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A Study on Monitoring Gene Expression in Pediatric Cardiac Transplantation

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ABSTRACT

The AlloMap® Gene Expression Test is a non-invasive screening tool approved for use in heart transplant recipients 15 years of age and older. Experience with AlloMap® in pediatric heart transplant recipients is limited. We aimed to describe differences in his AlloMap® scores observed in pediatric heart transplant recipients. This is a retrospective study of all pediatric heart transplant recipients evaluated by his AlloMap® at a single institution between 2013 and 2014. All possible ratings were recorded. Additional variables recorded at the time of each AlloMap® score include immunosuppressive therapy, patient demographics, and endocardial biopsy (EMB) results. Patients who underwent another solid organ transplant or multiple solid organ transplants were excluded. Her 100 AlloMap® scores were obtained from 42 patients, and her mean age at implantation was 4.3 years. Her median AlloMap® score for all patients was 32 (IQR: 30-35). Of the 100 AlloMap® scores, 10% were collected from her 12-year-old patient. There was little difference in the median score between age groups (p=0.143). Forty-five scores had a concomitant biopsy. Twenty-eight (62%) patients had ISHLT grade 0 and 16 (36%) had ISHLT grade 1 rejection. AlloMap® scores were higher in patients with evidence of ISHLT grade 1 acute cellular rejection (ACR) on EMB (p=0.044). AlloMap® scores were similar across all immunosuppression regimens (p=0.403), with TAC+MMF (n=43) and TAC+SIR (n=27) being the most commonly used regimens. In patients with multiple AlloMap® scores, the mean change from baseline in AlloMap® score was 2 (IQR, 2-5), with no significant change in biopsy findings. Among pediatric heart transplant recipients, patients with ISHLT Grade 1 rejection had higher AlloMap® scores than those with ISHLT Grade 0 rejection, although AlloMap® scores were affected by patient age and immunity. It did not appear to be affected by suppressive therapy. Further research is needed to confirm the results of this study and to determine the role of her AlloMap® in monitoring pediatric patients after transplantation.

Keywords: Aromap®; heart transplantation in children; gene expression; immunosuppressive.

INTRODUCTION

Rejection is one of the leading causes of morbidity in pediatric heart transplant recipients, often leading to graft failure and death. In the most recent era, 15% of patients experienced treated rejection within the first-year post-transplant, with rates of rejection being highest in patients greater than 1 year of age [1]. Frequent monitoring with cardiac catheterization and endomyocardial biopsy (EMB) has been utilized to monitor patients in the post-transplant period for evidence of rejection [2]. However, EMB has been associated with risks such as tricuspid valve damage and regurgitation, conduction system abnormalities, and cardiac perforation [3-5]. Endomyocardial biopsy is subject to sampling error and inter-observer variability and can only detect acute cellular rejection (ACR) once cellular infiltration and damage have occurred [6,7]. Major complications have also been reported with cardiac catheterization including arrhythmias, hemodynamic compromise, perforation, and death [8,9]. During these procedures, patients are exposed to high doses of ionizing radiation, which can increase the child's lifelong risk of developing cancer [10]. Additionally, after this invasive procedure, patients must be hospitalized for monitoring, resulting in hospitalization costs ranging from an average of $1,200 to $5,600 per biopsy [6].

The AlloMap® Molecular Expression Test (CareDx, Brisbane, CA) is an innovative, non-invasive test to determine the risk of rejection in adult and adolescent heart transplant recipients aged 15 years and older who are at least 2 months post-transplant. method [7,11] -13]. However, experience in pediatric heart transplant recipients is limited.

The primary objective of this project was to evaluate AlloMap® scores and determine the correlation of these scores with EMB results in pediatric heart transplant patients. The secondary objectives of this project were to identify transplant-related factors, if any, that alter the reliability of the AlloMap® score in the pediatric heart transplant population and to assess the use of different immunosuppressive therapies at this institution. is to explain the relationship between therapies. and the patient's impact on her AlloMap® score.

METHODS AND MATERIALS

Patients

Pediatric patients (age <20 years) who underwent heart transplantation by AlloMap® scoring and South American Medical University EMB between April 1, 2013, and December 31, 2014, were considered for participation in this study. Carolina (MUSC) was monitored. All possible his AlloMap® scores were recorded. Patients who underwent another solid organ transplant or multiple solid organ transplants were excluded. The MUSC protocol for pediatric heart transplantation includes AlloMap® assessment, which is performed in conjunction with EMB at 6- and 9-months post-transplant. Once the patient has survived one-year post-transplant, he performs AlloMap® twice a year, without the use of biopsies. If there is a recent history of ACR, her AlloMap® assessment will be performed more frequently. For study purposes, rejection was defined as evidence of ACR (ISHLT grade ?1A) in EMB. Biopsies reviewed during the study period were scored based on the 1990 ISHLT Standardized Cardiac Biopsy Score. Patient data were obtained through a retrospective review of electronic medical records. Data include patient details, transplant indications and dates, immunosuppressive therapy and corresponding serum trough concentrations, viral load, and allograft surveillance studies. Evaluation of the corresponding serum trough concentrations was patient-specific, with target concentrations based on time post-transplant and the patient's rejection history, with higher trough concentrations preferred during her first 6 months to 1-year post-transplant. It has been. AlloMap® test results were obtained from the AlloMap® database. The study protocol followed the Declaration of Helsinki and was approved by the MUSC Institutional Review Board.

