Editorial

Biomarker combination is necessary for the assessment of Gaucher disease?

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Biomarkers are useful tools to help in disease diagnosis and follow-up. According to the US Food & Drug Administration, biomarkers are defined as measurable elements that can be used as indicators in normal biological and pathological processes, or in response to an exposure or therapeutic interventions. Molecular, histologic, radiographic or physiological characteristics are some of those biomarkers (www.fda.gov). The term biomarker is currently being applied to molecular markers that define a specific biological status (1). Considering these factors, the "ideal" biomarker should fulfill susceptibility/risk, be reliable, and can be used for diagnosis, monitoring, prognosis, prediction and pharmacodynamic response.

Some useful biomarkers such as the number of *BCR/ABL* transcripts in chronic myeloid leukemia serve as sensitive indicators that help in the monitoring of the molecular response, a quantitative instrument to monitor the long-term molecular response to therapy (2) or for example the serum concentration of M-component in monoclonal gammopathies (3).

In lysosomal storage diseases (LSD) such as Gaucher disease (GD) there are several available biological markers that are useful tools in diagnosis that offer objective information about the situation of the disease and in the follow-up to detect early complications and the stability in the response to treatment. However, the search for more reliable and accurate indicators for LSDs is an open battle in order to get the most sensitive, easiest to determine and cheapest biomarker (4).

The study by Jian *et al.* (5) in the present issue of EBioMedicine raises some interesting information concerning a new biomarker [Chitinase-3-like protein 1 (CHI3L1)] for diagnosing and following-up on GD.

Chitinases are a family of enzymes whose main function is to catalyze hydrolysis of glycosidic bonds in chitin polymers. More than 18 different chitinases have been identified in mammals (6). These structures are generally implicated in a variety of diseases involving immune dysfunction or related to inflammatory environment.

Since 1994, chitotriosidase (ChT) is known as a biomarker in LSDs, and the first and most used biomarker in GD patients (7). This biomarker reflects in GD the presence and the quantity of Gaucher cells and therefore is used in the screening. From ChT description to the present, many studies have been carried out about its effectiveness and limitations as a biomarker. One of its limitations is that its activity is increased in plasma for different inflammatory processes such as atherosclerosis, ischemic heart disease, paludism, cancer, β-thalassemia major or myeloproliferative neoplasms, chronic disorders that involve activated macrophages although it does not reach the highest levels found in GD (6,8-10).

One of the problems that this biomarker shows is the null to reduced activity due to null alleles in the gene that encode them. Several studies performed on more than 600 subjects have worked on the *CHIT1* gene (MIM*600031), which encodes the ChT enzyme and identifies the null and/or pseudo-deficient variants, like the changes NP_003456:p.Glu74Lys, p.Gly102Ser, p.Gly354Arg, p.Ala442Val, or several complex alleles (e.g., the 4 bp deletion across the

exon/intron-10 boundary etc.) (11). However, the most outstanding allele is the NM_003465:c.1049_1072 dup24 (12,13). When this duplication is present in homozygous status, the subjects show total absence of ChT activity. In Caucasian population about 6% are homozygous and approximately 30–40% heterozygous for this allele (9). The interpretation of the fluctuations in the ChT levels must be individualized according to the genotype of those *CHIT1* alleles. The trend of the marker, along with the evaluation of other clinical parameters, is what should be studied in the evaluation of the activity of the disease, not its absolute levels.

CHI3L1 or YKL-40 lacks of chitinase activity, even though it is a mammalian glycoprotein that binds chitin polymers. This pro-inflammatory marker increases for auto-immune diseases as rheumatoid arthritis and different rheumatic process, pulmonary sarcoidosis, among others (5,6). CHI3L1 binds to interleukin-13 (IL-13) receptor α2 and exerts its biological function by activating downstream mitogen-activated protein kinase B/AKT. Wnt/β-catenin signaling (14) is able to suppress the alpha tumor necrosis factor (TNFα) and IL-1-induced secretion of matrix metalloproteases and IL-8 in both human skin fibroblasts and articular chondrocytes. Jian *et al.* (5) in their study propose CHI3L1 to be a novel downstream molecule with potential to be used as a biomarker for screening of the GD and examining the therapeutic effects of new GD drugs. The fact that these markers are sensitive during inflammatory processes may have the added value of guiding the inflammatory state underlying the LSD.

