ENZYME REPLACEMENT THERAPY FOR GAUCHER DISEASE PATIENTS: AN EXPENSIVE TREATMENT

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ABSTRACT

Gaucher disease, the most well-known lysosomal storage disorder, is instigated by the inadequate activity of the lysosomal enzyme, acid β-glucosidase (GlcCerase), prompting amassing of glucosyleramidase (GlcCer), especially in cells of the macrophage. Almost 200 transformations in GlcCerase have been depicted, yet generally, genotype-phenotype correlations are frail and little is known about the down-stream biochemical changes that happen upon GlcCer accumulation that outcome in cell and tissue dysfunction. Conversely, the clinical course of Gaucher disease has been very much portrayed, and various treatment options (Enzyme Replacement Therapy) are also available. One other treatment, substrate reduction therapy, has recently been approved by FDA and others are in various phases of clinical trial. Transformation in the GBA1, situated on chromosome 21, result in decreased/defective activity glucocerebrosidase. The glycolipid storage offers ascend to trademark Gaucher cells, macrophages engorged with lipid with a folded tissue paper appearance and uprooted nuclei. Gaucher disease patient often have, hepatomegaly, splenomegaly, anemia, thrombocytopenia and skeletal disease. Investigations on a few thousand subjects have lingered the scope of the pan-ethnic disease variations providing genotype and phenotype relationships and discovery of successful ERT for such patients.

KEYWORDS: Gaucher disease, lysosomal storage disease, glucocerebrosidase, enzyme replacement therapy, macrophage.
INTRODUCTION

Gaucher's disease is an uncommon autosomal recessive\textsuperscript{[1-3]}, conceivably deadly disorder however most common type among lysosomal storage disorders. GD develop due to deficiency of a enzyme $\beta$-glucocerebrosidase that prompts amassing of glucocerebrosidase in cells of macrophage-monocyte system.\textsuperscript{[4-7]} It is most common in Ashkenazi Jewish population with a recurrence of 1 in 850 persons and carrier recurrence of 1 in 15 individuals. GD is similarly common in both genders. Among non-Jewish population the disease recurrence is 1 in 40000. Just about 60\% of Ashkenazi Jewish population is homozygous for N370S transformation which represents 75\% disease alleles in this population.\textsuperscript{[8-9]}

<table>
<thead>
<tr>
<th>Table 1 Differences in the Three Types of Gaucher Disease</th>
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<tbody>
<tr>
<td><strong>Type 1</strong></td>
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<tr>
<td>Disease Onset</td>
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<tr>
<td>High Prevalence</td>
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<tr>
<td>Splenohepatomegaly</td>
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<tr>
<td>Bone involvement</td>
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<td>Ocular Signs</td>
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<td>Neurological Involvement</td>
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<tr>
<td>Other organ involvement</td>
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<tr>
<td>Lifespan with or without therapy</td>
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<td>Response to ERT</td>
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The LSD incorporate more than 40 distinct maladies, the greater part of which are caused by the deficiency of a lysosomal hydrolase prompting the progressive, intralysosomal accumulation of substrates, for example, sphingolipids, mucopolysaccharides and oligosaccharides.\textsuperscript{[10-13]} Chemical chaperones are small particles that binds to the active site of glucocerebrosidase variations balancing out their three dimensional structure in the endoplasmic reticulum, likely preventing their endoplasmic reticulum-related corruption and permitting their legitimate trafficking to the lysosome where they can metabolize accumulated substrate to adequately amend Gaucher disease.\textsuperscript{[14-17]}

Lipid accumulation and Inflammation

The primary originator of the pathogenic procedure is the abnormal gathering of lysosomal glucocerebrosidase and most likely its deacylated analog, glucosylsphingosine. Imperatively, Glucocerebrosidase is a definitive glycolipid antecedent in the synthesis and degradation of $>300$ neutral glycosphingolipids and gangliosides.\textsuperscript{[18-19]} Glucosylceramide, the gathered
glycolipid, is basically derived from the phagocytosis and degradation of senescent leukocytes and to a lesser degree, from erythrocyte layer. Two noteworthy pathophysiological components that account for macrophage initiation are still under scrutiny.\textsuperscript{[20-24]} The most evident possibility for an obsessive initiator is the excess gathering of glucosylceramide. Sphingolipids have been embroiled in inflammatory and apoptotic procedures and glucosylceramide may have direct activating impact on macrophage function, potentially interceded through specific calcium-channel dysregulation. Surely, a few pointers of macrophage initiation including chitotriosidase, CCL18, angiotensin-converting enzyme, and cathepsin S - have been recognized in abundance in plasma of patients with Gaucher disease.\textsuperscript{[25-27]} Histological evaluation demonstrated that such proinflammatory particles, including tumor necrosis factor, are variably expanded in some splenic gaucher cells. Though, the nonappearance of tissues from these patients has confined such investigations. There is a confirmation that majority of these patients with disease have expanded levels of macrophage derived inflammation related particles, for example, interleukin-1ß, interleukin-6, interleukin-10 and TNF-a.\textsuperscript{[28-31]}

