



Progression characteristics of the European Friedreich's Ataxia Consortium for Translational Studies (EFACTS): a 2 year cohort study

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Summary

Background The European Friedreich's Ataxia Consortium for Translational Studies (EFACTS) is a prospective international registry investigating the natural history of Friedreich's ataxia. We used data from EFACTS to assess disease progression and the predictive value of disease-related factors on progression, and estimated sample sizes for interventional randomised clinical trials.

Methods We enrolled patients with genetically confirmed Friedreich's ataxia from 11 European study sites in Austria, Belgium, France, Germany, Italy, Spain, and the UK. Patients were seen at three visits—baseline, 1 year, and 2 years. Our primary endpoint was the Scale for the Assessment and Rating of Ataxia (SARA). Secondary outcomes were the Inventory of Non-Ataxia Signs (INAS), the Spinocerebellar Ataxia Functional Index (SCAFI), phonemic verbal fluency (PVF), and the quality of life measures activities of daily living (ADL) and EQ-5D-3L index. We estimated the yearly progression for each outcome with linear mixed-effect modelling. This study is registered with ClinicalTrials.gov, number NCT02069509, and follow-up assessments and recruitment of new patients are ongoing.

Findings Between Sept 15, 2010, and Nov 21, 2013, we enrolled 605 patients with Friedreich's ataxia. 546 patients (90%) contributed data with at least one follow-up visit. The progression rate on SARA was 0.77 points per year (SE 0.06) in the overall cohort. Deterioration in SARA was associated with younger age of onset (−0.02 points per year [0.01] per year of age) and lower SARA baseline scores (−0.07 points per year [0.01] per baseline point). Patients with more than 353 GAA repeats on the shorter allele of the *FXN* locus had a higher SARA progression rate (0.09 points per year [0.02] per additional 100 repeats) than did patients with fewer than 353 repeats. Annual worsening was 0.10 points per year (0.03) for INAS, −0.04 points per year (0.01) for SCAFI, 0.93 points per year (0.06) for ADL, and −0.02 points per year (0.004) for EQ-5D-3L. PVF performance improved by 0.99 words per year (0.14). To detect a 50% reduction in SARA progression at 80% power, 548 patients would be needed in a 1 year clinical trial and 184 would be needed for a 2 year trial.

Interpretation Our results show that SARA is a suitable clinical rating scale to detect deterioration of ataxia symptoms over time; ADL is an appropriate measure to monitor changes in daily self-care activities; and younger age at disease onset is a major predictor for faster disease progression. The results of the EFACTS longitudinal analysis provide suitable outcome measures and sample size calculations for the design of upcoming clinical trials of Friedreich's ataxia.

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Introduction

Although a rare disorder, Friedreich's ataxia is the most common hereditary ataxia in white people, with an estimated prevalence of 2–4 cases per 100 000 population.¹ In up to 98%² of cases, this recessive disease is caused by homozygous guanine-adenine-adenine (GAA) triplet repeat expansions in the first intron of the *FXN* gene, which encodes the mitochondrial protein frataxin. The remaining cases are compound heterozygotes for a GAA repeat expansion and an *FXN* point mutation or deletion.³ GAA repeat expansions suppress transcription of the *FXN* gene, leading to frataxin deficiency. The disease is characterised by spinocerebellar ataxia, dysarthria, pyramidal weakness, deep

sensory loss, hypertrophic cardiomyopathy, skeletal abnormalities, and diabetes mellitus.⁴ Clinical onset occurs most often around puberty, but in few cases symptoms develop in adulthood. In its typical form, this chronic disease leads to severe disability by early adulthood, with substantial functional loss, wheelchair dependence, and loss of quality of life. Affected individuals have reduced life expectancy, with many premature deaths caused by complications of the cardiomyopathy at about the end of the fourth decade of life.⁵

Previous natural history studies in genetically confirmed cases of Friedreich's ataxia, including our analysis of the European Friedreich's Ataxia Consortium

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Research in context

Evidence before this study

We searched PubMed for articles on Friedreich's ataxia published between Jan 1, 1996 (identification of the genetic cause), and April 15, 2016, with the search terms "Friedreich ataxia AND progression" and "Friedreich ataxia AND natural history" resulting in the identification of 11 peer-reviewed studies in English. Three studies were retrospective surveys, one of which focused only on patients with late-onset Friedreich's ataxia. Three studies were cross-sectional, including our baseline analysis. Three of the five longitudinal studies followed up patients for 1 year or 2 years, or both. The two remaining studies were long-term follow-up studies, one of which followed up patients for up to 7 years and used the International Cooperative Ataxia Rating Scale, whereas the other one focused on cardiac outcome measures for up to 22 years. Overall, these studies show the effects of earlier disease onset and its association with faster disease progression. However, use of clinical rating scales was heterogeneous. To date, there has been no prospective study with a similarly large cohort of patients with Friedreich's ataxia as in our study and a focus on showing changes in ataxia and non-ataxia symptoms, as well as functional measures, over the course of 2 years.

