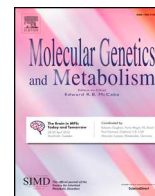




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Review article

Clinical relevance of endpoints in clinical trials for acid sphingomyelinase deficiency enzyme replacement therapy

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ABSTRACT

Background: Acid sphingomyelinase deficiency (ASMD) also known as Niemann-Pick disease, is a rare lysosomal storage disorder with a diverse disease spectrum that includes slowly progressive, chronic visceral (type B) and neurovisceral forms (intermediate type A/B), in addition to infantile, rapidly progressive fatal neurovisceral disease (type A).

Purpose and methods: We review the published evidence on the relevance of splenomegaly and reduced lung diffusion capacity to the clinical burden of chronic forms of ASMD. Targeted literature searches were conducted to identify relevant ASMD and non-ASMD studies for associations between diffusing capacity of the lungs for carbon monoxide (DL_{CO}) and splenomegaly, with clinical parameters and outcome measures.

Results: Respiratory disease and organomegaly are primary and independent contributors to mortality, disease burden, and morbidity for patients with chronic ASMD. The degree of splenomegaly correlates with short stature, atherogenic lipid profile, and degree of abnormality of hematologic parameters, and thus may be considered a surrogate marker for bleeding risk, abnormal lipid profiles and possibly, liver fibrosis. Progressive lung disease is a prevalent clinical feature of chronic ASMD, contributing to a decreased quality of life (QoL) and an increased disease burden. In addition, respiratory-related complications are a major cause of mortality in ASMD.

Conclusions: The reviewed evidence from ASMD natural history and observational studies supports the use of lung function and spleen volume as clinically meaningful endpoints in ASMD trials that translate into important measures of disease burden for patients.

1. Introduction

Interventional clinical trials require identification of reproducible endpoints that respond over a defined duration of therapy and, either directly or indirectly, reflect clinically meaningful improvement in patient mortality, morbidity, or quality of life. Most lysosomal storage diseases (LSDs) are ultra-rare, monogenic, multi-systemic diseases with heterogeneous disease spectra resulting from different pathogenic variants as well as individual genetic and epigenetic influences. Disease outcomes range widely, and include mortality in early childhood,

chronic lifelong symptoms that impart significant morbidity, and relatively benign disease with prolonged survival.

For chronic LSDs, the diversity and heterogeneity of slowly progressing disease manifestations makes identifying appropriate clinical endpoints for treatment trials challenging. Particularly problematic is quantifying clinical responses over the span of a typical rare disease clinical trial of 6–12 months. Unfortunately, surrogate biochemical markers may not be reliable indicators of disease progression or clinical status necessitating the selection of pharmacodynamic, functional, and histologic endpoints. In both pediatric and adult patients with chronic

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Table 1
Pivotal clinical trial endpoints for FDA approved compounds for the treatment of lysosomal storage disorders.

Disease	Compound Name	Therapeutic Class	Endpoints in Pivotal Clinical Trials
Mucopolysaccharidosis (MPS)			
MPS I	Laronidase	Enzyme	Forced vital capacity (% of predicted), 6 min walk distance
MPS II	Idursulfase	Enzyme	Forced vital capacity (% of predicted), 6 min walk distance
MPS IVA	Elosulfase alfa	Enzyme	6 min walk distance
MPS VI	Galsulfase	Enzyme	12 min walk distance, 3 min stair climb test (stairs/min)
Gaucher disease	Agglucerase*	Enzyme	Liver volume and spleen volume, hematologic deficiencies, bone mineralization, cachexia and wasting
	Imiglucerase	Enzyme	Anemia and thrombocytopenia, liver volume and spleen volume, cachexia
	Taliglucerase alfa	Enzyme	Hemoglobin concentration, platelet count, liver volume and spleen volume
	Velaglucerase alfa	Enzyme	Hemoglobin concentration, platelet count, liver volume and spleen volume
	Miglustat	Substrate reduction	Liver and spleen volume, hemoglobin concentration, platelet count
	Eliglustat	Substrate reduction	Spleen volume, and composite of spleen volume, liver volume, hemoglobin concentration, and platelet count
Fabry disease	Agalsidase beta	Enzyme	GL-3 inclusions in capillary endothelium of kidney, heart and skin
Pompe disease	Alglucosidase alfa	Enzyme	Mortality, invasive ventilator support, forced vital capacity (% of predicted), 6 min walking distance
Lysosomal acid lipase deficiency	Sebilase alfa	Enzyme	Alanine aminotransferase level, lipid level, hepatic fat content

Adapted from Mechler et al. [1].

* First enzyme replacement therapy drug approved. Manufactured from human placental tissue and subsequently withdrawn from the market with the advent of recombinant DNA technology approaches for drug development.

