe hepatitis, graft failure and death within a short time since transplantation. For this reason, hepatitis B was considered for some years a relative and even absolute contraindication for LT. Both type of disease and HBV DNA level before transplantation are the best predictors to assess the risk of recurrence, with the highest rates reported in HbsAg-positive cirrhotic patients with evidence of active viral replication (HBV DNA and/or HBeAg positive) and the lowest in those without detectable HBeAg or HBV DNA, those with fulminant hepatitis, or those coinfected with the delta virus (2-year actuarial risk : 75%, 67%, 17%, and 32%, respectively) (9).

Histologically, substantial liver damage develops in the short term, with less than 5% maintaining a normal graft on the medium-long term. Typically, patients develop acute hepatitis after detection of HBsAg in serum and high HBV replication, with progression to chronic hepatitis and cirrhosis within two years of transplantation. One particular entity called fibrosing cholestatic hepatitis develops in a small subset of patients, particularly those with high levels of viremia pre-transplantation and those infected with precore mutants (10-12). It is characterized histologically by the presence of periportal and perisinusoidal fibrosis, ballooned hepatocytes with cell loss, pronounced cholestasis and a paucity of inflammatory activity. Immuno-histochemical stains show high cytoplasm expression of viral antigens, which in conjunction with the lack of inflammatory infiltrate, suggests a direct cytopathic effect of the virus. The clinical course is rapidly progressive with severe cholestasis, coagulopathy, and liver failure within weeks of onset (10).

1.1. *Prevention of HBV graft reinfection*

Empirical application of hepatitis B immunoglobulin (HBIg) aiming at maintaining serum anti-HBs titers above 100 IU/L was shown to reduce the rate of viral recurrence. This was further proven in a European, multicenter study, where HBIg was shown to significantly reduce HBV recurrence in non-replicating patients (9). Indeed, when long-term HBIg are used with titers reaching the treshold of 100 UI/L, recurrence is reduced in those without active HBV replication to 17-38% at 2 years (6,7). Unfortunately, recurrence remains approximately the same (70%-96%) in those in whom HBV-DNA is detected prior to transplantation by hybridization methods. Based on these findings, the use of long-term HBIg was established as the standard prophylaxis. HBIg prophylaxis has substantial limitations though, including the cost and the high rate of failure particularly in those with active HBV replication. Major advances have been recently made with the introduction of safe and orally administered antivirals that, when administered in combination with HBIg, not only improve the efficacy but also lower the cost.

a) Lifelong passive immunization with high-dose HBIg with titers above 100 IU/L is followed by an overall

This work was supported in part by a Grant from the Instituto de Salud Carlos III (C03/02).

Correspondence : Marina Berenguer, Hospital Universitario La FE, Servicio de Gastroenterología y Hepatología, Avda Campanar 21, Valencia 46009, Spain.
E-mail : mbhaym@teleline.es.

reduction in the rate of recurrence to 42%, 49%, 54% and 56% at 1, 2, 5 and 10 years with substantial differences observed between patients who are HBV DNA (+) and those who are (–) prior to transplantation (10-year actuarial recurrence of 90% and 38%, respectively) (1,2). Almost no new cases of recurrence are observed after five years. In order to overcome the adverse prognostic characteristic of active viral replication pre-transplantation, two alternatives have been developed : (i) a more aggressive use of HBIg achieving anti-HBs titers higher than 500 IU/L, at least during the first 6 months. With this alternative, recurrence in HBV DNA positive patients may be reduced to approximately 16%-35% (13,14) ; and, (ii) antiviral therapy before transplantation (see later). Various regimens have been described, with most including the administration of 10,000 IU HBIg intravenously during the anhepatic phase and 10,000 IU HBIg daily for the first week post-transplantation. The subsequent dosing is either given on a fixed schedule (generally on a monthly basis) or based on anti-HBs titers (re-administration when anti-HBs is less than 100 IU/l) (6,7,14).

Despite its clear efficacy, HBIg has several drawbacks, including the cost, the need for parenteral administration, the need for close monitoring of anti-HBs levels, the issue of availability, the potential for breakthrough and finally the lack of efficacy in patients with viral replication. Causes of breakthrough are multifactorial including inadequate anti-HBs titers, HBV overproduction from extrahepatic sites and mutations in the "a" determinant region of the surface gene (15-18). In general, early reappearance of HBsAg is related to insufficient dosing of HBIg, while late recurrence is caused by the selection of surface mutations.

