Current Issues in Liver Transplantation

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Abstract: The state of liver transplantation continues to evolve. This article focuses on 3 separate yet important issues within this field. First, there is a proposal to change the allocation of donor livers in the United States. The fundamental premise of this proposal is to equalize access to donor livers across the country. To accomplish this goal, the proposal is to increase the geographic area of liver allocation. As might be expected, there is a great deal of controversy surrounding the possibility of a major change in liver allocation and distribution. A second area of interest, and perhaps the most important therapeutic breakthrough in the field of hepatology, is the introduction of direct-acting antiviral agents against hepatitis C virus (HCV) infection. With cure rates up to 100%, an increasing proportion of liver transplant candidates and recipients are being cured of HCV infection with therapies that have minimal side effects. Consequently, the impact of HCV infection on patient and graft survival will likely improve substantially over the next few years. Finally, this article reviews the role of donor-specific antibodies (DSAs) in antibody-mediated rejection. Long recognized as an important factor in graft survival in renal transplantation, DSAs have recently been shown to be a strong predictor of graft and patient survival in liver transplantation. However, the importance of DSAs in liver transplantation is uncertain, in large part due to the absence of proven therapies.

Keywords
Liver transplantation, hepatitis C, liver allocation, antibody-mediated rejection

Liver allocation has been a controversial issue in the United States over the past 2 decades. The challenge is the lack of sufficient donor organs for all of the potential recipients, which is compounded by regional differences in the availability of donor organs. The debate has intensified recently due to a regulatory mandate to provide equal access to donor livers throughout the country. As a result, the debate on the equitable distribution of donor livers has become increasingly complicated and contentious.

Changes in Liver Allocation

Because the number of liver transplant candidates (approximately 12,000 patients currently listed) exceeds the number of available organs for transplant (approximately 6000 livers procured each year), approximately 10% of listed liver transplant candidates die each year or are removed from the list for being too sick. As a result, the transplant community continually adjusts the liver allocation system to maximize the benefit to listed patients. Many iterations of the allocation system have been written, with perhaps the most important occurring in 1998 when the US Department of Health and Human Services issued the Final Rule, which required liver allocation to be based upon 3 basic principles: (1) to develop a system of prioritization based on "standardized medical criteria … to determine the status of a person's illness," with the ultimate goal being "to equalize waiting times among different areas of the country;" (2) to permit patient access to donor organs without regard to place of residence; and (3) to base allocation on "patients' medical need" with "less emphasis … placed on keeping organs in the local area where they [were] procured."[1]

Although the Final Rule allocation principles were simple enough, no guidelines were issued on how to achieve these objectives. Moreover, many physicians in the transplant community opposed implementation of the Final Rule, fearing that it would result in the closure of small transplant programs, limit access to transplantation, and lead to a decrease in organ donation. Response to the Final Rule led to changes in liver allocation in early 2002, in which prioritization of liver transplant candidates was based upon the Model for End-Stage Liver Disease (MELD) score, an objective scoring system that ranks candidates based upon their 90-day predicted mortality.[2-4] While MELD-based liver allocation improved access to donor livers across the country, it did not address geographic disparities in access or distribution of donor livers. A study published shortly after the implementation of the MELD-based liver allocation policy showed that wide geographic disparities continued to persist.[5] Specifically, smaller organ procurement organizations (OPOs)—organizations with fewer than 100 patients listed for liver transplantation—continued to transplant fewer sick patients than larger OPOs that had more than 100 patients listed. Only 19% of transplanted patients in the small OPOs had MELD scores greater than 24, compared with 49% in large OPOs.[5] Despite widespread recognition that disparity in MELD scores would be resolved by increasing the size of the population served by the OPO, there was insufficient political will to undertake this issue. However, incremental changes in liver allocation have been instituted over the past decade, many of which aimed to widen the geographic area of liver allocation.

