Enzyme replacement therapy in Fabry disease, towards individualized treatment

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Quality of life in patients with Fabry disease: a systematic review of the literature

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Abstract

Fabry disease (FD), caused by deficiency of the lysosomal enzyme α-galactosidase-A, is a progressive multisystem disease. The disease is X-linked with generally more severe manifestations in males, but can impact on quality of life (QoL) of both male and female patients. The purpose of this literature review is to analyse the currently available data concerning QoL measurement, specifically which questionnaires have been used to measure QoL, how patients with FD score compared to the general population, and the effects of enzyme replacement therapy (ERT) on QoL. Fifty-four articles were relevant for this literature review. Patients with FD had a lower QoL compared to the general population. No definite conclusions could be drawn from the studies on the effect of ERT on QoL; natural history data is scarce, changes observed were limited and the cohorts were of small size. We propose that a FD specific questionnaire be made to accurately assess QoL in patients with FD.

Introduction

Fabry disease (FD) (OMIM#301500) is a rare X-linked lysosomal storage disorder. The disease is characterized by deficiency of the lysosomal enzyme α-galactosidase A (α-Gal A, E.C. 3.2.1.22). This results in a systemic accumulation of globotriaosylceramide (Gb3) and related glycosphingolipids in lysosomes in cells throughout the body. The prevalence of FD is estimated at 1:40.000-170.000 live births although recent newborn and high-risk group screening studies suggested that the prevalence of non-classical FD may be much higher than previously thought.[1-5] Phenotypically, FD can be distinguished in the more severe classical form of FD, predominantly affecting males, and a non-classical form, more prominent in males with residual enzyme activity. Although females can be as severely affected as male patients with classical FD, most of them have a more variable and attenuated phenotype and are therefore better characterised as non-classical patients.[6]

Early symptoms in classically affected male and female patients include angiokeratoma, anhydrosis, neuropathic pain, gastrointestinal symptoms and microalbuminuria. Later in life, progressive renal failure, heart failure and stroke generally occur. In non-classically affected male patients and most females, the disease presents with a more attenuated and variable disease course.[7-11] The shortened life expectancy and the morbidity of Fabry patients are strongly related to the degree of end-organ damage. Currently, two enzyme preparations are available for the treatment of FD (agalsidase alfa, Shire HGT, Boston MA, USA, and agalsidase beta, Genzyme Inc, Boston MA, USA). The initial clinical trials showed beneficial effects on neuropathic pain, cardiac mass and kidney function. However, it has been shown that despite enzyme replacement therapy (ERT), disease complications may still occur.[12-14]

Patients who suffer from FD have a lower quality of life (QoL) compared to healthy individuals. Neuropathic pain and anhidrosis are predictors of decreased QoL, presumably as a marker of more severe disease.[3] It has been postulated that ERT has a positive effect on QoL.[15,16] However, these studies used different measures of QoL and were only reported for small cohorts of patients. Interest in QoL measurements has increased over the past decades, because it is well recognized that, in addition to physical disabilities, emotional and psychological factors play an important role in the lives of patients with FD. Additionally, patient involvement with decision making and assessment of quality of care is increasing. Lastly, QoL measurements are needed for cost-effectiveness analyses, nowadays a requirement for reimbursement of therapy for some governments in the EU.[17] It is therefore important to gain a good understanding of the information available to us now.

This systematic review provides an overview of the current literature with the aim to improve our understanding of the QoL amongst patients with FD and to enhance the appropriate use of QoL instruments in clinical practice.

We specifically focus on which QoL measures have been used to determine if these different measures reveal similar results. Furthermore we review the literature on the potential effect of ERT on QoL.

Methods

Search strategy and study selection

The following electronic databases have been searched via OvidSP: Medline (1946 till December 10, 2014), Embase (1947 till December 10, 2014) and PsycInfo (1806 till December week 1, 2014). The Cochrane Central Register of Controlled Trials (CENTRAL, accessed December 10, 2014) has been searched as well.

The search terms used were: Fabry disease, quality of life, questionnaires, SF-36, EQ5D, pain measurement, BPI, peds QL, and their synonyms, Mesh terms (Medline) and headings (Embase). No limits were used. Detailed search strategies can be found in supplemental material A. The title and abstract of all articles obtained by the search were screened to identify studies where quality of life in patients with FD was studied. Reference lists of identified papers were hand searched for additional relevant citations. Original articles published in English, French and German were included. Case reports, case series on less than 5 patients, and review articles were excluded.

Data extraction

Data were recorded on the type of study (clinical trial, cohort study, before-after study, case series or registry study), number of subjects, gender and age groups (children and/or adults), together with the type of questionnaire used to assess QoL, disease severity and therapy status at the time of QoL assessment.

Statistical analyses

A meta-analysis was performed on studies reporting SF-36 or RAND-36 results using a fixed effect inverse variance weighting. Meta-analysis of other QoL measurements was not feasible because data were either not given in sufficient detail or QoL instruments were only used in single studies. Articles were included in the meta-analysis when mean domain scores with standard deviations or confidence intervals were provided. Pooled analysis for all studies combined, as well as for subgroups of studies, were performed. Subgroups were defined as: (1) studies performed in the period before ERT was available (untreated, mostly classically affected patients), (2) studies on the effect of ERT that report baseline measurements (untreated patients but with a treatment indication) and (3) studies in which only ERT treated patients were included. Results from the Bodily Pain and General Health subdomains from the RAND-36 were excluded because different scoring algorithm are used for these subdomains.

Results

The electronic search resulted in 532 publications. Cross-checking reference lists revealed four additional relevant papers. After removal of duplications 368 articles remained. One hundred eighty seven articles were selected based on title and abstract. A total of 54 articles were eligible for inclusion in this review (see supplemental material B) of which 26 reported detailed QoL data. A flow diagram is presented in figure 1.

