Received: 23 November 2023 | Revised: 28 December 2023 | Accepted: 29 December 2023

DOI: 10.1111/ejh.14171

ORIGINAL ARTICLE

European Journal of Haematology

WILEY

Soluble mannose receptor: A potential biomarker in Gaucher disease

Brendan Beaton[1,2,3] | Derralynn A. Hughes[1,2]

[1]Department of Haematology, Royal Free NHS Trust, London, UK

[2]University College London, London, UK

[3]Department of Haematology, Liverpool Hospital, Sydney, Australia

Correspondence
Brendan Beaton, Locked Bag, 7090 Liverpool BC, NSW 1871, Australia.
Email: brendan.beaton1@health.nsw.gov.au

Abstract

Purpose: Soluble mannose receptor (sMR) relates to mannose receptor expression on macrophages, and is elevated in inflammatory disorders. Gaucher disease (GD) has altered macrophage function and utilises mannose receptors for enzyme replacement therapy (ERT) endocytosis. sMR has not previously been studied in GD.

Methods: sMR was measured by ELISA and correlated with GD clinical features including spleen and liver volume, haemoglobin and platelet count, bone marrow burden (BMB) scores and immunoglobulin levels. sMR was compared with biomarkers of GD: chitotriosidase, lyso-GL1, PARC, CCL3, CCL4, osteoactivin, serum ACE and ferritin.

Results: Median sMR in untreated GD patients was 303.0 ng/mL compared to post-treatment 190.9 ng/mL ($p = .02$) and healthy controls 202 ng/mL. Median sMR correlated with median spleen volume 455 mL ($r = .70$, $p = .04$), liver volume 2025 mL ($r = .64$, $p = .04$), BMB 7 ($r = .8$, $p = .03$), IgA 1.9 g/L ($r = .54$, $p = .036$), IgG 9.2 g/L ($r = .57$, $p = .027$), IgM 1.45 g/L ($r = .86$, $p < .0001$), with inverse correlation to median platelet count of 125 $\times$ 10^9/L ($r = -.47$, $p = .08$) and haemoglobin of 137 g/L ($r = -.77$, $p = .0008$). sMR correlated with established biomarkers: osteoactivin 107.8 ng/mL ($r = .58$, $p = .0006$), chitotriosidase 3042 nmol/mL/h ($r = .52$, $p = .0006$), PARC 800 ng/mL ($r = .67$, $p = .0068$), ferritin 547 µg/L ($r = .72$, $p = .002$) and CCL3 50 pg/mL ($r = .67$, $p = .007$).

Conclusions: sMR correlates with clinical features and biomarkers of GD and reduces following therapy.

KEYWORDS
biomarker, Gaucher disease, soluble mannose receptor

Novelty statements

What is the new aspect of your work?

The aspect of this work that is new is that soluble mannose receptor (sMR) has never been characterised in Gaucher disease before, and it is of considerable interest because it is easy to measure and exists in steady state with macrophage mannose receptors, which are essential for

endocytosis of enzyme replacement to be delivered to the lysosome; with future work this may help better predict those that will respond sub-optimally to therapy to allow earlier changes to management.

What is the central finding of your work?

The central finding of this work is that sMR is elevated at baseline and falls to that of healthy controls following therapy and correlates with both severity of baseline clinical features and also established biomarkers; of particular novelty is the strong correlation with immunoglobulin concentrations which may allow better prediction of those patients at risk of myeloma or lymphoproliferative disorders (which occur at higher incidence in patients with Gaucher disease).

What is (or could be) the specific clinical relevance of your work?

The specific clinical relevance of this work may be better prediction of those patients who may not respond optimally to therapy allowing earlier alterations in management strategy, and also better prediction of those at risk of myeloma or lymphoproliferative disorders, enabling closer monitoring or earlier intervention.

