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REVIEW

Treatment modalities for hypersplenism in liver transplant recipients with recurrent hepatitis C

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Abstract

Hepatitis C is the most common indication for orthotopic liver transplantation in the United States. Unfortunately, hepatitis C recurs universally in the transplanted liver and is the major cause of decreased graft and patient survival. The combination therapy of interferon and ribavirin has been shown to be the most effective therapy for recurrent hepatitis C. However, pre- and post-transplant hypersplenism often precludes patients from receiving the antiviral therapy. Splenectomy and partial splenic embolization are the two invasive modalities that can correct the cytopenia associated with hypersplenism. In this report we review the two treatment options, their associated outcomes and complications.

Key words: Hypersplenism; Leukopenia; Recurrent hepatitis C; Thrombocytopenia; Liver transplant

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INTRODUCTION

Liver disease caused by chronic hepatitis C virus (HCV) infection is the most common indication for liver transplantation in the United States. Unfortunately, HCV is universally recurrent in the transplanted liver and is a major cause of graft failure and decreased patient survival[1]. 10%-30% of patients who have recurrent infection develop advanced fibrosis or cirrhosis within the first 5 years post-transplantation[2,3].

The combination therapy of interferon and ribavirin has been shown to be the most effective therapy for HCV recurrence after liver transplantation with sustained virologic response rates between 20%-40%[4]. Further studies are needed to determine whether treatment should be started preemptively, at the time of acute hepatitis, or at the early stages of chronic hepatitis in the graft. The ability to treat patients with adequate doses of interferon and ribavirin or even to initiate treatment is often limited by leucopenia, anemia, and thrombocytopenia. Chang *et al*[5] reported in their study that almost 50% of patients (109 out of 216) had a platelet count below 50 000/μL before liver transplantation. At one year of follow-up, 21% of transplanted patients (45 out of 216) continued to have moderate to severe thrombocytopenia. Clinical factors associated with sustained thrombocytopenia were pretransplant severe thrombocytopenia (< 50 000/μL) and pretransplant large spleen volume (> 2000 mm^3).

Splenectomy and partial splenic embolization represent two interventional therapies to improve thrombocytopenia which could potentially allow treatment of HCV. In this review we examine the effectiveness and risks of these approaches in liver transplant patients.

SPLENECTOMY

Splenectomy has been performed routinely in the past in liver and kidney transplant patients for immunologic reasons. It allowed patients to tolerate azathioprine therapy for episodes of rejection[6]. This practice continued

until the early 1980s when cyclosporine was introduced. Current accepted indications for post-transplant splenectomy include recurrent ascites, splenic infarction, large aneurysms of the splenic artery, thrombocytopenia secondary to hypersplenism prior to or after liver transplantation, and small-for-size syndrome in recipients of living donors with associated thrombocytopenia and impaired liver function. Splenectomy was also performed at the time of liver transplantation for ABO incompatibility and preemptive HCV treatment with interferon and ribavirin in thrombocytopenic patients[7-9]. Tashiro *et al*[10] advocated performing concurrent splenectomy with liver transplantation in all patients who had a pre-transplant platelet count of less than 60000 mm^3 so that this group of patients could tolerate preemptive administration of combination therapy in the post-transplant period.

Although successful results have been reported, splenectomy is potentially associated with multiple complications. It is an invasive procedure that can be technically difficult, with a high risk of bleeding in patients with portal hypertension, varices, and enlarged spleen. Portal vein thrombosis and pancreatic leaks requiring surgical reexploration have been described as complications[9,11]. However, in our opinion, the risk of infection post-splenectomy is the most serious and potentially life-threatening complication in the immunosuppressed population. Troisi *et al*[12] reported that 4 out of 10 liver transplant patients who underwent splenectomy developed sepsis, which led to their demise. Samimi *et al*[13] reported 17.5% *vs* 2.7% one-month and 30% *vs* 11.5% one-year sepsis-related mortality in patients who underwent concomitant splenectomy with liver transplantation *vs* those who underwent liver transplantation alone. Neumann *et al*[14] reported an increased risk for opportunistic pneumonia in patients who underwent simultaneous splenectomy and liver transplant. Splenectomy also places patients at risk for overwhelming post-splenectomy sepsis syndrome (OPSS), usually due to encapsulated organisms. It is recommended by the Center for Diseases Control to immunize patients prior to splenectomy to decrease the risk of OPSS from *Streptococcus pneumonia*, *Haemophilus influenzae* type B, and *Neisseria meningitides*[15]. According to guidelines issued by the American Society of Transplantation in 2004, these vaccines are administered to all candidates prior to liver transplantation[16]. Unfortunately, the response rate is only 40%-80%[17,18].

