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Efficacy of Systemic Sirolimus in the Treatment of Generalized Lymphatic Anomaly and Gorham-Stout Disease

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Abstract

Background: Generalized lymphatic anomaly (GLA) and Gorham-Stout disease (GSD) are rare complicated lymphatic malformations that occur in multiple body sites and are associated with significant morbidity and mortality. Treatment options have been limited and conventional medical therapies have been generally ineffective. Emerging data suggest a role for sirolimus as a treatment option for complex lymphatic anomalies.

Procedure: Disease response was evaluated by radiologic imaging, quality of life (QOL) and clinical status assessments in children and young adults with GLA and GSD from a multicenter systematic retrospective review of patients treated with oral sirolimus and the prospective Phase 2 clinical trial assessing efficacy and safety of sirolimus in complicated vascular anomalies (NCT00975819). Sirolimus dosing regimens and toxicities were also assessed.

Results: Eighteen children and young adults with GLA (n=13) or GSD (n=5) received oral sirolimus. Fifteen patients (83%) had improvement in one or more aspects of their disease (QOL 78%, clinical status 72%, imaging 28%). No patients with bone involvement had progression of bone disease and the majority had symptom or functional improvement on sirolimus. Improvement

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CONFLICT OF INTEREST STATEMENT

The authors declare no conflicts of interest.

of pleural and pericardial effusion(s) occurred in 72% and 50% of affected patients; no effusions worsened on treatment.

Conclusions: Sirolimus appears effective at stabilizing or reducing signs/symptoms of disease in patients with GLA and GSD. Functional impairment and/or QOL improved in the majority of individuals with GLA and GSD with sirolimus treatment.

Keywords

lymphatic malformation; generalized lymphatic anomaly (GLA); Gorham-Stout Disease (GSD); sirolimus (rapamycin); lymphangiomatosis; mammalian target of rapamycin (mTOR)

INTRODUCTION

Generalized lymphatic anomaly (GLA), previously termed lymphangiomatosis, and Gorham-Stout or “vanishing bone” disease (GSD) are rare complicated lymphatic malformations (LM) that commonly involve multiple body sites such as the bones, thorax, spleen, retroperitoneum, soft tissues and gastrointestinal tract. Presenting across various medical and surgical sub-specialties, individuals with GLA and GSD commonly do not receive the correct diagnosis for months, years or even decades. Accurate and timely diagnosis is critical as patients with GLA and GSD frequently experience significant morbidity secondary to numerous complications such as respiratory issues, organ dysfunction, pathologic fractures, infection, functional impairment, disfigurement and death [1]. Although the clinical course of GLA and GSD is variable and unpredictable, certain clinical signs and symptoms appear to be associated with poorer prognosis including the presence of pleural and pericardial effusions, rib and vertebral involvement, and young age at presentation [2].

Treatment of GLA and GSD is also challenging. Surgical interventions such as excision, sclerotherapy and laser therapy are generally reserved for local control and symptom relief. Medical treatments have been limited and therapies such as steroids, interferon, and chemotherapeutic agents have produced variable outcomes. The largest obstacle in identifying or developing effective systemic therapies is a gap of knowledge in the pathogenesis of GLA and GSD. However, germline and somatic mutations involving vascular endothelial growth factor and the downstream phosphoinositide-3-kinase (PI3K)/Akt cell signaling pathway have been discovered in pure lymphatic malformations, combined vascular malformations with a lymphatic component as well as lymphedema syndromes [3–6].

Sirolimus (Rapamune®) is an inhibitor of mammalian target of rapamycin (mTOR), a kinase in the PI3K/Akt pathway which regulates numerous cellular processes including cellular catabolism and anabolism, cell motility, angiogenesis, and cell growth [7,8]. The prospective Phase 2 clinical trial (NCT00975819) by Adams et al. demonstrated that sirolimus was well-tolerated and efficacious in the treatment of multiple complicated vascular anomalies [9]. Although prospective clinical trials have been limited, numerous reports have been published on the efficacy of sirolimus treatment for LM as well as combined malformations with a lymphatic component [9–16]. This evidence, along with the identification of germline

and somatic mutations within the PI3K/Akt/mTOR and associated pathways in lymphatic disorders, supports the use of sirolimus for treatment of complex LM and associated complications.

