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BEYOND INFUSIONS: HOW MIGALASTAT (GALAFOLD®) IS REDEFINING FABRY DISEASE TREATMENT

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ABSTRACT

Fabry disease (FD) is a rare, progressive lysosomal storage disorder caused by mutations in the GLA gene, resulting in reduced α-galactosidase A activity and the subsequent accumulation of globotriaosylceramide (Gb3) in various organ systems. Enzyme replacement therapy (ERT), although conventional, has drawbacks, including exorbitant costs, biweekly infusions, immunological reactions and limited tissue penetration. Migalastat (Galafold®), the first oral pharmaceutical chaperone, offers a tailored, non-invasive option for individuals with susceptible mutations. This evaluation assesses the drug's mechanism of action, pharmacokinetics, clinical effectiveness and socio-economic implications. Clinical studies, such as facets and attract, have shown that Migalastat efficiently stabilizes renal function, improves cardiac structure and enhances quality of life. It furthermore provides benefits in cost efficiency, patient compliance and diminished healthcare strain. Furthermore, public-private collaborations have been crucial in facilitating worldwide access and regulatory approval. Nonetheless, constraints are there about its application in individuals with non-amenable mutations or severe renal pathology. This study asserts that Migalastat represents a transformative advancement in the treatment of Fabry disease, facilitating precision medicine and alleviating long-term treatment burdens, thereby improving quality of life and providing an invasive option for those with treatable mutations. Migalastat represents a paradigm shift in the care of Fabry disease, according to this review, which also demonstrates that it promotes precision medicine and reduces the burden of long-term treatment.

KEYWORDS

Migalastat, Fabry disease and α-galactosidase.

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INTRODUCTION

Fabry Disease (FD) is a rare X-linked lysosomal storage disorder (LSD) that results from a deficiency of the α-galactosidase A (GLA) enzyme, leading to a deficiency of the GLA enzyme. Because of this enzymatic deficiency against alpha-galactosidase A (GLA), Gb3 and other glycosphingolipids progressively build up inside

lysosomes. The disease primarily impacts four major organ systems: The kidneys, the heart, the nervous system, and the vascular endothelium. Physiological problems associated with GLA gene mutations result in decreased or absent GLA enzymatic activity, leading to the development of Fabry disease. Hemizygous males with X-linked disorders typically exhibit severe symptoms, as they possess only one X chromosome. In contrast, heterozygous females demonstrate variability, as their second X chromosome undergoes X-inactivation. Two major clinical subtypes exist within the spectrum of this disease.

The classic form of Fabry Disease features enzyme levels below three percent of normal, which results in swift organ disruption that includes cardiac hypertrophy, brain strokes and kidney dysfunction.

Later-onset Fabry Disease patients display residual enzyme activity, which results in variable clinical expression limited to distinct organs, including the heart or kidneys.

Pathophysiology

Lysosomal accumulation of Gb3 and Lyso-Gb3 leads to pathogenic outcomes by inducing oxidative stress. It causes inflammation, damages endothelial cells, and triggers the development of fibrosis. Several organ complications develop from this pathogenic accumulation of Gb3 and Lyso-Gb3 within lysosomes.

Cardiac disease: Left ventricular hypertrophy and arrhythmias

Kidney dysfunction: Proteinuria and progressive renal failure

Neuropathy: Chronic pain and autonomic dysfunction

Cerebrovascular disease: Increased risk of strokes

Epidemiology and Disease Burden

Statistics indicate that one case of classic FD exists per 40,000 males; however, newborn screening suggests that more cases may emerge from later-onset variants. Heart disease, alongside kidney failure, leads to the most widespread complications and early death among patients. Implementing enzyme replacement therapy (ERT), chaperone therapy, and gene therapy advances has not eliminated the challenges of stopping permanent organ damage (Xi Li *et al*, 2022[1], Fernando Perretta and Sebastian Jaurretche, 2023[2]).

Traditional Therapy for Fabry Disease

Medical approaches for treating Fabry disease (FD) depend on enzyme replacement therapy (ERT). Therapy approaches aim to overcome α-galactosidase A deficiency by reducing globotriaosylceramide accumulation in the body's tissues.

