

have distinct intracellular targets. A recent report (Goebel MG, Cell 1991; 64:1051-1052, Correspondence), tentatively identifying FKBP as a previously described 12 kD endogenous inhibitor of protein kinase C, raises the possibility that FK 506 exerts its effect by blocking activation of protein kinase C, a key step in antigen-induced T-cell activation. One possible model integrating this report with the work of Bierer et al. would be that FK 506 must bind to FKBP to elicit the protein kinase C inhibitory capacity of FKBP. FK 506 might activate FKBP by a conformational change or by directing FKBP to the proper subcellular compartment. In either case, only the FK 506-FKBP complex is effective. Presumably, the rapamycin-FKBP complex acts in a different fashion or at a distinct intracellular site.

These studies highlight how much has been learned in recent years of the molecular events initiated by T-cell activation. They also underscore the complexity of the immune response and the risks of predicting drug effects based solely on chemical similarities. Furthermore, the difficulty in determining whether drugs with apparently distinct effects *in vitro* will be useful in combination should serve to emphasize that there is no substitute for rigorous *in vivo* testing. Ultimately, the goal of transplantation research is to induce a state of tolerance, or immunological unresponsiveness, to the graft. Although this remains an elusive goal, studies such as these advance us one step further by dissecting intracellular events that occur during the immune response.

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SPLIT-LIVER TRANSPLANTATION: ONE PLUS ONE DOESN'T ALWAYS EQUAL TWO

Emond JC, Whittington PF, Thistlewaite JR, Cherqui D, Alonso EA, Woodle IS, Vogelbach P, et al. Transplantation of two patients with one liver: Analysis of a preliminary experience with "split-liver" grafting. Ann Surg 1990;212:14-22.

ABSTRACT

Surgical reduction of donor livers to treat small children has been performed successfully in several centers. While this procedure improves the allocation of livers, it does not increase the organ supply. We have extended reduced-size orthotopic liver transplantation (OLT) to treat 18 patients with 9 livers, accounting for 26% of our transplants during a 10-month period and have evaluated the results. In 18 split liver OLTs, patient survival was 67% and graft survival was 50%. In comparison, for 34 patients treated with full-size OLT during the same period, patient survival was 84% ($p = 0.298$) and graft survival was 76% ($p = 0.126$). Biliary complications were significantly more frequent in split grafts, occurring in 27%, as compared to 4% in full-sized grafts ($p = 0.017$). Primary nonfunction (4% versus 5.5%) and arterial thrombosis (6% versus 9%) occurred with similar frequency in split and full-size OLT ($p =$ not significant). These results demonstrated that split-liver OLT is feasible and could have a substantial impact in transplant practice. We believe that biliary complications can be prevented by technical improvements and that split-liver OLT will improve transplant therapy by making more livers available.

Broelsch CE, Emond JC, Whittington PF, Thistlethwaite JR, Baker AL, Lichtor JL. Application of reduced-size liver transplants as split grafts, auxiliary orthotopic grafts, and living related segmental transplants. Ann Surg 1990;212:368-375.

ABSTRACT

The University of Chicago program in pediatric liver transplantation continues actively to seek innovative surgical solutions to problems related to the management of children with end-stage liver disease. Among the most important problems facing these children is a shortage of donor organs, which results from three factors in addition to the actual supply of