METHODS

Study Design

To evaluate the safety and efficacy of sirolimus in the treatment of patients with GLA and GSD, data analyses were performed on the combined results from the prospective FDA-funded study, Clinical Trial Assessing Efficacy and Safety of the mTOR Inhibitor Sirolimus in the Treatment of Complicated Vascular Anomalies, and a retrospective systematic review of medical records of children and young adults treated with sirolimus at multiple approved institutions. The multicenter retrospective study of patient medical records was approved by the institutional review board at Cincinnati Children's Hospital Medical Center. The Phase 2 clinical trial was approved by the Data and Safety Monitoring Board of the Cancer and Blood Disease Institute at Cincinnati Children's Hospital Medical Center and the institutional review boards at Cincinnati Children's Hospital Medical Center and Boston Children's Hospital.

Patient Population

Inclusion criteria included male and female patients between the ages of 0 to 31 years with a diagnosis of GLA or GSD and complications necessitating systemic therapy for disease control as clinically determined by the treating provider. Sirolimus must have been initiated between January 1, 2007 and June 1, 2014 with a minimum treatment length of 3 months. Patients receiving other disease-modifying agents such as steroids or chemotherapeutic agents concurrently were excluded from the study. Patients with biopsy results or imaging findings concerning for kaposiform lymphangiomatosis were excluded.

Sirolimus Treatment

In the prospective study, the patients received the liquid formulation of sirolimus dosed at 0.8 mg per square meter of body surface area per dose, twice a day with dose adjustments for a goal trough level of 10–15 ng/mL. The patients in the retrospective study received an oral form (liquid or tablet) of sirolimus in once or twice daily dosing with dose adjustments to individualized goal trough levels, all targeted within the high-dose sirolimus level range (range 8–15 ng/mL). Drug toxicities were identified while on sirolimus therapy and graded in accordance with the Common Terminology Criteria for Adverse Events (version 3.0). Laboratory testing including hematologic and serum metabolic tests were also assessed for abnormalities.

Disease Evaluation

Patients enrolled in the prospective trial had disease response evaluations at 3, 6 and 12 months (end of study); only the end of study results were analyzed in this study. Disease response was assessed for patients on the retrospective study at the time of enrollment with an average treatment time of 19 months (range 9 to 36 months). Disease improvement was determined by radiologic imaging, health-related quality of life (HRQOL) measurements

and clinical status assessments. Disease responses for QOL, clinical status/functional impairment and radiographic imaging were categorized as improvement or no improvement; overall response was established by changes in at least one of these parameters. Response of pleural effusions, pericardial effusions and bone involvement were classified as complete resolution, partial improvement, no improvement and progression of disease based on radiographic and clinical status assessments. Response criteria is available in Supplemental Appendix 1.

Magnetic resonance imaging was the preferred method of radiologic evaluation, but computed tomography scans and radiographs were also used if deemed appropriate by each site's radiologist. Imaging was performed prior to starting sirolimus and at 12 months of treatment in the prospective study. At the time of enrollment in the retrospective study, baseline imaging was compared to all pertinent imaging obtained while on sirolimus therapy; changes in radiographic response occurred ≦ 15 months on sirolimus treatment in this group. Each study site's radiologist reviewed the imaging to determine changes.

Because no validated scales exist to evaluate clinical status/functional impairment in patients with vascular anomalies, an instrument, adopted from measures of organ function that have been validated in the quantification of adverse event results from medical therapies and procedures, was created for use in the prospective clinical trial; this instrument was also used to assess clinical status in the retrospective group (Supplemental Appendix 2).

In the prospective trial, HRQOL was evaluated with the use of the Pediatric Quality of Life Inventory (PedsQL 4.0) in children (3–18 years) and Infant Scales (<2 years) and the Functional Assessment of Chronic Illness system in adult patients (>18 years). In the retrospective trial, QOL improvement was determined based on subjective improvement in QOL per parent or patient report to the treating physician(s).

