Novel Therapies for Orphan Diseases

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ABSTRACT: “Orphan” does not mean infrequent: over 7,000 rare diseases affect millions of individuals. The US Orphan Drug Act and analogous regulations have succeeded at accelerating the development of novel therapies, but high prices threaten sustainability. Lysosomal storage disorders serve here to illustrate the light and shadows of this burgeoning field.

As recently as in May 25th 2019 Novartis’ subsidiary AveXis received FDA approval for Zolgensma (AVXS-101) as a gene replacement treatment for spinal muscular atrophy (SMA), a rare inherited neuromuscular disease with a prevalence of approximately 1-2 per 100,000 persons and incidence about 8 per 100,000 live births.[1] Zolgensma also secured Orphan Drug designation, which provides incentives to encourage the development of drugs for rare diseases. The company announced to set the price at $2.125 million per dose, making it the world’s most expensive drug. An occasional newspaper reader might see the story as an exorbitant extravagancy, but nothing could be further from the truth. The progressive enactment of “orphan” legislations in a number of countries, after the 1983’s US Orphan Drug Act (ODA), has undoubtedly succeeded at stimulating the investment in the development of treatments for conditions that otherwise will suffer from low profitability resulting from the small size of target population (Figure 1, right side).[2] The lawmaker’s intention of reversing the neglect of rare diseases by the pharmaceutical industry through financial enticement, with the goal of having new treatments developed, approved, and made available for patients, faces an unanticipated side effect: the outrageous increase in the prices. The spiraling R&D and production costs associated to biologics (recombinant enzymes, antibodies, nucleic acids) only partially justify the scenario. Biologics signify 36% of the orphan drugs approved in the last years (against 64% of small molecules) but are expected to grow significantly in a global orphan drug market that represents US $125 billion and is estimated to reach US $209 billion by 2022, accounting for 21.4% of total branded prescription drug sales.[3] This situation seriously threatens the sustainability of the public-health systems and risks creating an unbearable inequity in treatment access. A strong debate in this topic is in place, with voices for and against maintaining the current regulatory status.[4]

Is there any room left for small molecules in the post-omic era?

It is undeniable that rare or orphan diseases are, collectively, an important public-health issue and a challenge not only to the medical community, but also to the whole ensemble of researchers implied in deciphering the molecular basis of disease and the development of drugs and therapies.[5,6] It might appear that the competition with biologics in terms of efficacy and with drug repurposing strategies (i.e., developing old drugs for new indications) in regards to cost restricts the space for new small molecule entities in this area. On the other hand, small molecules generally hold advantages as compared to biologics regarding stability, pharmacokinetics, safety and production cost. Most importantly, the knowledge developed from proteomics/genomics and the availability of biologics conceived for protein/gen replacement therapies enable unprecedented opportunities for the target-oriented design of chemically conceived disease modifiers. The relative paucity of funds tends to discourage and requires investigators to strive for novel funding mechanisms, such as grant seeking from pharma, stakeholder patient communities or philanthropy sources. Nonetheless, the often-close relationships between the pathophysiological mechanisms operating in rare and common diseases can be put forward in funding applications for multidirectional repositioning of lab produced synthetic compounds. The historical evolution in the field of lysosomal storage disorders (LSDs), a subset of about 70 rare metabolic diseases, perfectly serves to illustrate these notions.

