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Review Research

Comprehensive Review of the Role of Rituximab in Pediatric Cardiac Transplantation

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Abstract

Rituximab is a chimeric anti-CD20 monoclonal antibody approved for the treatment of CD20 positive B cell malignancies. In the transplant context, rituximab has been used to prevent and treat antibody-mediated allograft rejection, minimize systemic toxicities secondary to chemotherapy, treat autoimmune anemias, and as a strategy for managing post-transplant lymphoproliferative disorders (PTLD). However, information in the pediatric cardiac transplant patient population is limited. This review summarizes the use of rituximab in the pediatric cardiac transplant population.

ABBREVIATIONS

ADCC: Antibody-Dependent Cell Mediated Cytotoxicity; AIC: Autoimmune Cytopenia; AIHA: Autoimmune Hemolytic Anemia; AIN: Autoimmune Neutropenia; ANC (Absolute Neutrophil Count); CLL: Chronic Lymphocytic Leukemia; DSA: Donor Specific Antibodies; EBV: Epstein-Barr Virus; ECMO: Extracorporeal Membrane Oxygenation; HLA: Human Leukocyte Antigens; ITP: Immune Thrombocytopenia; IVIG: Intravenous Immunoglobulin; MHC: Major Histocompatibility Complex; MMF: Mycophenolate Mofetile; NHL: Non-Hodgkin's Lymphoma; PRA: Panel Reactive Antibody; PTLD: Post-Transplant Lymphoproliferative Disease; RA: Rheumatoid Arthritis; SOT: Solid Organ Transplant; WBC: White Blood Cells.

INTRODUCTION

The CD20 antigen is expressed on both immature and mature B cells, and is associated with the regulation of B cell proliferation and differentiation [1]. Rituximab is a chimeric anti-CD20 monoclonal antibody [2]. The rituximab Fab domain binds to the CD20 antigen and impacts the B cell through three mechanisms: activates the complement cascade, which leads to complement mediated cytotoxicity; phagocytosis and antibody-dependent cell mediated cytotoxicity (ADCC) through macrophage recognition; and natural killer cell interaction resulting in ADCC. Rituximab leads to a reduction in B cells in the peripheral blood in approximately one to three days following administration, and complete B cells depletion within one to six weeks [3]. However, rituximab does not have a direct effect on the plasma cells as these do not express the CD20 antigen. Rituximab is approved for the treatment of CD20 positive B cell malignancies: non-Hodgkin's lymphoma (NHL), rheumatoid arthritis (RA), chronic lymphocytic leukemia (CLL), granulomatosis with polyangiitis, microscopic polyangiitis, and pemphigus vulgaris. Generally, a rituximab dose of 375 mg/m2 weekly, depending on the indication it is utilized for, and has minimal reported side effects [2]. In the transplant context, rituximab has been used to prevent and treat antibody-mediated allograft rejection, minimize systemic toxicities secondary to chemotherapy, treat autoimmune anemias, and as a strategy for managing post-transplant lymphoproliferative disorders (PTLD) [4,5].

Pediatric patients are at risk for sensitization given their propensity to alloantibody production to HLA as a result of blood transfusion, pregnancy, mechanical circulatory support, and exposure to foreign human leukocyte antigens (HLA) antigens from the allograft materials used for reconstructive surgery in congenital heart disease (CHD) [5]. Identifying the optimal desensitization strategy to reduce the pre-heart transplant antibody has been a recent focus, but with limited success in the pediatric heart transplant patient population. The purpose of this review is to summarize the use of rituximab in the pediatric cardiac transplant population.

CLINICAL USE OF RITUXIMAB IN PEDIATRIC CARDIAC TRANSPLANTATION

Although rituximab is not approved for use in pediatric cardiac transplant patients, numerous studies report its successful off-label use in a variety of situations.

