Long-Term Effects of Enzyme Replacement Therapy on Fabry Cardiomyopathy
Evidence for a Better Outcome With Early Treatment

Frank Weidemann, MD*; Markus Niemann*; Frank Breunig, MD; Sebastian Herrmann; Meinrad Beer, MD; Stefan Störk, MD; Wolfram Voelker, MD; Georg Ertl, MD; Christoph Wanner, MD; Jörg Strotmann, MD

Background—Enzyme replacement therapy with recombinant α-galactosidase A reduces left ventricular hypertrophy and improves regional myocardial function in patients with Fabry disease during short-term treatment. Whether enzyme replacement therapy is effective in all stages of Fabry cardiomyopathy during long-term follow-up is unknown.

Methods and Results—We studied 32 Fabry patients over a period of 3 years regarding disease progression and clinical outcome under enzyme replacement therapy. Regional myocardial fibrosis was assessed by magnetic resonance imaging late-enhancement technique. Echocardiographic myocardial mass was calculated with the Devereux formula, and myocardial function was quantified by ultrasonic strain-rate imaging. In addition, exercise capacity was measured by bicycle stress test. All measurements were repeated at yearly intervals. At baseline, 9 patients demonstrated at least 2 fibrotic left ventricular segments (severe myocardial fibrosis), 11 had 1 left ventricular segment affected (mild fibrosis), and 12 were without fibrosis. In patients without fibrosis, enzyme replacement therapy resulted in a significant reduction in left ventricular mass (238±42 g at baseline, 202±46 g at 3 years; P for trend <0.001), an improvement in myocardial function (systolic radial strain rate, 2.3±0.4 and 2.9±0.6 s−1, respectively; P for trend=0.045), and a higher exercise capacity obtained by bicycle stress exercise (106±14 and 122±26 W, respectively; P for trend=0.014). In contrast, patients with mild or severe fibrosis showed a minor reduction in left ventricular hypertrophy and no improvement in myocardial function or exercise capacity.

Conclusions—These data suggest that treatment of Fabry cardiomyopathy with recombinant α-galactosidase A should best be started before myocardial fibrosis has developed to achieve long-term improvement in myocardial morphology and function and exercise capacity. (Circulation. 2009;119:524-529.)

Key Words: cardiomyopathy □ echocardiography □ Fabry disease □ hypertrophy □ treatment

Fabry disease is a relatively rare X-linked lysosomal storage disorder caused by α-galactosidase A deficiency. The enzymatic deficit results in progressive intracellular accumulation of globotriaosylceramide in different tissues. Cardiac involvement is frequent, presenting with left ventricular (LV) hypertrophy as the most common finding, and many patients die of heart failure.1

Clinical Perspective p 529

Enzyme replacement therapy (ERT) with recombinant α-galactosidase A cleared microvascular deposits of globotriaosylceramide in biopsies of kidney, skin, and heart of most Fabry patients.2-3 We have shown a reduction in LV mass and an improvement in LV function after 1 year of ERT in 16 Fabry patients.4 However, the response to ERT was not consistent in this small cohort of Fabry patients. In addition, it remained unclear whether the effect of ERT could persist over longer periods of time. In a more recent study in a larger group of patients, we identified the coexistence of LV hypertrophy, myocardial fibrosis, and severely reduced regional LV function as a surrogate of advanced Fabry cardiomyopathy.5 It is conceivable that such severe morphological manifestation is irreversible and that the course of cardiomyopathy at this stage is unresponsive to therapy of the underlying disease.

The hypothesis of the present study was that patients at an early stage of the disease showing no or little myocardial fibrosis may consistently benefit from ERT over a period of 3 years. This hypothesis was tested in a cohort that was relatively large for this rare disease. Fibrosis was quantified by magnetic resonance imaging (MRI).
Methods

Study Population
Thirty-two patients with genetically confirmed Fabry disease 42±7 years of age were observed over a period of 3 years. None of the Fabry patients had received ERT at study entry. A subgroup of these patients (n=16) who were under ERT for 1 year was already reported.4 The data from the Fabry group were compared with those from 20 age-matched healthy control subjects. The study conformed with the principles outlined in the Declaration of Helsinki. Informed consent was obtained from all patients.

Patients were treated with recombinant α-galactosidase A (dosage of 1 mg/kg body weight) intravenously every 2 weeks (infusion time, 2 to 4 hours) for a period of 3 years.4 Patients underwent MRI, standard echocardiographic, color Doppler myocardial imaging studies, and bicycle stress tests at baseline and after 1, 2, and 3 years.