Added value of this study

This European, multicentre, longitudinal study of Friedreich's ataxia provides data for yearly change in clinical measures, based on observations at three timepoints over 2 years. Our results corroborate our baseline cross-sectional analysis, emphasising the advantages of the Scale for the Assessment and Rating of Ataxia and assessment of major clinical deterioration and the activities of daily living to measure functional decline in Friedreich's ataxia. Age of onset was a strong predictor for faster disease progression. Our power calculations show that 2 years of observation would be needed for a feasible clinical trial.

Implications of all the available evidence

Our data have important implications for future research, especially for the design of clinical trials of Friedreich's ataxia, as they provide suitable clinical measures and power calculations. Overall, the available evidence can now fulfil the longstanding requirements for large-scale studies of progression and calculations of sample sizes for future trials.

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for Trans-lational Studies (EFACTS) baseline data, have delineated the clinical characteristics of Friedreich's ataxia and provided estimates of progression.^{6–11} Although different clinical assessments were used in earlier studies, the conclusions drawn were that earlier onset and longer GAA repeats were associated with increased disease severity and more rapid progression. However, there has been no prospective longitudinal study of the Scale for the Assessment and Rating of Ataxia (SARA), which—based on previous estimated progression rates—seems to be a suitable clinical measure to monitor disease progression and effects on activities of daily living (ADL) to assess functional deterioration.⁷

As potential disease-modifying therapies in Friedreich's ataxia are emerging, longitudinal studies are urgently needed to identify and validate robust measures of clinical progression to guide the design of future clinical trials. To address this necessity and to enable translation to clinical practice, we have analysed prospective data from the EFACTS database representing 2 years of observation. We assessed disease progression and the predictive value of disease-related factors on progression, and estimated sample sizes for interventional randomised clinical trials.

Methods

Study design and participants

Within the framework of the EFACTS project, patients with a genetically confirmed diagnosis of Friedreich's

ataxia were enrolled into a cohort study at 11 study centres in Europe (five centres in Germany [Aachen, Bonn, Marburg, Munich, and Tübingen] and one each in Belgium [Brussels], Austria [Innsbruck], UK [London], Spain [Madrid], Italy [Milan], and France [Paris]). Genetic testing was repeated for all study participants at the Laboratoire de Neurologie Expérimentale of the Université Libre de Bruxelles (Brussels, Belgium).¹²

All patients or their authorised surrogates provided written informed consent at enrolment into EFACTS. This study was approved by the local ethics committees of each participating centre.

Procedures

Assessments were done at all centres in accordance with the same written natural history study protocol. A full description of procedures and data collection is available in our report of the baseline data.⁷

Outcomes

For primary and secondary outcomes, patients were assessed at baseline (visit 1) and once a year for 2 years (visit 2 at 1 year and visit 3 at 2 years). Briefly, we used SARA¹³ as our primary outcome measure. SARA is a 40 point scale to quantify ataxia signs, in which a higher score shows more severe ataxia. Secondary outcome measures were the Inventory of Non-Ataxia Signs (INAS),¹⁴ which provides a count of non-ataxia signs such as changes in reflexes and other motor,

For more on EFACTS see <http://www.e-facts.eu>

sensory, or ophthalmological signs; the performance-based Spinocerebellar Ataxia Functional Index (SCAFI);^{15,16} a phonemic verbal fluency (PVF) test to probe executive cognitive functioning;^{17,18} the ADL functional activity scale part of the Friedreich Ataxia Rating Scale (FARS);¹⁹ and the self-reported quality of life index EQ-5D-3L.²⁰

Statistical analysis

Data are reported as mean (SD) or frequency, as appropriate. To enable comparison of responsiveness between outcome measures, we calculated standardised response means (SRM)—ie, the mean change in scores from baseline to follow-up divided by the standard deviation of the change. We estimated the yearly progression for each outcome with the linear mixed-effect modelling restricted-maximum-likelihood method with random effects on intercept and slope (proc MIXED in SAS version 9.4). The time variable was calculated in years—ie, days since the baseline visit divided by 365. We used unstructured covariance and adjusted the degrees of freedom by the between-and-within method. Based on previous reports showing differential rates of clinical decline in late-onset Friedreich’s ataxia (symptom onset at age ≥25 years) compared with typical-onset Friedreich’s ataxia (age ≤24 years),^{4,21} we further assessed progression over time within each disease onset group.