1 | INTRODUCTION

The mannose receptor (MR), also known as CD206, is present on subpopulations of macrophages, and its upregulation has been demonstrated on alternatively activated macrophages.[1] It is also seen on immature dendritic cells and endothelial cells.[2,3] The mannose receptor has roles in recognizing extracellular ligands, endocytosis and in antigen presentation. The mannose receptor can be cleaved into the extracellular matrix, by a yet unidentified metalloprotease, and released as soluble Mannose Receptor (sMR).[4] sMR is present in human plasma and its concentration has been shown to be increased in a variety of non-lysosomal storage disorders.[5–10] It has been shown to promote macrophage proinflammatory activation and trigger 'metaflammation'.[11,12] MR shedding occurs constitutively and levels of sMR correlate and are in steady state with the amount of total MR expressed on cells.[4]

Gaucher Disease (GD) is an autosomal recessive lysosomal storage disorder caused by deficient activity of beta-glucocerebrosidase (GBA)[13,14] due to mutations within the GBA1 gene located on chromosome 1.[15] There is considerable heterogeneity in its clinical presentation with a limited degree of genotype–phenotype correlation[16] suggesting influence from a variety of genetic modifiers. There is a continuum of disease severity with a classification system of disease severity from type 1 to type 3. Type 1 disease is that without specific neurological features; it is the most common and mild phenotype. Type 2 disease is diagnosed in the first 6 months of life, has severe neurological manifestation and is invariably fatal; the most severe phenotype is the collodion baby. Type 3 disease is less severe than type 2 and is often diagnosed after the first 6 months of life, with patients having specific neurological features.[17]

The clinical features of type 1 GD include anaemia, thrombocytopenia, bleeding diatheses, splenomegaly, hepatomegaly, and bone abnormalities including Erlenmeyer flask remodelling deformity, bone marrow infiltration with atypical macrophages (Gaucher cells), reduced bone mineral density, avascular necrosis, increased incidence of fractures, bone pain and bone crises. There is also an increased incidence of bone-based plasma cell dyscrasias: polyclonal gammopathy, monoclonal gammopathy of uncertain significance and plasma cell myeloma.[18] Registry data suggests increased incidence of other haematological malignancies and also hepatocellular carcinoma. There is also an increase in metabolic rate and alterations in lipid metabolism. In addition to these clinical features, there are a wide variety of neurological manifestation of type 2 and 3 GD including seizures, cognitive deficits, ataxia, nuclear gaze palsy and oculomotor apraxia. Parkinson disease has an association with GD and has increased incidence in type 1 patients. There is an increased incidence of Parkinson disease in individuals who are carriers of just one disease-associated allele. Together, these discoveries have prompted interesting research in the role of lysosomes in neurodegenerative diseases.[19]

GD was the first lysosomal storage disorder treated with enzyme replacement therapy (ERT) with beta glucosidase derived from human placenta.[20] The development of ERT using placental enzyme was instructive in relation to understanding uptake of ERT and the utility of the mannose receptor on macrophages. Altering the carbohydrate moieties of the ERT molecule to expose the mannose moiety to enhance uptake was a crucial development.[21] Following this, recombinant ERT was developed: imiglucerase, velaglucerase, taliglucerase; as has substrate reduction therapy: miglustat and eliglustat.

Treatment has altered the natural history and progression of GD. Review of patient data has shown consistent data in improvement of haemoglobin and platelet counts and reduction in hepatomegaly and splenomegaly. Less consistent have been patients' response in relation to their bone disease. As expected, established avascular necrosis and bone infarction do not improve with therapy.[22] However, some studies have found that approximately 30% of patients have no improvement or progression of some features of bone disease, of which a significant proportion were receiving treatment.[23,24] Making general statements about this are impossible,

as the pathophysiology of individual manifestations of bone disease is different. Though animal studies have shown a reduction in B cell malignancy in GD mice treated with eliglustat, the effect ERT or SRT has on plasma cell dyscrasias in humans with GD is not well characterised.

