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# Liver Transplantation Under Tacrolimus In Infants, Children, Adults, and Seniors: Long-Term Results, Survival, and Adverse Events in 1000 Consecutive Patients

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THE BENEFITS of tacrolimus in solid organ transplantation are well recognized.[1–6] The aim of the present study is to examine the outcome of primary liver transplantation (LTx) under tacrolimus for various age groups over a long-term in 1000 consecutive patients from a single center.

## MATERIAL

The first 1000 primary LTx recipients under tacrolimus from August 1989 to December 1992 were followed until August 1997 (mean follow-up 77, range 56 to 96, months). The characteristics of the patients and immunosuppressive protocol have been described before in this population.[7] There were 75 infants (≤2 years), 91 children (>2 ≤18 years), 630 adults (>18 ≤60 years), and 204 seniors (<60 years). Of the recipients, 84.1% were hospital bound at the time of LTx, and 141 donors were above age 50 years.

## RESULTS

Patient and graft survival for various age groups is shown in Table 1. The difference in patients survival and graft survival for various age groups were highly significant, $P = .0006$ and .0000, respectively (log rank). The level of immunosuppression, liver function (mean total bilirubin, AST, ALT, alkaline phosphatase, GGTP), and the renal function at various time points is shown in Table 2.

### Adverse Events

The overall prevalence of hypertension requiring antihypertensive medication, insulin dependent diabetes mellitus, hyperkalemia (k+ > 5.0 mEq/L), and mean cholesterol values are shown in Table 2. Three infants and children (2%) and 23 adults and seniors (2.8%) underwent kidney transplant for end-stage renal disease. In addition, 12 adults and seniors are currently on hemodialysis. Posttransplant lymphoproliferative disorder (PTLD) was observed in 19 infants and children (11.4%) and 16 adults and seniors (1.9%). Seventy-nine percent of infants and children and 69% of adults and seniors are currently alive following the diagnosis of PTLD. DeNovo nonlymphoid malignancy was observed in 57 adults and seniors (6.8%) but not in infants or children. These consisted of 20 squamous or basal cell skin cancers, 2 melanoma of the skin, 8 lung cancers, 7 oropharyngeal cancers, 5 gastrointestinal cancers, 5 genitourinary cancers, 3 breast cancers, 2 Kaposi's sarcoma, and 5 other miscellaneous cancers. Fifty-eight percent of these patients are still alive. Graft loss and death related to chronic rejection accounted for 13 adults and seniors (1.6%). Most of them had associated risk factors such as life-threatening sepsis requiring withholding of immunosuppression, cytomegalo or hepatitis C or hepatitis B viral

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**Table 1. Patient and Graft Survival**

| Post LTx | Months | 3 | 12 | 24 | 36 | 48 | 60 | 72 | 84 |
|---|---|---|---|---|---|---|---|---|---|
| Patient survival (%) | Infant | 85 | 83 | 80 | 77 | 77 | 77 | 77 | 77 |
| | Children | 92 | 91 | 91 | 91 | 91 | 91 | 91 | 91 |
| | Adults | 93 | 85 | 80 | 77 | 73 | 70 | 67 | 64 |
| | Seniors | 85 | 75 | 71 | 66 | 64 | 60 | 58 | 51 |
| | Overall | 91 | 84 | 79 | 76 | 73 | 71 | 68 | 65 |
| Graft survival (%) | Infant | 83 | 80 | 77 | 75 | 75 | 75 | 75 | 75 |
| | Children | 86 | 85 | 85 | 85 | 85 | 85 | 85 | 85 |
| | Adult | 85 | 80 | 74 | 71 | 67 | 64 | 61 | 59 |
| | Senior | 79 | 70 | 66 | 61 | 59 | 56 | 54 | 48 |
| | Overall | 84 | 77 | 73 | 70 | 68 | 65 | 63 | 60 |



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**Table 2. Adverse Effects**

| Months Post Ltx. | 3 | 6 | 12 | 24 | 36 | 48 | 60 |
|---|---|---|---|---|---|---|---|
| Renal Function | | | | | | | |
| Serum creatinine mg/dL* | 1.7 | 1.7 | 1.7 | 1.6 | 1.6 | 1.7 | 1.7 |
| BUN mg/dL | 31 | 30 | 29 | 27 | 27 | 26 | 25 |
| Liver Function | | | | | | | |
| Total bilirubin mg/dL* | 1.0 | 1.1 | 1.1 | 0.8 | 0.8 | 1.0 | 0.9 |
| AST u/L* | 68 | 48 | 50 | 46 | 42 | 42 | 120 |
| Alkaline phosphatase u/L* | 205 | 194 | 168 | 152 | 142 | 144 | 131 |
| ALT u/L* | 65 | 62 | 57 | 61 | 44 | 45 | 42 |
| GGTP u/L* | 177 | 156 | 127 | 121 | 125 | 129 | 120 |
| Immunosuppression | | | | | | | |
| Tacrolimus Dose mg/d* | 11 | 10.5 | 8.5 | 6.9 | 5.9 | 6.0 | 4.8 |
| Tacrolimus level ng/mL* | 1.0 | 0.9 | 0.8 | 0.7 | 0.6 | 0.7 | 9.7# |
| Prednisone = 0 mg/d (%) | 53 | 57 | 67 | 72 | 71 | 66 | 67 |
| Prednisone > 10 mg/d (%) | 28 | 9 | 13 | 4 | 2 | 9 | 5 |
| Toxicity | | | | | | | |
| Hypertension (%) | 29 | 29 | 30 | 37 | 36 | 41 | 46 |
| Diabetes (%) | 24 | 13 | 16 | 15 | 16 | 17 | 18 |
| Hyperkalemia (%) | 39 | 44 | 42 | 46 | 40 | 38 | 35 |
| Cholesterol mg/dL* | 102 | 159 | 165 | 172 | 176 | 179 | 178 |

* Mean value.
# Whole blood trough level; others are plasma trough level.

infection, noncompliance of the patients taking immunosuppression.

## DISCUSSION

The initial benefit of tacrolimus reported in our early experience has been maintained in the long term. While patient and graft survival in adults and seniors continue to drop at a rate of 3 to 4% every year beyond 2 years, survival for infant and children remains stable. Graft loss due to acute or chronic rejection is rare under tacrolimus-based immunoprophylaxis. The common causes of graft loss in the long term include recurrence of the disease, cardiorespiratory failure, cerebrovascular accidents, noncompliance of the patients, and denovo cancers. Relatively stable liver and renal function has been observed in the long term. About 70% of the patients remain without steroids beyond 1 year. Nephrotoxicity leading to end-stage renal failure is less than five percent. Incidence of PTLD and denovo cancers are comparable with conventional immunosuppression.[8,9] Lesser incidence of acute or chronic rejection; lesser incidence hypercholesterolemia; and freedom from steroid in 70% of the patients, from hirtutism, and from gum hyperplasia remains a considerable benefit of tacrolimus-based immunosuppression.[6]

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