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Long-term Management of Immunosuppression After Pediatric Liver Transplantation: Is Minimization or Withdrawal Desirable and/or Possible?

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Abstract

Purpose of Review—The aim of this review is to review available data regarding the risks and benefits of indefinite immunosuppression versus attempted immunosuppression withdrawal for children who have undergone liver transplantation.

Recent Findings—Emerging data suggest that conventional immunosuppression practices may well be responsible for a substantial proportion of the long-term mortality and morbidity burden borne by pediatric liver transplant recipients. The cumulative risk of chronic kidney disease, infection, malignancy, and cardiovascular risk factors such as hypertension, diabetes, and hyperlipidemia appear to threaten the health and well-being of children more than that of acute or chronic allograft rejection. In parallel, single center experiences have suggested that gradual immunosuppression withdrawal can be done safely with higher success rates in pediatric compared to adult liver transplant recipients. The coalescence of these two data streams has engendered substantial interest in systematic exploration of the safety and efficacy of immunosuppression withdrawal in conjunction with a vigorous scientific effort to elucidate an immunologic signature predictive of succesful withdrawal.

Summary—There is a concerted effort within the transplant community to identify biomarkers that can accurately predict the success of immunosuppression withdrawal after liver transplantation. Freedom from lifelong immunosuppression is likely to yield considerable benefit, particularly for children who face the longest lifetime horizons.

Keywords

Pediatric liver transplantation; outcomes; immunosuppression; tolerance

Introduction

Currently, transplantation of any solid organ incurs a lifelong burden of immunosuppression. In spite of many advances, the basic premises of immunosuppression remain unchanged. As such, substantial renal, metabolic, infectious, and neoplastic complications threaten the recipient's life and well-being after transplantation. This concern is heightened when considering pediatric transplant recipients who face the longest lifetimes beyond transplantation (1,2). For pediatric liver transplant recipients, the distant post-transplant horizon is just coming into view as the numbers of medium and long-term survivors burgeon (3). In this article, we will briefly outline outcomes of pediatric liver transplantation and then

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present emerging data regarding the mortality and morbidity of immunosuppression. We will then review promising strategies to minimize the cumulative burden of immunosuppression.

Current Outcomes of Pediatric Liver Transplantation

It is well known that the past decade has witnessed tremendous improvements in short-term liver transplant outcomes. Figure 1 shows declining death rates after deceased donor liver transplantation for all pediatric age groups with the most dramatic decrease in the less than one year of age cohort (3). Medium-term outcomes have recently been reported by The Studies of Pediatric Liver Transplantation (SPLIT) registry (4*). For patients transplanted between 1995 and 2005 who were alive with their primary allografts one year after transplant and had at least one additional year of follow-up, five year Kaplan-Meier patient and graft survival was 94.2% and 89.2%, respectively. Figure 2 illustrates the slow but steady patient attrition over time.

Causes of patient death and graft loss after pediatric liver transplantation

Causes of death and graft loss after pediatric liver transplantation have recently been updated by the SPLIT registry (5). Of the 2291 children that underwent primary liver transplantation between 1995 and 2006, 274 (12%) died. Assigning the etiology of death and consideration of its potential relationship to immunosuppression yielded striking data. Infection contributed directly or indirectly, typically through multi-system organ failure or cardiopulmonary failure, to nearly half of all deaths (125 of 274; 46%). Malignancy accounted for an additional 15 deaths (5.1%). In contrast, rejection contributed directly or indirectly, by necessitating re-transplantation, to only 13 deaths (4.7%). Re-transplantation was required for 236 children (10%). Primary non-function and technical complications accounted for the majority of re-transplants (64%) although rejection was responsible for 36 cases (15%). Among patient subgroups, infants were simultaneously at highest risk to develop infections and at lowest risk to experience rejection. The authors concluded that infection, compared to rejection, posed steeply higher risks of both mortality and morbidity.

The landscape of late deaths and graft loss after pediatric liver transplantation has also been recently painted by the SPLIT registry (4*). Among the 872 pediatric liver transplant recipients alive at one year with their primary graft and with a minimum of an additional 12 months of follow-up, 34 died and an additional 35 lost their grafts. Sepsis / infection (n = 5), multi-system organ failure (n = 5), and post-transplant lymphoproliferative disorders (n = 4), clear complications of immunosuppression, accounted for 14 of the 34 deaths (41%). Immunosuppression may have been a contributing factor to an additional seven deaths from malignancy (21%). Chronic rejection accounted for a single recipient death. In contrast, insufficient immunosuppression resulting in chronic rejection (n = 13), acute rejection (n = 4), and “stopped immunosuppression” (n = 1) were the dominant etiology of graft loss, accounting for half of the cases (18 of 35; 51%).

Morbidity of long-term immunosuppression

In assessing the long-term toll exacted by immunosuppression on the well-being of pediatric liver transplant recipients, one must look beyond the endpoints of death and graft loss.

