Festschrift

Reprinted from the Archives of Surgery
October 1981, Volume 116

471

Past and Future Prospects of Orthoptic Liver Transplantation

Thomas E. Starzl, MD, PhD; Goran B. G. Klintmalm, MD; Shunzaburo Iwatsuki, MD; Carlos Fernandez-Bueno, MD

• The hopes for liver transplantation have been increased by experience with the new immunosuppresive drug cyclosporin A. Optimal therapy with cyclosporin A has required steroid therapy, but the amounts of prednisone used have been a small fraction of those used in the past.

(*Arch Surg* 1981;116:1342-1343)

In July 1967, liver replacement with extended patient survival was accomplished for the first time. That young recipient lived for more than a year before dying of metastases from a hepatoma for which she originally had been treated.[1]

RESULTS WITH CONVENTIONAL IMMUNOSUPPRESSION

The demonstration of its feasibility did not make orthoptic liver transplantation a widely used clinical procedure, and, in fact, only we[2] and Calne and Williams[3] have persisted in large-scale trials. The results using conventional immunosuppression with azathioprine and prednisone to which in our series we have added lymphoid depletion with antilymphocyte globulin or, more recently, thoracic duct drainage, have been unsatisfactory.

Before 1976

By early summer 1976, we had treated 111 consecutive patients. Thirty-one (28%) of these recipients survived for at least a year. Now, with follow-ups of five to 11⅓ years, 13 patients have still survived. This low accrual of further mortality after one year has been an important stimulus to persist in efforts at liver transplantation and so has the acceptable quality of life of many long-term survivors. Chronic graft rejection has been the single most common cause of late death.[2]

From 1976 to 1979

A second series of 30 patients was compiled in the subsequent 18 months, ending in early 1978. Half (50%) of these patients survived for at least one year, and today, after 2½ to almost four years, 13 (43%) of these patients are still living. It was thought that improvements in surgical technique (especially biliary tract reconstruction), better diagnosis of postoperative hepatic dysfunction, and refinements in immunosuppression were responsible for the better results.

In subsequently treated patients, we were unable, with the use of immunosuppression with azathioprine and prednisone, to maintain these gains in a further series of 30 patients (the first 23 of these patients have been described in detail).[4] Instead of using antilymphocyte globulin, many of these 30 patients had lymphoid depletion with thoracic duct drainage or lymphapheresis. All 30 patients were given azathioprine and prednisone. The one-year survival was only 33%. Many of the early deaths in this series were attributable to technical or management errors as in the past. The complications often were not intrinsically lethal but became so because of the need for high-dose steroid therapy.

The preoperative use of thoracic duct drainage as a steroid-sparing device, which had been shown to be valuable in cadaveric kidney transplantation,[5] proved impractical for conditioning of liver recipients.[4] The amount of thoracic duct lymph drained in patients with chronic liver disease was always large. Two patients died during preparation for transplantation because of our inability to manage a fluid exchange of as much as 2 L/hr.

Accepted for publication June 5, 1981.
From the Department of Surgery, University of Pittsburgh School of Medicine.

Reprint requests to Department of Surgery, University of Pittsburgh School of Medicine, 1084 Scaife Hall, Pittsburgh, PA 15261 (Dr Starzl).

NONCONVENTIONAL IMMUNOSUPPRESSION
Cutting Edge of Kidney Experience

By late 1979, we had concluded that no real movement of liver transplantation toward an acceptable risk was going to be possible without a drastic change in immunosuppressive techniques. Such a change became possible with the development of cyclosporin A. The powerful immunosuppressive qualities of cyclosporin A were accurately delineated in rodents by Borel et al.[6] To our knowledge, Calne and associates were the first to use cyclosporin A in larger animals and humans.[7,8]

When cyclosporin A became available for clinical trials in the United States in late 1979, we began its evaluation in the simple kidney transplant model. From the beginning, it was obvious that unless some hidden problem surfaced, cyclosporin A would change the face of transplantation. In our center, we have shown that cyclosporin A alone, even in doses of 15 to 20 mg/kg/day, does not consistently prevent rejection, that it should be combined with steroid therapy for optimal use, and that the proper amount of prednisone when cyclosporin A is used is much smaller than when steroids are combined with azathioprine.[9]

Conceptually, we have substituted cyclosporin A for azathioprine in what is a modern version of the time-honored, double-drug immunosuppression introduced in 1962 and 1963.[10] Since we have learned that rejection usually can be expected, we now start steroid therapy on the day of an operation and reduce the dose of prednisone in adults by 20 or 40 mg/day until a maintenance dose of 20 mg/day is reached (usually within five or six days). The amount of prednisone needed in the first three months has been a fraction of that, which we gave when prednisone was combined with azathioprine. The survival of 67 cadaveric kidneys transplanted from seven to 15 months ago has been 80%.[11] The most recent report by Calne et al[12] projects a one-year cadaver kidney survival of 86%.

Cyclosporin A and Liver Transplantation

Liver transplantation with the use of cyclosporin A was first reported by Calne and colleagues.[8] The first liver transplantation that we performed with the use of cyclosporin A was not attempted until experience had been acquired with 22 cadaveric kidney graftings. Since then, 14 orthoptic liver transplantations have been performed. There were two operative deaths; one death was caused by hemorrhage, and the other death occurred when the abdominal incision could not be closed despite repeated attempts during a 48-hour period. Of the 12 survivors who had operations, 11 (92%) of them were still alive after seven to 14 months of undergoing treatment with cyclosporin A and low-dose steroids. The only postoperative death was caused by hepatic arterial thrombosis.

References

1. Starzl TE: *Experience in Hepatic Transplantation.* Philadelphia, WB Saunders Co, 1969.
2. Starzl TE, Koep LJ, Halgrimson GC, et al: Fifteen years of clinical liver transplantation. *Gastroenterology* 1979;77:375-388.
3. Calne RY, Williams R: Liver transplantation. *Curr Probl Surg* 1979;16:1-44.
4. Starzl TE, Koep L, Porter KA, et al: Decline in survival after liver transplantation. *Arch Surg* 1980;115:815-819.
5. Starzl TE, Weil R III, Koep LJ, et al: Thoracic duct drainage before and after cadaveric kidney transplantation. *Surg Gynecol Obstet* 1979;149:815-821.
6. Borel JF, Feurer C, Magnee C, et al: Effects of the new antilymphocytic peptide cyclosporin A in animals. *Immunology* 1977;32:1017-1025.
7. Calne RY, White DJG, Pentlow BD, et al: Cyclosporin A: Preliminary observations in dogs with pancreaticoduodenal allografts and patients with cadaveric renal transplants. *Transplant Proc* 1979;11:860-864.
8. Calne RY, Rolles K, White DJG, et al: Cyclosporin A initially as the only immunosuppressant in 34 recipients of cadaveric organs: Thirty-two kidneys, two pancreases, and two livers. *Lancet* 1979;2:1033-1036.
9. Starzl TE, Weil R III, Iwatsuki S, et al: The use of cyclosporin A and prednisone in cadaver kidney transplantation. *Surg Gynecol Obstet* 1980;151:17-26.
10. Starzl TE: *Experience in Renal Transplantation.* Philadelphia, WB Saunders Co, 1964.
11. Starzl TE, Klintmalm GBG, Weil R III, et al: Cyclosporin A and steroid therapy in 66 cadaver kidney recipients. *Surg Gynecol Obstet,* to be published.
12. Calne RY, White DJG, Evans DB, et al: Cyclosporin A in cadaveric organ transplantation. *Br Med J* 1981;282:934-936.

Printed and Published in the United States of America