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Safety of mTOR inhibitor continuation in pediatric heart transplant recipients undergoing surgical procedures

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Abstract

mTOR inhibitors have been associated with SWC when used in the perioperative period. Limited literature is available to guide providers in managing chronic mTOR inhibitor use in the perioperative period, especially in the pediatric setting. The primary aim of this study was to describe the prevalence of SWC with mTOR inhibitor continuation during the perioperative period for major surgeries. Heart transplant recipients 25 years old at the time of primary heart transplant receiving sirolimus maintenance therapy during a surgical procedure and within the study period were included. Surgeries identified within the study period included otolaryngology procedures (46.2%), such as tonsillectomies with or without adenoidectomies, cardiac surgeries (30.8%) including a sternal revision, pulmonary vein repair, and pacemaker placement in two patients, orthopedic surgeries (15.4%) including a posterior spinal fusion and an Achilles tendon lengthening with ankle and subtalar joint release, and a neurosurgery (7.7%), which was a ventriculoperitoneal shunt revision. Thirteen surgical encounters were examined. One SWC was observed, an infected pacemaker requiring systemic antibiotics and removal of the device. The results of this study suggest that sirolimus may be continued in the perioperative period based on the low rate of SWC observed.

Keywords

pediatric heart transplant; postoperative complications; sirolimus; wound healing

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AUTHORS' CONTRIBUTIONS

All listed authors contributed to study concept/design, data analysis, drafting and critical revision, and approval of the article. Jane Gralla: Contributed to statistical analysis.

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1 INTRODUCTION

mTOR inhibitors are used as immunosuppression in pediatric heart transplant recipients due to their beneficial properties, including renal sparing and antiproliferative effects. In addition, mTOR inhibitors have been proven to slow the progression of CAV, which is a leading cause of death and retransplant.^{1,2} mTOR inhibitors disrupt T-cell proliferation and result in immunosuppressive effects; however, the concurrent disruption of endothelial cell and fibroblast proliferation impairs appropriate wound healing.³ Controversy exists regarding mTOR inhibitor use in the perioperative period and the risk of SWC. The reported incidence of SWC is between 8% and 40% of patients receiving an mTOR inhibitor at time of heart transplant.^{4,5}

Current literature discusses the association of SWC with de novo use of mTOR inhibitors following initial heart transplant. However, there are no universal recommendations for the management of mTOR inhibitors during the perioperative period for major surgeries occurring post-heart transplant. It is unclear whether the risk of SWC associated with preoperative mTOR inhibitor use outweighs the risk of changing the patient's baseline immunosuppressive regimen, including cardiac rejection, renal dysfunction, or CAV progression. Knowing that practice variability exists, and that there is potential for risk with either approach, the aim of this study was to describe the prevalence of SWC associated with mTOR inhibitor continuation during the perioperative period following major surgeries.

2 METHODS

A retrospective review was conducted using the electronic medical record between 5/1/2007 and 5/31/2016. The electronic medical record was reviewed between 90 days preoperatively and 90 days postoperatively to identify patient demographics, risk factors, and SWC. Institutional review board approval was obtained for this study.

2.1 Patient population

Heart transplant recipients less than or equal to 25 years old at the time of primary heart transplant who were receiving mTOR inhibitor maintenance therapy were identified. Patients who underwent a surgical procedure at Children's Hospital Colorado while continuing mTOR inhibitor therapy during the study period were included. Patients were excluded if they received chemotherapy within 1 year of surgery or if there was a lack of clarity regarding mTOR inhibitor use during the perioperative period. Major procedures were defined as those procedures requiring general anesthesia and removal of an organ or tissue, cardiac surgeries, extensive orthopedic procedures, or need for extensive skin incision. Minor procedures, including cardiac catheterizations, myringotomy tube placements, ocular procedures, percutaneous biopsies, gastrostomy tube replacements, and other surgical procedures requiring only conscious sedation or local anesthesia, were excluded.

2.2 Measures

SWC were defined as the need for surgical re-intervention, wound dehiscence, delayed wound healing, lymphocele, incisional hernia, delayed sternal closure, pericardial effusion,

pleural effusion requiring a chest tube for at least 5 days, or wound infection as documented in the medical record.

Data regarding mTOR inhibitor use was obtained including the dose (mg/m²) and corresponding trough concentration within 30 days prior to the surgery, target trough concentration range, duration of mTOR inhibitor therapy, and indication for use. The concomitant immunosuppressive medications were collected.

