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Editorial

Recent advances and future challenges in Gaucher disease

The development of and introduction into clinical practice of safe and effective enzyme replacement therapy (ERT) as a specific treatment for patients with Gaucher disease (GD) occurred almost simultaneously with the implementation of polymerase chain reaction-based diagnostics that allowed for the characterization of patients and carriers. Together they mark the dramatic changes that revolutionized the diagnosis and management of patients with this inherited metabolic disorder. In many respects, GD serves as a model for the wider field of lysosomal storage diseases (LSDs) and other rare diseases, from the proof of concept of therapeutic interventions by ERT or substrate reduction therapy (SRT) with relevance to LSDs, to broader ramifications for health care systems worldwide coping with extremely expensive orphan therapies and more recently to potentially improve the future of patients with, or destined to suffer from Parkinson and related neurodegenerative disorders. All of these aspects are covered in this special GD issue, honoring the memory of Roscoe O Brady.

While significant advances have occurred in diagnosis and therapy, there is an ongoing need to expand the knowledge of the more basic features of the disease.

For the clinical manifestations, we have several papers. Adar et al. [1] have reviewed liver involvement in GD. Although hepatomegaly is listed among the four key disease features, the majority of the patients today do not have the massive hepatomegaly which was particularly common among splenectomized patients in the pre-ERT era and their liver function tests (LFTs) are usually within the normal range, or slightly abnormal. However several points are worth mentioning. Quite often, hepatomegaly and abnormal LFTs are due to another hepatic co-morbidity, which might be either GD-related (found in greater incidence in patients with GD than in the general population) such as hepatocellular carcinoma, or unrelated to GD (that is, not more common among patients with GD) such as viral hepatitis, that may impacted by the GD (for example, the ability to deliver anti-viral therapies may be compromised by thrombocytopenia). Adar also provides practical advice, such as there being no need to screen GD patients for alfa fetoprotein.

A significant proportion of patients with GD are diagnosed, or at least present with signs and symptoms during childhood. In general, early onset of symptoms and signs is associated with more severe forms of the disease. Accordingly, within the non-Ashkenazi Jewish populations the percentage with pediatric onset is even greater. This is even more relevant to Asian populations, which are underrepresented in the current medical literature and disease registries. The paper by Yuyu Feng et al. [2] opens a window to the clinical and molecular characteristics of patients with GD from Southern China. Similar to what has been reported previously from Japan and from Korea, Chinese patients with GD rarely have the N370S mutation, hence the majority of the patients (60%) present before age of 2 years and many of them had neuronopathic forms. Two additional papers deal with children with GD. A major concern of children and their parents is the issue of height. First published by Zevin et al. [3] in 1993, it was noted that growth retardation in children with GD is mainly affected by height and rather than weight, as is often the case with other chronic diseases that affect growth. We have a group of children with a relatively mild GD whose main indication to start ERT was low stature. In this issue, Mendelsohn et al. [4] report a 15 year follow up of the growth parameters in 41 children both treated and untreated, where the key findings were of a lower final height of the patients, but without short stature (defined by height less than the 3rd percentile). The impact of ERT on final height was not as significant as previously assumed. A second paper from the same group [5] describes the changing phenotype of pediatric patients with GD in the era of ERT, highlighting the huge impact of this therapeutic modality. Children no longer undergo splenectomy and do not suffer from severe bone involvement. Many have been diagnosed prenatally and those who required ERT because of symptomatic disease started before the development of irreversible skeletal complications, highlighting the importance of early diagnosis and awareness, and hinting to a future when neonatal screening becomes widely available. It is to be hoped that prudent medical judgement will still be exercised in those children diagnosed so many years before the onset of signs or symptoms.