Albeit more investigations is required, the relationship of these pathways in the spread of tissue damage in gaucher disease gives the hypothetical premise to extra adjunctive medications. An alternative mechanism by which these proinflammatory and anti-inflammatory pathways could be activated through abnormal folding of mutant proteins in the endoplasmic reticulum.\textsuperscript{[32]} Such irregular folding initiates an unraveled protein reaction that can trigger apoptotic or inflammatory pathways in different tissues. Direct proof of unraveled protein reaction involved is not accessible for gaucher disease. These pathways are of eminent interest for some disorders, including Parkinson’s disease, Alzheimer's disease and other Neurodegenerative disorders.\textsuperscript{[33-34]}

**Clinical Manifestations**

GD patients get hematological abnormalities because of hypersplenism. Gastroenterologists can be consulted for anemia, massive splenomegaly or hepatomegaly of obscure reason. Albeit uncommon, patients presenting hepatosplenomegaly and ascites are reported. GD involvement changes in severity as indicated by the density of macrophages in the specific organ and partially relies upon the phenotypically heterozygous nature of the disease itself.

The most widely recognized transformation, N370S, could bring about inconspicuous sign and symptoms because of vicinity of some level of enzymatic activity resulting in diagnosis
delay. The delay in diagnosis eventually results in irreversible complexities.\textsuperscript{[35-36]} Researchers have demonstrated that in adult patients with type 1 disease the average time from first appearance of indications of GD to final analysis was 48 months. Likewise, hematology oncology scientist who were managing 66\% of the patients considered diagnosis of GD just in 20\% for the common symptoms (bone pain, organomegaly and low blood counts).\textsuperscript{[37]}

The fortitude of GD is straight forward. The demonstration of genetically miscoded enzyme levels is usually investigated. For this reason, direct investigation of glucocerebrosidase in fringe blood leukocytes is used. The action of glucocerebrosidase is variable in white cell type, enzyme activity usually increases from granulocytes to lymphocytes to monocytes.\textsuperscript{[38]}

Type 1 GD subjects have 15\% of the typical enzyme activity though type 2 and 3 patients usually have lower action. Because of impressive cover of enzymatic movement between heterozygote carriers and normal subjects, enzyme investigation can't recognize GD carriers from non-GD-carriers. With a specific end goal to separate the carrier state, the genetic investigation which was mentioned ought to be connected for complete diagnosis. After analysis, GD subjects ought to be classified according to clinical severity scores.\textsuperscript{[39]}

\textbf{Prevalence}

The exact frequencies and variations in the phenotype should be completely outlined. Significantly, the alleles containing L444P have the worldwide predominance and are connected with the neuronopathic variations. In spite of the higher heterozygote recurrence of Gaucher disease type 1 (1:18) in the Ashkenazi Jewish population.\textsuperscript{[40]} The phenotypic heterogeneity of Gaucher disease has been ascribed to numerous transformations in GBA1. PCR-based screening of 2121 unaffected Ashkenazi Jewish subjects uncovered 4 regular transformation genotypes, c.84–85 insG, c1226A.G (N370S), IVS2→G→A, c.1448T.C (L444P) and generally account for more than 97\% of mutations in Ashkenazi Jewish subjects, while representing under 74\% of the mutant alleles distinguished in other "western-world" populations.\textsuperscript{[41]}

\begin{table}[h]
\centering
\begin{tabular}{|l|l|l|}
\hline
\textbf{Population} & \textbf{Frequent Mutation} & \textbf{Mutation (\%)} \\
\hline
Japanese & L444P & 55 \\
& F2131 &  \\
Ashkenazi Jews & N370S & 93 \\
Turkish & N370S & 61.8 \\
& L444P &  \\
Spanish & L444P & 68.9 \\
\hline
\end{tabular}
\caption{Worldwide most common mutations in Gaucher Disease}
\end{table}
Complete gene sequencing has identified GBA1 mutations in more general populations. Each of the 320 transformations in GBA1 has a recurrence that changes between distinctive population.\[42\] The lion's share are missense transformations that outcome in diminished catalytic activity, while nonsense mutations including frameshifts, deletions, alleles resulting from recombination with the pseudogene, gene transformations and total deletion lead to null alleles.\[43\] On the other hand, the L444P alleles will probably be the most well-known mutations around the world. The diversity of transformations and the absence of institutionalized general technique for phenotyping have made genotype/phenotype relationships challenging. In the western-world population, predominantly Ashkenazi Jewish, N370S homozygosity does not reliably present a mild phenotype that shows in adult since 50% of such subjects were analyzed by age years.\[44\]