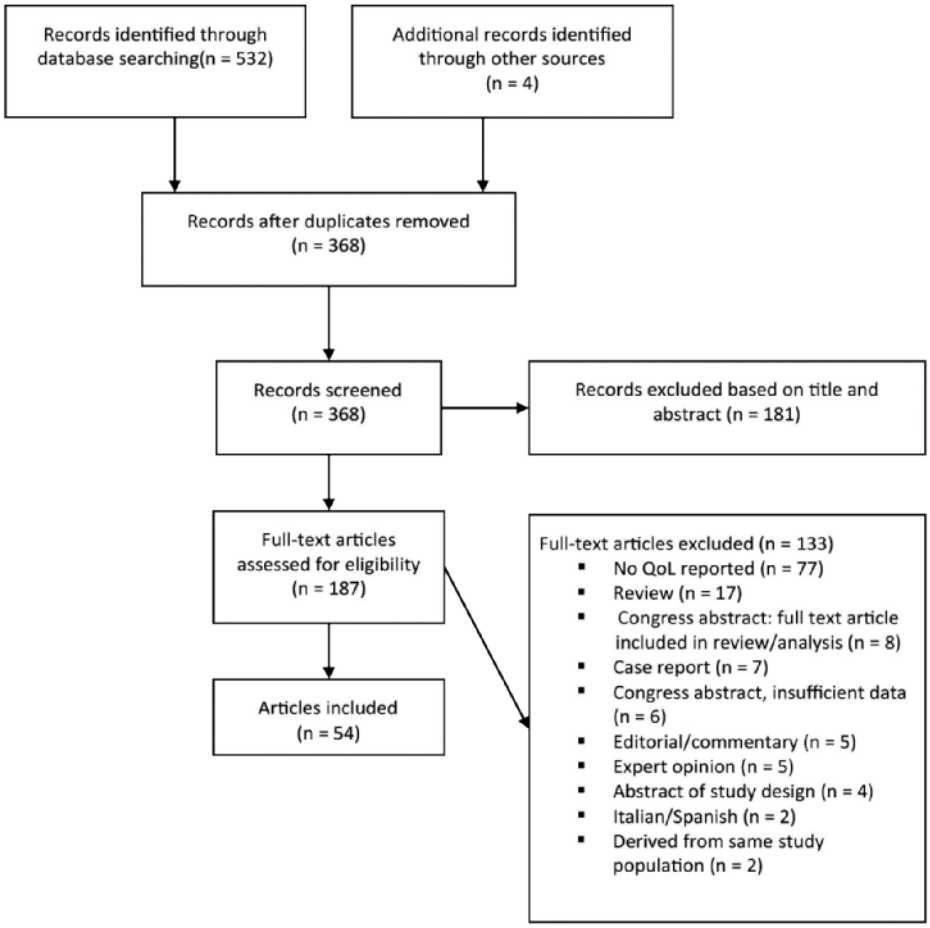

Figure 1 Flow chart of identification, screening and inclusion of articles in the systematic review.

Questionnaires used to assess quality of life in Fabry disease

Fifteen different questionnaires have been used to assess QoL in FD populations, amongst which the Short Form (36) Health Survey (SF-36), the EuroQoL five dimensions questionnaire (EQ-5D) and the interference score of the Brief Pain Inventory (BPI) were the most frequently used measures. A short description of these questionnaires is given below.

Other questionnaires used were: the Anderson-Fabry Disease specific questionnaire,[7,18,19] Child Health Questionnaire,[20] Fabry-Specific Pediatric Health and Pain Questionnaire (FPH-QP),[21] KINDL,[21] PedsQL,[22] RAND-36,[23] Rankin scale,[24] WHOQOL-100,[25] and four locally developed questionnaires.[26-29]

SF-36 and RAND-36

The SF-36 questionnaire assesses 8 domains of QoL: (1) Physical Functioning, (2) Role Physical, (3) Bodily Pain, and (4) General Health, (5) Vitality/Energy, (6) Social Functioning, (7) Role Emotional, and (8) Mental Health. SF-36 domain scores range from 0 to 100.[30] The 8 domains can be grouped into two summary scores: the Physical Component Summary (PCS) and the Mental Component Summary (MCS). These scores are computed by multiplying each of the 8 individual SF-36 scores by their specific factor score coefficients. MCS and PCS are norm based summary scores, which are standardised with a T-score transformation resulting in a mean of 50 with a standard deviation of 10. Studies of cross-sectional differences between clinically defined patient groups have suggested a 3 to 5 point change on any SF-36 scale as minimally clinically important difference (MCID).[31] The RAND-36 is virtually identical to the SF-36 however for the domains General Health and Bodily pain the scoring algorithms are different.[32]

EQ-5D and EQ-VAS

The EQ-5D questionnaire is comprised of 5 domains: (1) mobility, (2) self-care, (3) anxiety/depression, (4) usual activities and (5) pain/discomfort.[33] Each domain has 3 levels of severity: (1) no problems, (2) some or moderate problems, and (3) extreme problems. Results from the EQ-5D descriptive system can be converted into a utility score for the calculation of quality-adjusted life years (QALYs) via an algorithm that uses population-based preferences. Utility scores range from -0.11 (all five ED-5D health domains reported extreme problems) to 1 or perfect health (no problems at all five EQ-5D domains), in which zero means dead and negative utility scores represent health states worse than dead. A difference or improvement of 0.074 is considered to be of clinical importance.[34] The EuroQol Visual Analog Scale (EQ-VAS) is a visual analogue scale ranging from 0 to 100 which assesses health state. The minimal important difference is considered to be 7.[35]

BPI

The Brief Pain Inventory (BPI) has been designed to assess the severity of pain and the impact of pain on daily functions.[36] The latter is reflected by the BPI interference score, which

is the average of the following interference subscales: general activity, mood, walking ability, normal work, relations with other people, sleep and enjoyment of life. These subscales are scored from 0 to 10, with an estimated minimal important difference of 1 or 0.5 SD.[37]

Quality of life in patients with Fabry disease versus the general population

Eleven studies that investigated QoL in a cohort of FD patients with the SF-36 or the RAND-36 supplied sufficient data for the meta-analysis.[3,16,19,23,38-44] The results of this meta-analysis (males and females, and treated and untreated patients combined) are depicted in Figure 2. In general, patients with FD scored worse across all domains compared to the general population.[45] Seven studies reported sufficient data to stratify results by gender and ERT treatment status.[3,16,19,38,41,42,44] Pooled SF-36 scores of these 7 studies are presented in Figure 3.

Six studies provided the PCS and MCS.[19,22,38,39,43,46] Pooled analysis (males and females, and treated and untreated patients combined) revealed a weighted mean of the PCS and MCS of 42.8 (SEM: 0.62) and 48.7 (SEM: 0.52), respectively.

