Viral hepatitis B, C and D

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Recurrence of the original liver disease is a a major threat to long-term survival in liver transplant recipients (1). This is particularly true for viral hepatitis. Recurrence was first best described for hepatitis B, with more than 80% viral recurrence in the era prior to the introduction of immunoprophylaxis (2). Although hepatitis B recurrence has been effectively contained by the use of hepatitis B immunoglobulin with or without lamivudine, recurrent hepatitis C is becoming an increasingly challenging problem to the transplant community (3).

Recurrent hepatitis B virus (HBV) infection

Before the introduction of immunoprophylaxis, HBV-infected patients had done poorly with a 5-year post-transplantation survival of only 50% compared to 70-85% for other indications (2). This reduced survival was in large part due to the high rate of HBV recurrence (approximately 80%) with subsequent graft loss due to the development of recurrent liver disease (> 70%) (2,4). In recent years, several new and effective therapies have become available (1,4,5) including hepatitis B immunoglobulins (HBIg) and nucleoside/nucleotide analogues. Currently, the debate has shifted from whether liver transplantation is an option for this patient subgroup to selecting the best approaches to prevent reinfection and treat disease prior to and following transplantation.

Natural history

HBV infection post-transplantation typically results from the recurrence of an infection present prior to liver transplantation (3,4). The serological and virological status prior to transplantation is the major predictor of post-transplantation reinfection, with lower rates in patients with fulminant hepatitis, HDV coinfection, and chronic HBV infection without detectable HBeAg or HBV DNA pre-transplantation than in those with indices of active viral replication (4).

Ocasionally, HBV infection post-transplantation is a consequence of *de novo* infection (6,7), with a prevalence which ranges from 2% to 8%. It is generally related to transmission from an HBsAg negative anti-HBc positive donor. In these cases, 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 (6,7).

The natural history of recurrent hepatitis B is more agressive than that observed in the immunocompetent population. Typically, patients develop acute hepatitis after detection of HBsAg in serum, with progression to chronic hepatitis and cirrhosis within two years of transplantation (3). One particular entity initially described in these patients (8), and later, among HCV-infected recipients (9), is called fibrosing cholestatic hepatitis. 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 (8). Immunohistochemical 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, hypoprothrombinemia, and liver failure within weeks of onset. Patients at risk for this syndrome include those with high levels of viremia pre-transplantation and those infected with precore mutants.

Pre-transplantation therapy

Since the presence of HBV replication (HBV DNA positive by hybridization methods) prior to transplantation is associated with a high rate of recurrence (4), even when HBIg is used, nucleoside/nucleotide analogues (10) have been used in an attempt to reduce the level of viral replication and allow transplantation (10-13). These drugs have a potent antiviral effect inducing a rapid clearance of HBV DNA from serum. They are very well tolerated, are orally administered and, in contrast to interferon, do not precipitate worsening of liver function in patients with advanced disease . Most of the experience published to date is with lamivudine (10-14).

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Table 1. — **Lamivudine as treatment of HBV cirrhosis : clinical improvement**

Author, year (#)	HBeAg+ (%)	Follow up (mo)	C-Pugh decrease (%)	Resistance		
				total (%)	1 year (%)	2 years (%)
Villeneuve, 2000 (35)	57	19	66	13	10	25
Marzano, 2000 (33)	27	5.6	33	3	NA	NA
Fontana, 2000 (37)	92	NA	27	13	NA	NA
Yao, 2000 (13)	69	17.5	69	8	8	–

In some instances, clinical progression of decompensated liver disease is even reduced (Table 1) and the need for liver transplantation may be delayed. The major drawback of this approach is the development of "resistance" to lamivudine with HBV DNA reappearance (5,10). This risk increases significantly after 6 months of treatment and thus lamivudine should be initiated taking into account the expected waiting time for liver transplantation. Adefovir dipivoxil is effective against resistant mutants to lamivudine and can be used as salvage therapy (15). Some authors advocate the use of this drug as a first-line option in patients awaiting liver transplantation since resistance to adefovir is extremely uncommon.