Patients suffering from GD live with the fear of developing osteoarticular complications. Finding biomarkers that can predict the appearance of bone complications is of great interest. This would help detect the risk of them appearing, allowing us to make appropriate therapeutic decisions, like the dose to be administered and maintained with enzymatic replacement therapy (ERT) or whether or not to switch to oral treatment. Another desirable goal is to find a good marker/predictor for the development of complications such as gallbladder stones, the appearance of neoplasms or Parkinson's disease as more frequent complications related to GD.

There are other biomarkers that only specifically reflect the accumulation of substrates, such as glucosylsphingosine (Lyso-Gb_1), the deacylated form of glucosylceramide, which was first described in 1982 by Nilsson and Svennerholm (15) who found this molecule in high concentration in the brain and cerebellum of GD patients affected by the neurological forms. Its concentration in the plasma is 200 times greater than control samples for subjects affected by GD type 1 (GD1) versus controls (16). Lyso-Gb_1 levels seem to be related to the genotype of GBA (MIM*606463), being higher in patients with severe mutations. This biomarker is highly specific from GD, shown high levels in patients and normal levels in carriers and other LSDs even Krabbe disease when a suitable chromatographic method is applied (16). Lyso-Gb_1 shows a wide range of normal/pathological values due to methodological variability (16-18). In a few studies concerning response to therapy, it can be observed that the amount of this biomarker in plasma rapidly decreases once the ERT is started, and its discontinuation causes a significant increase, being detected earlier in the 3 weeks of the interruption than in the 10 weeks in the ChT activity (16). Nowadays the experience using this biomarker in the clinical practice is limited, so is difficult to know its real usefulness.

Lyso-Gb1 appears to induce tissue inflammation in mice (19) but it is still unknown if it is tissue specific and the modifications in inflammatory response that occurs after treatment. Despite all this, Lyso-Gb1 promises to be useful biomarker in patients without ChT activity.

Another accredited biomarker useful in LSD is the chemokine CCL18/PARC, which is an inflammatory marker produced by T lymphocytes and monocytes, first described by Boot *et al.* in 2004 (20) as a peptide that was first detected in plasma of GD subjects. Comparing the mass spectra profiles (SELDI-TOF) significant differences between healthy individuals and those affected by GD were found, being these levels almost 30 times higher in the latter. Likewise, Boot *et al.* verified that its levels decreased during treatment, correlating this reduction with observed reduction in ChT activity (20). This cytokine was quantified by immunoquantification methods in plasma, showing that its variations are not as early and sensitive as ChT. During the period of shortage of ERT suffered in 2009, it could be observed that after 6 months of discontinued imiglucerase therapy ChT activity increased by 35% ($P<0.03$), while the CCL18/PARC concentration only was increased by an average of 8.2% ($P<0.08$) (21).

Therefore, it can be stablished that there is correlation between the concentration of CCL18/PARC and ChT activity, but also that this is markedly high in other entities such as atherosclerosis, active C hepatitis, pneumonitis, allergic hypersensitivity, sepsis, ovarian carcinoma, rheumatoid arthritis, Niemann-Pick disease, β-thalassemia and others, being able to exist overlap between them (20).

Ferritin was another one of the biomarkers used in the

follow-up of GD. Ferritin is a protein that binds to iron in tissues, storing it in a biologically available form for vital cellular processes as protecting proteins, lipids and DNA from their potential toxicity. Iron homeostasis is controlled by a circulating peptide, hepcidin, whose production in the liver is influenced by inflammatory cytokines (22). Glucosylceramide accumulation in macrophages induces an inflammatory response that produces deregulation in iron recycling and cytokine release. Data collected in the Spanish Registry of GD revealed that up to 60% of patients with GD1 have hyperferritinemia (23), which has been associated by some authors with the severity of this disease (24). Hyperferritinemia reverts with ERT with no relationship stablished between this and the mutations in the hemochromatosis gene. It has been speculated that the failure of iron control mechanisms contributes to the development of some pathological conditions such as inflammation, neurodegeneration, metabolic disorder and cancer, conditions that frequently occur in GD (24,25).

In some studies, a reduction in the serum concentration of ferritin after months in ERT has been observed (25,26). Although hyperferritinemia occurs in a majority of GD1 patients, its value as a biomarker of the disease, unlike ChT and CCL18/PARC, is secondary, is only found in association with the severity of the disease and increase of some cytokines (27). Stein *et al.* studied the correlation between ChT, CCL18/PARC and ferritin, finding that ChT and CCL18/PARC were clearly superior as biomarkers of GD to ferritin (27).

