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Gaucher disease: Resetting the clinical and scientific agenda

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Editorials are written to provide insightful commentary about articles in the current issue of a scientific journal. In general, they are intended to provide context and a balanced perspective for the overall readership that may not necessarily have specialized knowledge of the subject matter. Thus, an editorialist assumes a great burden of intellectual rigor and responsibility. With that in mind, we feel it is necessary to provide substantive comments and remonstrations to the editorial by Zimran et al. [1] in this issue of the *American Journal of Hematology* (AJH). We thank the AJH Editor for this opportunity and commend him for allowing an open scientific discussion of these important issues.

In essence, without any substantiating or credible evidence, the Zimran et al. commentary postulates that enzyme replacement therapy (ERT) with imiglucerase, the current standard of care for Type 1 Gaucher disease, may increase mortality rates and cancer risks. The commentary also invokes a nonevidence based and scientifically irrelevant comparison with the increased mortality experience associated with sustained, high-dose erythropoietin stimulating agent (ESA) treatment in chronic renal disease. Moreover, Zimran et al. imply that physicians are improperly promoting and prescribing unnecessary high-dose treatment when low-dose should suffice for all patients irrespective of individual clinical status or adequacy of treatment response.

These disquieting matters necessitate thoughtful and evidence-based responses. Here, we address the following:

- The misinterpretations in the Zimran et al. commentary of recent published data that ERT causes cancer and shortens life-expectancy [2,3].
- The incorrect speculation that increased plasma glucocerebroside levels confer a selective advantage on patients with Gaucher disease that is abrogated by higher doses of ERT.
- The incorrect promulgation of the concept that ERT causes pulmonary hypertension, which is in fact a well-known complication of Gaucher disease [4–7].

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- Whether or not there is improper use of high-dose ERT for Gaucher disease [8].

Despite precise genomic annotation of the GBA1 gene (gene encoding lysosomal glucocerebrosidase), the enzyme defect, biomarkers and phenotypic spectrum, the molecular pathways from accumulation of glucocerebroside and its lysolipid to the protean manifestations are not known [9,10]. Exploration of these pathways has just begun that spans almost the entire spectrum of medicine [11]. However, studies using a model system of glucocerebroside infusion into rodents and its effect on the adaptive immune system is an irrelevant extrapolation to Gaucher disease in which blood glucocerebroside is elevated only several-fold over normal, whereas infusion of this lipid elevates the level many times over that seen in patients [12]. The opinion expressed in the Zimran et al. commentary that ERT causes cancers in Gaucher disease by inducing low circulating glucocerebroside levels is untenable and it is not supported by any available evidence.

There is a substantive body of evidence linking Gaucher disease with increased risk of cancers before any intervention with ERT. Cancer is not an uncommon consideration in Gaucher disease. In fact, the first patient described with the disorder by Dr. Philippe Gaucher in 1882 was believed to have a rare neoplasm of the spleen, and it remains the most common misdiagnosis to this day [13,14]. The study reported in the current issue found increased risk of cancers in patients with Gaucher disease harboring at least one N370S allele, primarily myeloma and other hematological malignancies [3]. Of the patients who developed cancers, 69.6% (32/46) were diagnosed with cancer before ERT was initiated. The relative risk of multiple myeloma was increased up to 37.5-fold and that of nonmyeloma hematological cancers was increased to 3.45-fold. Although this study focused entirely on the N370S Gaucher disease variants, the finding of increased cancer risk is in agreement with numerous other reports of such an association since 1965, before the availability of ERT. In the pre-ERT era (-before 1991-), at least 24 reports were published of Gaucher disease associated with a variety of malignancies including multiple myeloma, lymphomas, leukemia, and one case each of hepatocellular carcinoma and glioblastoma multiforme. In 1982, RE Lee Gaucher Registry at University of Pittsburgh (a pre-ERT era Registry) reported on 32 patients who had died: cancer caused death in 54% (19/35) [15]. In contrast, among the 137 patients who died during the ERT era (1991–2004), 28 were attributed to cancer, i.e., 20% [16]. A comparison of cancer prevalence rates in pre-ERT and ERT era from several study populations is depicted in Table I. There is no evidence of increased prevalence rates of cancers in the ERT-era; in fact, compared with the pre-ERT era, the prevalence rates of cancers in the ERT era seem to show a downward trend [3,15,17–19]. Moreover, a study reporting cancer prevalence rates in Amsterdam (where low-dose ERT is used) and Düsseldorf (where high-dose ERT is the standard of care) found cancer prevalence rates of 14% (9/63) versus 7% (5/68), respectively, corresponding to cancer-related death rates of 5% (3/63) versus 3% (2/68), respectively [20]. Additionally, it is of interest that deaths associated with multiple myeloma in Gaucher disease fell from 9.7% in the pre-ERT era to 0.7% in the ERT era [16]. It should be kept in mind that the treatment of multiple myeloma and other cancers is markedly improved since pre-ERT era and this situation has most likely contributed to seemingly reduced number of cancer-related deaths among Gaucher disease patients in the ERT era. What contribution ERT made if any, will have to await carefully conducted clinical studies and delineation of basic mechanisms that link the two conditions together and an elucidation of how ERT might impact on these processes.