Chronic kidney disease

Chronic kidney disease is now well-recognized as a major threat to the overall health of liver transplant recipients. Ojo and colleagues brought the issue sharply into view when they reported that the cumulative incidence of chronic renal failure was 26% for adult liver transplant recipients followed for ≥ 10 years (6). For children, available data suggests that while rates of renal failure are low, the prevalence of chronic kidney disease is high (7–11). The largest and

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best study to date has come from Cincinnati Children's Hospital (11). Glomerular filtration rate (GFR) was measured in all pediatric recipients of primary, solitary liver transplants between July 1986 and November 1999 (n = 117). At a mean follow-up of 7.6 years (range 3 – 14.6 years), 37 patients (31.6%) had measured GFR < 70 mL/min per 1.73 m^2, corresponding to stage ≥ 2 chronic kidney disease (12). The prognostic significance of this data with regard to evolution to end stage renal disease remains unknown. However, taken in the context of the protracted predicted lifespan, the cumulative burden of calcineurin inhibitor exposure, and the potential for future development of common medical co-morbidities such as hypertension and diabetes, the high prevalence of significant renal impairment bodes raises serious concerns for the well-being and longevity of pediatric liver transplant recipients (12).

Cardiovascular risk profile - hypertension, diabetes, and hyperlipidemia

Current immunosuppressive medications are well known to predispose to potent atherosclerosis risk factors including hypertension, diabetes, and hyperlipidemia. In general, their impact on pediatric liver transplant recipients appears less than on their adult counterparts. However, there is serious concern that the cumulative impact over time for affected patients bodes poorly. Avitzur et al. reported that 8 of 32 patients (25%) required anti-hypertensive treatment, a rate consistent with several previous reports (7,9,13). Moreover, it has been suggested that hypertension may be substantially under diagnosed. Del Compare et al. compared office blood pressure measurements with 24-hour ambulatory blood pressure monitoring in stable pediatric recipients 1.1–11.5 years (median 5.1 years) after liver transplantation who had good renal function and who were not on any anti-hypertensive medications (14). Of 61 eligible patients, 32 were excluded: 18 (30%) because of chronic renal insufficiency (calculated GFR < 80mL/min), 12 (20%) because of recent changes in immunosuppression, and two because of declined consent. Of the 29 stable patients with good renal function who were studied, eight (28%) met criteria for hypertension by ambulatory blood pressure monitoring while only one was hypertensive based on office blood pressure measurements. With regard to other metabolic diagnoses, approximately 6% of all 10-year pediatric liver transplant survivors are diabetic (9). Although 26% had elevated fasting cholesterol and 45% had elevated triglycerides, none were prescribed lipid lowering agents. Again, although these metabolic abnormalities were often mild and affected a modest proportion of patients, the potential for cumulative morbidity particularly over the anticipated long life of a pediatric transplant recipient span merits concern.

Malignancy

Pediatric liver recipients are particularly susceptible to the malignancy classically related to immunosuppression, post-transplant lymphoproliferative disorder (PTLD), a condition that is almost always associated with Epstein Barr virus (EBV). The most common pediatric liver diseases necessitate transplantation during the infant or toddler years (3), earlier than the usual timeframe of primary EBV infection. Because primary infection is a much more potent risk factor than reactivation infection, EBV seronegative compared to seropositive recipients, are five to seven times more likely to develop clinically important EBV infection and PTLD (15, 16). PTLD has been a leading cause of death beyond the immediate post-operative period (17).

The other malignancy widely acknowledged as a direct sequela of immunosuppression is skin cancer. The risks of squamous cell carcinoma and melanoma are increased by 65 and 3.4 times higher, respectively, in renal and cardiac transplant recipients compared to the general population (18). Specific information on pediatric transplant recipients suggest that skin cancers typically do not occur until the second decade after transplantation, at an average age of 26–28 years (19). As in adults, but even more so, there was reversal of the squamous cell

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to basal cell carcinoma ratio compared with the general population. Spread to lymph nodes was also more common in pediatric recipients than in adult recipients.

Immunosuppression Practices in the Early Post-transplant Period

The recent emergence of more and more data detailing the prevalence and morbidity of complications associated with immunosuppression has engendered increasing interest to reduce the implicit burden of lifelong immunosuppression for pediatric liver transplant recipients. Minimization of immunosuppression early after transplantation may offer the greatest theoretical advantage. However, as the early post-transplant period is widely accepted as the time of highest rejection risk, aggressive reduction of early maintenance immunosuppression is not readily possible. In actuality, early post-transplant immunosuppression has intensified during the past decade. There has been increasing use of induction immunosuppression, dominated by IL-2 receptor antibodies (20). Currently, approximately 26% of pediatric liver transplant recipients receive induction, compared to the nadir of 5% in 1997. For maintenance immunosuppression, calcineurin inhibitors remain the primary agent, given to greater than 90% of recipients at hospital discharge from transplantation. However, cyclosporine has essentially been replaced by its more potent cousin, tacrolimus (20,21). Similarly, the vast majority of the children treated with an anti-proliferative agent are administered mycophenolate mofetil, considered to be a more potent agent that azathioprine (21). These trends of intensified early post-transplant immunosuppression have facilitated decreased use of corticosteroids. Although complete avoidance remains uncommon, there are clear trends that corticosteroids are increasingly discontinued during the first or second post-transplant year (21).

An approach that has been explored in adult transplantation to enable substantial reduction of maintenance immunosuppression early after transplantation is administration of a potent induction regimen. Typically, a strongly depletional drug such as rabbit thymoglobulin or alemtuzamab has been given for induction, followed by monotherapy with tacrolimus (22–27). This strategy has not, however, been embraced by the pediatric liver transplantation community out of concern that the short- and long-term consequences of such potent drugs on the immune system of infants and toddlers, the predominant liver transplant population, is poorly defined.