AlloMap® Gene Expression Assay

The AlloMap® test assesses gene expression profiles of ribonucleic acids isolated from peripheral blood

mononuclear cells using a 20-gene algorithm to help identify patients at low risk of ACR [7-13]. Eleven genes have been tested and shown to be associated with the presence of ACR in adult and adolescent heart transplant patients. The expression of these identified genes in the sample was then converted to a score from 0 to 40, and the threshold for discriminating rejection was determined by each transplant center based on AlloMap® experience and desired negative predictive value. is set by Due to the exploratory nature of these tests for pediatric patients, there were no pre-determined thresholds at this institution. All samples were collected and sent to the CareDx laboratory in Brisbane, CA for analysis.

Statistical Analysis

Patient data, AlloMap® scores, and EMB results were analyzed descriptively and expressed as a median frequency or interquartile range. The Kruskal-Wallis test was used to determine the relationship between AlloMap® score and endocardial biopsy results, the patient's age at her first AlloMap® score, and immunosuppressive therapy. A p-value less than 0.05 was considered significant.

RESULTS

Forty-two pediatric heart transplant recipients met the inclusion criteria, 21 men and 21 women were included in the analysis (Table 1). 100 His AlloMap® scores were obtained from 42 pediatric patients, the median age at the time of implantation was 4.3 years, median time from implantation until his AlloMap® scores were collected was 2.7 years (range 0.3 ~14.3 years). Her median AlloMap® score for all patients was 32 (IQR: 30-35). Ten percent were taken from a 12-year-old patient. There was little difference in median values between age groups [12 years: 32 (IQR, 29-35), p=0.143].

	Median AlloMap® Score (IQR)	*p*- value
ISHLT Grade 0, n=28	31.5 (29-35)	0.044
ISHLT Grade 1, n=16	35 (32-36)	
ISHLT Grade 2, n=1	36	

Table 1: AlloMap® Score by Rejection Severity.

Concurrent biopsies were performed on 45 patients. 28 (62%) patients had ISHLT grade 0 rejection and 16 (36%) had ISHLT grade 1 rejection (9 patients' grade 1A, 7 patients' grade 1B). AlloMap® scores were significantly higher in patients with proven ISHLT grade 1 rejection than in those with EMB-proven ISHLT grade 1 rejection (Table 2). At the time of AlloMap® evaluation, she was the only patient who had grade 1B ISHLT rejection on biopsy, and she had been treated for ACR. This patient's AlloMap® score was 38 with new donor-specific antibodies and elevated B-type natriuretic peptide. One patient with ISHLT rejection grade 1A and one patient with ISHLT rejection grade 1B both had an AlloMap® score of 35 and had no clinical rejection at 4 and 12 months after biopsy and AlloMap® score. I experienced it. One episode of her ISHLT rejection of grade 2 occurred concurrently with an AlloMap® score of 36. This patient received bortezomib and rituximab with plasmapheresis for antibody-mediated rejection (AMR) and monthly continuous intravenous immunoglobulin for antibody-mediated rejection (AMR) in the 2 months prior to her AlloMap® score. Ta. The only treatment she received after obtaining this AlloMap® score was intravenous immunoglobulin with no recurrence of AMR or development of her ACR requiring medical intervention.

Immunosuppression Regimen	Median Time Post-Transplant	Median AlloMap® Score (IQR)	*p*-value
Prednisone + TAC + MMF, n=15	1.47 years	31 (27-35)	0.403
TAC + MMF, n=43	1.52 years	33 (30-35)	
TAC + SIR, n=27	6.65 years	31 (29-34)	
TAC + AZA, n=9	3.88 years	34 (32-37)	
Other regimen, n=6	5.38 years	34 (28-36)	

Table 2: AlloMap® Score by Immunosuppressive Regimen.

