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Clinical management of patients with recurrent viral hepatitis after liver transplantation

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KEYWORDS

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Abstract Liver transplantation is indicated in end-stage chronic viral liver disease, but unless adequate prophylaxis is administered, the patient will in most cases develop recurrent hepatitis B (HBV) and C (HCV) virus infection. Today, patients receiving prophylaxis using nucleoside analogue drugs with or without specific immune globulin drugs in connection with orthotopic liver transplantation for HBV related cirrhosis, present low risk of relapse and high 5–10 year survival rates. Lamivudine was the first drug used in the prophylactic treatment, but this drug has increasingly been combined with or replaced by adefovir due to the low genetic barrier, which causes viral resistance. Most patients develop viral recurrence after orthotopic liver transplantation for HCV related cirrhosis, and in an elevated number of cases, cirrhosis and hepatic insufficiency set in after a few years. Prophylaxis before transplantation and pre-emptive treatment using interferon and ribavirin present numerous side effects resulting in reduction of doses and suspension of therapy, with consequently low sustained virological remission rates and risk of rejection.

The treatment is better tolerated by patients with histologically confirmed chronic disease, but also in these patients virological remission rates are low. This pathology requires new therapeutic protocols and/or new drugs in order to obtain better compliance and better responses.

Sommario Il trapianto di fegato rappresenta il trattamento indicato nella malattia epatica cronica virale in fase avanzata, ma senza un'adeguata profilassi l'infezione da virus B o C recidiva nella maggior parte dei casi.

In questi ultimi anni il paziente con cirrosi HBV correlata che necessita di trapianto ortotopico di fegato utilizzando una profilassi con farmaci analoghi nucleosidici, associati o meno alle immunoglobuline specifiche, presenta un basso rischio di recidiva e ottima percentuale di sopravvivenza a 5–10 anni. La lamivudina è stato il primo farmaco utilizzato nella profilassi, ma sempre più viene associato o sostituito dall'adefovir per la bassa barriera genetica, responsabile di produzione da parte del virus di resistenza.

Nella quasi totalità dei pazienti con cirrosi C si assiste a una recidiva virale dopo il trapianto di fegato a cui consegue, in una elevata percentuale di casi, cirrosi e insufficienza epatica nell'arco di pochi anni.

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La profilassi prima del trapianto e il trattamento preemittivo con interferone e ribavirina sono gravati da molti effetti collaterali, riduzione della dose fino alla sospensione della terapia con percentuali di remissioni virologiche sostenute non molto elevate, con rischio inoltre di rigetto.

La terapia è meglio sopportata nella malattia cronica, accertata istologicamente, ma anche in questo caso il numero di remissioni virologiche rimane basso.

In questa patologia saranno necessari nuovi protocolli e/o nuovi farmaci che consentano di ottenere una compliance migliore associata a migliori risposte.

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Introduction

Virus related liver cirrhosis is the main indication for liver transplantation, and hepatitis C virus (HCV) related cirrhosis is the most frequent reason for transplantation both in Europe and in the U.S. ranging from 30 to 45%. Hepatitis B virus (HBV) related cirrhosis is the second most frequent indication in Italy (21.7%) and in the U.S. (5–10%) [1,2]. Unless prophylaxis is received recurrence of HBV and HCV infections reaches almost 100%.

Prophylaxis and treatment of recurrent HBV infection

In the past, indication for liver transplantation in patients with HBV related cirrhosis was controversial as 75% of patients developed recurrence independently of their viremic condition, reaching a 5-year survival rate of only 50%.

Today more patients with HBV related cirrhosis are considered for transplantation as pre- and postoperative prophylactic therapy using specific immune globulin drugs and nucleoside/nucleotide analogues have led to a 10-year survival rate of 70.9% [3].

Patients considered for liver transplantation are differentiated on the basis of HBV replication assessed using polymerase chain reaction (PCR). Different therapeutic strategies are applied in patients who have markers of active replication and in patients without markers of active replication, as antiviral preoperative therapy is not useful in the absence of viral replication [4,5]. The aim of pre-transplant therapy is to suppress HBV replication in order to reduce the risk of liver graft reinfection. Cut-off value differentiating "replicators" from "nonreplicators" is 5 log copies/ml, and transplantation can be performed without prophylactic treatment if the HBV DNA replication rate is below this value.