Enzyme Replacement Therapy (ERT)

ORT treatment requires healthcare providers to administer recombinant α-Gal-A intravenously, allowing patients to regain their enzyme functionality and decrease tissue accumulation of Gb3.

The main ERT options include:

Agalsidase beta (Fabrazyme®) – 1.0mg/kg every two weeks.

Agalsidase alfa (Replagal®) – 0.2mg/kg every two weeks.

Pegunigalsidase alfa-iwxj (Elfabrio®) is the new enzyme therapy recently approved.

Challenges of ERT

This therapy targets several tissue locations, including the challenging-to-access brain region.

Anti-drug antibodies known as ADA diminish the effectiveness of the treatment.

High cost (~$200,000 per year) and lifelong treatment requirement (Alan Raj *et al*, 2024)[3].

Need for Alternative Treatment for Fabry Disease

Genetic GLA gene mutations that harm α-Gal A expression led to Gb3 and Lyso-Gb3 accumulation in essential body organs. ETR serves as the standard therapy; however, patients require biweekly infusions of this medication. The treatment has limited penetration into tissues, which may potentially cause immune reactions.

Drug Discovery and Development of Migalastat (Galafold®)

Migalastat is a novel treatment concept that serves as a pharmacological chaperone, designed to enhance the stability and function of misfolded α-Gal A, thereby facilitating a patient-friendly therapeutic approach. It is the first oral medicine to act as a pharmacological chaperone for the treatment of Fabry disease (FD). The enzyme replacement therapy (ERT) method provides patients with external α-galactosidase A (α-Gal A), as Migalastat works differently by binding to

mutant α-Gal A and creating stable lysosomal trafficking, along with enzymatic function, in patients with amenable GLA mutations.

Discovery of Pharmacological Chaperones

Studies of lysosomal storage disorders have shown that misfolded proteins degenerate before they can execute their functional roles. Researchers have found that specific molecules, known as pharmacological chaperones, bind to misfolded proteins, stabilizing them before they degrade prematurely.

Identification of Migalastat (Galafold®)

1-deoxygalactonojirimycin (DGJ), an artificial galactose molecule, successfully bound to the active site of α-Gal A, enabling correct cell transport. Migalastat functions as a derivative of DGJ to enhance enzyme stability while accelerating the breakdown of Gb3 in patients with Fabry disease.

Without Migalastat (Galafold®)

The endoplasmic reticulum (ER) deforms unstable AGAL until it cannot be transported through lysosomes. Due to GL-3 building up in lysosomes, organ damage occurs in the kidneys, heart and nervous system.

With Migalastat (Galafold®)

Migalastat interacts with unstable AGAL to facilitate the proper formation of protein structure, compared to the untreated condition. From the Golgi apparatus, AGAL moves towards lysosomes after it has been stabilized. AGAL recovers its activity within lysosomes to degrade GL-3, thereby preventing substrate accumulation and slowing the progression of the disease. Migalastat is a mutation-specific therapy that delivers noninvasive treatment to patients with amenable mutations of the GLA gene (Frank Weidemann *et al*, 2022)[4].

Drug development and FDA approval process

FACETS Trial (Phase 3, 2016)

The 67-patient study tracked treatment-naïve patients over 12 months and statistically demonstrated GL-3 reductions in their kidney tissues, a biomarker of Fabry disease.

ATTRACT Trial (Phase 3, 2018)

A clinical study compared Migalastat treatment to ERT, including Fabrazyme and Replagal. Migalastat was an equally effective muscle protector, offering the added advantage of oral treatment.

Regulatory Milestones

The EMA approved Migalastat in 2016 and the FDA granted expedited approval for Galafold in August 2018, making it the first drug for treating Fabry disease.

Clinical Impact and Advantages of ERT

Migalastat is an innovative oral treatment that replaces biweekly intravenous enzyme replacement therapy (ERT) for specific GLA mutations, offering improved patient adherence with just twice-weekly dosing. Its non-immunogenic properties reduce the risk of antibody formation and associated immune-related side effects, making it a safer option for long-term use. As a small molecule pharmacological chaperone, Migalastat provides better tissue penetration and effectively manages cardiac hypertrophy and neurological symptoms. Clinical studies have shown that it enhances patients' quality of life by alleviating symptoms such as diarrhea and indigestion.

