SIROLIMUS EFFICACY IN THE TREATMENT OF CRITICALLY- ILL INFANTS WITH CHYLOUS EFFUSIONS

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Abstract

Background: While rare in children, chylothorax is a significant cause of respiratory morbidity and can lead to malnutrition and immunodeficiency. Historically, the traditional pharmacological treatment has been octreotide. There are several treatments that have been utilized in the past few years including sirolimus, however data regarding their efficacy and outcomes is limited. Furthermore, sirolimus has proven efficacy in complex vascular malformations, and hence, its utility/efficacy in pediatric chylous effusions warrants further investigation. Methods: In this retrospective study at Texas Children's Hospital, data were extracted for all patients with chylothorax who were treated with sirolimus between 2009 and 2020. Details regarding underlying diagnosis, co-morbidities and number of days from sirolimus initiation to resolution of effusion were collected. Descriptive statistics were used to analyze the study cohort. Results: Initially a total of twelve infants were identified. Among them, seven patients had complete data and were included in the study. The mean duration of sirolimus treatment needed for chest tube removal was 16 days, with a median of 19 days and range of 7- 22 days. Chest tube output corresponded with sirolimus serum trough levels and trended down prior to chest tube removal. Conclusion: With close monitoring, sirolimus is a safe and effective therapy for pediatric lymphatic effusions even in critically-ill infants. The study also demonstrates shorter duration of chest tube requirement after initiation of sirolimus compared to previous studies. Our conclusion is based on a small case series due to the rare incidence of the condition.

INTRODUCTION

Chylothorax is the accumulation of chyle or lymphatic fluid in the pleural space. While rare in children, chylothorax is a significant cause of respiratory morbidity and can lead to depletion of fluids, proteins, immunoglobulins, and lymphocytes, eventually leading to malnutrition and immunodeficiency.[1,2] There are five main etiologies: congenital, traumatic, high central venous pressure, malignancies, and miscellaneous (which includes infections).[1,3,4] Patients with chylothorax often present with respiratory symptoms including dyspnea, cough, and non-pleuritic chest pain. In traumatic causes of chylothorax, patients can have cardiorespiratory symptoms due to rapid chyle accumulation in the pleural cavity. However, in nontraumatic causes the symptoms have a slower onset and progression.[5]

Typically, treatment of large pleural or lymphatic effusions involves a chest tube with quantification guiding management. Many hospitals use drainage output as a guide to quantify clinical improvement or failure (<10 mL/kg per day of pleural drainage is considered improvement; >10 mL/kg per day of pleural drainage is considered failure after four weeks of nonsurgical management).[3,6]

Management for chylous effusion further includes dietary modifications to limit chyle-forming elements in the diet. Dietary management requires a fat-free diet with medium-chain triglycerides, available as enteral

formulas or total enteric rest requiring total parenteral nutrition, which is a more aggressive option.[1] Use of conservative enteral or complete parenteral nutrition for one to three weeks resulted in resolution of the chylothorax in 80% of the patients if the effusion was not secondary to lymphatic anomalies[6]. However, if the effusion is due to a "mal"-formation in the lymphatic vasculature, placing the patient "nothing per oral" (NPO) is not sufficient as the effusion will persist but will not be chylous anymore. In these cases, while diet is useful in treatment, patients rarely have chylothorax resolution with diet alone.

Traditionally, octreotide has been the first-line pharmacologic treatment. In Shah and Sinn's study, five of six patients with congenital chylothorax had resolution of effusion with octreotide with a median treatment of 20 days.[7] In a systemic literature review of 35 children with chylothorax who were given octreotide, Roehr et. al found most studies reported a significant decrease in drainage within five to six days.[8] While there are studies noting its efficacy, larger studies have found equivocal results. In a 2017 study of 178 neonates with chylothorax, Church, et. al found the addition of octreotide to dietary management of chylothorax revealed no significant differences in any outcome including success.[9] Stated otherwise, octreotide added no measurable benefit over dietary management. Likewise, a 2010 Cochrane review of twenty case reports (no randomized controls identified) noted resolution of chylothorax in 14 of 20 neonates with treatment with octreotide; however, the researchers found no drastically beneficial effect.[10]