Interferon is not useful in prophylactic treatment, as it can cause cytopenia, infections and hepatic decompensation associated with modest antiviral activity, whereas nucleoside analogues such as lamivudine and adefovir are indicated. Lamivudine is well tolerated also by decompensated cirrhotic patients, and in 62–100% of cases HBV DNA replication is repressed within 2–3 months. This can be demonstrated using a molecular hybridization test. However, the genetic barrier of this drug is low, and it therefore causes progressive development of drug resistant mutants proportional to the duration of the therapy. Lamivudine seems to be able to delay, but not to exclude transplantation, and it seems not to have a significant influence on survival [6]. Adefovir generally has a high genetic barrier and a low resistance rate, and in a study of patients with

YMDD mutants and decompensated cirrhosis, the administration of this drug before transplantation led to significantly improved virological, biochemical and clinical values [7].

In a randomized study, the antiviral response to adefovir was similar to that of the combination of adefovir and lamivudine in patients with YMDD mutants, this drug has therefore been proposed as first line pre-transplant therapy alone or combined with lamivudine. Combined therapy can prevent development of multidrug-resistant mutants [8]. Lamivudine alone seems not to be able to prevent re-infection particularly in patients with viral replication, and mutants are developed in >40% after 3–4 years.

The combination of immune globulin anti-HBV (HBIG) and lamivudine reduces recurrence rate to less than 10% at 1–2 years after transplantation. The two drugs present a combined effect in the control and clinical expression of resistance with a reduced production of HBsAg and reduction of pre-S/S and YMDD mutants.

In patients with spontaneous or antiviral drug induced plasma viremia below the limit of detection (e.g. HDV, acute fulminating hepatitis, HBV absent in more than 3 monthly tests before transplantation) excellent results have been reported using only HBIG. In patients presenting medium-level viremia, good protection (>90%) is obtained using combined prophylaxis.

The question is if and when to stop HBIG treatment. In the absence of viremia, treatment can be stopped at the time of transplantation, whereas viremic patients should be treated for at least 2–3 years after transplantation. In these cases recurrence rates reported in the literature vary from 0 to 12.5%; when to stop HBIG treatment is thus a highly controversial issue.

An alternative strategy could be to substitute immune globulin therapy with a combination of two antiviral drugs (lamivudine and adefovir or tenofovir) possibly combined with vaccination. Promising preliminary results have been obtained by adding two adjuvants (lipopolysaccharide *Salmonella minnesota* and *Quillaja saponaria*) to the vaccine, generating response in 80% of patients. Eight studies reported in the literature using different vaccination schemes, some combined with lamivudine, obtained an anti-HBs titre with a production of anti-HBs antibodies >100 UI/ml in 2–24% of cases.

HBV reinfection is characterized by recurrence of HbsAg in the serum, generally high viremia and substantial quantities of HBV in the liver graft.

Antiviral therapy in recurrent HBV infection has greatly influenced graft and patient survival rates. However, therapy is indicated only if HBV related recurrence is confirmed in patients who have not received prophylaxis.

In HBV related recurrence, both monotherapy and combined therapy can be useful despite the prophylaxis.

In patients with de novo HBV infection after transplantation, little effect is obtained using interferon, which furthermore increases the risk of rejection. Nucleoside analogues do not increase the risk of rejection, they have a strong antiviral effect, are well tolerated also over a long period, but they cause development of multidrug-resistant mutants.

If lamivudine resistance is developed, the therapy should be continued as long as the liver enzymes are normal and the disease is not progressing. However, adefovir should be added if the transaminase levels increase, and lamivudine therapy should be suspended only after some weeks, as the latency period of adefovir is long.

A particularly aggressive course of HBV related pathologies in immunodepressed patients suggests that therapy should not be stopped despite development of drug-resistance. Biochemical and virological response to nucleoside analogues exceeds 90% after 48 weeks of therapy when combined with adefovir or tenofovir.

In the past, high risk of recurrence was a contraindication for retransplantation in HBsAg+ patients, but combined therapy using HBIG and the new antiviral drugs has completely changed this approach permitting retransplantation with excellent results.

HBV related disease is today one of the best indications for liver transplantation thanks to a correct selection of donors and recipients, a rational approach to organ allocation, post-transplant prophylaxis for HBV patients and treatment of the rare cases of recurrent infection which occur despite the prophylaxis.