Share 35 Liver Allocation

In 2013, a step was taken with the national implementation of the Share 35 liver allocation policy. The analysis leading to this change in allocation demonstrated a wide variation in MELD scores at transplant between United Network for Organ Sharing (UNOS) regions.[6] In some regions, liver transplants were routinely performed in patients with MELD scores of 20, compared with other regions in which the MELD score was 35 or higher. As a result, the waiting list mortality rates varied more than 3-fold between UNOS regions. Because major changes were not politically feasible, a minor change in liver allocation was implemented for a small group of patients with the greatest need for transplant.[6] Patients with a MELD score of 35 or higher have a waiting list mortality that is 1.9-fold and 3.8-fold higher than patients with MELD scores of 15 to 34 and less than 15, respectively. Increasing organ access to these sickest patients would potentially yield the greatest reduction in waiting list mortality. Consequently, in June 2013, the Share 35 liver allocation policy was implemented, and patients with a MELD score of 35 or higher had access to any organ procured within the region, not just their OPO of listing. The Share 35 policy effectively widened the geographic area of organ sharing for this small yet very sick group of patients, thereby fulfilling, in part, the second and third principles of the Final Rule.

However, implementation of this new allocation system was controversial. By widening the geographic area of liver distribution, detractors feared that organ transport time would increase and lead to an increase in cold ischemic time, a decrease in the quality of the donor liver, and an increase in the cost of organ procurement. In addition, there were fears that disproportionate prioritization of the very sickest patients would jeopardize the success of the transplant with lower patient and graft survival rates. An initial analysis of the impact of the Share 35 policy has allayed this fear to some extent. Following the implementation of the Share 35 policy, the proportion of organs shared within UNOS regions increased, and the effective area of organ allocation widened. Most importantly, the waiting list mortality of patients with MELD scores of 35 or higher significantly decreased, and posttransplant survival rates remained the same as before implementation.[7]

Once the Share 35 liver allocation policy was implemented, there was continued political pressure to expand regional sharing to all listed patients as well as to increase the geographic boundaries of the allocation area beyond the UNOS region. Therefore, the UNOS Liver Committee approved a proposal to redraw the boundaries of liver allocation to reduce geographic disparity of liver allocation.[8,9] Several stipulations were included in the redistricting proposal, such as reducing the number of UNOS

Table. Advantages and Disadvantages of Liver Redistricting

Advantages
Fulfills the mandate of the Final Rule
Reduces nationwide variation in Model for End-Stage Liver Disease scores
Normalizes access to donor livers across the country
Disadvantages
Complicates logistics of donor procurement
May increase the cost of acquiring donor livers
Redistributes donor livers from high-performing areas to low-performing areas

regions from 11 to between 4 and 8, which would increase the area of liver allocation; limiting transplant-volume-weighted average transport time to 4 to 5 hours between OPOs in the same district; and preventing the number of waitlist deaths under redistricting from increasing from the current system. This proposal has created a great deal of controversy (Table). Its proponents have described the potential benefits. The number of patients dying on the list (or being removed as too sick) is estimated to decrease by approximately 100 per year.[6] In addition, increasing the geographic area of organ sharing eliminates pockets of the country where transplant MELD scores are the lowest, thus normalizing MELD scores across the country. Finally, while the transport distance will increase with regional sharing, the estimated travel times will not.

Implementation of wider regional sharing would fulfill the unmet mandates of the Final Rule by eliminating place of residence as a determinant in organ access and allocating donor organs based upon a patient's need, with less emphasis placed on retention in the local procurement area. Opponents of regional sharing mainly reside in states with an ample organ supply (eg, Tennessee, South Carolina, Georgia, Kansas) or smaller centers (eg, Iowa, Utah) that would potentially be disadvantaged by this system. Detractors to the policy point out that the estimated decreased mortality of listed patients (by 100 per year) represents a tiny percentage (<1%) of the 12,000 listed patients. Furthermore, this benefit could be realized by simply procuring 2 more livers per year in each of the approximately 50 OPOs.[10] The ultimate goal of this new policy, which is to normalize MELD scores across the country, has a negative effect of essentially removing donor livers from states with the highest donation rates to those with the lowest, thereby penalizing the effective OPOs and rewarding the underperformers. Opponents of the policy also point to underestimations of the cost and logistical challenges in transporting donor organs around the country. Implementation of wider regional sharing is estimated to increase the cost of transplant by more than $68 million per year due to the issues listed above.[11] Currently, the organ allocation scheme remains under discussion, and no changes have been made in the allocation system. However, most observers believe that wider distribution of donor livers will ultimately be implemented within the next few years.