• Since HBIg has limitations, there has been a search for potential alternatives to (1) increase the efficacy, in particular in patients with active viral replication and (2) to reduce the cost. Among the former, there are two options : (i) use of antiviral therapy pre-LT so that replication is inhibited and the patient may undergo LT at lower risk (19), and (ii) use of antiviral therapy post-LT in combination with HBIg (20-22). Among the latter, (i) use of lower doses of HBIg by combining this product with antivirals (20,21,23-27), (ii) discontinuation of HBIg followed by either antiviral therapy (28,29) or HBV vaccination (30-33) after the initial period of highest risk of recurrence. Although these two last options are very attractive both from an economic point of view and the quality of life of the patients, they have only demonstrated their efficacy in low-risk patients, but there are no real data in high risk patients.

b) Antiviral treatment prior to transplantation to inhibit viral replication. Lamivudine administration (100 mg daily) in patients with liver cirrhosis induces a decrease in HBV replication to undetectable levels in 62.5% to 100% of treated cirrhotic patients (34-41), including both those infected with wild type virus or the e-minus strain of HBV. An additional benefit who may be obtained by some, but no all patients with decompensated cirrhosis, is an improvement in the hepatic synthetic function. Clinical improvement and stabilization of hepatic function is slow and gradual being more apparent after 6 months of therapy. Although this clinical improvement may be achieved by a subgroup of cirrhotic patients, it is less likely in those with severe hepatic insufficiency (42). Since progression of the disease and even death tend to occur early after the initiation of therapy, generally within the first 6 months, patients with the above characteristics, who most likely have presented late in their disease course, should be prioritized for urgent liver transplantation, irrespective of the antiviral response to lamivudine. The major drawback of lamivudine is the selection of drug resistant mutants with HBV-DNA reappearance. Mutations typically occur in the YMDD motif of the HBV DNA polymerase gene. This risk increases significantly after 6 months of therapy reaching 27% after one year. Although most patients continue to have low serum HBV DNA levels because of the decreased replication fitness of the mutants (43), flares of liver disease with worsening of liver disease have been reported (44,45). In addition, the selection of lamivudine-resistant mutants may increase the risk of HBV recurrence despite the use of high-doses of HBIg + lamivudine post-LT (46-48).

Adefovir dipivoxil (10 mg daily, with dose reductions in those with creatinine clearance below 50 mL/min) is a potent nucleotide analogue that has been shown to suppress viral replication of the wild type virus, the e-minus strain and the lamivudine or famciclovir resistant mutants. In cirrhotic patients who have failed lamivudine, adefovir leads to a significant reduction of HBV DNA levels and normalization of transaminase levels in 61% of the patients (46). It is an excellent drug that can be either used as salvage therapy or as a primary option. As with lamivudine, it is likely that its administration will lead to significant clinical improvement in some, but no all patients. In addition, since resistance to adefovir is extremely low (2% after 2 years of continuous use), these patients may even be removed from the waiting list. The best post-LT prophylaxis in patients with lamivudine-resistant mutants is at present unknown, but probably should be based on triple therapy.

c) Post-transplantation antiviral therapy with/without HBIg

Once LT is performed, there are several alternatives :

• Continue preemptive therapy with lamivudine which was begun prior to transplantation. Although this approach is initially effective, therapy is limited by the emergence of HBV mutants with prolonged treatment, occuring in 40% and 60% at 1 and 3 years, respectively (50). These mutations are typically observed in patients with high HBV replication before treatment initiation (51). Hence, it appears that lamivudine monotherapy is clearly insufficient for replicative

patients, but may be an option for those who are non-replicative.

• Combination therapy with HBIg and nucleoside analogues. It is the most promising alternative and is becoming the standard of care in most transplant programs (20-27). The advantages over a single agent are the following : (i) possibility of administering lower doses of HBIg (400-2000 IU/monthly) which then leads to a significant reduction in cost ; (ii) potential reduction of development of resistant mutants, which is a frequent event when each drug is given as a single agent ; and (iii) synergistic effect with failure rates lower than 10-12% in most series. This synergistic effect appears to be related to the reduction of HBsAg production with lamivudine which then leads to a decrease in the rate of escape mutations both in the preS/S and YMDD regions. The higher rates of recurrence are typically found in patients who have developed lamivudine resistance prior to transplantation. The best protocol is still unknown since doses, routes, type and lengths of administrations vary substantially from centre to centre.

d) Long-term prophylaxis.