INDUCTION/DESENSITIZATION IN HIGH HLA ANTIBODY TRANSPLANTATION

HLAs are cell surface proteins that present foreign substances to T lymphocytes, an important step in the immune recognition process. HLA are encoded by the genes of the class

I (A, B, and C regions) and class II (DR, DP, DQ regions) of the major histocompatibility complex (MHC) on chromosome 6. All nucleated cells express the MHC class I HLA, whereas class II HLA are found only on antigen-presenting cells. When antigens are present, antibodies react and form the antibody-antigen complex in the endothelial layer of the allograft, and subsequent activation of the complement cascade. The resulting inflammatory response leads to further macrophage infiltration, microvascular thrombosis, and potential allograft dysfunction [6]. Patients who are listed for transplant may be "sensitized" or have pre-existing circulating antibodies against HLA, and even non-HLA [7]. Patients who are sensitized often experience longer wait times on the transplant list, may have increased risk of post-transplant rejection, and experience decreased survival [8].

When a sensitized patient is identified, the transplant clinicians determine the appropriate strategy to manage the patient. Treatment protocols aim to remove alloantibodies and down regulate cells that are producing antibodies (e.g. B cells). Protocols and data are often based on single center experiences and/or case reports. The combination of plasmapheresis, intravenous immunoglobulin (IVIG), and rituximab have been reported to help remove circulating antibodies while minimizing antibody production with success in the adult kidney and heart transplant populations [9-11]. In pediatric heart transplant candidates, few case reports and studies report efficacy with rituximab (Table 1). Table 1 summarizes the published results from institutions or scenarios that have used rituximab as part of the desensitization strategy for HLA antibody incompatible pediatric heart transplantation. Balfour et al. reported an overall reduction in the Panel Reactive Antibody (PRA) from 69% to 2% in a 10-year-old patient when rituximab (2 doses) was added to plasmapheresis, IVIG and mycophenolate mofetil (MFF) [12]. Bucin et al., reported a successful ABO incompatible heart transplant in a 5-year-old with a pre-transplant PRA 100% using MMF, IVIG, immunoadsorption, tacrolimus and rituximab [13]. Schumacher et al., developed a protocol and found an almost 60% response rate in patients who were desensitized with IVIG and rituximab [14]. Asante-Korang et al. noted a reduction in PRA in five of the six patients who received rituximab as part of the desensitization protocol, and incidentally noted the absence of later development of PTLD in the rituximab subgroup [15]. More recently, Edwards et al. found that of the 13 patients who received rituximab, 8 patients (61.5%) were responders [16]. The use of rituximab may therefore serve to increase the donor pool for patients who are broadly allosensitized and whose transplant risk might otherwise be concerning.

RITUXIMAB AS A PREVENTION AND TREATMENT FOR ACUTE CARDIAC ALLOGRAFT REJECTION

Similar to its mechanism in desensitization, rituximab leads to a reduction in B cells within allografts when given as induction therapy or treatment of rejection [5]. Almost all the reports for the use of rituximab as a treatment for acute cardiac allograft rejection in the pediatric patient population have been case reports or single center retrospective studies (Table 2).

Pollock-BarZiv et al., evaluated the use of rituximab in 13 patients with PRA >10% over a 16-year period. Three patients received rituximab preoperatively, and 9 received it post-operatively to treat AMR, which all occurred in the first month post-transplant. No patients developed AMR on follow-up beyond 6 months post-transplant. The one-year survival was 71% compared to 84% in the non-sensitized population, indicating that B-cell directed strategies may be effective in managing AMR in this population [17]. Stendahl et al., reported the case of a 10 year-old that developed AMR requiring extracorporeal membrane oxygenation (ECMO), support. A reduction in HLA class 1 antigens from 32% to 17% and a decrease in HLA class II antigens from 26% to 0% were recognized when rituximab was added [18]. Similarly, Imamura et al. reported use of rituximab in a 16-year-old with acute cellular rejection (ACR) and AMR that

Table 1: Management of sensitization with rituximab in pediatric cardiac transplantation.

