Hepatitis C Treatment Before and After Liver Transplant

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Advanced hepatic disease, either in the form of cirrhosis or hepatocellular carcinoma, caused by infection with the hepatitis C virus (HCV), is currently the main indication for liver transplant worldwide [1,2]. Hepatitis C also appears as an etiologic factor for terminal hepatic disease. However, although this procedure is defined as a standard therapy in both situations, recurrence of HCV infection is universally recognized. The potential for HCV infection to evolve in a more aggressive manner is greater among transplant patients than among immunocompetent individuals, and the re-establishment of hepatic cirrhosis in these patients can occur within five to ten years after the transplant. The progression to cirrhosis also occurs at a more accelerated pace in these patients, with decompensation rates higher than 40% a year after diagnosis [3].

Despite the risk of recurrence, cirrhosis caused by HCV has long represented a disease with good post-transplant evolution potential and low recurrence rates. In the mid 1990s, there was an increase in the rate of recurrence, which impairs the function of the graft and reduces the survival of the patient. Studies to determine the risk factors began to be carried out, and the adoption of certain measures has enabled better outcomes [4].

Natural History of Hepatitis C After Transplant

Early recurrence of the HCV infection after the transplant, defined as the detection of HCV RNA in the serum or graft, is a practically universal event, observed in more than 95% of the cases. Hepatic disease recurrence is represented by a wide range of histopathological aspects, and the differential diagnosis with acute cellular rejection can delay its detection. In these cases, there is overlapping of histopathological standards, as well as immunopathogenic phenomena in common [5,6].

In the recurrence context, acute hepatitis generally occurs between one and six months after the liver transplant, at a frequency of approximately 70%. Its histopathological findings are characterized by hepatocyte edema, large-droplet steatosis, moderate lobular inflammation, and acidophilic corpuscles. Although spontaneous resolution of acute hepatitis C occurs in up to 15% of immunocompetent individuals, it is rarely observed in the transplant context [3,4].

Severe progressive cholestatic hepatitis can occur early, between one and three months after the transplant. This kind of recurrence is rarer, occurring only in 10% of the cases. Its severe evolution pattern is characterized by high levels of serum bilirubin (over 6 mg/dL), high serum levels of HCV RNA, central ballooning in the liver biopsy, low inflammatory infiltrate, and cholangiolar proliferation, without associated ductopenia, suggesting that HCV has a direct cytopathic effect. These patients evolve to rapid graft loss, and death occurs even before a new transplant attempt can be made [4].

In most cases, however, the hepatitis C recurrence is diagnosed as chronic hepatitis, with a more accelerated progression of fibrosis than that observed in the immunocompetent population, resulting in cirrhosis in 8% to 30% of patients within five years. Cirrhosis is also more aggressive in these patients, with a 65% cumulative risk of complications within three years. The histopathological findings found in the graft are similar to those found in the native liver of an individual with hepatitis C and include mixed portal infiltrate with lymphoid aggregates, periportal inflammation, varied lobular inflammation, and steatosis. These findings can be detected in 70% to 90% of patients one year after the transplant [7].

In all of these cases, however, the real recurrence rate can only be estimated through routine serial biopsies, considering that 20% to 30% of patients do not evolve to increased aminotransferase levels, and that such an increase lacks specificity, potentially resulting from other events, such as rejection, ischemia or opportunistic infections [8]. In the Liver Transplant Sector of the *Hospital das Clínicas da Faculdade de Medicina da Universidade de São Paulo* (HCFMUSP, University of São Paulo School of Medicine *Hospital das Clínicas*), protocol biopsies are carried out every six months in the first year after the transplant, every year between the second and forth year after the transplant, and every three years after the sixth year of the transplant. An evaluation of 43 patients demonstrated histological recurrence caused by chronic hepatitis in 80% of cases in an average period of 9.9 months [9].