In the long-term, 2 approaches have been investigated in patients at low risk of recurrence. In a recent long-term study, it was shown that almost 91% of recurrences occurred within the first 2 years of transplantation and only 3% after the 5th year (2), hence raising the issue of HBIg discontinuation in the long-term.

• Active HBsAg vaccination : Disparate results have been reported by two centers. While in the first study by Sanchez-Fueyos, seroconversion to anti-HBs (antiHBs titers higher than 10 IU/L) occurred in 64% of the 22 patients (30,31), only 23% seroconverted in the Angelico study, despite the use of a reinforced triple course of hepatitis B vaccination (32). The main differences between these two studies include the differences in the study population (all patients in the Italian study underwent transplantation for cirrhosis) and the use of lamivudine following HBIg discontination (100% in the Italian study vs 20% in the Spanish group). More recently, a third group has reported the results of HBV vaccination using a more immunogenic vaccine with promising results (33). If these results are further confirmed, HBV vaccination will enable a substantial proportion of patients now on HBIg to develop a sustained antibody response without the need for continuous passive immunoprophylaxis. This will have major impacts on costs and quality of life. Several aspects need however to be further investigated, including the best vaccine, the definition of protective anti-HBs titers, the amount of HBsAg in each dose, the number of doses, whether target titers should be the same for different subsets of patients or not, and finally, the necessity for boosting to maintain protective titers.

• HBIg substitution with lamivudine in the long-term, with successful results after a short follow-up already reported in low-risk patients (28,29,52). Longer follow up though, is needed to determine the incidence of lamivudine resistant mutants and the efficacy of this approach in high-risk patients.

In these and other long-term studies, it has become apparent that in a substantial subset of patients (up to 45% at 10 years), HBV DNA continues to be detected in serum, liver or peripheral blood mononuclear cells (PBMC) by PCR-based methods following up to 10 years from transplantation (2,29,52), yet these patients continue to be asymptomatic with normal liver enzymes and lack of HBsAg in serum. It is still unclear whether these virological recurrences without clear breakthrough and clinical manifestations will remain so with prolonged follow-up. These findings though raise several issues (1) the indefinite risk of graft reinfection, at least in some patients, and hence need for indefinite use of some type of prophylaxis ; (2) the difficulty in predicting who will clear the virus since persistence of HBV DNA has been proven not only in high-risk patients but also in those at low risk of recurrence ; and (3) the difficulty in identifying the patients who have really cleared the virus and in whom prophylaxis can be safely stopped, task which probably relies on the use of sensitive PCR techniques to detect HBV DNA PCR in serum, PBMC and liver.

1.2. *Treatment of HBV disease of the graft*

Nucleoside analogues are the cornestone of therapy in this setting due to their potent antiviral effect and lack of side effects. The need for continuous treatment and resistance remain the main limitations. The selection of the antiviral is likely dependent on the category of patient. In those who have undergone LT in the pre-HBIg and/or lamivudine era or those with apparent “de novo” HBV acquisition, all known antivirals are potential good candidates. In contrast, for those who have undergone LT in the post-HBIg/lamivudine era and who have broken through, new antivirals such as adefovir that have activity against resistance variants may be best options. With lamivudine, HBV DNA negativization is obtained in 68% to 100% of patients treated for 12 to 36 months (53,54). Resistance occurs in more than 50% in the long-term with a rise in serum HBV DNA and ALT levels. The long-term rate of emergence of drug resistant-mutants and their implications in the natural history of HBV infection are under investigation. Although some cases of histological and clinical deterioration have been reported, particularly in patients under HBIg and lamivudine (45), mutations are not consistently associated with disease progression. The molecular mechanisms associated with this severe recurrence may be a drug-dependent enhanced replication of lamivudine-resistant HBV mutants. Adefovir has resulted in viral suppression of lamivudine resistant variants (49).