LSDs, improvement in the primary disease manifestation in one or more predominantly affected organs may be considered as representative of an improvement in overall clinical status for the disease process as a whole. Table 1 (adapted from Mechler et al. [1]), shows the various endpoints that have been used in pivotal clinical trials for enzyme replacement therapy (ERT) or substrate reduction therapy (SRT) in several LSDs.

The evaluation of therapeutic interventions for acid sphingomyelinase deficiency (ASMD), a rare LSD, has all of the aforementioned challenges. All patients with ASMD have a metabolic defect arising from sequence variants in the *SMPD1* gene (EC 3.1.4.12), resulting in deficiency of acid sphingomyelinase (ASM) activity leading to accumulation of sphingomyelin in certain tissues [2]. Despite the uniform underlying mechanism of disease, (i.e., deficient ASM activity), the spectrum of disease severity and clinical manifestations are driven by the heterogeneity of *SMPD1* mutations and resultant variable residual acid sphingomyelinase activity, as well as less understood cellular and molecular compensatory pathways [3]. The most severe form is ASMD type A (infantile neurovisceral, Niemann-Pick Disease [NPD] type A, OMIM#25707) [4], characterized by very low levels of residual ASM activity, rapid neurodegeneration, progressive psychomotor retardation, failure to thrive, and death by three to 4 years of age. Chronic forms include ASMD type A/B (chronic neurovisceral, intermediate form, NPD type A/B or NPD type B variant) [5] and ASMD type B (chronic visceral, NPD type B, OMIM#607616) [6] that are more slowly progressing and can manifest from infancy to adulthood with significant morbidity and often shorter life spans. Some neurologic involvement is present in ASMD type A/B, although much less severe than in ASMD type A, and may include neurocognitive delay, hypotonia, and peripheral neuropathy [5,6]. At present, there is no disease-specific treatment for ASMD, although olipudase alfa, a recombinant human ASM, is currently in clinical development for the chronic, systemic, non-neurologic manifestations of the disease [7,8]. Until a disease-modifying treatment is available, management of chronic ASMD is focused on palliation of symptoms and supportive care [9].

ASM deficiency disrupts the normal homeostatic cycle of cellular membrane phospholipid regulation by failing to break down sphingomyelin (a ubiquitous component of all cellular membranes), to its two components, phosphorylcholine and ceramide. The resultant accumulation of sphingomyelin occurs in almost every cell type, with particular buildup in lipid-laden macrophages of the reticuloendothelial system (RES). Affected organs/cells include spleen, liver, lung, bone marrow, skin and lymph nodes, and, in more severe disease, neurons of the

central and peripheral nervous system [2]. The spleen, the primary RES organ, can be severely enlarged in ASMD patients [3,9]. Pulmonary function is affected in ASMD, manifesting as interstitial lung disease due to accumulation of sphingomyelin in alveolar macrophages residing in the interalveolar septae, resulting in distortion and thickening of the delicate architecture and impaired oxygen/carbon dioxide exchange [10–12]. Therefore, diffusion capacity is often compromised in patients with chronic disease [3,6,13–16]. This infiltrative pulmonary process is typically progressive [10,12–14,17] and significantly contributes to the disease burden and severity of sequela for patients with chronic forms of ASMD [15].

Additional disease manifestations of chronic ASMD include, but are not limited to pulmonary infections, delayed growth and puberty, osteopenia with decreased bone strength leading to fractures, and hepatomegaly with progressive fibrosis leading to hepatic dysfunction and/or liver failure/cirrhosis, and portal hypertension. In addition, ASMD patients have a proatherogenic lipid profile, characterized by low high density lipoprotein (HDL) and elevated low density lipoprotein (LDL) with resultant premature cardiac and vascular disease, as well as cardiac valvular disease due to deposition of lipid on valvular cusps. Bleeding episodes are common and are thought to be due in part to complications from thrombocytopenia and/or to abnormal platelet function from platelet membrane abnormalities and potential hepatic synthetic dysfunction. Other manifestations include anemia, and leukopenia [6]. At present, there is no disease-specific treatment for ASMD, although an ERT with olipudase alfa, a recombinant human ASM, is currently in clinical development for the chronic, systemic, non-neurologic manifestations of the disease [7,8]. Until a disease-modifying treatment is available, management of chronic ASMD is focused on palliation of symptoms and supportive care [9].

