Exploring the Relationship between Surrogate and Long-Term Outcomes in Lysosomal Storage Diseases: A Targeted Literature Review

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Background

- Clinical trials in rare diseases frequently rely on surrogate endpoints because of limited sample size, trial design constraints and disease heterogeneity.[1,2]
- In the United States and European Union, regulatory bodies have allowed use of surrogate endpoints for early drug licencing to address the unmet medical need in the treatment of rare diseases.[3,4]
- However, the acceptance of surrogate endpoints is frequently challenged by payers;[3] therefore, there is a growing need to assess the influence of surrogate endpoints on long-term outcomes, until evidence for their longer-term effects is available in rare diseases.

Objective

- This targeted literature review (TLR) evaluated the possible relationship between long-term and surrogate outcomes in lysosomal storage diseases (LSDs) trials, specifically focusing on Fabry disease (FD), Gaucher disease type 3 (GD3) and GM2 gangliosidoses, namely Tay–Sachs and Sandhoff diseases.

Methods

Search strategy and selection criteria

- A comprehensive TLR was conducted using Excerpta Medica Database (EMBASE®) and MEDLINE from inception to March 2022 to identify studies linking surrogate endpoints used in clinical trials to long-term outcomes (health-related quality of life [HRQoL], morbidity and mortality) in LSDs of interest.
- Studies evaluating the relationship between surrogate and long-term outcomes in these LSDs were eligible for inclusion. Studies without the relevant population and outcomes were excluded.
- For LSDs with limited evidence on surrogate endpoints, analogous diseases with similar natural history and disease pathway would be explored.

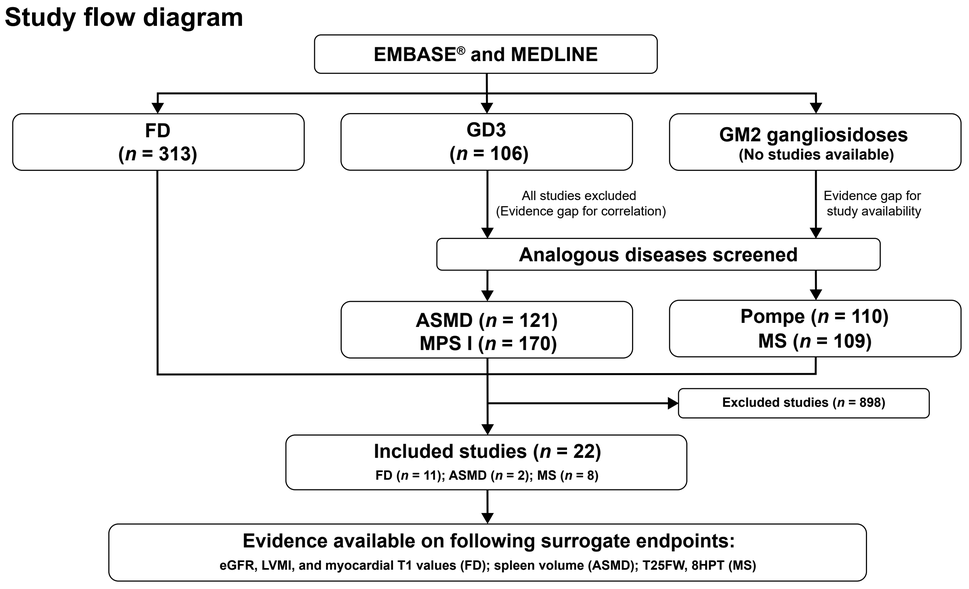
Data extraction and analysis

- Data extracted included study design, statistical methods and results that evaluated a possible relationship between surrogate and long-term outcomes.
- Studies reporting regression coefficient (b), hazard ratio (HR), odds ratio (OR) or chi-square test (χ^2) were categorised as 'association', whereas studies reporting Pearson or Spearman correlation coefficient (*r*), were categorised as 'correlation'.

Results

- Overall, 419 studies (FD, number of studies, *n* = 313; GD3, *n* = 106) were identified; as no evidence was reported in GM2 gangliosidoses, additional searches were conducted focusing on analogous disease, such as, Pompe disease (*n* = 110) (**Figure 1**). There was no evidence on 9-hole peg test (9HPT) and timed 25-foot walk (T25FW) identified in GM2 gangliosides, and its analogous disease, Multiple Sclerosis (MS) (*n* = 109), was explored where these endpoints have been studied.
- Furthermore, none of the studies met the eligibility criteria for GD3; hence, a subsequent search was conducted on mucopolysaccharidosis type I (MPS I, *n* = 170) and acid sphingomyelinase deficiency (ASMD, *n* = 121), which are analogous diseases (**Figure 1**).
- A total of 22 studies (FD [*n* = 11]; ASMD [*n* = 2]; MS [*n* = 9]) met the eligibility criteria (**Figure 1**).
- All 22 studies exhibited relationship between surrogate and long-term outcomes at patient level, irrespective of treatment.