Prevention of HBV graft reinfection

Lifelong passive immunization with high-dose HBIg was until very recently considered the "standard of care" (1,4,5,16,17). The presumed mechanism of action of this antibody is to neutralize circulating virus by binding to the viral envelope preventing infection of the transplanted liver. The administration of HBIg for more than 6 months has been shown to reduce dramatically the rate of HBV recurrence to a median rate of 20% after 2 years (4,16,17). This effect is observed in those with fulminant HBV (< 10%), in HDV coinfected patients (10-15%), and in HBV DNA negative cirrhotic patients (< 30%), but not in those with HBV DNA positive HBV cirrhosis (4,16,17). In these patients, the use of more aggressive HBIg maintaining titers over 500 IU/l (18, 19), or the use of HBIg in combination with nucleoside/nucleotide analogues post-transplantation (20) may overcome the limitations of HBIg alone.

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 (readministration when antiHBs is less than 100 IU/l) (4,16-20).

Despite the clear efficacy of prophylactic HBIg, this therapy has limitations. The major disadvantages are high cost, limited availability, difficulty in discontinuing this product in the long-term (21) and the lack of efficacy in approximately 20% of patients. Causes of breakthrough are probably multifactorial and include inadequate anti-HBs titers, HBV overproduction coming from extrahepatic sites and/or mutations in the region of the surface gene of the HBV genome which encodes the "a" determinant region, the putative region for antibody binding, due to immune pressure selection (17).

There are several alternatives to long-term HBIg. The first is to continue the preemptive therapy with lamivudine which was begun prior to transplantation (13). Although prophylaxis with lamivudine alone is initially effective (22), it is limited by the emergence of HBV mutants with prolonged treatment (23-25), mainly in patients with high level of viral replication prior to transplantation (25).

The second alternative and most promising approach is the use of combination therapy with HBIg and nucleoside analogues. In a preliminary report, lamivudine in combination with high doses of HBIg was shown to be safe and highly effective (20) without reatment failures and an excellent survival after one year of treatment. The cost was however high due to the use of HBIg at high doses. More recently, combination prophylaxis with low doses of intramuscular HBIg and lamivudine has also shown to be effective (recurrent HBV rates < 10%) (26-32) and less costly (33). Certain issues which are still unresolved are the dose and duration of HBIg treatment.Patients infected with pre-core mutants may be at higher risk of recurrence despite combination therapy but the data are controversial (30,31). Some authors have suggested that HBIg should only be maintained during the "high-risk period" (32), that is the first 6 months post-transplantation, while others prefer to maintain lifetime low-dose HBIg (21).

A final alternative is the use of HBIg followed by vaccination against HBV (34). Results of this approach are contradictory. One pilot study based on a "low-risk population of transplant recipients" showed good results with an 82% seroconversion rate to anti-HBs and no HBV recurrence following seroconversion (34). A second study however has found less optimistic results (35). Reasons which explain the observed discrepancies include differences in the study design (use or not use of lamivudine following discontinuation of HBIg) or in patient population analyzed. Evaluation of this approach in high risk patients should also been investigated.

Treatment of HBV disease of the graft

Interferon has been used in this setting with low efficacy and albeit low, risk of rejection (36). New nucleoside analogues are promising due to their potent antiviral effect and their lack of side effects, particularly regarding the risk of rejection (5). Resistance however is an issue (5,36-44). In most studies, liver transplant recipients with