1.3. *Prevention and treatment of* de novo *HBV infection*

The prevalence of *the novo* HBV hepatitis ranges from 2% to 8%, and is generally related to transmission from an HBsAg negative anti-HBc positive donor. The most significant factor associated with transmission is the serologic status of the receptor, so that the risk is almost null in patients who are anti-HBs positive, minor (≅ 10%) in those who are anti-HBs negative but anti-HBc positive, and high (≅ 50%-70%) in those without markers of previous exposure to HBV (55). In order to avoid *de novo* HBV infection, three complementary approaches may be undertaken (56) : (i) HBV vaccination prior to LT with response rates of 40% ; (ii) Use of organs from anti-HBc positive donors in recipients already infected with HBV ; and (iii) use of organs from anti-HBc positive donors in special circumstances in those uninfected. In these cases, lamivudine alone is possibly sufficient to prevent HBV reactivation, although some authors recommend combination prophylaxis with lamivudine and low-dose HBIg.

1.4. *Retransplantation*

Retransplantation for recurrent HBV disease is currently rare. If needed, three measures should be followed in order to improve the outcome : (i) avoid late retransplantations when the hepatic failure is too advanced and renal insufficiency has developed, (ii) use antiviral therapy to clear the virus prior to retransplantation, and (iii) choose an aggressive prophylactic regimen to prevent reinfection (57).

In conclusion, HBV-related end-stage liver disease is an excellent indication for liver transplantation. Recurrence is effectively prevented with current therapies. The best available option appears to be the combination of HBIg with pre and post-transplantation antivirals. In the long-term, HBIg discontinuation and substitution with either HBV vaccination or oral antivirals is possibly a good alternative. More studies are though required to define the best timing for HBIg discontinuation, the best vaccination protocol and the best antiviral for long-term prophylaxis.

2. Recurrent HCV infection (58)

Hepatitis C-related end-stage liver disease is the most common indication for LT. Recurrent infection is universal based on the presence of HCV RNA in the serum and/or liver. A rapid and sharp decline in viral load occurs immediately after removal of the infected liver followed by a progressive increase (59) reaching pre-transplantation levels as soon as day 4 and up to 10 to 20 fold higher at 1 month.

2.1. *Natural history of recurrent hepatitis C* (60)

Recurrence of infection is associated with histological evidence of liver injury in the majority of patients. There are different patterns of allograft reinfection and damage (61). In a short proportion of cases, the mechanism of damage is presumably cytopathic and the clinical pattern follows a very aggressive course (see later). The commonest response to persistent HCV infection though is the evolution over time to chronic hepatitis, in a similar way to what we know from the immune competent host. Progression of disease in those with the latter pattern is usually (62), although not always, linear. Although a proportion of patients may have normal histology after one year of follow-up, prolonged follow-up based on protocol biopsies shows that the majority will develop some degree of liver damage (63-67). Unfortunately, liver enzymes do not correlate with either viremia of histological findings, hence providing the justification for protocol liver biopsies at regular intervals in order to identify progression to severe forms of chronic hepatitis (68,69). By assessing the rate of fibrosis progression post-transplantation, the median duration to graft cirrhosis was recently estimated to be 10 years in the transplant population (62), a duration significantly shorter than that observed in the non-transplant patients. Indeed, progression to cirrhosis occurs in a percentage that varies between 6% and 23% at a median of 3-4 years post-transplantation, with cumulative risks at 5-7 years ranging from 10% to 44% (58,60-67). In a subgroup of patients with initial benign recurrence (≅ 30%), delayed hepatitis C-related severe liver damage may occur (70). In these patients, progression to severe disease is not linear and the patients develop a sudden acceleration in fibrosis following an initial and sometimes prolonged period of stabilization. The presence of some degree of fibrosis at baseline, and even more, the combination of some fibrosis and elevated liver enzymes at 3 years post-transplantation, appears to predict this sudden change in the natural history of recurrent hepatitis C.

As previously mentioned, in a small proportion of patients (<10%), an accelerated course of liver-injury leading to liver failure has been observed (71,72), reminiscent of that described in HBV-infected recipients with fibrosing cholestatic hepatitis. Disease generally begins to set in by the first trimester post-transplantation. It is characterized by progressive jaundice and biochemical cholestasis. Levels of viremia are extremely high (72). The course is very aggressive with progression to liver failure within 3 to 6 months. The histology, initially similar to that observed in those with typical HCV recurrence, varies from centrizonal hepatocyte ballooning with little inflammation, to an injury that can mimic large duct obstruction with cholangiolar proliferation.

