Recent Advances in Liver Transplantation

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Advances in liver transplantation continue to evolve but are hampered by continued increasing shortages in donor organs. This has resulted in a high incidence of patients dying while on the United Network for Organ Sharing waiting list. Indeed, we continue to assess ways of expanding the donor pool by using marginal donors, living donor liver transplantation, split liver transplantation, domino transplantation, and hepatic support systems to prolong survival long enough for the patient to undergo liver transplantation. Changes in the liver allocation policy to reduce the number of people dying while waiting for an organ are discussed. Implementation of the model for end-stage liver disease allocation system should help alleviate the problem of increasing deaths of patients while on the waiting list. Recurrent disease, particularly recurrent hepatitis C, continues to be a major problem, and effective therapy is needed to prevent both progression of hepatitis C and recurrence in the graft and avoid retransplantation. The use of pegylated interferon in combination with ribavirin holds promise for improving the success in overcoming recurrent hepatitis C. Finally, advances in immunosuppression have reduced the incidence of acute cellular rejection and chronic rejection. However, these therapies have been fraught with metabolic complications that are now affecting quality of life and long-term survival. Tailoring immunosuppressive regimens to the individual patient is discussed.


CTP = Child-Turcotte-Pugh; HBIG = hepatitis B immune globulin; HBV = hepatitis B virus; HCV = hepatitis C virus; MELD = model for end-stage liver disease; PBC = primary biliary cirrhosis; PSC = primary sclerosing cholangitis; TIPS = transjugular intrahepatic portosystemic shunt; UNOS = United Network for Organ Sharing

As we begin the 21st century, liver transplantation is the treatment of choice for patients with acute fulminant hepatic failure, end-stage chronic liver disease, and certain metabolic liver diseases for which no alternative therapies are available. One-year patient survival approaches 90%, and a 5-year survival of 80% is achieved at many leading medical centers in the United States. In addition to longer survival, many liver transplant recipients are now experiencing improved quality of life, including resumption of active employment and reproductive capacity.1-4

Despite these advances, liver transplantation faces several major challenges. The most important of these is dealing with the donor shortage.1 As the hepatitis C virus (HCV) epidemic develops, the demand for liver transplants could increase as much as 5-fold. Furthermore, recurrent disease, in particular recurrent hepatitis C, has evolved as a leading cause of late graft failure and a major indication for retransplantation.5-7 Complications related to prolonged immunosuppressive therapy have also occurred, with many patients developing diabetes, hypercholesterolemia, progressive renal insufficiency, hypertension, and osteoporosis. Furthermore, all liver transplant recipients remain at increased risk for major infections and development of de novo malignancies, the major causes of late death.8-13

Transplant centers encounter an increasing number of cases of hepatocellular cancer, particularly in patients who have chronic hepatitis C with cirrhosis. Recent studies have documented a marked increase in the incidence of hepatocellular cancer during the past decade,14 and we will almost certainly see a further increase in the next decade related to the HCV epidemic. Additionally, we are challenged by patients who present with acute fulminant hepatitis who have only hours to live and are in need of a lifesaving liver transplantation. The development of bioartificial liver support systems appears to have tremendous potential in providing a bridge to liver transplantation in this subgroup of patients.15

DEALING WITH THE DONOR SHORTAGE

Today, more than 18,000 patients are on the United Network for Organ Sharing (UNOS) list waiting for a liver. However, in the past 5 years, the number of cadaver organs

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available for liver transplantation in the United States has remained stable at approximately 4600 per year (Figure 1). With an ever-increasing number of patients on the waiting list and a stable number of available cadaver donors, the number of patients who die while on the waiting list had increased steadily but plateaued in recent years, with approximately 1800 potential liver recipients dying while on the waiting list in the year 2000. In addition, numerous patients are removed from the UNOS waiting list because they become too ill or experience tumor growth or spread, making them ineligible for liver transplantation. Thus, the success of liver transplantation has increased the demand, which has resulted in a marked discrepancy between the number of patients waiting for a liver and the number of available organs.

During the past several years, a number of innovative and creative techniques have been developed to deal with the donor shortage (Table 1). In the past, older donors (>55 years of age), those with fatty infiltration, those with diabetes mellitus, and those who were HCV or hepatitis B virus (HBV) positive were typically excluded but are now termed marginal donors. In more recent years, organs from marginal donors have been used with increasing success. Several studies have shown that organs from older donors (>50 years of age) or from those who have mild to moderate fatty infiltration can be used with good results if cold ischemia time is minimized. Organs from donors who are HBV or HCV positive are now used in recipients who have HBV or HCV, respectively, as their underlying liver disease. Recent studies have shown that transplanting organs from HCV-positive donors in patients with HCV does not appear to have an adverse effect. Similarly, studies have suggested that an organ from a hepatitis B core antibody-positive donor, which can subsequently cause de novo hepatitis B infection in the liver recipient, can be used if prophylactic treatment with lamivudine and hepatitis B immune globulin (HBIG) is administered.

