Growth following solid organ transplantation in childhood

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One of the ultimate goals of successful solid organ transplantation in pediatric recipients is attaining an optimal final adult height. This manuscript will discuss growth following transplantation in pediatric recipients of kidney, liver, heart, lung or small bowel transplants. Remarkably similar factors impact growth in all of these recipients. Age is a primary factor, with younger recipients exhibiting the greatest immediate catch-up growth. Graft function is a significant contributing factor, with a reduced glomerular filtration rate correlating with poor growth in kidney recipients and the need for re-transplantation with impaired growth in liver recipients. The known adverse impact of steroids on growth has led to modification of the steroid dose and even steroid withdrawal and avoidance. In kidney and liver recipients, this strategy has been associated with the development of acute rejection. In infant heart transplantation, avoiding maintenance corticosteroid immunosuppression is associated with normal growth velocity in the majority of patients. With marked improvements in patient and graft survival rates in pediatric organ recipients, quality of life issues, such as normal adult height, should now receive paramount attention. In general, normal growth following solid organ transplantation should be an achievable goal that results in normal adult height.

KEYWORDS: Growth; Solid Organ Transplantation; Children; Growth Hormone; Steroid Avoidance.

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INTRODUCTION

Growth is frequently suboptimal in pediatric recipients of kidney, liver, heart, lung or small bowel transplants. Because the overwhelming majority of recipients are prepubertal at the time of transplantation, optimizing post-transplant growth to affect catch-up growth is imperative if the target adult height is to be achieved. The following will review the current data for growth after successful solid organ transplantation in children.

KIDNEY

What factors influence post-transplant growth in renal allograft recipients? The three major factors are age at transplantation, allograft function and corticosteroid dose. Chronological age at transplantation is predictive of the magnitude of post-transplant growth. The most recent data from the North American Pediatric Renal Trials and Collaborative Studies (NAPRTCS), which delineates growth in children 0-1, 2-5, 6-12 and older than 12 years of age, shows that the two youngest age groups of children, or children less than 6 years of age, all exhibit catch-up growth for the initial 1-2 years following transplantation and then plateau after that time interval. However, children who are greater than 6 years of age at the time of transplantation had no catch-up growth. Therefore, older children do not exhibit any catch-up growth, and their final adult height will be determined by height at the time of transplantation (1).

Reduced renal allograft function has a significant effect on growth velocity. Studies by Tejani et al. (2) almost two decades ago showed that renal function has a profound impact on growth, with a 0.17 decrease in the Z score (SDS) being associated with a 1.0 mg/dl increase in the serum creatinine level. These data indicate that as kidney function deteriorates following renal transplantation, long-term growth velocity will decrease. Likewise, the data emphasize the need for optimal graft function to achieve the optimal adult target height in pediatric renal allograft recipients.

Steroid dose also has a significant impact on growth in pediatric allograft recipients. Switching from daily to every-other-day steroids (3), steroid withdrawal and steroid avoidance (4) have all been associated with improved growth velocity. A randomized controlled trial of early steroid withdrawal (TWIST Study) randomized 98 patients to tacrolimus and mychophenolate mofetil with steroids being discontinued on day 5 *versus* 98 patients randomized to receiving tacrolimus, mychophenolate mofetil and steroids with the steroids being tapered but continued at a daily dose of 10 mg/m^2. At 6 months, the standard deviation score improved by 0.13 in the steroid withdrawal group compared to continued steroid group (5). The patients

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enrolled in this study were primarily prepubertal patients. All of the clinical parameters were similar in the two groups except for increased infection and anemia rates in the steroid withdrawal group. The long-term results of this study have continued to show improved growth following early steroid withdrawal without any adverse impacts on allograft function. This regimen will likely become the standard of care in the future. An alternative to steroid withdrawal is total steroid avoidance. Preliminary studies from the Stanford Group (4) seem to indicate that young children experienced significant improvements in growth velocity following steroid withdrawal compared to a historical control group. Recently, Sarwal et al. (6) reported the 3-year follow up from a multi-center, NIAID-sponsored randomized controlled study of 130 children enrolled from 12 pediatric transplant centers in the United States. The change in standard deviation score at 3 years for all of the recipients was not different between the steroid-free and the steroid-based groups. However, when the change in standard deviation score at 3 years in the 27 children less than 5 years of age was analyzed, there was a significant difference in the growth velocity between the steroid-free and steroid-based groups ($p = 0.2$). Biopsy-proven acute rejection at 3 years was similar in the steroid-free (16.7%) and steroid-based groups (17.1%). Patient survival was 100% in both groups, and graft survival was similar in both groups (steroid free 95% and steroid based 90%). The systolic blood pressure and cholesterol levels were lower in the steroid-free group. This randomized controlled study certainly indicates that steroid avoidance does not adversely affect long-term graft function or increase the incidence of biopsy-proven acute rejection. However, the impact on growth was less than anticipated because the steroid-free group only demonstrated an effect on growth in the recipients less than 5 years of age. This study emphasizes that there are factors other than steroids that affect growth velocity and catch-up growth, especially in older pediatric transplant recipients. A strategy to address modifiable factors to enhance growth in older recipients will need to be a significant focus in the future. The ultimate goal with respect to growth in pediatric renal allograft recipients is attaining a normal final adult height. Recent data from the NAPRTCS registry (1) has shown that over the past quarter century, there has been a significant increase in the average final adult height of recipients entered into the registry. From 1987 to 1991, those patients who reached adult height had a standard deviation score of -1.93, whereas for the patients who were entered into the registry between 2002 and 2010 and reached final adult height, the standard deviation score was -0.94, representing an almost 1 standard deviation improvement in final adult height over 15 to 20 years. This improvement certainly is a remarkable achievement and indicates that pediatric renal allograft recipients now have final adult heights that are approaching their target height.