Long-term Immunosuppression Practices

It is well-known that incidence of acute rejection drops substantially as time passes after liver transplantation (Figure 3). Data from the SPLIT registry clearly show that immunosuppression exposure decreases in parallel (21). Corticosteroids and anti-proliferative agents are frequently discontinued during the first post transplant year. By 12 and 18 months after transplantation, approximately one third and one half of all pediatric transplant recipients are receiving only a single immunosuppressant, respectively. Calcineurin inhibitors in general and tacrolimus in specific are the primary agents used for maintenance immunosuppression. Doses of calcineurin inhibitors also decrease steadily. Particularly if the dose is normalized to recipient weight or trough levels are considered, it is clear that calcineurin inhibitor exposure diminishes over time. Nevertheless, even as much as six years after transplantation, mean trough cyclosporine and tacrolimus levels center around 100 ng/ml and 6 ng/ml, respectively. Therefore, while immunosuppression exposure does indeed diminish, it is still considerable particularly considering the long lifetimes of pediatric liver transplant recipients.

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Immunosuppression Withdrawal Experiences in Pediatric Liver Transplant Recipients

Of all solid organs that are transplanted, the liver has historically been regarded as being immunologically privileged – the most resistant to immunologic attack and damage. Presentation of antigens via the portal venous system is more likely to result in a tolerizing response than presentation via the systemic venous system. In several allogeneic models ranging from rodent to canine to swine, minimal or even no exposure to immunosuppression has resulted in successful and durable graft function after transplantation (28–31). In the human arena, the liver is unique among transplanted solid organs in several ways. First, while episodes of acute rejection commonly connote deleterious outcomes for nearly all other transplanted organs, acute rejection after liver transplantation does not share in such long-term connotations (32,33). Second, it is well-known that some episodes of acute rejection may resolve spontaneously without treatment (34,35). Third, although chronic rejection threatens the longevity of other transplanted organs, its incidence and importance is less in the post-liver transplant setting, particularly in the age of modern immunosuppression (36). Furthermore, it has been suggested that tacrolimus has nearly eliminated the threat of chronic rejection for pediatric liver transplant recipients in general (37,38) and that living donor liver transplants may be particularly immune to chronic rejection (39). And finally, while humoral mechanisms of acute and chronic allograft rejection are operational for all other solid organs, they exert little impact on liver allografts. All of these favorable immunologic factors, in conjunction with specter of lifelong immunosuppression with its attendant toxicities has stimulated tremendous interest in complete immunosuppression withdrawal for pediatric liver transplant recipients.

As for clinical data, there exist single center experiences that demonstrate successful, prospective immunosuppression withdrawal from liver transplant recipients (24,27,40–49*). The collective experience has also been recently reviewed (50,51*). Two, in particular, are informative regarding children. The University Pittsburgh have reported on 95 prospectively withdrawn recipients; at study entry, 31 were ≤ 20 years old and the remaining were 21 – 68 years old (40,41). At last publication, 19% were completely off immunosuppression, 39% were still weaning, 29% have experienced rejection and 13% have withdrawn from the study. Of the 28 patients with rejection, 18 had biopsy-proven episodes, seven had clinically suspected episodes and three had biopsy findings suggestive of “incipient” chronic rejection but not diagnostic of chronic rejection. All 28 recipients were treated with resumption or escalation of baseline immunosuppression, with or without bolus corticosteroids. Although it appears as if the pediatric cohort had better outcomes with higher weaning success rate and lower rejection rate, these conclusions are substantially tempered by the fact that large proportions of both cohorts were still weaning (55% of pediatric and 30% of adult). More recently, outcomes regarding the pediatric cohort have been updated (51*). Of 64 pediatric liver transplant recipients that have attempted immunosuppression withdrawal, 22 (34%) were successful, nine (14%) experienced acute rejection, while the remaining 33 (52%) have reached neither endpoint and are still weaning.

Kyoto University has also reported their experience with immunosuppression withdrawal in pediatric liver transplant recipients. Overall, they observed a success rate for complete immunosuppression withdrawal of 42% (48 of 115 recipients) (43,44). Twenty patients (17%) experienced rejection; all rejection episodes were easily reversed except one that required OKT3 therapy. One recipient developed chronic rejection that was successfully treated with triple immunosuppression - corticosteroid, tacrolimus, and mycophenolate mofetil. A more recent update of this center’s experience indicates that they have successfully weaned 87 pediatric liver transplants recipients (49*). As the report was primarily focused on immunologic studies, it provided no updated information as to how many recipients attempted weaning and / or experienced rejection.

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While these reports regarding immunosuppression withdrawal in adults and children prove that functional tolerance can occur in liver transplant recipients and create the general context of expectation as to its frequency, they have not yielded definitive data regarding the mechanism (s) of or biomarkers that may predict, characterize, or identify functional tolerance. Intriguing glimpses into the signature of functional tolerance have recently emerged that have yet to be prospectively validated. Two groups, one studying children and the other studying adults, have reported that functionally tolerant liver transplant recipients, compared to immunosuppression-dependent liver transplant recipients and healthy controls, have increased proportion and absolute numbers of circulating γδ T cells (49*,52**). Moreover, functionally tolerant patients show a predominance of Vγδ1+ over Vγδ2+ cells. One of the two groups has also suggested that the expression patterns of as few as 22 genes can accurately predict the outcome of withdrawal (52**). Currently, there is an ongoing clinical trial of immunosuppression withdrawal to prospectively test the combination of lymphocyte subsets and gene expression markers for accuracy to identify functionally tolerant adult liver transplant recipients (http://clinicaltrials.gov/ct2/show/NCT00647283?term=immunosuppression+AND +withdrawal&rank=9).