Authors	Year	Design	Number of Patients	Patient Characteristics	Methods	Rituximab Dosing	Outcomes and Conclusions	Adverse side effects
Balfour et al.	2005	Case Report	1	Age at transplant: 11 months Pre-transplant PRA: > 10%	High PRA despite IVIG, MMF, plasmapheresis, treated with rituximab	375 mg/m2 x 2 doses	PRA decreased 69% to 18% PRA decreased after transplantation to 2%. Patient well 12 months post-transplant.	None reported
Bucin et al.	2006	Case Report	1	Age at transplant: 5 years Pre-transplant PRA: 100% Heart transplant across antibodies against HLA and ABO	High PRA despite MMF, IVIG, immunoadsoprtions, tacrolimus, treated with rituximab	375 mg/m2	PRA increased 3-fold despite MMF, IVIG, tacrolimus, immunoadsoprtions. Rituximab reduced antibody titers against donor lymphocytes from 128 to 16. No hyperacute rejection, 3 acute rejection episodes. Post-transplant DRAs present in low titers at 16 months.	None reported
Schumacher et al.	2012	Prospective study	14	Pre-transplant PRA: > 10%	2002 to 2011 Desensitization with IVIG and rituximab	375 mg/m2 weekly	6/8 responders required 2-3 doses rituximab. Potential donors increased 10% pre-treatment to 85% post-treatment.	None reported

Asante-Korang et al.	2014	Retrospective single center study	14	Age at transplant: High PRA: 6.4 (0.06-16.8) years Low PRA: 2.2 (0.02-19) years Pre-transplant PRA: > 10%	2005-2013 Desensitization: PRA 11%-50%: MFI 3,000-7,000: IVIG, plasmapheresis, cyclophosphamide 500-1000 mg/m2 (replaced by rituximab times 4 doses post 2009). PRA >50% and MFI >7,000: IVIG, plasmapheresis, Rituximab 4 weekly doses, post-transplant plasmapheresis.	375 mg/m2	6 patients received rituximab; PRA reduction in 5/6 patients. No PTLD in subgroup of patients treated with rituximab.	None reported
Irving et al.	2015	Retrospective single center study	12	Age at transplant: Patient 1: 26 months Patient 2: 11 months Patient 3: 8.9 years Patient 4: 9.5 years	ABO incompatible cardiac transplant Pre-transplant isohemagglutinins 1:16 or higher	375 mg/m2	Patient 1: Plasmapheresis, rituximab, immunoadsorption, ATG, IVIG.Pre-transplant Anti-A 1:128, Anti-B 1:16. Post-treatment Anti-A 1:8; anti-B 1:2 Patient 2: Steroids, rituximab. Pre-transplant Anti-A 1:128, Anti-B 1:64. Post-treatment Anti-A 1:4, Anti-B: 1:2. Patient 3: ATG, rituximab. Pre-transplant Anti-A 1:128, Anti-B 1:16. Post-treatment Anti-A 1:32, Anti-B 1:2 Patient 4: Rituximab, bortezomib, eculizumab, immunoadsorption. Pre-transplant Anti-A 1:256, Anti-B 1:4. Post-treatment Anti-A 1:2, Anti-B 1:4.	None reported
Edwards et al.	2019	Retrospective single center study	14	Pre-transplant PRA: ≥ 10%	2013-2018 IVIG and Rituximab	375 mg/m2	Of 13 patients who received rituximab, 8 patients (661.5%) were responders	

Abbreviations: ATG: Anti-thymocyte globulin; DSA: Donor specific antibodies; IVIG: Intravenous immunoglobulin; MFI: Mean-fluorescence intensity; MMF: Mycophenolate mofetile; PRA: Panel reactive antibody; PTLD: Post-transplant lymphoproliferative disease.

resulted in a reduction in PRA from 52.1% to 1.3% [19]. Erdogan et al., described 7 pediatric patients with AMR treated with rituximab and plasma exchange, in addition to steroids, MMF, and tacrolimus. Although there were no adverse effects reported, mortality rate was 57% [20]. Despite the small case reports and studies, some evidence exists that rituximab may positively affect the treatment of cardiac allograft rejection, either in combination with other agents or when other therapies prove ineffective.

