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Fabry Disease: Current scenario in India using herbal plants

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CONTENTS

ABSTRACT

Fabry disease is an uncommon hereditary lysosomal storage disorder known as a sphingolipidosis. It arises due to deficiency of -galactosidase A (GLA), leading to the accumulation of excessive glycosphingolipids in cellular structures. It is also called Alpha-Galactosidase or Anderson Fabry disease. It primarily affects hemizygous males, with various symptoms such as neurological distress (pain), dermal manifestations (angiokeratoma), renal complications (proteinuria, kidney failure), cardiovascular issues (cardiomyopathy, arrhythmia), cochleo-vestibular impairments and cerebrovascular events (transient ischemic attacks, strokes). Symptoms may manifest in heterozygous females and magnitude ranges from mild to profound. Furthermore, patients experience pain, gastrointestinal disturbances and impairments in the eyes, ears, lungs and bones. Early detection of Fabry disease is crucial for timely and appropriate treatment, currently focused on enzyme replacement therapy (ERT) using Pegunigalsidase-alfa and Moss-aGal. Other cutting-edge Chaperone-based therapy, substrate depletion therapy and alternative therapeutic approaches migalastat, and techniques involving stem cells, genes and mRNA, are also being used to prolong the lives of affected individuals. The impact of certain plant constituents, like curcumin revealed that it improves AGAL activity in 80 % of scrutinized mutant genotypes. The degree of enhancement varied from 1.4 to 2.2-folds increase depending on the specific mutation. Additionally, the *Nicotiana benthamiana* plant has potential to produce therapeutic enzymes. Moreover, *Nicotiana tabacum* plant cells successfully manufactured a PEGylated form of human-GAL enzyme for the management or therapeutic intervention for Fabry disease and Curcumin's pleiotropic effects are associated with its modulation of various

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pathways, including, ERK5, Akt, mTOR, Notch-1, AP-1, TGF-, Wnt, catenin, PPAR, Shh, PAK1, Rac1, STAT3, EBP, NLRP3, p38MAPK, Nrf2, inflammasome, AMPK, TLR-4, and MyD-88 PI3K and it modulates autophagy and ER stress.

Keywords: *Camellia sinensis*, Chaperone-Based Therapy, Enzyme Replacement Therapy, Fabry Disease, Lysosomal Storage Disorder, Substrate Depletion Therapy

1. INTRODUCTION

Accumulation of Gb3 within lysosomal compartments following a deficiency in -GalA is widely acknowledged; however, the subsequent mechanisms leading to cellular dysfunction and consequent symptomatology remain shrouded in mystery (32). Similar to other hereditary glycosphingolipidoses, the presence of lipid-filled lysosomes could potentially impact the flow of autophagy, encompassing mitophagy (24). The etiology of the condition seems to involve crucial factors such as fibrosis, inflammation, and oxidative stress (51,56). A robust correlation was observed between the cumulative lysoGb3 exposure throughout the lifetime and the overall severity of the disease among male and female individuals diagnosed with classic Fabry disease (42). Undoubtedly, the activation of smooth muscle cell proliferation by lysoGb3 elucidates the underlying mechanism behind the augmented intima media thickness and rigidity of arteries observed in individuals affected by Fabry disease (38). Additionally, the presence of lysoGb3 has demonstrated its ability to induce the demise of nociceptive neurons in individuals affected by FD, aligning seamlessly with the documented anguish experienced in the limbs of typical males with FD (8). The sensitivity thresholds to heat and cold in the upper limb were found to be significantly associated with cumulative exposure to lysoGb3 throughout one's lifetime (3). Subsequently, it is anticipated the participation of lysoGb3 in progression of podocyte loss and glomerular fibrosis, crucial aspects of renal pathology in individuals with Fabry disease (45). Lastly, it has been unveiled that lysoGb3 exhibits the ability to inhibit endothelial nitric oxide synthase (eNOS) at levels comparable to those observed in individuals diagnosed with Fabry disease, implying its potential contribution to the development of vasculopathy associated with the condition (25). Beyond the confines of the lysosome, there seem to be additional cellular ramifications stemming from the deficiency of –Gal A. The autophagy-lysosome pathway (ALP) stands as a pivotal regenerative mechanism that fosters cellular endurance and sustenance (28).

The disruption of the autophagy-lysosome pathway (ALP) represents a prevalent characteristic observed in lysosomal storage disorders, encompassing notable examples such as Fabry syndromes. Likewise, deviations in mitochondrial functionality and the equilibrium of energy dynamics have been detected within sphingolipid compounds disorders Gaucher disease and Fabry disease serve as two illustrative instances (24). Moreover, the infiltration of lymphocytes and macrophages into FD tissues, including the cardiac tissues, has been observed, indicating the involvement of inflammation in tissue injury (48).