MRI Studies
Routine cine MRI with gadolinium was carried out in all patients with Fabry disease as part of the standard assessment. The late-enhancement (LE) technique (8-mm slice thickness, breath hold, short heart axis) was applied to detect changes in tissue integrity in the LV myocardium.6 Images were acquired with an inversion recovery sequence (field of view, 240×320 mm²; matrix, 165×256). Short-axis views at the basal, mid, and apical segments were used for the semi-quantitative assessment of the appearance of LE in every LV segment (LE, yes or no) according to the standardized 16-segment model.7 With this LE technique, every LV segment was evaluated for the occurrence of intramyocardial fibrosis. All MRI data were analyzed by researchers blinded to the time point.

Table 1. Baseline Characteristics of Fabry Patients and Control Subjects

<table>
<thead>
<tr>
<th></th>
<th>Fabry Patients (n=32)</th>
<th>Control Subject (n=20)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>42±7</td>
<td>43±13</td>
<td>0.51</td>
</tr>
<tr>
<td>Sex, M/F</td>
<td>27/6</td>
<td>15/5</td>
<td>0.53</td>
</tr>
<tr>
<td>Weight, kg</td>
<td>72±12</td>
<td>75±10</td>
<td>0.62</td>
</tr>
<tr>
<td>Height, cm</td>
<td>177±8</td>
<td>177±6</td>
<td>0.81</td>
</tr>
<tr>
<td>HR, bpm</td>
<td>69±10</td>
<td>65±11</td>
<td>0.72</td>
</tr>
<tr>
<td>Systolic BP, mm Hg</td>
<td>125±15</td>
<td>127±13</td>
<td>0.68</td>
</tr>
<tr>
<td>LVEDD, mm</td>
<td>49±7</td>
<td>50±5</td>
<td>0.79</td>
</tr>
<tr>
<td>PWT, mm</td>
<td>13.9±2.1</td>
<td>8.6±1.4</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Arterial hypertension, n</td>
<td>14</td>
<td>0</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Ventricular arrhythmia, n</td>
<td>2</td>
<td>0</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Atrial fibrillation, n</td>
<td>2</td>
<td>0</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Angina pectoris, n</td>
<td>11</td>
<td>0</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Dyspnea, n</td>
<td>15</td>
<td>0</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

HR indicates heart rate; LVEDD, LV end-diastolic diameter. Values are mean±SD when appropriate. Probability values refer to t test and χ² test as appropriate.

Patient Groups
Patients were assigned to 1 of 3 groups according to the amount of fibrosis in the MRI.5,6,8 Patients without detectable fibrosis were categorized as the no fibrosis group. Patients with fibrosis in no more than 1 LV segment were categorized as the mild fibrosis group, and patients with ≥2 fibrotic LV segments were categorized as the severe fibrosis group.

Data Analysis
Data are presented as mean±SD. Differences between control subjects and patients were tested with the unpaired Student t test or χ² test as appropriate. Multiple comparisons between different groups were performed using ANOVA with Duncan’s posthoc test. Changes over time were analyzed with a general linear model for repeated measurements. The overall effect was assessed in a multivariable analysis after testing for sphericity to check the circular covariance assumption. If sphericity was not present, the Huynh-Feldt ε correction factor was applied to correct the degrees of freedom, and the resulting probability value was then reported. Sidak’s t test was applied to account for multiple testing in analyses assessing between-subject effects. All tests were performed 2 sided. A value of P<0.05 was considered statistically significant. SPSS version 16.0.1 (SPSS Inc, Chicago, Ill) was used.

The authors had full access to and take full responsibility for the integrity of the data. All authors have read and agree to the manuscript as written.

Results
The baseline characteristics of the control subjects and Fabry patients are presented in Table 1. Fourteen patients had a history of hypertension. All were under hypertensive medication and therefore were almost normotensive at study entry. The types of antihypertensive medication and the number of patients receiving antihypertensive medication were very uniformly distributed in all 3 groups. The major clinical limitation at baseline was dyspnea. Two patients died during follow-up of heart failure as a consequence of the underlying disease.
MRI Studies
At baseline, 12 patients were LE negative, 11 patients had only 1 LE-positive segment, and 9 patients had LE in >1 segment (Figure 1). In general, LE was detected in basal or mid segments of the posterolateral walls. Only in the severe fibrosis group were fibrotic segments also found in the basal third of the other LV walls. None of the patients had an LE-positive segment in the apical septum. There was no change in the LE pattern after 3 years of ERT.