In the United States, of the three trials funded by the Immune Tolerance Network / National Institute of Allergy and Infectious Diseases that are actively exploring immunosuppression withdrawal after liver transplantation, one specifically targets pediatric recipients of parental living donor transplants (http://clinicaltrials.gov/ct2/show/NCT00320606?term=immunosuppression+AND +withdrawal&rank=1). The trial is small, aiming to enroll twenty stable recipients at two centers who will withdraw from immunosuppression over a minimum of 36 weeks. Although the primary endpoint is one of efficacy - the proportion of participants who are successfully withdrawn from immunosuppression, defined as those who remain off immunosuppression for at least one year – there is an overarching emphasis on clarifying the safety of tightly controlled drug withdrawal. An integral part of the study is the serial evaluation of peripheral blood and liver tissue over a five year period before, during, and after withdrawal to identify biomarkers of functional tolerance. If this pilot trial in children proves to be safe and, particularly if a fingerprint of tolerance emerges from this and/or other withdrawal experiences, then the pediatric liver transplant community can look forward to future trials that will enroll a sufficient number of patients to answer critical questions regarding the medical, psychosocial, and immunologic efficacy of immunosuppression withdrawal.

Conclusion

As pediatric liver transplantation has matured into a highly successful endeavor in the past 10 – 15 years, attention has increasingly turned towards delineating the long-term challenges and concerns of and for this unique patient cohort. Only recently has any information emerged regarding the cumulative impact of immunosuppression on the health and well-being of long-term survivors. These reports have stimulated interest in immunosuppression withdrawal. Although single center experiences have provided proof of concept, efficacy with regard to the frequency of success, consequences of failure, and magnitude of future benefit remains to be elucidated by well-conducted and adequately powered clinical trials.

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REFERENCES

1. McDiarmid SV. Current status of liver transplantation in children. Pediatr Clin North Am 2003;50:1335–1374. [PubMed: 14710783]
2. Ryckman FC, Bucuvalas JC, Nathan J, Alonso M, Tiao G, Balistreri WF. Outcomes following liver transplantation. Semin Pediatr Surg 2008;17:123–130. [PubMed: 18395662]
3. Magee JC, Krishnan SM, Benfield MR, Hsu DT, Shneider BL. Pediatric transplantation in the United States, 1997–2006. Am J Transplant 2008;8:935–945. [PubMed: 18336697]
4. Soltys KA, Mazariegos GV, Squires RH, Sindhi RK, Anand R. Late graft loss or death in pediatric liver transplantation: an analysis of the SPLIT database. Am J Transplant 2007;7:2165–2171.2171 [PubMed: 17608834] Comprehensive review examining the etiology of and risk factors for patient death and graft loss one or more years after pediatric liver transplantation.
5. Diamond IR, Fecteau A, Millis JM, Losanoff JE, Ng V, Anand R, Song C. Impact of graft type on outcome in pediatric liver transplantation: a report From Studies of Pediatric Liver Transplantation (SPLIT). Ann Surg 2007;246:301–310. [PubMed: 17667510]
6. Ojo AO, Held PJ, Port FK, Wolfe RA, Leichtman AB, Young EW, Arndorfer J, et al. Chronic renal failure after transplantation of a nonrenal organ. N Engl J Med 2003;349:931–940. [PubMed: 12954741]
7. Berg UB, Ericzon BG, Nemeth A. Renal function before and long after liver transplantation in children. Transplantation 2001;72:631–637. [PubMed: 11544422]
8. Alonso EM. Long-term renal function in pediatric liver and heart recipients. Pediatr Transplant 2004;8:381–385. [PubMed: 15265166]
9. Avitzur Y, De Luca E, Cantos M, Jimenez-Rivera C, Jones N, Fecteau A, Grant D, et al. Health status ten years after pediatric liver transplantation--looking beyond the graft. Transplantation 2004;78:566–573. [PubMed: 15446316]
10. Mention K, Lahoche-Manucci A, Bonnevalle M, Pruvot FR, Declerck N, Foulard M, Gottrand F. Renal function outcome in pediatric liver transplant recipients. Pediatr Transplant 2005;9:201–207. [PubMed: 15787794]
11. Campbell KM, Yazigi N, Ryckman FC, Alonso M, Tiao G, Balistreri WF, Atherton H, et al. High prevalence of renal dysfunction in long-term survivors after pediatric liver transplantation. J Pediatr 2006;148:475–480. [PubMed: 16647407]
12. Hogg RJ, Furth S, Lemley KV, Portman R, Schwartz GJ, Coresh J, Balk E, et al. National Kidney Foundation's Kidney Disease Outcomes Quality Initiative clinical practice guidelines for chronic kidney disease in children and adolescents: evaluation, classification, and stratification. Pediatrics 2003;111:1416–1421. [PubMed: 12777562]
13. Bartosh SM, Alonso EM, Whitington PF. Renal outcomes in pediatric liver transplantation. Clin Transplant 1997;11:354–360. [PubMed: 9361923]
14. Del Compare ME, D'Agostino D, Ferraris JR, Boldrini G, Waisman G, Krmar RT. Twenty-four-hour ambulatory blood pressure profiles in liver transplant recipients. Pediatr Transplant 2004;8:496–501. [PubMed: 15367287]
15. Wallot MA, Mathot M, Janssen M, Holter T, Paul K, Buts JP, Reding R, et al. Long-term survival and late graft loss in pediatric liver transplant recipients--a 15-year single-center experience. Liver Transpl 2002;8:615–622. [PubMed: 12089716]
16. Fridell JA, Jain A, Reyes J, Biederman R, Green M, Sindhi R, Mazariegos GV. Causes of mortality beyond 1 year after primary pediatric liver transplant under tacrolimus. Transplantation 2002;74:1721–1724. [PubMed: 12499888]
17. Migliazza L, Lopez Santamaria M, Murcia J, Gamez M, Clavijo J, Camarena C, Hierro L, et al. Long-term survival expectancy after liver transplantation in children. J Pediatr Surg 2000;35:5–7. [PubMed: 10646764]discussion 7–8.
18. Otley CC, Pittelkow MR. Skin cancer in liver transplant recipients. Liver Transpl 2000;6:253–262. [PubMed: 10827224]
19. Euvrard S, Kanitakis J, Cochat P, Claudy A. Skin cancers following pediatric organ transplantation. Dermatol Surg 2004;30:616–621. [PubMed: 15061845]