pediatric donors: the concentration of pediatric liver disease in the population younger than 2 years; the necessity for a graft that is small enough; and the epidemiology of accidents and other events that lead to organ donation. Transplantation using a liver lobe as a graft overcomes size disparity and shifts the available supply of organs from older donors to younger recipients. This work describes the technical aspects of recent innovations in the use of liver lobes in pediatric transplantation, simple reduced-size liver transplantation (RLT), split-liver transplantation (SLT), orthotopic auxiliary liver grafting (ALT), and transplantation using a living related donor (LRLT), and compares their results. Since November 1986 a total of 61 procedures have been performed in which a liver lobe was used as a graft: 26 RLT; 30 SLT, 25 in children and 5 in adults; 5 LRLT; and 1 ALT. Overall 62% of transplants performed in children have involved using a liver lobe as a graft. The rates of complications are somewhat higher than with whole-liver transplantation, but this may not be entirely the result of the complex procedures. Split liver transplantation is associated with the highest mortality and complication rates. Living related liver transplantation has been associated with complications in donors and recipients, but to date survival is 100%. Orthotopic auxiliary liver transplantation effectively corrected the metabolic defect in one patient with ornithine transcarbamylase deficiency. Overall the various modalities of using graft reduction have resulted in postoperative results similar to those achieved with full-size grafts, while pretransplantation mortality has been limited to less than 2%. Thus the use of grafts as liver lobes accomplishes the goal of reducing global mortality among children with end-stage liver disease, but at the cost of increased surgical complexity and more postoperative complications.

COMMENTS

From its clinical dawn in 1963 as a last ditch effort to save lives that were almost certainly past salvation, through 20 yr of pioneering surgical efforts primarily by Thomas Starzl in the United States and Roy Calne in England, orthotopic liver transplantation has reached the mainstream of hepatological therapy. As its application becomes ever wider, indications for transplantation appear to be limited only by the irreversibility of the underlying hepatic disorder and by the physiological reserve of the potential recipient. Recently, however, it has become clear that increasing numbers of otherwise treatable patients are dying from a shortage of donor organs. Children are at special risk because most cadaveric organ donors are adults, and in one report 25% of infant patients awaiting transplantation died for lack of a suitable organ (1).

The number of liver transplant procedures performed in the United States increased each year from 1980 to 1989, reflecting, in part, a growing acceptance of the procedure. However, the total number performed (more than 2,100 in 1989) also reflects an increasing percentage of procurement of livers from an almost static

number of cadaveric organ donors in this country (2). During the mid-1980s, the imbalance between the number of small children and infants awaiting liver grafting and the number of pediatric donors led to the development of successful techniques for transplantation of selected segments or lobes of an adult liver into a smaller, in some cases remarkably smaller, child or infant (3, 4). These innovative techniques use extant concepts of hepatic anatomy and surgical resection and have assumed a prominent place alongside whole organ grafting for children at many large centers, including our own. Reduced-size allograft patient survival rates of 75% to 80% for infants have been reported and are comparable to results obtained with intact pediatric donor livers (5, 6). Using this approach, infant patient mortality for those on the waiting list has been reduced to 1% to 2% (5).

Unfortunately, two undesirable effects accompany the use of reduced-size liver allografts. First, with a nearly stable cadaveric organ donor pool this technique produces an allocation shift toward pediatric recipients because adult recipients who might otherwise have had transplants are bypassed. Second, given the increasingly desperate shortage of organs, the inevitable discarding of a large volume of otherwise well-preserved and viable hepatic parenchyma after the reduction is completed evokes in the transplant surgeon a sense of waste.

It is these two issues that Emond and his colleagues from the University of Chicago have attempted to address in describing their results with the next step in the evolution of liver transplantation technique wherein two individuals are transplanted using one donor. Using two vascularized lobes or segments from a single donor, this surgical *tour de force* and the initial results in 18 patients who had transplants from 9 donors testify to the authors' technical skill and stamina. On closer examination, however, the suggestion that the "two for one" technique may, on wider application, solve the donor organ shortage appears to warrant a measure of skepticism.

Given the technical complexity of the surgery and the poor condition of many recipients in the pediatric recipient population, a high incidence of complications is nearly assured. The difficulties encountered by Emond et al. were sufficient to lower graft survival after split liver transplantation to 50% from the 75% associated with whole organ and reduced-size allografts. This reduction in graft survival considerably dampens enthusiasm for a technique intended to increase donor organ availability, especially when one considers that a whole organ or nonsplit reduced-size allograft will probably be used to replace a failed split liver graft. The high incidence of postoperative bleeding (33%) and biliary complications (27%) underscores the technical challenges of this new procedure. Given the short follow-up period (2 to 12 mo), it is virtually certain that the actual 1-yr patient survival rate will be lower than the crude 67% figure cited by the authors. Despite these sobering

facts, it is likely that further experience with this technique will reduce the complication rate, and perhaps improved patient survival will result.