RITUXIMAB AND PTLD

PTLD is a disease of heterogeneity, with the majority being of B cell origin and associated with Epstein-Barr virus (EBV) infections. The EBV virus infects cells and stimulates proliferation. Cytotoxic T cells would normally control such proliferation, but in the setting of chronic immunosuppression, such normal immune regulation is disrupted, allowing EBV infections to lead to PTLD [21,22]. It is a significant cause of morbidity and mortality, affecting approximately 10% of surviving transplant patients at 10 years of age and increases the risk of death [23]. A few studies have assessed the prevalence and history of PTLD amongst pediatric heart transplant patients in developing nations [24-26]. Typically, treatment consists of chemotherapy with or without antiviral therapy, and a few studies indicate improved outcomes with the addition of rituximab therapy [27,28] (Table 3).

Several case reports have reported success with the addition of rituximab 375 mg/m2 for at least 4 doses in combination with reduction in immunosuppression, chemotherapy, or local radiation to achieving sustained partial or complete remission of PTLD, and a decrease in EBV load in the blood [28-36]. Two case series also report remission of PTLD with the addition of rituximab to reduction in immunosuppression or rapid discontinuation of immunosuppression in combination with chemotherapy. Similar benefits on EBV viral load were also reported and side effects remained minimal, indicating that a chemo-immunotherapeutic approach may be effective in managing PTLD [37,38]. Schubert et al., described their experience with rituximab for PTLD in pediatric heart transplant patients and noted an overall incidence of 8.2%, with rituximab being used in 50% of the PTLD cases. All patients demonstrated full remission without death related to PTLD or treatment at median 3.9 years follow up time (interquartile range 1.3-6.2) [39]. More recently, Arshad et al. discussed the outcomes

Table 2: Management of rejection with rituximab in pediatric cardiac transplantation.

Authors	Year	Design	Number of Patients	Patient Characteristics	Methods	Rituximab Dosing	Outcomes and Conclusions	Adverse side effects
Pollock-BarZiv et al.	2008	Retrospective single center study	13	Age at transplant: 7 (3.5 months to 15.5 years) Female: 5 (39%)	1990 to 2006 Pre-transplant PRA (Class I or Class II >10%), or a positive T- or B-cell cross match, ACR or AMR rejection administered rituximab.	Not reported	3 patients received rituximab pre-operatively. 9 patients received rituximab post-operative for AMR. 5 patients received 2 doses for AMR 6 months post-transplant. No patients developed AMR 6 months post-transplant 71% 1-year survival vs. 84% in nonsensitized population.	None reported
Stendahl et al.	2010	Case Report	1	Age at transplant: 8 years Age at rejection: 10 years Antibody mediated rejection requiring ECMO	Case report	375 mg/m2	Plasmapheresis, anti-thymoglobulin, IVIG, rituximab, steroids. HLA antigen antibody analyses: Pre-transplant: class I 0%, class II 0% At admission: class I 32%, class II 26% At discharge: class I 17%, class II 0%	None reported
Imamura et al.	2013	Case Report	1	Age at transplant: 4 years Age at rejection: 16 years ACR and AMR	Case Report	375 mg/m2	PRA 52.1% at admission. Plasma exchange 8 sessions, IVIG (2 doses), and rituximab. PRA 1.3% at discharge	None reported
Erdogan et al.	2018	Retrospective single center study	7	Age at transplant: 3 (1.5 to 17) years Age at rejection: 7 (7-17.5) years	IVIG, rituximab, plasmapheresis, steroids, MMF, tacrolimus or sirolimus.	375 mg/m2	Anti-thymocyte induction therapy not given at transplant or rejection. 4 patients died within 6 months (mortality rate 57.1%).	None reported