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20. Horslen S, Barr ML, Christensen LL, Ettenger R, Magee JC. Pediatric transplantation in the United States, 1996–2005. Am J Transplant 2007;7:1339–1358. [PubMed: 17428284]
21. SPLIT Research Group. SPLIT Annual Report 2006. Rockville, MD: 2006.
22. Eason JD, Loss GE, Blazek J, Nair S, Mason AL. Steroid-free liver transplantation using rabbit antithymocyte globulin induction: results of a prospective randomized trial. Liver Transpl 2001;7:693–697. [PubMed: 11510013]
23. Tzakis AG, Tryphonopoulos P, Kato T, Nishida S, Levi DM, Madariaga JR, Gaynor JJ, et al. Preliminary experience with alemtuzumab (Campath-1H) and low-dose tacrolimus immunosuppression in adult liver transplantation. Transplantation 2004;77:1209–1214. [PubMed: 15114087]
24. Tryphonopoulos P, Tzakis AG, Weppler D, Garcia-Morales R, Kato T, Madariaga JR, Levi DM, et al. The role of donor bone marrow infusions in withdrawal of immunosuppression in adult liver allotransplantation. Am J Transplant 2005;5:608–613. [PubMed: 15707417]
25. Marcos A, Eghtesad B, Fung JJ, Fontes P, Patel K, Devera M, Marsh W, et al. Use of alemtuzumab and tacrolimus monotherapy for cadaveric liver transplantation: with particular reference to hepatitis C virus. Transplantation 2004;78:966–971. [PubMed: 15480160]
26. Eghtesad B, Fung JJ, Demetris AJ, Murase N, Ness R, Bass DC, Gray EA, et al. Immunosuppression for liver transplantation in HCV-infected patients: mechanism-based principles. Liver Transpl 2005;11:1343–1352. [PubMed: 16237712]
27. Eason JD, Cohen AJ, Nair S, Alcantera T, Loss GE. Tolerance: is it worth the risk? Transplantation 2005;79:1157–1159. [PubMed: 15880061]
28. Calne RY, Sells RA, Pena JR, Davis DR, Millard PR, Herbertson BM, Binns RM, et al. Induction of immunological tolerance by porcine liver allografts. Nature 1969;223:472–476. [PubMed: 4894426]
29. Starzl TE, Marchioro TL, Porter KA, Taylor PD, Faris TD, Herrmann TJ, Hlad CJ, et al. Factors Determining Short-and Long-Term Survival after Orthotopic Liver Homotransplantation in the Dog. Surgery 1965;58:131–155. [PubMed: 14305148]
30. Kamada N, Davies HS, Roser B. Reversal of transplantation immunity by liver grafting. Nature 1981;292:840–842. [PubMed: 7022223]
31. Qian S, Demetris AJ, Murase N, Rao AS, Fung JJ, Starzl TE. Murine liver allograft transplantation: tolerance and donor cell chimerism. Hepatology 1994;19:916–924. [PubMed: 8138266]
32. Neuberger J, Adams DH. What is the significance of acute liver allograft rejection? J Hepatol 1998;29:143–150. [PubMed: 9696504]
33. Wiesner RH, Demetris AJ, Belle SH, Seaberg EC, Lake JR, Zetterman RK, Everhart J, et al. Acute hepatic allograft rejection: incidence, risk factors, and impact on outcome. Hepatology 1998;28:638–645. [PubMed: 9731552]
34. Klompmaker LJ, Gouw AS, Haagsma EB, Ten Vergert EM, Verwer R, Slooff MJ. Selective treatment of early acute rejection after liver transplantation: effects on liver, infection rate, and outcome. Transpl Int 1997;10:40–44. [PubMed: 9002150]
35. Dousset B, Hubscher SG, Padbury RT, Gunson BK, Buckels JA, Mayer AD, Elias E, et al. Acute liver allograft rejection--is treatment always necessary? Transplantation 1993;55:529–534. [PubMed: 8456473]
36. Libby P, Pober JS. Chronic rejection. Immunity 2001;14:387–397. [PubMed: 11336684]
37. Jain A, Mazariegos G, Pokharna R, Parizhskaya M, Smith A, Kashyap R, Fung JJ, et al. Almost total absence of chronic rejection in primary pediatric liver transplantation under tacrolimus. Transplant Proc 2002;34:1968–1969. [PubMed: 12176649]
38. Cao S, Cox KL, Berquist W, Hayashi M, Concepcion W, Hammes GB, Ojogho OK, et al. Long-term outcomes in pediatric liver recipients: comparison between cyclosporin A and tacrolimus. Pediatr Transplant 1999;3:22–26. [PubMed: 10359027]
39. Gupta P, Hart J, Cronin D, Kelly S, Millis JM, Brady L. Risk factors for chronic rejection after pediatric liver transplantation. Transplantation 2001;72:1098–1102. [PubMed: 11579307]
40. Ramos HC, Reyes J, Abu-Elmagd K, Zeevi A, Reinsmoen N, Tzakis A, Demetris AJ, et al. Weaning of immunosuppression in long-term liver transplant recipients. Transplantation 1995;59:212–217. [PubMed: 7839442]