Other ways to deal with the donor shortage include split liver transplantation in which a cadaver liver is split into 2 pieces, with the right lobe usually being used for an adult recipient and the left lobe or left lateral segment being used for a small adult or a pediatric recipient. However, the optimal technique used to split the liver is controversial. At least 1 center showed a marked advantage for in vivo splitting vs ex vivo splitting in regard to overall outcomes. The advantage of split liver transplantation is that 2 patients receive transplants from 1 donor. The disadvantage is that split liver transplantation appears to be associated with decreased graft survival and an increased number of biliary complications compared with whole liver transplantation. However, data are accumulating that show that split liver transplantation should be used for select patients who are UNOS 2B status (model for end-stage liver disease [MELD] score ≤24) (see subsequent section on liver allocation policy for further details) and should not be used or should be used cautiously in patients with more severe underlying liver diseases, such as those who are UNOS status 1 or those who have a MELD score of 25 or higher. Split liver transplantation is technically

Table 1. Resources Available for Expanding the Donor Pool

<table>
<thead>
<tr>
<th>Resources Available for Expanding the Donor Pool</th>
</tr>
</thead>
<tbody>
<tr>
<td>Marginal donors</td>
</tr>
<tr>
<td>Older donors (&gt;50 y)</td>
</tr>
<tr>
<td>Donors with fatty infiltration</td>
</tr>
<tr>
<td>Hepatitis B and C virus–positive donors</td>
</tr>
<tr>
<td>Split liver transplants</td>
</tr>
<tr>
<td>Domino transplants</td>
</tr>
<tr>
<td>Living donors</td>
</tr>
<tr>
<td>Xenografts</td>
</tr>
</tbody>
</table>
demanding, and the results vary widely among liver transplant centers, which may be related to a distinct learning curve. Nonetheless, split liver transplantation is an important option for expanding the donor pool, may be potentially beneficial for pediatric patients, and could potentially lead to decreased waiting times for both pediatric and adult recipients.

Another means of increasing the donor pool is domino liver transplantation. In this situation, a patient with familial amyloidosis (a disease in which the liver produces a mutated transthyretin gene molecule that accumulates in blood vessels, nerve tissue, and other organs) receives a liver transplant from a cadaver donor. This patient's liver in turn is procured and transplanted into an elderly recipient. Since symptoms related to familial amyloidosis develop over a period of 20 to 30 years, short-term follow-up data suggest that a liver from a patient with familial amyloid disease can be used for liver transplantation without early adverse effects.

A major advance that has increased the donor pool is living donor liver transplantation. Living donor liver transplantation was first reported in 1990. A left lateral segment (segment 2-3) of an adult liver was resected and grafted into a child. This procedure has been tremendously successful, with patient and graft survival approaching that achieved with cadaver donor liver transplantation. Adult to pediatric live donor liver transplantation is a standard of care at many pediatric liver transplant centers worldwide.

Living donor adult-to-adult liver transplantation was first reported in 1994. In this procedure, the right lobe (segment 5 and 8), representing 60% to 65% of the liver, is resected from the donor and grafted into the recipient. Because of the ever-increasing number of patients on the UNOS list waiting for a liver transplant, this procedure has evolved rapidly in the United States, with more than 500 adult-to-adult liver transplants performed in 2001 (Figure 2). Adult-to-adult living donor liver transplantation is also popular in Japan because of the lack of cadaver donors due to cultural differences in the definition of brain death. Adult-to-adult live donor liver transplantation has been highly successful, particularly when used in non-urgent situations, such as in patients previously designated UNOS status 2B or 3 or those with a MELD score lower than 25. This procedure has also played an important role in transplant recipients with hepatocellular cancer who often wait 1½ to 2 years designated as UNOS 2B status and then have disease progression and metastasis, eliminating them as candidates for a liver transplant. Results have been less favorable when used in urgent situations, such as in patients previously designated UNOS status 1 and 2A or those with a MELD score greater than 25.

Although living donor liver transplantation in adults is attractive, the procedure is technically demanding and has several drawbacks. First, at present, only one third of liver recipients can identify a potential donor who becomes a candidate after undergoing evaluation. Second, although the risk of death for the donor has not been defined, at least 2 deaths have been reported in living liver donors in the United States. Furthermore, a 20% to 30% morbidity rate has been experienced in living donors, directly related to the hepatic resection. A third drawback relates to potential coercion and the apparent conflict of interest. Finally, many medical centers have reported substantial donor costs that appear to exceed the costs associated with procuring a cadaver donor.

Despite these drawbacks, graft survival is comparable to that achieved with cadaver donors in younger recipients but is significantly decreased in older recipients (>50 years of age) (Figure 3, left). Similarly, with use of living donors,
graft survival decreases significantly with donor age compared with use of cadaver donors (Figure 3, right). Furthermore, most series report a modest increase in the number of biliary complications and a slightly increased retransplantation rate. In a recent survey, most US liver transplantation centers indicated that they have either done right lobe living donor transplantation or plan to perform this procedure in the future. The overwhelming reason is the continued donor shortage and the ever-increasing number of patients on the UNOS liver waiting list. However, many believe that living donor transplantation may further expand indications for liver transplantation, thus nullifying some of its potential positive effect on the donor shortage. During the next several years, adult living donor liver transplantation should continue to evolve as it becomes more common.

A further development that has helped in dealing with the donor shortage in patients who present with acute fulminant hepatitis is the use of hepatic support systems. These devices use either a dialysis-type method or columns of hepatocytes from pigs or humans. The major goal of treating patients with acute fulminant hepatitis is to prevent the development of cerebral edema and brainstem herniation, thus providing a bridge to liver transplantation. In addition, theoretically, a hepatic support device could allow time for hepatic regeneration, thus potentially excluding the need for liver transplantation.