Similar to other LSDs that result in accumulation of lipids in the RES, such as Gaucher disease (see Table 1), improvement in spleen volume has been selected as a relevant outcome measure in ASMD clinical trials for systemic ERT with olipudase alfa. In a phase 1b trial and extension study in five adults with chronic visceral ASMD, all study participants had splenomegaly, with an average spleen volume of 12.8 multiples of normal (MN) at baseline [7,8]. Treatment with olipudase alfa reduced spleen volume to an average of 6.7 MN (~50% reduction) after 30 months [7]. Given the accumulation of sphingomyelin laden alveolar macrophages in the interalveolar septae, the most pathophysiologic relevant clinical marker of lung disease in patients with ASMD is the percent diffusion capacity of carbon monoxide (DL_{CO}), as this marker directly reflects the function and health of the alveolar-

epithelial barrier where oxygen-CO₂ exchange occurs. A DL_{CO} value below the lower limit of predicted reference range 75% to 140% indicates pulmonary dysfunction [18,19]. In the olipudase alpha phase 1b open label study, all patients had impaired gas exchange at baseline, with a mean DL_{CO} of 53% of predicted values that corresponded to moderate impairment [7,8]. Following 30 months of treatment with olipudase alpha, the percent predicted DL_{CO} improved in all study participants to a mean of 67% predicted (mild impairment) with concomitant improvement in infiltrative lung disease pathology as assessed by high resolution contrast tomography (HRCT) [7].

Based on these findings, an ongoing phase 2/3 randomized placebo-controlled clinical trial in adult patients with chronic visceral ASMD (NCT02004691; EudraCT: 2015-000371-26), used both the percent changes in DL_{CO} and improvement in splenomegaly as primary outcome measures, and were established in keeping with the Food and Drug Administration (FDA) guidance for industry for ERT for rare diseases [20].

The purpose of this paper is to review published evidence on the relevance of splenomegaly and reduced lung diffusion capacity to the clinical burden of ASMD, and use validated examples from diseases where splenomegaly and DL_{CO} are used as clinical endpoints in treatment trials to illustrate how improvements in these parameters can be surrogates for overall improvements in disease-related mortality, morbidity or patient quality of life (QoL).

2. Methods

2.1. Literature search and selection

Targeted literature searches were conducted to identify relevant ASMD studies for associations between DL_{CO} or splenomegaly with other ASMD clinical parameters and outcome measures. Separate searches also identified studies for other diseases that used DL_{CO} [idiopathic pulmonary fibrosis (IPF), interstitial lung disease (ILD), systemic sclerosis (SSc) and pulmonary arterial proteinosis (PAP)] or splenomegaly (Gaucher disease, myelofibrosis) as endpoints with reporting on mortality, morbidity or QoL. While the pathological mechanisms in these diseases are different from those in ASMD, reviewing the criteria for splenomegaly and DL_{CO} as endpoints provides useful examples of the impact of changes in these endpoints on disease burden. A third tier of searches identified treatment or practice guidelines for selected relevant diseases using DL_{CO} or splenomegaly as endpoints. Searches were conducted in PubMed and were limited to human studies with English-language abstracts and articles. Searches were limited to publications in the last 5–10 years for diseases other than ASMD, which had no time restrictions. Lastly, searches were conducted on the US FDA and EMA web sites for agency reports on the diseases of interest. Search strategies and outcomes are included in Supplementary tables. From 794 identified publications, 26 (5 ASMD studies, 8 disease guidelines or agency reports for Gaucher, myelofibrosis and IPF, and 13 publications on studies in other disease states) provided relevant information on DL_{CO} and splenomegaly endpoint use, and are summarized in Tables 2–4.

3. Results

3.1. Splenomegaly in ASMD

Splenomegaly is observed in pediatric and adult patients with chronic ASMD and spleen volumes exceeding 20 times normal have been reported [3,6]. In addition to increasing risk of splenic rupture, splenomegaly has a significant impact on patient QoL, where massive abdominal distension (as shown in Fig. 1) can compromise respiratory function, limit physical activity including participation in sports, lead to early satiety, and negatively affect body image, self-esteem, and relationships with peers [21,22]. As determined from the review of ASMD

Table 2
ASMD observational and natural history studies of patients with chronic ASMD describing associations of DL_{CO} or splenomegaly with morbidity, mortality or quality of life.