Standard Echocardiographic Measurements

Comparison Between the Complete Fabry Cohort and Control Subjects
Fabry patients had a longer deceleration time (248±65 ms) compared with control subjects (198±36 ms; P<0.01), but the E/A ratio did not differ (Fabry, 1.5±0.5; control subjects, 1.4±0.4). Patients showed a normal ejection fraction at baseline (62±1%), not different from control subjects (64±1%), and no change during ERT (Fabry, 64±1%).

Table 2. Baseline Echocardiographic Data of the Fabry Subgroups

<table>
<thead>
<tr>
<th>Subgroups</th>
<th>No Fibrosis (n=12)</th>
<th>Mild Fibrosis (n=11)</th>
<th>Severe Fibrosis (n=9)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>36±4</td>
<td>42±7*</td>
<td>50±7*</td>
</tr>
<tr>
<td>LVEDD, mm</td>
<td>48±4</td>
<td>49±5</td>
<td>51±12</td>
</tr>
<tr>
<td>LVESD, mm</td>
<td>33±3</td>
<td>32±4</td>
<td>36±12</td>
</tr>
<tr>
<td>PWT, mm</td>
<td>13.0±1.2</td>
<td>13.0±1.2</td>
<td>14.7±2.7</td>
</tr>
<tr>
<td>Septum, mm</td>
<td>13.5±1.4</td>
<td>13.5±1.4</td>
<td>14.9±3.0</td>
</tr>
<tr>
<td>LV mass, g</td>
<td>238±42</td>
<td>276±62</td>
<td>303±84*</td>
</tr>
<tr>
<td>Ejection fraction</td>
<td>61.5±6.5</td>
<td>60.5±6</td>
<td>61±11</td>
</tr>
<tr>
<td>E/A</td>
<td>1.5±0.6</td>
<td>1.5±0.5</td>
<td>1.4±0.5</td>
</tr>
<tr>
<td>DT, ms</td>
<td>245±67</td>
<td>236±66</td>
<td>286±65</td>
</tr>
</tbody>
</table>

LVESD indicates LV end-systolic diameter; LV mass, g.

End-diastolic thicknesses of the LV posterior wall and septum were significantly higher in patients compared with control subjects (PWT: Fabry, 13.9±2.1 mm; control subjects, 8.6±1.4 mm; septum: Fabry, 14.3±2.1 mm; control subjects, 8.9±1.0 mm; both P<0.001). In Fabry patients, myocardial mass at study entry averaged 269±67 g, which was significantly higher compared with the control subjects (133±55 g; P<0.001). The standard echocardiographic measurements of the Fabry subgroups are shown in Table 2, and the changes in these parameters during ERT are given in Table 3. In all 3 subgroups, PWT and LV myocardial mass decreased significantly after 3 years of ERT.

Table 3. Changes in Echocardiographic Data of the Fabry Subgroups of Fibrosis During 3 Years of ERT

<table>
<thead>
<tr>
<th>Subgroups</th>
<th>No Fibrosis</th>
<th>Mild Fibrosis</th>
<th>Severe Fibrosis</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>LVEDD, mm</td>
<td>48±4</td>
<td>49±4</td>
<td>49±4</td>
<td>0.89†</td>
</tr>
<tr>
<td>PWT, mm</td>
<td>13.0±1.2</td>
<td>11.7±1.6</td>
<td>11.3±1.6</td>
<td>&lt;0.01*</td>
</tr>
<tr>
<td>Septum, mm</td>
<td>14.4±2.2</td>
<td>13.1±2.4</td>
<td>13.3±2.4</td>
<td>0.21†</td>
</tr>
<tr>
<td>LV mass, g</td>
<td>238±42</td>
<td>213±46</td>
<td>201±65</td>
<td>0.02†</td>
</tr>
</tbody>
</table>
| LVEDD indicates LV end-diastolic diameter; LVESD indicates LV end-systolic diameter.