2. SYMPTOMS

In the initial phases of the disease, neural impairment primarily targets the delicate nerve fibres within the Sensory and autonomic nervous systems in the peripheral regions (5,10). Pain manifests in approximately 60-80% of individuals affected by the classical

form of Fabry disease, regardless of gender (20). Two distinct forms of pain exist within the context of Fabry disease: the episodic pain commonly referred to as "Fabry crises," characterized by excruciating burning sensations originating in the peripheral regions and radiating inward towards the lower extremities and various body regions, and the persistent discomfort typified by persistent burning sensations and chronic discomfort (7). Fabry crises can be instigated by various factors such as fever, physical exertion, fatigue, psychological stress, and abrupt fluctuations in temperature (19). In patients experiencing crises that are triggered or accompanied by fever, a notable elevation in erythrocyte sedimentation rate (ESR) is often observed (9). Pain may diminish with advancing age, thus emphasizing the importance of assessing the medical history for symptoms of acroparesthesia (35). Anhidrosis, or diminished perspiration capacity known as hypohidrosis, accompanied by reduced Epidermal resilience, poses a pivotal and consequential challenge for individuals seeking medical care, and lead to heat sensitivity and limited physical exertion tolerance (16) .

3. DIVERSE THERAPEUTIC APPROACHES FOR TREATMENT

3.1. Enzyme replacement therapy

Presently, there exist two distinct variants of or categories of enzyme replacement therapy Enzyme replacement therapy (ERT) presents itself as a therapeutic choice. One is agalsidase-alfa (Replagal, Takeda, Shire Human Genetic Therapies, Cambridge), which is derived from Human-derived fibroblasts and administered at a dose of 0.2 mg/kg twice weekly. The other is Beta agalsidase (Fabrazyme, Sanofi Genzyme), which is Produced within Chinese hamster ovary cells and characterized as a dose of 1.0 mg/kg biweekly. Short-term pathological manifestations examinations evaluating the impact of agalsidase-beta therapy based on renal biopsy specimens have demonstrated the elimination of Gb3 from endothelial, mesangial, and podocyte cellular populations (54).

Beta agalsidase is currently the only available treatment option in the US, having received approval from the FDA in 2003. Conversely, outside of the United States, agalsidase alfa is accessible in various regions including the South American countries, Australia, Canada, Mexico and European Union (13,16).

Enzyme replacement therapy (ERT) has exhibited favourable outcomes in mitigating renal and cardiac symptoms in the early stages of the disease (27). It is worth noting that certain individuals may manifest immunological responses to the administration of recombinant enzymes (58). Additional drawbacks of enzyme replacement therapy (ERT) encompass the limited duration of the enzyme's effectiveness due to its short half-life, as well as the necessity for frequent administration of substantial enzyme doses (40). In 2008, the identification of LysoGb3, a deacylated derivative of as a biomarker i.e. Gb3 for Fabry disease proved significant. The levels of LysoGb3 in plasma exhibit a strong correlation with the disease phenotype, with classical patients demonstrating higher levels and non-classical individuals exhibiting lower levels (37). Individuals who initiated treatment before reaching the age of 25demonstrated notably reduced LysoGb3 concentrations levels during therapy in contrast to those who commenced treatment at a later stage in life (1).

3.2. Chaperone therapy

Certain individuals with Fabry disease exhibit missense mutations that result in the enzymatic proficiency of AGAL remain unimpaired. However, there is a decline in overall AGAL enzyme activity due to compromised protein robustness caused by misfolding and premature degradation (43). To address the issue of misfolding and premature degradation, a minuscule compound referred to as a chaperone has been developed with the purpose of rectifying the misfolding process and preventing untimely destruction. In vitro studies involving COS-1 cells carrying the p.Q279E mutation have demonstrated that the addition of galactose to the growth media resulted in a notable augmentation of enzyme activity (23). Nevertheless, the effectiveness of galactose in enhancing enzyme activity in AGAL mutations has not been substantiated (38). Subsequent studies primarily employed 1-deoxygalactonojirimycin (O2 atom in the ring is substituted with a nitrogen atom) developed by Amicus Therapeutics, U.S., Inc. (PA, USA, Philadelphia).

Migalastat, the exclusive oral therapy available for FD, is given at a dose of 123 mg every alternate day. It received approval from the European Medicines Agency (EMA) in 2016 and from the US Food and Drug Administration (FDA) in 2018 for the treatment of individuals aged 12 years and above with an eGFR of 30 mL/min/1.73 m^2 and treatable AGAL mutations. Due to the exceptional rarity of FD, extensive Clinical investigations involving Migalastat have nonetheless been conducted on a large scale yet (2).

Migalastat is believed to act as a potent competitive inhibitor of AGAL by binding to it, but interestingly, at diminished levels or concentrations it enhances the Catalytic function or enzymatic performance specifically in instances of AGAL genetic mutations that are susceptible to its effects (21). It is important to note that Migalastat is not advised for use by pregnant or breastfeeding women due to limited information on its safety in these populations (55).

The iminosugar's attachment to the catalytic domain of GAL A is believed to induce proper folding of the enzyme (12).

Pegunigalsidase alfa is a pharmacologically modified form of -Gal A enzyme, PEGylated for enhanced therapeutic properties, formulated as an enzyme replacement therapy (ERT) for Fabry disease. This modified enzyme is produced using the ProCellEx system, a platform that utilizes plant cells for enzyme production (57).

Its purpose was to enhance therapeutic efficacy by prolonging Plasma's duration of half-life and reducing Immunogenicity in contrast to existing treatments(46).