Gaucher cells do not resemble classically activated macrophages and have some but not all features of alternatively activated macrophages. In one study of two patients already receiving ERT for GD, large Gaucher cells (GCs) were negative for CD163 with smaller GCs demonstrating intracellular staining for CD163. Double labelling for the alternatively activated macrophage markers CCL18 and MR showed that CCL18 was expressed by all GCs, whereas MR expression was expressed on adjacent endothelial cells. Double-positive cells were observed only occasionally. Therefore, in some patients receiving ERT, GCs express many but not all markers that are characteristic for alternatively activated macrophages and there may be variable expression of MR with many lacking MR expression.[25] This is an important finding given that ERT is mannose-terminated and treatment of GD is based on MR-mediated uptake. This has major implications in understanding GD and its treatment and may relate to poor response to treatment.

Ongoing work demonstrates an evolution in our understanding of the pathophysiology of GD. This has moved from the macrophage-centric model of disease toward a more integrated model of general osteoimmunological dysfunction incorporating alterations in lymphocytes, NK cells, macrophages and stromal cells, including mesenchymal stem cells.[26–29]

There are a number of biomarkers of GD activity that are elevated at diagnosis or baseline assessment and can be used to track response to therapy. Each one reflects a different compartment or pathway altered by GD activity, and each has specific limitations. These biomarkers include chitotriosidase, glucosylsphingosine (lysoGL1), PARC/CCL18, progranulin, CCL3 and CCL4. There are also biochemical assays in routine use that can give an indication of GD activity, serum ACE and ferritin for example, although these are not specific.[30–37]

Given the importance of altered macrophage function in a complicated immunological microenvironment in the pathophysiology of GD and the importance of the mannose receptor in the cellular internalization of exogenous enzyme replacement therapy, it seems vital to characterize sMR expression in GD as sMR has not been reported in the literature in relation to Gaucher disease (GD).

Here we present measurement of sMR in a population of type 1 GD patients before and after therapy, also compared to a group of healthy volunteers, and correlate this with known clinical feature domains of GD. We also compare sMR to known biomarkers of GD.

2 | MATERIALS AND METHODS

Patients with GD and healthy volunteers were enrolled and gave blood samples between January 2004 and July 2016 to study bone disease in GD. The study was approved by the Royal Free Hospital Multi-Centre Research Ethics Committee to recruit healthy controls or individuals with Gaucher diseases. All subjects provided written informed consent prior to participation. The diagnosis of GD was confirmed in our patients by assessing enzyme activity and genotype. Healthy controls were not screened for GD, but self-reported as well and asymptomatic.

Blood specimens for storage were collected in serum vacutainer tubes and allowed to stand for 30 min, then centrifuged at 2000*g* for 10 min. Serum was removed and stored in polypropylene tubes in 200 μL aliquots at −80°C until thawed immediately before analysis.

For patients with GD, specimens were collected following diagnosis and prior to starting enzyme replacement therapy; also collected again on at least one occasion following commencement of ERT.

ELISA analysis of biomarkers was undertaken as per kit instructions: Human sMR (Hycult Biotech); PARC (Life Technologies); human osteoactivin GPNMB (Invitrogen by Thermo Fisher Scientific); CCL3 and CCL4 (Invitogen by Thermo Fisher Scientific); progranulin (Ray Biotech). All tests were conducted according to the specified instructions.

Chitotriosidase, ferritin, ACE, haemoglobin, platelets, IgA, IgG, and IgM were determined by the diagnostic laboratory at The Royal Free hospital using standard operating procedures and accredited by UKAS. Lyso-GL1 was measured by liquid chromatography with tandem mass spectrometry.

Clinical data was collected retrospectively from the patient electronic medical record. The data recorded in the medical record was collected as part of normal clinical activity.

Estimated spleen volumes and liver volumes were calculated from MRI images of patients. Spleen volume (cm^3) = 30 + 0.58(L × D × T), where L = cranio-caudal distance between the first and last slices in the axial plane where the spleen is depicted, D = the largest measurable long axis diameter in the axial plane, and T = the largest perpendicular dimension to D in the axial plane.[38] Liver volume (cm^3) = CC × LL × AP × 0.31, where CC = craniocaudal dimension, LL = latero-lateral dimension, AP = antero-posterior dimension.[39]

Differences between groups were determined by the non-parametric Mann–Whitney *U* test and differences for non-parametric paired data were assessed using the Wilcoxon test. Correlations were determined using simple linear regression. All were calculated using Prism software (GraphPad).