The studies that only mentioned whether or not QoL was better or worse compared to the general population, without providing exact scores, supported these findings; they all showed that QoL in Fabry patients was worse for some or all domains.[47-52]

In total, 7 studies used the EQ-5D to compare QoL in patients with FD versus the general population. In 2 studies mean EQ-5D utility scores of 0.66and 0.56were reported.[19,53] The first study was performed in a mixed cohort consisting of males and females, either treated or untreated, while the latter comes from the pre-ERT era and studied only male patients. These scores were both significantly lower than the general population, with 1 of these 2 studies reporting an estimated difference of -0.23.[53] The third study reported a mean difference of -0.24 in a combined cohort of treated and untreated male and female patients compared with the general population, also a significant difference.[54] Two other studies only mentioned that the EQ-5D score was lower, in a cohort of primarily treated male patients and a cohort of treated female patients without providing any exact data.[51,55] Finally, two studies reported EQ-VAS scores in mixed cohorts of 21 and 33 untreated and treated FD patients which were significantly lower compared to the general population and matched controls, respectively.[40,44]

One study used the BPI interference score to measure pain related QoL in male and female patients with FD, either treated or untreated. Compared to age- and gender matched healthy controls, they scored significantly worse (0.4 versus 2.0).[46]

In addition, several other studies suggested a negative influence of FD on QoL, but no comparison with a reference population was made.[7,8,18,28,29,56,57]

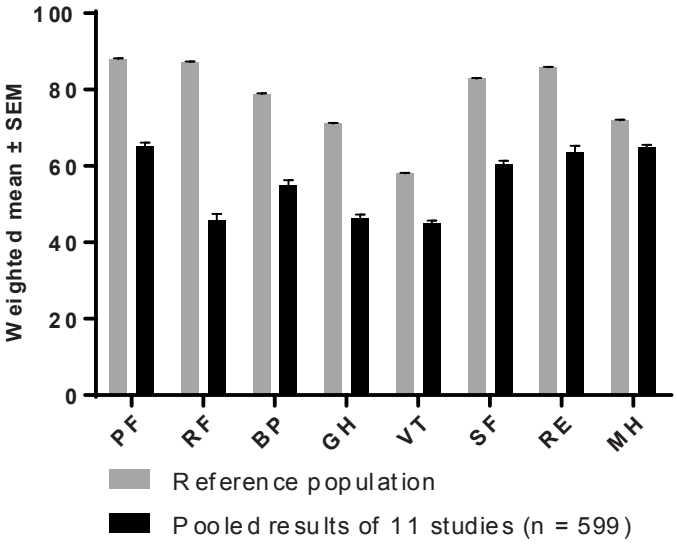

Figure 2 Pooled results of SF-36 subdomain scores. Weighted mean and SEM. Results from treated and untreated, male and female patients. Reference population derived from Jenkinson et al.[45] PF = Physical Functioning, RP = Role Physical, BP = Bodily Pain, GH = General Health, VT = Vitality, SF = Social Functioning, RE = Role Emotional, MH = Mental Health.

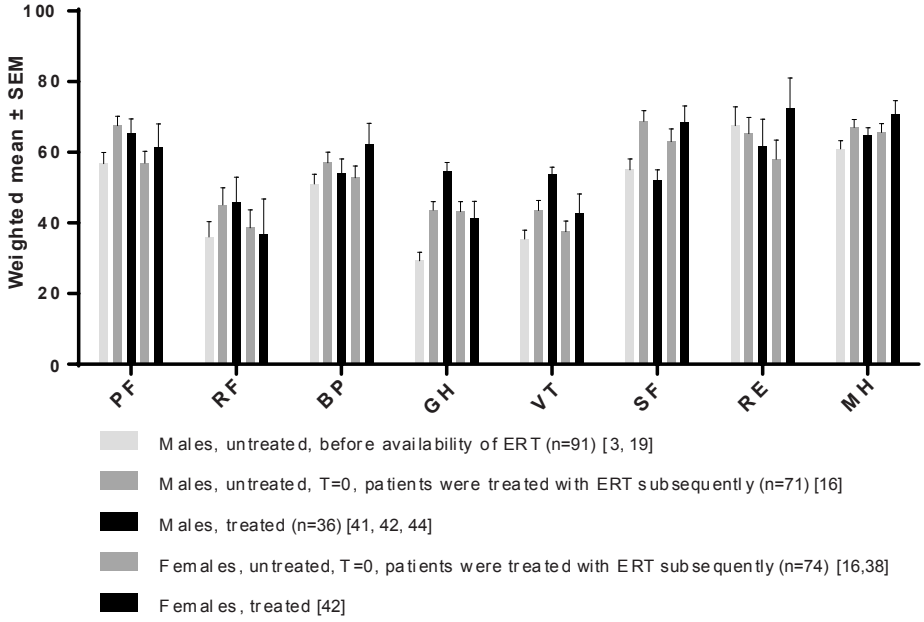

Figure 3 Pooled results of SF-36 subdomain scores stratified by gender and treatment status. Weighted mean and SEM. PF = physical functioning, RP = role physical, BP = bodily pain, GH = general health, VT = vitality, SF = social functioning, RE = role emotional, MH = mental health.

The relation between quality of life, disease severity and age

Renal disease, disease severity and age are related to QoL in FD. Renal disease impacts on the QoL of FD patients. Significant differences for all SF-36 domain scores except for Mental Health were reported among FD patients with an eGFR of >60 ml/min/1,73m^2, patients with an eGFR of <60 ml/min/1,73m^2 and patients receiving renal replacement therapy (RRT). Median PCS scores were 49.8 (eGFR >60), 35.9 (eGFR <60) and 29.4 (RRT). The MCS scores were 47.1 (eGFR >60), 49.8 (eGFR < 60) and 30.1 (RRT).[58] Others have shown a negative correlation between MSSI (Mainz Severity Score Index) scores and QoL,[39,55] which was supported by Rombach et al. who defined four disease states; asymptomatic, acroparasthesia/symptomatic, single complication and multiple complications, and found lower EQ-5D utility scores with more severe disease (0.87, 0.76, 0.74, and 0.58 per state, respectively).[59] Hoffmann et al. investigated specifically gastro-intestinal (GI) complaints amongst male and female patients with FD and unknown treatment status.[60] Using the EQ-5D, patients with GI complaints had a lower EQ-5D score than those without GI complaints.

In line with the relation between disease severity and QoL, higher age has been associated with lower QoL.[9,19,22,39] QoI in males starts to decline at younger age than in female patients as shown by a Fabry Registry (a Genzyme sponsored post-marketing drug registry) study in which males between 18 and 25 years of age had significantly lower SF-36 scores in 6 of 8 subdomains whilst females had normal scores in all but the subscales Bodily Pain and General Health.[9] Above the age of 25, both males and females showed impaired QoL in the subdomains Physical Functioning, Bodily Pain, General Health and Vitality. Females scored better in the Social Functioning domain, while males scored better in the Mental Health subscale.[9]

Effect of enzyme replacement therapy on quality of life

Two studies reported detailed SF-36 scores to show the effect of ERT on QoL. One Phase IIIB study in 15 female patients with clinical evidence of FD (*i.e.* involvement of at least 3 organ systems) reported baseline scores.[38] In addition, scores were reported after 13 and 27 weeks of treatment. No control group was included. After 13 weeks of treatment no changes were seen. At week 27, domain scores for Role Physical and General Health were increased, while the other domain scores stayed stable. PCS was 35 (SD: ±12) at baseline, stayed stable after 13 weeks and improved by 6.6 (SD: ± 6.0) after 27 weeks of treatment. MCS was 40 (SD: ±15) at baseline, and similar scores were found after 13 and 27 weeks of treatment.