New alternatives such as sirolimus are now increasingly being utilized. Sirolimus is a mammalian target of rapamycin (mTOR) inhibitor derived from *Streptomyces hygroscopicus* . Because of the role of mTOR in cell proliferation and angiogenesis, an overactive mTOR pathway due to activating mutations of its components has been implicated in diabetes, cancer, neurological diseases, genetic disorders, vascular anomalies and lymphatic anomalies.[11] Sirolimus is considered a strong agent against lymphatic anomalies given its part in cell growth regulation and in the vascular endothelial growth factor (VEGF) pathway.[1] Sirolimus has been shown to significantly reduce lesion size in tuberous sclerosis and lymphangioleiomyomatosis, which both involve mutations upstream from mTOR.[12]

A recent systematic review of sirolimus as a treatment for lymphatic malformations found that treatment with sirolimus led to a partial remission of disease in 60 of 71 patients studied (three patients had progressive disease and eight patient outcomes were not reported).[11] While sirolimus is currently being used in treatment of chylothorax, its use and efficacy need continued studying to create better treatment guidelines.

OBJECTIVE

The purpose of this study is to describe our center's experience with sirolimus for the treatment of chylous effusions in critically-ill infants and determine the duration of treatment needed to resolve chylous effusions.

METHODS

Study Design

This study was a retrospective chart review of all infants with a diagnosis of chylothorax at Texas Children's Hospital (TCH) who received sirolimus as treatment between January 1st 2009 and December 31st 2020. Institutional Review Board approval was obtained through the Baylor College of Medicine prior to undertaking this study. Informed consent and authorization were waived as the chart review was completed retrospectively and no direct patient contact was required for study completion.

Study Population

Data were extracted for all eligible patients. Inclusion criteria included patients less than 1 year of age who received sirolimus treatment primarily for the management of chylous effusion and required chest tube for the management of effusion due to respiratory distress. Patients of both genders and all races/ethnicities were included. Patients were excluded from the study if they did not have a chest tube at the time of treatment initiation with sirolimus, or had incomplete documentation of chest tube output after sirolimus was started.

Chart Review Protocol

Data were collected from the patients' electronic medical records. Charts were reviewed for demographic information, including age and gender, volume of chest tube output, sirolimus blood level, duration of chest tube placement, other medical and dietary interventions, lymphatic anomaly diagnosis, and co-morbidities. Day 0/Hour 0 was the time of first sirolimus dose. The data from the patients' charts were recorded in an Excel spreadsheet with all patient identifiers removed.

Chylous effusion was diagnosed by pleural fluid analysis findings consistent with lymphocyte content of >80%, pleural fluid triglyceride level >110 mg/dL and ratio of pleural fluid to serum cholesterol <1.0. The vascular anomalies team was involved in the care of all these patients. Our institutional guidelines for use of Sirolimus are as follows. The starting dose of sirolimus is based on age (0.4mg/m2/dose for patients younger than 6 months and 0.8mg/m2/dose PO or NG/G-tube q12h). Sirolimus trough levels of 8-12 ng/mL are considered therapeutic. A trough level is checked after 72 hours to evaluate for toxicity as some newborns can reach the upper level of the range or even toxic troughs very early. In this case, the sirolimus is held and levels checked until they are back in range and dose adjusted/decreased as needed until reaching goal. If the level is low or within range, it is checked again at 1 week and adjusted at that point. During hospitalization, all patients had sirolimus levels at least weekly. Administration was interrupted during proven or suspected infections and restarted immediately afterwards.

Data Analysis

Descriptive statistics were used to describe the study population with no variables manipulated. Pre-existing data was reviewed for correlational and observational findings. We calculated the mean, median and range of sirolimus duration of treatment required for chest tube removal. The rate of chest tube output after initiation of sirolimus treatment was recorded and plotted.