RESULTS

Patient Characteristics

Eighteen male and female children and young adults, 13 with GLA and 5 with GSD, were eligible for this study. Of these patients, 9 were from the prospective clinical trial and 9 were from the retrospective sirolimus study. All patients had radiographic imaging consistent with GLA or GSD. The diagnosis of GLA versus GSD was differentiated based on radiographic imaging of bone disease and the presence or absence of cortical bone destruction. Two patients without bone involvement had the diagnosis of GLA. Pathology was performed confirming the LM diagnosis in fourteen patients (9 from prospective study, 5 from retrospective study). Differences were not seen for age, sex and race/ethnicity of individuals in the retrospective versus the prospective study or between patients with diagnoses of GLA versus GSD (all p-values> 0.05, Fisher's exact test). The patient demographic characteristics are summarized in Table 1. Indications for sirolimus treatment were bone and/or visceral involvement including effusions (n=17, 94%), chronic pain (n=7, 39%), and cardiac dysfunction (n=2, 11%). During the follow up period, none of the patients had surgical interventions involving the malformation, including sclerotherapy, vessel ligation and/or

excision. Twelve patients (67%) had prior medical and/or surgical treatment(s), which are summarized in Supplemental Table 1.

Disease Response

Fifteen of the 18 patients (83%), 12 (92%) with GLA and 3 (60%) with GSD, had an overall partial response or improvement in at least one aspect of disease. As expected, no patients had complete response as this would require normalization of QOL and clinical status/functional impairment as well as complete resolution of all LM lesions on radiographic imaging. Clinical status/functional impairment improved in 83% of the patients with GLA and GSD and QOL improved in 78% with an average time to response of 2.7 months and 4.2 months, respectively. Only five patients (28%), 4 with GLA and 1 with GSD, demonstrated radiographic improvement of their lesions (Figure 1A and 1B). No patients were found to have progression of disease on radiologic imaging. One individual with GSD was on concomitant bisphosphonate therapy with zoledronic acid; this patient experienced improvement in bone symptoms and QOL upon the addition of sirolimus. Fisher's exact test (p-value<0.05) did not reveal differences between the retrospective versus prospective groups for overall disease response, QOL, clinical status and radiologic responses. Table 2 and 3 summarize the disease responses by diagnosis.

Sixteen (89%) of the individuals had LM involvement of the bones. Thirteen patients (81%) had known LM disease in the vertebrae and 8 (50%) in the ribs. Ten (62.5%) patients had improvement of symptoms or functional impairment. Only 1 asymptomatic patient with GLA and vertebral lesions had complete resolution of the bone LMs on radiologic imaging upon evaluation after 12 months of treatment. Bone disease did not progress in any patients while on sirolimus therapy. Additional information about bone involvement responses is located in the Supplemental Table 2.

Of the 7 patients with pleural effusions, 5 had a decrease in size, 2 of which had complete resolution of pleural effusion(s) on sirolimus treatment (Figure 1C and 1D). Four of these 5 patients with decreased pleural effusions also experienced cessation of respiratory symptoms. In patients with pleural effusions, 4 also had a concurrent pericardial effusion. No patients had a pericardial effusion in the absence of pleural effusion(s). Pericardial effusions completely resolved in 2 patients on sirolimus. No pleural or pericardial effusions worsened on sirolimus therapy. Effusion responses are further characterized in Supplemental Table 3 and 4.

Side Effects/Toxicity

The most common side effects were bone marrow suppression, mucositis/stomatitis and hypertriglyceridemia. Nine attributable (possible, probable or definite) grade 3 or 4 toxicities occurred in 3 patients, who were 14, 16 and 23 years of age. In these 3 patients, sirolimus was temporarily stopped until symptoms or laboratory values normalized but no dose reductions of sirolimus were required. One patient experienced grade 3 larynx edema associated with supra-therapeutic sirolimus levels (>15 ng/mL). Attributable grade 3 and 4 toxicities are summarized in Supplemental Table 5. One patient was removed from the prospective study due to grade 2 nausea (cessation of therapy >4 weeks) that affected QOL.

No patients contracted PJP pneumonia while on sirolimus therapy and concurrently taking PJP prophylaxis.

DISCUSSION

To date, this is the largest analysis of the use of sirolimus therapy in patients with the complex lymphatic malformations, GLA and GSD. Sirolimus appears to overall stabilize or reduce signs/symptoms of disease and improve QOL in these affected individuals. Importantly, sirolimus treatment demonstrated beneficial effect on disease risk factors associated with poorer prognosis. Furthermore, no patients experienced clinical or radiologic progression of their disease while on sirolimus, which is important given the unpredictable and progressive nature of these conditions.