The second study, based on data from the Fabry Registry, investigated the mean change after 24 months of treatment compared to baseline for males and females separately.[16] Although the Fabry Registry had data of 3128 patients at that time, only for 71 male patients baseline QoL data and three post treatment assessments during a period of 36 months were available. In addition, 59 female patients had baseline and at least 2 post treatment assessments during a period of 24 months. Limited data on genotype, phenotype and dis-

ease severity were given. Males showed improvements for all 8 domains after 24 months of treatment with changes from baseline ranging between 4.6 in the Mental Health domain to 14.6 in the Role Physical domain. Females also showed improvements from baseline after 24 months of treatment for Bodily Pain, Vitality, Social Function and Mental Health; 6.1, 7.3, 8.4 and 5.1 respectively. Other domain scores did not change significantly. PCS and MCS scores were calculated at baseline, 12 months and 24 months in the male and female groups, and after 36 months in the male group only. Male PCS and MCS scores were 39 (SD: ±10.9) and 46 (SD: ±10.3) at baseline and did not change significantly after 36 months. Likewise, female PCS scores (baseline score: 37 (SD: ±12.9)) remained stable. MCS scores of females improved from 46 (SD: ±11.8) to 49 (SD: ±11.5) after 24 months.

One study measured mean scores for all domains at baseline, 4 years and 7 years of treatment.[61] Mean SF-36 domain score was 62 (SD: ±19) at baseline and 59 (SD: ±21) after 4 years. After 7 years of treatment the mean score was 57 (SD: ±16) coming from 66 (SD: ±18) at baseline. Changes were not statistically significant, except for the subdomain Social Functioning which worsened significantly after 7 years of therapy. This abstract did not provide patient characteristics, study type, nor detailed baseline and follow-up scores.

Seven studies did not report mean SF-36 domain or summary scores but only mentioned if improvements were observed.[48,51,62-66] Five studies mentioned improvements in one or more domains after introduction of ERT, while two studies reported no significant change after 24-36 months of treatment.[51,66] One of these studies included a placebo group.[62] Both the patients in the placebo and the treatment group showed improvements in the domain Role Physical. In addition, treated patients showed improvement in Role Emotional whereas the placebo patients showed an improvement in the domain Bodily Pain. A study that assessed the relation between treatment duration and QoL reported a negative correlation between time on ERT and SF-36 PCS and MCS scores.[22]

Three studies, all using Fabry Outcome Survey (FOS, a Shire sponsored post-marketing drug registry) data, used the EQ-5D to measure the effect of ERT on QoL.[53,54,67] Baseline scores were between 0.61 and 0.64, and improvements to 0.74 after 1 year of treatment, and a trend towards improvement to 0.69 in males and 0.72 in females after 4 years of treatment was observed.[53,67] The third study calculated the difference compared to the general population.[54] At the start of treatment the score was -0.24 lower than the general population and after 5 years of treatment -0.17 below the general population. Wyatt et al studied the relation between time on ERT and EQ-5D score and found no significant correlation, while EQ-VAS reduced with increased treatment duration.[22] A randomised controlled trial in 14 male patients on the efficacy of agalsidase alfa showed a significant difference in change from baseline in BPI interference scores after 24 weeks of ERT, favouring the ERT treatment group (-1,1 vs -0.6).[15] A second randomized controlled trial did not find an effect of different dosing regimens on this score in the short term.[68]

Two studies reported on the effect of home based infusion therapy in comparison to hospital based infusion therapy. A before-after study showed improvement of all SF-36 subscales except Physical Functioning.[69] A cross-sectional study reported less stress and less negative impact on family life after introduction of home treatment.[27]

Effect of the shortage on quality of life

In 2009 a temporary worldwide interruption of enzyme supply led to dose reductions or cessation of treatment in groups of FD patients.[70] Three studies investigated the effect of dose decrease or interruption on QoL. Two articles used the SF-36 questionnaire and one article used EQ-5D. The first study using combined data from patients on lower doses of agalsidase beta and patients who switched to agalsidase alfa, showed lower scores for females in the General Health and Vitality domains during the shortage.[42] The second reported no change in MCS and PCS scores after dose reduction of agalsidase beta.[71] The latter, using EQ-5D, showed no change after the switch from agalsidase beta to agalsidase alfa, although a trend towards improvement was seen.[72]

Quality of life in children with Fabry disease

In a paediatric cohort of 87 children (boys and girls combined) the mean EQ-5D utility score was 1.00 (SD ±0.0), the mean of the interference score of the BPI was 0.76 (SD 1.47), and the KINDL showed a moderate impact on QoL and daily life, with the most severely affected domains being personal feeling, family and friends.[21] In 22 boys and girls of whom seven received ERT the total PedsQL score as well as the subscales physical functioning and school functioning decreased with age, while no relation with time on ERT was found.[22] BPI interference scores decreased after introduction of ERT in 13 children.[73] In nine children (age <10) all subscales of the Child Health Scores were lower, but only bodily pain and mental health were significantly different from a healthy control population. Children above the age of 10 years only scored worse on the bodily pain domain compared to the control population.[20] Thirty-six adolescent patients scored worse on the SF-36 compared to general population; boys reported decreased QoL in all subscales, except for Role Emotional, while females scored worse in the subscales Bodily Pain and General Health.[74]

Quality of life in Fabry disease vs other chronic illnesses

Street et al. investigated data from female FD patients and compared them with cohorts with multiple sclerosis (MS) and rheumatoid arthritis (RA) using the RAND-36.[23] Females with FD scored better on the Physical Functioning domain than MS and RA patients (67 versus 37 and 51, respectively). Similar scores were found in patients with FD and patients with MS in the domains Role Emotional, Energy and Emotional Well-being patients with FD while RA patients scored better. Social functioning and Role Physical scores in patients with FD were comparable to those in patients with RA, while patients with MS scored worse in these domains. Pain scores of FD patients were worse than those in MS patients but better than those in RA patients (62 versus 74 and 56, respectively). General health is lower in patients

with FD than in patients with MS and RA (45 versus 53 and 51, respectively). A second study compared patients with FD to patients with RA, MS, central neuropathic pain and Gaucher disease (GD).

Baseline SF-36 scores were similar to MS and GD patients. General Health and Vitality scores in patients with FD were comparable to those in RA and central neuropathic pain patients.[16] A third study reported substantially lower General Health, Vitality, Social Functioning, Role Emotional and Mental Health domain scores in female patients with FD compared to patients with RA.[38]

In addition, patients with FD have been compared to severe haemophiliacs.[19] MCS and EQ-VAS scores were lower in patients with FD; PCS scores and EQ-5D were similar in both populations. Finally, a study using WHOQoL-100 compared QoL of FD patients with that of PKU patients.[25] General QoL as well as the physical, independence, facet medication domains were lower in patients with FD. The scores in the psychological, spiritual and environmental domains were similar.