In the cancer study from the International Collaborative Gaucher Group (ICGG) Registry, a definite increased risk was observed only for myeloma; however, the risk estimates are probably significantly lower than the actual levels because of incomplete ascertainment and significant skewing of that population to younger ages at which cancer rates are lower [19].

Zimran et al. suggest that rates reported in the current issue of AJH are higher than that those in their referral clinic, and that this discrepancy may be due to the use of high-dose ERT in many countries outside of Israel [18]. This conclusion is not tenable in light of the foregoing considerations. Moreover, in the ICGG Gaucher Registry analysis of life expectancy, among the patients who succumbed to various cancers, the median age at death (72 years) was consistent with the median age of cancer-related mortality in the general population, i.e., 73 years [2].

What about the report of shortened estimated life expectancy at birth for patients with Gaucher disease Type 1 compared with the 2002 US reference population? [2] It should be kept in mind that the life table technique is not equivalent to and cannot be interpreted like a survival analysis. The results are entirely dependent on past medical practice and are inapplicable to estimates of future risk. Therefore, the key finding of the study is the large number of life-years during which the majority of patients included in the analysis did not have access to ERT, yet had negative outcomes that can now be attributed at least in part, to rapid acceleration of the disease because of interventions such as splenectomy, a procedure of diminished indications in the ERT era. These results do not provide insight into influences of ERT on life expectancy nor was the analysis designed to evaluate any such effect. The stated intention of the life expectancy analysis was “to create a baseline for future analyses of survival trends in Gaucher disease Type 1 particularly as the effects of long-term enzyme therapy and other proposed treatments are increasingly identified.” Because of insufficient data and small numbers, specific subgroups, e.g., the Israeli population could not be similarly examined. Such rigorous studies should be performed in the future.

In a preliminary analysis, cardiovascular disease or cerebrovascular disease rates in Gaucher disease patients younger than 60 years old appeared to exceed the expected rates [2]. However, the numbers were small and, as stipulated, highly preliminary. The cause of death data was not available on almost 40% of the deceased patients, the known causes of death were not verified, and the 102 deceased patients represented <2% of all patients worldwide who are receiving ERT. Interestingly, despite low HDL-cholesterol levels, Dutch patients with Gaucher disease Type 1 were recently shown not to have accelerated atherosclerosis [21].

Zimran et al. speculate that elevated levels of plasma glucocerebroside may confer a biological selective advantage favoring persistence of Gaucher mutations (beyond that attributed to the founder effect, historical “bottleneck” events and inbreeding) that may be obviated by ERT, especially in high-dose regimens. Such advantage, if it were to occur would be expressed only in patients with Gaucher disease because there are no studies, that we are aware of, indicating heterozygote carriers have elevated levels of plasma glucocerebroside. It should be noted that the article cited in the Zimran commentary, restricts a putative selective advantage to Gaucher carriers, because “those who had two abnormal genes, and hence Gaucher disease, clearly had decreased fitness” [22]. Moreover, Beutler noted outside of the Ashkenazi Jewish population in Europe, Gaucher mutations remained rare, suggesting that any selective advantage is unique to this Jewish population. It is difficult to fathom how a biological determinant, i.e., plasma glucocerebroside, would be specifically ethnocentric. Importantly, no evidence exists to support the claim that higher doses of imiglucerase decrease plasma glucocerebroside to subnormal levels. In the seminal alglucerase trial, plasma glucocerebroside levels decreased after 9 months of biweekly infusions at a dose of 60 U/kg (a putative high dose), but none dropped below the lower limit of normal [23]. Comparable results were obtained for four Israeli patients treated at an undocumented, but presumably lower dose ERT, for 3–4 years; plasma glucocerebroside levels normalized during the first year of treatment and subsequently reached a plateau [24].