Abbreviations: ACR: acute cellular rejection; AMR: antibody mediated rejection; ECMO: extracorporeal membrane oxygenation; HLA: human leukocyte antigen; IVIG: intravenous immunoglobulin; MMF: mycophenolate mofetile; PRA: panel reactive antibody.

of PTLD management using rituximab over a 16-year period, and reported that 15 of 24 patients received rituximab in addition to reduction in immunosuppression and chemotherapy. Freedom from disease recurrence and death after PTLD diagnosis was 73.9% at 1 year, 52.1% at 3 years and 47.8% at 10 years [40]. Although rituximab for the management of PTLD in the pediatric cardiac transplant population has been reported in the literature, given that most are case reports or small studies, the need for larger trials is needed to refine practices.

RITUXIMAB AND MANAGEMENT OF CYTOPENIAS

Cytopenias in the pediatric solid organ transplant population are multifactorial. Autoimmune hemolytic anemia (AIHA), immune thrombocytopenia (ITP), and autoimmune neutropenia (AIN) are autoimmune cytopenias (AICs) that may occur as a consequence of T-cell inhibition and dysregulation in patients following solid organ transplantation (SOT). In the solid organ transplant population, autoimmune diseases have been attributed to prior infection or immunosuppression. Case reports in the adult SOT population suggest that the treatment response of transplant-related AIC may differ from primary immune cytopenias, necessitating a different treatment approach [40-43]. Treatment strategies include standard immune cytopenia treatments with steroids, IVIG, plasmapheresis, vincristine, and conversion of immunosuppression agents [44,45]. Given the formation of autoreactive antibodies in most of these situations, rituximab has also been reported to be an effective therapy for elimination of the autoreactive antibodies in difficult cases (Table 4). However, the literature is limited in discussing the utilization of rituximab as a step-up therapy in the pediatric cardiac transplant population for this indication.

Chitlur et al., reported a patient who developed severe neutropenia and thrombocytopenia while on tacrolimus. The patient was switched to cyclosporine with azathioprine, which yielded a mild transient improvement in ANC and platelets. After receiving rituximab 375 mg/m^2 for 4 weekly doses, the neutropenia responded to rituximab therapy, as evidenced by a normalized white blood cell (WBC) count and absolute neutrophil count (ANC) that remained in normal range without G-CSF

Table 3: Management of PTLD with rituximab in pediatric cardiac transplantation.

Authors	Year	Design	Number of Patients	Patient Characteristics	Methods	Rituximab Dosing	Outcomes and Conclusions	Adverse side effects
Zilz et al.	2001	Case report	1	Age at transplant: 10 years Age at PTLD: 14 years EBV seroconverted, subcutaneous, lymphatic B-cell lymphoma	Case Report	Not stated 4 doses	Rituximab at age 19, when additional skin nodules noted. 3 months later, skin and inguinal lesions resolved.	Not reported
Dotti et al.	2001	Case series	3	Age at transplant: Patient 1: 12.5 years Patient 2: 16 years Patient 3: 5.5 years Age at PTLD: Patient 1: 21 years Patient 2: 24 years Patient 3: 12 years	Case series	375 mg/m2 for at least 4 doses	Everyone had reduction in immunosuppression Patient 1: CD20 positive DLCL. Received local radiotherapy, consolidation with 4 doses rituximab. Complete remission Patient 2: CD20 positive DLCL. Received weekly chemotherapy and rituximab. Partial remission. Patient 3: CD20 positive DLCL with EBV. Weekly chemotherapy with rituximab. Partial remission.	None reported
Herman et al.	2002	Case Report	1	Age at transplant: 5 years Age at PTLD: 7 years EBV polymorphic lymphoproliferative disorder	Case Report	375 mg/m2 per week for 4 weeks	Rituximab with reduction in immunosuppression. EBV load high at diagnosis, dropped and remained below detection threshold 11 months after completion of therapy.	None reported
Garceau et al.	2008	Case Report	1	Age at transplant: 17 years Age at PTLD:17 years EBV+ PTLD with undetectable virus	Case Report	Does not state; rituximab for 8 doses	Rituximab with reduction in immunosuppression. 1-month post discharge, reduction but persistent lymphoma in liver and spleen. 4-years post-transplantation and 40 months after diagnosis of PTLD, normal thoracic-abdominal CT scan.	None reported
Windebank et al.	2009	Retrospective single center study	4	13 patients with PTLD 4 patients with advanced stage EBV driven BLL	1990-2007 Patient 1: low dose chemotherapy Patient 2-4: low dose chemotherapy and rituximab	375 mg/m2	Patient 1: Age at transplant 3.5 years, age at PTLD 9 years. Did not achieve remission Patient 2: Age at transplant 9.5 years, age at PTLD 14 years, achieved remission Patient 3: Age at transplant 11.5 years, age at PTLD 13.5 years, achieved remission Patient 4: age at transplant 13.5 years, age at PTLD 17.5 years, achieved remission	None reported
Kusuki et al.	2009	Case report	1	Age at transplant: 17 month Age at PTLD: 47 months Monomorphic, PTLD, DLBL	Case report	375 mg/m2 for 6 doses	Reduction in immunosuppression during chemotherapy. Child free of both PTLD and allograft rejection 41 months post PTLD diagnosis.	Not reported