3.3. MOSS –a GAL: A GENETICALLY ENGINEERED ENZYME FOR FD

Moss-a Gal, a genetically engineered iteration of -galactosidase A derived from plants, has demonstrated selective uptake in endothelial cells but not in fibroblasts in vitro. Although there were no differences in the clearance of Gb3 from these cell types, moss-aGal treatment resulted in higher enzymatic activity in kidney biopsies of FD mice compared to those treated with agalsidase-alfa. However, when contrast to agalsidase-alfa, the injected recombinant enzyme moss-aGal exhibited a generally shorter half-life in the heart and kidney. Recently, a phase I clinical trial investigating moss-aGal, administered as a single dose (0.2 mg/kg), was conducted on a group of seven females with GLA mutations, including four classical, two late-onset, and one benign phenotypic cases (NCT02995993). Encouragingly, no significant adverse effects were reported, and

pharmacokinetic analysis indicated a relatively following a solitary injection, the plasma's half-life amounts to 14 minutes (18).

3.4. Substrate Reduction Therapy

Substrate reduction therapy (SRT) is gaining traction as an alternative strategy for reducing metabolite by Fabry disease-associated levels inhibiting the amalgamation of critical precursor glycosphingolipids. Currently, two small compounds are either under evaluation in clinical trials or scheduled for testing: ibiglustat (NCT02489344; completed) and lucerastat (NCT03425539; ongoing recruitment). These two ibiglustat and lucerastat act by blocking the glucosylceramide synthase enzyme responsible for the initial an intermediate step in the synthesis of glucosphingolipids. This strategy has demonstrated efficacy in the management of Gaucher disease, another glycosphingolipidosis (52).

The efficacy of SRT (substrate reduction therapy) has been investigated in mouse models alongside enzyme replacement therapy (ERT) (29). This study introduces Genz-682452, a novel, highly specific, and potent glucosylceramide synthase (GCS) inhibitor with central nervous system (CNS) penetration. Genz-682452 demonstrates favourable pharmacokinetics and safety characteristics with the aim of managing Fabry disease. In a mouse model of Fabry disease, Genz-682452 effectively reduces the pathological accumulation of the main glycolipid substrates. Moreover, due to the distinct pharmacodynamic profiles and underlying mechanisms of action, there is evidence of therapeutic synergy and potential additive effects in certain tissues between the two treatment approaches. Thus, the availability of Genz-682452 as an adjunct therapy presents an opportunity to enhance the degree of medical attention for individuals with Fabry disease, providing additional benefits and improving overall treatment outcomes (30).

3.5. Removal of Storage Material

An alternative methodology to mitigate intralysosomal accumulation involves promoting the efflux of accumulated substances from the intracellular lysosomal compartment and subsequently, from the cell itself. This strategy is under investigation due to the interconnected relationship between Gb3 and cholesterol homeostasis, which exhibit various interaction . Gb3, similar to other glycosphingolipids, is present in plasma lipoproteins, particularly in decreased-density lipoprotein (LDL), and thus has the potential to enter endothelial cellular demise mediated by LDL receptors (4). The accumulation of glycosphingolipids (GSL) within cells has been associated with the accumulation of intracellular cholesterol, primarily due to an increase in LDL receptor expression. Consequently, the storage of Gb3 may lead to an enhanced influx of Gb3 into endothelial cells in the presence of LDL. This influx of cholesterol triggers a diversion of GSLs towards the lysosome rather than the Golgi apparatus, thereby exacerbating lysosomal accumulation (47). Moreover, the accumulation of Gb3 has been observed to hinder the ability of apoA1 to facilitate the efflux of cholesterol (14). Additionally, it has been demonstrated that the accumulation of Gb3 hinders the ability of apoA1 to facilitate the efflux of cholesterol (47).

3.6. Stem Cell, Gene, and mRNA Based Therapies

In recent years, numerous pre-clinical studies on gene therapy for Fabry disease have emerged, exploring both in vivo and ex vivo techniques utilizing various vectors such as delivery systems including retroviral, lentiviral, adenoviral, adeno-associated viral, and non-viral vectors as previously examined (17).

In recent times, clinical trial phase I and II s have commenced treating Fabry disease patients using an ex vivo approach. This innovative strategy involves extracting the patient's hematopoietic stem cells, modifying them through lentiviral transfection using AVR-RD-01 (developed by Avrobio), and subsequently re-infusing the modified cells back into the patient. Notable trials employing this approach include NCT02800070 and NCT03454893 (31). Adeno-associated virus (AAV)-based gene Clinical trials are currently underway for therapeutic interventions. currently in progress, aiming to enhance the production and secretion of the enzyme through the action of liver-specific enzymes.