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41. Mazariegos GV, Reyes J, Marino IR, Demetris AJ, Flynn B, Irish W, McMichael J, et al. Weaning of immunosuppression in liver transplant recipients. Transplantation 1997;63:243–249. [PubMed: 9020325]

42. Devlin J, Doherty D, Thomson L, Wong T, Donaldson P, Portmann B, Williams R. Defining the outcome of immunosuppression withdrawal after liver transplantation. Hepatology 1998;27:926–933. [PubMed: 9537430]

43. Takatsuki M, Uemoto S, Inomata Y, Egawa H, Kiuchi T, Fujita S, Hayashi M, et al. Weaning of immunosuppression in living donor liver transplant recipients. Transplantation 2001;72:449–454. [PubMed: 11502975]

44. Oike F, Yokoi A, Nishimura E, Ogura Y, Fujimoto Y, Kasahara M, Kaihara S, et al. Complete withdrawal of immunosuppression in living donor liver transplantation. Transplant Proc 2002;34:1521. [PubMed: 12176465]

45. Pons JA, Yelamos J, Ramirez P, Oliver-Bonet M, Sanchez A, Rodriguez-Gago M, Navarro J, et al. Endothelial cell chimerism does not influence allograft tolerance in liver transplant patients after withdrawal of immunosuppression. Transplantation 2003;75:1045–1047. [PubMed: 12698096]

46. Girlanda R, Rela M, Williams R, O'Grady JG, Heaton ND. Long-term outcome of immunosuppression withdrawal after liver transplantation. Transplant Proc 2005;37:1708–1709. [PubMed: 15919439]

47. Tisone G, Orlando G, Cardillo A, Palmieri G, Manzia TM, Baiocchi L, Lionetti R, et al. Complete weaning off immunosuppression in HCV liver transplant recipients is feasible and favourably impacts on the progression of disease recurrence. J Hepatol 2006;44:702–709. [PubMed: 16473433]

48. Assy N, Adams PC, Myers P, Simon V, Minuk GY, Wall W, Ghent CN. Randomized controlled trial of total immunosuppression withdrawal in liver transplant recipients: role of ursodeoxycholic acid. Transplantation 2007;83:1571–1576. [PubMed: 17589339]

49. Koshiba T, Li Y, Takemura M, Wu Y, Sakaguchi S, Minato N, Wood KJ, et al. Clinical, immunological, and pathological aspects of operational tolerance after pediatric living-donor liver transplantation. Transpl Immunol 2007;17:94–97.97 [PubMed: 17306739] Notable paper providing a brief clinical update of the largest experience in immunosuppression withdrawal for pediatric liver transplant recipients along with immunologic analyses looking for a signature of functional tolerance.

50. Lerut J, Sanchez-Fueyo A. An appraisal of tolerance in liver transplantation. Am J Transplant 2006;6:1774–1780. [PubMed: 16889539]

51. Mazariegos GV, Sindhi R, Thomson AW, Marcos A. Clinical tolerance following liver transplantation: long term results and future prospects. Transpl Immunol 2007;17:114–119.119 [PubMed: 17306742] Good overview with long-term follow-up of the largest single center experience of immunosuppression withdrawal experience after adult and pediatric liver transplantation.

52. Martinez-Llordella M, Puig-Pey I, Orlando G, Ramoni M, Tisone G, Rimola A, Lerut J, et al. Multiparameter immune profiling of operational tolerance in liver transplantation. Am J Transplant 2007;7:309–319.319 [PubMed: 17241111] Noteworthy paper suggesting that functionally tolerant liver transplant recipients may be identifiable by peripheral blood biomarkers.