Schubert et al.	2009	Retro-spective single center study	12	Age at transplant: 7.2 ± 3.3 years Time to PTLD: 3.2 ± 2.2 years 7 monomorphic B-cell lymphomas 4 monomorphic Burkitt lymphoma	1986 to 2007	Not reported	PTLD incidence 8.2% (12/147). Rituximab in 6 patients. All patients demonstrated full remission without death related to PTLD or treatment at 3.9 (1.3–6.2) year median follow-up time.	None reported
Gupta et al.	2010	Retro-spective Chart Review	30 (10 heart transplant)	Age at transplant: 6.9 (0.04-17.7) years Time to PTLD: 23.65 (3.8-104.6) months	1995-2008	Not reported	Rituximab, cyclophosphamide and prednisone used in 20% of cases. 2-year failure free survival was 80% for heart transplant patients with PTLD.	None reported
Giraldi et al.	2011	Case Series	2	Age at transplant: Patient 1: 24 months Patient 2: 36 months Age at PTLD: Patient 1: 41 months Patient 2: 32 months PTLD diagnosis Patient 1: DLBCL/ IIIB CD20, EBV LMP-1 Patient 2: Polyclonal Polymorphic	Case Series	375 mg/m2	Case 1: Complete remission after first induction cycle. Case 2: Partial remission after first induction cycle. 6 polychemotherapy-blocks given in 4 months. Rituximab administered 4 times	None reported
Chen et al.	2012	Case Report	1	Age at transplant: 2 years Age at PTLD: 6 years Solid lip tumor classified as monomorphic PTLD with diffuse large B-cell lymphoma	Case Report	375 mg/m2 per week for 4 weeks	Reduction in immunosuppression, ganciclovir, and rituximab resulted in undetectable viral load Patient remained in full remission with a negative EBV-DNA 12 months following treatment	None reported
Nelson et al.	2013	Case Report	1	Age at transplant: 11 years Age at PTLD: 11 years (5 moths post heart transplant)	Case Report	Not reported	Reduction in immunosuppression, rituximab, and methotrexate. Did not achieve remission with rituximab alone. Alternative therapies considered	None reported
Mahapatra et al.	2014	Case Report	1	Age at transplant: 20 months Age at PTLD: 7 years Monomorphic, CD20+ EBV + PTLD with CNS involvement	Case Report	Not reported	Reduction in immunosuppression reduction, rituximab, systemic and intrathecal chemotherapy. Complete clinical and radiologic remission, sustained > 46 months.	None reported
Bhatt et al.	2017	Case Report	1	Age at transplant: 3 weeks Age at PTLD: 9-year-old Sinusoidal CD30+ DLBCL in PTLD	Case Report	700 mg/m2 x 2 doses (induction I and II) 375 mg/m2 x 2 doses (consolidation I and II)	Patient remained in remission at 12 months post therapy completion	None reported