Finally, xenografting has received much press in recent years; however, clinical use of xenografts does not appear feasible at this time. Gene therapy has been able to deal with hyperacute rejection in xenografts; however, vascular rejection has been difficult to control and is the major challenge facing xenotransplantation. In addition, transmission of infectious viruses across species remains a potential concern.

A NEED FOR CHANGE IN THE UNOS LIVER ALLOCATION POLICY

An alternative approach to a decrease in the death of patients on the UNOS waiting list is to change the current allocation policy. A change in the liver allocation policy has been spurred by the Health and Human Services final rule mandate that provides the following guidelines: (1) organs should be allocated to transplant candidates in the order of medical urgency, (2) the role of waiting times should be minimized, and (3) attempts should be made to avoid futile transplantations and promote efficient use of the scarce donor organs.

Previously, the UNOS liver allocation policy was based on the Child-Turcotte-Pugh (CTP) score and on waiting time. During the past few years, several limitations have been identified with both the UNOS allocation scheme and the CTP score. The most important shortcoming of the UNOS allocation policy was that it defined only 3 categories of disease severity for patients with chronic end-stage liver disease: status 3 (CTP score ≥7), status 2B (CTP score ≥10), and status 2A (CTP score >10) in the intensive care unit and less than 7 days to live. With only 3 categories of disease severity, waiting time had become an extremely important factor, serving as a tiebreaker within each category. This was particularly a problem for patients classified as status 2B, the largest group of patients waiting for
liver transplantation, who had a broad range of liver disease severity. This problem was further magnified by the fact that the waiting time accrued by patients classified as status 3 while on the waiting list was applied as they advanced to status 2B. Since waiting time was shown in 2 studies not to correlate with death while on the waiting list, de-emphasizing waiting time as an organ allocation factor seemed appropriate.

Although the UNOS allocation scheme clearly failed to prioritize liver allocation based on medical urgency, the CTP score itself was found to have limited usefulness as an index of disease severity. These drawbacks were primarily due to limited discriminant ability and variability of the CTP score. First, the CTP score has a limited number of disease categories. Second, the CTP score is limited by its inability to discriminate disease severity among the sickest patients. For example, patients with a bilirubin level of 3 mg/dL or 30 mg/dL are given the same CTP score, suggesting the same severity of liver disease. Similarly, 2 patients, one with a serum albumin level of 2.8 g/dL and one with a serum albumin level of 2.1 g/dL, are given the same disease score despite marked differences in hepatic synthetic function. Third, the CTP score was limited because 2 factors in the CTP score—ascites and encephalopathy—depended on the manner in which these conditions were evaluated. Should ascites be assessed by subjective findings on physical examination as it was when the original CTP score was developed, or should the more sensitive ultrasonographic method for detecting ascites be used? Do vague symptoms such as forgetfulness, fatigue, and insomnia constitute a diagnosis of portosystemic encephalopathy, or should more objective criteria be required? Not only was there a lack of uniform standards for diagnosing and grading the severity of ascites and encephalopathy but also these symptoms could improve or even resolve with simple dietary or medical measures. Even the more objective laboratory elements of the CTP score varied from one institution to another. In particular, the measurement of the prothrombin time depends on the sensitivity of the thromboplastin reagent used, and wide variation exists among centers. Although serum electrophoresis is usually considered the gold standard for the measurement of serum albumin, some clinical laboratories use the less expensive and also less sensitive colorimetric assay for albumin. Thus, based on the shortcomings of both the UNOS allocation scheme and the CTP scoring index, many have agreed that change was necessary so that organs could be more fairly allocated in the United States.

**MODEL FOR END-STAGE LIVER DISEASE**

MELD was derived from a heterogeneous group of cirrhotic patients from 4 medical centers throughout the

<table>
<thead>
<tr>
<th>Score</th>
<th>No. of patients</th>
<th>Mortality (%)</th>
<th>Mortality or removal from list due to severity of illness (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>MELD</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;9</td>
<td>124</td>
<td>1.9</td>
<td>2.9</td>
</tr>
<tr>
<td>10-19</td>
<td>1800</td>
<td>6.0</td>
<td>7.7</td>
</tr>
<tr>
<td>20-29</td>
<td>1908</td>
<td>19.6</td>
<td>23.5</td>
</tr>
<tr>
<td>30-39</td>
<td>295</td>
<td>52.6</td>
<td>60.2</td>
</tr>
<tr>
<td>≥40</td>
<td>120</td>
<td>71.3</td>
<td>79.3</td>
</tr>
<tr>
<td>CTP</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;7-9</td>
<td>318</td>
<td>4.3</td>
<td>5.6</td>
</tr>
<tr>
<td>10-12</td>
<td>2357</td>
<td>11.2</td>
<td>13.4</td>
</tr>
<tr>
<td>13-15</td>
<td>588</td>
<td>40.1</td>
<td>48.5</td>
</tr>
</tbody>
</table>

*CTP = Child-Turcotte-Pugh; MELD = model for end-stage liver disease.