Limitations and Future Directions

The treatment is effective only for patients with Fabry disease who have mutations that are "amenable." The drug should not be used for patients with severe kidney impairment who have an eGFR lower than 30mL/min/1.73m². Continuing research investigates future-generation pharmacological chaperones, with possible combined therapies using enzyme replacement therapy (Frank Weidemann *et al*, 2022[4], Moran Nuala, 2018[5]).

Pre-Clinical and Clinical Trials of Migalastat (Galafold®)

Migalastat is a pharmacological chaperone therapy that underwent several preclinical and clinical trials to evaluate its effectiveness and safety in patients with Fabry disease who have suitable mutations.

Preclinical studies demonstrated the mechanism of action of Migalastat, and clinical trials established its safety and efficacy, leading to global regulatory approvals. The drug permeates through oral routes without causing immunologic reactions while stabilizing α-Gal A endogenously, representing a significant upgrade from conventional ERT (Han-Wook Yoo, 2023[6], Ilaria Iacobucci *et al*, 2023[7]).

Pharmacokinetics of migalastat (Galafold®)

Pharmacokinetic studies of migalastat investigated the substance's absorption, metabolism, and

elimination patterns, as well as its comprehensive effect on patient outcomes in Fabry disease.

Migalastat provides Fabry disease patients with a convenient oral option offering benefits similar to those of enzyme replacement therapy (ERT). It showcases excellent absorption, low antibody formation, and enzyme stabilization. It mainly benefits patients with amenable GLA mutations, featuring alternate-day dosing, minimal interactions, and sustained renal and cardiac benefits (Michal Nowicki *et al*, 2024[8], Judit Tomsen-Melero *et al*, 2024[9], William C. Hallows *et al*, 2023[10]).

Pharmacoeconomics of Migalastat (Galafold®)

Cost-Benefit Evidence

Migalastat offers better cost management than enzyme replacement therapy (ERT) by eliminating the need for biweekly infusions and their associated healthcare costs. ERT treatment can range from $200,000 to $300,000 annually, creating significant financial strain for patients. Studies from Japan and the Netherlands indicate that Migalastat treatment improves financial outcomes by reducing hospital visits and complications linked to infusions. The healthcare cost per QALY for ERT ranges from €3.2 million to €6.5 million, while Migalastat shows better cost-effectiveness. A Japanese analysis highlights how Migalastat minimizes medical expenses by lowering infusion-related costs. Overall, long-term evaluations suggest that Migalastat is a more budget-friendly option for healthcare systems.

Social Impact

Migalastat improves QALY outcomes by enhancing therapy adherence and reducing treatment pressures. Eliminating infusion challenges enables a better quality of life for patients compared to intravenous enzyme replacement therapy (ERT). Research indicates that Migalastat results in fewer side effects and greater patient independence. While ERT can extend lifespan, complications from infusions often lead to discontinuation, diminishing its long-term QALY effectiveness. Migalastat also reduces the disease burden by slowing Fabry-related complications and decreasing long-term disability, as indicated by the Disability-Adjusted Life Years (DALY) metric. Limited DALY data suggest that its oral administration stabilizes organ function better than ERT.

Commercial Impact

Fabry disease imposes significant economic burdens due to ongoing treatment costs, medical appointments and complications that reduce earnings for patients and caregivers. Advanced kidney disease adds to the financial strain on healthcare systems due to the need for additional renal support. As the disease progresses, patients often leave work prematurely, worsening their financial situation. Migalastat's oral medication helps reduce indirect costs by eliminating the need for infusion sessions, allowing patients to maintain full-time employment and improve productivity. This therapy can lead to fewer hospital admissions, lower medical bills, and increased work participation, ultimately reducing patient costs and healthcare costs (Ana Jovanavc *et al*, 2024[11], Uzma Sultana *et al*, 2024[12], Renzo Mignani *et al*, 2024[13], Jonas Muntze *et al*, 2023[14]).

