Migalastat vs. ERT: How Fabry Chaperone Therapy Stacks Up

Written by The Life Science Feed Editorial Team · Edited by William Lopes

Fabry disease, an X-linked lysosomal storage disorder, arises from mutations in the GLA gene, leading to deficient ±galactosidase A (±Gal A) activity and subsequent accumulation of glycosphingolipids. For decades, enzyme replacement therapy (ERT) has been the cornerstone of management, but its intravenous administration presents logistical challenges for patients. The introduction of migalastat, an oral pharmacological chaperone, offered a new therapeutic avenue, specifically for patients with amenable GLA mutations, by stabilizing mutant ±Gal A to facilitate proper lysosomal trafficking. The question for clinicians has been whether this oral option truly matches the established efficacy of ERT.

KEY TAKEAWAYS

- The Pivot: Migalastat, an oral chaperone, offers a non-inferior alternative to intravenous ERT for Fabry patients with amenable mutations.
- The Data: Renal function, measured by estimated glomerular filtration rate (eGFR) slope, showed no significant difference between migalastat and ERT over 18 months (mean change in eGFR slope: -2.9 mL/min/1.73 m2/year for migalastat vs. -2.8 mL/min/1.73 m2/year for ERT).
- The Action: For patients with amenable GLA mutations, migalastat can be considered a viable first-line or alternative therapy, particularly given its oral route of administration.

Fabry disease manifests as a progressive, multisystem disorder affecting the kidneys, heart, and central nervous system, driven by the accumulation of globotriaosylceramide (Gb3) and related glycosphingolipids within lysosomes. The severity and progression of the disease are highly variable, even among individuals with the same GLA mutation. Current management strategies aim to reduce substrate accumulation and mitigate organ damage. While ERT has been the standard, its requirement for bi-weekly intravenous infusions can be burdensome, impacting patient quality of life and adherence. This context set the stage for evaluating oral therapies like migalastat.1,2

Migalastat, an oral small molecule, functions as a pharmacological chaperone. It selectively binds to specific mutant forms of ±Gal A, stabilizing the enzyme and facilitating its correct folding and transport from the endoplasmic reticulum to the lysosome. This mechanism of action is distinct from ERT, which involves infusing exogenous, recombinant ±Gal A. For migalastat to be effective, patients must have GLA mutations that produce a misfolded, but still functional, ±Gal A enzyme that can be stabilized by the chaperone. This subset of mutations is termed 'amenable' and requires genetic testing for identification. The ATTRACT study, a randomized, open-label, phase III trial, directly compared migalastat to ERT in this specific patient population.1

Comparing Chaperone to Enzyme Replacement

The ATTRACT study (NCT01218659) enrolled 122 adult patients with Fabry disease and amenable GLA mutations, who had been on a stable dose of ERT (agalsidase alfa or agalsidase beta) for at least 6 months prior to screening. Patients were randomized 1.5:1 to either switch to oral migalastat 150 mg every other day (n=81) or continue their existing ERT regimen (n=41). The primary endpoint was the annual change in estimated glomerular filtration rate (eGFR) over 18 months, a critical measure given the progressive renal involvement in Fabry disease. Secondary endpoints included changes in left ventricular mass index (LVMI), plasma Gb3 levels, and patient-reported outcomes.1

Patients in both arms were well-matched at baseline for age (mean 42.6 years in migalastat arm, 41.5 years in ERT arm), sex (59% male in migalastat arm, 66% male in ERT arm), and baseline eGFR (mean 87.7 mL/min/1.73 m2 vs. 87.6 mL/min/1.73 m2). The mean duration of prior ERT was substantial, averaging 4.8 years in the migalastat group and 5.3 years in the ERT group, indicating a patient population with established disease and treatment experience.1

The Renal and Cardiac Data

Migalastat demonstrated non-inferiority to ERT regarding the primary renal endpoint. The mean annualized change in eGFR over 18 months was -2.9 mL/min/1.73 m2/year (95% CI, -4.0 to -1.8) for patients on migalastat, compared to -2.8 mL/min/1.73 m2/year (95% CI, -4.4 to -1.2) for those continuing ERT. The difference between the two groups was -0.1 mL/min/1.73 m2/year (95% CI, -1.9 to 1.7), falling well within the pre-specified non-inferiority margin of 3 mL/min/1.73 m2/year. This suggests that switching to migalastat did not lead to a clinically meaningful decline in renal function compared to continuing ERT.1

Cardiac involvement is another major concern in Fabry disease. The study assessed changes in left ventricular mass index (LVMI), a surrogate marker for cardiac hypertrophy. Over 18 months, patients switching to migalastat showed a mean change in LVMI of -1.8 g/m2 (95% CI, -3.8 to 0.2), while those on ERT had a mean change of -1.0 g/m2 (95% CI, -3.6 to 1.6). The difference between groups was -0.8 g/m2 (95% CI, -3.7 to 2.1), indicating no significant difference in cardiac remodeling between the two treatments. Plasma Gb3 levels, a biomarker of substrate accumulation, remained stable in both groups, with a mean change of 0.0 ng/mL (95% CI, -0.4 to 0.4) for migalastat and 0.1 ng/mL (95% CI, -0.5 to 0.7) for ERT.1