Transplantation in HCV related cirrhosis

Transplantation is the treatment of choice in patients with end-stage HCV related liver disease and it is now indicated in an elevated number of cases. In the last 20 years, transplantations due to chronic viral pathologies have thus greatly increased, and chronic HCV hepatitis is now the cause of 50% of cases in Europe and the U.S. In Italy about 60% of liver transplantations are carried out in patients affected by HBV and HCV related cirrhosis, and the latter is responsible for 33% of indications [9,10]. Cases of HCV related cirrhosis seem to be increasing and this could lead to a two-fold rise in mortality due to hepatic insufficiency, hepatocellular carcinoma in 61–68% and a five-fold increase in the need for liver transplantations.

At present, the main problems in connection with orthotopic liver transplantation for HCV related cirrhosis is to prevent reinfection of the liver graft and reduce progression of the chronic viral infection [11]. During the anhepatic phase and right after reperfusion, there is a drop in viremia levels due to a limited production of mature virions associated with viral load clearance. However, in the days following the transplantation, viremia levels rapidly rise and often exceed pre-transplant values.

Unless appropriate prophylactic therapy is administered, reinfection will occur, and between the first and the fourth month from transplantation, the patient is likely to develop asymptomatic globular hepatitis. This disease

rarely resolves but it frequently becomes chronic, and already in the first month it can evolve into cholestatic fibrosing hepatitis, which has a poor prognosis.

After liver transplantation, reinfection occurs in 99% of patients; 25–45% will develop acute hepatitis and 50–98% will develop chronic hepatitis, which is likely to evolve into cirrhosis within 5–7 years in 12–44% of patients of whom 63% will have decompensated cirrhosis within 3 years.

Serious pathologies after orthotopic liver transplantation for HCV related cirrhosis and post-transplant reinfection are massive hepatic necrosis, cholestatic fibrosing hepatitis and cirrhosis, which occur in 15, 33 and 44% at 3, 5 and 7 years, respectively, and rapidly lead to hepatic insufficiency and decompensated cirrhosis in 8, 17 and 42% within 1, 2 and 6 months, respectively, with a 1-year survival rate in retransplanted patients of only 30–45% [12]. This poor prognosis is due to the rapid progression of fibrosis, the rate is 0.3–0.6 stages per year as compared to 0.1–0.2 stages in non-transplanted patients. However, not all patients develop so serious complications and in 30–50% of cases only a light histological damage is evidenced which subsequently resolves in 30%. A comparison of transplanted and non-transplanted patients shows that 15–45% of patients with recurrent chronic HCV related hepatitis are likely to develop cirrhosis during the first 5 years post-transplantation. In these patients the cirrhotic evolution takes an average of 10–12 years as compared to 20–30 years in non-transplanted patients.

In transplanted patients with cirrhosis, hepatic insufficiency occurs within 1 year in 50% of cases as compared to 20–25% within 10 years in non-transplanted patients, with a first year mortality rate of 41% as compared to 50% within 5 years in non-transplanted patients with liver cirrhosis and hepatic insufficiency.

The evolution of the disease after transplantation depends on various factors:

- 1) Viral: viral load, genotype, quasispecies
- 2) Donor: age, gender, presence of steatosis, hepatic iron overload
- 3) Surgical: duration of hepatic ischemia
- 4) Recipient: HLA class, gender, race, age, immunogenetic background and immune system
- 5) External: Cytomegalovirus (CMV) infection, alcohol, immune depression, coinfection, antiviral therapy

Among all these risk factors, advanced donor age, treatment of acute rejection, CMV infection and elevated viral load before transplantation increase more than any other risk of recurrence and consequent fibrosis [13].

Management of patients who have undergone transplantation for end-stage HCV related cirrhosis requires an accurate clinical and ultrasound (US) follow-up in order to monitor the disease and currently make the most appropriate management decisions.

US in the evaluation of transplanted patients with viral reinfection

The two viral pathologies leading to most liver transplantations are at present characterized by substantially

different evolutions. Thanks to prophylaxis and treatment options, patients who undergo transplantation for HBV related cirrhosis only rarely develop serious complications, whereas complications are frequent in patients transplanted for end-stage HCV related cirrhosis.

The evolution of the disease is generally monitored by performing sequential liver biopsies, while US examination is performed mainly to evaluate post-transplant complications and, more rarely, to detect early signs of reinfection.

US is considered the imaging method of choice in the detection and follow-up of all early and late complications in liver grafts, such as vascular complications including thrombosis or stenosis of the inferior vena cava, portal vein, hepatic artery and celiac trunk, biliary complications including stenosis, calculi, biliary duct dilation, bilomas, parenchymal pathologies, and focal lesions such as lymphoma, infarction, abscesses and neoplastic recurrence as well as perihepatic fluid collections and ascites [14].