RESULTS

Demographics

The preliminary database consisted of twelve charts identified as eligible patients. Of those patients, seven met the inclusion criteria and were included in the final analysis. The remaining patients did not have chest tube output data available post sirolimus initiation and therefore were excluded. Age at diagnosis ranged from 3 days to 8 weeks old. There were five males (71.4%) and two females (28.6%). Patient A had a central conducting lymphatic anomaly (CCLA). Patient C was suspected RASopathy syndrome, in particular concern for Costello syndrome (but genetic studies were not completed). The other five patients had clinical diagnosis of generalized lymphatic anomalies, but due to their critical state, no lymphangiogram was performed to fully investigate the integrity of the lymphatic central system. The cohort of patients described have a very high morbidity index, are newborns (some premature) and the prognosis was poor from diagnosis. Three patients (two, three and four weeks old at sirolimus initiation) have since died at 2 months, 8 months and 3.5 months of age respectively due to severe co-morbidities. Other four patients are alive at the time of writing this manuscript.

Each patient's clinical course on sirolimus has been briefly detailed as below (Table 1):

Patient A

This patient was a term infant girl who had a history of transient myeloproliferative disorder (TMD) of Down syndrome in the first couple of weeks of life, and Atrial Septal Defect. Shortly after the TMD resolved, she was found to have a chylous pleural and pericardial effusion and CCLA was diagnosed by MR lymphangiogram. Sirolimus was initiated at 3 weeks of age. The initial dose of sirolimus was 1.6 mg/m2/day via NG tube. This patient had 3 chest tubes at the beginning of sirolimus therapy. Chest Tube #1 had initial drainage of 102 mL noted on day 8 which decreased to 33 mL by day 13, and further minimized until chest tube removal on day 17. Chest Tube #2 had initial output of 130 mL on day 12. Drainage was minimal by days 17-20 with eventual removal on Day 20. Chest Tube #3 had 8 mL output on day 17 and tube was removed the next day. Sirolimus level was supratherapeutic on days 2, 12, 15, and 16 at 24, 29, 28 and 21 ng/ml respectively. Day 12 supratherapeutic levels coincides with increased output from Chest Tube

#2 and days 15 and 16 with increased output from Chest Tube #3 (Figure 1). She was discharged home on sirolimus without chest tubes and clinically stable almost one month later. The patient was re-admitted at 8 months of age due to acute respiratory failure secondary to human metapneumovirus pneumonia and passed away.

Patient B

This patient was a 6-week old baby boy born at 37 weeks gestational age, diagnosed in utero with low urinary tract obstruction and prune belly syndrome s/p placement of vesico-amniotic shunts x3. At birth, he was found to have bilateral pneumothoraces, pneumomediastinum and pneumopericardium and bilateral chylous effusions s/p bilateral pigtail placement. He also required hemodialysis 3-4 times/week. Due to significant chylous effusion and inability to clamp or remove the chest tubes, the vascular team was involved and treatment with sirolimus was initiated at 6 weeks age. The initial dose of sirolimus was 0.6 mg/m2/day PO, comparatively lower due to poor renal function. He had two chest tubes. Chest Tube #1 had initial output of 2 mL on day 5, 34 mL on day 6, and 28 mL on day 8. Chest Tube #2 had drainage of 14 mL on day 12, 14 mL on day 14 and minimal drainage on days 15-19. Chest Tube #1 was removed on day 12 and Chest Tube #2 on day 19 (Fig 1). By day 20 sirolimus levels were therapeutic (longer time than usual due to renal dosing limitations). Sirolimus was continued for five more weeks without re-accumulation of pleural effusion or without need to replace chest tubes.

Patient C

This patient was a 2-week old critically-ill 32 week preemie with multiple medical complications including congenital heart block, hydrops, respiratory distress syndrome, chylothorax and chyloperitoneum. Clinical presentation was concerning for RASopathy syndrome, in particular Costello syndrome (genetic studies not completed). After a week trial of octreotide, vascular team was consulted and patient switched to sirolimus due to persistent significant chylous effusions. The initial dose of sirolimus was 1 mg/m2/day via NGT. Patient had extensive chest tube output initially– 220 mL, 860 mL and 300 mL on days 0, 1, and 2, respectively. Chest tube drainage markedly decreased by day 3 with 39 mL and was minimal by day 6 at 8 mL, and chest tube was removed on day 7. The sirolimus level remained subtherapeutic on day 6; however, by day 9 reached therapeutic levels (Fig 1). The patient passed away at two months of age due deteriorating cardiac function.