Discussion

This systematic review of quality of life in Fabry patients from 54 articles and abstracts has led to two major findings. Firstly, a consistent finding from all studies is that Fabry patients suffer from a considerably worse quality of life as compared with the general population. This was found for all domains in the SF-36 and in the EQ-5D questionnaires. Secondly, the studies on the effect of ERT on QoL are inconclusive.

Both the SF-36 and EQ-5D revealed that patients with FD clearly have lower QoL scores in comparison with the healthy population. However, in the interpretation of these results, some of the study characteristics need to be taken into consideration; firstly, disease severity is rarely comprehensively reported and if reported, the data varies between studies. Rombach et al. showed that disease severity plays an important role for measuring QoL and should therefore be taken into account when measuring QoL scores.[59] This is further supported by the finding of a correlation between the MSSI (a measure for disease severity) and QoL.[39,55] In addition, more severe kidney disease has been shown to lead to reduced QoL, in particular after initiation of renal replacement therapy.[58] Also, no studies on the difference in QoL between patients with either classical or non-classical FD have been performed, although this would have been interesting considering their different disease courses. The influence of phenotype is illustrated by Gold et al., who measured SF-36 scores for untreated male patients before the introduction of ERT. In these severely, mostly classically affected males, domain scores ranged between 24 and 61, which is worse compared to QoL scores found after the introduction of ERT, even if only baseline scores (prior to start of ERT) are

considered. This difference can be partly explained by the inclusion of non-classical patients in the more recent studies. In addition, most studies investigated a Fabry population consisting of both males and females. As noted by Wilcox et al. differences are observed between males and females and at what age the quality of life starts to decline for either gender.[9] Both are factors that need to be taken into consideration. Thirdly, many of the cohorts studied consisted of treated and untreated patients together. More studies in subgroups of patients are needed to gain a better insight into the influence of phenotype, gender and treatment on QoL.

If specifically looking at the effect of ERT on QoL, only a limited number of studies reported baseline and follow-up data in detail, showing different results. One study of only women, with a small sample size and without a control arm discovered a very minor change after 27 weeks. Another study reported a minimal improvement in BPI interference score after 24 weeks, although it should be noted that baseline BPI scores were different between both treatment arms and decreased in both groups.[15] One might argue that 6 months is too short to detect any effect from ERT on QoL scores. However, a third study showed no change in subdomains of the SF-36 after 4 and 7 years of therapy except for Social Functioning, which worsened after 7 years of therapy.[61] Another explanation could be that the questionnaires are not sensitive enough to show a clear effect in patients with FD. Baumstarck et al. demonstrated that generic questionnaires often are more suitable for universal applications where QoL is compared in different populations, while disease specific instruments focus on particular health problems and are more sensitive for detecting and quantifying small changes.[75,76] This would suggest that a Fabry specific QoL questionnaire would provide a more sensitive tool to investigate the effects of ERT on the QoL. At this point no validated FD specific QoL questionnaire exists and it would be worthwhile to develop such a questionnaire for this patient group. The studies based on data from the Fabry Registry or Fabry Outcome Survey all showed an improvement.[16,53,54,67] Despite being large, these registries have their shortcomings as has been published by Hollak et al.[77]

Follow-up data on QoL of only a very small percentage of patients enrolled in these registries were available for the analysis making the results susceptible to selection bias. Furthermore, the limited information on genotype, phenotype and disease severity of the patients in these registry studies makes comparison between cohorts impossible. Finally, differences before and after therapy are small, especially when comparing to the 3-5 point (SF-36) or 0.074 (EQ-5D) minimally clinically important difference (MCID). However, whether the standard MCID's are applicable to FD can be questioned. For example, Wyrwich et al. demonstrated that three different expert panels provided three different Clinically Important Differences for three different diseases; chronic obstructive pulmonary disease (COPD), asthma, and heart disease, respectively.[78] This would imply that a FD specific MCID needs to be defined for an optimal interpretation of the results. Altogether, no clear answer can be given whether ERT has a positive or negative effect on standard QoL scores in patients with FD.

Apart from the need for more sensitive questionnaires and disease specific MCID's, another important caveat is the lack of QoL data from untreated patients with similar disease severity as those treated with ERT. Only two short-term placebo-controlled trials of ERT in FD with QoL as a secondary outcome measure have been performed. One of those studies revealed significant improvement in both placebo and treated arms,[62] while the other showed a small improvement in BPI interference score compared to the placebo group.[15] The 3 studies published on the effects of the shortage did provide us with an opportunity to see how ERT affected the QoL once the preparation or dose was changed. However, these studies were of relatively short duration and no clear conclusion can be drawn from the results. Two studies reported stable QoL scores, while one study established a decline in two subdomains of the SF-36, only in female patients.[42] Whether anxiety of patients due to the situation of shortage played a role is unknown as well.

Finally, several national governments currently ask for cost effectiveness analyses to aid in reimbursement decisions. SF-36 and EQ-5D utility scores play a central role in these analyses. Based on these scores, QALY's are calculated and subsequently used to obtain costs per QALY. This development stresses the importance for the collection of high quality QoL data both before and during treatment.

Conclusion

Patients who suffer from FD have a considerably lower QoL compared to the general population; this was shown in two generic questionnaires, the EQ-5D and the SF-36. The effect of ERT is however inconclusive; small cohorts, lack of data and limited natural history data hamper a definite conclusion. We propose that a FD specific QoL questionnaire is developed to accurately monitor patients who suffer from this disease.

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79.

