



Commentary

Brain-penetrant heat shock protein amplifier arimoclomol enhances GCCase activity in *in vitro* Gaucher disease models


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Gaucher disease (GD), the most common lysosomal storage disease, is caused by the dysregulation of glucosylceramide (GlcCer) and other sphingolipid clearance normally mediated through activity of β -glucocerebrosidase (GCCase); attributable to rare mutations in GBA1, the gene encoding GCCase [1]. GD presents along three subtypes designated in accordance with the onset of neuropathic symptoms. Type I GD is predominantly limited to the peripheral systems and affected individuals typically live an average lifespan with appropriate therapy [1]. Available treatments include enzyme replacement therapies (ERT) and glucosylceramide synthase inhibitors [2]. Cases of types II and III feature neurological damage consequent of GlcCer accumulation in the primary central nervous system (CNS) [1]. Disease modifying treatments for neuronopathic GD remain clinically unavailable, resulting in progressive neurodegeneration and significantly reduced life expectancy for many patients.

A degree of incongruence between GBA1 mutation type and disease phenotype indicates the involvement of additional key disease modifiers in the etiology of GD. Efforts to define these modifiers have led to identification of numerous molecules involved in the regulation of GD pathogenicity, including molecules that influence GCCase trafficking, inflammatory mediators, lysosomal stress mediators, and molecular chaperones [3]. GBA1 mutations underlying GD generally result in impaired folding and maturation of GCCase, inhibiting movement to the lysosome and subsequent substrate accumulation and downstream effects [1]. Accordingly, molecules recognized as contributory to maturation and lysosomal trafficking of GCCase have received great attention as novel therapeutic targets, particularly for treatment of neuronopathic GD. The importance of heat shock proteins (HSPs) in lysosomal function and proteostasis is well attested [4] and the recognition of HSP70's necessity for appropriate lysosomal localization of GCCase through recruitment by PGRN to the GCCase/LIMP-2 complex has situated HSP70 as a promising therapeutic target in models of GD and other LSDs [2,5,6].

In an *EBioMedicine* paper, Kirkegaard and colleagues examined the therapeutic effects of the investigational drug arimoclomol, an HSP amplifier, on GCCase activity in cells from GD patients [7]. Kirkegaard et al.

demonstrate induction of disease relevant HSPs, including HSP70 and BiP, and enhanced maturation of GCCase primary in fibroblasts from GD patients with varied GBA1 mutations subjected to arimoclomol treatment. GCCase activity was enhanced in a time and dose-dependent manner in response to arimoclomol treatment, co-occurring with HSP70 induction. Analysis of cellular localization of mutated GCCase further indicated lysosomal localization of mutant protein following arimoclomol treatment in both non-neuropathic and neuronopathic patient derived cells. In order to evaluate the effects of arimoclomol in a human neuron-like cell model of GD, multipotent adult stem cells were collected from healthy and neuronopathic and non-neuronopathic GD patient donors and induced toward neural differentiation prior to treatment with arimoclomol or vehicle. Similar to observations in fibroblast cultures, arimoclomol treatment correlated with enhanced GCCase activity in patient derived cells.

In brief, these results bolster consideration of the HSP amplifier arimoclomol for development toward the treatment of non-neuronopathic and neuronopathic GD. The status of arimoclomol as the subject of ongoing phase II/III clinical trials for Niemann-Pick disease type C (ClinicalTrials.gov identifier NCT02612129) enhance the drug's attractiveness and give credence to the supposition of activity within the CNS *in vivo*. However, a more thorough description of the cellular and *in vivo* effects of arimoclomol would enhance the argument for development toward implementation as a GD therapy. Data presented by Kirkegaard and colleagues suggest that amplification of HSPs underlie the drugs' impact on GCCase activity, and as RNAi studies did not result in enough HSP knock-down to be conclusive, future loss-of-function studies conducted with HSP70 family member knock-out cells could be considered to strengthen this hypothesis. The authors demonstrate that arimoclomol increased the activity of mutant GCCase up to 50–100% but this increase does not bring GCCase activity to levels comparable with that observed in wild type cells, although longer exposures provided additional increases in GCCase activity. Interestingly, the differences in GCCase activity levels between type III neuronopathic patients and type I non-neuronopathic patients, suggest that increase in the 50–100% would lift the type III activity levels to that of neurologically unaffected type I patients [7]. This might suggest a particular potential for arimoclomol in neuronopathic Gaucher disease. Further clarification of the relative contributions of arimoclomol's effects upon increased GCCase catalytic activity and lysosomal delivery to the overall therapeutic impact will be valuable to advancement of drug applications.

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Additionally, accumulation of sphingolipids is a hallmark of the cellular phenotype of GD and elucidation of the effect of arimoclomol upon GCCase substrate content in GD cells would be a useful indicator of potential therapeutic utility.

Overall, the data from these cell-based assays are promising and one might consider confirming the therapeutic effects of arimoclomol *in vivo* with GD animal models, such as mice with GCCase mutations or ovalalbumin (OVA)-challenged progranulin (PGRN) deficient mice [8]. However, extrapolation of *in vivo* results from murine models of GD should be interpreted with some degree of trepidation given the discrepancy between human and mouse phenotypes of specific GD mutations [9]. Importantly, in light of PGRN's association with GD and functionality as a co-chaperone of HSP70 during GCCase trafficking, the utilization of PGRN-deficient mice, which exhibit a GD-like phenotype upon challenge with OVA, may be particularly interesting and offer novel insights into GD pathogenesis and arimoclomol function [5,8,10].

Neuronopathic GD is a devastating condition for which no effective treatment is currently available. The complex network of molecules implicated in regulation of GD has complicated development of disease modifying drugs but chaperone therapy has received steadily growing acknowledgment as a potential avenue for addressing both peripheral and neuronal GD progression. Continued evaluation of pharmaceuticals targeting key proteostasis mediators, like arimoclomol, could lead to development of novel drugs for the treatment of neuronopathic GD, as well as additional LSDs.

Disclosure

The authors declared no conflicts of interest.

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