Thoracic disease, particularly in the pediatric population, is associated with higher mortality rates than those without effusions or lung disease. In a review of 53 cases of thoracic involvement in GLA, Alvarez et al. reported that children under 16 years of age had a worse prognosis than older individuals (39% versus 0% mortality) [17]. Thoracic disease is less common in GSD than GLA but when present, is also associated with high morbidity [18–22]. In a study by Ozeki et al., overall mortality rate of GLA, GSD and KLA patients with thoracic symptoms was 20% over a 7-year period, whereas all patients without thoracic lesions survived. Furthermore, a quarter of children with thoracic lesions died [18]. In our study, nearly 40% of the patients with GLA and GSD had a pleural effusion with or without a pericardial effusion; the majority of patients with effusions experienced improvement in one or more associated complications including respiratory symptoms, functional impairment, QOL and/or imaging abnormalities. None of the patients had worsening of effusions or died on sirolimus therapy, which is also notable given the high morbidity associated with thoracic disease.

In addition to causing pain and/or functional limitations, bone lesions of the vertebrae and ribs, common sites of disease in GLA and GSD, may cause significant morbidity and mortality [1, 18]. Involvement of the thoracic cage (ribs, scapula, thoracic vertebrae and sternum) may lead to the development of pleural and/or pericardial effusions from secondary inflammation or from direct extension of LM into the lungs, pleura or mediastinum. Our study supports this association in that 86% of patients with pleural effusions and 75% of those with pericardial effusions had known rib and/or mediastinal involvement. Pathologic rib fractures may also cause direct injury to the lungs, heart, thoracic duct and abdominal organs as well as mechanical weakness of the chest wall, resulting in restrictive lung disease or respiratory failure [23]. Extension of the LM into the spinal canal can lead to increased intracranial pressure, mass effect of the spinal cord and CSF leaks while progressive osteolysis or pathologic fracture of the spine can cause severe neurological defects, deformity, paralysis, and even death. Our results suggest that the bone disease is stabilized on sirolimus as there was no bone lesion progression on radiologic imaging. Furthermore, over half of the patients with bone lesions had improvement in functional impairment and/or associated symptoms. Additionally, no patients developed pathologic fractures while on study. However, lack of long-term follow up precludes comment on whether sirolimus therapy decreases the incidence of pathologic fractures in this patient population. Lack of

resolution of bone disease is also not surprising given that the disease response assessments to sirolimus were performed on average of 12 months and 19 months, in the prospective and retrospective studies respectively. Compared to other tissues like skin or lungs, the time to sirolimus effect is likely prolonged for bone LM given the limited blood supply to the bones. Other lytic bone lesions such as those in multiple myeloma can take years to resolve on MRI after disease remission [24]. Additionally, despite successful treatment of symptoms and complications, imaging may be persistently abnormal since these radiographic lesions represent congenitally-derived LM within bones.

Multiple case reports and case series report poorer prognosis when patients with GLA and GSD present at an early age, particularly in those with thoracic disease [1, 17–19]. Because of small patient numbers representing the early childhood, older childhood, adolescence and early adulthood age groups, we are unable to definitively make conclusions about the severity of signs and symptoms of disease at a younger age. Similarly, efficacy of sirolimus treatment during different developmental time periods is difficult to explicitly define. Those patients with no response to sirolimus were 9, 15, and 23 years of age. First symptoms of disease or worsening complications in GLA and GSD have been also reported with periods of hormonal changes such as puberty. However, we are unable to comment on disease progression during puberty as this was not a primary assessment and requires further prospective investigation.

Small numbers of patients with GLA and GSD make prospective studies difficult to perform on the natural disease progression as well as to therapy response(s). The prevalence of GLA and GSD is also unknown but is generally accepted to be very rare. Although distinctly different diagnoses, GLA and GSD have similar disease courses including affected anatomic locations, complications and symptoms and individuals with these diseases, like those in our patient cohort, have historically received a multitude of prior therapies such as sclerotherapy, surgery, chemotherapeutic or immunomodulating agents. Because of the rarity of GLA and GSD, we analyzed the combined results of prospective and retrospective studies in order to improve inferences about the beneficial effects and the safety of sirolimus therapy in these conditions.