Supplemental table A

Supplemental table A Search strategy

EMBASE (1947 – December 10, 2014), via OvidSP		
Fabry disease		
1	exp Fabry Disease/	
2	fabry*.ti,ot,ab,hw,kw.	
3	(angiokeratoma adj3 diffusum).ti,ot,ab,kw,hw.	
4	(diffuse angiokeratoma*).ti,ot,ab,kw,hw.	
5	(galactosidase adj3 deficiency).ti,ot,ab,kw,hw.	
6	exp alpha-Galactosidase/	
7	(alpha galactosidase).ti,ot,ab,kw,hw.	
8	(GLA adj3 deficiency).ti,ot,ab,kw,hw.	
Enzyme replacement therapy		
9	replagal.ti,ot,ab,kw,hw,tn.	
10	exp agalsidase alfa/	
11	fabrazyme.ti,ot,ab,kw,hw,tn.	
12	exp agalsidase beta/	
13	agalsidase.ti,ot,ab,kw,hw,tn.	
Quality of life		
14	exp "Quality of Life"/	
15	(quality adj3 life).ti,ot,ab,kw,hw.	
16	(QoL or hrQoL).ti,ot,ab,kw,hw.	
Questionnaires		
17	exp Questionnaires/	
18	questionnair*.ti,ot,ab,kw,hw.	
Quality of life questionnaires		
19	exp Short Form 36/	
20	(SF-36 or SF36 or sf 36 or short form 36 or short form-36).ti,ot,ab,kw,hw.	
21	(RAND 36 or RAND36 or RAND-36 or (RESEARCH adj2 DEVELOPMENT 36) or RAND-36 item Health Survey or RAND 36 item Health Survey).ti,ot,ab,kw,hw.	
22	(EQ5D or EQ-5D or EuroQol or Euro-QoL).ti,ot,ab,kw,hw.	
23	(QOLS or Quality of life scale).ti,ot,ab,kw,hw.	
24	(PedsQL OR (pediatric quality of life)).ti,ot,ab,kw,hw.	
25	(FPHPQ OR (Fabry-specific Pediatric Health and Pain Questionnaire)).ti,ot,ab,kw,hw.	
26	((AFD specific questionnaire) or (Fabry* and specific questionnaire) or (AFD specific questions) or (Fabry* and specific questions)).ti,ot,ab,kw,hw.	
27	((Disease severity scoring system) OR (DS3)).ti,ot,ab,kw,hw.	
Pain questionnaires		
28	exp pain assessment/	
29	(BPI or (brief pain inventory)).ti,ot,ab,kw,hw.	
30	exp Brief Pain Inventory/	
31	exp McGill Pain Questionnaire/	
32	(McGill pain).ti,ot,ab,kw,hw.	
33	(FPQ or (Fabry pain questionnaire)).ti,ot,ab,kw,hw.	
Combined		
34	or/1-13	*Combined concepts Fabry and enzyme replacement therapy*
35	or/14-33	*Combined concepts Quality of life and questionnaires*
36	34 AND 35	*Combined search, results used in the current study*

Supplemental table A Search strategy (Continued)

MEDLINE (1946 – December 10, 2014) , via OvidSP		
Fabry disease		
1	exp Fabry Disease/	
2	fabry*.ti,ot,ab,kf.	
3	(angiokeratoma adj3 diffusum).ti,ot,ab,kf.	
4	(diffuse angiokeratoma*).ti,ot,ab,kf.	
5	(galactosidase adj3 deficiency).ti,ot,ab,kf.	
6	exp alpha-Galactosidase/	
7	(alpha galactosidase).ti,ot,ab,kf.	
8	(GLA adj3 deficiency).ti,ot,ab,kf.	
Enzyme replacement therapy		
9	replagal.ti,ot,ab,kf,nm.	
10	fabrazyme.ti,ot,ab,kf,nm.	
11	agalsidase.ti,ot,ab,kf,nm.	
Quality of life		
12	exp "Quality of Life"/	
13	(Quality adj3 life).ti,ot,ab,kf.	
14	(QoL or hrQoL).ti,ot,ab,kf.	
Questionnaires		
15	exp Questionnaires/	
16	Questionnair$.ti,ot,ab,kf.	
Quality of life questionnaires		
17	(SF-36 or SF36 or sf 36 or short form 36 or short form-36).ti,ot,ab,kf.	
18	(RAND 36 or RAND36 or RAND-36 or (RESEARCH adj2 DEVELOPMENT 36) or RAND-36 item Health Survey or RAND 36 item Health Survey).ti,ot,ab,kf.	
19	(EQ5D or EQ-5D or EuroQol or Euro-QoL).ti,ot,ab,kf.	
20	(QOLS or Quality of life scale).ti,ot,ab,kf.	
21	(PedsQL OR (pediatric quality of life)).ti,ot,ab,kf.	
22	(FPHPQ OR (Fabry-specific Pediatric Health and Pain Questionnaire)).ti,ot,ab,kf.	
23	((AFD specific questionnaire) or (Fabry* and specific questionnaire) or (AFD specific questions) or (Fabry* and specific questions)).ti,ot,ab,kf.	
24	((Disease severity scoring system) OR (DS3)).ti,ot,ab,kf.	
Pain questionnaires		
25	exp Pain Measurement/	
26	(BPI or (brief pain inventory)).ti,ot,ab,kf.	
27	(McGill pain).ti,ot,ab,kf.	
28	(FPQ or (Fabry pain questionnoire)).ti,ot,ab,kf.	
Combined		
29	or/1-11	*Combined concepts Fabry and enzyme replacement therapy*
30	or/12-28	*Combined concepts Quality of life and questionnaires*
31	29 AND 30	*Combined search, results used in the current study*
PsychInfo (1806 till December week 1, 2014) , via OvidSP		
Fabry disease		
1	fabry*.ti,ab.	
2	(angiokeratoma adj3 diffusum).ti,ab.	
3	(diffuse angiokeratoma*).ti,ab.	
4	(galactosidase adj3 deficiency).ti,ab.	
5	(alpha galactosidase).ti,ab.	

Supplemental table A Search strategy (Continued)

PsychInfo (1806 till December week 1, 2014) , via OvidSP		
6	(GLA adj3 deficiency).ti,ab.	
Enzyme replacement therapy		
7	replagal.ti,ab.	
8	fabrazyme.ti,ab.	
9	agalsidase.ti,ab.	
Quality of life		
10	exp "Quality of Life"/	
11	(Quality adj3 life).ti,ab.	
12	((QoL) or (hrQoL)).ti,ab.	
Questionnaires		
13	exp Questionnaires/	
14	Questionnair*.ti,ab.	
Quality of life questionnaires		
15	(SF-36 or SF36 or sf 36 or short form 36 or short form-36).ti,ab,tm.	
16	(RAND 36 or RAND36 or RAND-36 or (RESEARCH adj2 DEVELOPMENT 36) or RAND-36 item Health Survey or RAND 36 item Health Survey).ti,ab,tm.	
17	(EQ5D or EQ-5D or EuroQol or Euro-QoL).ti,ab,tm.	
18	(QOLS or Quality of life scale).ti,ab,tm.	
19	(PedsQL OR (pediatric quality of life)).ti,ab,tm.	
20	(FPHPQ OR (Fabry-specific Pediatric Health and Pain Questionnaire)).ti,ab,tm.	
21	((AFD specific questionnaire) or (Fabry* and specific questionnaire) or (AFD specific questions) or (Fabry* and specific questions)).ti,ab,tm.	
22	((Disease severity scoring system) OR (DS3)).ti,ab,tm.	
Pain questionnaires		
23	(BPI or (brief pain inventory)).ti,ab,tm.	
24	(McGill pain).ti,ab,tm.	
25	(FPQ or (Fabry pain questionnaire)).ti,ab,tm.	
Combined		
26	or/1-9	*Combined concepts Fabry and enzyme replacement therapy*
27	or/10-25	*Combined concepts Quality of life and questionnaires*
28	26 AND 27	*Combined search, results used in the current study*
CENTRAL (accessed December 10, 2014)		
Fabry disease		
1	fabry*:ti,ab,kw	
2	diffuse angiokeratoma:ti,ab,kw	
3	galactosidase deficiency:ti,ab,kw	
4	GLA deficiency:ti,ab,kw	
5	MeSH descriptor: [Fabry Disease] explode all trees	
6	MeSH descriptor: [alpha-Galactosidase] explode all trees	
Enzyme replacement therapy		
7	replagal:ti,ab,kw	
8	fabrazyme:ti,ab,kw	
9	agalsidase:ti,ab,kw	
Quality of life		
10	MeSH descriptor: [Quality of Life] explode all trees	
11	quality near life:ti,ab,kw	
12	(QoL) or (hrqol):ti,ab,kw	