Once the cirrhosis is established the risk of clinical decompensation is high in the short term (42% in 1 year). Finally, recent data have shown that disease progression, and thus the risk of developing severe HCV-hepatitis post-transplantation is increasing in recent years (62,67,74). Due to the recurrence of the original

Table 1. — **Prognostic factors associated with the outcome of recurrent hepatitis C**

End-Point	Variable
Survival	High viral load prior to transplantation Genotype 1b Hepatocellular carcinoma Advanced hepatic insufficiency (high Child-Pugh score) Non-Caucasian race Aged donor Rejection Methyl-prednisolone boluses
Fibrosis progression	High viral load pre and/or early post-transplantation Genotype 1b Non-Caucasian race Live donor liver transplantation Prolonged ischemic time Aged donor Donor steatosis Rejection Methyl-prednisolone boluses Over and/or abrupt changes in immunosuppression Cytomegalovirus infection Severe and early histological damage High transaminase levels in the early post-transplant period
Late-onset severe disease	Initial fibrosis (F1) in the first-years liver biopsies Elevated transaminase levels during the first post-LT years
Cholestatic hepatitis	High viral load Pulses of methyl-prednisolone therapy and OKT3
Decompensation of HCV-graft cirrhosis	High Child-Pugh score (> A) Low levels of albumin at diagnosis of cirrhosis Short interval between transplantation and diagnosis of clinically compensated graft cirrhosis

LT = liver transplantation.

disease, HCV infection significantly impairs patient survival (60-70% vs 76-77% in non-HCV controls at 5 years) (4,5).

2.2. *Prognostic Factors*

Several factors have been proposed to be associated with a disease progression (Table 1) (3,58). The major determinant of accelerated progression is the immunosuppression. Several indirect findings support the association between disease severity and overall immunosuppression, particularly the more aggressive course of HCV in immune suppressed patients as opposed to immune competent. Global immunosuppression though, and not a single immunosuppressive agent, dominates the effect. In fact, the effect of specific immunosuppressive drugs on viral replication and disease progression is still unknown or controversial for most agents. It even appears that it is the change in immunosuppression rather than the absolute amount of immunosuppression that is deleterious (75). This would explain why corticosteroids boluses and OKT3 use are particularly harmful to HCV-infected patients in most studies, whereas either steroid avoidance or maintaining low levels as opposed to late steroid withdrawal may be beneficial (76-80). This hypothesis may also explain the discrepancies between studies regarding the effect of mycophenolate mofetil (MMF) on disease progression (81-83). Given the negative effect of intense and/or abrupt changes in immune suppression, strategies to reduce the impact of overimmunosuppression have included global reduction in total immunosuppression, discontinuation of individual agents, preference for some immunosuppressive agents with potential antiviral properties, and slow and not dramatic changes in immunosuppression. Long-term follow-up and prospective studies are however needed to determine the beneficial effect of these strategies. Level of viremia pre-transplantation or early post-transplantation predicts the occurrence and/or severity of recurrent hepatitis C, and the rate of survival (62,84,85). These correlations are the basis for early initiation of antiviral therapy. In contrast, the effect of the infecting HCV genotype is unclear (86). However, a high predominance of genotype 1b patients exists in centres that have reported the highest rates of fibrosis progression (62,4). In addition, preliminary data suggest that specific strains within genotype 1 are possibly responsible for the differences in outcome between centers (87). Patients who develop cytomegalovirus (CMV) viremia are at increased risk of severe HCV recurrence (74), likely as a result of cell-mediated immunosuppression. The age of the donor has been found to be independently associated with disease severity, disease progression and survival (4,67,74,88). In fact, the increasing age of the donors may in part explain the worse outcome seen in recent years. Indeed, organs from older donors were infrequently used in the days of LT, but their use has substantially increased in recent years.