Treatment and Prevention of Recurrent Hepatitis C Virus Infection After Liver Transplantation

The most common cause of long-term mortality in patients surviving more than 1 year post–liver transplant is recurrent liver disease, the majority of which is recurrent HCV infection, as reported in the long-term, follow-up study by the National Institute of Diabetes and Digestive and Kidney Diseases.[12] However, this statistic will likely improve substantially in the future due to changes in HCV therapy. Until recently, treatment of recurrent HCV infection was difficult and ineffective. Sustained virologic response (SVR) rates of 25% were typical with interferon-based therapy. SVR rates improved to more than 50% with the addition of protease inhibitors, but at a very high cost of morbidity and mortality.[13-15] With the introduction of new, all-oral direct-acting antiviral (DAA) agents, posttransplant SVR rates are as high as 100% with a much improved side-effect profile. Therefore, treatment of posttransplant HCV infection with DAA agents will likely reduce the risk of death from recurrent disease. Recent data have shown that just 12 weeks of ledipasvir/sofosbuvir (Harvoni, Gilead Sciences) with ribavirin led to a SVR rate of 96% in noncirrhotic and early cirrhotic (Child-Turcotte-Pugh [CTP] class A) patients.[16] However, SVR rates decreased to 85% and 60% for patients with CTP class B or C, respectively. Remarkably, patients with the most virulent form of recurrent HCV infection, fibrosing cholestatic hepatitis, achieved a SVR rate of 100%. Equally important, the side effects of this treatment were minimal. Similar results have been reported with ombitasvir/paritaprevir/ritonavir and dasabuvir (Viekira Pak, AbbVie) plus ribavirin, although drawbacks to this regimen include the pill burden and drug-drug interactions with immunosuppressants.[17] Thirty-four liver transplant recipients with no or mild fibrosis were treated with this regimen for 24 weeks. The SVR rate was 97%, and only 1 patient had to stop therapy due to adverse events (although the patient still achieved SVR).[17]

Historically, relatively few patients with recurrent HCV infection were able to undergo interferon-based therapy due to limited efficacy and prohibitively high side effects. Patients with advanced renal dysfunction, severe debilitation, cytopenias, or psychiatric problems were also ineligible for interferon-based therapy. In fact, a report

from Barcelona indicated that only 40% of HCV-infected liver recipients were eligible for treatment.[18] With highly effective DAA agents that cause very few side effects, the selection of patients who are eligible for therapy is limited primarily by cost and logistics. While all patients with viremia should be considered for therapy, evaluation for treatment requires scrutiny, especially given the cost, which approaches $100,000. Renal dysfunction is common and an important consideration. Patients with a glomerular filtration rate less than 30 mL/min are generally not eligible for treatment with ledipasvir/sofosbuvir therapy due to impaired clearance of sofosbuvir metabolites. In addition, the use of ribavirin in these patients creates additional problems given its renal clearance and associated anemia. However, clinicians have successfully treated such patients, according to anecdotal reports, with careful monitoring. In terms of severity of illness, patients in whom treatment would have the greatest impact are those with advanced fibrosis and preserved renal dysfunction. However, as noted in the studies above, SVR rates were the lowest in patients with decompensated cirrhosis; thus, treatment would be most effective before these symptoms manifest.

Perhaps the greatest challenge in treating patients is finding a sufficient number of care providers to organize and implement therapy. For example, at Baylor University Medical Center in Dallas, Texas, more than 800 liver transplant recipients are infected with HCV. If 1 patient were started on therapy each working day and no further transplants were performed, it would take 4 years to treat this entire cohort and would cost more than $80 million. These staggering statistics unfortunately require some level of patient triage to apply HCV therapy in the most effective manner. Two groups of patients have the least likelihood to benefit from HCV treatment: those whose survival is less than a few years due to comorbidities such as advancing age, renal failure, or malignancy; and those who are at least 10 years from transplant with biopsy-proven minimal fibrosis (stage 0 or 1). Such patients are effectively HCV carriers and would benefit less than patients with more advanced disease. Any patient infected with HCV posttransplant should be considered for treatment with DAA agents. Patients with decompensation and significant renal dysfunction will have the lowest SVR rates and may be the most difficult to treat. Those with fibrosis up to CTP class A and preserved renal function will have the highest SVR rates. The daunting logistics of identifying and treating the large number of eligible patients have to be a consideration in selecting the most appropriate candidate for therapy.