Risk Factors for the Severity of Post-Transplant HCV Recurrence of Hepatitis C

The factors that determine the evolution of hepatitis C in patients submitted to liver transplant can be variables related to the donor and receptor, viral factors, and events associated with the transplant, resulting in greater severity of the disease and higher rates of graft loss. The factors that are more consistently associated with the severity of the disease are: advanced age of donors, treatment for acute cellular rejection involving pulse therapy with corticosteroids or administration of OKT3, and infection with the cytomegalovirus [3,5,7,10]. A better understanding of the factors that contribute to the progression of the disease may indicate the potentially modifiable mechanisms of its evolution.

Donor and Receptor Factors

The use of older liver donors is a factor that negatively affects the fibrosis progression rate. Recent studies show a tendency toward a ten-year increase in the age of donors in the last decade. This measure, although applied to compensate for the low availability of organs, has been shown to have a direct influence on the degree of fibrosis in recurrent hepatitis C. Recent studies have shown that the ten-year difference in donor age (40 *versus* 50 years) has been associated with greater fibrosis progression (from 0.6 to 2.1 units a year) and with a decrease in the interval of appearance of cirrhosis (of up to eight years). Donor age seems to influence graft survival only in HCV-positive patients. However, there is little chance that this will change, since very few transplant programs are able to pair younger donors with HCV-positive receptors [11,12].

The involvement of immunogenetic factors is also considered, with studies that observed the association between HLA-B14 and HLA-DRB104 as beneficial to hepatitis C evolution, and the mismatch between the donor/receptor HLA-DRB1 with an increased recurrence risk [13,14].

Other donor factors that require further investigation include the use of live donors, hepatic iron content, and hepatic steatosis [15,16].

Viral Factors

Some studies have associated high viral load before or soon after the transplant with the severity of post-transplant HCV recurrence. An analysis involving 284 North-American and Spanish patients showed that the pre-transplant viral load is an independent factor in the progression of fibrosis. In another study carried out in the United States, the five-year survival of patients submitted to transplant for HCV was found to be lower in patients with viral loads higher than one million mEq/mL [7].

The importance of the HCV genotype in the progression of the disease remains controversial. Although most of the studies conducted in the United States failed to show this association, a large collaborative European study showed a higher rate of progression and severity in transplant patients infected with HCV genotype 1b. One hypothesis is that, in the liver transplant context, the host immune response to HCV is stronger for the 1b genotype than for other genotypes, and that the tissue lesion is associated with this response [17].

Factors Associated with the Transplant

The treatment of acute rejection episodes with the use of corticosteroid pulse therapy or anti-lymphocyte preparations has been associated with greater severity of hepatitis C recurrence. However, for such patients, the use of immunosuppressive regimens is recommended, which is sufficient to prevent moderate or severe rejection, as is the subsequent use of corticosteroid pulse therapy or OKT3 administration, but not to the point of exacerbating the hepatitis C progression or causing other long-term complications [5].

Considering that one of the hypotheses put forth to explain the more severe HCV recurrence observed in recent years is the increased potency of immunosuppressive agents, several studies have been carried out to minimize or even abandon the use of the immunosuppressive regimen. These studies have shown diverging results. However, there were differences among the studies in terms of the initial immunosuppressive doses and the dose reduction rates. In some studies, the prolonged use of maintenance corticosteroid therapy was associated with lesser severity of the hepatic disease recurrence. In this case, the method of reducing the dose was important, and gradual reductions have been associated with less aggressive forms of hepatitis C [18,19].

The use of azathioprine or mycophenolate mofetil has not been shown to have any consistent effect on HCV recurrence. Although cyclosporine has been shown to have antiviral properties in vitro, it has not shown to have any advantage over tacrolimus in clinical practice [20,21]. The long-term use of sirolimus can provide some benefit, since it has antifibrotic and potential antiviral effects, although such studies are still preliminary and do not support its preferential use in this group of patients. The use of new drugs, such as sirolimus and the interleukin 2 receptor antagonist, requires controlled and prospective studies. Therefore, the general immunosuppression status seems to be one of the possible determinant events in the course of recurrent hepatitis C [20,22,23].

Another factor that is associated with the transplant and negatively influences the post-transplant evolution of hepatitis C is the presence of infection with the cytomegalovirus, which leads to the worsening of fibrosis [24].