United States and was validated by using an independent data set from the Netherlands originally developed to assess short-term prognosis of patients with liver cirrhosis undergoing a transjugular intrahepatic portosystemic shunt (TIPS) procedure. This recently described model uses serum creatinine, total serum bilirubin, international normalized ratio of prothrombin time, and the etiology of cirrhosis. Further studies reveal that the model is valid even if the etiology of liver disease is removed. The model has been validated in several patient groups with cirrhosis and has been found to be an extremely powerful tool to predict the probability of death during a 3-month period. It has also been assessed in patients on the UNOS waiting list and found to be an excellent predictor of who will live or die during a 3-month period (Table 2). MELD has been shown to be superior to the CTP score in predicting mortality and has the distinct advantage of using variables that are readily available, standardized, reproducible, and objective. On the basis of these findings, UNOS is now using MELD to allocate livers in the United States.

A similar process was initiated by a pediatric group using data from the Studies of Pediatric Liver Transplantation database. The pediatric survival model (pediatric end-stage liver disease [PELD]) was developed with the following variables: age younger than 1 year, serum albumin level, total serum bilirubin level, international normalized ratio, and growth failure defined as less than 2 SD below the mean based on age. This model was validated with an independent database from the University of Pittsburgh and was found to be useful in predicting deaths of pediatric patients on the UNOS waiting list. Both MELD in adults and the PELD model in pediatric patients should help to achieve the "final rule" goal of rank-ordering patients on the UNOS waiting list by severity of liver disease and may reduce the number of patients dying while on the waiting list.
MANAGING PATIENTS ON THE UNOS WAITING LIST

With patients waiting prolonged times to receive a donor organ, prevention and treatment of complications related to portal hypertension have become increasingly more important. Interventions including the use of β-blockers and/or prophylactic banding of esophageal varices in patients at high risk for bleeding and the use of prophylactic antibiotic therapy to prevent spontaneous bacterial peritonitis are particularly relevant in patients with Child class C cirrhosis. The use of TIPS to treat ascites, refractory variceal bleeding, and early hepatorenal syndrome has also helped patients to remain viable candidates for liver transplantation. Maintaining renal function in the setting of liver failure remains a major challenge to all practicing hepatologists. The avoidance of renal toxins such as aminoglycoside antibiotics and antiprostaglandin medications, along with the judicious use of albumin in patients undergoing large-volume paracentesis, is an important measure in preserving renal function. In addition, nutritional support and multiple feedings have been important in maintaining the nutrition of these extremely ill patients. Finally, the use of hepatic support devices has been advocated in some patients with chronic end-stage liver disease. Using hemodialysis devices to remove ammonia and urea also tends to improve renal function. Although these devices are theoretically attractive, data supporting their widespread use have yet to be generated.

RECURRENT DISEASE

Hepatitis C

Recurrent disease after liver transplantation is a major challenge to the transplant hepatologist. The most important disease that recurs after liver transplantation is hepatitis C. Hepatitis C viremia occurs almost universally in patients with HCV who have undergone liver transplantation, with levels of viremia reaching several logs higher compared with patients infected with HCV who do not undergo transplantation. Histological recurrence is noted in approximately 50% of patients if liver biopsy is performed 1 year after liver transplantation. Several studies have revealed the importance of routine liver biopsy in the hepatitis C transplant recipient because correlation between serum transaminase levels and histological findings is often poor. Furthermore, a number of patients with normal or near-normal alanine aminotransferase levels have developed fibrosis or early cirrhosis. In patients with recurrent hepatitis C, 15% to 30% develop cirrhosis after 5 years. Finally, although short-term follow-up studies suggest that patient survival and graft survival were similar to other indications for liver transplantation, recent literature suggests that long-term outcomes are worse in HCV recipients vs cholestatic or non-HCV recipients (Figure 4).

Several risk factors have been identified that portend increased severity of recurrent HCV (Table 3). These risk factors include pretransplantation viral load, prolonged cold ischemic time, use of older donors, genotype 1B, type of immunosuppression, occurrence of early rejection episodes treated with bolus corticosteroids, rejection treatment with antilymphocyte preparations, and cytomegalovirus infection. Furthermore, at least 2 studies reported increased severity of recurrent HCV in patients with HCV who received a living donor graft. Of concern is evi-
dence that shows that the severity of recurrent HCV has increased in recent years, which most likely reflects the increasing use of older donor organs and increased overall immunosuppression. Defining the balance between over-immunosuppression and prevention of acute rejection remains a major challenge in patients with HCV who receive a liver transplant.

Treatment, either to prevent recurrent HCV or to treat recurrent HCV, has been disappointing. In general, interferon therapy alone has been inadequate to treat HCV in the posttransplantation setting and has been poorly tolerated. The combination of interferon and ribavirin therapy has been associated with a 25% to 30% end-of-treatment virological response but only a 10% to 15% sustained virological response.\textsuperscript{77-86} However, most reports note that more than two thirds of patients have had serious adverse effects that required either discontinuation or major dose reduction of both interferon and ribavirin. Retransplantation for patients with recurrent HCV remains controversial because of poor outcomes.\textsuperscript{7} Indeed, several transplant centers have stopped performing retransplantations in patients with recurrent HCV. For the future, the use of pegylated interferon holds promise for improving our success in overcoming recurrent HCV. However, innovative approaches will be important to reduce the effect of recurrent HCV.