Perhaps the most effective strategy in preventing posttransplant HCV infection is to administer treatment immediately before transplant. Previously, treating HCV-infected liver transplant candidates with interferon-based therapies was associated with low SVR rates and high serious adverse event rates. In a randomized trial, patients undergoing live donor liver transplant or patients with hepatocellular carcinoma were treated up to 6 months before transplant to determine the safety and efficacy in preventing posttransplant HCV recurrence.[19] Only 19% of patients treated immediately before transplant remained virus-free after transplant, but the number of serious adverse events per patient was higher in the treated group vs the controls (2.7 vs 1.3; P=.003). Treatment was most effective for patients who remained virus-free for more than 16 weeks before transplant (50% efficacy) and least effective (0% efficacy) in those treated for less than 8 weeks, indicating that the duration of therapy before transplant is predictive of viral clearance after transplant.

A similar trial was undertaken with sofosbuvir (Sovaldi, Gilead Sciences) plus ribavirin in 61 patients with hepatocellular carcinoma who received therapy immediately before transplant to determine safety and efficacy in the prevention of recurrent HCV infection posttransplant.[20] Of the 61 treated patients, 49% had undetectable virus 12 weeks after transplant (sustained SVR). Of the 43 patients who had undetectable virus at the time of transplant, 30 (70%) had a sustained SVR. Similar to the previously mentioned trial, recurrence was inversely related to the number of days of undetectable HCV RNA before transplantation. Of the 26 patients with undectable virus for more than 30 days, only 1 (4%) had posttransplant recurrence. Side effects were manageable, and only 2 patients discontinued therapy due to adverse events. The most frequently reported adverse events were fatigue (38%), headache (23%), and anemia (21%).

Increasingly, liver transplant recipients will be virus-free at the time of transplant, as treatment with all-oral therapies are more widely applied.[12] For example, at Baylor University Medical Center, over 70% of the patients listed for liver transplant with the diagnosis of HCV infection are virus-free after successful therapy. Most of the remaining patients have either not been treated or have difficult-to-treat disease, mainly genotype 3 following treatment failure with sofosbuvir. Remarkably, within only a few years, HCV infection has been transformed from virtually universal at liver transplant (with a nearly 100% chance of recurrence posttransplant) to most patients being rendered virus-free at transplant (effectively eliminating the chance of posttransplant recurrence).

Donor-Specific Antibodies and Antibody-Mediated Rejection

An important emerging topic in liver transplantation is the role of donor-specific antibodies (DSAs) causing

antibody-mediated rejection (AMR) and its effect on graft function.[21] DSAs are antibodies that are present at transplant (or develop after transplantation) and are directed against epitopes on the donor organ with potential to cause graft injury. The most obvious DSAs occur in blood type–incompatible transplantation, such as when a blood type O recipient receives a blood type A liver. The blood type O recipient has preformed antibodies against blood type A antigens expressed on the endothelial cells of the donor organ, leading to endothelial vascular injury (usually graft loss) if transplanted into a blood type O recipient. Antibodies against human leukocyte antigen (HLA) epitopes have been recognized for years as a cause of graft loss in renal transplantation. DSA testing has been mandated prior to renal allograft transplantation due to a study by Patel and Terasaki that showed that a positive donor crossmatch was associated with an 80% immediate graft failure (hyperacute rejection) rate in renal transplant recipients.[22] Besides hyperacute rejection, DSAs in kidney recipients are also associated with a more chronic, progressive form of graft injury linked to an increased risk of graft loss.

Compared with renal transplantation, the effect of DSAs in liver recipients seems much less problematic. The initial studies in liver transplant recipients with a positive donor crossmatch were not associated with hyperacute rejection. Of 28 transplants in recipients with a positive donor antibody crossmatch and a current panel reactive antibody of more than 30%, no difference was noted in graft survival rates compared with patients with a negative crossmatch.[23] There are several reasons that the liver may be relatively protected from AMR caused by DSAs.[24] Compared with the kidney, the liver appears to have resistance to AMR. The large size and unconventional sinusoidal microvascular bed of the liver may effectively reduce the relative endothelial damage from DSAs. In addition, the secretion of high levels of soluble HLAs and their phagocytosis by sinusoidal Kupffer cells inactivates immune complexes. Finally, the liver has a remarkable regenerative capacity following injury.