Risk factors associated with SWC were collected, including BMI, corticosteroid use, diagnosis of diabetes mellitus, anticoagulant use, and nutritional status. Pre- and postoperative anticoagulation included the use of therapeutic heparin and heparin-containing products, vitamin K receptor antagonists, direct thrombin inhibitors, factor Xa inhibitors, aspirin, or other antiplatelet medications within the 7 days prior to and following the surgical procedure. Pre- and postoperative nutritional status was defined as the primary route of nutrition providing majority of kilocalories within the 7 days prior to and following the surgical procedure.

2.3 Statistical analysis

Descriptive statistics were used to identify the prevalence of SWC in patients continued on mTOR inhibitors during major surgery. Study data were collected and managed using REDCap electronic data capture tools hosted at the University of Colorado Denver.

3 RESULTS

3.1 Demographic and clinical variables

Of 111 heart transplant recipients on maintenance mTOR inhibitor therapy, 13 surgical procedures occurred in 12 patients receiving mTOR inhibitors during the study period. All patients were receiving sirolimus. One patient had two surgeries occurring greater than 90 days apart, and these were included as separate episodes.

The demographic and clinical variables for each surgery are shown in Table 1. The most common type of surgeries was otolaryngology procedures (46.2%), which included tonsillectomies with or without adenoidectomies in all patients. Cardiac surgeries (30.8%) included a sternal revision, pulmonary vein repair, and pacemaker placement in two patients. Orthopedic surgeries (15.4%) included a posterior spinal fusion and an Achilles tendon lengthening with ankle and subtalar joint release. The single neurosurgical procedure (7.7%) within the study was a ventriculoperitoneal shunt revision.

All patients had received an mTOR inhibitor for at least 10 days prior to surgery, and the most common indication for mTOR inhibitors was CAV progression. The mean sirolimus trough concentration obtained within 30 days prior to surgery was 4.8 ng/mL. Table 2 illustrates the additional immunosuppressive medications utilized by both groups. The most frequent combination was cyclosporine in addition to sirolimus (38.5%). The mean trough concentration of cyclosporine was 148.4 ng/mL, and the mean tacrolimus trough concentration was 6.7 ng/mL. Mycophenolate was received by five of 13 (38.5%) patients. The mean mycophenolate trough concentration was 2.5 µg/mL.

Risk factors for SWC were assessed. The mean BMI was $16.4 \pm 4 \text{ kg/m}^2$. No patients had diabetes mellitus, and all patients were receiving enteral nutrition postoperatively. Anticoagulation was received by 46.2% of patients preoperatively and 69.2% of patients postoperatively. The majority of these patients were receiving aspirin for CAV. Two patients received corticosteroid therapy. One patient, who underwent an adenoidectomy, was receiving prednisolone as part of their primary immunosuppressive regimen. Another patient, who underwent placement of an epicardial pacemaker, was treated for rejection 8 days prior to the surgery. This patient received high-dose methylprednisolone for a short course prior to surgery and high-dose methylprednisolone with three doses of thymoglobulin during the week following the procedure.

3.2 SWC

One SWC was identified within the study period. The single SWC was identified in a 9-year-old male who underwent a transvenous pacemaker placement. The patient was receiving triple immunosuppressive therapy with sirolimus, and tacrolimus with recent trough concentrations of 5.3 ng/mL and 8.4 ng/mL, respectively, combined with azathioprine. Seventeen days after the procedure, the patient developed fever, pain, and tenderness of the right arm and chest. A pacemaker infection was suspected, the pacemaker was removed, and methicillin-susceptible *Staphylococcus aureus* was cultured from the pacemaker site. The patient was successfully treated with 2 weeks of antibiotic therapy.

No episodes of wound dehiscence, delayed wound healing, lymphocele, incisional hernia, delayed sternal closure, or pericardial effusion were identified in any patient.

4 DISCUSSION

Limited literature examines the use of mTOR inhibitors in the perioperative period. A retrospective study in adult heart transplant recipients identified significantly more postsurgical wound complications, pleural effusions, and deep SWC with de novo sirolimus use. The study suggested that delayed initiation of sirolimus following initial heart transplant may be beneficial.⁶ In non-cardiac surgeries, low rates of SWC were identified in six adult liver transplant recipients receiving mTOR inhibitors while undergoing major abdominal or thoracic surgeries.⁷ Specific to the pediatric population, Goldberg et al examined postoperative complications with ongoing sirolimus use during heart retransplant or VAD placement. All patients receiving sirolimus developed pleural effusions, and three patients developed bacterial infections. The authors concluded that because an increase in mortality was not observed, continuing sirolimus prior to retransplant is an acceptable option.² In our own center, sirolimus has been continued in some patients prior to retransplantation, but is discontinued at the time of retransplantation. Patients undergoing retransplantation were not included in our assessment of the effects of continuation of mTOR inhibitors during the perioperative period of major surgeries.