In a separate analysis, we tested the effects of demographic and disease-related factors on progression rates across the entire cohort. We modelled fixed

interaction effects between time and sex, age in years at baseline, educational level,²² age of symptom onset, baseline scores of the respective outcome measure, and number of FXN GAA repeats on each allele. Additionally, we included study site and baseline scores as main effects. Continuous variables were mean centred to help with interpretation. To assess the model fit, we visually inspected the residual plots and excluded observations of extreme outliers on the basis of the restricted likelihood distance. Because of potential bias caused by missing values, we reanalysed the data for our primary outcome measure SARA by use of an imputation method for missing observations. Furthermore, we were interested in cutoff values for specific factors that would enable selection of patients with higher rate of disease progression according to SARA. We described the established progression for SARA through individual factors (ie, SARA baseline, age in years at baseline, age of onset, and GAA repeat length) and tried to identify a cutoff point through breakpoint analysis of piecewise linear regression models (two regression lines; proc NLIN in SAS). Finally, on the basis of the established progression rate for SARA, we calculated sample sizes that would enable the detection of a reduction in progression as assessed with SARA in a parallel group interventional trial of treatments with different efficacies and observation periods of 1 year and 2 years.²³

Statistical analyses were done with SAS version 9.4. All tests were two-sided with a p value of 0·05 set as the threshold for significance. This study is registered with ClinicalTrials.gov, number NCT02069509.

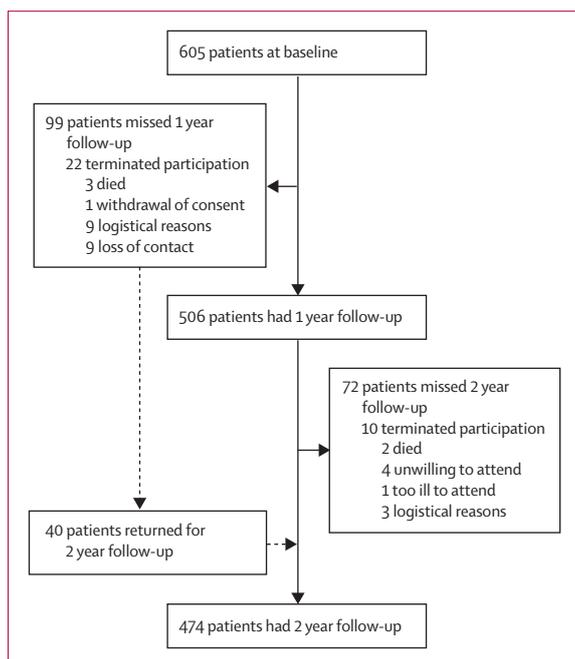


Figure 1: Study profile

	Full cohort (n=605)	Typical-onset Friedreich's ataxia (n=505)	Late-onset Friedreich's ataxia (n=100)
Women	325 (54%)	266 (53%)	59 (59%)
Age at study entry (years)	37·9 (13·9)	30·2 (11·8)	51·2 (9·7)
Age at onset (years)*	15·5 (10·4)	11·7 (5·1)	34·8 (8·7)
Disease duration (years)*	18·2 (10·3)	18·5 (10·6)	16·4 (8·1)
Disability stage†	4·8 (1·5)	4·9 (1·4)	3·9 (1·3)
Wheelchair bound	292 (48%)	280 (55%)	12 (12%)
Education (ISCED)‡	3·3 (1·3)	3·3 (1·3)	3·3 (1·3)
Number of FXN GAA repeats§			
Short allele 1	590 (270)	654 (239)	273 (177)
Long allele 2	903 (211)	934 (179)	753 (282)
Time between visits (years)			
Visit 1 to visit 2	1·1 (0·2)	1·1 (0·2)	1·1 (0·1)
Visit 1 to visit 3	2·1 (0·2)	2·1 (0·2)	2·1 (0·2)

Date are mean (SD) or n (%). ISCED=International Standard Classification of Education (1997). *Data are missing for one patient with typical-onset Friedreich’s ataxia. †Disability stage was recorded on a range from 1 (no functional handicap but signs at examination) to 6 (wheelchair bound) and 7 (confined to bed). ‡Data missing for three patients with typical-onset Friedreich’s ataxia. §Data missing for eight patients with typical-onset Friedreich’s ataxia.

Table 1: Baseline characteristics of the Friedreich’s ataxia cohort

Role of the funding source

The funders of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results

The first patient's baseline visit was on Sept 15, 2010, and the last patient of the cohort was recruited on Nov 29, 2013. The last 2 year follow-up visit of this cohort was on Jan 11, 2016, and the data were closed for this 2 year data analysis on Jan 28, 2016. Further follow-up assessments and recruitment of new patients for EFACTS are still ongoing. 611 potentially eligible individuals were screened for inclusion in the EFACTS database. In six individuals, the diagnosis of Friedreich's ataxia could not be genetically confirmed. Thus, 605 patients with genetically confirmed Friedreich's ataxia were enrolled at baseline (visit 1). Of these patients, 506 (84%) completed the 1 year follow-up assessment (visit 2) and 474 (78%) returned for the 2 year follow-up assessment (visit 3; figure 1). 546 (90%) patients contributed longitudinal data with at least one follow-up visit.

Table 1 shows the baseline demographic and clinical characteristics of the included patients. 505 (83%) patients had typical-onset Friedreich's ataxia and 100 (17%) had late-onset disease. The age of symptom onset was missing for one patient with typical-onset Friedreich's ataxia. 15 (2%) patients (including 13 with typical onset and two with late onset) were compound heterozygotes with an expanded GAA repeat on one allele and an *FXN* point mutation on the other allele.⁷ The remaining patients were homozygous for expanded GAA repeats in the *FXN* gene, with the shorter repeat containing at least 60 GAA triplets. The genetic dataset from the EFACTS laboratory was missing for eight patients with typical-onset Friedreich's ataxia who had previous genetic confirmation of homozygous GAA repeat expansion.