The immunosuppressive regimen was recorded at each time point in AlloMap®. Tacrolimus and mycophenolate mofetil (TAC+MMF) and tacrolimus and sirolimus (TAC+SIR) were the most used immunosuppressive therapies. Other treatments used were prednisone plus tacrolimus and mycophenolate (PRED+TAC+MMF) and tacrolimus plus azathioprine (TAC+AZA). If serum trough concentrations were collected during AlloMap® screening, serum trough concentrations were reviewed and evaluated in relation to the patient's specific treatment goals. At the time of AlloMap® screening, tacrolimus trough levels were considered therapeutic in 36% of samples, and sirolimus trough levels were considered therapeutic in 43% of samples. AlloMap® scores were similar across immunosuppressive regimens (p=0.403). Twenty-eight of the 42 patients included in the analysis had more than one AlloMap® score throughout the study period. The mean change from baseline in AlloMap® score was 2 points (IQR 2–5), which corresponded to her interpatient variation of 6.4% (range 0–52%). Despite this variation, only one ISHLT grade 2 rejection occurred.

DISCUSSION

To our knowledge, this is the first report of the use of her AlloMap® test as an adjunct to conventional monitoring in patients younger than 15 years. In this retrospective study of 42 pediatric heart transplant recipients aged 1 to 19 years and at least 6 months post-transplant, patients with grade 1 rejection were more likely than those with nonrejection. We found that activity at the time of biopsy correlated with a higher AlloMap® score, as the score was higher. Rejected with grade 0 in EMB. Our study mainly compared grade 0 and grade 1 rejection grades found on biopsy. This previously defined rejection as ISHLT grade 3 or higher and tested the ability of AlloMap® to distinguish between moderate to severe rejection (ISHLT grade 3 or higher) and no rejection (ISHLT grade 0). This differs from the adult study conducted in [7].

However, when all biopsy scores were analyzed in the CARGO study, it was found that ISHLT Grade 1B correlating AlloMap® scores were higher than those of ISHLT Grades 0, 1A, and 2, but like those associated with ISHLT Grade 3A [7]. A similar correlation was seen in our population with evidence of ISHLT Grade 1 rejection having higher corresponding AlloMap® scores than ISHLT Grade 0. While this correlation was statistically significant, the study authors note that this may not be of great clinical significance, as the patients included in this study would have biopsy grading classified as grade 0R or grade 1R (no rejection or mild rejection) based on the 2004 revision of ISHLT ACR grading. Although this grade of rejection may not require treatment in all cases, three patients (one with grade 1A and two with grade 1B rejection) in this study required treatment for ACR within 12 months of EMB and AlloMap® screening [14]. AlloMap® has not been validated for the detection of mild rejection, but rather to distinguish the presence of moderate-to-severe rejection [7]. The relevance of AlloMap® ratings across all rejection grades in our pediatric population is unknown, as there were no episodes of ISHLT grade 3 rejection during the study period.

The AlloMap® test uses mathematical formulas to develop an algorithm that provides a score range of 0 to 40 [13]. AlloMap® scores collected in our population ranged from 14 to 38. Comparing these scores to her AlloMap® Examination Clinical Performance Characteristics table for patients 6 months or more post-transplant, the score range suggests an estimated probability of 98.2%. Patients experienced 100% ISHLT grade 3 rejection [13]. This was also the case in our population, as there were no cases of ISHLT level 3 rejection. In the IMAGE study, AlloMap® detected only 17.6% of rejection episodes, leading the study authors to believe that clinical diagnosis, rather than changes in AlloMap® scores, can detect the most severe rejection episodes. I'm thinking [15]. Previously conducted adult studies did not explore the expected interpatient variation in his AlloMap® scores within our sample, with no significant changes in EMB or allograft function. Multiple Her AlloMap® scores were performed in her 28 patients included in this analysis, and despite no change in EMB, there was large within-patient variability in her reported AlloMap® scores. It became clear that there is. This small variation in scoring, in addition to previously reported data in the IMAGE study, calls into question the reliability of his AlloMap® scoring in detecting acute cellular rejection.

Although different immunosuppressive therapies were used in our patient population, there was little effect on his AlloMap® score between groups. The most used immunosuppressive therapy is consistent with recent international reports for pediatric heart transplant patients, with the combination of tacrolimus and mycophenolate mofetil being the most common [16]. Previous studies in adults have erroneously shown that using prednisone at doses greater than 20 mg daily reduced AlloMap® scores, which were associated with IL1R2, ITGAM, and FLT3 gene expression. decline [7,13]. Nineteen patients received prednisone as part of immunosuppressive therapy. A weight-based dose was used, with patients in this cohort receiving doses ranging from 0.05 to 0.17 mg/kg/day at the time of blood draw, up to 6 mg daily. AlloMap® scores did not appear to change with these doses of corticosteroids.