Immediately after transplantation, the graft presents a homogeneous or moderately inhomogeneous US pattern with increasing echogenicity, which returns to normal in the course of the following months. Initially, mean velocity of portal perfusion is elevated, varying from 39 to 50 cm/s, whereas the smaller or abnormal hepatic arteries reach a peak velocity between 0.40 and 0.68 cm/s. The hepatic veins are characterized by reduced diastolic waveforms and reduced or no positive waveforms, while some patients present slightly dilated bile ducts. Some patients present a high resistive index (RI) measured on the hepatic artery, which can be a result of advanced donor age, prolonged hepatic ischemia and an elevated post-transplant portal perfusion [15–19].

US examination is used for evaluating rejection of the graft as well as the two most important complications: fibrosing hepatitis and liver cirrhosis. A liver graft likely to develop acute rejection is characterized by changes in the parenchyma, the intrahepatic vessels and the bile ducts. The parenchyma appears apparently inhomogeneous with hyperechogenic areas in the periportal space, with reduced diastolic waveforms and no positive waveforms in the hepatic veins, reduced portal flow velocity and increased RI values measured on the hepatic artery. Acute rejection substantially reduces the portal velocity and increases the splenic pulsatility index. These two parameters present an elevated diagnostic accuracy (88%) in predicting rejection [20].

Cholestatic fibrosing hepatitis is a pathology, which is characterized by slowly increasing cholestatic parameters as compared to necrosis, which can be detected already in the first month after transplantation.

US examination can evidence progressive hyperechogenicity of the peribiliary tissue showing specific images especially at the level of the biliary carrefour (Fig. 1).

In the study of chronic viral liver diseases, US examination is concentrated mainly on parenchymal and extraparenchymal alterations. Possible altered dimensions of the organ are evaluated, hypertrophy of the left hepatic lobe and the caudate lobe, the caudate–right lobe ratio (C/RL), alterations in the hepatic echostructure, shape and margins. The following extraparenchymal features are evaluated: caliber of the portal and splenic veins and of the upper mesenteric artery, variations in the portal system

Fig. 1 Parasagittal right side scan of a patient lying on the left side. The graft appears echographically homogeneous with hyperechogenic areas in the periportal and peribiliary tissues due to advanced fibrosis: Cholestatic fibrosing hepatitis in a patient with recurrent HCV infection after orthotopic liver transplantation.

Fig. 1 Scansione obliqua sottocostale destra in paziente in decubito laterale sinistro. Il fegato presenta accentuazione omogenea dell'ecostruttura e intensa iperecogenicità del tessuto periportale e peribiliare per intensa fibrosi: Epatite fibrosante colestatica in paziente con recidiva di epatite C dopo trapianto ortotopico di fegato.

related to the patient's respiration, presence of collateral circles (at the level of the left gastric, short gastric, splenorenal and retroperitoneal veins, recanalization of the umbilical vein, and varicose dilation of the cholecystic veins), the caliber of the hepatic artery, presence of subclinical ascites, the dimensions of the spleen and alterations of the gallbladder wall.

In patients with suspected cirrhosis, also color-Doppler US is very useful for evaluating the presence and the degree of portal hypertension and thereby for detecting the evolution of a possible chronic liver disease.

In patients with recurrent disease after transplantation for HCV related cirrhosis, the gallbladder cannot be evaluated. Vascular complications are frequent such as stenosis, thrombosis and blood flow alterations due to modifications caused by the transplantation; ultrasound semeiological data are therefore few. Changes in the echostructure of the liver parenchyma are compared with the echostructure of the right kidney. These changes can range from slightly heterogeneous liver structure to coarse liver pattern (Fig. 2).

It is useful to examine the liver surface especially at the level of the first segment, the posterior profile of the liver at the level of Morrison's pouch and, using a 10 MHz probe, the upper surface of the liver in search of micro or macro nodules impressing Glisson's capsule (Fig. 3).

Volumetric changes initially appear as an enlargement of the caudate and left lobe and are only later evidenced by C/RL ratio <0.64 , which is a sign of caudate lobe hypertrophy associated with atrophy of the right lobe. Other parameters have proved less sensitive, such as evaluation of the spleen volume as well as caliber and perfusion of the

Fig. 2 Parasagittal right side scan shows the presence of coarse, prolonged echos and inhomogeneous parenchyma: Coarse liver pattern in a patient with recurrent HCV infection 3 years after transplantation.