One of the primary factors that have led to improved final adult height has been that the height deficit at the time of transplantation has improved markedly during the past decade. The most recent NAPRTCS registry data[1] indicate that in 1987, the standard deviation score (Z score) for patients at the time of transplantation was approximately -2.5, whereas in patients who were transplanted in 2009, the Z score at transplantation was between -1 and -1.5. Again, over a quarter of a century, the standard deviation score for children at the time of transplantation has improved more than 1 standard deviation, which is similar to the improvement in adult height over the same period for the same patient population.

As indicated previously, the overwhelming majority of children over 6 years of age at the time of transplantation do not exhibit any catch-up growth following transplantation. Therefore, if those patients are to achieve normal adult height, some intervention to stimulate growth will be required. This dilemma raises the question as to whether the use of recombinant human growth hormone (rhGH) improves growth in growth-retarded renal allograft recipients. There have been four (7-10) randomized controlled studies that have studied rhGH treatment in growth-retarded renal transplant patients. In all four studies, 1-year growth significantly improved in the group receiving rhGH compared to the control group. The growth velocity in most of the studies doubled with rhGH treatment compared to the control group. One concern regarding the use of rhGH following renal transplantation has been prior anecdotal information that rhGH may stimulate the immune system and precipitate acute rejection. In all four studies, there was no difference in the incidence of acute rejection in the rhGH group compared to the control group.

A concern with one of the newer immunosuppressant drugs, sirolimus, was that this agent could impair linear growth in pediatric solid organ transplant recipients. Two studies (11,12) have addressed this issue, which was raised primarily because animal models have shown decreased longitudinal growth due to sirolimus-mediated inhibition of cell proliferation and vascular endothelial growth factor expression in the long bone growth plate, which blocks insulin-like growth factor (IGF) intracellular signaling in chondrocytes (13). A study by Gonzalez et al. (11) evaluated 34 renal transplant recipients who received sirolimus for 24 months and compared their height standard deviation scores to a control group. There was no difference in the height standard deviation score between the sirolimus and control groups at any time over the 24 months. However, the change in height was significantly decreased in the sirolimus group at all of the follow-up times compared to the control group. The authors concluded that the growth velocity was significantly decreased in the sirolimus group compared to the control group. In contrast, Hymes and Warshaw (12) studied 25 renal transplant recipients taking sirolimus who were followed for 24 months and compared their height standard deviation scores to a control group receiving tacrolimus. The height standard deviation scores were no different at baseline and 24 months between the sirolimus and tacrolimus groups. The height standard deviation score increased by 52% in the sirolimus group, and the authors concluded that sirolimus does not impair growth in renal allograft recipients.

LIVER

Al-Sinani and Dhawan (14) summarized the current data regarding growth following liver transplantation in 2009 by evaluating 20 reports between 1987 and 2008. The number of patients in each report varied from 21 to 236, and the follow-up period in each report varied from 1 to more than 8 years. The number of recipients who exhibited catch-up growth varied between 39 and 100%. The steroid regimen used in the various reports was variable, including daily to a