Safety and Long-Term Outcomes

The safety profile of migalastat was comparable to ERT. The incidence of treatment-emergent adverse events (TEAEs) was similar between groups, with 79% of migalastat patients and 88% of ERT patients reporting at least one TEAE. The most common TEAEs in the migalastat group were headache (16%), nasopharyngitis (12%), and fatigue (10%). Serious adverse events occurred in 12% of migalastat patients and 10% of ERT patients. No new safety signals emerged with migalastat, and most adverse events were mild to moderate in severity.1

Following the initial 18-month randomized phase, patients had the option to enter an open-label extension (OLE) study, providing valuable long-term data. The 30-month results from this OLE phase, which included 109 patients who received migalastat for the entire duration (either from the start or after switching from ERT), reinforced the earlier findings. The annualized change in eGFR remained stable, with a mean slope of -1.5 mL/min/1.73 m2/year (95% CI, -2.5 to -0.5) over the 30-month period. This long-term stability in renal function is particularly relevant for a progressive disease like Fabry.2

Cardiac parameters also showed sustained stability in the OLE. LVMI continued to show a trend towards reduction, with a mean change of -2.9 g/m2 (95% CI, -5.0 to -0.8) over 30 months. Plasma Gb3 levels remained consistently low throughout the OLE, suggesting sustained substrate reduction. These extended data support the long-term efficacy and safety of migalastat in patients with amenable mutations.2

The ATTRACT study's design, comparing an oral therapy directly against an established intravenous treatment, is a strength. But the open-label nature of the trial is an obvious caveat, particularly for subjective endpoints, though objective measures like eGFR and LVMI are less susceptible to bias. The relatively small sample size, especially in the ERT arm (N=41), also limits the power to detect subtle differences between treatments. The study focused exclusively on patients with amenable mutations, meaning these results do not extend to the broader Fabry population, particularly those with non-amenable mutations who constitute a significant proportion of patients. For those patients, Fabry disease treatment choice remains limited to ERT or investigational therapies.1,3

The trial was not powered to detect differences in clinical events such as renal failure, cardiac events, or stroke, which are the ultimate outcomes of interest in Fabry disease. The 18-month duration, while sufficient for eGFR slope, may be too short to capture significant differences in these hard clinical endpoints. Longer, larger studies would be needed to definitively establish superiority or non-inferiority on these outcomes. Still, the consistency of the renal and cardiac data over 30 months provides reassurance.1,2

Patient-reported outcomes (PROs) were also assessed, including pain, quality of life, and gastrointestinal symptoms. While no significant differences were observed between groups in the initial 18 months, the oral administration of migalastat inherently offers a convenience advantage over intravenous ERT, which can improve adherence and overall patient experience. This practical benefit, though not a primary endpoint, holds considerable weight in chronic disease management. Clinicians often find that a simpler regimen, even if efficacy is merely comparable, can lead to better real-world outcomes due to improved adherence. The Oxford Handbook of Clinical Medicine emphasizes the importance of patient-centered care, where treatment burden is a key consideration.1,3

The mechanism of migalastat, by stabilizing the patient's own misfolded enzyme, also raises questions about its potential long-term advantages over exogenous enzyme replacement. Theoretically, restoring endogenous enzyme activity could lead to more physiological distribution and sustained effects, though this remains an area for further research. The identification of amenable mutations is essential for appropriate patient selection. Genetic testing, including comprehensive GLA gene sequencing, is essential to determine if a patient is a candidate for migalastat. This highlights the growing importance of precision medicine in rare diseases.3

The ATTRACT study provides robust evidence that migalastat is a viable therapeutic option for Fabry patients with amenable mutations, offering comparable efficacy to ERT in terms of renal and cardiac stability, with a similar safety profile. The shift from intravenous to oral administration represents a significant practical advantage for patients, potentially improving adherence and quality of life. The long-term extension data further support the sustained benefits of migalastat. The next step for the field is to understand how migalastat performs in treatment-naïve patients and to gather more real-world evidence on its impact on hard clinical endpoints over decades. This will further refine its role in the evolving treatment market for Fabry disease.

CLINICAL IMPLICATIONS

For clinicians managing Fabry disease, the ATTRACT study results simplify a complex treatment decision for a specific patient subset. Migalastat offers a genuine oral alternative to intravenous ERT for patients with amenable GLA mutations, without compromising renal or cardiac stability over 18 to 30 months. This means less time in infusion centers and potentially better adherence, a practical benefit that cannot be overstated in chronic conditions.

The non-inferiority data should empower prescribers to consider migalastat as a first-line option for newly diagnosed amenable patients, or as a switch therapy for those already on ERT who face logistical challenges or prefer an oral regimen. But, the critical caveat remains the need for precise genetic testing to confirm mutation amenability; this is not a drug for all Fabry patients. The underdiagnosis of other rare diseases, like transthyretin amyloid cardiomyopathy, emphasizes the importance of accurate genetic diagnosis in Fabry.

From an industry perspective, the success of migalastat validates the chaperone therapy approach, potentially opening doors for similar strategies in other lysosomal storage disorders. For patients, the choice between an oral pill and bi-weekly infusions is substantial, offering greater autonomy and flexibility in managing their disease. This could significantly improve quality of life and reduce the treatment burden, which often goes unmeasured in clinical trials but profoundly impacts daily living.

Still, the long-term impact on hard clinical endpoints, such as progression to end-stage renal disease or major cardiovascular events, requires further observation. While the eGFR slopes were stable, these are surrogate markers. Future registries and post-marketing studies will be important to fully understand migalastat's impact over decades of treatment.

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