Figure 1. Study flow diagram



The surrogate endpoints were identified based on primary, co-primary and secondary endpoints of the CARAT trial (NCT05280548)[5] for FD, LEAP2MONO trial (NCT05222906)[6] for GD3 and AMETHIST trial (NCT04221451)[7] for GM2 gangliosidoses.

Studies related to MPS I and Pompe were excluded as they lack the relevant population/outcomes of interest.

9HPT, 9-hole peg test; ASMD, acid sphingomyelinase deficiency; eGFR, estimated glomerular filtration rate; EMBASE, Excerpta Medica Database; FD, Fabry disease; GD3, Gaucher disease type 3; LVMI, left ventricular mass index; MPS I, mucopolysaccharidosis type I; MS, Multiple sclerosis; *n*, number of evidence; T25FW, timed 25-foot walk

Surrogate endpoints in FD

- Surrogate endpoints selected in FD were reduced estimated glomerular filtration rate (eGFR), left ventricular mass index (LVMI) and myocardial T1 values.
- Reduced eGFR was associated with decreased HRQoL (*n* = 3),[8–10] increased risk of cardiovascular (CV)/neurological/renal events (*n* = 4)[11–13] and mortality (*n* = 1)[14] (**Table 1**).
- Increased LVMI was associated with increased risk of CV events (*n* = 1)[12] and CV morbidity as well as mortality (*n* = 1)[15] (**Table 1**).
- A study emphasised a negative correlation between myocardial T1 values and morbidity[16] (**Table 1**).

Surrogate endpoints in GM2 gangliosidoses

- No evidence was identified in GM2 gangliosidoses and its analogous disease, Pompe. There were no studies that identified and explored the relevance of the endpoint 9HPT and T25FW in GM2 gangliosidoses; 9HPT and T25FW, which were studied as measures for impaired coordination and motor disability in MS, were there fore explored.
- Increase in T25FW was associated with walking disability (*n* = 3),[17–18] showed positive correlation with Guy's Neurological Disability Scale (GNDS) worsening[19] and a negative correlation with cognitive performance as measured by Paced Auditory Serial Addition Test (PASAT)[20] (**Table 2**).
- Lower T25FW speed was associated with higher incapacity status scale scores , lower rivermead mobility index scores and higher frequency of falls[21].
- Increase in 9HPT showed negative correlation with walking ability[20] and positive correlation with both GNDS worsening[19] and worse cognitive performance as measured by PASAT[20] (**Table 2**).

Table 1. Studies reporting association/correlation between surrogate and long-term outcomes in FD

Surrogate endpoint	Long-term outcome	Study design	Statistical analysis	Variables assessed	Measure of association	95% CI	*p*-value
eGFR	HRQoL	Cross-sectional survey[a,8]	Linear regression	Physical function[b]	b = −19.06	-	0.02
				Role physical[b]	b = −23.62	-	0.04
		Retrospective observational extraction[9]	Hierarchical linear modelling	Physical function	b = 0.37	-	<0.01
		Cross-sectional[a,10]	Multivariate regression	EQ-5D index[c]	b = −0.06	−0.22; −0.03	0.03
				EQVAS[C]	b = −6.79	−14.12; −2.77	0.04
	Morbidity[d]	Retrospective observational[e,11]	Cox regression	-	HR = 4.57	1.79; 11.73	0.001
	Renal events[f]	Retrospective (registry data)[12]	Multivariate Cox regression	-	HR = 5.88	2.73; 12.68	<0.001
	CV events	Retrospective (registry data)[g,12]	Multivariate Cox regression	-	HR = 1.33	1.04; 1.70	0.021
	CV events[h]	Retrospective analysis of prospectively collected data[13]	Linear regression	-	HR = 3.59	1.15; 11.18	0.0273
	Mortality	Retrospective (registry data)[14]	Multivariable	-	HR = 2.22	1.38; 3.57	-
LVMI	CV events[g]	Retrospective (registry data)[12]	Multivariate Cox regression	-	HR = 1.57	1.21; 2.05	<0.001
	CV morbidity and mortality	Observational, longitudinal, prospective cohort[15]	Multivariable modelling	AF	HR = 1.02	1.01; 1.03	0.02
				Cardiac death	HR = 1.05	1.02; 1.09	0.000
Myocardial T1 values	Morbidity	Prospective[16]	Pearson correlation	LVM	*r* = −0.79	-	<0.0001
				MWT	*r* = −0.79		
				Sokolow–Lyon Index	*r* = −0.54	-	
				MSSI	*r* = −0.61	-	
				Left atrial volume	*r* = −0.49	-	<0.0002

[a]Kidney disease was defined as reduced eGFR; [b]The eight scales measured by the short form-36 health survey are physical functioning, role physical, bodily pain, general health, vitality, social functioning, role emotional and mental health; [c]EQ-5D index and EQ VAS are standardised measures of HRQoL; [d]Morbidity was assessed by clinical events, which included neurological, cardiovascular and renal events; [e]Chronic kidney disease was defined as eGFR with <60 ml/min/1.73m²; [f]Renal events included dialysis, transplantation and renal failure; [g]CV events included myocardial infarction, left ventricular hypertrophy, heart failure, arrhythmia, conduction abnormality and cardiac surgery; [h]CV events included arrhythmia, atrial fibrillation, implantable cardioverter device or pacemaker implantation and myocardial infarction.