tapered dose, every other day steroid therapy to steroid withdrawal and steroid-free regimens. Therefore, specifically analyzing each group was quite difficult. However, the authors attempted to identify the factors in these 20 reports that impacted growth. Their assessment was that the steroid dose impacted growth, with the cumulative dose, timing of tapering and withdrawal and the presence of daily steroid treatment having adverse impacts on growth. Height at the time of transplantation also had an impact on catch-up growth, with those who had decreased growth standard deviation scores at the time of transplantation having increased catch-up growth following transplantation. Age was also a factor that impacted growth in children less than 2 years of age at the time of transplantation: these children experienced increased catch-up growth. The primary diagnosis (cholestasis, fulminant liver failure, sclerosis or metabolic disease) had an impact on growth. Patients with cholestasis or hepatitis had better post-transplant growth. Graft dysfunction also impacted post-transplant growth, with those liver transplant recipients who required re-transplantation or developed post-transplant lymphoproliferative disease (PTLD) having a reduced growth velocity following transplantation. Alonso and colleagues (15) reviewed the data for 1,143 recipients from the Studies of Pediatric Liver Transplantation (SPLIT) registry. The standard deviation score was -1.55 at transplant, and at 24 and 36 months, the scores were -0.87 and -0.68, respectively. These results demonstrate a significant improvement in the height standard deviation score following liver transplantation. However, subsequent follow-up showed limited catch-up growth after 36 months. The factors that negatively impacted growth were more than 18 months of steroid therapy following transplantation and the association of primary metabolic or non-biliary cholestatic disease with decreased catch-up growth.

Because the liver is thought to be less immunogenic than other organs, steroid withdrawal has been used therapeutically in pediatric liver transplant recipients in the past to maximize linear growth. Five uncontrolled studies using cyclosporine as the primary immunosuppressive agent have withdrawn steroids between 3 and 58 months following transplantation, and acute rejection occurred in 7 to 27% of the patients. Chronic rejection that occurred in less than 18 months was present following steroid withdrawal in 4 to 13% of the patients and graft loss in 3 to 13%. More recently, steroid withdrawal was attempted in three series of patients with tacrolimus as the primary immunosuppressant (16-17). In a study from Johns Hopkins (16), the steroid was withdrawn at 6 months in 29 patients with a 29% acute rejection rate. In Kyoto (17), the steroid was withdrawn at 8 months in 156 patients, all of whom were recipients of livers from live related donors with a 14% acute rejection rate. In Pittsburgh, the steroid was withdrawn within the first year in 166 patients, and in 21% of these patients, reinstitution was required within 5 years due to rejection. The SPLIT data (15) indicate that at 24 months post-transplant, if steroids are withdrawn less than 6 months, the increase in standard deviation score (1.7 increase) was greater compared to steroids being withdrawn after 18 months (0.9 increase). These data indicate that steroid withdrawal, especially if performed early, will result in an improved standard deviation score and will potentially lead to improved adult height. However, there is a risk of rejection and potential graft loss with steroid withdrawal.

What can one anticipate as the final adult height in pediatric liver transplant recipients? A 2008 study by Scheenstra et al. (18) evaluated 23 recipients with a median age of 13.3 years at transplantation. The standard deviation scores were -1 at transplant and -1.4 at the final height, and the median target height was -1.3. Additionally, 12 of the 23 had final adult heights below 1.3 standard deviations of their target heights. These data indicate that a significant number of liver transplant recipients cannot reach their adult target heights. Because a number of liver transplant recipients exhibit suboptimal post-transplant growth, one could question whether or not there is any effective treatment for improving growth in this population. Eight recipients with standard deviation scores greater than 2 were treated with rhGH for more than 5 years. The standard deviation scores improved from -3.6 to -2.7 (19). There were no rejection episodes, and 1 patient who had elevated liver enzyme levels prior to rhGH treatment was diagnosed with chronic rejection at 3 years. This single study on a limited number of patients would seem to indicate that severely growth retarded liver transplant recipients could benefit from prolonged rhGH treatment post-transplant without any adverse impact on graft function.

HEART

More than a decade ago, Chinnock and Baun (20) evaluated heart transplant recipients at their institution and delineated three factors that seemed to impact post-transplant growth. These factors were the number of days in the hospital during the first post-transplant year; the number of treated rejection episodes after the first post-transplant year; and mid-parental height, the genetic growth potential for an individual, which is quite important and had not been delineated by prior authors regarding growth following other organ transplants. These authors evaluated 77 infants who were transplanted at less than 6 months of age and received no maintenance steroid therapy. Catch-up growth was quite prevalent during the first post-transplant year, and only 6 of 51 patients who were more than 5 years post-transplant had heights that were less than the fifth percentile. This study demonstrated that the use of a steroid-free maintenance protocol can lead to normal growth for very young infants transplanted at less than 6 months of age. Peterson et al. (21) evaluated 46 heart transplant recipients who were less than 11 years of age at the time of transplantation. Those recipients showed no significant change in the height standard deviation score up to 24 months post-transplant. The authors noted that a younger age at transplant had a positive impact on growth, and the length of steroid treatment had a negative impact on the change in the standard deviation score post-transplant. Their current practice is to wean low-risk patients with no rejection episodes off steroids at 1 year. More recently, Bannister et al. (22), from Toronto Sick Kids, evaluated 130 heart recipients who were transplanted between 1990 and 2005 and had a mean follow-up of 4.4 years. Their mean height Z score was unchanged from transplant to the last measurement, and the mean was -1.3. The authors felt that enteral feeding led to increased height standard deviation scores in patients without sufficient caloric intake.