Public-Private Partnership (PPP) and Access Consideration for Migalastat (Galafold®)

PPP in Migalastat Development and Distribution

Migalastat (Galafold) from Amicus Therapeutics' market entry was established through public-private partnerships (PPPs) across multiple nations. Through these collaborations, both entities secured regulatory approvals, negotiated pricing, and established patient access programs.

GlaxoSmithKline (GSK) Partnership (2010-2013)

Amicus entered its first development agreement with GSK to produce and sell Migalastat. The collaboration secured funding to conduct late-stage clinical trials, thereby extending the scope of regulatory approval. The complete rights to Migalastat returned to Amicus in 2013, thus allowing them to pursue independent commercialization.

Partnership with Pint Pharma in Argentina, the European Union, and Global Expansion (2019)

Amicus and Pint Pharma's Migalastat received approval from Argentina's ANMAT as a monotherapy for Fabry disease, making Latin America Amicus's first market. The companies are working on applications for Brazil, Mexico, and other regions. They collaborated on early access programs to provide affordable pricing and expedite distribution in Argentina. Migalastat has been

licensed in over 40 countries, including the U.S., Canada, and Japan. The companies are partnering with European health agencies to enhance patient access through pricing agreements.

Access Considerations

Targeted Access for Patients with Amenable Mutations

Medical research has proven that migalastat can treat GLA mutations that are considered amenable in patients (rare cases amounting to 30-50% of Fabry patients). Several countries now operate genetic testing programs aimed at identifying patients who are eligible for treatment.

Regulatory Approvals and Reimbursement Challenges

Certain health reimbursement rules have delayed medical access due to pharmaceutical companies setting high drug costs. National reimbursement decisions about Migalastat depend on health technology assessment (HTA) agencies, which assess its cost-benefit ratio against enzyme replacement therapy (ERT).

Affordability and Patient Assistance Programs

Amicus partnered with national healthcare systems to implement price negotiations and subsidy programs focused on broader healthcare coverage. Migalastat remains inaccessible to patients in low- and middle-income countries because these countries must address high costs and a lack of developmental infrastructure for genetic screening.

Advantages over Traditional ERT in Access and Administration

The oral treatment method makes care more accessible to patients living in remote locations by eliminating the requirement for regular infusions. Better long-term costs and reduced hospital expenses make healthcare more affordable (Amicus Therapeutics, 2016)[15].

Table No.1: Summary of pre-clinical and clinical trials of migalastat

S.No	Trial Stages	Objectives	Results
1	Pre-Clinical Studies	To assess how well Migalastat stabilizes the mutated α-Gal A and its effect on lysosomal transport systems and its reduction of Gb3 accumulation.	Migalastat successfully stabilized α-Gal A while enhancing enzymatic function and reducing Gb3 levels in animal models.
2	FACETS Trial (Phase III, 2016)	To evaluate the effectiveness of the treatment for patients with Fabry disease and amenable mutations who have never received ERT.	Over 12 months, the long-term treatment of 67 patients resulted in a substantial reduction in Gb3 levels in their kidneys, maintenance of renal function and improved heart anatomy.
3	ATTRACT Trial (Phase III, 2018)	To compare Migalastat with enzyme replacement therapy (ERT) in ERT-experienced patients.	A study comparing migalastat to ERT, which enrolled 60 patients, showed that Migalastat was equally effective in protecting kidney health and better managed gastrointestinal issues.
4	Long-term Extension Studies	To evaluate long-term safety, efficacy and renal function preservation.	Patients who received treatment for 30 months or longer experienced stable renal function, stable Lyso-Gb3 levels, and improved cardiac function.

Table No.2: Summary of Pharmacokinetics and Pharmacodynamics of Migalastat

S.No	Pharmacokinetic Parameters	Results
1	Absorption and Bioavailability	The estimated oral bioavailability is ~75%.
2	Peak Plasma Concentration	Concentration reached within ~3 hours of post-administration.
3	Effect of Food	People who take this medicine should avoid eating for at least 2 hours because food can reduce absorption by up to 40%.
4	Distribution	Extensive tissue distribution with no significant plasma protein binding.
5	Metabolism	The drug primarily leaves the body through urine without undergoing any transformations, as it does not activate any cytochrome P450 enzymes.
6	Elimination	Around 77% of trazodone passed through urine without transformations, while fecal elimination accounted for approximately 20% of the substance.
7	Half-Life	The enzyme stabilizing duration ranges between 4 and 6 hours.
8	Patient Compliance	The oral administration method leads to better patient adherence through simplified medication administration, which eliminates the need for biweekly intravenous infusions used in ERT.

