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High-dose Ambroxol for Disease Modification and Prevention of Gba1-Related Parkinson Disease: From the Wrong Mouse to the Right *Drosophila*

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Abstract

After early skepticism, the association between Gaucher Disease (GD), a rare genetic disease and Parkinson's Disease (PD), the second most common neurodegenerative disorders, is well established, but its underlying mechanisms is controversial: loss of function (haploinsufficiency) or gain of function. Both approaches are supported by apparent suitable animal models. The commentary discusses the failure of substrate reduction therapy and the unlikeliness of success using enzyme replacement therapy (the loss-of-function hypothesis), and predicts future success for pharmacological chaperones, targeting the misfolded mutant glucocerebrosidase for GBA1-related PD (the gain-of-function mechanism). A unique clinical trial (AGPI) is presented, exclusively enrolling GBA1 carriers, focusing on high-dose Ambroxol in early-stage PD for both prevention and disease modification, with the hope to transform the management of GBA1-PD and related disorders.

Keywords: Parkinson's disease; Gaucher disease; Glucocerebrosidase; Cerebrospinal fluid

Introduction

The first paper proposing a potential link between Gaucher Disease (GD), and Parkinson's Disease (PD) faced six rejections before its eventual acceptance by the Quarterly Journal of Medicine (QJM) in 1996 [1]. The primary basis for the rejection was the skepticism of the editorial reviewers, who could not believe that the association between a rare genetic disease and the second most prevalent neurodegenerative disorder was anything more than a mere coincidence. Subsequent to persistent research efforts and substantial contributions, particularly from Ellen Sidransky of the National Institutes of Health (NIH), including her pivotal meta-analysis in 2009 confirming an odds ratio of 5.43 for any GBA1 mutation in patients with PD compared to controls, GBA1-related PD has evolved into a firmly established entity [2]. It exhibits three distinctive features relative to idiopathic PD: an earlier age of onset, a more severe clinical course, and a heightened likelihood of developing dementia [1].

While GBA1-PD is by now textbook knowledge, the underlying pathogenesis has remained controversial, and the academic debate-loss of function (haploinsufficiency) versus gain of function-has influenced the development of strictly different treatment approaches. Interestingly, each school of thought has successfully developed an animal model to justify its chosen form of therapy [3,4]. Sanofi, leveraging a mouse model homozygous for the D409V mutation created created by Sardi and colleagues (primarily a model for GD, introducing mutations not found in humans to date), invested substantial resources in venglustat, a Substrate Reduction Therapy (SRT) capable of crossing the Blood-Brain-Barrier (BBB), during phase I and phase 2 clinical trials for GBA1-PD [5-7]. Conversely, proponents of the gain-of-function hypothesis employed alternative animal models, notably the *Drosophila* fruit fly, to explore the use of pharmacological chaperones, primarily Ambroxol, for treating both GBA1-PD and idiopathic PD [8,9]. This approach assumes that misfolding may also occur in the wild-type Glucocerebrosidase [GCase] enzyme [10,11].

While the double-blind placebo-controlled venglustat clinical trial was ongoing as a multi-national multicenter study, with company representatives and a few of their investigators promoting its great potential in various medical conferences, we [AR, AZ and colleagues; published in February 2020 a viewpoint entitled: "Substrate Reduction Therapy for GBA1-Associated Parkinsonism: Are We Betting on the Wrong Mouse" [12]. The key consideration against the SRT approach for GBA1-PD is the basic fact that GAB1 carriers do not accumulate glucocerebroside (the substrate) not in the reticuloendothelial cells in the spleen, liver and bone-marrow and certainly not in the dopaminergic neurons. Had this been the underlying mechanism, we should have had more patients with GD suffering from GBA1-PD than carriers (who only have 50% of the mutant GCase enzyme) and not

only that this is not the case, in fact, carriers of the non-N370S variant have a higher risk to develop PD than patients with GD who have two mutant alleles and double the amount of the mutant enzyme [4]. Paradoxically, venglustat clinical trial patients with GD and PD were excluded.

Literature Review

A year after our viewpoint, in February 2021, Sanofi halted the venglustat GBA1-PD clinical, citing no beneficial treatment effect compared to placebo [7]. The trial revealed more Adverse Events (AEs) in the venglustat group relative to the placebo cohort.

GBA1-PD is not a metabolic manifestation of GD; it stems from the misfolding of the mutant enzyme in the Endoplasmic Reticulum (ER), leading to ER stress, inflammation, (MH, unpublished), alfa-synuclein aggregation in dopaminergic neurons, and eventual cell death [13]. Treatment should focus on correcting misfolding and halting downstream consequences using Pharmacological Chaperones (PCs). Similarly, the ongoing clinical trial of Elly-Lilly/Prevail, delivering human recombinant GCase Enzyme Replacement Therapy (ERT) to the brain through Adeno-Associated Virus (AAV)-based gene therapy, is unlikely to succeed either, as the addition of normal enzyme cannot correct the misfolding of the endogenous mutant GCase [14]. Two other clinical trials based on the haploinsufficiency hypothesis involve Magnetic resonance imaging (MRI)-guided Low-Intensity Focal Ultrasound (LIFU) to temporarily open the BBB during intravenous injection of imiglucerase [Cerezyme™; Sanofi, USA) and a new small molecule, an allosteric activator of GCase [LTI-291, Bial Pharmaceuticals, Portugal [15,16].