Table 2. — **Treatment of recurrent hepatitis B with lamivudine**

Author, year	#	Follow-up (mo)	Negativization HBV DNA (%)	Normalization ALT (%)	Breakthrough (HBV DNA re-positivization) (%)
Andreone, 1998	11	17	100	100	27
Nery, 1998	8	27	87%	–	29
Perrillo, 1999	52	12	60	71	27
Malkan, 2000	15	25	100	–	13
Ben-Ari, 2001	8	36	37	62	62
Fontana, 2001	33	21	100	27	45

documented HBV recurrence (elevated serum ALT levels, and detectable HBsAg and HBV DNA) have been treated with lamivudine 100 mg daily (adjusted for renal function) with good tolerance and rapid loss of HBV DNA in serum. Good biochemical and virologic response have been achieved not only in patients with chronic hepatitis B but also in the setting of acute hepatitis B and in cases of fibrosing cholestatic hepatitis. Response is associated with histologic improvements. The downside of this agent is the need for continuous treatment since relapse is the rule once the drug is discontinued. Prolonged therapy is associated with the potential development of breakthrough due to the emergence of HBV escape mutants (Table 2). This resistance generally occurs after prolonged therapy (more than 6 months) and is associated with a rise in serum HBV DNA and ALT levels. Molecular analysis of these mutations has shown changes in the gene for the viral DNA polymerase (41-44). The implications of these mutations in the natural history of HBV infection are unclear. They are generally not associated with acute flares of the hepatitis except in some cases. Lamivudine resistant variants remain sensitive to adefovir (15,45,46).

Prevention and treatment of de novo *HBV infection*

There are two potential approaches to prevent *de novo* HBV infection : (i) HBV vaccination of all anti-HBs negative candidates to liver transplantation with an accelerated vaccination regimen. Unfortunately, as with other immunosuppressed populations, the results of vaccination in these patients have been disappointing with response rates which barely reach 40% (47) ; (ii) Anti-HBc determination of the donor with use of organs from anti-HBc positive donors only in recipients already infected with HBV or in those with minimum risk of HBV transmission, that is, recipients with anti-HBs and/or anti-HBcore positive (6,7,48). If an anti-HBc(+) donor is offered to a naïve recipient with critical clinical situation or with hepatocellular carcinoma, prophylaxis of HBV infection with either lamivudine or HBIg or a combination of both agents is advisable given the high likelihood of HBV acquisition.

Retrasplantation

The initial results on retransplantation for patients with graft failure due to recurrent hepatitis B were discouraging due to high rates of HBV reinfection and even more aggressive disease in the second graft (49). Improved outcomes have been achieved with specific interventions, mainly with the use of aggressive immunoprophylaxis to prevent HBV reinfection in combination with lamivudine which is typically started prior to retransplantation in order to inhibit viral replication (49,50).

Transplantation in patients coinfected with hepatitis delta infection

Delta infection is an uncommon indication for liver transplantation. Patients with HBV and hepatitis delta (HDV) infection are at low risk of recurrent infection because of the typically low HBV DNA levels (4,51-53). In the absence of HBIg, both HBV and delta virus can infect the graft, but HDV is not pathogenic until HBV replication also occurs. With long-term follow-up HBV and delta infection of the graft can cause progressive liver injury. HBIg prophylaxis is effective at preventing recurrence in the majority of those with pre-transplantation coinfection. The additional benefit of pre-transplantation treatment with lamivudine is largely unstudied but is commonly administered in clinical practice. Current recommendations are similar to those applied for hepatitis B.

Recurrent hepatitis C virus infection

Hepatitis C virus-associated end-stage liver disease is a leading diagnosis in patients undergoing liver transplantation (1,2). Viral recurrence defined by the presence of HCV RNA in serum following transplantation occurs near universally (54). In spite of viral recurrence, early post-transplantation infection typically results in indolent disease with good graft and patient survival. Disease progression is however signficantly faster than that observed in immunocompetent patients, with a higher rate of cirrhosis occurring within 5 years of infection in transplant recipients than in the immune competent patient (55,56). Histologic evidence of liver injury develops in approximately half of the patients within the first year post-transplantation (55-62). With longer follow-up (5-7 years), the vast majority of patients develop some degree of histologic damage with a subset, ranging from 8 to 30%, progressing to HCV-related graft-cirrhosis (55-62). Development of cirrhosis is associated with a