Fig. 2 Scansione obliqua sottocostale destra. Il parenchima epatico mostra la presenza di echi grossolani e allungati che rendono disomogeneo il parenchima. Coarse liver pattern in paziente in recidiva di epatite C a 3 anni dal trapianto.

portal system, which are often altered before and after transplantation. It is difficult to determine exactly how often a patient with recurrent HCV related infection should undergo US follow-up after transplantation, however, the operator's experience and skill are crucial.

Prophylaxis and therapy in recurrent HCV infection

HCV infection is an important problem in connection with liver transplantation, not only because hepatitis C is the main indication for transplantation, but also because re-infection occurs in almost 100% of cases.

Combined pegylated interferon and ribavirin is the only treatment for HCV reinfection in patients, who have undergone orthotopic liver transplantation, even though this combined therapy is problematic because of low effectiveness, because especially ribavirin is poorly tolerated, and because the correct dose of the drug and duration of the therapy are still not well defined.

However, the most important uncertainty concerns the timing of the therapy, whether it should be administered before transplantation (prophylaxis), immediately after transplantation (pre-emptive therapy), in the acute phase of the disease or after histological confirmation of recurrent disease.

Antiviral therapy before and at the time of transplantation aims at preventing recurrence by administering antiviral drugs and immune prophylaxis using specific immune globulin (HCIG), even though the utility of prophylaxis using these substances is still not clear. For this reason ongoing trials are assessing the value of IgG and anti-E2.

Fig. 3 Longitudinal scan of the inferior vena cava. The shape of the liver is irregular impressing the venous ligaments and the lower margin of the liver (arrows), due to micro and macro nodules caused by recurrent HCV related cirrhosis 4 years after transplantation.

Fig. 3 Scansione longitudinale passante per la vena cava inferiore. I contorni del fegato mostrano piccole irregolarità che improntano il legamento venoso e il margine inferiore del fegato (freccie), dovuto a micro e macronoduli secondari a cirrosi epatica HCV correlata per recidiva a distanza di 4 anni dal trapianto.

Prophylactic therapy to prevent recurrent disease is carried out before transplantation, but its role has still not been defined although some ongoing studies have shown that it has a certain effect. Some results suggest that prophylaxis can prevent reinfection if it is associated with virological response, but it is still not clear whether prophylactic therapy can reduce the gravity of the recurrence.

Towards the end of the 1990s a group of experts at the International Liver Society recommended prophylactic treatment in patients with a CPT or MELD score under 7 and 18, respectively, suggesting that it was unadvisable in patients with scores over 11 and 25, while considering it useful in some cases with a CPT score between 8 and 11 and a MELD score between 18 and 25. While waiting for transplantation, patients with HCV related decompensated cirrhosis were treated with doses of 1 million units interferon standard alfa 2b followed by 3 million units three times weekly combined with 800 mg ribavirin per day for 6–12 months obtaining virological remission in 73.3% of patients and sustained virological remission in 46.6% [21].

Interferon alone or combined with ribavirin is not always applicable in the prophylactic treatment due to the severity of the adverse effects, particularly infections and hepatic decompensation, even though this treatment seems to prevent recurrence in 23% of cases [22,23]. Prevention of recurrence is related to a sustained virological remission, but non-adherence to therapy can negatively influence response rates, more in cirrhotic patients than in non-cirrhotic patients.

The rationale behind pre-emptive therapy, i.e. treatment started early after transplantation, is based on the fact that in this phase the viral load is low and fibrosis is less serious. Prevention of recurrence using antiviral therapy started early after transplantation, i.e. 2–4 weeks from

transplantation, means that treatment is started before there is any biochemical or histological evidence of recurrent disease. The rationale is based on the high rate of virological remission (65%) obtained in patients with acute HCV hepatitis and the low concentration of HCV RNA in the first week after transplantation, generally reaching its peak after 1–3 months [24].

However, early therapy is applicable only in a limited number of patients, as the drug is poorly tolerated and only 15% of patients can tolerate an adequate mean dose. Virological remission rates after completed therapy therefore vary from 13.6 to 22.7% with sustained virological remission from 9.1 to 18.2% according to the drug, i.e. if standard interferon is used or pegylated combined with ribavirin.