Study design	Relevant population	DL _{CO} -related	Spleen-related	Reference
Multicenter, multinational prospective, cross-sectional natural history study (US, Italy, Brazil, France and Germany)	59 pediatric or adult patients with chronic ASMD ranging in age from 7 to 65 years	Shortness of breath; disease severity	Bleeding/bruising, increased liver volume, atherogenic lipid profile, below average height z scores, hematologic abnormalities, lung parameters (including fibrosis scores, % predicted DL _{CO} , % predicted FVC)	McGovern et al. [23]
Retrospective and prospective natural history study (Belgium and the Netherlands)	25 pediatric or adult patients with chronic ASMD with up to 11 years of follow-up	6 min walk test; disease progression	No significant correlations between baseline spleen volume and platelets, lipids, DL _{CO} , bone marrow fat burden, chitotriosidase	Hollack et al. [15]
Systematic evaluation of morbidity and mortality (US single center)	103 pediatric or adult patients with chronic ASMD ranging in age from 1 to 72 years	NR	Higher mortality in splenectomized patients	McGovern et al. [14]
Assessment of bone scans (US single center)	46 pediatric or adult patients with chronic ASMD ranging in age from 1.6 to 54.5 years	NR	Lumbar bone mineral density Z-score	Wasserstein et al. [25]
Cross-sectional analysis of growth in children (US single center)	23 children and adolescents with chronic ASMD ranging in age from 3.7 to 18.3 years	NR	Short stature and low weight	Wasserstein et al. [24]

DL_{CO} diffusing capacity of the lungs for carbon monoxide; FVC forced vital capacity; NR not reported.

Table 3
Treatment guidelines incorporating DL_{CO} or splenomegaly reduction as clinically significant outcomes.

Disease	Outcome	Guideline	Reference
Gaucher disease	Splenomegaly	<ul style="list-style-type: none"> ● Spleen volume should be expressed as multiples of normal with a treatment goal of 2–8 times reduction of normal and assessments at different time points up to 5 years 	<ul style="list-style-type: none"> ● European Working Group on Gaucher Disease [31,32] ● US Food and Drug Administration [29] ● European Medical Association [30]
Myelofibrosis	Splenomegaly	<ul style="list-style-type: none"> ● Reduction of $\geq 35\%$ in spleen volume as assessed by MRI or CT is indicative of response to treatment 	<ul style="list-style-type: none"> ● WHO International Working Group-Myeloproliferative Neoplasms Research and Treatment (IWG-MRT) and European LeukemiaNet consensus report [35]
Idiopathic pulmonary fibrosis	DL _{CO}	<ul style="list-style-type: none"> ● A decrease of $> 15\%$ DL_{CO} in absolute values is associated with disease worsening/increased risk of mortality 	<ul style="list-style-type: none"> ● 2017 Spanish IPF guidelines [58,59] ● 2017 French IPF guidelines [60]

DL_{CO} Diffusing capacity of the lungs for carbon monoxide; IPF idiopathic pulmonary fibrosis.

natural history and observational studies, splenomegaly is associated with the degree of disease severity across several clinical parameters in both pediatric and adult patients as summarized in Table 2 [14,15,23–25].

In a multinational, observational natural history study among 59 pediatric and adult patients with chronic ASMD, there was a strong positive correlation between spleen volume and triglyceride levels ($r = 0.545$, $P < .001$), and a negative correlation with high density lipoprotein (HDL) levels ($r = -0.620$, $P < .001$) [23]. Spleen volume also strongly correlated with liver volume ($r = 0.760$, $P < .001$), height Z score ($r = -0.509$, $P < .001$), hemoglobin ($r = -0.330$, $P < .019$), and white blood cell count ($r = -0.466$, $P < .001$) [23]. In another study, among 46 pediatric and adults with chronic ASMD, larger spleen volume was associated with lower bone mineral density (BMD) Z scores ($r = -0.7311$, $P = .001$) [25]. Among 23 pediatric patients, short stature and low weight were significantly correlated with larger spleen volumes [24].

Spleen size has also been associated with an increase in bleeding risk. Abnormal bleeding was the third most common cause of death in a report of 85 patients with chronic ASMD, including gastrointestinal variceal bleeding, postoperative hemorrhage, subdural hematoma and internal bleeding after injury [13]. Overall, bleeding/bruising were statistically more frequent in patients with larger spleens compared to those patients without bleeding/bruising (means of 13 multiples of normal (MN) versus 9 MN, $P = .006$) [23].

Spleen volume was modestly associated with several pulmonary measures, including a positive correlation with HRCT interstitial lung disease score ($r = 0.308$, $P = .033$), and a negative correlation with % predicted DL_{CO} ($r = -0.306$, $P = .052$) and % predicted FVC ($r = -0.346$, $P = .015$) [23]. However, in contrast to these results, a small study of 6 patients from Belgium and the Netherlands did not find that spleen volume correlated with other clinical manifestations [15]. It may be relevant that the majority of individuals in this study were homozygous for an *SMPD1* variant associated with milder disease (i.e., delR610).