The angiotensin-converting enzyme (ACE) has high concentration in plasma of GD patients compared to the values in the controls. ACE is a membrane protein involved in the homeostasis of blood pressure, whose active sites are directed to the extracellular spaces; its presence in plasma comes from the endothelium. In healthy subjects, circulating levels are usually very low, with a considerable variation range between individuals. ACE increase in serum of patients with GD was first described about 40 years ago and it is considered to be produced in excess by Gaucher cells. However, this biomarker is not specific, so it also appears increased when suffering from other diseases, such as sarcoidosis or other inflammatory process. Nevertheless, overlapping occurs between GD patients and controls (28).

The bone affection is present quite frequently in types 1 and 3 of GD, compromising the functionality and life quality of patients. Hence, it would be of great importance to have specific markers to predict this affection. Despite of having numerous biomarkers related both to osteoclasts (markers of bone resorption) and to osteoblasts (markers of bone formation), no great advances have been made in determining their specificity in GD. Bone alkaline phosphatase which is related to bone mineralization, osteocalcin, the major protein of the non-collagenous bone matrix whose concentration is subject to the circadian rhythm and the procollagen peptides, was released to the bloodstream after the secretion of procollagen by osteoblasts (29).

The activity of isoenzyme 5b of acid phosphatase (TRAP5b) marker during bone resorption, which plays a critical role in the degradation of type I collagen by the osteoclast, was found at high levels for the first time by Tuchman in 1959 in GD patients. This concluded that the rise of acid phosphatase in serum, unlike acid phosphatase of prostate origin or erythrocyte origin, which is not inhibited by L-tartrate, formaldehyde or copper ions, could be considered as a suspicious biomarker for GD (30). Elevation of TRAP5b activity occurs in all three subtypes of GD. However, it is also at high levels in the plasma of patients with Niemann-Pick disease, osteopetrosis, multiple myeloma among others.

The markers of bone metabolism are complex and their concentration depends on multiple factors: the fasting period, circadian rhythm, phase of the menstrual cycle, rest-exercise, diet, season, drugs intake and habits. This creates great biological variability, making their use in clinical practice rather controversial and is not recommended to use during the follow-up of patients in ERT (29).

When looking for a specific biomarker for bone disease, several cytokines were evaluated. These substances are secreted by activated macrophages and T lymphocytes, and have been extensively studied in plasma and/or serum of patients with GD1.

High levels of IL-1β, the antagonist receptor of IL-1, IL-6, TNFα and the soluble IL-2 receptor (31) were found, 2- to 5-fold increase in the antigen activator of monocyte differentiation of macrophages (CD14) and 2 to 8 times that of the macrophage colony formation stimulating factor (M-CSF) (32). Studies carried out in a cohort of 83 GD1-patients compared to controls have revealed an increase in the levels of proinflammatory cytokines IL-4, 1-α and 1-β macrophage inflammatory proteins (MIP) and TNFα, as well as the reduction of anti-inflammatory cytokines such as IL-10 and IL-13 (33). The studies performed in a mouse model with the neurological form of GD show high levels of mRNA expression up to 30-fold in the proinflammatory cytokines IL-1β, TNFα, TNF receptor

1 and M-CSF on the gray matter of brain tissue (34), and the increase is greater when the disease progresses. Similarly, cytokines CCL2/MCP-1, CCL3/MIP1α and CCL5/RANTES, which regulate the infiltration of immune cells and the crossing of the blood-brain barrier, were found to be between 120 and 400 times larger.