The improving phenotypes seen with the wider use of ERT presents a challenge in development programs of new drug modalities, when the identification of suitable patients with marked disease abnormalities becomes significant. This is also challenging in switch-over clinical trials that are frequently required for new drug approval as well as for comparisons of the efficacy of newly approved drugs beyond lack of deterioration or maintaining stability. Here there is a clear need for sensitive, specific, reproducible, reliable and widely available biomarkers. This issue includes three papers dedicated to biomarkers. The first paper by Wated et al. [6] is a confirmatory report of the use of low density lipoprotein as a biomarker for GD. Although assessment of low density lipoprotein is widely available, it is inferior compared to chitotriosidase and CCL18 with regard to sensitivity and specificity and is far from meeting the criteria for an ideal biomarker [7]. The second is a validation study of the potential importance of the newer biomarker Glycoprotein Non-Metastatic Melanoma B (gpNMB, or osteoactivin) from Mistry's group [8]. This biomarker seems to be equivalent to chitotriosidase and CCL18 with potential added value remaining unclear. Two other biomarkers are more directly involved in the pathogenesis of GD. Glucosylsphingosine (LysoGb1), independently reported by Dekker et al. [9] and by Rolfs et al. [10], is the most specific and

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sensitive, and hence is probably the best currently available GD biomarker. It has already been studied in large cohorts of patients, and was included in several clinical trials [11,12]. Moreover, the relevance of this biomarker to the pathological processes in GD has been demonstrated in a recent study wherein continuous intravenous application of the LysoGb1 to healthy mice led to the development of hepatosplenomegaly, thrombocytopenia and bone pathology [13]. With the availability of LysoGb1, one should question the justification of measuring less specific and less sensitive biomarkers, which by themselves are not without cost for health care providers. The third paper dedicated to biomarkers is from Sweden [14] and focuses on serum ferritin, another "old" and less specific biomarker but with the new aspect of its relationship to hepcidin and correlation with serum TNF-α concentration. This observation may be directly relevant to the inflammatory aspects of GD, as recently published by Pandey et al. in Nature [15], as well as to the hypothesis that this marker is better correlated with fatigue (demonstrated in other clinical settings) [16] than other biomarkers. Finally, the biomarker Progranulin (PGRN; granulin epithelium precursor) although not discussed elsewhere in this issue, is a protein involved in many physiological and pathological cellular processes, including anti-inflammation and immunoregulation. It has shown significantly low levels in patients with GD, and may be more important than other biomarkers. Comprehensive studies have reported the detection of mutations in the GRN gene encoding Progranulin in patients with GD, and an adult PGRN null mouse model developed GD-like phenotypes including Gaucher-like cells in the lungs, spleen and bone marrow, making it an important disease modifying gene. Importantly, beyond being a new biomarker, PGRN may become a target for the development of a new therapeutic modality. To conclude the discussion on biomarkers in GD, we are still missing biomarkers that would predict the development of skeletal complications in mildly affected patients, in particular among Ashkenazi Jews, or co-morbidities in all patients, treated and untreated, with specific relevance to future implementation of neonatal screening and pre-symptomatic diagnosis of GD.

A biomarker does not necessarily have to be a laboratory analyte measured in blood or urine samples. According to the World Health Organization (WHO), the true definition of biomarkers includes "almost any measurement reflecting an interaction between a biological system and a potential hazard, which may be chemical, physical, or biological" [17]. In 2014, van Dussen et al. from Academic Medical Center (AMC) in Amsterdam attempted to define Quantitative Chemical Shift Imaging (QCSI) as an ideal imaging biomarker for GD; they have used the following criteria [18]: 1) The presence of the imaging biomarker is closely coupled or linked to the presence of the target disease or condition; 2) The detection and/or quantitative measurement of the biomarker is accurate, reproducible and feasible over time, and 3) The changes measured over time in the imaging biomarker are closely coupled, or linked to the success or failure of the therapeutic effect and the true end point for the medical therapy being evaluated. Several pitfalls (including age, menopause, degenerative disc disease; vertebral collapse, focal fatty deposits and others) and the extremely limited availability of this modality makes it difficult to call QCSI and ideal "imaging biomarker", despite its great potential value for clinical trials, particularly those comparing different treatments or dosing regimens [19]. The immediate alternative to QCSI, also reported originally by the same group of Maas et al. from AMC, is the Bone Marrow Burden (BMB) score, which has already been used in several of the more recent clinical trials in GD [20,21]. An important paper in this journal is the contribution of Robertson et al. [22] from Australia describing the major impact of reporting experience in reducing intra- and inter-observer variability of BMB scoring. This has been used in that country for over 2 decades to assess both disease severity as an indication for ERT and response to therapy and to inform dose adjustments among ERT treated patients, thereby optimizing cost effective care of patients with GD in Australia.