Frequencies of missing data for each outcome and visit are shown in the appendix. Available data at baseline ranged from 96% to 99% for SCAFI, ADL, INAS, and SARA, whereas less data were available for PVF (60%) and EQ-5D-3L (77%; associations of missing data at baseline with study site, demographics, and disease onset have already been addressed in our cross-sectional analysis⁸). Longitudinally, a large proportion of patients with at least two visits contributed data for SARA (90%), INAS (90%), SCAFI (88%) and ADL

See Online for appendix

	Baseline		1 year follow-up			2 year follow-up			Annual progression rate		
	Number of patients	Mean (SD)	Number of patients	Mean (SD)	SRM	Number of patients	Mean (SD)	SRM	Estimate (SE)	95% CI	p value
SARA (total score)	600	21.9 (9.6)	502	22.5 (9.5)	0.33	471	23.2 (9.1)	0.55	0.77 (0.06)	0.65 to 0.89	<0.0001
Typical onset	500	23.3 (9.4)	414	24.1 (9.2)	0.33	393	24.6 (8.9)	0.53	0.75 (0.07)	0.62 to 0.88	<0.0001
Late onset	100	14.7 (7.4)	88	14.9 (7.2)	0.29	78	16.2 (6.8)	0.69	0.86 (0.15)	0.57 to 1.16	<0.0001
INAS (count)	603	5.0 (1.9)	500	5.1 (1.9)	0.08	468	5.2 (1.8)	0.17	0.10 (0.03)	0.04 to 0.16	0.0007
Typical onset	503	5.2 (1.9)	412	5.3 (1.8)	0.04	390	5.3 (1.7)	0.10	0.06 (0.03)	-0.004 to 0.13	0.0676
Late onset*	100	3.9 (1.6)	88	4.3 (1.9)	0.27	78	4.6 (1.9)	0.50	0.33 (0.07)	0.18 to 0.47	<0.0001
SCAFI (z score)	579	-0.4 (1.7)	492	-0.4 (1.7)	0.05	452	-0.5 (1.6)	-0.05	-0.04 (0.01)	-0.05 to -0.02	<0.0001
Typical onset	485	-0.6 (1.8)	407	-0.5 (1.7)	0.07	377	-0.6 (1.7)	-0.02	-0.03 (0.01)	-0.05 to -0.01	0.0004
Late onset*	94	0.3 (0.7)	85	0.2 (1.0)	-0.13	75	0.1 (1.0)	-0.29	-0.07 (0.02)	-0.11 to -0.04	<0.0001
PVF (number of words)	359	13.9 (6.7)	359	15.0 (6.7)	0.19	345	15.8 (6.8)	0.43	0.99 (0.14)	0.72 to 1.26	<0.0001
Typical onset	288	13.0 (6.2)	287	14.1 (6.3)	0.18	279	15.1 (6.5)	0.36	0.90 (0.15)	0.60 to 1.20	<0.0001
Late onset	71	17.8 (7.3)	72	18.8 (6.8)	0.20	66	19.0 (7.4)	0.69	1.39 (0.30)	0.79 to 1.98	<0.0001
ADL (total score)	597	14.6 (7.8)	502	15.6 (7.8)	0.36	472	16.5 (7.9)	0.66	0.93 (0.06)	0.80 to 1.05	<0.0001
Typical onset	498	15.5 (7.9)	414	16.7 (7.9)	0.39	394	17.5 (7.9)	0.72	0.98 (0.07)	0.85 to 1.12	<0.0001
Late onset*	99	10.2 (5.3)	88	10.6 (4.9)	0.25	78	11.4 (5.4)	0.39	0.64 (0.16)	0.33 to 0.94	<0.0001
EQ-5D-3L index	466	0.60 (0.2)	405	0.6 (0.2)	-0.06	381	0.6 (0.2)	-0.22	-0.02 (0.004)	-0.03 to -0.01	<0.0001
Typical onset	374	0.6 (0.2)	322	0.5 (0.2)	-0.07	309	0.5 (0.2)	-0.24	-0.02 (0.004)	-0.03 to -0.01	<0.0001
Late onset	92	0.7 (0.2)	83	0.7 (0.1)	0.002	72	0.7 (0.1)	-0.16	-0.01 (0.01)	-0.02 to 0.01	0.4914

Higher values for SARA, INAS, and ADL represent greater impairment and vice versa for SCAFI, PVF, and EQ-5D-3L index. Annual progression rate was calculated as the slope of time effect based on linear mixed effects modelling. SARA=Scale for the Assessment and Rating of Ataxia. INAS=Inventory of Non-Ataxia Symptoms. SCAFI=Spinocerebellar Ataxia Functional Index. PVF=phonemic verbal fluency. ADL=activities of daily living. *Significant differences in slopes between onset groups at $p<0.05$. SRM=standardised response mean (ie, mean change compared to baseline divided by the standard deviation of the mean change).

