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Hepatitis C and Liver Transplantation

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1. Introduction

Chronic hepatitis C virus (HCV) infection, together with chronic alcoholic liver disease, are the leading causes of hepatic cirrhosis and the development of hepatocarcinoma. Chronic HCV infection is the reason for about 50% of liver transplants in the western world; it is the second cause of liver transplants in northern Europe and and the main cause in countries such as Italy (Guillouche & Feray, 2011). In Spain, it accounts for 35% of all transplants (Registro Español de Trasplante Hepático [RETH], 2009). In fact, liver transplantation is currently the best therapeutic alternative for patients with advanced chronic liver disease due to HCV or those who develop hepatocarcinoma.

Reinfection of the graft is universal and occurs in 95% of patients transplanted due to HCV infection. This reinfection can compromise graft function and patient survival. In a few cases the histological recurrence is minimal and non progressive, though in most patients it follows a more rapid course than in immunocompetent persons, and frequently evolves to cirrhosis with graft loss. There also exists a pattern of recurrence which is very severe, but unusual (<10%) called fibrosing cholestatic hepatitis that often involves rapid graft loss (Roche & Samuel, 2010).

The elaboration of an efficient antiviral therapeutic strategy has been of paramount concern in clinical research in recent years, with questions about when, how much and at what point this treatment should be applied.

A considerable number of studies published over recent years have shown that antiviral treatment of post-transplant HCV hepatitis carried out during the late phase is the best option for improving the prognosis of these patients. Those patients who present a negative HCV serology after antiviral treatment have better survival (Picciotto et al, 2007).

The future perspectives concerning the introduction of new drugs for the treatment of chronic hepatitis C may involve therapeutic changes and, perhaps, a better prognosis for these patients.

2. Natural history of post liver transplant HCV infection

2.1 Recurrence of HCV post transplantation

The viral infection recurs in almost all cases and occurs immediately after the graft reperfusion phase. The diagnosis of viral recurrence is purely virological and is established by detection in serum of HCV RNA using polymerase chain reaction (PCR) techniques. The levels of viraemia are generally far higher than those existing before the transplant (García-Retortillo et al, 2002). The diagnosis of relapse of the hepatitis or disease in the graft, however,is based on histological findings.

Pathophysiologically, two patterns of recurrence can be distinguished: (1) a pattern of chronic HCV hepatitis similar to that seen in non-transplanted patients but with a faster course, reaching states of advanced fibrosis or cirrhosis in a shorter time (9-12 years versus 20-50 years); (2) a second pattern, called fibrosing cholestatic hepatitis, which is less common (3-5%) but very severe, and generally appears in the context of intense immunosuppression. It can present as an initial manifestation of disease relapse or, less commonly, in the context of recurrent chronic hepatitis, and is characterised by marked jaundice with cholestasis and high titres of viraemia. This form usually progresses rapidly to acute liver failure, with graft loss soon after.

Histological confirmation is necessary to establish the diagnosis of HCV recurrence, as well as to assess the degree of activity and perform a periodic follow-up of histological disease progression. This not only provides information about the prognosis, it can also establish the differential diagnosis with other complications such as rejection, biliary disease, or vascular problems (Berenguer et al., 2001a, Berenguer et al., 2003, Roche & Samuel, 2010, Samuel et al., 2006).

A new non-invasive technique, transient elastography, has recently become available that appears to correlate well with the stage of fibrosis. This technique can detect an important degree of fibrosis (F≥2) with effect from the sixth month after transplantation, and has an excellent diagnostic capacity at 12 months post-transplantation (Carrión et al, 2010a).

2.2 Evolution of the recurrence of HCV in the post-transplant liver

The histological involvement of the graft and the natural history of the recurrence both vary, with different presenting forms. Post-transplant reinfection with HCV is associated with greater aggressiveness than in immunocompetent patients (Table 1) (Berenguer et al, 2000, Berenguer et al, 2001b).

At around the fifth month after transplantation there is an acute hepatitis, which is generally asymptomatic in some 50% of patients. Its histological findings present characteristics of lobular hepatitis with varying degrees of inflammatory infiltrate in the portal space, mainly of lymphocytes and macrovesicular steatosis, similar to the histological pattern found in acute hepatitis in immunocompetent patients.