Spleen volume also has been observed to be greater among individuals with chronic ASMD with early mortality, irrespective of the cause [14], suggesting that the burden of disease was greater in individuals with larger spleens. However, conclusions are limited due to the small amount of retrospective data. In a survey of causes of death among patients with chronic ASMD, 12 of the deceased (15%) had full or partial splenectomy, suggesting that severe hypersplenism necessitating surgery is associated with a greater disease burden and increased mortality [13]. Splenomegaly may also be associated with symptoms resulting from hypersplenism and splenic infarctions or crises; however, these can be hard to define and quantify.

Spleen volume also appears to correlate with liver disease in ASMD. Liver disease and liver failure are common observations in patients with chronic forms of ASMD. Almost 10% of patients with chronic visceral ASMD had liver failure or cirrhosis, and liver transplant was required in some individuals [14]. In addition to respiratory-related causes, liver failure was a leading cause of mortality in individuals with chronic

forms of ASMD [13]. Liver fibrosis was identified in baseline biopsy data of 15/17 (88%) patients with chronic ASMD enrolled in two phase 1 studies of olipudase alfa [8,26,27]. Fig. 2 shows the association of fibrosis grade and spleen volume for these individuals. While splenomegaly is initially related to infiltration of lipid-laden macrophages, the onset of accelerated splenomegaly later in the course of disease can also be a secondary effect from worsening portal hypertension resulting from the progression of fibrotic liver disease.

3.2. Splenomegaly in other diseases

Gaucher disease and myelofibrosis are examples of diseases where splenomegaly is a common disease manifestation that has been identified as a clinically relevant endpoint in clinical trials. In addition, guidelines for meaningful reductions in splenomegaly following treatment have been established for both diseases (Table 3). Although the pathological mechanisms of Gaucher disease and myelofibrosis are different from those for ASMD, the summary of splenomegaly criteria as an endpoint in these diseases provides useful examples of the impact of changes in splenomegaly on disease burden.

Gaucher disease is a LSD in which glycosphingolipid accumulates in cells and organs, shares several features with ASMD, including splenomegaly (although skeletal, hematological, pulmonary, and bone marrow involvement differ between the two diseases). Splenomegaly in patients with Gaucher disease is associated with greater bone marrow burden [28]. In US FDA and collaborative EMA-FDA draft guidance, spleen size, expressed as MN and measured with magnetic resonance imaging (MRI) or ultrasound, was recommended as an endpoint in clinical trials in children and adults with Gaucher disease [29,30]. The European Working Group on Gaucher Disease (EWGGD) recommended a short-term goal of reduction in spleen volume to 2–8 MN (or in absence of volume measurement tools, reduction of spleen size) within 1–2 years of treatment depending on baseline spleen volume as a target for drug efficacy in clinical trials [31,32].

Myelofibrosis is a clinical manifestation of chronic myeloproliferative neoplasms, and splenomegaly occurs, in part, due to splenic extramedullary hematopoiesis. Larger spleen volumes correlate with increased morbidity and decreased survival [33,34]. Reduction in splenomegaly is a relevant clinical treatment endpoint in myelofibrosis clinical trials. In the WHO International Working Group-Myeloproliferative Neoplasms Research and Treatment (IWG-MRT) and European LeukemiaNet (ELN) consensus report, a reduction of $\geq 35\%$ in spleen volume as assessed by MRI or computed tomography (CT) was considered a positive treatment response in myelofibrosis [35]. Drugs for myelofibrosis that successfully met this criterion include the Janus kinase 2 (JAK2) inhibitor, ruxolitinib. Following ruxolitinib treatment, individuals with reductions in spleen volumes $> 35\%$ had the greatest improvements in symptoms and QoL as measured using a patient reported outcome (PRO) tool [36]. This guideline is consistent with a Cochrane review on treatment of myelofibrosis by several JAK2 inhibitors in which a reduction of spleen size of $\geq 35\%$ was used as an outcome to measure treatment efficacy [37].

Table 4
Correlation of DL_{CO} with morbidity, mortality or quality of life in chronic lung diseases.