Patient D

This patient was a 4-week old infant born at 32 weeks at an outside hospital due to hydrops fetalis with Trisomy 21 and bilateral chylous pleural effusion secondary to lymphatic malformation. She was initially treated with octreotide at the outside facility but due to significant persistent chylous effusions even after two weeks, she was transferred to TCH and transitioned here to sirolimus at a starting dose of 0.8 mg/m2/day PO. There was large volume of chest tube output of 550 ml on day 0 which gradually decreased to 300 ml a week later, to less than 100 ml by day 15 and ultimately 10 ml on day 19, and chest tube removed on day 20 (Fig 1). Levels were supratherapeutic at the time of chest tube removal at 23 ng/ml, but no sirolimus-related toxicity noted. The patient was transitioned to comfort care measures only due to inability to control fluid overload, and passed away at 3.5 months of age.

Patient E

This patient was born at 35 weeks with a prenatally diagnosed congenital pleural effusion s/p pleural amniotic shunt. She required chest tube placement at birth and was started on sirolimus 0.8 mg/m2/day PO at one week of age due to persistent chylous effusion and inability to remove the chest tube. Initially chest output was low ranging from 0-3 ml/day, increased to maximum of 17 ml in a day and then decreased again to 0-5 ml/day. Chest tube was ultimately removed on day 15 (Fig 2). Subsequent sirolimus levels were therapeutic.

Patient F

This patient was a 8 week old ex-25 weeks preemie who was admitted for E. coli sepsis, presumed fungal

sepsis, respiratory failure and grade 4 Intraventricular Hemorrhage (IVH). He was noted to have diffuse anasarca and bilateral pleural effusions, which were initially attributed to ongoing infections. However, due to persistent anasarca and pleural effusions even after finishing the course of antibiotics and antifungals and repeated failed attempts to clamp the chest tube, vascular team was consulted for concern for congenital lymphatic malformation. Since initiation of sirolimus at a dose of 0.8 mg/m2/day PO, chest tube output decreased ranging from 6-24 ml/day and team was able to pull out the chest tube on day 14 (Fig 2). Sirolimus levels were therapeutic when checked on day 16.

Patient G

Patient G was born emergently at 35 weeks due to decreased fetal movements and fetal hydrops, and found to have bilateral pleural effusions at birth requiring chest tube placements. The vascular team was involved on day 3 of life due to significant ongoing chest tube output concerning for lymphatic malformation. He was started on sirolimus at a dose of 0.4 mg/m2/day via NGT. Had some interruptions to sirolimus in the beginning, due to intermittent discontinuation in the setting of infectious concern- necrotizing enterocolitis (NEC). Hence, initially the chest tube output was high and ranged 60-260 ml/day. However, by day 13 sirolimus trough was therapeutic and chest tube output was noted to come down with eventual removal of chest tube on day 23 (Fig 2). Patient was ultimately taken off sirolimus two weeks post chest tube removal due to concern for another infection. He did not develop any subsequent effusions.

Chest tube outcomes with sirolimus use

Duration of chest tube after initiation of sirolimus ranged from 7- 20 days, with a mean of 16 days and median duration of 19 days. There were some interruptions in treatment due to infections, but no other sirolimus-related toxicity. The number of infections was considered similar to patients in NICU of same age and co-morbidities and not a side-effect of sirolimus. The medication was held during all episodes of proven or suspected infections and/or neutropenia.

DISCUSSION

Our study focuses on lymphatic effusions caused by complicated lymphatic anomalies (CLAs) which included, in our series, generalized lymphatic anomaly (GLA) and central conducting lymphatic anomaly (CCLA). The average duration of sirolimus treatment needed for chest tube removal was 16 days in our patient cohort. This is shorter than what has been reported in previous studies with other interventions.

Use of conservative enteral or complete parenteral feeding for one to three weeks may result in resolution of the chylothorax when the effusion is not due to a lymphatic anomaly[6]. However, in patients with significant chylothorax and associated respiratory compromise (such as the patients described in our study) especially if the patient is too clinically unstable to completely image the lymphatic vasculature, conservative treatment alone is not adequate. Additionally, chylous effusions can lead to malnutrition and immunodeficiency due to loss of proteins and immunoglobulins in the chylous fluid. Given the associated complications, it is imperative to reduce the amount of pleural effusion promptly to alleviate the resulting respiratory compromise.