There are limited data on the use of rhGH in growth-retarded pediatric heart transplant recipients. Mital et al. at Columbia (23) reported 10 recipients with a mean age of 7.8

years at transplant, a mean age at the initiation of rhGH treatment of 13 years and a mean duration of rhGH treatment of 2.5 years. The growth velocity increased from 2.5 cm per year at baseline to 8.6 cm per year during rhGH treatment. The authors noted increases in left ventricular shortening fraction, left ventricular volume and cardiac output in the patients who received rhGH treatment. The left ventricular volume remained increased following the discontinuation of rhGH; therefore, this change was thought to be physiologic and not pathologic.

LUNG

Recently, Elizur et al. (24) from St. Louis Children's Hospital reported on 36 infants <1 year of age and 26 toddlers 1-3 years of age who underwent lung transplantations between 1990 and 2004. At transplant, the height standard deviation scores were -1.76 for infants and -1.72 for toddlers. At 1, 3 and 5 years post–transplant, the standard deviation scores became more negative (-1.89, -1.91 and -2.14, respectively). Obviously, this report indicates that catch-up growth does not occur. Indeed, increased growth retardation occurs following lung transplantation. Thus, rhGH has been used in a small series at St. Louis Children's Hospital. Sweet and his colleagues (25) reported that 8 of 9 lung transplant recipients who received rhGH developed bronchiolitis obliterans syndrome, which was a higher incidence compared to the group who did not receive rhGH. Therefore, Sweet and his colleagues caution the use of rhGH to enhance growth velocity in lung transplant recipients.

SMALL BOWEL

The current data on growth in small bowel recipients was delineated by Nayyar and colleagues (26). Of 76 small bowel transplant recipients who received transplants at a mean age of 2.6 years, 34 received standard immunosuppression with tacrolimus and steroids, and 42 underwent a combination of anti-thymocyte globulin induction followed by tacrolimus and only received steroids for acute rejection. Additionally, 48% of the patients who received anti-thymocyte globulin remained steroid-free during the follow-up period, and the height standard deviation score improved at 2 years in the steroid-free group. These data seem to indicate that steroid-free immunosuppression has beneficial effects in the small bowel transplant population.

CONCLUSION

There are universal factors that impact growth velocity, catch-up growth and final adult height in all pediatric solid organ transplant recipients. The height at the time of transplant is certainly an important factor, with more severe growth retardation at transplant leading to a potential for greater catch-up growth following transplant. A normal target height at transplant has the potential to result in normal final adult height. The latter has certainly been shown in the renal transplant population.

The age at transplant also impacts growth, with younger recipients tending to be more growth-retarded at transplant; therefore, these patients may exhibit greater catch-up growth.

Likewise, graft dysfunction impacts growth, with the number of acute rejection episodes, number and length of hospitalizations, need for re-transplantation and need for surgical re-exploration all having adverse effects on growth.

Renal dysfunction, whether in renal allograft recipients or in recipients of other solid organ transplants, may have adverse impacts on growth. In renal allograft recipients, primary renal dysfunction certainly has been associated with an adverse effect on growth. In recipients of other solid organ transplants, renal dysfunction secondary to drug toxicity (i.e., calcineurin inhibitors, antibiotics and antivirals) can have adverse impacts on growth.

Bone dysfunction may impact growth, whether there is a persistent bone abnormality resulting from the primary disease or acquired bone dysfunction following solid organ transplantation.

Corticosteroids can certainly impact growth in all pediatric solid organ transplant recipients. Steroid-free regimens are optimal, with steroid withdrawal being a secondary option. In the studies where steroid withdrawal was effective, it was noted that earlier withdrawal was better. Receiving every-other-day steroid therapy had a positive impact on growth; however, adherence is a concern when every-other-day treatment is used. One of the major factors that may adversely affect the ultimate adult height is a suboptimal pubertal growth spurt. This spurt occurs to a significant degree in renal allograft recipients and may also occur in other solid organ transplant recipients. One potential therapeutic option to enhance pubertal growth is the use of rhGH to enhance the magnitude of the pubertal growth spurt; however, to my knowledge, there are no studies that have addressed this issue. Importantly, when one is determining the factors that affect growth following transplantation, genetic potential is a major factor that will determine target height. Thus, one should determine the mid-parental height when determining the anticipated target height for any recipient. In addition, one should also be cognizant that if the patient has significant growth retardation there may be a genetic abnormality causing primary short stature rather than the growth retardation being a consequence of the primary disease or other factors following organ transplantation.

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