Supplemental table A Search strategy (Continued)

CENTRAL (accessed December 10, 2014)		
Questionnaires		
13	MeSH descriptor: [Questionnaires] explode all trees	
14	questionnaire*:ti,ab,kw	
Quality of life questionnaires		
15	((SF36) or (SF-36) or (short form 36) or (short form-36)):ti,ab,kw	
16	((RAND 36) or (RAND36) or (RAND-36) or (RESEARCH near DEVELOPMENT 36) or (RAND-36 item Health Survey) or (RAND 36 item Health Survey)):ti,ab,kw	
17	(EQ5D or EQ-5D or EuroQol or Euro-QoL):ti,ab,kw	
18	(QOLS or Quality of life scale):ti,ab,kw	
19	(PedsQL or "pediatric quality of life"):ti,ab,kw	
20	(FPHPQ or "Fabry-specific Pediatric Health and Pain Questionnaire"):ti,ab,kw	
21	("AFD specific questionnaire" or (Fabry* and specific questionnaire) or (AFD specific questions) or (Fabry* and specific questions)):ti,ab,kw	
22	("Disease severity scoring system" or DS3):ti,ab,kw	
Pain questionnaires		
23	MeSH descriptor: [Pain Measurement] explode all trees	
24	BPI:ti,ab,kw	
25	Brief pain questionnaire:ti,ab,kw	
26	McGill pain:ti,ab,kw	
27	FPQ or "Fabry pain questionnaire":ti,ab,kw	
Combined		
28	or/1-9	*Combined concepts Fabry and enzyme replacement therapy*
29	or/9-27	*Combined concepts Quality of life and questionnaires*
30	29 AND 30	*Combined search, results used in the current study*

Supplemental table B

Supplemental table B Overview of included studies

Study	Design	Controls	Questionnaire	No of patients (males) in whom QoL is measured	ERT	Disease severity
Baehner et al. (2003)†	before after study, non-comparative	General population, RA patients	SF-36	15 (0)	100%	67% >6 affected organ systems. Creatinine clearance varied from 65 to 73 ml/min/1.73m^2. Average LVMi at baseline: 148 g/m^2
Barba-Romero et al. (2011)‡	case series	N/A	EQ-5D	10 (2) [=12% of patients included in study]	♀ 94% ♂ 48%	Not available for QoL subgroup. Overall: mean MSSI: ♀7, ♂14.5
Beck et al. (2013) †	before after study, non-comparative	N/A	SF-36	69 (?)	100%	Not available
Bouwman et al. (2011) †	cross sectional, comparative	General population	SF-36	28 (9)	64%	Mean MSSI: ♀4 ♂16. Proteinuria ♀5% ♂11%. WML ♀16% ♂33%. LVH ♀16% ♂33%.
Bouwman et al. (2012)	case control	Age matched controls	locally developed questionnaire	62 (0)	Unknown	Not available
Buechner et al. (2008)	case series	N/A	EQ-5D, Rankin scale	43 (25)	56%	Renal dysfunction ♀28% ♂ 76%. Cardiac involvement ♀ 39% ♂ 68%. Stroke ♀28% ♂24%
Cazzorla et al. (2012)	cross sectional, comparative	Other inherited metabolic diseases	WHOQOL-100	13 (?)	Yes, % unknown	Not available
Deegan et al. (2006)	case series	N/A	EQ-5D	130 (0) [=43% of patients included in study]	Yes, % unknown	Not available for QoL subgroup. Overall: Stroke 7%, LVH 26%, proteinuria 35%
Duning et al. (2012) †	cross sectional, comparative	General population	SF-36	49 (27)	Unknown	MSSI range 0-51, mean 15. CVA 10%. Cardiac abnormalities 27%, proteinuria 29%
Eng et al. (2001)	NRCT	FD (different dosing regimens)	SF-36	15 (15)	100%	Classically affected, nu further information.

Supplemental table B Overview of included studies (Continued)

Study	Design	Controls	Questionnaire	No of patients (males) in whom QoL is measured	ERT	Disease severity
Eng et al. (2001)	RCT	FD, placebo	SF-36	58 (56)	50%	Mean GFR: ERT 83, placebo 96
Eto et al. (2005)	before after study, non-comparative	N/A	SF-36, BPI interference	13(13)	100%	Mean creatinine 93μmol/L
Faggiano et al. (2006)	case control	Age and gender matched controls	SF-36	18 (9)	55%	"classic" male patients. Overall 28% CKD stage III-V, LVH 72%
Geevasing et al. (2012) †	cross sectional, non-comparative	N/A	BPI interference	13 (10)	46%	Mean MSSI 16
Germain et al. (2007)	before after study, non-comparative	N/A	SF-36	58 (56)	100%	All patients had normal GFR
Ghali et al. (2012) ‡	Cohort study, retrospective	FD patients (different treatment groups)	SF-36	40 (32)	100%	Not available for QoL subgroup Overall: GFR 93, LVH 7%, small cerebral infarction 7%
Gibas et al. (2006)	cross sectional study	N/A	locally developed questionnaire	96 (45)	Unknown	Not available
Gold et al. (2002) †	cross sectional study, comparative	General population	SF-36	53 (53)	-	Not available
Gupta et al (2005)	Cross sectional study	N/A	BPI	50 (50) [=88% of patients included in study]	-	MeanGFR : 93,
Hoffmann et al. (2005) †‡	before-after study	N/A	EQ-5D, BPI	120 (73)	100%	Not available
Hoffmann et al. (2007) ‡	case series	N/A	EQ-5D	262 (133) [=35% of patients included in study]	Unknown	Not available
Hoffmann et al. (2007) ‡	case series	N/A	BPI	108 (41) [=32% of patients included in study]	Unknown	Not available
Hopkin et al. (2008) ‡	case series	N/A	SF-36	352 (194) [36 (10)]	40%	Not available