Table 2: Outcome measures and annual progression rates

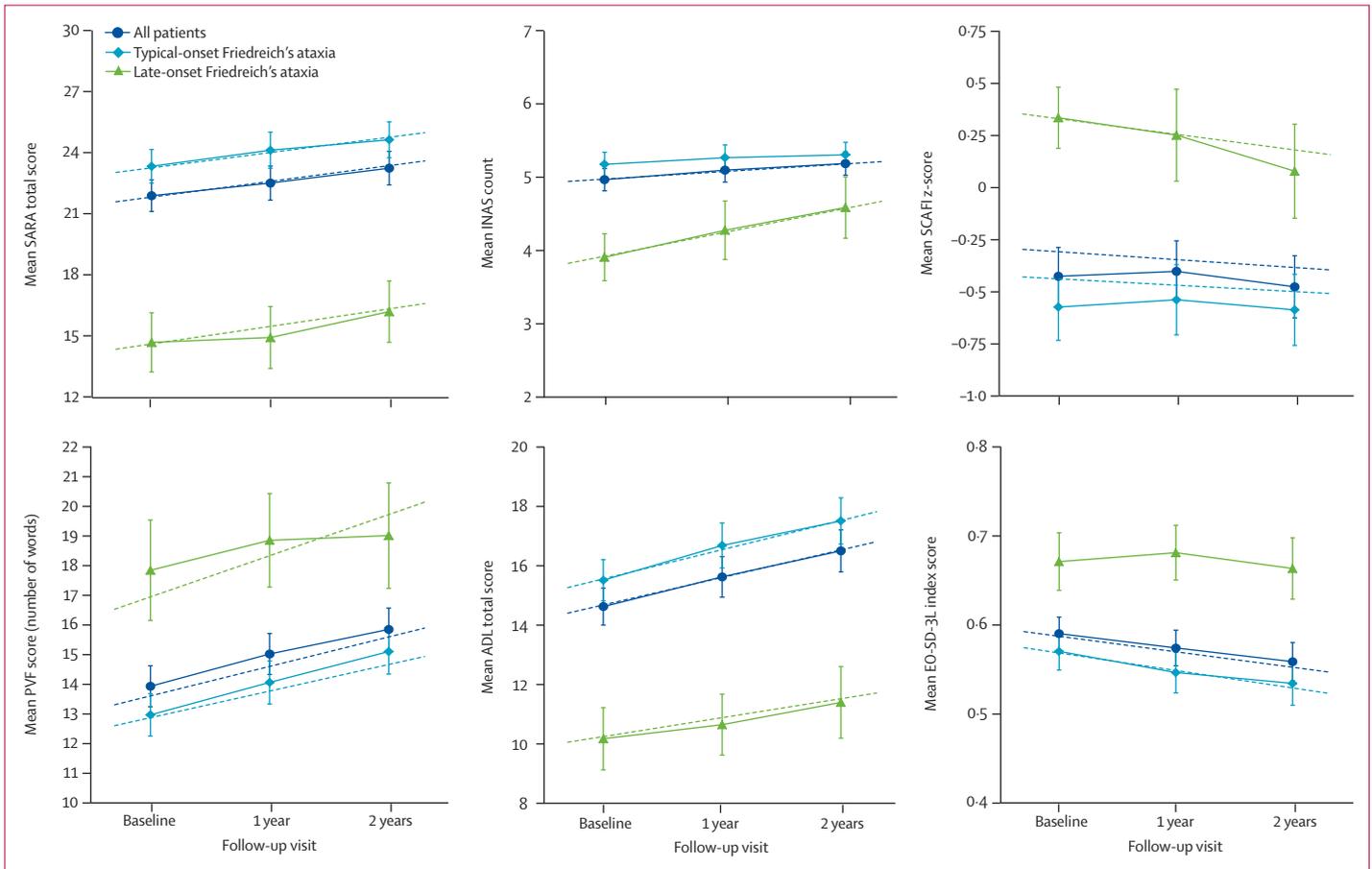


Figure 2: Progression of outcome measures for the whole cohort and by onset group

Data are means (95% CI shown as bars) at baseline, 1 year follow-up, and 2 year follow-up. Dashed lines show significant annual progression over time ($p < 0.05$) as estimated on the basis of linear mixed effect modelling (table 2). SARA=Scale for the Assessment and Rating of Ataxia. INAS=Inventory of Non-Ataxia Signs. PVF=phonemic verbal fluency. SCAFI=Spinocerebellar Ataxia Functional Index. ADL=activities of daily living.

(89%). Again, this number was lower for PVF (60%) and EQ-5D-3L (71%). Responsiveness of outcome measures (table 2) was highest for SARA (SRM 0.33 at 1 year follow-up and 0.55 at 2 year follow-up) and ADL (0.36 at 1 year and 0.66 at 2 years), and lowest for SCAFI (0.05 at 1 year and -0.05 at 2 years).