The TNFα, is a cytokine produced by macrophages, necessary for adhesion molecule expression and leukocyte recruitment where inflammation occurs. It is involved in several physiological and pathological processes, such as bone resorption. There is a contradiction between previously published results on their expression in the plasma of GD-suffering patients, probably due to the limited number of patients showing significant expression differences between patient and control samples (20,22) in contrast to the study by Altarescu *et al.* in 25 GD1 patients, 4 GD2 and 1 GD3 demonstrated a significant increase in TNFα plasma concentration (35) nevertheless the highest levels of TNFα corresponded to patients with neuronopathic forms. It has been indicated that TNFα changes the expression of ion channels and membrane potentials of oligodendrocytes *in vitro*, produces the breakage of myelin and necrosis of oligodendrocytes. These authors analyzed the variation of TNFα levels during ERT, observing a decrease in TNFα levels, becoming more pronounced the higher the concentration was before the start of treatment. That supports the idea that there is a causal relationship between the disease and the secretion of this cytokine. Subsequent studies have analyzed the relationship between TNFα levels and the genotype of patients for the polymorphism NG_007462.1:g.4682G>A (rs1800629), located in the promoter region of the *TNF* gene, finding significant differences between serum TNFα levels among patients homozygous for said polymorphism (A/A). The lowest values correspond to these and heterozygotes (A/G), which present the highest expression values (35). Out of all these data it was concluded that the genetic variability in TNFα could be associated to the severity in the GD, so that the presence of only one mutated allele would be associated with greater severity of the disease. However, it does not correlate with the ChT activity, always limited by the small number of patients analyzed.

IL-6 is a paracrine regulator of plasma cell growth in bone marrow. Increased levels have also been detected in the serum of GD patients (33). IL-6 levels are greatly increased in patients with multiple myeloma. This neoplasia is more frequent in patients with GD. Said cytokine induces maturation of B cells, T lymphocyte growth and the hepatic response for acute phase reactants, so it has been suggested that it may play an important role in the expression of GD and its association with multiple myeloma. In addition, it is a potent modulator of bone resorption, so that its increase in GD patients' plasma could be related to the development of bone disease.

The β-hexosaminidase activity is high (especially the isoform B) in most patients suffering from GD, with an average value of approximately twice its normal concentration. Its values decrease during the ERT, reaching normal levels in some cases after a few months in treatment. Likewise, levels of α-mannosidase, β-glucuronidase, N-acetylglucosaminidase and in some cases—even if just slightly—β-galactosidase increase has been described. Although the reason for this decompensation of other lysosomal hydrolases is unknown. It is possible that they are compensatory processes that attempt to eliminate accumulated excess glucocerebroside, being secreted by Gaucher cells or other activated cells (32).

Recently a new regulator of GD through direct binding to glucocerebrosidase has been identified. Progranulin (PGRN) is a growth factor with multiple functions, including promoting cell proliferation, stimulating wound healing and facilitating the delivery of glucocerebrosidase to lysosome (28). *GRN* (MIM*138945) gene mutations are widely present in GD patients where serum levels of PGRN are significantly reduced (36). In a gene array screening from T cells of WT and PGRN KO mice, Chitinase-3 like family members (CHI3L1, CHI3L3, CHI3L4) are up-regulated in PGRN KO mice. CHI3L1 was confirmed to have the strongest induction among the three members, especially in the spleen. The analysis among serum levels of ChT, PGRN, and CHI3L1 have demonstrated that PGRN levels correlate positively to CHI3L1 and ChT in GD patients. A weaker correlation is observed between PGRN and CHI3L1 in healthy controls, but none is observed between PGRN and ChT in healthy controls and the disease

Conclusions

GD is, perhaps, the LSD that has the best monitoring biomarkers. However, the "ideal" biomarker—which reflects all the aspects of the disease—in which the activity of the cells correlates with the clinical severity of the disease, efficiency of the treatment and that predicts complications has not been found yet.

The ChT activity is a good biological marker, easy

to measure and economical, which correlates with the burden of the disease and is modified with the treatment applied, therefor it is a useful tool to monitor the treatment response. The limitation that this biomarker has is that 6% of the population lacks of ChT activity so it cannot be used as a marker in these patients. In addition, it is not possible to compare or predict the occurrence of bone complications involved in the disease.

The quantification of plasma Lyso-Gb_1 only specifically reflects the accumulation of substrate, that is not uniform in different compartments and tissues. Also, the amount of accumulation does not show the underlying degree of inflammation which could be related to complications related to the immune system or neurological involvement.

Alternatively, CCL18/PARC, ACE, TRAP5b and ferritin are also inflammatory biomarkers that inform about the grade of immune stimulation.

The authors of the study "*Chitinase-3-like Protein 1*: *A Progranulin Downstream Molecule and Potential Biomarker for Gaucher Disease*" are proposing that the identification and characterization of this new molecule may lead to innovative diagnostic biochemical approaches for lysosomal disorders, in particular GD, and may be also used as a biomarker for evaluating the therapeutic effects of new treatments and to determine whether CHI3L1 is a better biomarker than those currently employed, in particular ChT.

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Footnote

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