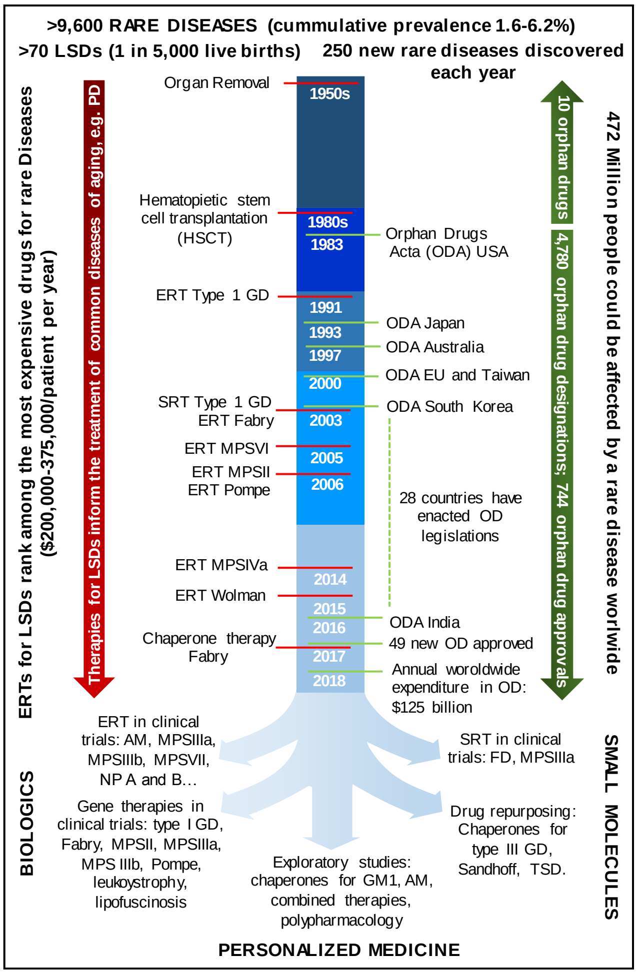

Figure 1. Figure: Chronology of orphan disease legislation and orphan drug discovery for the rare disease subgroup of lysosomal storage disorders. Selected prevalency and economical data are also displayed. Abbreviations: LSDs, lysosomal storage disorders; OD: orphan drug; ERT: enzyme replacement therapy; GD, Gaucher disease; MPS: mucopolysaccharidosis; SRT, substrate reduction therapy; TSD, Tay-Sachs disease; GM1: G_{M1}-gangliosidosis; NP, Niemann-Pick disease; PD, Parkinson disease.

Lysosomal storage disorders: a showcase

The bright lights and shadows of orphan biologics under the ODA. LSDs are monogenetic diseases where the mutation in a gene encoding for a lysosomal protein (an enzyme, an integral membrane protein or an enzyme modifier or activator) results in lysosomal failure and the subsequent steady accumulation of substrates, which ultimately leads to cell dysfunction and cell death.[7] Examples of LSDs are Gaucher disease (GD, the LSD with the highest prevalence) Fabry disease, GM_1 gangliosidosis (GM1), Pompe disease, α-mannosidosis (AM), Tay-Sachs disease (TSD), Niemann-Pick disease (NP) or the mucopolysaccharidosis (MPS). Most LSDs present as pediatric progressive neurodegenerative diseases. Peripheral organs and tissues are also affected leading to multimorbidity, implying that an efficient drug may require reaching at and exerting a correction effect in multiple compartments of the body. Enzyme replacement therapy (ERT) is available for a small proportion of the LSDs and has been transformational for a few of them by addressing the most meaningful (often life-threatening) symptom (Figure 1, left side). The ERT pioneered by Brady and colleagues for type 1 GD and approved by the FDA in 1991 remains the iconic and most successful example in this category.[8] However, the formation of neutralizing antibodies, a predictable limitation of biologics, remains a concern with all ERT products. Biodistribution also represents an issue even for the most effective ERTs, often resulting in imbalanced efficacy in different aspects of the pathology. Furthermore, the blood-brain barrier (BBB) is a major hurdle in bringing the recombinant proteins used in ERT to the central nervous system (CNS), leaving a large unmet clinical need in the form of LSD variants involving the brain, meaning the two-third of all LSDs. Last, but not least, biologics for ERT rank among the most expensive drugs nowadays, with annual cost per patient ranging from $200,000 to $375,000 in average for their whole life. The increasing number of clinical trials focusing in gene therapy will likely provide amazing advancements in the near future, but at the expenses of pursuing the headlong flight to ever-increasing prices.

Small molecule LSD therapies: from common to rare. The flourishing of ERTs addressing the LSDs under the ODA was only possible because of the advancements in fundamental research on lysosomal functioning and protein homeostasis. Reestablishing the equilibrium in substrate metabolism is the key to avoid accumulation and the pathological downstream consequences. ERT act at the processing level by supplying the functional enzyme. An alternative tactic consists at downregulating substrate biosynthesis with the help of inhibitors of an intervening enzyme. Most of the LSDs affect carbohydrate/glycoconjugate degrading enzymes (glycosidases), leading to the accumulation of oligosaccharides, glycolipids or glycoproteins. It happens that carbohydrate chemists have been discovering and synthesizing carbohydrate lookalikes, so-called glycomimetics, to modulate carbohydrate active enzymes since the 1960's. Research in glycosidase regulators had led, for instance, to the development of miglitol (Glyset®), a reversible inhibitor of intestinal α-glucosidases marketed for the management of type 2 diabetes mellitus. The potential of glycomimetics to target oligosaccharide/glycoside biosynthesis trough medicinal chemist optimization strategies was apparent, leading to the approval of miglustat (Zaveska®), the first small molecule-based substrate reduction therapy (SRT) for an LSD (GD), in 2003. A main advantage of drug chemical synthesis versus biotechnological production of biologics crudely manifested in the 2009-2013 period, when

Gaucher and Fabry patients under ERT suffered the supply shortage of the corresponding recombinant enzymes (imiglucerase and agalsidase beta; Cerezyme® and Fabrazyme®, respectively) following viral contamination of the bioreactors.[9]