On the other hand, the deficient ascertainm of N370S homozygotes complicates these evaluations significantly more. Two conclusions are moderately strong.\[45\]

1) the vicinity of a single N370S allele in Gaucher disease subjects precludes childhood onset of neuronopathic disease; and
2) heteroallelism for N370S and most other nonsense or missense mutations, eg, 84GG or L444P, ordinarily shows in childhood.\[46\]

Homozygosity for the L444P genotype is essentially associated with development of neuronopathic disease. Interestingly, 'true' L444P Homozygotes have not been reported in the Ashkenazi Jewish Type 2 patients.\[47\] Detailed sequence investigations of subjects thought to be homozygous for L444P uncover that all had one allele resulting because of a recombination with the GBA1 pseudogene. This demonstrates the significance of utilizing procedures that will precisely recognize any allele carrying a L444P transformation when genotyping type 2 patients.\[48-49\]
Enzyme Replacement Therapy

Treatment with macrophage targeted on mannose-ended glucocerebrosidase ERT (imiglucerase, Cerezyme®) is the standard of care for type 1 Gaucher disease and of non-neuronopathic signs of type 3 Gaucher disease.[50-51] Evidence shows that enzyme replacement with imiglucerase and its antecedent alglucerase turns around hematological and instinctive indications of the disease and lessens the bone marrow burden of Gaucher cells bringing about amelioration of osteopenia, bone torment, risk of bone crises and general improvement in QoL. A few parts of bone disease, for example, osteonecrosis, osteofibrosis and lytic sores can't be reversed however timely start of ERT diminishes the risk of these irreversible complications.[52] Other variations of macrophage-targeted ERT are experiencing clinical trials: velaglucerase, a human fibroblast derived enzyme, was recently approved for treatment of type 1 Gaucher disease and taliglucerase, a plant derived enzyme is in clinical trials. Substrate reduction treatment (Zavesca® miglustat) is approved for patients with mild Gaucher disease who are incapable to receive ERT. A more specific and powerful inhibitor of glucosylceramide synthesis, eliglustat tartrate is in stage 3 trials having amazing efficacy and safety in stage 2 trials.[53-54]

<table>
<thead>
<tr>
<th>Pharmaceutical Company</th>
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<th>Description</th>
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<th>Status</th>
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<tr>
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<td>Cerezyme</td>
<td>Recombinant Glucocerebrosidase</td>
<td>ERT</td>
<td>Marketed</td>
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<tr>
<td></td>
<td>Ceredase</td>
<td>Alglucerase enzyme</td>
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<td>Marketed</td>
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<tr>
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<td>Plant cell expressed rGCase</td>
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<td></td>
<td>PRX-112</td>
<td>Plant cell expressed rGCase (oral)</td>
<td>ERT</td>
<td>Phase I</td>
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<tr>
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<td>rGCase</td>
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<td>Biosimilar Cerezyme</td>
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<td>Phase III</td>
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<tr>
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<td>Glucosyltransferase inhibitor</td>
<td>Substrate reduction Therapy (SRT)</td>
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<td>EXR-202</td>
<td>Gcase binding chaperone</td>
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<td>Phase I</td>
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Closing Remarks

Adult type GD is a heterozygous disease. On account of vulnerability to deferred diagnosis, timely analysis and early start of suitable treatment are vital and avert inconvenient entanglements and stops the progress of malady to some degree. In near future, we may be conceivable to "cure" this genetic disease by gene vaccines. Consequently, we require more speculation on examinations for gene treatment. ERT and SRT have verifiable therapeutic impacts, yet there seems to be a requirement for more evidence before placing them into "gold standard" treatment for all subjects.

Amid the recent two decades, the treatment of Gaucher disease and the standpoint for influenced subjects has experienced a surprising change and it speaks to an astounding model of personalized medicine. Further energizing progress is anticipated and small molecule pharmacological chaperone treatment customized for mutations that outcome in protein folding defects. An exceptionally encouraging methodology is small molecule treatment act to restrain substrate development, similar to treatment for hypercholesterolemia with HMG CoA reductase inhibitors; this methodology is prone to represent a significant development to current macrophage directed treatment and guarantees to conquer a portion of the unmet needs. Propels in technique for diagnosis utilizing dry blood spots will enhance access to testing and timely diagnosis.

Conflicts of Interest Statement

The Authors declare no conflicts of interest.

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