Outcome	Disease	Criterion for DLCO	Correlation	References
Mortality	IPF	Continuous variable	Increased risk with lower DL _{CO}	Traila et al. [45], Sharp et al. [44]
	ILD	DL _{CO} < 40%		Zamora-Legoff et al. [46]
	SSc	DL _{CO} < 60%		Panopoulos et al. [47]
QoL/PROs SGRQ score (QoL)	IPF	Continuous variable	Higher score (worse QoL) for lower DL _{CO} , $P < .001$ (univariate)	Matsuda et al. [49]
	SSc	Continuous variable	Decreased score (better QoL) for improved DL _{CO} (DL _{CO} at 1 year $\geq 15\%$ higher than baseline) vs worsened DL _{CO} at 1 year $\geq 15\%$ lower than baseline), $P = .02$	Wallace et al. [50]
	SSc	Continuous variable	Higher score (worse QoL) for lower DL _{CO} , $P = .0004$	Lopes et al. [48]
Respiratory/cardiovascular outcomes Abnormal heart rate recovery after exercise Pulmonary hypertension	IPF	Per 10% predicted	OR 0.4 per 10% predicted, 95% CI 0.2–0.7, $P = .003$	Swigris et al. [51]
	ILD	DL _{CO} < 40%	Increased risk of PH with DL _{CO} < 40% OR 6.25, 95% CI 1.32–17.43, $P = .02$	Ruocco et al. [52]
	SS	Continuous variable	Increased risk of PH with lower DL _{CO} HR 0.95, 95% CI 0.93–0.97, $P < .001$ (univariate)	Mecoli et al. [55]
Reduced physical activity Severity of dyspnea Work disability	IPF	Continuous variable	$r = 0.494$, $P < .001$	Bahmer et al. [53]
	ILD	Continuous variable	$P = .007$	Ryerson et al. [54]
	SS	Continuous variable	Multivariate, HR 0.98, 95% CI 0.97–0.99, $P = .038$	Sharif et al. [56]

DL_{CO} Diffusing capacity of the lungs for carbon monoxide; HAQ-DI Health Assessment Questionnaire Disability Index; HR hazard ratio; IPF idiopathic pulmonary fibrosis; ILD interstitial lung disease; OR odds ratio; pH pulmonary hypertension; QoL quality of life; SGRQ St. George's Respiratory Questionnaire; SS systemic sclerosis.

3.3. Splenomegaly as a primary endpoint in ASMD clinical trials

In the olipudase alfa phase 2/3 clinical trial in adults with chronic visceral and chronic neurovisceral ASMD (NCT02004691), improvement within 1 year in spleen volume (as measured by abdominal MRI) was a primary efficacy endpoint. Of note, only ASMD patients with splenomegaly ≥ 6 MN were included in this trial. The criteria for improvement in spleen volume in current ASMD clinical trials is a decrease of 30% in spleen volume over 1 year OR a decrease of 30% with a trend toward improvement in splenomegaly related score (SRS), which is a patient-reported outcome (PRO) measure consisting of a 5 question survey on splenomegaly related problems including early satiety, abdominal discomfort, abdominal pain, difficulty bending down and abdominal body image. Development of the SRS used in ASMD trials was made based on the subset of symptoms related to spleen volumes in the validated myelofibrosis symptom assessment form [38].

3.4. Lung disease in ASMD

Progressive lung disease is an inexorable clinical feature of chronic ASMD. Associated recurrent respiratory tract infections [39] and progressive decline in pulmonary function are major contributors to decreased QoL and increased disease burden in ASMD patients [10,12,14,17] [15]. Greater than 90% of patients with chronic visceral ASMD have radiographic evidence of infiltrative lung disease, although some patients may not have overt symptoms [10,40]. Both respiratory infections and respiratory failure are major causes of death in both pediatric and adult patients with chronic forms of ASMD [13].

In natural history and observational studies in ASMD, patients with chronic ASMD and progressive lung disease were found to have decreased QoL, and in some instances the percent predicted DL_{CO} correlated with symptom severity as summarized in Table 2. In the combined retrospective and prospective natural history study of 25 patients with chronic ASMD [15] dyspnea and decreased stamina were the most impactful clinical factors that limit daily activities among individuals with chronic ASMD. Reduced 6 min walk test results were observed in all individuals (61–85% of predicted values), and for six individuals with follow-up, the lowest 6-min walk test performance correlated to the patient with the lowest DL_{CO} value [15]. In the cross-sectional natural history study of 59 patients, a low DL_{CO} was consistent with restrictive lung disease, DL_{CO} was inversely related to disease severity, and patients with history of shortness of breath versus no shortness of breath had lower percent predicted DL_{CO} (51.3% vs 70.6%, $P = .009$) [23]. The latter fact suggests a direct relationship between clinical respiratory symptoms and DL_{CO}.

3.5. Clinical relevance of DL_{CO} in chronic lung disease

DL_{CO} is a predictor of mortality in individuals in the general population, in those with altered pulmonary function, and in patients undergoing lung resection [41,42]. In addition, low DL_{CO} is observed in patients with other chronic lung diseases and cardiovascular diseases as summarized in Table 4. Clinical scenarios in which DL_{CO} can provide clinically relevant information include: i) early detection of lung disease in patients at risk of ILD, ii) the assessment of ILD severity, iii) morbidity and mortality risks, and iv) disease management/responses to therapy [43].