As good as both QCSI and BMB score are for assessing bone involvement in GD, both are magnetic resonance imaging (MRI) methodologies that are not always readily available. They add cost and require sedation in children, causing some problems in routine practice when repeated measurements are necessary. It is therefore not unreasonable to widen the use of bone densitometry studies which are readily available, inexpensive and in the past several years have become also suitable and evaluable for children. Dar et al. [23] report a seminal paper on the utility of whole body Dual Energy X-ray Absorptiometry (DXA) for evaluation of bone mineral density (BMD), lean body mass (LBM) and fat fraction in children with GD to assess the potential of DXA as a measure of bone-muscle relationships for prognostication of adverse skeletal events in pediatric patients. While the authors confirmed a positive impact of ERT on improved BMD in addition to the hematological and visceral improvement, further studies are needed to incorporate biological evaluation of growth and maturation along with DXA results. Such future findings may allow differentiation of children with slower maturation who will eventually achieve satisfactory bone density and muscle mass from those children in whom poor BMD and LBM may occur from childhood and onwards, and for whom ERT should be recommended despite an otherwise mild disease phenotype. The third (nonskeletal) imaging biomarker study reported for the first time in this issue is that of the transient elastography (TE) and shear wave elastography (SWE) of both spleen and liver [24]. This tool is both noninvasive and reproducible (as an ultrasound based methodology), and was able to differentiate patients with GD from healthy controls and among those with splenomegaly, from cirrhotic patients. Again, future studies are needed before the full value of this modality is recommended for routine follow-up of patients with GD.

The introduction of ERT to patients with GD in 1991 [25] was revolutionary in the history of medicine, not just for the patients but also for treating physicians, who for the first time were able to make a significant impact on the clinical manifestations and quality of life of patients with GD. It is worth noting the immeasurable role that Roscoe Brady, to whom this Special Edition is dedicated and in which two tributes appear as well as the contribution of the late Henry Temeer who took the academic breakthroughs and made them into a pharmaceutical reality for patients. Prior to the availability of therapy, most of the dialogue between the patient and the treating physicians was focused on time to splenectomy or to orthopedic surgery, all aimed to provide some partial symptomatic improvement, During the first decade of ERT there was a single available enzyme, and most of the discussions around it had to do with dosage regimens and indications for treatment, two big issues that have not been completely resolved even after 25 years. Now two or three different enzymatic preparations marketed by three different pharmaceutical companies are available in many parts of the world. While a dose-response relationship has been validated in several studies including three prospective clinical trials using a randomized, double blind, design [26–28] and retrospective reports [29], there is still a debate related to what should be considered a clinically meaningful difference. We support Beutler's approach advocating the administration of minimal effective rather than maximal tolerated dose, and the rational for a lower dose therapy goes beyond cost considerations which, however should not be neglected, as it may impact also on future risks for certain co-morbidities [30].

We also identified a need to revisit the 2004 publication by Pastores et al. on therapeutic goals [31], and this topic is the focus of two different publications in this journal. Biegstraaten et al. [32], present an ambitious list of 42 potential goals using a Delphi approach, aiming to define the relative importance of the traditional goals of hematological parameters, organ volumes and skeletal features. Ultimately we believe that the goals of therapy will still focus on platelets, hemoglobin, spleen, liver and bones, with growth parameters for children. In this regard, a simpler and more straightforward approach is that presented by Zimran et al. [33], proposing the importance of aiming for normalization or near normalization as the therapeutic targets, based on cumulative data from the velaglucerase alfa clinical trials. It seems logical to us that different drugs whether biosimilars or different molecular entities and different protocols should be compared based on percentage of cases achieving normalization for each of the key