**Hepatitis B**

Tremendous advances have been made in the past decade in preventing recurrent HBV infection after liver transplantation for hepatitis B liver disease. The use of high-dose HBIG with or without lamivudine has prevented recurrences of HBV in up to 90% of patients undergoing liver transplantation for chronic HBV infection.\textsuperscript{86-90} However, patients undergoing liver transplantation with high-level, replicative HBV disease (DNA positive, hepatitis B e antigen positive) have had recurrence rates of up to 20% even if prophylactic therapy is administered.\textsuperscript{89,91,92} The challenge is the increasing cost of HBIG, which can be up to $100,000 per year.\textsuperscript{93} Today, several treatment protocols use HBIG, lamivudine, or a combination of the 2 agents.\textsuperscript{94-97} Used alone, HBIG and lamivudine have been associated with the development of resistant mutants, and the best results have been achieved by using a combination of HBIG and lamivudine.\textsuperscript{91,94,95,96} The major problem with lamivudine monotherapy is the high incidence of breakthrough infection due to the development of resistant YMDD mutants.\textsuperscript{96-102} However, adeovir is now available as rescue therapy, and, to date, strains resistant to adeovir have not been identified.\textsuperscript{103-106} A major adverse effect associated with adeovir is modest renal toxicity, which may limit its use because liver transplant recipients frequently have impaired renal function related to the use of calcineurin inhibitors. Further studies are needed to determine the optimal dose of adeovir and to assess its relationship with nephrotoxicity.

Another challenge facing the liver transplant hepatologist is whether it is important to convert patients from a replicative state to a nonreplicative state before liver transplantation. Treatment with lamivudine is associated with decreased HBV DNA levels and is often associated with improved liver function test results even in patients with compensated disease. However, patients on the liver transplant waiting list treated with lamivudine have approximately a 20% chance of developing a YMDD mutant in the first year and up to 40% after 2 years of therapy.\textsuperscript{105} The pathogenicity of the YMDD HBV mutant remains controversial. There are reports of acute fulminant hepatitis developing in relationship to the development of the YMDD mutant; however, several reports have shown that patients with the YMDD mutant can undergo successful transplantation by using prophylactic therapy.\textsuperscript{101,107} More data are needed to determine the best and most cost-effective manner for treating patients with HBV to optimize long-term results, prevent recurrent disease, and prevent the occurrence of HBV mutants.

Currently, a major National Institutes of Health–funded effort is examining optimal treatment protocols for patients undergoing transplantation for hepatitis B. Treatment regimens for patients considered at low risk and at high risk for recurrence are being evaluated. In addition, the effects of HBV genotype and mutations on recurrence are being studied. Early data suggest that some HBV genotypes may be more likely to cause HBV reinfection.\textsuperscript{109}

**Other Liver Diseases**

Several reports have documented the recurrence of autoimmune liver disease after liver transplantation. Primary biliary cirrhosis (PBC), primary sclerosing cholangitis (PSC), and autoimmune hepatitis all have a 20% to 30% incidence of recurrence within 5 years after liver transplantation. Autoimmune hepatitis has been seen with increasing frequency since corticosteroid therapy is being tapered completely in many patients.\textsuperscript{110-117} Recurrent autoimmune hepatitis is usually easily managed by reintroducing use of corticosteroids with or without the addition of azathioprine. In addition, graft dysfunction that mimics autoimmune hepatitis has been identified after liver transplantation in patients with a variety of underlying liver diseases.\textsuperscript{118}

Recurrence of PBC and PSC has also been reported in up to 30% of patients.\textsuperscript{110,112} Although these cholestatic conditions are usually slowly progressive, at least 3 patients with PSC in our experience have developed liver failure related to recurrent PSC and have required retransplantation. In 2 of these patients, fibrosis was noted on liver
biopsy specimens; 1 patient developed jaundice and ascites
and is listed for retransplantation. Patients with recurrent
PBC generally have a mild form of disease, with the only
finding being a florid duct lesion on a yearly protocol
biopsy in the setting of completely normal biochemical
liver test results.

A continued controversial indication for liver
transplantation is alcoholic liver disease. The incidence of
alcohol use after liver transplantation in patients with alcoholic
liver disease remains poorly defined. A recent meta-
analysis by Bravata et al.\textsuperscript{119} of a large number of reports after liver
transplantation in alcoholic patients revealed several
interesting findings. The study found no difference in the
proportion of transplant recipients (alcoholic vs nonalcoholic)
reporting early alcohol use posttransplantation (4% vs 6% at 6 months and 17% vs 16% at 12 months, respectively).
However, the study found that patients who received a
transplant because of alcoholic liver disease and who resumed
drinking tended to drink excessively. At 7 years
posttransplantation, approximately one third of patients
who underwent liver transplantation because of alcoholic
liver disease reported regular use of alcohol. The group at
highest risk for alcohol use was patients who maintained
abstinence for fewer than 6 months pretransplantation vs
those who maintained abstinence for more than 6 months,
with a relative risk of 7.8 (P < 0.001). In addition, the rate
of active employment after liver transplantation was signifi-
cantly less in alcoholic vs nonalcoholic patients (33% vs
80%). Finally, although 1- and 2-year survival after liver
transplantation because of alcoholic liver disease is similar
to other indications, long-term survival seems to be dimin-
ished in alcoholic patients vs patients with cholestatic liver
disease. Of note, only a few of the deaths or graft failures
are directly related to alcohol abuse. However, an increase
in cancer-related deaths in alcoholic patients was recently
noted in a study from Europe that revealed a high number
of ear, nose, and throat cancers.\textsuperscript{120}