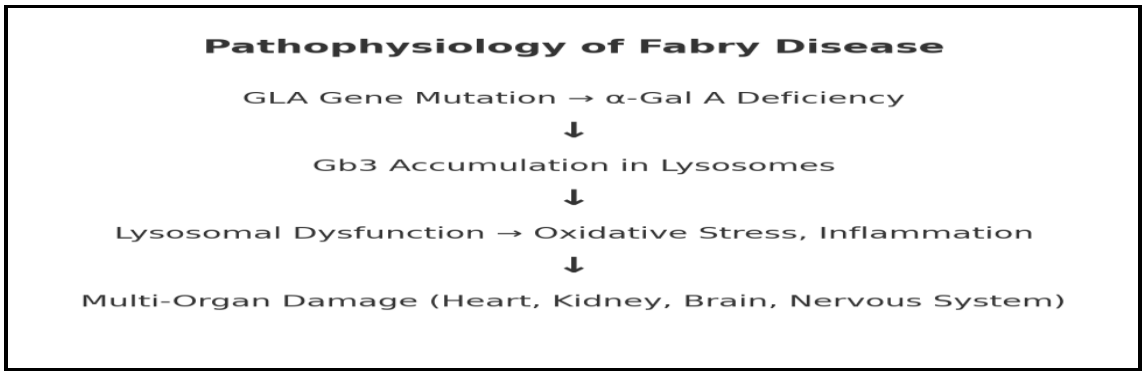

Figure No.1: Pathophysiology of Fabry Disease: This schematic illustration illustrates how Gb3 deposition leads to lysosomal breakdown, toxic stress, and damage to various body systems

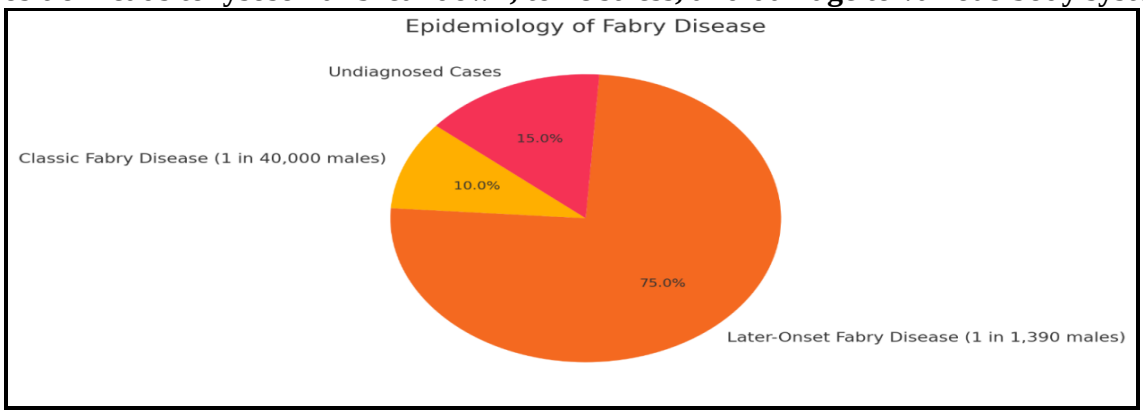

Figure No.2: Epidemiology of Fabry Disease (FD): This pie chart presents statistical information about the prevalence of classic versus later-onset Fabry disease, while also highlighting an unknown segment to represent the underdiagnosis of this condition