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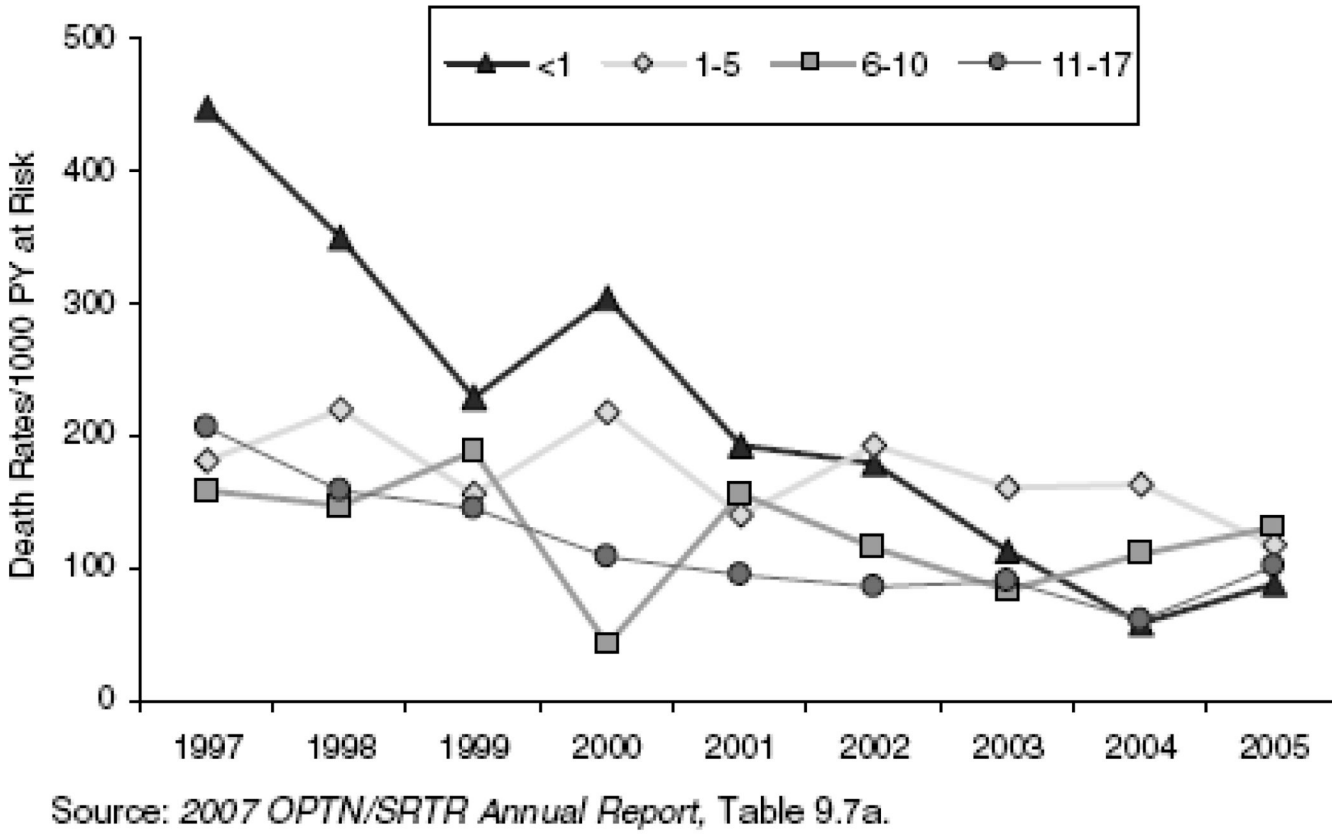

Figure 1. Declining death rates within one year of pediatric deceased donor liver transplantation

Data from the Scientific Registry of Transplant Recipients regarding death rates after pediatric deceased donor liver transplantation by age group for transplants performed between 1997 and 2005. [Figure 10 from Magee et al., AJT 2008; reference 3].

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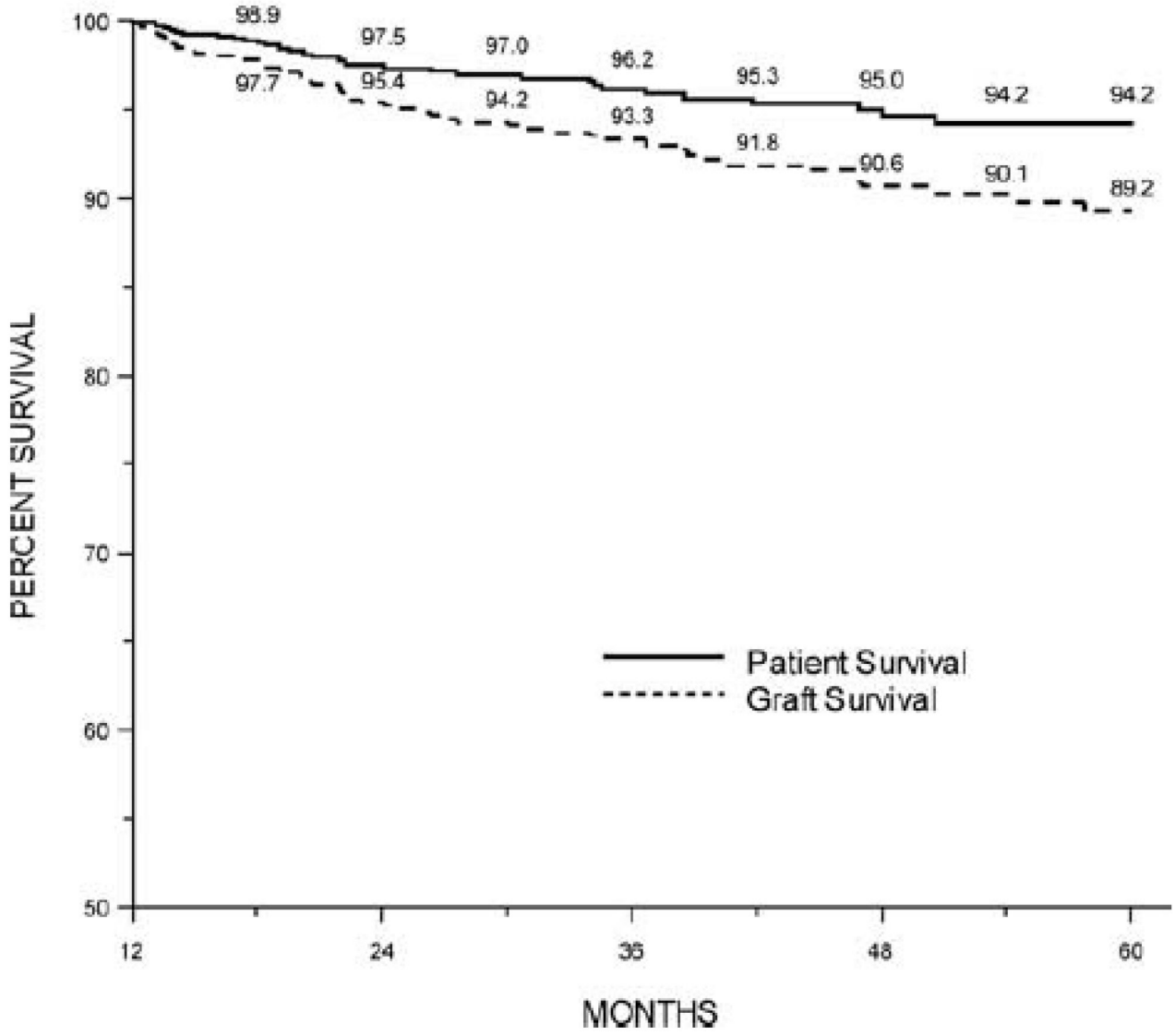