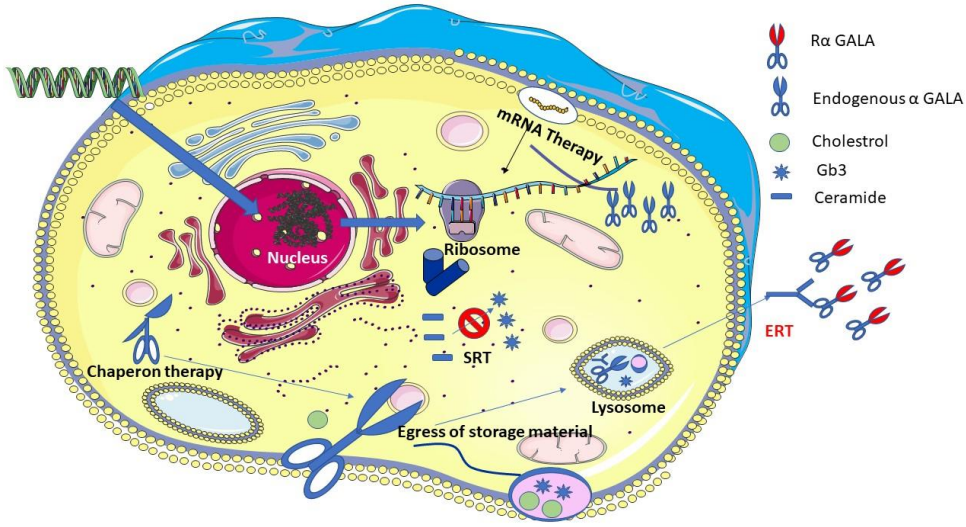

Figure 1. Overview of various methodologies in the treatment of Fabry disease; Enzyme replacement therapy (ERT) strives to reinstate the malfunctioning αGAL A enzyme. Chaperones interact with the active site of the unstable αGAL A enzyme to facilitate appropriate protein folding. Substrate reduction therapy focuses on inhibiting the synthesis of glycosphingolipids to diminish the generation of Gb3 and its derivatives. Gene therapy endeavors to rectify the underlying genetic anomaly responsible for Fabry disease. mRNA therapy triggers temporary production of αGAL A within the body. Enhancing cholesterol efflux has the potential to stimulate the expulsion of Gb3.

In addition to gene therapy, there are ongoing developments in the field of systemic messenger RNA (mRNA) treatment for FD, led by companies like Moderna Inc and Translate Bio. Unlike DNA-based therapies, mRNA-based treatments do not pose a risk of insertional mutagenesis. However, one drawback of mRNA-based therapy is its transient nature, which requires repeated injections to maintain the therapeutic effect (15). When delivered in lipid nanoparticles, mRNA treatment is primarily directed towards

hepatocytes, the cells responsible for producing and releasing the enzyme into the bloodstream, which is then adopted by diverse range of tissues. The sustained generation of the production of the enzyme following a single mRNA administration led to a plasma duration of GAL A activity lasting approximately. The duration of GAL A activity is approximately 7.5 hours in both mice and rats nonhuman primates (41). Repetitive administration of mRNA resulted in a substantial reduction in the levels of Gb3 and lysoGb3 levels in the heart and kidney, reaching reductions of up to 90% and 70%, respectively (11). mRNA-based therapy is currently in its nascent phase, with limited clinical data available in human subjects.

4. ROLE OF HERBS IN FABRY DISEASE

4.1. *Curcuma longa*

Curcumin, a compound derived from turmeric, has garnered interest in Western medicine due to its traditional use in Chinese medicine (91). Curcumin's pleiotropic effects are associated with its modulation of various pathways, including, ERK5, Akt, mTOR, Notch-1, AP-1, TGF-, Wnt, catenin, PPAR, Shh, PAK1, Rac1, STAT3, EBP, NLRP3, p38MAPK, Nrf2, inflammasome, AMPK, TLR-4, and MyD-88 PI3K. Curcumin additionally modulates autophagy and ER stress (53). The IF-L300F cell line was subjected to curcumin treatment, both with and without deoxygalactonojirimycin (DGJ), in order to investigate the impact of curcumin therapy on potential lysosomal biomarkers. Interestingly, curcumin treatment led to a decrease in LAMP-1 levels, a phenomenon previously observed with enzyme replacement therapy ERT (33). Moreover, the administration of curcumin, whether as monotherapy (panel D) or in combination with other treatments (panel E), resulted in a reduction in GAA activity. These compelling findings indicate the beneficial impact of curcumin therapy on the cellular model of Fabry disease (FD).

Curcumin and the combination of curcumin with DGJ demonstrated therapeutic advantages in FD cell cultures, manifesting in the amelioration of the FD phenotype. Curcumin, in combination with either pharmacological chaperone therapy, exhibited positive outcomes for four out of the five studied mutants. The fold-increase in AGAL activity ranged from 1.1 to 2.3 for 1-deoxygalactonojirimycin (DGJ) and from 1.1 to 2.8 for galactose. Furthermore, in a long-term therapy study involving the L300F mutant, and observed improvements in Gb3 clearance and lysosomal markers, specifically LAMP-1 and GAA (6).

4.2. *Nicotiana benthamiana*

Galactosidases (EC 3.2.1.22) can be detected in a wide array of flora, fauna, and microorganisms. During the germination of seeds, plant galactosidases demonstrate their ability to break down galactosyl-sucrose oligosaccharides, oligosaccharides belonging to the raffinose family, and galactomannans present in cell walls (26). Apoplast samples derived from *N. benthamiana* and Leaf extracts were generated and then subjected to scrutiny for activity of galactosidase, employing 4-methylumbelliferyl--D-galactose (4MU-Gal) as the support for assessment. Enzymatic functionality was detected in both specimens, exhibiting an optimal pH range of 5.0-6.7. Subsequently, the leaf and apoplast samples were subjected to varying pH conditions, followed by treatment with Cy5-

functionalized TB474 ABP. Within the leaf extract, proteins labelled with Cy5-ABP displayed apparent molecular masses of 39 and 45 kDa.