LIMITATIONS

This study is the first report on the use of his AlloMap® assessment in pediatric patients. The study was conducted at a single pediatric academic institution, and only 42 of his patients were available for analysis. Collaboration with other pediatric heart transplantation groups using AlloMap® scoring will provide more robust data regarding its use in the pediatric population. Our study group had a low incidence of clinically significant ACR and no moderate to severe rejection episodes. Therefore, we were unable to assess the utility of her AlloMap® scoring for all rejection grades or the ability of her AlloMap® to detect the presence of moderate to severe rejection. Finally, AMR remains an important factor in graft survival after transplantation. The AlloMap® test cannot detect AMR, so switching to AlloMap® instead of EMB for post-transplant rejection monitoring may result in AMR going undetected and untreated.

CONCLUSION

Our study suggests that the AlloMap® gene expression test may be useful in detecting the presence of ISHLT grade 1 rejection in pediatric heart transplant recipients at least 6 months post-transplant. To confirm the results of this study, characterize the role of AlloMap® in pediatric patients, validate the use of AlloMap® in all degrees of rejection, and determine the potential for endocardial biopsy alternatives, Additional experience with AlloMap® evaluation is required. Post-surgery case. Monitoring of transplant rejection.

CONFLICT OF INTEREST

The corresponding author declares that no conflict of interest exists on behalf of all authors.

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REFERENCES

1. Heart and Lung Transplant Registry Pediatric Heart Transplantation Statistics (2013) International Society for Heart and Lung Transplantation.

2 Costanzo MR, Dipchand A, Starling R, Anderson A, Chan M, et al. The International Society of Heart and Lung Transplantation Guidelines for the care of heart transplant recipients. J Heart Lung Transplant. 2010;29:914-56.

3. Pophal SG, Sigfusson G, Booth KL, Bacanu SA, Webber SA, et al. Complications of Endomyocardial Biopsy in Children. J Am Coll Cardiol. 1999;34:2105-2110.

4. Daly KP, Marshall AC, Vincent JA, Zuckerman WA, Hoffman TM, et al. Endomyocardial biopsy and selective coronary angiography are low-risk procedures in pediatric heart transplant recipients: Results of a multicenter experience. J Heart Lung Transplant. 2012;31:398-409.

5. Strecker T, Rosch J, Weyand M, Agaimy A. Endomyocardial biopsy for monitoring heart transplant patients: 11-years-experience at a german heart center. Int J Clin Exp Pathol. 2013;6:55-65.

6. Evans RW, Williams GE, Baron HM, Deng MC, Eisen HJ, et al. The Economic Implications of Noninvasive Molecular Testing for Cardiac Allograft Rejection. Am J Transplant. 2005;5:1553-1558.

7. Deng MC, Eisen HJ, Mehra MR, Billingham M, Marboe CC, et al. Noninvasive Discrimination of Rejection in Cardiac Allograft Recipients Using Gene Expression Profiling. Am J Transplant. 2006 6:150-160.

8. Cassidy SC, Schmidt KG, Van Hare GF, Stanger P, Teitel DF. Complications of Pediatric Cardiac Catheterization: A 3-Year Study. J Am Coll Cardiol. 1992;19:1285-1293.

9. Vitiello R, McCrindle BW, Nykanen D, Freedom RM, Benson LN. Complications Associated with Pediatric Cardiac Catheterization. J Am Coll Cardiol. 1998;32:1433-1440.

10. Andreassi M. Radiation Risk From Pediatric Cardiac Catherization. Circulation. 2009;120:1847-1849.

11. Pham MX, Deng MC, Kfoury AG, Teuteberg JJ, Starling RC, et al. Molecular Testing for Long-term Rejection Surveillance in Heart Transplant Recipients: Design of the Invasive Monitoring Attenuation Through Gene Expression (IMAGE) Trial. J Heart Lung Transplant. 2007;26:808-814.

12. Crespo-Leiro MG, Stypmann J, Zuckermann A, Bara C, Ross H, et al. Utility of Gene Expression Profiling Test (GEP) Score Instability to Predict Future Clinical Outcomes in Heart Transplant: Results from the CARGO 2 European-Based Multicenter Trial. J Heart Lung Transplant. 2013;32:S113.

13. AlloMap® (2014) A Non-Invasive Test Service for Heart Transplant Patients. CareDx.

14. Stewart S, Winters GL, Fishbein MC, Tazelaar HD, Kobashigawa J, et al. Revision of the 1990 Working Formulation for the Standardization of Nomenclature in the Diagnosis of Heart Rejection. J Heart Lung Transplant. 2005;24:1710-1720.

15. Pham MX, Teuteberg JJ, Kfoury AG, Starling RC, Deng MC, et al. Gene Expressing Profiling for Rejection Surveillance after Cardiac Transplantation. N Engl J Med. 2010;362:1890-1900.

16. Dipchand AI, Edwards LB, Kucheryavaya AY, Benden C, Dobbels F, et al. (2014) The Registry of the International Society for Heart and Lung Transplantation: Seventeenth Official Pediatric Heart Transplantation Report; Focus Theme: Retransplantation. J Heart Lung Transplant. 2014;33:985-995.