AF, atrial fibrillation; b, regression coefficient; CI, confidence interval; CV, cardiovascular; eGFR, estimated glomerular filtration rate; EQ-5D, EuroQol-five dimensions of health; EQ VAS, EuroQol visual analogue scale; FD, Fabry disease; HR, hazard ratio; HRQoL, health-related quality of life; LVM, Left ventricular mass; LVMI, left ventricular mass index; MWT, maximum wall thickness; MSSI, Mainz Severity Score Index; *r*, correlation coefficient

Table 2. Studies reporting association/correlation between surrogate and long-term outcomes in GM2 gangliosidoses

Surrogate endpoint	Long-term outcome	Study design	Statistical analysis	Variables assessed	Measure of association	*p*-value
T25FW	Walking ability	Post-hoc analysis of prospective cohort[17]	Ordinal logistic regression	MWD-EDSS[a]	χ^2 = 17.6; *df* = 7	0.014
					χ^2 = 8.6; *df* = 3	0.034
		Retrospective[18]	Cox proportional hazard model	Confirmed disability progression[b]	HR = 2.6 (95% CI, 2.2; 3.1)	-
		Cross-sectional[21,c]	Multivariate regression	ISS scores	b = −0.07	<0.001
				RMI scores	b = 0.04	
				Fall frequency	OR = 1.01	0.048
	Cognitive function	Retrospective observational[20]	Spearman correlation	PASAT	*r* = −0.28	<0.001
	Neurological disability	Retrospective[19]		GNDS	*r* = 0.23	-
9HPT	Walking ability	Retrospective observational[20]	Spearman correlation	EDSS	*r* = −0.50	<0.001
	Cognitive function			PASAT	*r* = 0.21[d]	0.01
	Neurological disability	Retrospective analysis of longitudinal database[19]		GNDS	*r* = 0.20	-

[a]Chi square statistic value (17.630) was tested using seven categories of T25FW (<5.0, 5.0–5.9, 6.0–6.9, 7.0–7.9, 8.0–8.9, 9.0–9.9 and ≥10.0 seconds), and chi-square statistic value (8.678) was tested using three categories of T25FW (<6.0, 6–7.9 and ≥8.0 seconds); [b]The variable, confirmed disability progression was assessed based on EDSS; [c]In this analysis, speed of T25FW was considered; [d]In this analysis, reciprocal of 9-HPT was considered.

9HPT, 9-hole peg test; b, regression coefficient; CI, confidence interval; *df*, degree of freedom; EDSS, Expanded Disability Status Scale; GNDS, Guy's Neurological Disability Scale; HR, hazard ratio; ISS, Incapacity Status Scale; MWD, maximum walking distance; OR, odds ratio; PASAT, Paced Auditory Serial Addition Test; *r*, Spearman correlation coefficient; RMI, Rivermead Mobility Index; T25FW, timed 25-foot walk; χ^2, chi square statistic

Surrogate endpoints in GD3

- Since there was no evidence identified in GD3, analogous diseases MPS I and ASMD were explored. No relevant studies on MPS I were retrieved. For ASMD, two studies met the eligibility criteria where spleen volume was reported to be associated with increased mortality risk (*n* = 2)[22,23] (**Table 3**).

Table 3. Studies reporting association between spleen volume and mortality risk in GD3

Study design	Statistical analysis	Variables assessed	Measure of association
Prospective longitudinal[22,23]	Cox proportional hazard	Splenomegaly severity	HR = 9.99 (95% CI, 1.03; 97.14)
	-	Mortality risk with severe splenomegaly vs. moderate splenomegaly	OR = 10.29 (95% CI, 1.70; 62.70)

CI, confidence interval; GD3, Gaucher disease; HR, hazard ratio; OR, odds ratio

Limitations

- The findings cannot be generalised based on a small number of studies evaluated.
- The findings from ASMD and MS may not be directly extrapolated to LSDs of interest due to existing gaps in evidence.

Conclusions

- **Studies focusing on FD showed that the worsening of eGFR, LVMI and myocardial T1 values are associated with long-term morbidity, mortality and decreased HRQoL.**
- **Considering limited evidence in specific LSDs, such as GD3 and GM2 gangliosidoses, clinical communities need to rely on endpoint validity using other disease areas, such as ASMD and MS, respectively, to understand the influence between surrogate endpoints and long-term outcomes.**

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CONFLICTS OF INTEREST
JMP, KR, MF, MBR, NL, LP and **RP-J:** Sanofi — employees, may hold stocks and/or stock options in the company. **FL** — was an employee of Sanofi at the time of study conduct.

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