For the purpose of research, -GAL, -NAGAL, and -NAGALEL enzymes were transiently synthesized within the leaves of *N. benthamiana*. By employing activity-based probes that form a covalent bond within their catalytic site, all enzymes can be visualized. Upon conducting a thorough examination of purified proteins, it was ascertained that -NAGALEL exhibits heightened efficacy when it comes to artificial 4MU-α-Gal. Notably, recombinant -NAGAL and NAGALEL exhibit lower stability in human plasma compared to -GAL, while they remain un-neutralized by Ab-positive FD serum. Moreover, these enzymes effectively catalyze the hydrolysis of the lipid substrates Gb3 and Lyso-Gb3 commonly observed in individuals with Fabry disease. The presence of -NAGALEL, and to a lesser extent -NAGAL, in the serum of Fabry disease patients mitigates the detrimental effects of Lyso-Gb3. By utilizing activity-based probes firmly attached within their catalytic cavity, it becomes feasible to visualize all enzymes. This innovative enzyme, amenable to synthesis in *N. benthamiana*, demonstrates promising prospects for therapeutic applications in the treatment of Fabry disease, aiming to effectively reduce the levels of circulating Lyso-Gb3 (26).

5. CONCLUSIONS

In summary, the treatment landscape for Fabry disease encompasses a spectrum of therapeutic options, including enzyme replacement therapy (ERT), chaperone therapy, migalastat, pegunigalsidase-alfa, moss-aGal, substrate reduction therapy (SRT), and innovative approaches such as stem cell, gene, and mRNA-based therapies. ERT, available in various formulations, has demonstrated favourable outcomes in addressing renal and cardiac symptoms and enhancing the quality of life. However, its long-term efficacy in stroke prevention remains uncertain. Chaperone therapy, employing compounds like migalastat, aims to rectify enzyme misfolding and degradation, leading to improved stability and reduced accumulation of substrates. Pegunigalsidase-alfa, a modified version of α-galactosidase A, holds promise in reducing the build up of renal globotriaosylceramide (Gb3) inclusions. Moss-a Gal, derived from plant sources, exhibits selective absorption and heightened enzymatic activity in kidney cells. SRT, which aims to decrease substrate levels, has shown potential synergy with ERT. Exploratory approaches such as stem cell, gene, and mRNA-based therapies are currently under investigation, and gene therapy trials employing viral vectors have yielded encouraging results in augmenting enzyme production. However, challenges pertaining to immune responses and the need for further research persist.

AUTHOR'S CONTRIBUTION

SS carried the conceptualization and writing on fabry disease advance Treatment contains enzyme replacement therapy, substrate reduction therapy and followed research done recently on this disease. AV, BP, and VP performed the systematic evaluation and elaborated on the conclusion. All authors read and approved the final manuscript.

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DECLARATION

We affirm that each and every author of this scholarly endeavor made substantial contributions, and we have not excluded any author who made significant contributions. We adhered diligently to the ethical norms set forth by our respective institutions.

6. REFERENCES

1. Arends, M., Biegstraaten, M., Wanner, C., Sirrs, S., Mehta, A., Elliott, P.M., Oder, D., Watkinson, O.T., Bichet, D.G., Khan, A., Iwanochko, M., Vaz, F.M., van Kuilenburg, A.B.P., West, M.L., Hughes, D.A. and Hollak, C.E.M. (2018). Agalsidase alfa versus agalsidase beta for the treatment of Fabry disease: An international cohort study. *Journal of Medical Genetic* **55:** 351-358.