The degree of necroinflammatory activity and fibrosis staging observed on the initial liver biopsy, as well as some histologic findings such as steatosis, ballooning degeneration, cholestasis and confluent necrosis may help to predict subsequent progression to severe disease. Indeed, in two studies only 6 to 10% of those with minimal to mild hepatitis in the first year liver biopsy progressed to cirrhosis within the first 5 years post-transplantation while this percentage increased to 29 to 66% of those with moderate to severe hepatitis (63,64). In addition, the existence of fibrosis 1 in the third-year liver biopsy as opposed to no fibrosis was recently shown to predict a late acceleration of fibrosis progression (70).

While using living donation could theoretically lead to better outcomes by avoiding some of the known negative factors (age of the donor, rewarming time, steatosis, levels of viremia), there is a general concern that the results are, in fact, worse than those observed with cadaveric organs. Data are however limited and, similarly to what initially happened with cadaveric organs, the end-point used differ significantly between studies. Small single center studies have generally reported greater rates of recurrences of hepatitis C, higher levels of viremia, and higher rates of cholestatic hepatitis in LDLT recipients compared to deceased recipients (89). In contrast, one large multicenter study has shown that there are no significant differences in short-term graft and patient survival between recipients of liver donor organs and deceased donor organs (90).

2.3. *Post-transplantation management*

A study performed in patients undergoing LT due to HBV and HCV-cirrhosis showed that anti-HBs hyperimmunoglobulin produced before 1990 was associated with a low incidence of HCV recurrence, suggesting that these pools of immunoglobulins contained anti-HCV capable of neutralizing HCV (91). Unfortunately, preliminary data analyzing the efficacy of anti-HCV immunoglobulin (HCIg) for prevention of HCV recurrence did not demonstrate clinical or virological benefits (92).

There are three potential alternative and /or complementary approaches : (1) preemptive antiviral therapy as the patient is awaiting the availability of an organ donor ; (2) early post-transplant antiviral therapy before histological damage has occurred ; and (3) treatment of disease when and if it occurs. The goals of treatment and end points for success of therapy may be different in these situations. The major endpoint of therapy in patients awaiting LT may be the stabilization and/or improvement of the hepatic function so that the need for LT may be delayed or even obviated. Alternatively, viral eradication, or at least viral suppression is also a relevant goal, so that the risk of post-transplantation HCV recurrence and/or aggressive recurrent HCV disease is reduced. The major goal of preemptive post-transplantation therapy is to prevent re-infection of the graft, and in doing so, to reduce the rate of recurrent disease. Finally, the endpoint in patients with established disease is primarily viral eradication, since sustained clearance of HCV RNA appears to be associated with improvement in liver histology in most, but no all patients. A second aim of therapy in patients with established disease is the prevention of fibrosis progression even in the absence of viral clearance.

While the timing and aim of these alternatives are firmly established, their efficacy and efficiency are less clear. It is well known that current antiviral therapy based on interferon with or without ribavirin is poorly tolerated both in the pre and post-transplant setting, therefore limiting its general application.

• Prevention of infection and/or HCV-related disease.

(1) Pre-transplantation therapy with (peg)interferon ± ribavirin. To date, three studies have evaluated this strategy, which is poorly tolerated and can precipitate worsening hepatic function and severe / life-threatening infections. Results from these studies are complementary. In the first study from the U.S. (93), a small number of patients who were near the top of the waiting list were treated with interferon alone or in combination with ribavirin. After several severe side-effects and even death were reported, the study had to be discontinued. In contrast, in the two subsequent studies (94,95) where less sick patients were included, therapy was better tolerated and was only discontinued in 20 to 28% of the patients. In these studies with approximately 120 treated cirrhotic patients, HCV recurrence was prevented in the majority (65%), but no all patients, who cleared the viremia (20%). Hence if tolerated, prevention of recurrent infection may be achievable in those with viral clearance. However, patients with advanced cirrhosis are at increased risk for toxicities, in particular bone marrow suppression, that leads to frequent dose reductions and drug discontinuation. Low antiviral doses with increases as tolerated may improve the tolerability. The applicability of this approach is limited since only half of patients meet entry criteria, particularly with regards to thrombocytopenia and leukopenia. It is potentially a good option in selected patients, probably those with Child scores A such as those with HCC. However, can we justify pre-transplantation therapy of all Child A patients when possibly only a subset of these will develop recurrent progressive disease and some will develop serious side-effects and maybe death related to therapy ?