Mean scores for outcome measures at each visit and estimated yearly progression rates are shown in figure 2 and table 2. For linear mixed-effect modelling, observations of extreme outliers were excluded (three exclusions for SARA and three exclusions for INAS, 21 for SCAFI, nine for PVF, two for ADL, and eight for EQ-5D-3L). For SARA, progression was 0.77 points per year (SE 0.06) across the entire cohort. The rate of progression was slightly higher in patients with late-onset Friedreich's ataxia (0.86 points per year [0.15]) than for patients with typical-onset disease (0.75 points per year [0.07]), but the difference in slopes was not significant (-0.11 [0.17], 95% CI -0.44 to 0.21, $p = 0.49$). Furthermore, additional analysis of our primary outcome SARA by use of an imputation method for

missing observations yielded similar results (appendix). Analysis of factors that might affect disease progression (appendix), in which we assessed the effect of age of onset as a continuous variable on SARA progression across the entire cohort, showed that younger age of onset was associated with an annual worsening in SARA (-0.02 points per year [0.01] per additional year). Additionally, lower SARA scores at baseline were related to faster progression (-0.07 points per year [0.01] per additional SARA point). We did not find a continuous linear association between SARA progression and GAA repeat length. However, breakpoint analysis of linear regression models showed a cutoff for GAA repeat length on the shorter allele at 353 repeats (SE 117; 95% CI 123-584, $p = 0.0016$; appendix). In patients with more than 353 repeats on the shorter allele, SARA progression rate increased with repeat length (by 0.09 points per year [0.02] per additional 100 repeats, 95% CI 0.04-0.14). We did not find any cutoff values for SARA baseline scores, age, or age of onset related to SARA progression. Finally, based on the SARA

progression rate, we calculated sample sizes for an interventional, placebo-controlled trial with different treatment efficacies (figure 3). For a potential treatment efficacy of a 50% reduction in SARA progression rate and 80% statistical power, the required sample size for a 1 year trial would be 548 individuals (274 per group). The corresponding sample size in a 2-year observational period would be 184 individuals (92 per group).

Linear mixed-effect modelling showed a significant yearly change for all secondary outcomes. Across the entire cohort, progression was 0.10 points per year (SE 0.03) for INAS and -0.04 points per year (0.01) for SCAFI. For both measures, yearly worsening was stronger in late-onset Friedreich's ataxia than in patients with typical-onset. For INAS, the slope for typical-onset was 0.06 (0.03) and the slope for late-onset was 0.33 (0.07), giving a difference of -0.26 points (0.08; 95% CI -0.43 to -0.10, $p=0.0013$). For SCAFI, the slope for typical-onset was -0.03 (0.01) and the slope for late-onset was -0.07 (0.02), giving a difference of 0.04 (0.02; 95% CI 0.002-0.09, $p=0.04$). ADL scores changed by 0.93 points per year (0.06) in the entire cohort; however, patients with typical-onset Friedreich's ataxia had higher progression rates than did those with late-onset (0.98 points per year [0.07] for typical-onset vs 0.64 points per year [0.16] for late-onset, difference 0.35 points per year [0.17, 95% CI 0.01-0.68, $p=0.04$]). Furthermore we noted an improvement in PVF performance of 0.99 (0.14) words per year and worsening of the EQ-5D-3L index by -0.02 points per year (0.004) in the entire cohort. PVF and EQ-5D-3L did not significantly differ between onset groups (PVF: 0.90 words per year [0.15] for typical onset vs 1.39 [0.30] for late onset, difference -0.49 points per year [0.34; 95% CI -1.16 to 0.18, $p=0.15$]; EQ-5D-3L: -0.02 points per year [0.005] for typical onset vs -0.01 [0.01] for late onset, difference -0.01 points per year [0.01; 95% CI -0.03 to 0.01, $p=0.20$]).

Younger age at disease onset was related to the yearly worsening of INAS (-0.01 points per year [0.004] per additional year of onset), ADL (-0.04 points per year [0.01]), and EQ-5D-3L (0.002 points per year [0.001]), as well as reduced improvement in PVF (0.12 [0.02] words per year; appendix). Older age at baseline was also related to yearly worsening of INAS (0.01 points per year [0.003] per additional year of age), ADL (0.02 points per year [0.01]), and EQ-5D-3L (0.002 points per year [0.0004]), and less improvement in PVF (-0.05 words per year [0.01]). For each measure, less impairment (or better performance) at baseline was associated with greater deterioration over time (-0.21 points per year [0.02] per additional INAS point; -0.06 [0.01] per ADL point; -0.03 [0.01] per SCAFI point; -0.19 [0.02] per EQ-5D-3L point; and -0.19 [0.02] per word in PVF). Less improvement in PVF was associated with larger numbers of GAA repeats on the longer allele (-0.26 [0.07] per additional 100 repeats). The ability of larger numbers of GAA repeats