reduction in survival (55,63). Based on the histological evolution of chronic hepatitis in these patients, it has been estimated that the duration of time required to develop graft cirrhosis is approximately 10-12 years in the average patient (56). Furthermore, in a proportion of patients albeit less than 5%, an accelerated course of liver-injury leading to rapid development of liver failure has been observed (9), reminiscent of that previously described in HBV-infected recipients with fibrosing cholestatic hepatitis (8). Finally, recent data have shown that disease progression has increased in recent years (55,56), the reasons for this being as yet unidentified. From these observations, it is not surprising that in several transplant programs reaching their second decade of activity, an increase in HCV-related graft loss is being observed with a subsequent decrease in both graft and patient survival (55,63).

The natural history of posttransplantation hepatitis C is however, highly variable and while some patients develop cirrhosis in less than one year due to recurrent infection, others show minimal or no injury in their protocol liver biopsies during years of follow-up. Factors influencing this variability are probably many and are present prior to and or following liver transplantation (2) :

Immunosuppression : Recent data have implicated the immune system in the pathogenesis of liver injury due to HCV (64,65). These observations are supported by the observation that the course of HCV infection is accelerated in liver transplant recipients when compared to that observed in immune competent patients (56), suggesting a deleterious role of immunosuppression on progression of HCV-related liver disease. Progression is not only faster prior to the development of cirrhosis but also afterwards, with a shorter natural history of clinically compensated HCV-related graft cirrhosis in transplant patients compared to that observed in immunocompetent patients (66). Not only is the immunosuppressed status per se deletereous for the evolution of the hepatitis C, the intensity of the immunosuppression has also been shown to be associated with disease severity, so that patients who are more severely immunosuppressed such as those receiving high doses of steroids or anti-lymphocyte globulin are at higher risk of progressing to cirrhosis than those less immunosuppressed (2,67-70). Furthermore, a strong association has been found in one study between the year of transplantation and fibrosis progression, with patients transplanted recently progressing at a faster rate than those transplanted in earlier years (55,56). This progressive nature of recurrent hepatitis C may in part be related to the recent introduction of more potent immunosuppressive agents, such as tacrolimus and mycophenolate. Results of the potential association between the type of administered immunosuppression and disease severity are however difficult to prove due to the multiplicity of immunosupressive regimen together with the changes in immunosuppressive drugs in individual patients over time. In that sense, the majority of studies have found no differences in patient and/or graft survival in recipients treated with cyclosporine-based versus those treated with tacrolimus-based induction regimens (2,71-73). Data on MMF are conflicting (74). Preliminary data suggest that IL2-receptor antibodies are associated with an aggressive course of recurrent hepatitis C (75).

Pretransplantation HCV RNA levels : Several studies have shown that, as described for HBV, level of viremia pre-transplantation or early post-transplantation predicts the occurrence and/or severity of recurrent hepatitis C (56,70,76,77).

HCV genotype : The effect of the infecting genotype on the severity of liver disease posttransplantation is unclear. Some (57,58,77), but not all (78) studies have implicated genotype 1b in a more severe posttransplantation disease compared to non-1b genotype. It may be possible that different strains belonging to genotype 1b may be involved (79).

Donor-related variables : The age of the donor has been found to be independently associated with disease severity, disease progression and survival (55). The increasing age of the donors may explain in part the worse outcome seen in recent years (55,56).

Coinfection with other viruses : Patients who develop cytomegalovirus (CMV) viremia are at increased risk of severe HCV recurrence (80). The reasons for this association are unknown but likely relate to induction of immune-deficiencies, release of tumor necrosis factor by CMV or the existence of cross-reactive immunological responses**.** Coinfection with HBV may influence histologic disease severity but results are conflicting (57,81). In contrast, coinfection with other viruses such as HGV (82) does not seem to influence the post transplantation course of HCV disease.

Histologic changes : The degree of necroinflammatory activity and fibrosis staging observed on the initial liver biopsy has been used as variable predictive of subsequent development of severe chronic hepatitis C in some studies (55,56,58, 59,61,83).