Supplemental table B Overview of included studies (Continued)

Study	Design	Controls	Questionnaire	No of patients (males) in whom QoL is measured	ERT	Disease severity
Hughes et al. (2011) †‡	before after study	N/A	EQ-5D	[60 (37) [=24% of patients included in study]	100%	Not available for QoL subgroup. Mean LVMi ♀ 48.2 ♂ 54.7 g/m$^{2.7}$, mean eGFR ♀ 71.8 ♂ 88.2
Hughes et al. (2013) †	RCT (cross over)	Cross over design	EQ-5D	19 (13)	100%	Not available
Kantola et al. (2012)	case series (congress abstract)	N/A	SF-36	16 (?)	100%	Not available
Koskenvuo et al. (2008)	open label prospective follow up study	N/A	SF-36	9 (5)	100%	Mildly impaired to normal renal function, LVH 62%, atrial fibrillation present in 11%
Low et al. (2007) †	cross sectional study, comparative / before after study	General population	SF-36	21 (19)	76%	38% ESRD, 10% stroke
MacDermot et al. (2001)	cross sectional study	N/A	AFD specific questionnaire	46 (46) [=47% of patients included in study]	-	Not available for QoL subgroup. Overall: ESRD 31%, LVH 88%, TIA/CVA 24%
MacDermot et al. (2001)	cross sectional study	N/A	AFD specific questionnaire	29 (0) [=48% of patients included in study]	-	Not available for QoL subgroup. Overall: ESRD 3%, 47%, LVH 19%, TIA/CVA 22%
Mehta et al. (2009) †‡	case series	General population	EQ-5D	[51 (?) [=28% of patients included in study]	100%	Not available for QoL subgroup. Overall: mean eGFR 85 , mean LVMi 58 g/m$^{2.7}$
Milligan et al. (2006)	case series	N/A	locally developed questionnaire	20	100%	Not available
Miners et al. (2002) †	cross sectional study, comparative	General population	SF-36, EQ-5D, AFD specific questionnaire	38 (38)	-	Heart symptoms 74%, stroke 13%, ESRD 16%. Classically affected males.
Morier et al. (2010)	cross sectional study	N/A	locally developed questionnaire	23 (8)	-	Not available
Oliveira et al. (2013) †	cross sectional, comparative	Elderly population	SF-36	14 (10)	71%	Not available

Supplemental table B Overview of included studies (Continued)

Study	Design	Controls	Questionnaire	No of patients (males) in whom QoL is measured	ERT	Disease severity
Quinn et al. (2010)	cross sectional study (congress abstract)	N/A	SF-36	32 (18)	Unknown	Not available
Ramaswami et al. (2012) †‡	validation study	N/A	EQ-5D, BPI interference, FPHPQ, KINDL	87 (44)	57%	93% MSSI <20
Ramaswami et al. (2007)	before after study	N/A	BPI interference	13 (9)	100%	Acroparesthesia 77%, 15% asymptomatic
Ries et al. (2005)	case control	General population	Child health questionnaire	25 (25)	Unknown	Renal function, urinary protein excretion, and cardiac function and structure were normal for the majority of patients.
Rombach et al. (2013) †	HTA / cohort study	N/A	EQ-5D	100 (48)	58%	Stratified by disease severity
Schermuly et al. (2011) †	case control	Age, gender and educational matched controls	SF-36, BPI interference	25 (10)	80%	Mild to moderate disease involvement, mean MSSI 21
Schiffman et al. (2001) †	RCT	Placebo controlled	0	26 (26)	54%	19 patients >4 organ systems involved
Smid et al. (2011) †	before after study	N/A	SF-36	35 (17)	100%	Not available
Street et al. (2006) †	cross sectional, comparative	General population, MS patients, RA patients	RAND-36	202 (0)	Unknown	Renal insufficiency 17%, TIA 20%, Stroke 8%, arrhythmia 44%, LVH 18%, proteinuria 38%.
Torvin et al. (2009)	cross sectional	General population	SF-36	19 (0)	53%	Not available
Tsuboi et al. (2012) †	before after study	N/A	EQ-5D	11 (4)	100%	Mean eGFR 90, LVMi ($g/m^{2.7}$) 58, MSSI 22
Vedder et al. (2007)	Case series	N/A	SF-36	71 (27)	45%	CKD III-V ♀ 5% ,♂ 30%, LVH ♀ 63% ,♂ 45%
Wagner et al. (2014) †	retrospective cohort study	FD patients with&without renal impairment	SF-36	96 (46)	45%	Stratified by disease severity

Supplemental table B Overview of included studies (Continued)

Study	Design	Controls	Questionnaire	No of patients (males) in whom QoL is measured	ERT	Disease severity
Wang et al. (2007) †	prospective cohort study	General population	SF-36, BPI interference	19 (0) [=45% of patients included in study]	26%	Not available for QoL subgroup. Overall: stroke 22%, LVH 24%, ESRD 13%, proteinuria 56%
Watt et al. (2010) †‡	before after study	Patients with other chronic disease	SF-36	130 (71)	100%	Renal events ♀ 0% ,♂ 7%, cardiovascular events ♀ 25% ,♂ 23%, stroke ♀ 1% ,♂ 9%
Wilcox et al. (2008) †‡	case series	General population	SF-36	558 (368) [=25% of patients included in study]	Unknown	Stroke ♀ 4% ,♂ 7%, LVH ♀ 18.2% ,♂ 21.6%, CKD III-V ♀ 34% ,♂ 19%
Wilcox et al. (2004)	before after	N/A	SF-36	58 (56)	100%	All patients had normal GFR
Wyatt et al. (2012) Adults *†	prospective cohort study	N/A	SF-36, EQ-5D, BPI	289 (120)	73%	Proteinuria ♀ 19%, ♂ 48% , mean LVMi g/m^2 107 , mean eGFR in patients without proteinuria: 85 and with proteinuria 83
Wyatt et al. (2012) Children *†	prospective cohort study	N/A	pedsQL	22 (11)	32%	LVMi g/m^2 68 g/m^2 , mean GFR in patients without proteinuria: 110 and with proteinuria 81
Zuraw et al. (2011) †	cross sectional	General population	SF-36, EQ-5D	32 (20)	63%	Not available

† study reported detailed information on QoL. ‡ FOS or Fabry Registry based study. RCT = randomised controlled trial, NRCT = non-randomised controlled trial, N/A = not applicable, RA = rheumatoid arthritis, MS = multiple sclerosis. MSSI = Mainz severity index, GFR = glomerular filtration rate, in ml/min/1.73m^2, CKD = chronic kidney disease, ESRD = end stage renal disease, LVH = left ventricular hypertrophy, LVMi = left ventricular mass index, WML = white matter lesions