Of those patients who experience a relapse of their HCV infection after liver transplantation, 20% have histological lesions compatible with mild chronic hepatitis 5 years post-transplantation. The others experience a more important chronic evolution. The progression to hepatic cirrhosis occurs in 30% of these patients after 5 to 7 years post-transplant, and is much faster than in immunocompetent persons (Forman et al., 2002).

The progression of the fibrosis is much more accelerated in those patients who receive their transplants due to HCV infection and who have a recurrence of the disease, up to five times faster than in immunocompetent persons. Accordingly, the evolution to cirrhosis is also sooner, with the average being 10 years as opposed to 20-30 years for immunocompetent persons with chronic HCV infection (Forman et al., 2002, Firpi et al., 2009).

Once cirrhosis is reached, 40-50% of transplanted patients will experience their first decompensation within one year. Survival after this first episode of decompensation is 50% (Berenguer et al, 2001b, Firpi et al, 2009).

In immunocompetent persons, about 25% experience their first decompensation 10 years after hepatic cirrhosis is diagnosed, and of these 50% survive for five years after the decompensation episode.

	Pre-transplantation	**Post-transplantation**
Fibrosis progression	0.2 units fibrosis/year	0.3 – 0.8 units /year
Median time to cirrhosis	20-30 years	10-12 years
Decompensation after development of cirrhosis	20-25% in 10 years	50% in 3 years
Survival after decompensation	50% at 5 years	50% at 1 year

Berenguer et al, 2001b.

Table 1. Natural history of hepatitis C before and after transplantation

2.3 Factors influencing the recurrence of HCV and graft survival

The course of post-transplant hepatitis C is determined by the interaction of various factors. Certain pre-transplant factors in the recipient are associated with worse evolution, including female sex, older age, and the presence of diabetes or the metabolic syndrome (Firpi et al 2004, Gallegos-Orozco et al, 2009, Pagada et al 2009, Pérez et al 2011). Other pre-transplant factors depend on the virus, for example the genotype HCV 1b, a high pre-transplant viral load, the absence of response to antiviral therapy and coinfection with HIV have also been associated with a worse prognosis (Berenguer et al, 2005).

Other factors, related with the donor and the peri-operative period, can also affect the severity and the time to relapse of post-transplant HCV infection, such as an older donor age (>50 years), a high degree of steatosis in the donor liver, a prolonged ischaemia time, a non-heart beating donor, a living donor, preservation injury, a partial split graft, or anti-HCV positive donors, all of which have been associated with a worse evolution (Pérez-Daga et al, 2006, Machicao et al 2004;. Pine et al 2009; Humar et al 2005)

Notable among the post-transplant factors is the metabolic syndrome, present within the first 12 months in around 50% of all patients who receive a transplant due to HCV infection and which is associated with greater progression of the fibrosis. Thus, the importance of control of factors like dyslipidaemia, hypertension and, more importantly, diabetes associated with insulin resistance, all of which play a crucial role in the evolution of the recurrence of post-transplant HCV infection (Hanouneh et al., 2008, Gallegos-Orozco et al, 2009).

Recent studies appear to show that polymorphisms in the interleukin 28 B gene (*IL-28B*), in both the donor and the recipient, may influence not only the response to antiviral therapy but also the evolution of hepatitis C due to post-transplant HCV reinfection, with a worse evolution in those with the genotypes CT and TT (of the polymorphism rs12979860) as compared with the genotype CC (Charlton et al, 2011, Brocato et al, 2010).

2.3.1 Role of immunosuppression in recurrence of hepatitis C

Agreement exists that immunosuppression is significantly associated with the natural history of recurrent hepatitis C (Samuel et al, 2006). However, controversy still surrounds the role of each immunosuppressive agent on HCV replication and the evolution of hepatitis C on the graft.

Immunosuppression contributes greatly to the increased viral load that takes place in these patients during the immediate post-transplant months. The recipient's cellular immune response against the infected hepatocyte, and thus against the virus, is altered. It is almost absent in patients with fibrosing cholestatic hepatitis and severe disease recurrence (McCaughan 2004, Samonakis et al, 2005).

The role of the type of immunosuppressive regimen and its influence on the progression of recurrence are still unclear and there is no established ideal immunosuppression protocol.