*Probability value for the test of the overall effect (n=32) of ERT over time (general linear model: within-subject effect).
†Probability value for the comparison of fibrosis groups (ie, no fibrosis vs mild fibrosis and no fibrosis vs severe fibrosis; general linear model with Sidak’s posthoc test for between-subject effect).
subjects (SR_{SYS} = 2.7 ± 0.5 seconds^{-1}; P < 0.001). The lowest radial SR_{SYS} was seen in the severe fibrosis group. Figure 2 displays the change in radial SR_{SYS} during the 3 years of treatment in the various subgroups. Radial SR_{SYS} increased in the no fibrosis group (normal values after 3 years of ERT) and rather decreased in the severe fibrosis group (Figure 2). Septal longitudinal SR_{SYS} in Fabry patients (−1.2 ± 0.3 seconds^{-1}) was similar to that of controls (−1.3 ± 0.3 seconds^{-1}) and among the 3 Fabry groups at baseline. Septal longitudinal SR_{SYS} increased in the 3 Fabry groups (significantly for the no fibrosis group, P = 0.045; Figure 3). Lateral longitudinal SR_{SYS} was lower in Fabry patients (−0.9 ± 0.3 seconds^{-1}) compared with the control subjects (−1.3 ± 0.2 seconds^{-1}, P < 0.001) and was lowest in the 2 groups with fibrosis. There was a nonsignificant decrease in lateral SR_{SYS} in patients with severe fibrosis during 3 years of ERT (Figure 3).

The 2 patients who died during follow-up (1 after 1 year and another after 2 years) had low radial and longitudinal strain-rate values at baseline and were in the severe fibrosis group. Interestingly, both patients showed a decrease in lateral longitudinal systolic strain rate of >0.5 seconds^{-1} between the last 2 assessments (displaying a systolic strain rate of <−0.3 seconds^{-1} in the last assessment).

Bicycle Stress Test

The exercise capacity was lower in the Fabry severe fibrosis group compared with the other 2 groups. Figure 4 displays the change in exercise capacity in the 3 Fabry groups during follow-up. Only patients of the no fibrosis group showed an improvement after 3 years of ERT (baseline, 106 ± 14 W; 3 years, 122 ± 26 W; P for trend = 0.014).

Discussion

The clearance of globotriaosylceramide from various tissues during ERT in Fabry disease has been well documented.2 Furthermore, Eng et al2 demonstrated in a placebo-controlled, double-blind study that ERT resulted in histological clearance desirable to achieve long-term improvement in myocardial morphology, function, and exercise capacity.

ERT in Fabry Disease

The safety of ERT was documented in 2 initial studies.2,3 Furthermore, Eng et al2 demonstrated in a placebo-controlled, double-blind study that ERT resulted in histological clearance

![Figure 2. Change in LV radial peak systolic strain rate of the posterior wall during 3 years of ERT according to the degree of myocardial fibrosis. Note that there is a linear increase in radial function in patients with no fibrosis (P = 0.005), P = 0.009 for comparison of trend between no fibrosis and mild fibrosis; P < 0.001 for comparison of trend between no fibrosis and severe fibrosis (general linear model with Sidak’s posthoc test); P = 0.126 for the overall effect of ERT over time. BS indicates baseline; 1, 1 year of ERT; 2, 2 years of ERT; and 3, 3 years of ERT.](image1)

![Figure 3. Change in LV longitudinal function during 3 years of ERT in the 3 different groups. Top, The longitudinal peak systolic strain rate of the septum increases during ERT (P = 0.045) in patients with no fibrosis. Bottom, The longitudinal peak systolic strain rate of the lateral wall is lower in patients with fibrosis; there is no significant change during ERT (all P > 0.3). Abbreviations as in Figure 2.](image2)

![Figure 4. Change in exercise capacity during 3 years of ERT in the 3 different groups. A mild but significant improvement in exercise capacity could be demonstrated for patients with no fibrosis (P = 0.014). Abbreviations as in Figure 2.](image3)
of the deposits of globotriaosyleramide from cardiomyocytes. Subsequently, clinical short-term follow-up studies in relatively small Fabry cohorts or registries have documented that ERT leads to a regression of LV hypertrophy and an improvement in myocardial function.4,9,10 The present investigation shows that the long-term ERT effects on Fabry cardiomyopathy are related to the extent of myocardial fibrosis at baseline, when therapy is started. We and others have shown that Fabry patients at an early stage of the disease have virtually no myocardial fibrosis.5,8 These patients with no detectable fibrosis and mild hypertrophy at baseline showed a normalization of LV wall thickness and mass during ERT in the present study. Parallel to cardiac morphology, LV radial and longitudinal septal function improved to normal. Subsequently, the patients with no fibrosis also improved in exercise capacity, which might be at least partly related to the positive effects of ERT on the Fabry cardiomyopathy. Thus, in the largest group of our Fabry patients (those in the beginning of disease progression), cardiac and exercise improvement during long-term ERT was proven. The effect of ERT critically depended on the stage of the disease at baseline. In patients with localized myocardial fibrosis in only 1 LV segment, a reduction in LV hypertrophy could be achieved during ERT that was associated with a stabilization of LV function and exercise capacity. Patients in a more advanced stage with fibrosis in several LV segments still showed some reduction in hypertrophy but hardly any benefit in terms of LV function during long-term ERT.