The review of publications describing studies that used DL_{CO} as an outcome measure in chronic lung disease show that decline in DL_{CO} is associated with long-term morbidity, mortality, and decreased QoL in individuals with IPF, ILD, and SSc as summarized in Table 4. Increased risk of mortality is correlated with moderate or severe (<60% and <45%, respectively) decreases in percent DL_{CO} in individuals with IPF [44,45], ILD [46], and SSc [47]. Lower percent DL_{CO} is also associated with decreased QoL in chronic lung disease [48–50]. In IPF, higher scores on the St. George Respiratory Questionnaire (SGRQ) (indicating

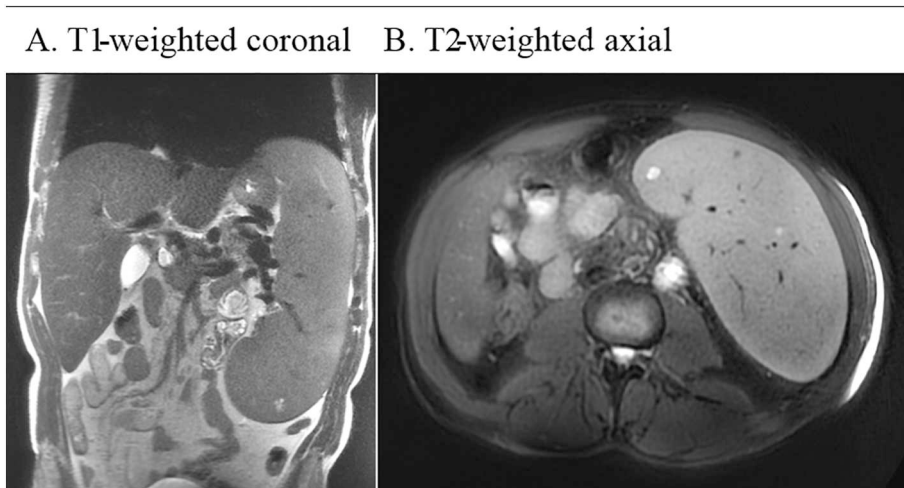


Fig. 1. Splenomegaly in adult patients with chronic ASMD.

Severe splenomegaly in an adult patient with chronic ASMD. **Fig. 1A** shows a gadolinium enhanced T1-weighted coronal image in the portal phase showing splenomegaly with 27 cm of cranio caudal length and multiple tiny hypointense foci. **Fig. 1B** shows a T2-weighted axial image showing splenomegaly with loss of the normal inferomedial concavity and multiple well-defined hyperintense nodules.

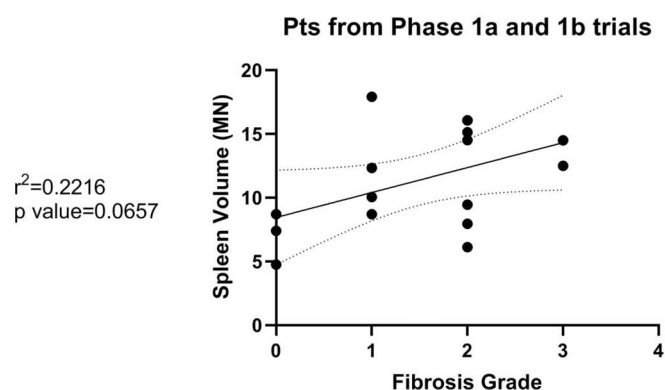


Fig. 2. Association of baseline spleen volume and degree of liver fibrosis from adult patients enrolled in ASMD clinical trials (previously published baseline data from [8, 26, 27]).

decreased QoL) were correlated with lower percent DL_{CO} values [49]. For individuals with SSc, better QoL (lower SGRQ scores) was observed when percent DL_{CO} increased to $\geq 15\%$ higher than baseline after 1 year [50]. Similarly, using another QoL instrument, the Health Assessment Questionnaire-Disability Index (HAQ-DI), higher scores indicating decreased QoL were associated with lower percent DL_{CO} in those with SSc [48].

In addition to correlations between DL_{CO} and mortality and QoL, lower percent predicted DL_{CO} is associated with other respiratory and cardiovascular morbidities that significantly impact activities of daily living, including abnormal heart rate recovery after exercise in individuals with IPF [51], increased risk of pulmonary hypertension in those with ILD and SSc [52], reduced physical activity in those with IPF [53], increased severity of dyspnea in those with ILD [54,55], and work-disability in those with SSc [56].