The use of high-dose steroid boluses to treat episodes of acute rejection, , has been shown to be clearly prejudicial, as they condition an increase in viral replication, a more aggressive relapse and increased early post-transplant mortality (Samuel et al 2006, Berenguer et al, 2006a).

Some studies suggest the possible benefit of maintaining low-dose steroid regimens with progressive withdrawal during the first 6-12 months (Berenguer et al, 2006a). However, two recent meta-analyses found that steroid-free immunosuppression protocols are significantly better and provide benefits related with such factors as the acute graft hepatitis, HCV recurrence, cholesterol levels and the development of de novo diabetes mellitus (Sgourakis et al, 2009, Segev et al, 2008). Thus, the use of steroid-free immunosuppression protocols improves the management of metabolic complications.

Regarding the use of calcineurin inhibitors, numerous studies have compared the recurrence of HCV with the two drugs, cyclosporine and tracrolimus. However, the results are not completely conclusive, with most studies failing to find differences. Thus, it is not possible to recommend the use of a specific calcineurin inhibitor. There seems to be evidence that the use of cyclosporine during interferon treatment may be beneficial, and that tacrolimus seems to reduce episodes of acute rejection and the need for steroid boluses. A possible beneficial immunosuppressive regimen could be to start with tacrolimus and later substitute it with cyclosporine if antiviral treatment is considered necessary for HCV recurrence (Berenguer et al, 2007, Levy et al, 2006, O´Grady et al, 2007). For other immunosuppressive agents, such as mycophenolate, azathioprine, mTor inhibitors or anti-IL-2 receptor antibodies, no solid studies have yet been done from which to obtain conclusions. In summary, therefore, the only firm recommendation would be to avoid a state of over-immunosuppression, avoiding steroid boluses and full-dose triple or quadruple regimens. This could lead to improved results in these patients (Berenguer et al, 2006a).

3. HCV antiviral treatment

Although treatment is based on the administration of pegylated interferon and ribavirin, as is done in immunocompetent patients, no standardized consensus criteria exist about the ideal time to initiate such therapy, which patients should be treated or the most suitable dose or duration of the regimen. The 2010 Expert Opinion Meeting of the Italian Association for the Study of the Liver (AISF, 2010) established the following criteria for starting antiviral therapy in patients with post-transplant HCV reinfection: the presence of positive HCV-RNA serology, compatible liver histology (HCV recurrence and fibrosis stage ≥F2 (Scheuer)) and the exclusion of rejection, vascular disease or biliary obstruction, with level III evidence and grade B recommendation.

As HCV recurrence is one of the most usual causes of graft loss, it can be assumed that those patients who respond to treatment will have a better prognosis, and consequently, an improved survival. One of the main problems of antiviral therapy concerns its frequent, and sometimes severe, secondary effects, which reduce tolerability and thus efficacy. Thus, given the lack of universal methods to prevent graft reinfection, the only alternative is antiviral therapy, to be used at varying times around the transplantation.

3.1 Pre-transplant antiviral therapy

Pre-transplant therapy consists of treating patients with chronic HCV liver disease who are candidates for a liver transplant before the transplantation, in order to reduce the viral load or even make it negative, thereby avoiding later reinfection in the graft.

Studies indicate that using interferon and ribavirin up to 30% of patients manage to reach the time of transplant with negative viraemia, though a negative HCV-RNA prior to transplant does not guarantee the absence of post-transplant recurrence of infection (Charlton et alt, 1998). The main inconvenience of this regimen concerns the poor tolerance to treatment in patients with advanced cirrhosis, and the presence of more and worse side effects in relation to the evolution of the liver disease, so that it can only be used in fewer than 50% of patients. In 60% of those patients who do receive this regimen, the doses of pegylated interferon and ribavirin have to be reduced due to the high rate of undesired effects, and even occasionally stopped prematurely, which leads to the poor virological results seen. This therapeutic strategy, therefore, should be given prudently, and can be recommended for those patients on the transplant waiting list who have compensated liver disease (Child Pugh A plus hepatocarcinoma, for example), independently of the genotype and viral load, and in those patients in Child Pugh stage A-B and MELD ≤18 with a good virological response profile who have no contraindication to starting the treatment (Everson et al, 2005, Crippin et al, 2002).

3.2 Post-transplant antiviral therapy

Post liver transplant therapy can be given either shortly after the operation or some time later, when the recurrence of the hepatitis C is established.