**Monitoring the Effects of ERT**

The change in LV mass was used in several studies to monitor ERT effects.4,9,10 The present study proved LV mass to be in principle a useful parameter to monitor the cardiac effects of ERT. However, fibrosis spreading to the posterior wall may mimic a reduction in hypertrophy in more advanced stages of the cardiomyopathy. Thus, PWT, which is an echocardiographic standard parameter to monitor changes in LV hypertrophy, is probably not useful for monitoring ERT.11

Strain-rate imaging based on tissue Doppler is superior to global parameters like ejection fraction in monitoring and quantifying LV function in patients with Fabry disease.4,5,12,13 The increase in peak systolic strain rate appears to be more specific for regional contractility and rather independent of wall thickness.14 The present study shows that an increase in radial strain rate after 1 year of ERT may predict long-term improvement in regional myocardial function. A decrease in longitudinal lateral function is an ominous sign in advanced stages and predicts an adverse outcome. Interestingly, both patients who died during ERT showed a decrease in longitudinal lateral strain rate of >0.5 seconds⁻¹ in the last year of life.

Most patients in our study sample who were treated with ERT reported an improvement in exercise capacity. The improvement could, however, be objectified only in the group of patients at an early stage of the disease. The reason might be that the mechanisms limiting exercise capacity are complex in Fabry patients and include cardiovascular factors, neuropathic pain, and hypohydrosis.

**Clinical Impact and Limitations**

The present study shows that an assessment of the baseline conditions before ERT is necessary. Knowledge of the presence or absence of myocardial fibrosis is crucial with respect to the treatment expectations. A recent phase IV ERT study focusing on renal function showed more benefit in patients starting with better renal function.15 We showed this finding here for Fabry cardiomyopathy, suggesting that the earlier the treatment is started, the better the long-term outcome is.

**Conclusions**

In patients with Fabry disease, early is probably superior to late treatment to achieve long-term improvements in cardiac morphology and function and exercise capacity.

**Disclosures**

Dr Wanner is a member of the European Advisory Board of the Fabry Registry sponsored by Genzyme Corp and has received travel assistance, speaking fees, and research support. Drs Weidemann, Breunig, and Strotmann have received speaking fees from Genzyme Corp. The other authors report no conflicts.

**References**


---

**CLINICAL PERSPECTIVE**

Enzyme replacement therapy with recombinant α-galactosidase A clears microvascular deposits of globotriaosylceramide in biopsies of kidney, skin, and heart of most Fabry patients. Clinically, it could be demonstrated that enzyme replacement therapy reduces left ventricular hypertrophy and improves regional myocardial function in patients with Fabry cardiomyopathy during short-term treatment. Whether enzyme replacement therapy is effective in all stages of Fabry cardiomyopathy during long-term follow-up is unknown. The present study shows that a baseline assessment of cardiac morphology and function before the start of enzyme replacement therapy is necessary. Thus, knowledge of the presence or absence of myocardial fibrosis (which is typical for a late stage of this disease) is crucial with respect to treatment expectations. Myocardial fibrosis can be visualized directly with the magnetic resonance imaging late-enhancement technique. In addition, the functional consequences of fibrosis can be quantified by ultrasonic strain-rate imaging. Only Fabry patients with no fibrosis before enzyme replacement therapy show a sustained improvement in regional myocardial function and exercise capacity in the long term. Thus, in Fabry disease, early is probably superior to late treatment to improve cardiac morphology, function, and exercise capacity.
Long-Term Effects of Enzyme Replacement Therapy on Fabry Cardiomyopathy: Evidence for a Better Outcome With Early Treatment
Frank Weidemann, Markus Niemann, Frank Breunig, Sebastian Herrmann, Meinrad Beer, Stefan Störk, Wolfram Voelker, Georg Ertl, Christoph Wanner and Jörg Strotmann

_Circulation._ published online January 19, 2009;
_Circulation_ is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2009 American Heart Association, Inc. All rights reserved.
Print ISSN: 0009-7322. Online ISSN: 1524-4539

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://circ.ahajournals.org/content/early/2009/01/19/CIRCULATIONAHA.108.794529.citation

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in _Circulation_ can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to _Circulation_ is online at:
http://circ.ahajournals.org//subscriptions/