TABLE 1 Characteristics of treatment-naïve Gaucher disease (GD) patients and health controls (HC).

	GD *n* = 16	HC *n* = 10
Age in years, median (range)	38.3 (21–80)	49 (18–75)
Sex, male, *n* (%)	12 (75)	5 (50)
GBA1 mutations		
N370S/N370S, *n* (%)	5 (31.3)	
N370S/Other, *n* (%)	10 (62.6)	
Other/Other, *n* (%)	1 (6.3)	
Splenectomy, *n* (%)	1 (6.3)	

3 | RESULTS

Sixteen treatment-naïve type 1 GD patients and 10 non-GD healthy controls had sMR measured from serum by ELISA. Patient and healthy control characteristics are outlined in Table 1.

Fourteen of the 16 treatment-naive GD patients had post-treatment sera available for analysis with a median time between treatment starting and testing of paired sera of 27 months (IQR: 21–43 months), Figure 1A.

The median sMR in treatment naïve sera, Figure 1B, was significantly higher at 303.0 ng/L (IQR: 149.2–736.4 ng/mL) compared to paired post-treatment median of 190.9 ng/mL (IQR: 105.4–414.5 ng/L) ($p = .02$). There was no statistical difference between the median treatment naïve and unpaired healthy control cohort with median sMR of 202 ng/L (IQR: 141.5–236.0 ng/mL). There was no statistically significant difference between control and post-treatment groups.

Having established that sMR was elevated in treatment-naïve patients and fell with therapy, we assessed sMR with known clinical features of disease. There was good correlation with pre-treatment sMR and all domains of GD clinical features, see Figure 2. (2A) Median spleen volume ($n = 8$) was 455 mL (IQR: 219–1348 mL) ($r = .71$, $p = .04$); (2B) median liver volume ($n = 10$) was 2025 mL (IQR: 1375–2425 mL) ($r = .64$, $p = .04$); (2C) median bone marrow burden (BMB) score ($n = 7$) was 7 (IQR: 6–12) ($r = .8$, $p = .03$). There was an inverse correlation with (2D) median platelet count of 125 × 10^9/L

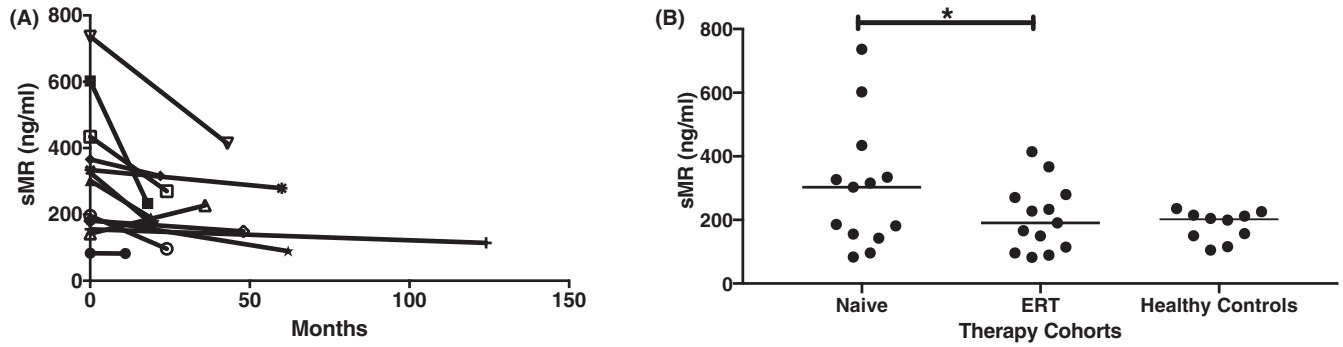

FIGURE 1 Changes in sMR. (A) There is a reduction of sMR with ERT after a median of 27 months comparing paired serum of treatment-naïve with post treatment ($n = 14$) GD patients. (B) There is a significant difference between the treatment-naïve and post-treatment GD patients' paired sera. There is no difference between post-treatment GD patients and healthy controls. ERT, enzyme replacement therapy; GD, Gaucher disease; sMR, soluble mannose receptor. *$p < .05$.