Pre- and Post-Transplant Approach to Treating HCV-Positive Patients

Antiviral therapy is the main strategy used in treating HCV-positive patients. However, the ideal moment at which to intervene remains unknown. The authors of most studies have initiated the treatment for HCV recurrence when there is histological evidence of the disease. Alternative treatments include the use of antiviral therapy before or soon after the transplant, when there is still no clinical evidence of recurrent disease. This is known as pre-emptive therapy. Antiviral therapy is generally less efficient and less well tolerated in the transplant patient than in the immunocompetent patient.

Treatment of Patients with Cirrhosis Who are on the Transplant Waiting List

Viral clearance in the patient with cirrhosis, in addition to providing better expectations for the transplant (increased graft survival), can even interrupt the progression of fibrosis in these patients, and, in some cases, preclude the need for the liver transplant.

Studies have proven that, although the side effect rates are high, the rate at which a sustained virological response is achieved in patients with compensated cirrhosis treated with

progressively higher doses of conventional interferon and ribavirin is approximately 22%, and can be even higher in those infected with genotype 2 or 3. When submitted to transplant, such patients do not present recurrence of the disease, confirming the validity of this therapeutic strategy [25].

In one study, carried out by Forns et al., 30 transplant waiting list patients of different functional classes were submitted to antiviral treatment. In that study, the efficacy of the treatment was evaluated on the basis of the virological response throughout the treatment period, as well as on the rate at which a sustained virological response was achieved. The simple reduction in the HCV viral load before the transplant was sufficient to avoid recurrence after the transplant (efficacy of approximately 66%). In addition, none of the patients achieving a sustained virological response experienced disease recurrence [26].

Most of the studies involving this population of patients have evaluated the efficacy of conventional interferon. Overall, they concluded that the treatment is recommended for patients with Child-Turcotte-Pugh class A or B cirrhosis and a model for end-stage liver disease (MELD) score lower than 18, or even in patients with decompensated cirrhosis. However, in the last case, following the treatment protocol in a center with support and possibility of immediate transplant [26].

In a recent study of data collected in the HCFMUSP Liver Transplant Sector, 37 transplant waiting list patients with HCV-induced cirrhosis were submitted to antiviral treatment. This population was composed of 46% women and 54% men, with a mean age of over 50 years. The predominant genotypes were 1 and 3. There was history of ascites and hepatic encephalopathy in 43.2% and 8.1% of the patients infected with genotypes 1 and 3, respectively. History of varicose digestive hemorrhage two months before the treatment was present in 5.4% of patients, and a history of spontaneous bacterial peritonitis was common (in 8.1%). Pegylated interferon was used in only five patients (all infected with genotype 1), and conventional interferon was used in the remaining patients. Both were used in combination with ribavirin. The mean duration of treatment was 7.9 months. The most common side effect associated with the treatment discontinuation was neutropenia (in 37.7%). Of the 37 patients, 14 (37.8%) presented viral load reduction of at least 2 log. In that study, the presence of compensated or decompensated cirrhosis did not affect the treatment response [27].

Recent studies describe the treatment with pegylated interferon and ribavirin in patients with decompensated cirrhosis. Although they present a considerable virological response, the frequency of severe complications necessarily leads to the need to always analyze the risk/benefit ratio before the decision to initiate treatment is made, also considering the feasibility of an emergency transplant [28,29].

Pre-Emptive Therapy

Antiviral therapy before the establishment of histologically confirmed disease presents theoretical advantages,

considering that, immediately after the transplant, the HCV viral load and the degree of hepatic fibrosis tend to be lower. This could provide a better response to the treatment, similar to what occurs in nontransplant patients. However, this is a moment at which the immunosuppression is still high, interfering with the antiviral response, and the antiviral regimen tolerability is too low in view of all of the other post-transplant clinical complications, such as infections and cytopenias. In addition, the immunomodulatory effect of interferon can increase the risk of acute cellular rejection, which is higher in this phase of the transplant process. Another criticism of pre-emptive treatment is that it does not distinguish patients who will actually evolve to a more significant recurrence of the disease and for whom treatment is indicated, from those who might have no need of antiviral therapy after the transplant [30,31].

