CRC IRB Proposal

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Study Purpose and Rational

Cardiac transplantation is known to be associated with not only mortality, in-terms of post-transplant survival; but also with significant morbidity-for example hospitalization for acute rejection, infections and also with respect to side effects of long term management therapies. Standard of care of a post-cardiac transplant pediatric patient, like many other solid organ transplants recipients, require utilization of immunosuppressive agents: for example, calcineurin-inhibitors such as tacrolimus and mycophenolate; azathioprine, cyclosporine, azathioprine and prednisone.

While many choices of immunosuppressive agents exist, recent trends in medical practice consequent to published data from the literature, shows adaptation to those regimen with fewer side effect profile([1,2]). As an example, since the mid-1990s, with the introduction and combination of tacrolimus and mycophenolate, versus use of agents such as cyclosporine has been adopted after extensive randomized control trials and a meta-analysis show superiority of tacrolimus in prevention of acute rejection, better side-effect profile as compared to cyclosporine[2,3]. Specifically, according to the International Society for Heart and Lung transplant (ISHLT) registry, from 1994-1999, majority of heart transplant patient were managed with cyclosporine, azathioprine and prednisone as maintenance immunosuppressive agents[2,4].

Since the early 2000s, the most common regimen utilized include use of tacrolimus and mycophenolate as maintenance therapy after induction with T-cell cytoxic agents such as ATG (antithymomite globulin). Another significant difference with this protocol is the early weaning off of steroids. In the pre-2000 era, post-cardiac transplant patients were maintained on prednisone for a minimum of 6months with many patients remaining on steroids for a significantly longer time period. Currently there is an increasing adoption of such steroid sparing regimen, as noted in ISHLT registry and emergence of literature showing improved growth with the utilization of less steroids [5-7]

The adverse effect on steroids on growth, particularly linear growth is well known and published in the literature. Long-term treatment with glucocorticosteroids is associated not only

with decreased bone density as seen in osteopenia and osteoporosis, but in children plays a significant role at the epiphyseal growth plates [8]. Steroids act systemically to increase estrogen and parathyroid hormones; its effects on Insulin-like growth factor I (IGF-I) result in inhibition of new bone formation and stimulate bone resorption[7,8] At the epiphyseal plate, IGF-1 stimulate chondrocyte proliferation and in formation of cartilage and ultimate bone formation, while the exact mechanism remains under investigation, steroids are thought to reduce cartilage matrix production by reducing effect of IGF-I- (decreasing chondrocyte proliferation) increasing apoptosis of chondrocytes and consequently reducing linear growth[8].

In the review of the literature, a few studies including reviews have investigated growth following solid-organ transplant. In cardiac transplant patient, some studies report improved or normal linear growth with use of steroid sparing immunosuppression while others show continued growth delay and failure to "catch up"-as is expected even in patient who originally demonstrated poor linear growth[6,7,9]

Given these conflicting findings and relative paucity in the literature regarding the effect of immunosuppression, particularly with the use chronic long-term steroids on linear growth in the post-cardiac transplant patient; this current study seeks add to the literature a corroboration or contrasting of the reported findings. Currently, at our institution, as of 2008, the more contemporary steroid sparing protocol is used. Prior to that time, the traditional protocol involving long term use of prednisone was employed. The primary aim of this study is to determine the differences in linear growth in patient who have received either protocol.

Study design and Statistical analysis:

This study will be a retrospective chart review of patients of comparing linear growth as a primary outcome in a cohort group having received the traditional cyclosporine/azathioprine/long term steroid use versus the cohort group having received the contemporary protocol utilizing tacrolimus/mycophenolate/steroid sparing post induction with cytolysis with antithymomite globulin (ATG). Patient having undergone primary heart transplantation at the Morgan Stanley Children's Hospital from January 2005-May 2011 are included. For analysis two cohort groups are identified: patients transplanted between January 2005 and April 2008-patients who were on cyclosporine/azathioprine/minimum of 6mo prednisone. Patient transplanted post-April 2008; having received induction with ATG +5days methylprednisolone; then tacrolimus and mycophenolate without further steroid use comprise

second cohort. Data review will be performed on the EHR of both inpatient and clinical data. The primary outcome will be linear growth as evident by change in height of the patients. A possible secondary outcome includes effect on weight.

Statistical Analysis will be performed by obtaining z-scores (unpaired t-test) of height –for-age of all individual at time of transplantation with subsequent report of change in z-score of height at 1yr post-transplant and 5yrs post-transplant. A sample size of 65 as calculated using the following equation: $n=1+16\ (\text{Std-dev/effect})^2$ will be a to detect an effect of ½ SD with power of 80% and α-error of 0.05. A t-test will also be used to determine differences among the two cohort. In addition, given the fact that in the two cohorts, the medications utilized are so different a regression analysis will be employed to detect any differences as well.

Study Procedure

Data collection and Chart Review

Study Drugs

Though no new drugs to be introduced medications utilized by patients in this study include:
Cyclosporine-disrupts DNA synthesis side effects include hypertension, hirsuitsm, gingival hyperplasia, GI effects
-Azathioprine-purine analogue-interrupts DNA synthesis, side effects include GI complaints
-Tacrolimus-calcineurin inhibitor-prevent T-cell proliferation, common side/adverse effects-hypertension, hyperglycemia/diabetes, GI effects, seizures and acute renal failure
-Anti-thymocite globulin: rabit-derived antibody to T-cell side effect: cytokine storm-fevers, chills, rigors; theoretical graft failure
-Prednisone-glucocorticosteroid side effect include weight gain, bone loss, growth retardation, hyperglycemia, hypertension
-Mycophenolate-disrupts purine biosynthesis leading to disruption in T and B-cell production; side effects hypertension, hypercholestronemia, electrolyte abnormalities, leucopenia, neoplasia

Medical Device: None

Study Questionnaires: None

Study Subjects

Inclusion Criteria: All pediatric <18yo primary heart transplant recipients at Morgan Stanley Children's Hospital from January 2005-May 2011 irrespective of indication for transplant

Exclusion Criteria: Any re-transplant patients or patients who die within 24hrs post-transplant

Recruitment of subjects: No active recruitment as this is a chart review

Confidentiality of Study Data: Data accessible only to investigators

Potential Conflict of Interest: None

Location of Study: Morgan Stanley's Children's Hospital of New York

Potential Risk: None

Potential Benefits: None

Alternative Therapies: None

Compensation to Subjects: No compensation

Cost to Subjects: None

Minors as research subjects: Since this is pediatric cohort, all are minors.

Radiation and radioactive substances: None

References

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