Obtaining adequate patient numbers for prospective studies is further complicated by frequent provider unfamiliarity and misdiagnosis of complex lymphatic anomalies due to overlapping clinical signs and symptoms, complications, imaging findings, and histology between GLA, GSD and other lymphatic anomalies. GSD can be differentiated from GLA by its progressive osteolysis with cortical bone destruction, typically in a contiguous manner, which may result in complete resorption and loss of entire bone(s). In contrast, GLA is associated with non-contiguous lytic lesions confined to the medullary cavity that typically involve multiple bones, particularly the appendicular skeleton, and generally does not result in entire bone loss [1, 25].

Importantly, GLA and GSD must be differentiated from kaposiform lymphangiomatosis (KLA) and central conducting lymphatic anomaly (CCLA), which are lymphatic anomalies that have similar presentations but are managed differently. Frequently confused with GLA, KLA is an aggressive lymphatic anomaly which can be differentiated by characteristic

clusters of intra- or perilymphatic spindle-shaped “kaposiform” endothelial cells on histology. Unlike GLA and GSD, KLA is associated with a life-threatening coagulopathy characterized by severe hypofibrinogenemia, thrombocytopenia and bleeding complications. Clinical presentation is typically severe, particularly at a young age, and mortality rate of KLA is high despite multi-modal therapy [26]. Although ISSVA recently classified KLA as a subtype of GLA, this remains controversial within the field given its tumor-like properties, along with the recent genetic discovery of NRAS mutations in KLA lesions. Because of its distinct phenotype and the need to typically treat with multiple concurrent disease-modifying agents, KLA was not analyzed in this study but sirolimus response is under current investigation.

Only recently recognized as a distinct entity, CCLA is a condition in which enlargement of lymphatic channels, dysmotility, or distal obstruction leads to stasis and reflux of lymph, resulting in effusions, blebbing, bone lesions and lymphangiectasia [1]. Treatments for CCLA are complication-based and remain mostly surgical but improvement with sirolimus has been reported in a few cases. Clinically differentiating CCLA from GLA is often difficult. Dynamic contrast MR lymphangiography can be used to assess for obstruction, degree of collateralization, and chylolymphatic reflux but this imaging technology, along with providers who have expertise in this technique, is limited to only a few centers in the country [27, 29]. Since the time period of this study occurred prior to the recognition of CCLA as a distinct diagnosis, there is the possibility of unintentional inclusion of CCLA patients in this analysis. However, care was taken to not include individuals with lymphangiectasia or dysfunction of the central channels responsible for lymphatic drainage as the main pathology.

There has been little published data specifically addressing sirolimus toxicity in patients with vascular anomalies [9]. In individuals with GLA and GSD, side effects of sirolimus have only been reported in case reports and small case series. Generally, the GLA and GSD patients in our study tolerated sirolimus without significant side effects. One patient did experience laryngeal edema secondary to supratherapeutic sirolimus levels, emphasizing the need for close monitoring. This study did not, however, evaluate for complications that may occur with long-term exposure to sirolimus. Chronic mTOR inhibition has been associated with glucose intolerance and insulin resistance, hyperlipidemia, and hypercholesterolemia, which all confer increased risk for the development of cardiovascular disease [29]. In addition to long-term complications associated with specific medications, there are general concerns for issues with fertility, growth and development, immune function, and secondary malignancies with chronic immunosuppression [30]. Although sirolimus appears to provide symptom relief and stabilize disease in patients with GLA and GSD, it remains unclear when to stop therapy and whether continuous therapy has ongoing benefit.

Limitations of this adaptive study design are related to inclusion of a non-prospective trial and the variable methods of data collection in the retrospective and prospective studies. Potential recall, selection and misclassification biases remain a concern even though the data collection methods for the retrospective study were modeled from the clinical phase 2 trial. Although ideal, a randomized prospective clinical trial of the efficacy and safety of sirolimus therapy [versus control/placebo] in patients with GLA and GSD is not feasible nor clinically

ethical given the significant morbidity associated with these conditions as well as the increasing support for subjective and/or objective benefits and good safety profile of sirolimus.