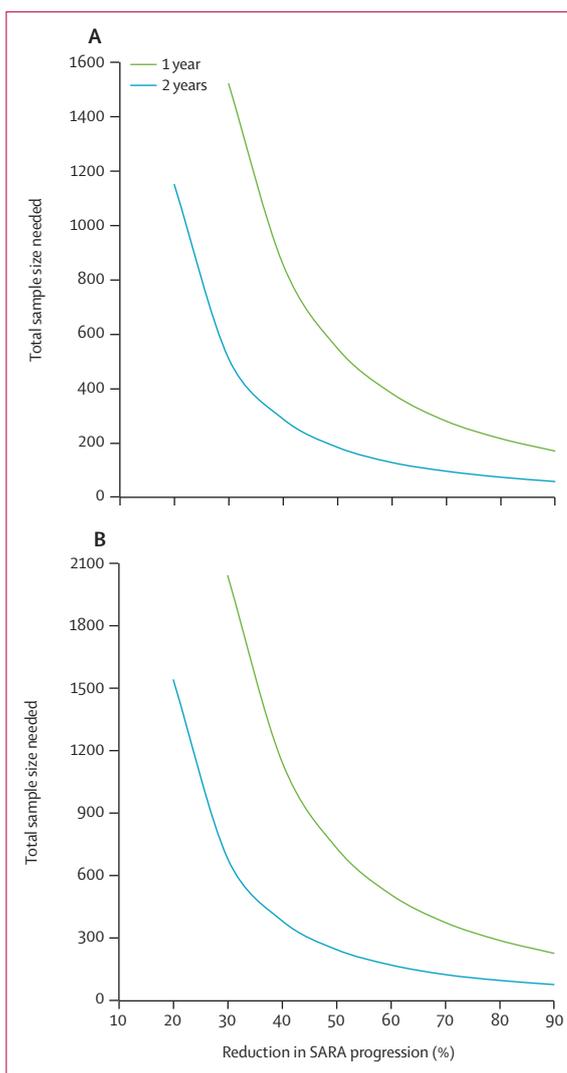


Figure 3: Sample size estimates

Required sample sizes to detect differences in SARA progression as a function of treatment efficacy (significance at $p<0.05$) for an observational period of 1 and 2 years and a statistical power of (A) 80% and (B) 90%. SARA=Scale for the Assessment and Rating of Ataxia.

on the shorter allele to predict worsening was not significant in ADL ($p=0.07$) or EQ-5D-3L ($p=0.08$). Sex effects existed only for PVF, with women showing a greater improvement over time (0.74 per additional word [0.27]). Lower educational levels were associated with decreased SCAFI performance over time (0.02 points [0.01] per year per ISCED unit).

Discussion

The results from EFACTS provide evidence of measurable phenotypic change in patients with Friedreich's ataxia over 2 years. The main results of the study are that SARA is a suitable clinical rating scale to detect deterioration of ataxia symptoms over time; ADL

is an appropriate measure to monitor changes in daily self-care activities; younger age at disease onset is a major predictor for faster disease progression; and sample sizes for interventional trials can now be calculated.

The main objective of EFACTS has been to define potential outcome measures for disease-modifying trials in Friedreich's ataxia. Our primary clinical outcome measure SARA showed good responsiveness, especially over 2 years (0.55), and a significant progression rate (0.77 points per year) across the entire Friedreich's ataxia cohort. Although the progression rate was slightly higher in late-onset Friedreich's ataxia (0.86 points per year) than in the typical-onset group (0.75 points per year), the late-onset group also showed higher variability of change in SARA with time, and the difference between onset-groups was not significant. Lower baseline SARA scores in patients with late-onset Friedreich's ataxia (table 2) might further account for the slightly increased progression rate, as we noted that low impairment at baseline predicts faster deterioration in ataxia symptoms over time. Further analysis supported earlier age of disease onset as being associated with greater worsening in SARA, which is in agreement with the results of our baseline report and other previous studies.^{6-8,10,24,25} Our analysis showed that the GAA repeat length of the shorter allele had differential predictive value for SARA progression, because the predictive value was only evident in patients with expansions of more than 353 repeats. This finding corresponds with previous evidence showing that GAA repeats interfere with in-vitro transcription in a length-dependent manner,²⁶ and might explain to some extent the findings of a previous longitudinal study²⁷ in which the link between SARA progression and GAA repeat expansion could not be substantiated. Generally, the length of the shorter allele is acknowledged to be more predictive of earlier disease onset and severity of disease⁵ than is the length of the larger allele.^{21,28}

Several different ataxia rating scales have been used in previous natural history studies of Friedreich's ataxia, including the International Cooperative Ataxia Rating Scale (ICARS),^{5,6,10,11} FARS,^{8,9,11,29} and SARA.^{5,7,27,30} ICARS and particularly FARS have been shown to be appropriate markers for the assessment of disease progression in Friedreich's ataxia in longitudinal studies of 1 year,¹¹ 2 years,^{8,9} and even up to 7 years.¹⁰ However, the compact nature of SARA and its ability to capture disease progression in Friedreich's ataxia favours use of SARA in clinical studies.