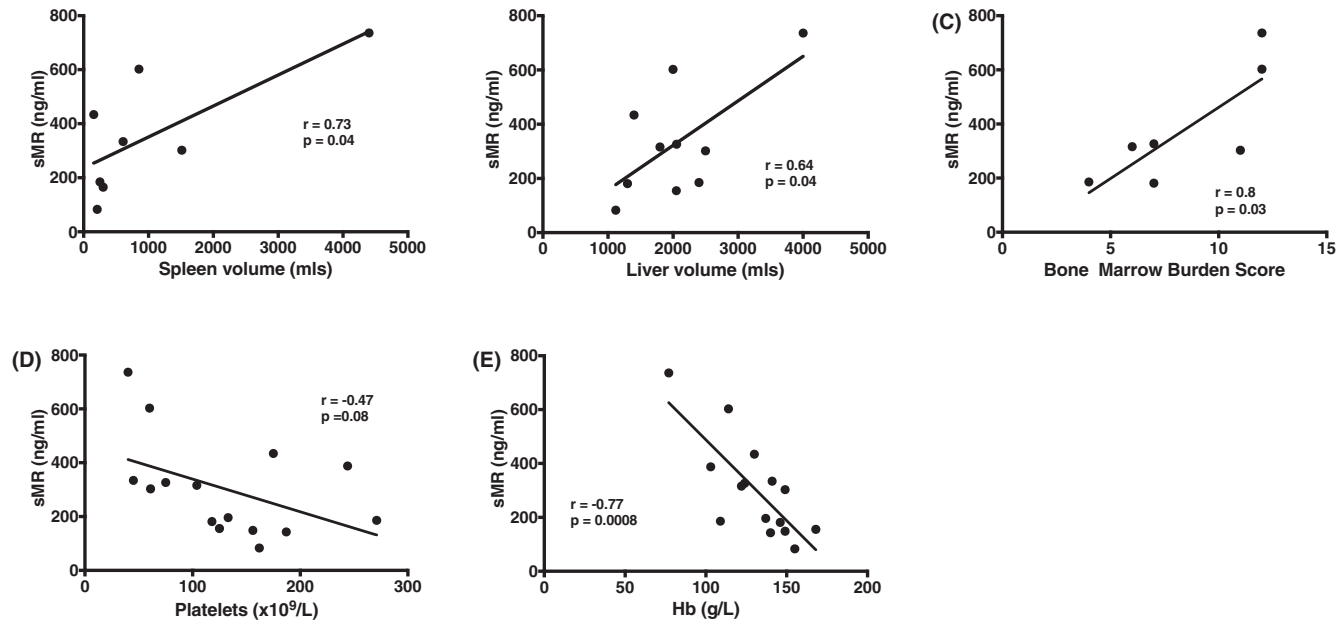

FIGURE 2 Correlation between treatment-naïve sMR concentration and severity of GD-related clinical features. There are significant correlations between sMR concentration and (A) spleen volume ($n = 8$), (B) liver volume ($n = 10$), and (C) bone marrow burden score ($n = 7$). There is a trend toward correlation between sMR concentration and (D) platelet count ($n = 15$). There is strong correlation between sMR concentration and Hb ($n = 15$). GD, Gaucher disease; Hb, haemoglobin; sMR, soluble mannose receptor.

(IQR: 40–175 × 10^9/L) ($r = -.47$, $p = .08$) and (2E) median haemoglobin of 137 g/L (IQR: 77–149 g/L) ($r = -.77$, $p = .0008$).