Year of transplantation is significantly associated with time to cirrhosis and fibrosis progression with patients transplanted more recently progressing at a faster rate than patients transplanted in earlier cohorts (55,56). Reasons which explain the worse outcome seen in HCV-infected patients in recent years are not fully understood. Possible factors include : (i) increasing age of the donors, (ii) use of stronger induction and initial maintenance immunosuppression, (ii) an earlier and faster reconstitution of the immune system with withdrawal of “second line immunsuppressive drugs” such as prednisone and azathioprine at earlier time-points than previously done (84) ; and (iv) a selection of more virulent strains due to previous failed antiviral courses of therapy (55,56,79).

Other variables : Prolonged rewarming time during allograft implantation, non-Caucasian race, an early detection of anti-HCV core IgM have been associated with severe recurrent disease (2).

Indication for liver transplantation

The indications for liver transplantation in HCV-infected patients do not differ from other causes. However, given the lack of effective prophylactic and therapeutical options, the universal recurrence of HCV and the rapid progression to graf failure in a substantial proportion of recipients (2), liver transplantation should not be considered just because the patient meets minimal listing criteria. Aggressive medical management should be indicated in these patients. In a significant percentage of cases, the existence of a coincidental hepatocellular carcinoma is the primary indication for transplantation. The outcome of patients with hepatocelullar carcinoma does not differ from that of patients without the tumor if strict selection criteria are followed (85). The long-term outcome is typically impaired by recurrence of HCV more than tumoral recurrence (86). Alternative measures should thus be proposed in cases of tumors treatable with traditional alternatives (percutaneous alcohol injection, transarterial chemoembolization, radiofrequency) or with surgery. In these patients, antiviral therapy should also be tried in an effort to eradicate viremia and, in doing so, obviate transplantation.

Prevention of infection and/or HCV-related disease

In contrast to HBV, there are no universally effective measures to prevent recurrence with HCV. It may be attempted with antiviral therapy administered either prior to transplantation or early post-transplantation.

Posttransplantation preemptive treatment is aimed at preventing HCV disease recurrence or diminish the risk of agressive histologic progression. Treatment with interferon alone does not appear to modify disease progression (87,88). In one study (87), 86 recipients were randomized within 2 weeks of transplantation to receive either interferon alone (n = 38) or placebo (n = 48) for one year. While patient and graft survival at two-years did not differ between groups, and the rate of persistence of HCV was not affected by treatment, histologic disease recurrence was observed less frequently in interferon-treated patients (8 of 30 evaluable at one year) than in those who were not treated (22 of 41 ; p = 0.01). In a second controlled trial (88), 24 recipients were randomized at 2 weeks post-transplantation to receive interferon or placebo for 6 months. Patient and graft survival, and the incidence of histologic recurrence and its severity did not differ between groups. However, interferon treatment delayed the development of HCV hepatitis. Combination with ribavirin may produce some benefits (89). In one small uncontrolled case series, 36 recipients were treated with IFN-alpha2b and ribavirin starting the third posttransplant week and continued for 1 year. An excellent actuarial 5-year survival was obtained (87.5%). At 36 months post-discontinuation of therapy, a sustained virological and biochemical response was achieved in 12 patients (33%), 20% in those infected with HCV genotype 1 and 100% in those with genotype 2. Liver biopsies were normal in these patients. In contrast, progression to severe hepatitis C was observed in 4 of the non- responders (11% of the overall series). Common side effects included hemolytic anemia and asthenia which were well controlled with dose reduction. Well-designed controlled randomized studies are needed to confirm these findings. Unfortunately, the development of side effects and the probably low proportion of patients meeting entry criteria, particularly with regards to anemia, neutropenia and thrombocytopenia, may ultimately limit the potential utility of this therapy.