The EFACTS data can now enable the calculation of sample sizes for interventional trials, which is a major achievement for future trials of Friedreich's ataxia. For example, for a placebo-controlled trial, 548 patients would be needed to detect a 50% reduction in SARA progression at 80% power over 1 year. The required sample size for a clinical trial can be reduced to

184 patients by use of a 2 year study. Our calculated sample sizes correspond well with reported sample sizes from the American and Australian cohort,³¹ although our 2 year data differ, which might be due to the different statistical methods, different study designs, and lower retention rates of the American and Australian cohort. Our findings show that 2 years of observation would be needed for a feasible clinical trial. Prespecified selection criteria, such as lower baseline score, younger age of onset, or genetic aspects, might further decrease the number of patients needed.

Using INAS to assess non-ataxic signs in Friedreich's ataxia, we found that the number of non-ataxic features of the disease slightly increases over time, although effects were larger in patients who had late onset. This finding supports the notion that phenotypical changes in late-onset Friedreich's ataxia could evolve differentially and emphasises the need for consideration of non-ataxia signs, especially in this late-onset population. Again, both lower INAS baseline scores and younger age of disease onset had an effect on INAS deterioration, suggesting a more progressive appearance of symptoms with an earlier disease course. The functional composite index SCAFI showed a little responsiveness over time, but deterioration was significantly greater in late-onset Friedreich's ataxia than in early-onset disease. As shown for each outcome, better performance (or less impairment) at baseline was related to greater worsening over time, which might be explained by the potential extent of further progression in less impaired patients. Floor effects in SCAFI performance, however, are also likely,⁴ especially in patients with typical-onset Friedreich's ataxia, who are unable to complete all SCAFI tasks because of physical limitations (eg, 8 m walk). The neurocognitive measure PVF showed a somewhat surprising improvement of about one word per year in all groups. This improvement might have resulted from increased familiarity with the task in follow-up measurements, for which we also had a higher number of missing data, which compromised the interpretation of the results. SCAFI and INAS are appropriate for use as secondary outcome measures to detect changes in functional performance and to provide valuable information on non-ataxia signs, particularly in late-onset Friedreich's ataxia.

An important goal of our study was to quantify how Friedreich's ataxia progressively interferes with daily activities and affects patients' quality of life.⁷ The ADL measure of functional status showed high responsiveness (SRM 0.66 after 2 years) and yearly progression (0.93 points per year) across the entire Friedreich's ataxia cohort, which were more marked in the typical-onset group (SRM 0.72 and progression 0.98 points per year), but also apparent in the late-onset group (SRM 0.39 and progression 0.64 points per year). By contrast, the self-rated quality of life measure EQ-5D-3L showed a rather small decline,

probably reflecting the good cognitive and emotional status of patients with Friedreich's ataxia¹⁸ compared with those in other neurodegenerative diseases, such as Huntington's disease. In particular, the strong responsiveness of ADL, which was even superior to that for SARA, shows the need to include functional status and quality of life assessments in addition to motor function measures in clinical trials.

The 2 year follow-up of the EFACTS cohort provided clinically relevant data, but this is a short time for a slowly progressive disease such as Friedreich's ataxia. Additionally, although we tried to handle missing data with statistical procedures, dropout rates increased with time and varied substantially among measures. Fewer data were missing for SARA and ADL than for the other outcome measures, whereas more data were missing for other measures such as PVF and might have weakened the conclusions we could draw. Another limitation is that our study did not include quantitative neurophysiological or neuroimaging data.

In conclusion, our results of the 2 year analysis of the EFACTS cohort allowed substantiation of the suitability of the SARA and ADL as robust outcome measures for future therapeutic trials, which should be designed with an observational period of at least 2 years.

Contributors

PG, CM, AD, SB, KB, MP, and JBS conceived the study. PG, CM, AD, SB, TKlop, FJRdR, LS, TKloc, KB, MP, and JBS are site principal investigators and organised the study. KR, PG, CM, AD, SB, TKlop, FJRdR, LS, TKloc, KB, MR, MP, and JBS recruited, enrolled, and examined participants or did genetic testing. KR, ID, R-DH, and JBS designed the statistical analysis. R-DH, ID, and KR did the statistical analysis. KR, ID, and JBS wrote the first draft of the manuscript. All authors contributed to the writing and editing of the manuscript. All authors reviewed and revised the manuscript.

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Declaration of interests

LS, TKloc, KB, PG, AD, MP, and JBS report grants from the European Union (EU). AD has a patent EP14187649. MP reports grants and personal fees from Biomarin and Voyager Therapeutics and has a patent on methods for diagnosing Friedreich ataxia with royalties paid. JBS has received funding for travel and speaker honoraria from GlaxoSmithKline, Merz Pharmaceuticals, Medical Tribune, Lundbeck, Pfizer, Boehringer, and Bayer; has received research support from the BMBF and the EU; and has received advisory board honoraria from Lundbeck, TEVA, Novartis, and Eli Lilly. All other authors declare no competing interests.

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