Octreotide has been the traditional pharmacologic treatment for chylothorax. A 2010 Cochrane Review and a 2017 study by Church et al. both found no significant benefit of the addition of octreotide to treatment regimens.[9,10] Although, it is important to note smaller studies illustrate its efficacy.[7,8] In our study, there were two patients (28.6%) who failed octreotide treatment prior to sirolimus initiation. The other five patients were started on sirolimus from the beginning due to confirmed or presumed lymphatic etiology.

This study validates previous studies which showed sirolimus led to partial remission of lymphatic disease.[11,13] A phase II clinical trial titled *Safety and Efficacy Study of Sirolimus in Complicated Vascular Anomalies* (n=61 patients) with 57 evaluable cases showed that 47 patients had a partial response, 3 developed stable disease and 7 - progressive disease. Only two patients required sirolimus discontinuation due to persistent adverse effects.[13] There are several case reports noting the reduction of lymphatic effusions post sirolimus treatment with an average time of 25 days to chylothorax resolution.[14-19] Based on our limited study population, response to sirolimus appears to be faster than previously reported.

Since this is a single center study, it is limited by a small size. While twenty patients were originally considered within the study criteria, inadequate chest tube drainage data and death prior to chest tube removal narrowed the study population to seven. All seven were critically-ill infants with a multitude of comorbidities. The clinical course for all these patients varied widely due to their disparities in age, and comorbidities. The incongruency in patients limits the extendibility of the research. Additionally, the study was limited by the variable data points of both sirolimus level and chest tube output. Future studies could be improved by measuring sirolimus at regular intervals post-initiation. Though efforts were made to quickly find appropriate dosing of sirolimus, the patients studied were at times subtherapeutic or supratherapeutic (which corresponded with changes in chest tube output). Tighter control of sirolimus levels would aid in finding the appropriate therapeutic range of sirolimus. To better control the confounding factors of the study, exclusion factors could be added to exclude patients with previous medical interventions (such as octreotide).

In conclusion, our study shows that with close monitoring, sirolimus is a safe and effective therapy for pediatric chylous effusions even in critically ill infants. Due to the rare incidence of the condition, our conclusion is based on a small case series. Larger multi-institutional studies will be needed to further support and confirm these findings.

Conflict of Interest

Authors have no conflict of interest to disclose.

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TABLES & FIGURES

Fig 1 Graphs showing sirolimus levels and chest tube drainage in patients A-D.

Fig 2 Graphs showing sirolimus levels and chest tube drainage in patients E-G.

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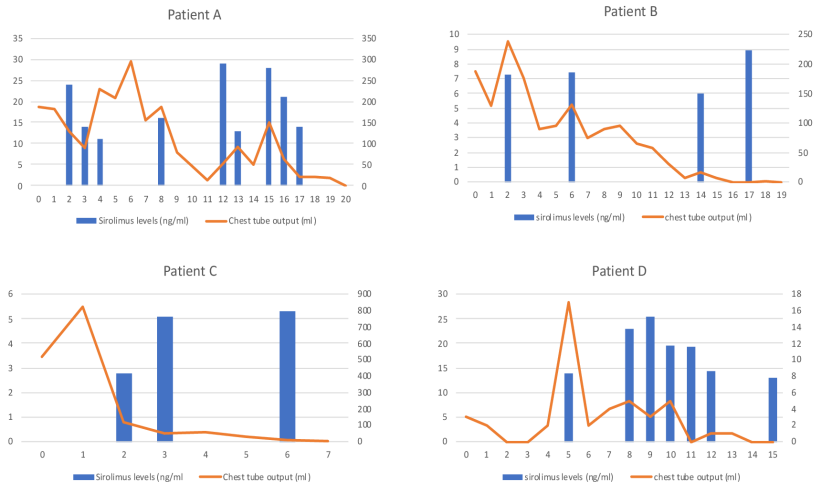
- **Fig 1 Graphs showing sirolimus levels and chest tube drainage in patients A-D.**



- **Fig 2. Graphs showing sirolimus levels and chest tube drainage in patients E-G.**