Figure 2. Late patient death and graft loss after pediatric liver transplantation

Kaplan-Meier patient and graft survival for recipients who were alive one year after transplantation with functioning primary allografts. [Figure 1 from Soltys et al., AJT 2007; reference 4*].

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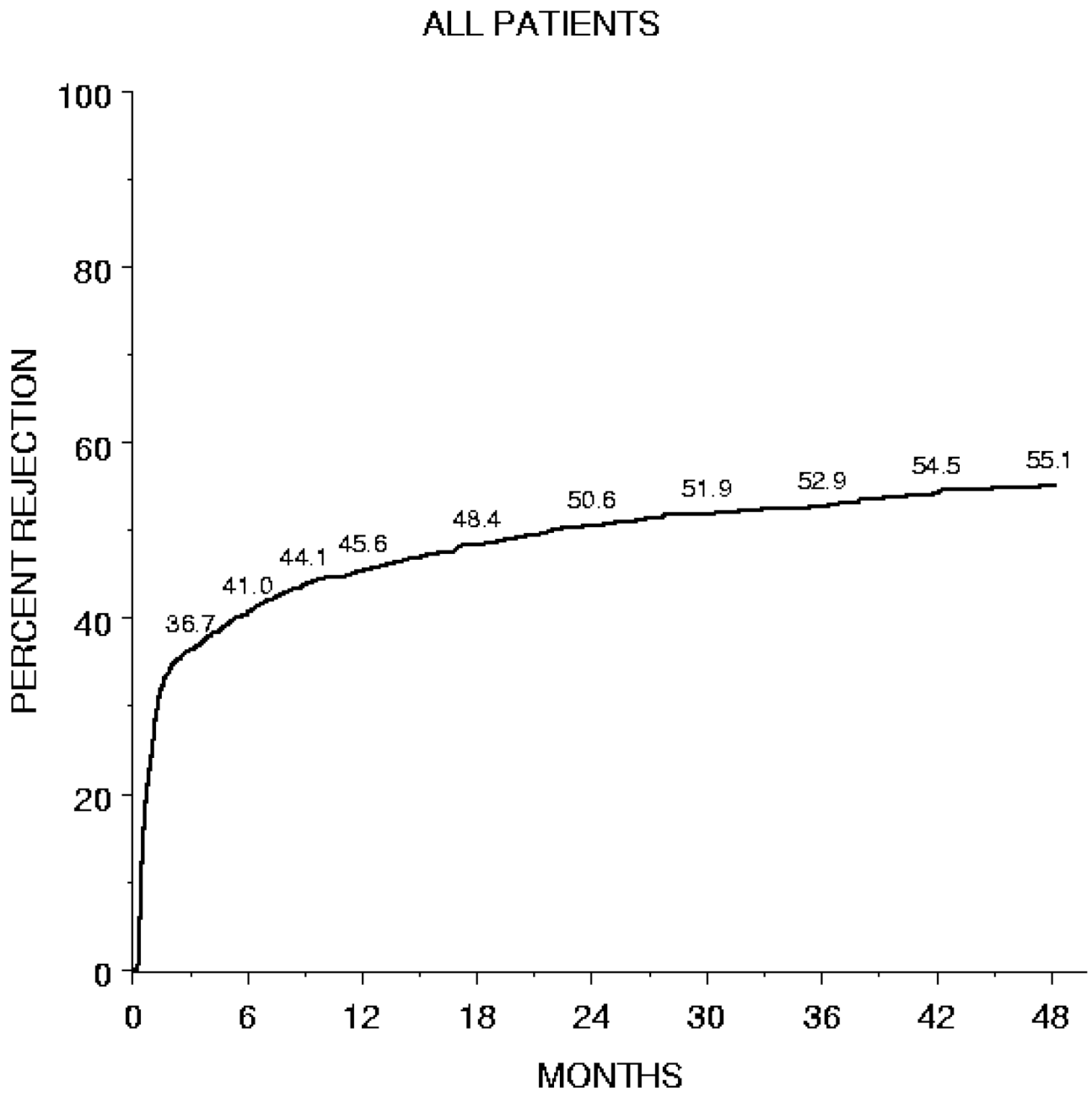

Figure 3. Probability of acute rejection after pediatric liver transplantation

Kaplan-Meier probability of first episode of acute rejection over time after liver transplantation. [Figure 6–Figure 4 from SPLIT Annual Report 2006; reference 21]