Despite vaccinations, fulminant bacterial sepsis carries a high risk of morbidity and mortality, especially in immunocompromised patients. The risk is greatest in the early months and years after splenectomy, but a period of as long as 45 years after the procedure has been reported in the literature[19].

PARTIAL SPLENIC ARTERY EMBOLIZATION

Partial splenic embolization is a non-surgical, less invasive treatment of hypersplenism. It is usually performed *via* a percutaneous femoral artery approach. The embolization catheter is advanced into the splenic hilum as far as possible in order to avoid injury to the pancreatic circulation. Gelatin sponge slurry suspended in an antibiotic solution, coils, microspheres, and polyvinyl alcohol particles are used for embolization of approximate 60%-70% of spleen parenchyma. Splenic embolization procedures date back to 1973, when the entire spleen parenchyma was ablated. At that time the procedure was associated with high rates of complications, including splenic abscesses, rupture, and pancreatic infarction, resulting in a high mortality rate[20]. Subsequently, this procedure became more successful with selective ablation of the spleen. In 1984, Mozes *et al*[21] showed in a prospective randomized trial that partial splenic embolization was as effective as splenectomy for treatment in renal transplant candidates on hemodialysis with a low platelet count prior to administration of immunosuppression. In this study excessive infarction of the spleen was avoided with a mean of 65% of spleen parenchyma ablated. Partial splenic embolization is an effective method to reduce the platelet pool and improve platelet count and is greatly dependent on the infarcted splenic volume. Hayashi *et al*[22] reported that splenic volume was the best predictive factor for increase in platelet count at one month and one year in patients with liver cirrhosis and hypersplenism.

In several reports in the literature, partial splenic embolization has been described in patients after liver transplantation. It has been successful in patients with thrombocytopenia and recurrent HCV who were able to undergo treatment with interferon and ribavirin as a result of ablation[23-25].

Most patients develop post-embolization syndrome, including symptoms of fever, left upper quadrant pain, pleural effusion, pneumonia, and atelectasis. Splenic abscesses and rupture are infrequent and are more commonly encountered and less tolerated by immunocompromised cirrhotic patients with a greater area of embolization[26]. The risk is greatly reduced with aseptic technique, antibiotic prophylaxis, and careful control of pain. Extent of embolization is important as well, with more complications following greater than 70% area of ablation. In partial splenic embolization, achieving the intended target embolization area remains challenging. Graded partial splenic embolization at several settings has been entertained in order to avoid excessive embolization and severe complications associated with it[27].

DISCUSSION

Hepatitis C is the most common indication for liver transplantation in the United States and Europe, but unfortunately the virus almost always recurs with up to a third of patients developing cirrhosis within the first 5 years. Interferon and ribavirin therapy has been widely accepted as the treatment for recurrent disease. Cytopenia, including thrombocytopenia, which often

afflicts liver transplant patients, leads to failure to initiate this antiviral regimen, dose reduction, or discontinuation of therapy, which ultimately decreases the likelihood of sustained virological response[28].

Although, hemolytic growth factors, such as erythropoietin and growth colony stimulating factors, are used to counter the anemia and neutropenia associated with interferon and ribavirin treatment, there is no approved therapy for low platelet count in HCV infected patients.

A new group of synthetic thrombopoietic agents, including romiplostim and eltrombopag, have been found to be effective in stimulating platelet production[29]. In 2008, romiplostim was approved by the FDA for the treatment of thrombocytopenia in patients with chronic idiopathic thrombocytopenic purpura (ITP). These agents are now being investigated in clinical trials for the treatment of thrombocytopenia in cirrhotic patients with hepatitis C infection[30,31].

CONCLUSION

Currently, splenectomy is the more popular choice of treatment for hypersplenism and thrombocytopenia. The question is whether it is the optimal choice. Partial splenic embolization is an alternative option that is often overlooked. It is less invasive and potentially carries fewer infectious complications since there is a remnant of functional splenic parenchyma remaining after the procedure. Although it diminishes with time, the risk of OPSS in asplenic patients is life-long. It carries a high mortality rate and therefore, we feel, other options should be seriously considered. Thus, further prospective studies are needed to investigate both modalities in this select group of patients.

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