

Pediatric Liver Transplantation in 808 Consecutive Children: 20-Years Experience From A Single Center

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SURVIVAL for children is significantly higher than for adults after liver transplantation (LTx).¹ A center-specific 20-year retrospective analysis of all pediatric transplant recipients was implemented to determine patient and graft survival, graft survival, and differences in survival related to immunosuppressive protocols.

MATERIALS AND METHODS

From March 1981 to April 1998, 808 children received liver transplants at the Children's Hospital of Pittsburgh. All patients were followed until March 2001, with a mean follow-up of 12.2 ± 3.9 years (median = 12.6; range = 2.9 to 20). There were 405 female (50.2%) and 403 male (49.8%) pediatric recipients. The mean age at transplant was 5.3 ± 4.9 years (mean = 3.3; range 0.04 to 17.95) with 285 children (25.3%) being less than 2 years of age at transplant. Cyclosporine (CsA)-based immunosuppression was used prior to November 1989 in 482 children (50.7%) and the

subsequent 326 recipients (40.3%) were treated with tacrolimus-based immunosuppression.

RESULTS

Patient Survival

Overall patient survival at 1, 5, 10, 15, and 20 years was 77.1%, 72.6%, 69.4%, 65.8%, and 64.4%, respectively (Fig 1). A significant difference in survival was seen in CsA-

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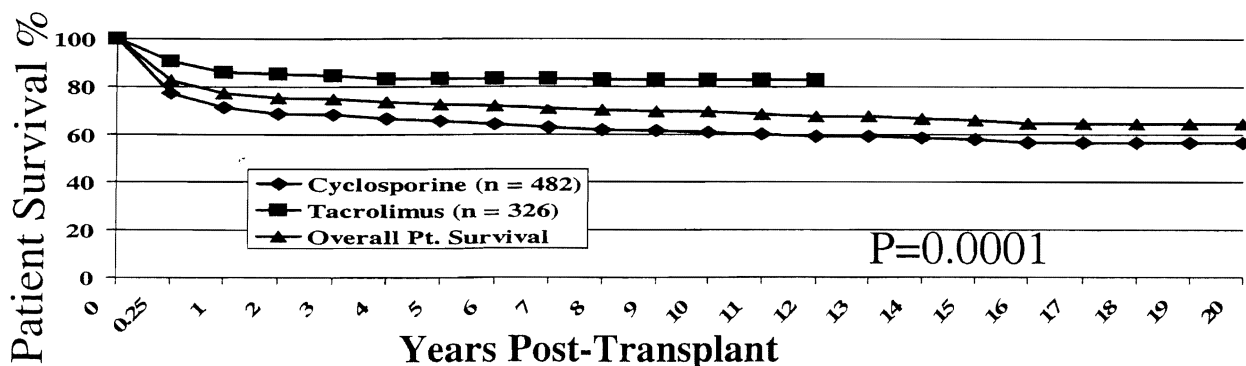


Fig 1. Patient survival under cyclosporine and tacrolimus immunosuppression.

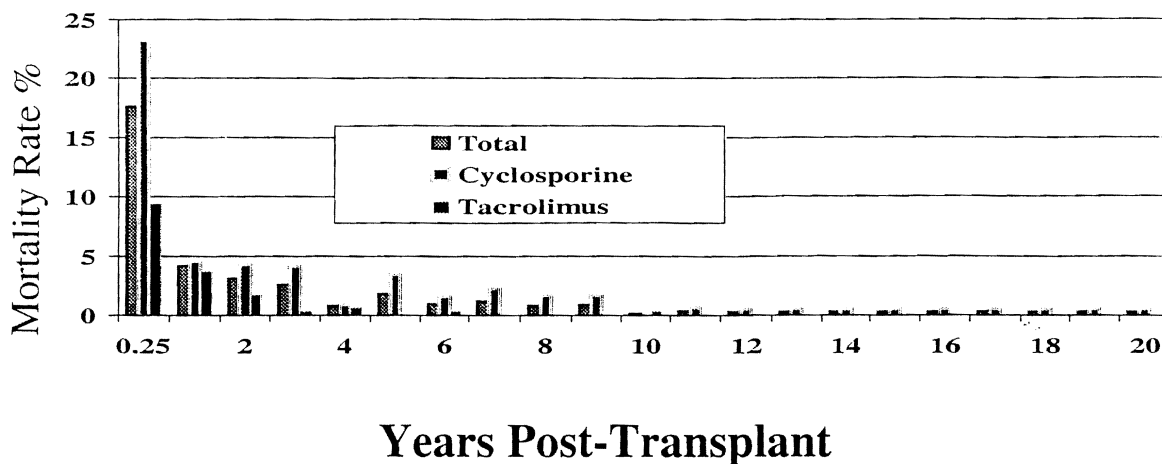


Fig 2. Overall mortality rate over time under cyclosporine and tacrolimus immunosuppression.

based immunosuppression (71.2%, 68.1%, 65.4%, and 61%) versus tacrolimus-based immunosuppression (85.8%, 84.7%, 83.3%, and 82.9%) at 1, 3, 5, and 10 years, respectively ($P = .0001$) (Fig 2). The maximum difference in the risk of death was observed in the first 3 months posttransplant, 22.8% under CsA versus 9.5% under tacrolimus. After 3 months, the survival at 10 years was 78.6% under CsA versus 91.5% under tacrolimus, a difference of 12.9%.