GLA and GSD are poorly understood diseases of the lymphatic system that have devastating complications with limited treatment options. Early and accurate diagnosis is critical for effective management given the progressive nature of these diseases. Based on these study results as well as published case series and reports, sirolimus appears to be a safe and well-tolerated treatment option that reduces symptoms and/or stabilizes disease in patients with GLA and GSD. Although the successes of sirolimus and other medications provide insight into these conditions, disease-specific clinical trials and basic science research studies are still urgently needed as much is still unknown about these rare disorders and their pathophysiology. Uncovering the genetics and molecular basis of GLA and GSD is key to the development of targeted therapies and/or novel uses of existing medications to ultimately improve disease outcomes and enhance quality of life for patients and their families.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Abbreviations:

CCLA	Central conducting lymphatic anomaly
GLA	Generalized lymphatic anomaly
GSD	Gorham-Stout disease
HRQOL	Health-related quality of life
KLA	Kaposiform lymphangiomatosis
LM	Lymphatic malformation(s)
mTOR	Mammalian target of rapamycin
PI3K	phosphoinositide-3-kinase
PJP	Pneumocystis jiroveci

QOL	Quality of life

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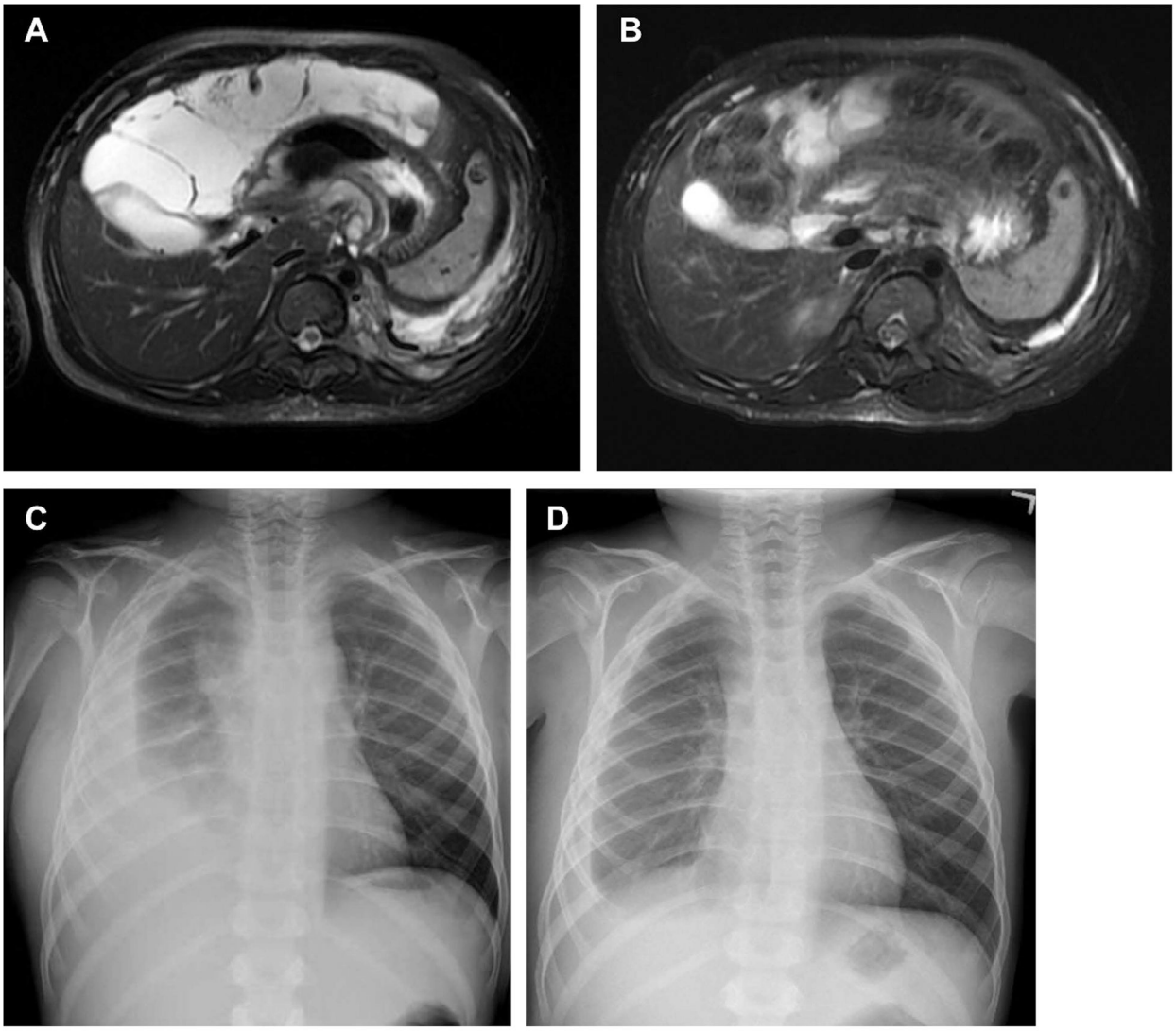