In the early era of liver transplantation, which was characterized by relatively high patient mortality and graft loss, the importance of AMR was not clinically apparent. Additionally, the diagnostic test (a positive crossmatch of the recipient serum with donor lymphocytes) to identify DSAs was relatively crude. However, as long-term patient survival rates have improved and diagnostic techniques for identifying DSAs have become more sophisticated, the role of DSAs in AMR leading to graft injury has been investigated again over the past few years. The diagnostic criteria for AMR in liver allograft recipients include DSAs in serum, histopathologic evidence of diffuse microvascular endothelial cell injury, strong and diffuse C4d positivity in tissue, and reasonable exclusion of other causes of injury that might result in similar findings.[25]

A study of a large cohort of liver transplant recipients with prospectively collected serum over several decades has demonstrated that DSAs are associated with early rejection, chronic rejection, graft loss, and patient mortality.[26] Liver transplant recipients with preformed class II DSAs experienced a significantly higher risk of early rejection (hazard ratio [HR], 1.58; *P*=.004). Preformed class I and/or II DSAs with a mean fluorescence intensity equal to or greater than 5000 were independently correlated with the risk of death (HR, 1.51; *P*=.02). Another study found that 8.1% of liver transplant recipients developed de novo DSAs and had a significantly lower patient and graft survival (*P*=.002 and *P*=.005, respectively) than patients without de novo DSAs.[27] However, the differences between the patient populations were small, with only a 7% difference at 5 years for patient survival and 6% for graft survival. The risk factors identified for developing DSAs included cyclosporine instead of tacrolimus at 1 year (odds ratio [OR], 2.50; *P*=.004) and patients with low calcineurin inhibitor levels (tacrolimus <3 ng/mL or cyclosporine <75 ng/mL) in the first year (OR, 2.66; *P*=.015). However, patients with a MELD score greater than 15 (OR, 0.47; *P*=.021) at the time of transplantation and recipients older than 60 years of age (OR, 0.26; *P*=.03) had a significantly lower likelihood of de novo DSA production.

While DSAs and AMR can be diagnosed in some liver recipients and may lead to graft injury, the treatment of DSAs and AMR is problematic. Currently, the published literature on AMR treatment is limited, and there is no clear evidence that AMR treatment provides any clinical benefit. Perhaps this is due to the nontargeted therapies against AMR, including plasmapheresis, intravenous immunoglobulin, and rituximab (Rituxan, Genentech). Bortezomib (Velcade, Millennium Pharmaceuticals) is a proteasome inhibitor that has been used to treat acute AMR in a small cohort of liver recipients.[28]

There are challenges in defining the roles of DSAs and AMR in liver transplantation. There is little doubt that AMR occurs in liver transplantation. However, some experienced clinicians remain skeptical of its practical importance for several reasons. First, as with any new concept, there is a general reluctance toward its acceptance until incontrovertible evidence is presented. Second, as discussed above, early studies discounted the effect of AMR in liver transplantation, leading many clinicians to believe that the liver is inherently protected from this type of graft injury. Third, many patients with DSAs have no evidence of graft dysfunction; therefore, identification of DSAs in the absence of graft injury would not necessarily require therapeutic intervention. Also, there is currently no effective therapy to treat AMR once it occurs. In the absence of effective therapy, the identification of DSAs or diagnosis of AMR leads to a practical conundrum about

how to effectively manage such patients. Finally, AMR from DSAs could be an epiphenomenon of noncompliance with immunosuppressive medications or a predetermined clinical phenotype of untreatable, progressive immunologic graft injury, which many liver transplant physicians have observed. Continued careful evaluation of DSAs and AMR will likely yield clarification of this important immunologic phenomenon.

Conclusion

This review has focused on some of the most critical emerging topics in liver transplantation. The continued debate over the equitable distribution of livers will challenge the liver transplant community as wider sharing of organs becomes nationwide policy. The ability to cure HCV infection in most liver transplant candidates and recipients will radically improve the outcomes for this disease that afflicts more liver patients than any other. The ability to effectively manage AMR awaits the development of a proven, effective therapy.

Dr Trotter is a member of the speakers bureau for Gilead Sciences and AbbVie.

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