Knowing that plasma cell dyscrasias and gammopathy have an increased incidence in GD, we thought it was important to assess sMR in relation to baseline immunoglobulin concentration. There was strong correlation with pre-treatment immunoglobulin levels, see Figure 3. (3A) Median IgA ($n = 15$) was 1.9 g/L (IQR: 1.35–2.9 g/L) ($r = .54$, $p = .036$); (3B) median IgG ($n = 15$) was 9.2 g/L (IQR: 7.8–14.5 g/L) ($r = .57$, $p = .027$); median IgM ($n = 15$) was 1.45 g/L (IQR: 0.6–2.75 g/L) ($r = .86$, $p \leq .0001$).

Having observed the relationship between the severity of baseline clinical features in GD and sMR, we compared the sMR of our patients with established key biomarkers, see Figure 4. (4A) Median PARC ($n = 15$) was 800 ng/mL (IQR: 750–980 pg/mL) ($r = .67$, $p = .0068$); (4B) median osteoactivin ($n = 15$) was 107.8 ng/mL (IQR: 70.5–177.4 ng/mL) ($r = .58$, $p = .0006$); (4C) median chitotriosidase ($n = 15$) was 3042 nmol/mL/h (IQR: 1120–5951 nmol/mL/h) ($r = .52$, $p = .046$); (4D) median ferritin ($n = 15$) was 547 µg/L (IQR: 381–972 µg/L) ($r = .72$, $p = .002$); (4E) median CCL3 ($n = 15$) was 50 pg/mL (IQR: 30–100 pg/mL) ($r = .67$, $p = .007$).

sMR did not correlate with these biomarkers: median angiotensin converting enzyme (ACE) ($n = 15$) was 118 nmol/mL/min (IQR: 65–214 nmol/mL/min) ($r = .27$, $p = .13$); median progranulin ($n = 15$) was 3.18 ng/mL (IQR: 3.06–3.74 ng/mL) ($r = .09$, $p = .7$); median CCL4 ($n = 15$) was 90 pg/mL (IAR: 51–104 pg/mL) ($r = -.036$, $p = .90$).

Lyso-GL1 was measured in 8 patients who were well established on therapy at the time of analysis, where there was a post-treatment sMR measured enabling comparison (though these samples were taken at different times). Unfortunately, there was no baseline Lyso-GL1 measured for any of the patients we had data for baseline sMR. Of the post-treatment patients, median lyso-GL1 was 51.8 nmol/L (IQR: 24.6–109.1 nmol/L) compared to median sMR of 163 ng/mL (IQR: 122–212 ng/mL) and there was no correlation ($r = -.18$, $p = .66$). It must be noted that the median time between the sMR

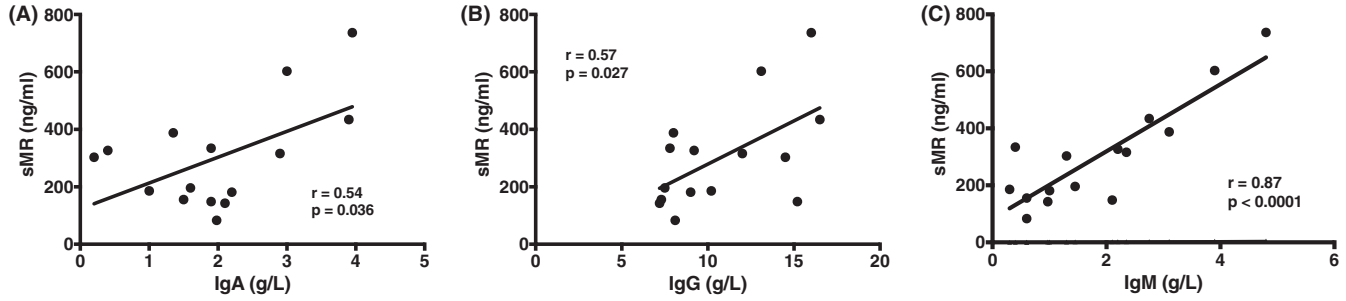

FIGURE 3 Correlation between treatment-naïve sMR concentration and immunoglobulin subgroups for GD patients. (A) IgA and (B) IgG show correlation, with (C) IgM showing very strong correlation. GD, Gaucher disease; Ig, immunoglobulin; sMR, soluble mannose receptor.