Therefore, there are no data to support the commentary's analogy between the imiglucerase dosing controversy and the adverse outcomes associated with over-utilization of erythropoietin, attributed to excessive increases in hemoglobin concentration and/or to ESA-induced hypertension [25].

An earlier hypothesis by Zimran et al. led to persistent misinformation about the relationship between pulmonary hypertension and ERT for Gaucher disease [26]. In the commentary, the historically excellent safety track record of ERT was acknowledged, but it continues to promulgate the opinion that pulmonary hypertension is a side-effect of ERT. As with cancer, pulmonary hypertension was a recognized cause of death in Gaucher disease before ERT became available [5–7]. The commentary does not cite data demonstrating the essential role of splenectomy in the development of Gaucher disease/pulmonary hypertension phenotype [4]. Moreover, ERT with or without adjuvant therapies in fact leads to an amelioration of pulmonary hypertension, a potentially life-threatening complication of Gaucher disease [4]. Such confusion of the data harms patient care by misleading treating physicians and patients alike, and could result in withholding of appropriate treatment with subsequent progression of this life-threatening condition. Fortunately, the striking reduction of splenectomy rates because of the success of ERT is likely to translate into extinction of the Gaucher disease/ pulmonary hypertension phenotype in the new generation of patients [27].

Careful phenotypic annotation in individual patients in defined cohorts can lead to identification of distinct syndromes within the vast phenotypic spectrum of Gaucher disease [28]. When considering Gaucher disease in its entire worldwide spectrum, a valuable resource is the ICGG Gaucher Registry, launched in 1991 with the emergence of ERT (ClinicalTrials.Gov NCT#00358943). ICGG is the largest observational registry for Gaucher disease with data on over 5,000 patients from 56 countries and has IRB/Ethics Committee approvals (https://www.lsdregistry.net/gaucher-registry/). Given the extreme heterogeneity of Gaucher disease and unpredictable rate of progression, the Gaucher Registry has the potential to fill the gap created by limitations to conduct randomized trials in this disorder. This is exemplified by a recent study from the Registry that addressed the issue of dose-response in the treatment of Gaucher disease by a methodology that could represent a *forme-fruste* of a randomized controlled trial [8]. There has been much controversy about the proper use of the appropriate amounts of enzyme therapy to achieve the best possible outcomes for this patient population [29,30]. The large number of patients in the Gaucher Registry facilitated the analyses of phenotypically matched patients who differed in the dose they received for therapy. This statistical matching (using propensity scoring methods) greatly diminished the interindividual variability except for dose. This rigorous analysis clearly shows a more robust response of liver and spleen volumes, and platelet and hemoglobin levels in the higher dose groups compared with that achieved at lower doses. However, the data did show a clear response at the lower doses. Does this massive study answer the question of dosing once and for all? No, it is a significant incremental step in evidence-based individualized medicine for this disease. The clinical relevance of these results will be determined by large studies conducted by multinational groups interested in the optimization of care of patients with Gaucher disease.

What are the implications for patient care? Gaucher disease phenotypes associated with Parkinsonian syndrome, pulmonary hypertension, and cancer are uncommon events in the patient population as a whole. Therefore, the vast majority of patients afflicted by Gaucher disease can be reassured by the overall low risk for these complications. The few patients who are affected will have the option of early intervention, monitoring, and potential for improved outcomes. Therefore, patients can be reassured of access to sophisticated personalized medicine.

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TABLE I

Cancer Prevalence Rates in Five Studies of Gaucher Disease Patients

	Pre-ERT era (Before 1991)	ERT-era (After 1991)
Israel	10/48 (20.8%)[a,b]	20/500 (4.0%)[c]
USA/ICGG Registry	19/35 (54.3%)[d]	126/2742 (4.6%)[e]
Taddei[f]	pre-ERT 32/367 (8.7%)	On ERT 14/335 (4.2%)

[a] Ref. 17.

[b] Although this article was published in 1993, the study population was derived from chart review of patients seen at Rambam Medical Center between 1968 and 1991, ie., pre-ERT era.

[c] Ref. 18.

[d] Ref. 15.

[e] Ref. 19.

[f] Ref. 3.