FIGURE 1:

Radiographic response with sirolimus treatment. A, Prior to initiation of sirolimus. MRI axial T2- weighted imaging of patient with a large intra-abdominal lymphatic malformation. This patient also had pleural effusions, diffuse bony disease, and lesions in the spleen and liver consistent with the diagnosis of GLA. B, 12 months on sirolimus therapy. MRI demonstrated substantial decrease in size of the intraabdominal malformation. C, Prior to initiation of sirolimus. Chest x-ray of a GLA patient with a right-sided pleural effusion. D, 3 months on sirolimus treatment. Chest x-ray exhibits near complete resolution of the right-sided pleural effusion.

TABLE 1

Patient Demographic Characteristics

Characteristic	Value (N = 18)
Gender, n (%)	
Male	8 (44)
Female	10 (56)
Median age, years	12.5
Age range, years	1–23.2
Age group, n (%)	
0–8 years	6 (33)
9–17 years	10 (56)
18–26 years	2 (11)
Race/Ethnicity, n (%)	
White-Non-Hispanic/Latino	14 (78)
White-Hispanic/Latino	1 (6)
Black-African American	1 (6)
White-Unknown Ethnicity	1 (6)
More than one race-Non-Hispanic/Latino	1 (6)

TABLE 2

Disease Responses in GLA and GSD Patients on Sirolimus Treatment

Response Category	GLA, n (%)	GSD, n (%)	GLA and GSD, n (%)
Overall			
Improvement	12 (92)	3 (60)	15 (83)
No improvement	1 (8)	2 (40)	3 (17)
Stable disease	1 (8)	1 (20)	2 (11)
Progressive disease	0	1 (20)	1 (6)
Clinical status			
Improvement	12 (92)	3 (60)	15 (83)
No improvement	1 (8)	2 (40)	3 (17)
Stable disease	1 (8)	2 (40)	3 (17)
Progressive disease	0	0	0
Quality of life			
Improvement	11 (85)	3 (60)	14 (78)
No improvement	2 (15)	2 (40)	4 (22)
Stable disease	2 (15)	1 (20)	3 (17)
Progressive disease	0	1 (20)	1 (6)
Radiologic imaging			
Improvement	4 (31)	1 (20)	5 (28)
No improvement	9 (69)	4 (80)	13 (72)
Stable disease	9 (69)	4 (80)	13 (72)
Progressive disease	0	0	0

TABLE 3

Disease Complication Responses to Sirolimus Treatment for GLA and GSD Patients

Complication Response	GLA, n	GSD, n	Total, n (%)
Pleural Effusion	**6**	**1**	**7**
Complete Resolution	2	0	2 (28.5)
Partial Improvement	3	0	3 (43)
No Improvement	1	1	2 (28.5)
Progressive Disease	0	0	0
Pericardial Effusion	**3**	**1**	**4**
Complete Resolution	2	0	2 (50)
Partial Improvement	0	0	0
No Improvement	1	1	2 (50)
Progressive Disease	0	0	0
Bone Involvement	**11**	**5**	**16**
Complete Resolution	1	0	1 (6)
Partial Improvement	7	3	10 (63)
No Improvement	3	2	5 (31)
Progressive Disease	0	0	0