A second therapeutic paradigm relying in small molecules for the treatment of the LSDs was launched at the investigational level at the end of the 20th century: pharmacological chaperone therapy (PCT). PCT rationale stems from the recognition that an important proportion of the LSD-causing mutations results in misfolding and premature endoplasmic reticulum (ER) associated degradation of a lysosomal enzyme that otherwise retain significant catalytic activity.[10] Small molecules capable of binding to the mutant protein at the ER short after its biosynthesis, inducing proper folding, restoring trafficking and increasing enzyme activity and substrate processing in the lysosome are called pharmacological chaperones (PCs). The ability of glycomimetics to accomplish the task upon binding at the active site of a complementary glycosidase was soon realized. Some 20 years after the initial seminal report by Suzuki and colleagues,[11] the PCT concept reached the market: in 2017 migalastat (Galafold®) got approval by the FDA for the treatment of Fabry disease patients harboring responsive (misfolding) mutations in the dysfunctional enzyme (lysosomal α-galactosidase). A year later, the EMA followed.

From rare back to common…: the unveiled connections between LSDs and major public-health priorities. The study of the molecular mechanisms underlying orphan diseases frequently yields information that is relevant for other conditions that affect to a much broader population. Indeed, intralysosomal accumulation of unprocessed substrates occurs in many common human pathologies, such as neurodegenerative diseases, infectious diseases, cardiovascular diseases, diabetes, cancers or even aging.[12] Development of atherosclerotic plaques, modulation of insulin sensitivity or cell proliferation are examples of potentially pathological events that heavily rely on the lysosome system. Therapies developed for LSDs may therefore have unanticipated utility beyond the LSD field. Most notably, being a carrier for a mutation in the enzyme concerned in GD (β-glucocerebrosidase; GCase) represents the highest genetic risk factor for developing Parkinson disease (PD) and Lewi body disorders. The relationship between the levels of GCase and the formation of toxic α-synuclein aggregates, a hallmark of PD, has been demonstrated experimentally, opening the possibility of therapeutic intervention by SRT and PCT drugs (Figure 2). The critically advantageous point here is that small molecules acting through these mechanisms can be much easily engineered than biologics to cross the BBB and reach the central nervous system.

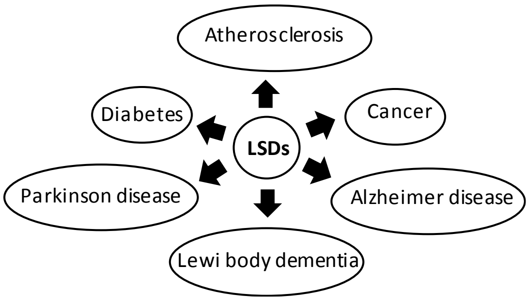

Figure 2. Representative examples of common diseases that can benefit from therapies tackling the “rare” LSDs.

And again to rare…: polypharmacology. Biologics and small molecules are not mutually exclusive but they can be synergistically reinforcing. The drugs developed to date (dominated by biologics) have targeted the more prevalent LSDs and have generally eluded conditions with neurological involvement awaiting gene therapy treatments. Pretending that the recombinant proteins used in ERT can reach all the affected organ and tissues efficiently is unrealistic, especially if one considers their rather short half-lives in biological fluids. Conversely, the small molecules used in SRT and PCT exhibit a strong mutation-dependent activity profile that limits the ratio of patients that can benefit from them. In practice, an all-inclusive treatment for LSDs is much more likely to be conveyed through the use of combination therapies tailored to each disease (or even to each individual patient in a personalized medicine perspective), with each therapeutic component addressing unique aspects of the pathogenic cascade, much like the approach implemented for the successful management of HIV infection. Such polypharmacology treatments should include drugs targeting downstream consequences that are shared with conditions that affect the general population, e.g. anti-inflammatories, further reinforcing the links between rare and common diseases.

Conclusions

As exemplified here with LSDs, there is plenty of room at the bottom for small molecules addressing orphan conditions. The connections between rare and common diseases is an additional incentive for medicinal chemists to approach the field that, moreover, can facilitate funding access. There is also an emotional side that, from our own personal experience, has the potential to create a strong commitment: whereas synthetic chemists generally stay at the rearguard in translational therapy-oriented research, they come to the frontline when the target is an orphan disease. This includes the direct contact with patients and their relatives. One might think that by focusing in small molecule orphan drugs the reduction in production costs as compared with biologics would translate into lower market prices and higher opportunities to treatment access for the less reach. Unfortunately, this reasoning proved naïve: the approved agents for ERT, SRT and PCT treating the same condition have all annual costs per patient in the same order of magnitude. Polemicizing here on this issue is beyond the intention of this viewpoint, but it looks evident that much discussion is required on how to reward innovation while maintaining the sustainability of drug budgets. Small molecules might help.

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Notes

Views expressed in this editorial are those of the authors and not necessarily the views of the ACS.

The authors declare no competing financial interest.

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