3.2.1 Early post-transplant antiviral therapy (Pre-emptive therapy)

Early treatment is given during the first weeks after the transplant (mainly between the second and sixth weeks). The idea behind this strategy is to anticipate the infection and

eliminate the HCV before the hepatic lesion appears. Nevertheless, this early antiviral therapy has numerous limitations, such as the degree of post-transplant immunosuppression present in these patients; their clinical situation after the transplant, which affects their tolerance to treatment; their high viral load, partly related with the degree of immunosuppression, and the corresponding reduction in therapeutic success plus the high risk of episodes of rejection, which advise delaying treatment until a more suitable time from the immunological standpoint (Sheiner et al, 1998, Chalasani et al, 2005, Sugawara et al, 2004, Shergill et al, 2005).

This strategy is, however, applicable to all patients who receive a transplant due to HCV infection, including those who have no aggressive rejection episode and remain stable, with minimum hepatic lesions for whom antiviral therapy would perhaps not otherwise be indicated.

The viral response experienced, according to the various studies published, ranges from 1% to 13%. However, treatment had to be withdrawn early in 35% of the patients treated, due to adverse effects (Shergill et al, 2005). The application of this treatment regimen could perhaps be considered in those patients who receive a further transplant due to aggressive HCV infection or in coinfected (HIV) patients.

3.2.2 Late post-transplant antiviral therapy

This consists of applying treatment once the histological recurrence of the HCV is well established, with the aim of preventing rapid progression of the hepatic lesion. The period of treatment application is from 2 to 7 months after the transplant, or according to the histological lesions seen on liver biopsy. Using this strategy, the patient has a lower and better controlled degree of immunosuppression, has recovered from the surgery, and alterations present prior to the transplant have been corrected, such as anaemia, thrombocytopoenia or the nutritional status, all of which favour greater tolerance and applicability.

The rate of sustained viral response seen with this schedule is from 20% to 40% (2,21-22,25); the rate of premature interruption of treatment is around 28% and that of dose reduction 73%. The results, though, are still worse than those found in immunocompetent patients (Berenguer, 2008).

In all cases management should be personalized, and consideration given to such factors as renal function, concomitant diabetes, a prior history of rejection and genotype (Aymant et al, 2010).

3.3 Antiviral drugs and regimens

The optimal dose and duration of antiviral treatment in transplant patients are unknown, and the same regimens are usually followed as those applied to immunocompetent patients (Otón et al, 2006).

Adverse effects are the main reason for dose reduction (50%), particularly with ribavirin, and premature treatment interruption (25%). The most usual adverse effects involve haematological alterations, mainly anaemia (60-80%), neuropsychiatric disorders (around 10-15%), thyroid disorders, asthenia (60-70%) and infections (15-25%). The use of

erythropoietin and colony-stimulating factors (G-CSF) helps avoid the need for dose reduction and thus increases the possibility of reaching a sustained viral response. Though these drugs clearly permit better tolerance to antiviral treatment, no data yet exist to confirm improved efficacy. (Berenguer et al 2006b, 2008).

The development of acute cellular rejection represents another possible complication, with an incidence of around 6% (0-35%). It is related with the state of the patient's immunosuppression, the time since transplantation, the concomitant use of ribavirin and the use of pegylated interferon (more than with conventional interferon). Cases of chronic rejection (<1%) have, however, been reported in patients who achieve a viral and biochemical response. In this situation it has been attributed to improved hepatic function with the resulting change in metabolism of the immunosuppressive drugs, which could determine a reduction in their blood levels (Berenguer, 2008, Otón et al, 2006). Accordingly, close vigilance and monitoring of the immunosuppression are necessary during treatment, as well as histological study in the event of unexplained laboratory findings.

3.4 Factors predicting response to antiviral therapy

Factors predicting antiviral response in the patient who undergoes liver transplantation due to HCV infection are mostly similar to those seen in the immunocompetent patients. Factors associated with a worse response include advanced donor age, advanced fibrosis, the presence of genotype 1, a high initial viral load and the presence of the metabolic syndrome. Obtaining a rapid viral response (4 weeks after starting antiviral therapy) and an early viral response at 12 weeks of treatment predict a sustained viral response, as seen with HCV treatment in non-transplant patients (Berenguer et al, 2006; Jiménez et al, 2010).