2. Benjamin, E.R., Della Valle, M.C., Wu, X., Katz, E., Pruthi, F., Bond, S., Bronfin, B., Williams, H., Yu, J., Bichet, D.G., Germain, D.P., Giugliani, R., Hughes, D., Schiffmann, R., Wilcox, W.R., Desnick, R.J., Kirk, J., Barth, J., Barlow, C. and Lockhart, D.J. (2017). The validation of pharmacogenetics for the identification of Fabry patients to be treated with migalastat. *Genetics in Medicine* **19:** 430-438.
3. Biegstraaten, M., Hollak, C.E.M., Bakkers, M., Faber, C.G., Aerts, J.M.F.G. and van Schaik, I.N. (2012). Small fiber neuropathy in Fabry disease. *Molecular Genetics and Metabolism* **106:** 135-141.
4. Bodary, P.F., Shayman, J.A. and Eitzman, D.T. (2007). Alpha-galactosidase A in vascular disease. *Trends in Cardiovascular Medicine* **17(4)**: 129-133.
5. Cable, W.J., Kolodny, E.H. and Adams, R.D. (1982). Fabry disease: Impaired autonomic function. *Neurology* **32:** 498-502.
6. Carmi, N., Zhang, G., Petreikov, M., Gao, Z., Eyal, Y., Granot, D. and Schaffer, A.A. (2003). Cloning and functional expression of alkaline α-galactosidase from melon fruit: Similarity to plant SIP proteins uncovers a novel family of plant glycosyl hydrolases. *Plant Journal: For Cell and Molecular Biology* **33(1)**: 97-106.
7. Charrow, J. (2009). A 14-year-old boy with pain in hands and feet. *Pediatric Annals* **38(4)**: 190-192.
8. Choi, L., Vernon, J., Kopach, O., Minett, M.S., Mills, K., Clayton, P.T., Meert, T. and Wood, J.N. (2015). The Fabry disease-associated lipid Lyso-Gb3 enhances voltage-gated calcium currents in sensory neurons and causes pain. *Neuroscience Letters* **594**: 163-168.
9. Cole, A.L., Lee, P.J., Hughes, D.A., Deegan, P.B., Waldek, S. and Lachmann, R.H. (2007). Depression in adults with Fabry disease: A common and under-diagnosed problem. *Journal of Inherited Metabolic Disease* **30(6)**: 943-951
10. DeRosa, F., Smith, L., Shen, Y., Huang, Y., Pan, J., Xie, H., Yahalom, B. and Heartlein, M.W. (2019). Improved efficacy in a Fabry disease model using a systemic mRNA liver depot system as compared to enzyme replacement therapy. *Molecular Therapy* **27(4)**: 878-889.
11. Dütsch, M., Marthol, H., Stemper, B., Brys, M., Haendl, T. and Hilz, M.J. (2002). Small fiber dysfunction predominates in Fabry neuropathy. *Journal of Clinical Neurophysiology* **19(6)**: 575-586.
12. Fan, J.Q., Ishii, S., Asano, N. and Suzuki, Y. (1999). Accelerated transport and maturation of lysosomal alpha-galactosidase A in Fabry lymphoblasts by an enzyme inhibitor. *Nature Medicine* **5(1)**: 112-115.
13. Redin, C., Gérard, B., Lauer, J., Herenger, Y., Muller, J., Quartier, A. and Piton, A. (2014). Efficient strategy for the molecular diagnosis of intellectual disability using targeted high-throughput sequencing. *Journal of medical genetics* **51(11)**: 724-736.
14. Glaros, E.N., Kim, W.S., Quinn, C.M., Wong, J., Gelissen, I., Jessup, W. and Garner, B. (2005). Glycosphingolipid accumulation inhibits cholesterol efflux via the ABCA1/apolipoprotein AI pathway: 1-phenyl-2-decanoylamino-3-morpholino-1-propanol is a novel cholesterol efflux accelerator. *Journal of Biological Chemistry* **280(26)**: 24515-24523.
15. Gollomp, K.L., Doshi, B.S. and Arruda, V.R. (2019). Gene therapy for hemophilia: Progress to date and challenges moving forward. *Transfusion and Apheresis Science* **58(5)**: 602-612.