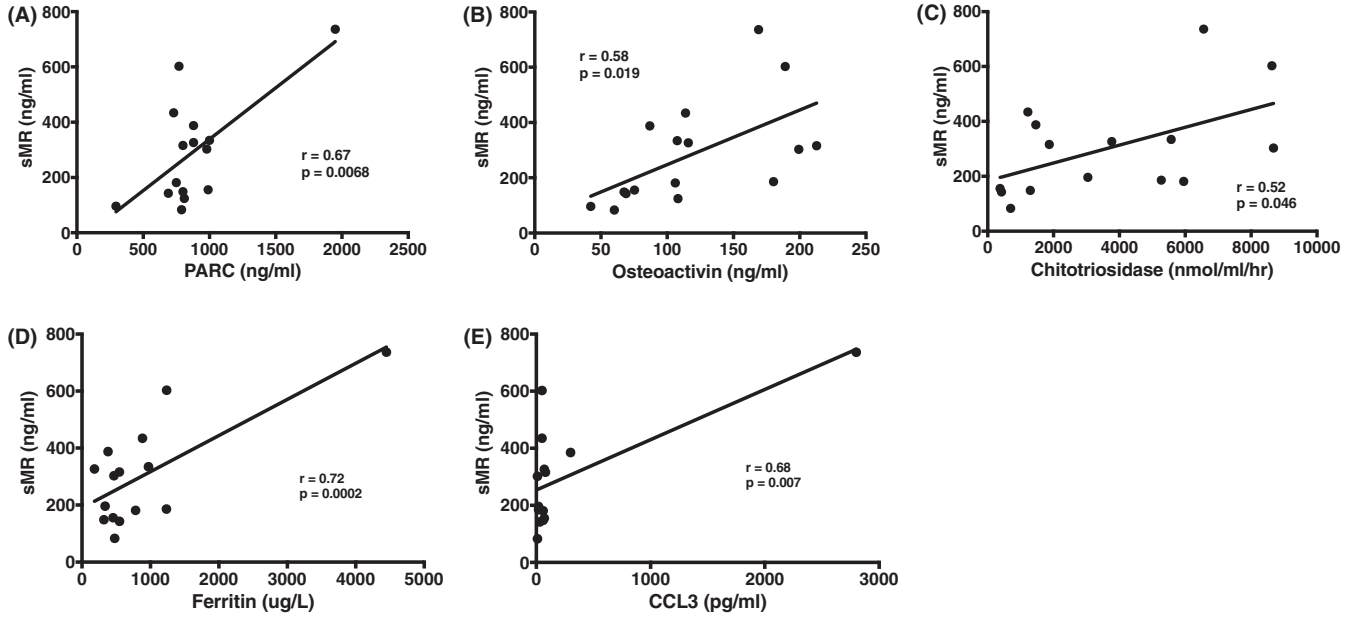

FIGURE 4 Correlation between treatment-naïve sMR concentrations and these established GD biomarkers: (A) PARC, (B) Osteoactivin, (C) Chitotriosidase, (D) Ferritin, (E) CCL3. CCL3, chemokine (C-C motif) ligand 3; GD, Gaucher disease; PARC, pulmonary and activation-regulated chemokine.

specimen collection date and the lyso-GL1 collection date was 96 months (IQR: 61–129 months) with patients continuing on treatment over this time.

4 | DISCUSSION

The results presented here show an elevated concentration of sMR in patients with GD prior to therapy compared to a median of 27 months post therapy and compared to healthy controls. The elevation itself compared favourably with other pre-treatment clinical features including platelet count, haemoglobin, spleen and liver volume, bone marrow burden and to immunoglobulin levels, particularly IgM. There was also favourable correlation with previously evaluated biomarkers: PARC, osteoactivin, chitotriosidease, ferritin and CCL3; though not with serum ACE, progranulin or CCL4. An attempt was made to assess correlation with lyso-GL1, which has emerged over the last decade and currently considered one of the best biomarkers of disease burden and response to therapy. However, as there were no contemporaneous samples available to assess sMR and lyso-GL1 directly at baseline and then following therapy in paired samples, this was not performed, though the data would be very interesting.