**Table 4. Incidence of Hepatic Allograft Rejection,
Stratified by Year and Immunosuppressive Therapy**

<table>
<thead>
<tr>
<th>Treatment regimen</th>
<th>Year</th>
<th>Patients experiencing rejection (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prednisone and azathioprine</td>
<td>1980</td>
<td>85</td>
</tr>
<tr>
<td>Cyclosporine and prednisone</td>
<td>1983</td>
<td>70</td>
</tr>
<tr>
<td>Cyclosporine, prednisone, and azathioprine</td>
<td>1987</td>
<td>65</td>
</tr>
<tr>
<td>Tacrolimus and prednisone</td>
<td>1993</td>
<td>55</td>
</tr>
<tr>
<td>Tacrolimus, prednisone, and azathioprine</td>
<td>1996</td>
<td>45</td>
</tr>
<tr>
<td>Cyclosporine, mycophenolate mofetil, and prednisone</td>
<td>1999</td>
<td>30</td>
</tr>
<tr>
<td>Tacrolimus and rapamycin</td>
<td>2001</td>
<td>18</td>
</tr>
</tbody>
</table>

Data from Wiesner and Menon.\textsuperscript{121}

**ADVANCES IN IMMUNOSUPPRESSION**

Since the 1980s, when acute hepatic allograft rejection
occurred in approximately 80% of patients undergoing
liver transplantation, marked advances have been made
(Table 4).\textsuperscript{121} The introduction of cyclosporine in the early
1980s was the first major advancement in the field and
reduced the incidence of acute rejection to between 60% and
70%. The introduction of tacrolimus in the mid-1990s
was the second major advancement. Tacrolimus-based
immunosuppression has reduced the incidence of acute
rejection to between 50% and 60%. A secondary advantage
of tacrolimus is the ability to reduce corticosteroid doses,
which has led to an overall decreased incidence in cardiovascular risk factors such as hypercholesterolemia, hypertension, and obesity.

In the late 1990s, mycophenolic acid was introduced in
combination therapy with cyclosporine.\textsuperscript{122,123} The use of
mycophenolic acid in combination with cyclosporine and
prednisone led to the reduction of acute rejection to 30% to
40%. When mycophenolic acid was combined with tacrolimus and low-dose prednisone therapy, a further reduction in the incidence of rejection to 25% to 30% was noted.\textsuperscript{124} The most recent combination of immunosuppressive agents includes the use of low-dose tacrolimus and rapa-
mycin.\textsuperscript{125-127} Preliminary studies indicate that the incidence of rejection with use of this regimen ranges from 15% to
18%. However, an increased incidence of hepatic artery
thrombosis has been noted in early posttransplantation
patients taking rapamycin (now known as sirolimus), and
this may limit early use of this agent.\textsuperscript{128} In fact, the Food
and Drug Administration has issued a formal warning con-
cerning the high incidence of hepatic artery thrombosis
with early use of rapamycin.

Chronic rejection has also decreased recently, from
a peak of about 15% to 18% associated with cyclosporine
and prednisone regimens in the early 1980s to approxi-
ately 5% with tacrolimus-based immunosuppressive
regimens.\textsuperscript{129,130} Today only about 2% of patients undergo-
liver transplantation develop chronic rejection; how-
ever, the incidence is higher in patients with autoimmune
liver disease.\textsuperscript{131} This reduction in the incidence of chronic
rejection results from the availability of alternative immu-
inosuppressive agents, particularly for patients who could
not tolerate cyclosporine or tacrolimus and who otherwise
would have been treated with prednisone and/or azathiop-
rine alone. Furthermore, an increased understanding of
the relationship between acute rejection and chronic rejec-
tion and the development of standardized criteria (Banff
criteria) for the histopathologic diagnosis of acute and
chronic rejection have been important achievements.\textsuperscript{122}

Several studies have documented that when chronic rejec-
tion is treated early the process can be reversed.\textsuperscript{133,134}
Several investigators have assessed the effect of acute rejection on overall patient and graft survival. Unlike heart and kidney transplantation in which an early acute rejection episode seems to affect 1- and 2-year graft survival negatively, an acute rejection episode after liver transplantation that is treated successfully does not appear to have a negative effect. The exception to this finding are patients who receive liver transplants because of hepatitis C who are treated for acute rejection with bolus corticosteroids or OKT3 therapy. These patients seem to have early and more severe recurrent disease. Patients who develop cytomegalovirus infection also seem to have more severe recurrent hepatitis C.

Another important advancement in immunosuppressive therapy is the ability to withdraw corticosteroid therapy completely within 3 to 4 months after transplantation. Corticosteroid withdrawal has been associated with marked improvement in cardiovascular risk factors, including a decrease in hypertension, a decrease in cholesterol and triglyceride levels, and a decrease in the incidence of obesity. In addition, a number of patients are able to discontinue insulin use once corticosteroids have been discontinued. Furthermore, corticosteroid withdrawal has been associated with preventing bone mineral loss and a reduced incidence of osteoporotic bone fracturing.