Controlled studies have shown that treatment with the combination of conventional interferon and ribavirin has an advantage over monotherapy with interferon. There was a delay in the appearance of recurrence in those patients, who presented viral load reduction and better histological profiles. Studies involving the use of pegylated interferon and ribavirin have also demonstrated histological improvement, although their results are generally disappointing, with sustained virological response rates of 7-13% with the use of isolated interferon, 16-33% with interferon and ribavirin, and 9% with isolated pegylated interferon [32].

This strategy is not applicable to all patients. Those with better MELD scores before the transplant seem to be the best candidates. The need to reduce the dose or even discontinue the treatment is common, typically caused by cytopenias and concomitant renal dysfunction, with secondary anemia, which makes the use of ribavirin particularly difficult [33].

Post-Transplant Treatment

In general, most patients submitted to transplant for cirrhosis caused by HCV are treated after the transplant, when recurrence is already an established event. Unfortunately, most studies that support this treatment strategy have been uncontrolled, preventing the determination of the treatment risks, acute/chronic rejection rates, and even the evaluation of the therapeutic efficacy.

This is a population that, in principle, presents the worst prognostic factors of evolution and treatment response, since it comprises older patients who are infected with genotype 1, have high viral loads and present more extensive fibrosis, as well as more often having a history of previous treatment. These characteristics are also associated with the fact that transplant patients present comorbidities that frequently prevent the use of full-dose therapies [34].

In this group of patients, protocol biopsies are an essential means of assessing the degree of hepatic fibrosis and should be carried out whenever clinically indicated (by an increase in aminotransferase levels) or at least on an annual basis, with the specific purpose of detecting and monitoring HCV recurrence [35].

The results of this group are no less disappointing, with a sustained virological response rate of 12.5% with isolated interferon, 21% with interferon and ribavirin, and 9% with isolated pegylated interferon. In uncontrolled studies the combined use of pegylated interferon and ribavirin proved to be the best strategy, with responses between 30% and 45% [2,36-38].

The optimal duration of antiviral therapy remains undefined. Although most recent studies established treatment periods of 48 to 52 weeks, the validity of prolonging treatment in patients who achieved virological response by the end of the standard treatment period is still in question [39-41].

The advantages of therapy that begins within 6 to 24 months after the transplant, compared with pre-emptive therapy, is that these patients require less immunosuppression, present better clinical status, and are at lower risk of acute or chronic rejection [7].

The occurrence of acute or chronic rejection has not been a limiting factor to the treatment, although there are some reports on this subject [42].

The use of ribavirin as isolated therapy or as maintenance after the combined use with interferon has no subside in the literature [43].

Use of Adjuvant Therapy

In this group of patients, one of the central issues is the high rate of side effects from antiviral drugs, especially cytopenia, which often requires dose reduction or even discontinuation of the treatment. The risk/benefit ratio of the use of erythropoietin or granulocyte colony-stimulating factor has not been well established. However, its use has facilitated the maintenance of antiviral treatment and the use of optimal doses of ribavirin and interferon [44]. Efforts have been made to investigate the use of ribavirin substitutes that do not cause hemolysis, such as viramidine, although controlled studies are still needed in order to determine the best strategy in relation to the adverse effects of the therapy [5].

Second Transplants in Cases of Hepatitis C Recurrence

Although a second transplant is always an option in patients presenting hepatitis C recurrence, this strategy is historically associated with disappointing results. Receptor age, total bilirubin, high prothrombin time, older donor age, admission to the intensive care unit, high creatinine level, and high MELD score are predictive factors of short survival after a new transplant. Second transplants remain controversial and require comprehensive discussions in view of the low availability of organs and the use of MELD score as an organ allocation criterion, which implies that second transplants will be given to recurrent patients presenting more severe clinical profiles. In general, a second transplant is recommended if one of the variables related to recurrence, and thus the natural history of HCV recurrence, can be altered [45-47].

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