Pre-transplantation therapy with interferon may be attempted to suppress replication, and in doing so, improve the posttransplantation outcome. Until very recently, there had only been anecdotal case reports of the use of interferon in decompensated HCV-cirrhotic patients, since these patients have been typically excluded from randomized trials. Interferon is poorly tolerated in this setting and can precipitate worsening hepatic function. In addition, patients with advanced cirrhosis are at increased risk for bone marrow suppression during combination therapy and can suffer severe, and even life-threatening infections during treatment. Two recent studies have evaluated this strategy (90,91). Both studies started with low doses of interferon ± ribavirin and slowly increased the drugs as tolerated. In the multicenter study by Crippin and colleagues (90), less than half the patients screened met entry criteria, with thrombocytopenia and leukopenia being the most common reasons for exclusion. Eventually, only 15 patients from 5 large transplant centers were administered antiviral therapy. While on treatment, loss of detectable HCV RNA was seen in 33%. Unfortunately, recurrence of infection was not prevented in the only patient undergoing transplantation with undetectable viremia (by bDNA) at the time of transplantation. In addition, a significant number of adverse effects occurred (n = 23), many of which were considered severe. While thrombocytopenia was the most frequent adverse event, infection was the most severe one. These side effects particularly, life threatening infections, ultimately led to the early termination of the study. In the second study by Everson and colleagues (91), 101 patients with advanced cirrhosis (with a better hepatic function : mean Child Pugh score of 7) were treated with a dose-escalating regimen. Preliminary data on 91 have been recently presented in abstract form with results more optimistic than in the previous study. On treatment virological responses occurred in 38% and sustained virological response in 22% of patients. Sustained responses were more

Table 3. — **Combination therapy with interferon-alfa and ribavirin in patients with recurrent hepatitis C**

Author, year (Nº)	Treatment regimen	Biochemical Response / Virological Response (%)	Sustained Biochemical Response / Virological Sustained Response (%)	Histological improvement	D/C(%)
Bizollon, 1997, (21)	6 mo IFN + Rbv + 6 m Rbv	100 / 48	86 / 24	Yes	14
Alberti, 2001 (18)	12 m IFN + Rbv + long-term Rbv	83 / 44	78 / 33	Yes	22
Ahmad, 2001 (60)	6 mo IFN (n = 40) vs 12 mo combinación (n = 20)	20 vs 25 / 15 vs 40	NA vs NA/ 2,5 vs 20	No	25
De Vera, 2001 (32)	IFN + Rbv ≥ 12 m	77 / 9	71 / 9	No	40
Gopal, 2001 (12)	IFN + Rbv indefinitely	NA / 50	NA / 8	NA	0
Narayanan, 2002 (26)	12 mo IFN + Rbv	42/35	NA	YES	50
Lavezzo, 2002 (57)	12 mo IFN- Rbv (n = 30) vs 6 mo IFN-Rbv (n = 27)	66 vs 53 / 23 vs 33	37 vs 30 / 17 vs 22	YES	5
Andreone, 2001 (9)	IFN + Rbv + Amantadine	33 / 33	11 / 11	YES	67

IFN = Interferon, Rbv = Ribavirin, NA = Not available, D/C = Discontinuation

* Sustained virological response was significantly higher in HCV-genotype 2-3-4 infected patients than among those infected with HCV genotype 1.

common in patients treated for more than 6 months. Recurrent infection of the allograft was observed in all patients with detectable HCV RNA at the time of transplant. In contrast, recurrence of infection was prevented in the 8 patients HCV RNA negative at the time of transplantation. Twenty-eight percent of the patients had to discontinue therapy due to severe side effects. Thus, pretransplantation treatment with combination therapy is feasible in selected patients, probably those with Child scores A or B. A group of patients who may benefit from this approach are those with a coexistant hepatocellular carcinoma.