16. Gupta, S.N., Ries, M., Murray, G.J., Quirk, J.M., Brady, R.O., Lidicker, J.R., Schiffmann, R. and Moore, D. F. (2008). Skin-impedance in Fabry disease: A prospective, controlled, non-randomized clinical study. *BioMed Central Neurology* **8**: 41.
17. Henig, I. and Zuckerman, T. (2014). Hematopoietic stem cell transplantation-50 years of evolution and future perspectives. *Rambam Maimonides Medical Journal* **5(4)**
18. Hennermann, J.B., Arash-Kaps, L., Fekete, G., Schaaf, A., Busch, A. and Frischmuth, T. (2019). Pharmacokinetics, pharmacodynamics, and safety of moss-aGalactosidase A in patients with Fabry disease. *Journal of Inherited Metabolic Disease* **42(3)**: 527-533.
19. Hilz, M.J., Stemper, B. and Kolodny, E.H. (2000). Lower limb cold exposure induces pain and prolonged small fiber dysfunction in Fabry patients. *Pain* **84(2-3)**:361-365.
20. Hopkin, R.J., Bissler, J., Banikazemi, M., Clarke, L., Eng, C.M., Germain, D.P., Lemay, R., Tylki-Szymanska, A. and Wilcox, W.R. (2008). Characterization of Fabry disease in 352 pediatric patients in the Fabry Registry. *Pediatric Research* **64(5)**: 550-555.
21. Hughes, D.A., Nicholls, K., Shankar, S.P., Sunder-Plassmann, G., Koeller, D., Nedd, K., Vockley, G., Hamazaki, T., Lachmann, R., Ohashi, T., Olivotto, I., Sakai, N., Deegan, P., Dimmock, D., Eyskens, F., Germain, D.P., Goker-Alpan, O., Hachulla, E., Jovanovic, A. and Feldt-Rasmussen, U. (2017). Oral pharmacological chaperone migalastat compared with enzyme replacement therapy in Fabry disease: 18-month results from the randomised phase III ATTRACT study. *Journal of Medical Genetics* **54(4)**: 288-296.
22. Ishii, S., Chang, H.H., Kawasaki, K., Yasuda, K., Wu, H.L., Garman, S.C. and Fan, J.Q. (2007). Mutant α-galactosidase A enzymes identified in Fabry disease patients with residual enzyme activity: Biochemical characterization and restoration of normal intracellular processing by 1-deoxygalactonojirimycin. *Biochemical Journal* **406(2)**: 285-295.
23. Ishii, S., Kase, R., Sakuraba, H. and Suzuki, Y. (1993). Characterization of a mutant alpha-galactosidase gene product for the late-onset cardiac form of Fabry disease. *Biochemical and Biophysical Research Communications* **197(3)**: 1585-1589.
24. Ivanova, M. (2020). Altered sphingolipids metabolism damaged mitochondrial functions: Lessons learned from Gaucher and Fabry diseases. *Journal of Clinical Medicine* **9(4)**: 1116.
25. Kaissarian, N., Kang, J., Shu, L., Ferraz, M.J., Aerts, J.M. and Shayman, J.A. (2018). Dissociation of globotriaosylceramide and impaired endothelial function in α-galactosidase-A deficient EA.hy926 cells. *Molecular Genetics and Metabolism* **125(4)**: 338-344.
26. Kytidou, K., Beekwilder, J., Artola, M., van Meel, E., Wilbers, R.H.P., Moolenaar, G.F., Goosen, N., Ferraz, M.J., Katzy, R., Voskamp, P., Florea, B.I., Hokke, C.H., Overkleeft, H.S., Schots, A., Bosch, D., Pannu, N. and Aerts, J.M.F.G. (2018). Nicotiana benthamiana α-galactosidase A1. 1 can functionally complement human α-galactosidase A deficiency associated with Fabry disease. *Journal of Biological Chemistry* **293(26)**: 10042-10058.
27. Lidove, O., Joly, D., Barbey, F., Bekri, S., Alexandra, J.F., Peigne, V., Jaussaud, R. and Papo, T. (2007). Clinical results of enzyme replacement therapy in Fabry disease: A comprehensive review of literature. *International Journal of Clinical Practice* **61(2)**: 293-302.
28. Loos, B., Engelbrecht, A.M., Lockshin, R.A., Klionsky, D.J. and Zakeri, Z. (2013). The variability of autophagy and cell death susceptibility: Unanswered questions. *Autophagy* **9(9):** 1270-1285.
29. Marshall, J., Ashe, K.M., Bangari, D., McEachern, K., Chuang, W.L., Pacheco, J., Copeland, D.P., Desnick, R. J., Shayman, J.A., Scheule, R.K. and Cheng, S.H. (2010). Substrate reduction augments the efficacy of enzyme therapy in a mouse model of Fabry disease. *PLOS ONE* **5(11)**: e15033
30. Ashe, K., Marshall, J., Budman, E., Bangari, D., Nietupski, J., Desnick, R., Scheule, R., Leonard, J. and Cheng, S. (2013). A novel, selective and orally-available glucosylceramide synthase inhibitor for substrate reduction therapy of Fabry disease. *Molecular Genetics and Metabolism* (***108***)**2**: Suppl. 20.
31. Medin, J.A., Tudor, M., Simovitch, R., Quirk, J.M., Jacobson, S., Murray, G.J. and Brady, R.O. (1996). Correction in trans for Fabry disease: Expression, secretion and uptake of alpha-galactosidase A in patient-derived cells driven by a high-titer recombinant retroviral vector. *Proceedings of the National Academy of Sciences of the United States of America* **93(15)**: 7917-7922.
32. Miller, J.J., Kanack, A.J. and Dahms, N.M. (2020). Progress in the understanding and treatment of Fabry disease. *Biochimica et Biophysica Acta. General Subjects* **1864(1)**: 129437
33. Monticelli, M., Hay Mele, B., Allocca, M., Liguori, L., Lukas, J., Monti, M.C., Morretta, E., Cubellis, M.V. and Andreotti, G. (2023). Curcumin has beneficial effects on lysosomal alpha-galactosidase: Potential implications for the cure of Fabry disease. *International Journal of Molecular Sciences* **24(2)**:1095 .