The mathematics and geometry of reality dictated that 13 of the 18 recipients were children weighing 12 kg or less. This occurred because of the authors' profoundly efficient use of five donors weighing less than 32 kg. At most centers, 30-kg donors are frequently used for a reduced-size graft for a single infant or not at all because the spectrum of liver disease results in few suitable recipients for a whole organ graft from a donor of this size. From this standpoint, the authors are to be commended for making the most of these donors. More careful examination of the data, however, reveals that three of the five adult recipients of a right lobe died, each of whom also received the medial segment of the left lobe (segment 4) in an attempt to provide an adequate volume of hepatic parenchyma. Whether routine removal of segment 4 from a liver providing a left lateral segment (segments 2 and 3) to a child and a right lobe (segments 5 through 8) to an adult will result in more uniform success for recipients of both grafts remains speculative at this point. Thus a critical question regarding the ability of this technique to avoid the bypassing of size-appropriate adult recipients cannot be answered at this time.

The second article from the University of Chicago team further illustrates the creativity and innovation of this group. In this report, Broelsch et al. describe the use of auxiliary orthotopic grafting and living-related segmental grafts in addition to the split liver technique. In what may be more appropriately called a partial orthotopic liver transplant, the authors transplanted a left lateral segment graft into a 14-mo-old patient with ornithine transcarbamylase deficiency. The recipient's own left lobe was resected, and the allograft segment was put in its place. This exciting approach to patients with metabolic defects whose livers are otherwise anatomically and functionally normal is worthy of careful consideration if it can be demonstrated that the limited volume of transplanted hepatic parenchyma is capable of establishing and sustaining normal metabolism. Unfortunately, the number of patients who could be treated in this way are limited.

Equally exciting and more controversial is the authors' use of living relatives as liver donors for children with end-stage hepatic disease. The first five such patients are included in this report. All of the donors and recipients were alive at the time of publication, but serious complications occurred in several of the donors. One of the five recipients required retransplantation from a cadaveric donor. It is too early to pass judgment on the advisability (medical, ethical or otherwise) of this approach, and the authors have been careful to point out that the program is as yet entirely experimental.

Further experience with the split liver technique was also included in the article by Broelsch et al. A total of 30 transplants, including 5 in adults, were described. Many of these patients were presumably included in the

article by Emond et al. Some of the issues previously raised appear closer to being answered by the data in the second article, in which four of the five adult recipients of split liver grafts died. The authors point out that they are now loathe to remove the left lobe from a liver intended to be transplanted into an adult and that livers from donors weighing less than 10 kg are unsuitable for splitting. This advice reinforces the concept that many donor livers too small for adults may still be successfully split into grafts for two pediatric recipients. It is important to point out, however, that donor organs of this size are not plentiful. Furthermore, having two disparately sized pediatric recipients available simultaneously is required.

The number of surgical teams may also limit widespread application of the split liver technique. Most transplant centers have developed teams who perform pancreas, kidney and liver transplants. These teams are highly specialized, and the members are few in number. Adopting the split liver approach requires mobilization of a multiorgan donor team to procure the organs and complete 3 to 4 hr of bench surgery, personnel to perform two liver transplants and potentially two or more additional teams to perform pancreatic and renal transplantation. If thoracic organ transplantation is added to the equation, the resource requirements at any given transplant center are considerable. Finally, the suggestion by the authors that the second recipient should be transplanted "at the priority of the left lobe recipient" may serve to undermine the admittedly imperfect attempts by the federally mandated United Network for Organ Sharing (UNOS) to ensure the fair and equitable distribution of organs. If the evolution of the split liver technique leads to success rates equivalent to whole organ or reduced size grafts, as the authors suggest it will, both lobes thus provided will have to be allocated separately under UNOS guidelines.

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