Causes of Death

A total of 258 children (32%) died during the follow-up period, with 55.4% of deaths occurring within the first 3 months posttransplant. Of the mortalities, 203 recipients received CsA-based immunosuppression, and 55 recipients were treated with tacrolimus. The most common cause of death was infection (43%). The mean annual death rate beyond 2 years posttransplant was 0.47% with the mean annual death rate for patients receiving tacrolimus-based immunosuppression being significantly lower than those receiving CsA-based immunosuppression (0.14% vs 0.8%; $P = .001$). The annual death rate for patients under CsA and tacrolimus-based immunosuppression is shown in Fig 2. The difference in the death rate between the immunosuppressive protocols was observed at all time points. The cumulative death rate at 1, 3, and 12 months posttransplant under CsA was 16.3%, 22.6%, and 28.8%, respectively, and for tacrolimus-treated patients was 6.4%, 9.5%, and 14%, respectively.

Graft Survival

Patient deaths or retransplantations were considered as graft loss. Graft survival at 1, 5, 10, 15, and 20 years was 66.6%, 60%, 57%, 52.3%, and 37.9%, respectively. Graft survival under CsA versus tacrolimus-based immunosuppression was similar to patient survival with a highly significant difference ($P = .0001$) at 12 years posttransplant.

Retransplantation

Two hundred three children (25.1%) required a second liver transplant. Additionally, 40 children required a third graft, six received four grafts, and one child received five liver transplants. All seven children who received four or more grafts died. Hepatic artery thrombosis was the most common indication for a second allograft under both CsA and tacrolimus-based immunosuppression, with an incidence of 33.4% ($n=68$) of all retransplantations. The second most common reason for retransplantation was rejection, both acute and chronic, with 54 patients (26.6%) requiring another graft. Retransplantation was required in six patients (2.9%) with acute rejection and 46 patients (22.6%) with chronic rejection. Interestingly, all retransplantations for acute or chronic rejection were performed in patients who were treated with CsA-based immunosuppression and none under tacrolimus.

Primary nonfunction was the third most common indication for retransplantation and was seen in 34 patients (16.7%). Of these patients, 19 (9.3%) were treated with CsA and 15 (7.3%) were treated with tacrolimus. Additional reasons for retransplantation included biliary stricture, posttransplantation lymphoproliferative disorder, and others.

DISCUSSION

A 20-year overall actuarial patient survival of 64.4% is reported here, representing the largest pediatric liver transplant experience with the longest follow-up from a single center. The most significant factor affecting survival in this experience was a change in immunosuppressive protocols from CsA-based immunosuppression in the 1980s, with a survival of 61% at 10 years, to tacrolimus-based immunosuppression resulting in an 83% survival at 10 years. This analysis reports the almost complete absence of graft loss from either acute or chronic rejection under tacrolimus, which is remarkable considering the incidence under CsA is

11% in a 20-year follow-up. Over a decade ago, observations from this institution supported the findings of a reduced rate of acute rejection as well as a decreased severity of rejection in patients receiving tacrolimus.^{2,3} Additionally, the ability of tacrolimus to reverse acute and chronic rejection and act as a rescue agent for patients failing treatment with CsA provided a better understanding of the process of rejection and its treatment as well as the clinical limits of failure. At this institution, nearly 25% of children under CsA-based immunosuppression have been converted to tacrolimus with many of the grafts rescued from acute and chronic rejection during the last decade.⁴ Similar advantages of tacrolimus in pediatric transplantation have been published from our center and by others.⁵⁻⁷ Nearly 80% of pediatric patients are now maintained on only low-dose tacrolimus.⁸ The virtual absence of chronic rejection in adult liver transplant recipients following a review of over 5000 liver biopsies from more than 1200 patients with a mean follow-up of 6 years has been previously reported.⁹ Hepatitis B and C viruses, primary biliary cirrhosis, autoimmune hepatitis, and primary sclerosing cholangitis were found to be risk factors for the development of chronic rejection after liver transplantation. Fortunately, these liver diseases as indications for transplantation are extremely rare in the pediatric population. Chronic rejection in pediatric liver transplant recipients is usually a result of treatment for life-threatening infection PTLN or noncompliance.

CONCLUSION

The 20-year actuarial survival for pediatric liver transplant recipients is 64% in a series of 808 children. Infection

remains the most common cause of death. Retransplantation is most commonly indicated for hepatic artery thrombosis and primary nonfunction. Survival following the introduction of tacrolimus-based immunosuppression has increased by 14 to 21% at 1 year (85% vs 71.2%) and 12 years (82.9% vs 61%) posttransplant. The increased survival rate of our program may reflect improvements in surgical techniques, better donor and recipient selection, and advances in posttransplant medical management. However, in our experience, increased survival can be attributed to the almost total absence of graft loss due to acute or chronic rejection in up to a 12-year follow-up, which reflects the immunologic advantage of tacrolimus-based immunosuppression.

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