Bata et al.	2018	Case Report	1	Age at transplant: 3 years Age at PTLD: 8 years PTLD with extra nodal marginal zone lymphoma (ocular)	Case Report	325 mg/m2 systemic weekly x 4 doses 0.1 mg in 0.1 mL intraocular injections weekly x 4 weeks	One week following last injections, cellular reaction and iris masses resolved. 8 months following initial injection, no signs of ocular toxicity.	None reported
Arshad et al.	2019	Retro-spective single center study	24	Age at transplant: 7.9 (2.9-12) years Age at PTLD: not reported	1992-2018	Not reported	15/24 patients: rituximab with reduction in immunosuppression and chemotherapy. Freedom from disease recurrence and death: 1 year: 73.9% (n = 17) 3 years: 52.1% (n = 12) 10 years: 47.8% (n = 11)	None reported
Kim et al.	2019	Retro-spective review	19	Age at PTLD: 7 (1-15) years Time to PTLD: 3.1 (0.8-9) years	2005-2018 Rituximab if EBV viral load > 40,000 copies/mL.	375 mg/m2	In all patients, EBV DNAemia eradicated after a median (range) 9 (3-20) days; PTLD did not re-occur.	Fever (n=1) Unrecovered B-cell counts
Xue et al.	2020	Case Report	1	Age at transplant: 8 months Age at PTLD: 18 months EBV+ monomorphic plasma cell myeloma type PTLD	Case report	Not reported	Rituximab, ganciclovir, IVIG, dexamethasone, and bortezomib Sirolimus restarted due to concern for rejection.	None reported

Abbreviations: ANC: Absolute neutrophil count; CNS: Central nervous system; DLCL: Diffuse large cell lymphoma; EBV: Epstien-Barr virus; IVIG: intravenous immunoglobulin; PTLD: Post-transplant lymphoproliferative disease; WBC: White blood cells.

Table 4: Management of cytopenias with rituximab in pediatric cardiac transplantation.

Authors	Year	Design	Number of Patients	Patient Characteristics	Methods	Rituximab Dosing	Outcomes and Conclusions	Adverse side effects
Chitlur et al.	2005	Case Report	1	Age at transplant: 3 months Neutropenia & thrombocytopenia. Tacrolimus therapy switched to cyclosporine/azathioprine. Mild improvement in ANC/platelets	Case report	374 mg/m2 for 4 doses weekly	WBC and ANC normalized; remained within range for 12 months without G-CS. Neutropenia responded to Rituximab. No impact on thrombocytopenia.	None noted
Tubman, et al.	2007	Case Series	3	Age at transplant: 4.5 years, 1 year, 7 months Time to cytopenias: 10 years 8 months, 8 years 10 months, 9 years 9 months	2002-2003	Patient 1: 375 mg/m2 for 4 doses Patient 2: 375 mg/m2 for 4 doses Patient 3: 375 mg/m2 for 3 doses	Post rituximab, CD20/CD19+ B lymphocyte counts fell to 0 in all patients, persisted for ≥ 4 months. Time to B cell return Patient 1: 4 months Patient 2: 6 months Patient 3: 6 months Duration of response Patient 1: 13 months Patient 2: 22 months Patient 3: 24 months	None reported