To our knowledge, this is the largest study describing mTOR inhibitor use continued throughout the perioperative period in pediatric heart transplant recipients undergoing major surgery. One surgical wound infection was observed which required re-intervention for removal of an infected pacemaker. It is difficult to attribute this SWC solely due to sirolimus

use as there may have been other factors contributing to this finding. No SWC were observed for the other surgeries examined including otolaryngology procedures such as tonsillectomies and adenoidectomies, a ventriculoperitoneal shunt revision, or orthopedic procedures such as a posterior spinal fusion.

Within the study presented here, there was a low overall prevalence of risk factors for SWC. Corticosteroid use was low overall, but one patient did receive corticosteroids as part of treatment for cardiac rejection. SWC did not occur in this patient or the patient receiving corticosteroids as primary immunosuppression. The mean BMI was below the obesity cutoff for the average patient age suggesting that these patients were not at increased risk for SWC due to obesity. Additionally, higher mTOR inhibitor trough concentrations and doses have been linked to SWC.⁸ The overall mean sirolimus trough concentration in this study of 4.8 ng/mL was on the lower end of the recommended range for heart transplant potentially minimizing risk for SWC. Low trough concentrations for mTOR inhibitors are targeted at our institution because mTOR inhibitors are often combined with calcineurin inhibitors.

There are several limitations of this study. Data were collected retrospectively from the medical record increasing the risk of misclassification and recall bias. Because of the descriptive nature of this study, definitive conclusions cannot be made. Although this study is larger than previous studies, the small sample size may have limited the number of SWC observed.

Larger, prospective studies are needed to provide firm recommendations for the management of mTOR inhibitors in pediatric patients undergoing major surgery to result in optimal patient outcomes. The results of this study suggest that continuation of sirolimus in the perioperative period may not carry an increased risk of SWC, at least when used at relatively low target levels as in this cohort of pediatric patients.

5 CONCLUSION

Limited literature is available surrounding the use of mTOR inhibitors during the perioperative period for children undergoing major surgery. The results of this study suggest that sirolimus may be continued in the perioperative period in pediatric heart transplant recipients undergoing surgical procedures, not including retransplant, based on the low rate of SWC observed.

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Abbreviations

BMI body mass index

CAV	cardiac allograft vasculopathy
mTOR	mammalian target of rapamycin
SWC	surgical wound complications
VAD	ventricular assist device

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TABLE 1

Demographic and clinical variables

Variable	Surgical encounters (n = 13)
Age at time of surgery (years), mean (SD)	10.8 (6.4)
Male gender, n (%)	7 (53.8)
Weight (kg), mean (SD)	33.8 (21.9)
Height (cm), mean (SD)	133.6 (39.6)
BMI (kg/m ²), mean (SD)	16.4 (4)
BSA (m ²), mean (SD)	1.2 (0.5)
Pre-op absolute neutrophil count (cells/mm ³), mean (SD)	3.8 (1.9)
Surgical procedure, n (%)	
Otolaryngology	6 (46.2)
Cardiac surgery	4 (30.8)
Orthopedic	2 (15.4)
Neurosurgery	1 (7.7)
Sirolimus daily dose (mg/m ²), mean (SD)	0.29 (0.16)
Sirolimus trough concentration prior to surgery (ng/mL), mean (SD)	4.8 (2.2)
Indication for mTOR inhibitor, n (%)	
CAV progression	10 (76.9)
CNI sparing	1 (7.7)
Other	2 (15.4)

TABLE 2

Additional immunosuppressive medications

Medication	Surgical encounters (n = 13)
Cyclosporine, n (%)	5 (38.5)
Cyclosporine + azathioprine, n (%)	2 (15.4)
Cyclosporine + mycophenolate, n (%)	2 (15.4)
Tacrolimus + mycophenolate, n (%)	2 (15.4)
Tacrolimus + azathioprine, n (%)	1 (7.7)
Tacrolimus + mycophenolate + prednisolone, n (%)	1 (7.7)