Treatment of HCV-related recurrent disease

Treatment of recurrent HCV disease with interferon or ribavirin as single agents has been disappointing. Initial results from combination therapy are slightly better. Interferon at doses of 3MU, thrice weekly for 6 months, has failed to clear serum HCV RNA, despite normalization of ALT values in a subset of patients treated (0%-28%) (92-94). Relapse after discontinuing treatment is almost the rule, and post-treatment improvement in liver damage is uncommon. The experience with ribavirin monotherapy has also been limited, and results discouraging, with biochemical improvement in some patients but virological clearance in none (94). In addition, biochemical relapse is universal after cessation of therapy and no histological improvement was observed. Hemolysis is the main side effect. The efficacy is improved when both drugs are administered in combination (95-104). Table 3 summarizes the results of recent studies using interferon and ribavirin as the treatment of recurrent hepatitis C. Overall sustained responses are achieved in 9% to 33%, and are probably the same when using a 6 vs a 12-month course. The broad range of response probably relates to the differences in genoytpe distribution in the study population, differences in timing of intervention and in the severity of the underlying hepatitis C once therapy is initiated. It is likely than an early intervention leads to better rates of response. In addition, results are better in those infected with HCV genotype non-1 than in those infected with genotype 1. Most studies have shown an improvement in liver histology among those responding to therapy. Tolerability of interferon and ribavirin is variable depending on the study. It frequently leads to dose reductions or discontinuation. Maintenance therapy with ribavirin is used in some centers, the efficacy being unknown to date and the rationale not completely understood. Preliminary data suggest that this maintenance therapy may be discontinued in patients who have achieved a sustained virological response.

In conclusion, with the available drugs, treatment of the established disease is probably the most cost-effective option. 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 identifiy early histologic changes which herald an aggressive course, and in these cases, therapeutical interventions may be implemented at earlier stages when a response appears to occur more frequently.

Alternative approaches

Since the efficacy of antiviral therapy is limited, selection of patients at low risk for severe recurrence and optimal management of long-term immune suppression are likely important in improving long-term outcomes. Unfortunately, no single or combination of variables is capable of accurately predicting which individual will develop serious disease post-transplantation and which individual will not.

Given the deleterous effect of intense immune suppression on the progression of recurrent HCV-disease, steroid doses should be minimized and anti-lymphocyte globulin avoided if possible. This is a trend already followed in many transplant centers, but its efficacy has yet to be proven. Additionally, when doubts exist between rejection and hepatitis C because of overlapping histological findings, serial biopsies should be performed to clarify the clinical picture.

Retransplantation

Retransplantation is the last option for patients with failing grafts due to recurrent disease, and the results of retransplantation are inferior to those reported for first transplants (105). As predicted from natural history studies, the prevalence of HCV infection in patients undergoing retransplantation is progressively increasing in most transplant centers. It has thus become imperative to determine whether all patients with graft failure due to recurrent HCV disease are candidates for further transplantation, or whether there is a subset in whom the outcomes would be so poor that retransplantation should not be undertaken. Early reports had suggested poor outcomes (105-107). However, other factors such as creatinine, bilirubin, and UNOS status appear to have greater predictive value than HCV status in patients undergoing retransplantation (108,109), and outcomes are improved if retransplantation is performed before severe hyperbilirubinemia and development of renal complications. A recent study defined the natural history of HCV-related graft cirrhosis in an attempt to determine predictors of clinical decompensation, timing of re-OLT and mortality (66). Thirty-nine patients with clinically compensated graft cirrhosis were evaluated ; 46% developed at least one episode of decompensation at a mean of 8 months. Patient survival rates dropped once decompensation developed (93%, 61%, and 41% at 1, 6 and 12 months, respectively). Variables associated with decompensation included a high Child-Pugh score and low albumin level of diagnosis of graft cirrhosis, and short interval between transplantation and development of cirrhosis. Thus, if retransplantation is considered, it should be performed before decompensation. Serial liver biopsies may help in the diagnosis of clinically compensated HCV-related graft cirrhosis, facilitating an early referral for liver retransplantation, at a stage where the probabilities of a favorable outcome are higher. It is unclear whether the severity of recurrent HCV disease in the first graft predicts the severity of recurrence in the second graft (110).

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