Schoettler et al.	2015	Single center, retro-spective chart review	19 (5 cardiac transplant)	Age at transplant: 12 (2-56 months) Time to cytopenias: 74 (13-112 months)	1995 to 2012 Review of SOT at center 6/19 patients received rituximab	Dose not reported	6 patients received rituximab Rituximab response rate (RR): AIHA RR: 75% ITP RR: 0%	Varicella zoster (n=1) Parainfluenza (n=1) Acquired hypogammaglobinemia (n=2)
Abongwa et al.	2017	Case Report	1	Age at transplant: 7 months Time to cytopenias: 7 months	Case Report	375 mg/m2 for 4 weekly doses	4 weekly doses rituximab improved anemia and reticulocytopenia. 1 week after infusion, patients did not require transfusions. Hemoglobin 11.3 g/dl, reticulocyte count 299 × 103/mm3, which resolved by 3-month follow-up	Noroviru, cellulitis, both resolved

Abbreviations: WBC: White blood cells; ANC: Absolute neutrophil count; AIHA: Autoimmune hemolytic anemia; ITP: Immune thrombocytopenia

therapy [46]. Tubman et al., reported 3 patients who developed cytopenias following cardiac transplant, and were treated with 375 mg/m^2. Following rituximab therapy, CD20/CD19+ B lymphocyte counts fell to zero in all patients and persisted for at least 4 months [47]. Schoettler et al. described the successful use of rituximab in 6 patients who developed cytopenias, with a response rate for AIHA of 75% [48]. Abongwa et al., also reported the use of rituximab in one patient who developed severe AIHA, and experienced improvement following rituximab therapy. One week after the first infusion, the patient was no longer transfusion dependent and was discharged home on a prednisone taper. The patient's hemoglobin was normal and reticulocyte count resolved by the 3-month follow-up [49]. Continued literature is necessary to understand and determine the impact of rituximab on cytopenias in pediatric cardiac transplant patients.

RISKS ASSOCIATED WITH RITUXIMAB USE

Although rituximab appears to be generally well tolerated and an effective therapy, there are some concerns related to its use. Infusion-related reactions, characterized by fever, rash, chills, nausea, and headache, may be common during the first infusion [50]. However, these reactions are typically milder and less frequent with subsequent infusions and premedication. Other serious side effects may include hypotension, neutropenia, thrombocytopenia, and bronchospasm. While rituximab has been used effectively to treat EBV viremia, concerns have been raised regarding the possible association between rituximab administration and increased risk of infections. However, most published reports discuss the development of hepatitis, cytomegalovirus (CMV) disease, and Pneumocystis jirovecii, but are from case series or smaller single-center adult renal transplant studies [51-54]. Furthermore, among studies evaluating allograft survival and function, infections are typically reported as a secondary outcome. Surprisingly, very few of the case reports and studies in the pediatric cardiac transplant population report any concerns for increased infections. This is likely due to the fact that the practice in most pediatric transplant programs is to administer monthly IVIG infusions following rituximab treatment until B cell recovery. For patients with active infections, rituximab should be used with caution. To evaluate and determine the association of rituximab administration with infection rates, further studies designed specifically to assess this are required.

SUMMARY & CONCLUSION

Rituximab has gained increased interest in the pediatric cardiac transplant population. The results from current case reports and small retrospective studies suggest benefit in reduction of donor specific antibodies (DSA)/PRA, decreased rejection rates, and improvements in cytopenias. More evidence from larger studies is needed to establish the effect of rituximab for management of these complex conditions in pediatric cardiac transplantation.

While the literature in pediatric cardiac transplantation reports minimal side effects, there is concern related to an increase in infectious complications associated with the administration of rituximab, although this may be associated with repeated doses of rituximab. The major concern of rituximab for induction therapy has been related to a higher risk of cardiovascular complications, and warrants further investigation.

Rituximab has proven to be a valuable addition to the pharmacological repertoire for cardiac transplantation. Its utilization in clinical practice provides additional insight into the role of B cells in the occurrence of acute and chronic rejection, as well as, management of cytopenias. Studies that are developed to answer such questions in the pediatric cardiac transplant population would also add to the knowledge regarding the complex role and interaction of the various components of the immune system, specifically B and T lymphocytes.

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