(2) Posttransplantation preemptive treatment with interferon started during the first 3 weeks does not appear to modify disease progression. Combination with ribavirin may produce some benefits (96), but data are lacking. The applicability of this alternative is unfortunately low due to the frequent development of side effects and low proportion of patients meeting entry criteria, particularly with regards to anemia, neutropenia and thrombocytopenia (97). As with pre-LT therapy, is it justifiable ?

- **Treatment of HCV-related recurrent disease**

Most of the published work on antiviral therapy has focused on treatment of established disease. Results with interferon or ribavirin as single agents have been disappointing. The efficacy is improved when both drugs are administered in combination for 6-12 months with overall sustained responses achieved in 9% to 33% (98-105). Severe side effects though occur in a significant proportion of patients leading to frequent dose reductions or discontinuations, frequent hospital admissions and blood transfusions, frequent use of granulocyte colony stimulating factor and erythropoietin, and a constrained follow-up. Overall, up to 20% of liver transplant recipients treated with interferon require cessation of therapy because of cytopenia. As for ribavirin, the most frequent and severe side effect is hemolytic anemia, potentiated in this setting by the reduced renal clearance from calcineurin-inhibitor nephrotoxicity and HCV-infection renal disease. Overall, 40-50% of patients treated with the combination interferon (either standard of pegylated) and ribavirin need to discontinue therapy due to the development of severe side effects. Dose reductions have been reported in more than two thirds of those treated. Response is better if initiated early, with non-1 genotypes, and in those without advanced disease. Although preliminary, treatment appears to be better tolerated with pegylated interferons. Duration of therapy is at present unknown. Although most clinicians follow the same guidelines that are used in immune competent patients, controlled studies are required to define the optimal duration. In that sense, in one large recent Italian study, the rate of sustained virological response was the same (approximately 20%) irrespective of whether the patients received a 6 or a 12-month course of combination interferon-ribavirin (104). In contrast, therapy may need to be indefinite in those with the most severe forms of cholestatic hepatitis (100). Most studies have shown a histological improvement and/or reduction in fibrosis progression among those responding to therapy. In addition, long-term studies have shown that loss of HCV after treatment of recurrent hepatitis C is durable, and that the durability of the response is associated with improvement in hepatic inflammation and regression of fibrosis (107,108). With the available drugs, treatment of the established disease is probably the most cost-effective option (109). Although limited by a relatively low efficacy, tolerance appears to be better, and treatment is only offered to patients who develop progressive disease. In that sense, protocol liver biopsies may identify early histologic changes which herald an aggressive course. Treatment should be initiated, if no contraindications are present, once portal fibrosis and/or moderate necroinflammation are detected.

2.4. *Retransplantation*

Re-transplantation is the last option for patients with failing grafts due to recurrent disease. The number of patients infected with HCV at need of second transplantation is expected to grow as primary transplant recipients survive long enough to develop graft failure from recurrent disease (110). Whether to perform retransplantation for these patients is a matter of debate across the world. While we wait for a consensus, it has become apparent that this procedure is becoming less common at many centers. The fear with re-transplantation, particularly in those with early severe recurrence, is related to four major aspects : 1) early reports suggesting a worse outcome following re-transplantation in HCV-infected recipients than in those uninfected (111,112) ; 2) uncertainty regarding the natural history of recurrent hepatitis C in the second graft ; 3) frequent comorbidities in these patients who generally have an advanced age by the time the require retransplantation ; and 4) increased organ shortage. Most series have shown that the outcome is generally poor, significantly worse than that obtained with retransplantation in other causes of late graft loss (113-115). Most cases of death occur in the first 6 months and are due to sepsis. However, it has also been shown that the outcome may be improved if performed before significant renal impairment and hepatic failure develop, and with the use of younger donors. Unfortunately, under the current MELD organ allocation system, patients have no realistic hope of receiving an organ until they have developed significant coagulopathy and renal insufficiency, and as a result, most patients with recurrent allograft failure due to hepatitis C will only receive an organ at a point when they are unlikely to survive retransplantation (116). In addition, some series have reported that the severity of recurrent hepatitis C in the new graft is related to that observed following the first transplant (117).

In conclusion, recurrent hepatitis C is an important problem due to the accelerated progression of the disease in the pos-transplant setting and the lack of effective and well-tolerated drugs to prevent and/or treat recurrence.

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