The second school, which posits gain of function as the underlying mechanism causing GBA1-PD, is targeting the misfolding of mutant GCase using PCs as the therapeutic approach. In this regards, effective animal models, particularly in *Drosophila*, have been previously discussed and there are ongoing clinical trials employing either high-dose ambroxol, an Over-The-Counter (OTC) cough medicine identified as a GCase-specific PC or several new drugs [10,11]. While most of these drugs are still in pre-clinical development, one particular formulation has recently initiated a phase 1 safety trial in Australia with healthy volunteers, starting in October 2023.

Ambroxol, initially developed by Boehringer-Ingelheim (Germany) in the late 1960s/1970s and commercialized in 1978, has served as an OTC drug in many counties, with the notable exception of the USA [17]. Its potential as a specific Pharmacological Chaperone (PC) for GCase by Maegawa and Mahuran in 2009 during the development of a thermal denaturation assay [18]. This assay utilized wild type GCase to screen a library of 1,040 commercially approved drugs. Originally sought as a PC to treat GD, Ambroxol's proof-of-concept success in patients with type 1 GD prompted Narita and colleagues in Japan to implement it in patients with advanced neuronopathic GD [nGD] through well-designed Investigator-Initiated Research (IIR) [19,20]. The demonstrated reversibility of key manifestations of nGD such as debilitating myoclonic epilepsy and severe ataxia, served as inspiration for the application of Ambroxol in patients with GBA1-PD. Moreover, its use has extended to non-GBA1-PD cases, based on the assumption, that misfolding of GCase may occur even in individuals without mutations at the DNA level [10,11].

Ambroxol has two advantages as a repurposed drug: First, as with the repurposed drugs identified in the past like acetylsalicylic acid, thalidomide, or sildenafil, and more recently discovered through data mining and computational drug discovery methodologies, it allows the bypassing of toxicology stages during drug development, thereby shortening the time to market [21,22]. Secondly, its OTC availability adds an extra layer of confidence in terms of safety, enabling its "off-label" use with or without official monitoring, as no formal clinical trials are required. In the context of devastating diseases such as nGD or GBA1-PD where there is currently no commercially available specific treatment, the prospect of trying a potentially beneficial therapy without solid evidence is appealing. However, physicians typically do not endorse such unproven approaches, and their reservations are sometimes justified. There have been instances, especially in cancer and PD, where testimonials proved to be misleading, resulting in false hopes and significant expenses for desperate patients or their families, as OTC medications are typically not reimbursed.

In an effort to enhance the evidential basis for Ambroxol's use, especially in nGD and GBA1-PD, we initiated an investigator-initiated drug registry. Initially comprising 41 patients, the registry involved individuals receiving daily doses ranging from 75 to 1485 mg (median 435 mg, approximately three times the typical cough medicine dose). The follow-up period spanned 1 to 76 months (median 19 months) [23]. Currently, we are expanding this registry to include over 120 patients., incorporating a more extended follow-up and higher mean Ambroxol doses. Despite the ongoing case reports, IIR, and informal registries, we recognize the necessity for a well-designed prospective clinical trial. Around this need, Agyany Pharmaceuticals has been co-founded by 2 of us (AR and AZ), with the first task to conduct an open-label pilot study for assessing the safety and efficacy of high-dose Ambroxol in newly diagnosed GBA1-related motor and pre-motor Parkinson disease (PD) Agyany Pharmaceuticals' GBA1-Related Parkinson's Initiative (AGPI).

Discussion

AGPI study distinguishes itself from the three other ongoing clinical trials involving high-dose Ambroxol in several aspects. Firstly, it exclusively enrolls carriers of GBA1 variants or patients with GD, excluding individuals with idiopathic PD. Unlike the other trials, AGPI does not incorporate a placebo arm, and Cerebrospinal Fluid (CSF) collection is not part of the protocol. Furthermore, we are actively recruiting individuals at significantly earlier stages of the disease, including those in advanced prodromal stages for PD prevention or newly diagnosed patients with Hoehn and Yahr Scale up to 2. Our rationale is rooted in the belief that initiating treatment at the early stages of the neurodegenerative process holds greater potential to impact injured and dysfunctional dopaminergic neurons. This in turn, increases the likelihood of observing significant changes within a relatively short timeframe, drawing on insights from studies in nGD and anecdotal cases over the past few years [24]. The first patient was recruited in October 2023, and we anticipate the last patient's last visit to take place at the beginning of 2025.

Conclusion

We hope that our ongoing study, in conjunction with additional clinical trials focusing on PCs for GBA1 PD and related disorders, will pave the way for the integration of Ambroxol into clinical practice. Furthermore, we anticipate that these efforts will stimulate the development of even more effective PCs, capable of greater BBB penetrance, enabling the use of smaller doses and significantly improving the prognosis for individuals at risk. Achieving the ability

to halt or, ideally, reverse the prodromal changes in the population at risk, starting with carriers of GBA1 variants, could be a transformative development. It has the potential to revolutionize the management of these devastating disorders, prompting the inclusion of PD prodromal testing in routine assessments for individuals aged 40 and above, similar to current practices for preventing or early detecting various forms of cancer.

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