34. Nabhan, J.F., Wood, K.M., Rao, V.P., Morin, J., Bhamidipaty, S., LaBranche, T.P., Gooch, R.L., Bozal, F., Bulawa, C.E. and Guild, B.C. (2016). Intrathecal delivery of frataxin mRNA encapsulated in lipid nanoparticles to dorsal root ganglia as a potential therapeutic for Friedreich's ataxia. *Scientific Reports* **6(1)**: 20019.
35. Naleschinski, D., Arning, K. and Baron, R. (2009). Fabry disease - Pain doctors have to find the missing ones. *Pain* **145(1)**: 10-11.
36. Nelson, M.P., Tse, T.E., O'Quinn, D.B., Percival, S.M., Jaimes, E.A., Warnock, D.G. and Shacka, J.J. (2014). Autophagy-lysosome pathway associated neuropathology and axonal degeneration in the brains of alpha-galactosidase A-deficient mice. *Acta Neuropathologica Communications* **2(1)**: 20.
37. Nowak, A., Mechtler, T.P., Hornemann, T., Gawinecka, J., Theswet, E., Hilz, M.J. and Kasper, D.C. (2018). Genotype, phenotype and disease severity reflected by serum LysoGb3 levels in patients with Fabry disease. *Molecular genetics and metabolism* **123(2)**: 148-153.
38. Ohshima, T., Murray, G.J., Swaim, W.D., Longenecker, G., Quirk, J.M., Cardarelli, C.O., Sugimoto, Y., Pastan, I., Gottesman, M.M., Brady, R.O. and Kulkarni, A.B. (1997). α-galactosidase A deficient mice: A model of Fabry disease. *Proceedings of the National Academy of Sciences of the United States of America* **94(6)**: 2540-2544.
39. Okumiya, T., Ishii, S., Takenaka, T., Kase, R., Kamei, S., Sakuraba, H. and Suzuki, Y. (1995). Galactose stabilizes various missense mutants of α-galactosidase in Fabry disease. *Biochemical and Biophysical Research Communications* **214(3)**: 1219-1224.
40. Pierre-Louis, B., Kumar, A. and Frishman, W.H. (2009). Fabry disease: Cardiac manifestations and therapeutic options. *Cardiology in Review* **17(1)**: 31-35.
41. Racz, L.Z., Racz, C.P., Pop, L.C., Tomoaia, G., Mocanu, A., Barbu, I., Sárközi, M., Roman, I., Avram, A., Tomoaia-Cotisel, M. and Toma, V.A. (2022). Strategies for improving bioavailability, bioactivity, and physical-chemical behavior of curcumin. *Molecules* **27(20)**: 6854.
42. Rombach, S.M., Dekker, N., Bouwman, M.G., Linthorst, G.E., Zwinderman, A.H., Wijburg, F.A., Kuiper, S., Vd Bergh Weerman, M.A., Groener, J.E., Poorthuis, B.J., Hollak, C.E. and Aerts, J.M. (2010). Plasma globotriaosylsphingosine: Diagnostic value and relation to clinical manifestations of Fabry disease. *Biochimica et Biophysica Acta* **1802**: 741-748
43. Romeo, G., D'Urso, M., Pisacane, A., Blum, E., De Falco, A. and Ruffilli, A. (1975). Residual activity of alpha-galactosidase A in Fabry's disease. *Biochemical Genetics* **13**: 615-628.
44. Sanchez-Niño, M.D., Carpio, D., Sanz, A.B., Ruiz-Ortega, M., Mezzano, S. and Ortiz, A. (2015). Lyso-Gb3 activates Notch1 in human podocytes. *Human Molecular Genetic* **24(20)**: 5720-5732.
45. Schiffmann, R., Warnock, D.G., Banikazemi, M., Bultas, J., Linthorst, G.E., Packman, S., Sorensen, S.A., Wilcox, W.R. and Desnick, R.J. (2009). Fabry disease: Progression of nephropathy, and prevalence of cardiac and cerebrovascular events before enzyme replacement therapy. *Nephrology, Dialysis, Transplantation* **24(7)**: 2102-2111.
46. Schueler, U., Kaneski, C., Remaley, A., Demosky, S., Dwyer, N., Blanchette-Mackie, J., Hanover, J. and Brady, R. (2016). A short synthetic peptide mimetic of apolipoprotein A1 mediates cholesterol and globotriaosylceramide efflux from Fabry fibroblasts. *Journal of Inherited Metabolic Disease Reports* **29**: 69-75.
47. Shen, J.S., Meng, X.L., Moore, D.F., Quirk, J.M., Shayman, J.A., Schiffmann, R. and Kaneski, C.R. (2008). Globotriaosylceramide induces oxidative stress and up-regulates cell adhesion molecule expression in Fabry disease endothelial cells. *Molecular Genetics and Metabolism* **95(3)**: 163-168
48. Tarno, H., Qi, H., Endoh, R., Kobayashi, M., Goto, H and Futai, K. (2011). Types of frass produced by the ambrosia beetle Platypus quercivorus during gallery construction, and host suitability of five tree species for the beetle. *Journal of Forest Research* **16(1)**: 68-75.
49. Sheth, K.J., Werlin, S.L., Freeman, M.E. and Hodach, A.E. (1981). Gastrointestinal structure and function in Fabry's disease. *American Journal of Gastroenterology* **76(3)**: 246-251.
50. Shu, L., Vivekanandan-Giri, A., Pennathur, S., Smid, B.E., Aerts, J.M., Hollak, C.E. and Shayman, J.A. (2014). Establishing 3-nitrotyrosine as a biomarker for the vasculopathy of Fabry disease. *Kidney International* **86(1)**: 58-66.
51. Smid, B.E. and Hollak, C.E. (2014). A systematic review on effectiveness and safety of eliglustat tartrate for type I Gaucher disease. *Expert Opinion on Orphan Drugs* **2(5)**: 523-529.
52. Müller-Decker, K., Leder, C., Neumann, M., Neufang, G., Bayerl, C., Schweizer, J., Marks, F. and Fürstenberger, G. (2003). Expression of cyclooxygenase isozymes during morphogenesis and cycling of pelage hair follicles in mouse skin: Precocious onset of the first catagen phase and alopecia upon cyclooxygenase-2 overexpression. *Journal of Investigative Dermatology* **121(4)**: 661-668.

53. Van der Veen, S.J., Hollak, C.E.M., van Kuilenburg, A.B.P. and Langeveld, M. (2020). Developments in the treatment of Fabry disease. *Journal of Inherited Metabolic Disease* **43(5)**: 908-921
54. Van Eijk, M., Ferraz, M.J., Boot, R.G. and Aerts, J.M.F.G. (2020). Lyso-glycosphingolipids: Presence and consequences. *Essays in Biochemistry* **64(3)**: 565-578.
55. West, M., Nicholls, K., Mehta, A., Clarke, J.T., Steiner, R., Beck, M., Barshop, B.A., Rhead, W., Mensah, R., Ries, M. and Schiffmann, R. (2009). Agalsidase alfa and kidney dysfunction in Fabry disease. *Journal of the American Society of Nephrology* **20(5)**: 1132-1139.
56. Wilcox, W.R., Banikazemi, M., Guffon, N., Waldek, S., Lee, P., Linthorst, G.E., Desnick, R .J. and Germain, D.P. (2004). International Fabry disease study group. Long-term safety and efficacy of enzyme replacement therapyfor Fabry disease. *American Journal of Human Genetics* **75(1)**: 65-74.

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