3.6. Clinical guidelines for idiopathic pulmonary fibrosis

International guidelines for clinically meaningful changes in DL_{CO} in IPF have been published within the last several years and are summarized in Table 3. In IPF, DL_{CO} is a clinical marker of disease progression. DL_{CO} is considered an indirect measure of IPF progression in the American Thoracic Society (ATS)/European Respiratory Society (ERS)/Japanese Respiratory Society (JRS)/Latin American Thoracic Association (ALAT) 2011 guidelines [57]. In a therapeutic algorithm of treatment in IPF Spanish guidelines, a reduction in DL_{CO} $> 15\%$ was recommended as a threshold for worsening of IPF, and conversely, a reduction of DL_{CO} $< 15\%$ as a threshold for stabilization or

improvement [58,59]. The 2017 update to the French Practical Guidelines for the Diagnosis and Management of IPF [60] states that for initial IPF signs and symptoms, a DL_{CO} $< 35\%$ to 40% has been associated with increased mortality risk, and for signs and symptoms appearing during the evolution of IPF, a decrease of more than 15% in DL_{CO} (in absolute or relative value) has been associated with increased mortality risk at 6 months of study follow-up.

It is important to recognize that while the studies and guidelines summarized here demonstrate the relationship between DL_{CO} and morbidity/mortality in IPF/ILD, few studies have used DL_{CO} as a primary endpoint, most likely due to the fact that other lung function assessments, (e.g., FVC) are more traditional measures [61,62].

3.7. DL_{CO} as a primary endpoint in ASMD clinical trials

In ASMD, data correlating DL_{CO} with QoL, mortality and morbidity are not available to the same extent as in chronic lung diseases. In addition, other organ involvement in ASMD (for example, severe splenomegaly or compromised growth) also can contribute to decreased mobility and quality of life. However, in a small number of studies, DL_{CO} decreased as ASMD severity increased [15,23] and correlated with QoL as described in the “Lung Disease in ASMD” section. In addition, in a Phase 1b trial of 5 adult patients, the percent predicted DL_{CO} improved within 6 months of olipudase alfa treatment and was maintained through 30 months of assessments [7]. Based upon these results and the specific pathological and anatomical features of ASMD (namely deposition of sphingomyelin-laden macrophages in the interalveolar space as a key driver of pulmonary gas exchange perturbation), and the potential of olipudase alfa to reverse this pathology, DL_{CO} was chosen as an innovative, pathophysiologically relevant endpoint in the olipudase alfa phase 2/3 trial in adults with chronic ASMD and baseline DL_{CO} $\leq 70\%$ that was independent of the endpoint for improvement in spleen volume. It is important to reiterate, however, that limited information is available regarding DL_{CO} as a clinical trial endpoint, especially with respect to the expected time course in which to see a clinical response and the degree to which baseline disease might affect both the magnitude and the time course of the clinical response.

4. Conclusions and discussion

Respiratory disease and organomegaly are primary and independent contributors to mortality (27.7% for each) [13], and disease burden and morbidity for patients with chronic forms of ASMD [3,6,14,23,39]. Clinical trials in chronic ASMD used DL_{CO} and spleen volume as primary efficacy endpoints to assess disease progression and treatment responses, while secondary endpoints include changes in liver volume,

platelet counts, and improvements in fatigue, pain, and dyspnea severity. It is important to establish that these outcome measures are reliable, valid, responsive, and clinically meaningful for ASMD. The degree of splenomegaly in patients with chronic ASMD correlates with short stature in pediatric patients, atherogenic lipid profile, and hematologic parameters, and may be considered a surrogate marker for bleeding risk, infection risk, abnormal lipid profiles and possibly, liver fibrosis. These results are consistent with other diseases where splenomegaly is correlated with morbidity and mortality risk. Progressive lung disease is a prevalent clinical feature of chronic ASMD contributing to decreased QoL and increased disease burden, and respiratory-related complications are a major cause of mortality. The reviewed evidence from ASMD natural history and observational studies supports the use of DL_{CO} and spleen volume as clinically meaningful endpoints in ASMD trials that translate into important measures of disease burden for patients. However, due to the rarity of ASMD and often inadequate diagnostic screening initiatives, available evidence remains limited, especially on mortality/survival, frequency, and timing of significant clinical events. We recognize that there may be additional publications since our targeted searches were completed in late 2018 that lend support to spleen volume and lung diffusion as clinically meaningful measures of disease burden for patients with ASMD. A review paper by Eskes et al. provides an overview of biochemical and imaging markers of visceral ASMD and evaluates their validity as surrogate endpoints in clinical practice [63]. The authors conclude from their analyses that spleen volume and lung diffusion capacity are among the potential biomarkers with the highest validity scores.

As the results of clinical trials where spleen volume and DL_{CO} are used as primary endpoints become available, we will have improved understanding of how these parameters relate to disease-related mortality, morbidity and patient QoL in both pediatric and adult patients with ASMD, where additional data on disease evolution across all age groups are needed.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.ymgme.2020.06.008>.

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