An important long-term complication of liver transplantation is progressive renal dysfunction. A recent unpublished study from Baylor University showed that patients followed up for 15 to 20 years posttransplantation have experienced a 15% to 20% renal failure rate, requiring dialysis or kidney transplantation. Renal insufficiency has occurred primarily in patients treated with cyclosporine, which was often used at extremely high dosages in the early posttransplantation course. Although tacrolimus also has associated renal toxicity, long-term follow-up of patients treated with tacrolimus is approaching 10 years, and further assessment of its effect on long-term renal function remains to be determined. Furthermore, for some patients who have degenerating renal function, switching treatment from a calcineurin inhibitor to rapamycin therapy has proved successful in not only preventing rejection but also in partially reversing renal dysfunction. However, many of these patients have a component of irreversible renal damage, and complete renal function recovery is unusual.

The increase in the availability of newer immunosuppressive agents with different mechanisms of action and different adverse effects has provided the clinician with a choice of immunosuppressive regimens. With this choice comes the concept of tailoring immunosuppression for the individual patient. For instance, several factors have now been established that predict patients at risk for acute rejection. The elderly alcoholic patient with moderate renal dysfunction has an extremely low incidence of acute rejection, whereas the young female patient with autoimmune liver disease has an extremely high incidence. Thus, the latter patient will need more immunosuppressive therapy, particularly in the early posttransplantation course. Several special circumstances arise in which one immunosuppressive regimen seems to be better than another. An example is the patient with PBC in whom the use of tacrolimus seems to be associated with an early and more severe recurrence of PBC. Patients with autoimmune chronic active hepatitis are often intolerant of corticosteroid withdrawal, which can lead to recurrent disease (in 20%). However, when autoimmune hepatitis recurs, it is easily controlled with reintroduction of corticosteroids and azathioprine.

Furthermore, patients who have diabetes mellitus before transplantation or who develop new-onset diabetes mellitus while receiving tacrolimus therapy (approximately 16%), which is associated with an increased morbidity, can frequently switch to cyclosporine, which allows either discontinuation or a marked reduction in insulin requirements. Finally, patients with cardiovascular risk factors, such as hypercholesterolemia and hypertension, might be better treated with tacrolimus-based immunosuppressive regimens that are associated with decreased cholesterol levels, decreased triglyceride levels, decreased blood pressure, and a decreased incidence of obesity compared with cyclosporine-based regimens. In part, this seems related to the fact that corticosteroid doses can be tapered faster in patients treated with tacrolimus.

Several investigators have tried to wean patients completely from immunosuppressive therapy. At the University of Pittsburgh, one third of a select group of patients was successfully weaned from all immunosuppressive therapy without experiencing evidence of rejection. However, approximately one third of patients did develop rejection, and a number of patients evolved to corticosteroid-resistant rejection requiring antilymphocyte therapy. Unfortunately, we have been unable to predict which patients can be successfully weaned from immunosuppressive therapy, and therefore patients undergoing such an experiment are at a substantial risk. The induction of tolerance is clearly an important goal and should be pursued vigorously in the next several years.

**LIVER TRANSPLANTATION FOR MALIGNANCY**

Liver transplantation in patients with hepatocellular cancer offers several advantages over partial hepatectomy: (1) It can be used for patients with poor hepatic function since about 90% of patients with hepatocellular cancer have cirrhosis; (2) tumor and underlying liver disease are therapeutically addressed concurrently; and (3) hepatocellular cancer associated with hepatitis C frequently is
multicentric, and performing partial hepatectomy leaves a
malignant portion of the liver, with a high risk for devel-
opment of new tumors.

Although the early experience with transplantation in pa-
tients with hepatocellular cancer was poor (approximately
a 30% cure rate), recent studies have shown that patient
selection can be a crucial determinant of outcome. Tumor
size (<5 cm) or the number of tumor nodules (up to 3
lesions <3 cm) appears to be important with regard to
prognosis and recurrent disease. Further studies based on
these selection criteria have shown that patient survival
and graft survival are similar to survival with other chronic
liver diseases. A recent study showed that patients who
fulfill the aforementioned criteria have a 3-year survival of
83% compared with a 3-year survival of 18% for patients
undergoing partial hepatectomy.145 On the basis of these
data, recent changes have been made to the UNOS alloca-
tion policy with the initiation of MELD. With the new
allocation policy, patients with cirrhosis and a hepatocellu-
lar cancer less than 2 cm will be entered with a MELD
score of 24, which is consistent with a 15% probability of
death or nontransplantability due to metastatic disease in a
3-month period. Similarly, patients with a hepatocellular
cancer 2 cm or greater will be entered with a MELD score
of 29, which equates to a 30% probability of death or
nontransplantability in the 3-month period. In both groups
of patients, a 10% increase in probability of dying or
transplantability will be added every 3 months until the
patient undergoes transplantation, dies, or develops a con-
dition that results in a nontransplantable situation, such as
metastatic disease.

In the patient with cirrhosis (Child class A) and hepatocellu-
lar cancer, the role of liver transplantation vs resection
remains somewhat controversial. However, we clearly fa-
vor transplantation in this group because of the multicentric
nature of hepatocellular cancer, particularly if associated
with HCV. If the waiting time will be more than 3 months,
we prefer chemoembolization, which causes necrosis of the
tumor and prevents further growth and possibly the
development of metastatic disease unless the patient has
extremely poor liver function. Radiofrequency ablation has
also been used at some centers; however, the Barcelona
group recently noted that 12.5% of patients undergoing
radiofrequency ablation experienced tumor seeding outside
the liver, along the needle tract.146 Clearly, further studies
regarding the use of chemoembolization and radiofre-
cuency ablation in relationship to the waiting time are
needed so that patients can receive optimal treatment.