Some studies have demonstrated that early therapy can have beneficial effects in terms of reduced HCV reinfection rates, varying from 9 to 43%.

The low rate of sustained virological remission is probably related to the problematic adherence and interruption of treatment because it is poorly tolerated and to the high incidence of adverse effects and development of rejection. The limited applicability is caused by the fact that it is difficult to start treatment immediately after transplantation while the patient is still debilitated and severely immunodepressed, affected by pharmacological interactions, infection and sometimes rejection.

Not all patients develop severe, progressive liver disease, so this therapy could therefore be appropriate in patients who are likely to be able tolerate it (transplantation from living donor, low Child or MELD scores) and in patients who are likely to develop more aggressive complications. However, the timing of the therapy still has to be defined, as treatment should be started as early as possible after transplantation, but not too early as this could increase the risk of rejection. The studies reported in the literature therefore mainly evaluate patients with stable chronic infection.

In the acute phase of HCV reinfection of the liver graft, pegylated interferon combined with ribavirin generates a virological remission after completed treatment in 65% of patients but sustained virological remission does not exceed 34.7%. In this phase, combined therapy has few side effects and most patients are able to continue the treatment [25]. Sustained virological remission is generally associated with viral clearance after completed treatment, particularly in patients who have not received cortisone antirejection therapy and in patients who do not have CMV infection. The aim of the therapy in this phase is to prevent progression of the disease and loss of the liver graft, and main indications are fibrosing cholestatic hepatitis and fibrotic evolution confirmed by biopsy which should be performed once a year to monitor the progression of the disease or by US examination performed every 3–6 months.

Studies evaluating post-transplant therapy are generally non-randomized, based on small patient populations and carried out by small centers applying significantly different criteria in the selection of patients, often evaluating biochemical response rather than virological response, using different treatment schedules and immunosuppressant drugs.

Also in this phase, combined therapy is more effective than monotherapy and the combination of pegylated interferon and ribavirin leads to sustained virological remission in 26–35% of cases. However, the results are influenced by elevated dose reductions and discontinued treatment [26].

In naïve patients, sustained virological remission rates of 60% were reached by administering a therapy combining 1 µg/kg per week pegylated interferon with 600 mg ribavirin per day [27].

Side effects are a disadvantage in the treatment of recurrent HCV infection after orthotopic liver transplantation, and in the literature it is reported that up to 43.6% of patients are unable to continue the treatment. Marrow toxicity and rejection are limiting factors, which more than any other complications require careful management. The risk of rejection varies from 0 to 35% and is related to the type of interferon and to the combination with ribavirin, and it increases when pegylated interferon is administered due to the molecular pharmacokinetics, which activates the expression of HLA II on the bile ducts. Virological response is accompanied by a histological improvement, which is more evident in necroinflammation than in fibrosis, as the latter is a slower process, which takes 3–5 years.

Particular problems can be persistent HCV infection of the liver in patients with sustained virological remission, presence of cryptic virus, pharmacological toxicity, biliary complications, *de novo* autoimmunity and chronic rejection. Factors that are predictive of response are the presence of genotype 2/3, completed therapy and virological remission after treatment, particularly if remission is sustained.

The role of growth factors in these patients still requires further investigation, and the optimal dose and duration of therapy have still not been defined, although the outcome seems not to be linked to the therapeutic schedule (low dose versus standard dose at the start of therapy).

Treatment of recurrent HCV in patients who have undergone liver transplantation leads to sustained virological remission in one-third of patients, but also in non-responders and in patients with recurrent disease, who are the majority in this group, therapy leads to a histological improvement characterized by improved or stabilized fibrosis scores.

The effectiveness of post-transplant antiviral therapy is still not satisfactory in patients treated for HCV related cirrhosis due to various factors in addition to nonresponse also in immunocompetent patients, such as elevated viremia, prevalence of genotype 1, low tolerance, necessity to reduce the recommended dose, high prevalence of previous nonresponse and altered immunological function.

All therapeutic strategies are unsatisfactory. Pre-transplant and pre-emptive prophylactic therapies are useful but limited by application restrictions and poor tolerance and consequently by low response rates. Treatment with the currently available drugs is therefore indicated mainly in patients who develop histologically progressive diseases after the transplantation.

Ongoing investigation will define new therapeutic strategies, which can improve the outcome in patients with recurrent HCV infection after transplantation and lead to results similar to those obtained in the treatment of HBV infection.

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