Polymorphisms in interleukin (*IL-28B*) (chromosome 19), related with response to antiviral therapy in immunocompetent patients (Fukuhara et al, 2010), are also related to response in transplant patients. Polymorphisms in rs 1127354 (chromosome 20), which determines the activity of inosine triphosphatase, have been associated with the possibility of predicting a predisposition to the development of haemolytic anaemia in relation to ribavirin (Fellay, 2010).Another important factor to consider that is associated with a greater sustained viral response concerns treatment adherence; at least 80% compliance should be aimed for.

4. Retransplant

For those patients with recurrence of HCV who have a decompensated cirrhosis, a liver retransplant is the only curative option.The International Liver Transplantation Society Expert Panel indicates that recipients aged >55 years, donors >40 years, a bilirubin ≥10 mg/dl, creatinine clearance <40 ml/min and early recurrence of HCV-related cirrhosis after transplant are all associated with a worse prognosis after retransplant (Carrion et al, 2010b). The development of fibrosing cholestatic hepatitis also has an unfavourable prognosis after retransplant (Marti et al, 2008).

Models predicting survival after retransplantation have been validated. These include the Markmann score (Markmann et al, 1999) and the Rosen score (Rosen et al, 1999), which appear to be the most accepted and enable prediction of the prognosis in the retransplant

patient, thus improving associated survival. Generally speaking, it is recommended that a retransplant should be offered to those patients who have a likelihood of 1-year survival of at least 55%, which includes patients with a Rosen score <20.5 (Marti et al, 2008).

The cornerstone depends on reducing the number of candidates for retransplantation, identifying those patients who have accelerated recurrence and undertaking energetic measures for their management, as well as starting antiviral therapy.

5. New therapies for HCV

The advent of new drugs for the treatment of HCV infection, as well as polymerase and protease inhibitors, will considerably change the management of HCV infection due to their high antiviral power (Kwo et al, 2009, Hezode C et al, 2009). Around 50% of non-transplant patients who are difficult to treat because of the presence of factors predicting a lack of response have been shown to experience a greater sustained viral response (Aymant et, 2010). In transplanted patients, the increase in efficacy, applicability and tolerance, and the possible interactions with other drugs are as yet unknown and more studies are still required.

6. Conclusions

Despite the advances in liver transplantation, the results in patients with HCV infection are not as satisfactory as desired, due mainly to the recurrence of the primary disease and the lack of availability of an efficient prophylactic therapy. Likewise, antiviral therapy still presents important limitations, particularly its poor tolerance, which hinders its use at full doses or for a sufficient duration to achieve an adequate response. The most recommended attitude is to attempt antiviral therapy prior to the transplant, particularly for those patients with maintained liver function, in an attempt to avoid disease progression, though if this is not possible, at least reach transplantation with a negative viraemia. Strict monitoring of the progression of the fibrosis by serial biopsies and/or elastography will enable early identification of those patients who might benefit from antiviral therapy to detain the advance of the disease and thus avoid the possible need for a retransplant. Nevertheless, new therapeutic approaches are required for the treatment of hepatitis C infection that can obviate the need for liver transplantation. For this, the introduction of protease and polymerase inhibitors is opening up hope for the future treatment of this disease.

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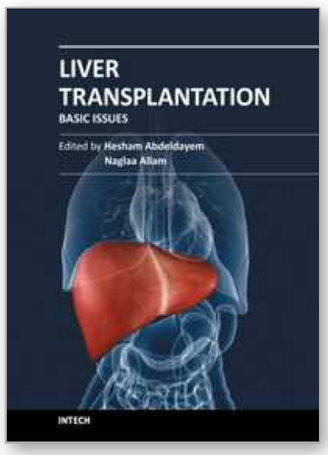

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This book covers a wide spectrum of topics including history of liver transplantation, ischemia-reperfusion injury, immunology of liver transplantation, viral hepatitis and liver transplantation, other indications for liver transplantation, prognostic factors and perioperative period. The authors of the chapters are experts in their respective fields. They are proponents covering different aspects of liver transplantation and come from many centers across the world. The interdisciplinary approach and the authority of the contributors resulted in a valuable reference to anyone interested in developing a global view in liver transplantation including medical students, residents, fellows, nurses, and practicing physicians and surgeons as well as researchers in the field of liver transplantation.

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