CHOLANGIOCARCINOMA

Treatment options for patients with cholangiocarcinoma
and PSC are limited primarily to surgical intervention.

Unfortunately, long-term survival of patients who undergo
surgical resection alone is less than 20% at 2 years. Long-
term survival after liver transplantation for cholangiocar-
cinoma has also been disappointing. However, the observa-
tion that occasional patients experience long-term survival
(>5 years in 10%) after liver transplantation for chol-
angiocarcinoma suggests that this procedure has the poten-
tial to prolong survival in select patients. With a protocol
using neoadjuvant radiation therapy and chemotherapy fol-
lowed by liver transplantation, we have performed success-
ful transplantations in a limited number of select patients
with cholangiocarcinoma.147 The criteria for study entry
were that the cholangiocarcinoma must be above the cystic
duct and be unresectable as assessed by an experienced
hepato-biliary surgeon. Patients with intrahepatic meta-
stasy, uncontrolled infection, prior attempts at resection, prior
irradiation or chemotherapy for this disease or evidence of
extrahepatic disease including lymph node metastasis were
excluded from the study. A preoperative staging laparo-
tomy was performed to exclude extrahepatic metastatic
disease. In addition, computed tomography of the chest and
abdomen and a bone scan were performed to exclude evi-
dence of distant metastatic cholangiocarcinoma. Two to 3
weeks after completion of the external beam therapy, these
patients received external beam radiation with a radia-
tion boost by transcatheter radiation. Thus far, results in
20 patients with cholangiocarcinoma undergoing liver
transplantation reveal a 91% graft survival with a mean
follow-up of 47 months; only one patient has developed
recurrent disease. Although the early results of this initial
pilot experience are favorable, further assessment of this
treatment protocol is necessary before widespread use is
recommended.

Evolving Therapies for Acute Liver Failure:
Liver-Assist Devices

Liver failure remains a challenge with limited treatment
options. Other than liver transplantation, no specific
therapy exists for patients with this catastrophic condition.
Goals of therapy are to (1) prevent irreversible neurologic
damage, (2) provide time for possible regeneration of the
liver to allow complete recovery, and (3) provide a bridge
to liver transplantation.

To treat such patients, liver-assist devices or dialysis-
like systems are used often with mammalian hepatocytes or
sliced livers loaded in a mechanical-type apparatus.13,148
During extracorporeal perfusion of the system, hepatocytes
provide metabolic function to the patient. The goal of such
a device in patients with acute liver failure is to prevent
development of cerebral edema, prevent renal failure, cor-
correct coagulopathies, and maintain patient survival until
either a donor organ becomes available or spontaneous
recovery occurs. Several pilot trials in humans have shown improvement in neurologic status and have shown that these devices provide a bridge to liver transplantation. However, in the absence of a randomized controlled trial, the efficacy of liver-assist devices has been difficult to ascertain and remains unproved at this time. The results of the first randomized controlled trial (sponsored by Circe Biomedical, Inc, Lexington, Mass) should be available some time in the spring of 2003.

HEPATOCYTE TRANSPLANTATION

Hepatocyte transplantation has also been attempted in patients with acute liver failure to accomplish the same goals as with the hepatic liver-assist systems. In the major study published to date, 5 patients underwent intraportal or intrahepatic injection of human hepatocytes while receiving cyclosporine immunosuppression.149 Of the 3 patients who survived 18 hours after receiving the cells, clinical improvement in encephalopathy scores, arterial ammonia levels, and prothrombin time was observed. However, none of the patients survived long term. Autopsy specimens showed successful engraftment of hepatocytes, demonstrating the feasibility of this approach. Future trials using this concept are likely if results with hepatocyte liver-assist systems are disappointing.

SUMMARY

The field of liver transplantation continues to advance. Donor shortage remains a problem, with a high incidence of patients dying while on the UNOS waiting list. The advent of living donor right lobe transplantation in adults and the implementation of MELD will help alleviate this problem. Recurrent disease, particularly recurrent HCV, continues to be a major problem, and effective therapy is needed both to prevent progression of hepatitis C to liver failure and need for transplantation and to prevent recurrence in the graft and avoid retransplantation. The most promising future therapy is the use of pegylated interferons in combination with ribavirin. However, better and less toxic treatment is clearly needed for HCV. Although recently HBV at this time can be prevented successfully, the cost of using HBIG is prohibitive. Combination therapy is needed to prevent formation of resistant mutants.

With marked advances in immunosuppression, the incidence of acute rejection has decreased to approximately 18%. Preventing rejection in patients with hepatitis C presents a challenge until effective therapy is found. The results of transplantation for hepatocellular cancer in the setting of cirrhosis are excellent provided specific UNOS criteria are used for patient selection. In the future, an increasing number of patients will present with hepatocellular cancer, and therefore screening of patients with cirrhosis will become more important. Management of acute fulminant hepatitis remains a problem, and we have only scratched the surface with our attempts at using liver-assist devices and hepatocyte transplantation to allow regeneration or bridge to liver transplantation.

We acknowledge the clinical contributions of Dr Denise M. Harms of the Mayo Clinic in Jacksonville, Fla, Dr David D. Douglas of the Mayo Clinic in Scottsdale, Ariz, and Drs Charles B. Rosen and Gregory J. Gores of the Mayo Clinic in Rochester, Minn.

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