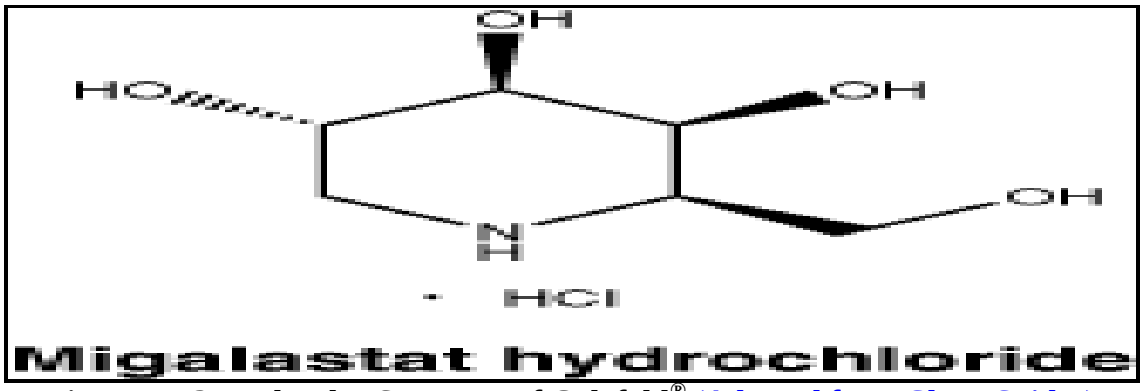

Figure No.3: Molecular Structure of Galafold® (Adapted from Chem Spider)

Mechanism of Action of Migalastat (Galafold®)

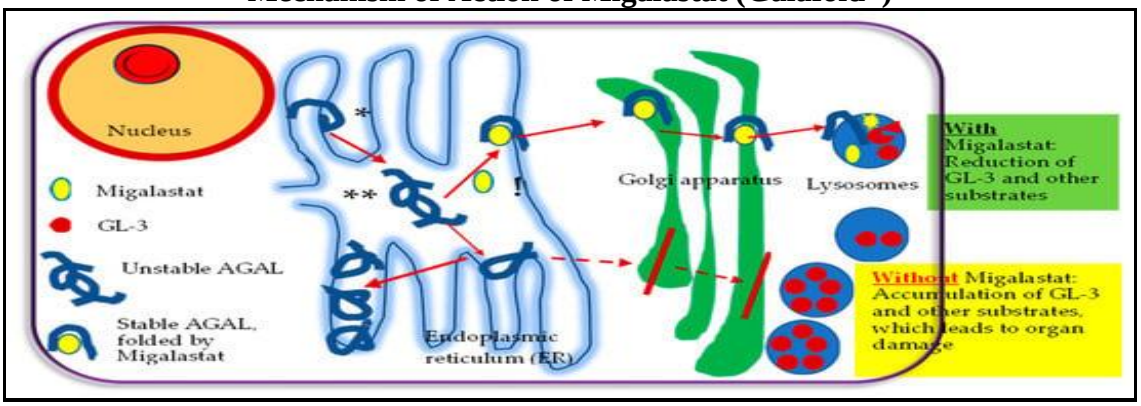

Figure No.4: Mechanism of action of migalastat in fabry disease

CONCLUSION

Migalastat (Galafold®) brings an essential breakthrough in Fabry disease treatment through its oral formulation, an alternative to enzyme replacement therapy (ERT). This medication acts as a pharmacological chaperone to stabilize and improve the function of misfolded α-Gal A, thereby reducing the disease burden and enhancing patient adherence. The pharmacological advantages of Migalastat exceed those of ERT, as it demonstrates improved cost-effectiveness and long-term clinical benefits, with favorable pharmacokinetics, specifically for patients with amenable GLA mutations.

The pharmacoeconomic analysis shows that Migalastat provides better sustainability because it lowers the expenses of therapy administration, hospital visits and employee absence from work. Strategic partnerships between public entities and private organizations helped expand access and secure regulatory authorizations to support global market entry. Multiple obstacles have arisen in the delivery of Migalastat, including patient requirements for specific genetic mutations, insurance coverage limitations and gaps in availability across developing countries.

The future strategy for managing Fabry disease involves uniting pharmacological chaperones with gene therapy or next-generation ERT therapy to improve patient outcomes. Healthcare professionals should assess Migalastat as a promising precision medicine therapy due to its practical treatment pathway for suitable Fabry patients, while also evaluating its cost-effectiveness and longer-term benefits.

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CONFLICT OF INTEREST

We declare that we have no conflict of interest.

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