Elevated sMR has been associated with critical illness, ICU admission, sepsis, severe liver disease, liver cirrhosis, alcoholic liver disease, pulmonary tuberculosis, pulmonary fibrosis, multiple myeloma, rheumatoid arthritis, chronic joint inflammation, pneumonia, interstitial lung disease and gastric cancer. sMR concentration correlates with disease severity and mortality. Some have argued that sMR may be a better biomarker of inflammation than CRP, sCD163 or procalcitonin.[40,41]

Evaluation of sMR in patients with GD is logical given the evidence of its elevation in conditions of significant inflammation, particularly when macrophage activation is increased. Though our understanding of the pathophysiology of GD has evolved to be more inclusive of multiple domains of immune dysregulation, altered macrophage morphology, activation and interaction with the microenvironment is still a significant part of the disease process.

Basic and translational research has informed important links between MR, sMR and inflammation. Murine models of MR expression have shown that MR-deficient mice are somewhat resistant to several inflammatory diseases.[42] Exogenous sMR has been shown to induce an inflammatory phenotype of both murine and human macrophages increasing secretion of several proinflammatory cytokines: TNF, IL6, IL12, IL1beta.[11]

Also, there are changes in metabolism associated with MR and sMR including an increase in glycolysis in macrophages, recognized as a hallmark of inflammation. In metaflammation linked to obesity, proinflammatory macrophages accumulate in metabolic tissues, with increased expression of MR seen in liver and adipose tissue. MR-deficient mice have a change in the proliferation and differentiation of adipocyte precursors. sMR levels are higher in both high-fat-diet fed obese mice and in obese humans. Intraperitoneal injection of exogenous sMR in mice increases circulation of proinflammatory cytokines. The mechanisms of MR and sMR cellular interactions are still being investigated and elucidated, with both known to have actions through CD45.[11] Given the increased incidence of plasma cell myeloma in obese patients[43] and the observation that sMR is elevated in patients with plasma cell myeloma[6] it is interesting that there is a strong correlation in sMR and immunoglobulin concentration in our patient cohort, particularly IgM. None of our patient cohort analysed had myeloma or lymphoma. However, the relationship of sMR to immunoglobulins here certainly raises future research questions about prediction of risk of developing myeloma or other B cell malignancies in GD patients.

A significant limitation in assessing patients with GD is that it is a very rare disease, which often means only small numbers of patients or samples are assessed before findings are published, which limits how robust the conclusions can be that are drawn from that data. However, this is what we have available to us. The description of the expression of MR on macrophages within GD patient specimens was performed on only 2 patients, both of whom were on ERT and only assessed splenic tissue.[25] The authors concluded that Gaucher cells lacked MR expression, however, the certainty about this given the limited numbers and confounders that were not discussed, must make one keep an open mind about MR expression. It is important to note that a spectrum of MR expression was seen on smaller macrophages within the specimens assessed.

Given the role the MR plays in facilitating endocytosis of ERT into cells for delivery to the lysosome, having a way of assessing MR expression at diagnosis is important. Given that work has shown sMR to be constitutively expressed and in steady state with total MR, we hypothesise that sMR may be a useful way to evaluate the net number of macrophages and Gaucher cells.

Some patients do not respond well to ERT, and until now it has not been possible to predict which patients will not respond to therapy. One wonders if there are some patients with GD who indeed have downregulated MR for disease-related or other reasons. We have seen evidence that larger or more mature Gaucher cells lack MR expression. Lack of MR expression may mean that those Gaucher cells have limited means of endocytosing ERT and may be part of the reason patients may exhibit refractoriness to treatment. The MR itself may act as a 'sink' and take ERT away from where it is needed most.[44]

Having a way of assessing MR by measuring sMR at baseline and throughout therapy may allow modifications to therapy to occur to optimise management strategies particularly in those who are responding sub-optimally to treatment.

Limitations to our work here relate to the small cohort of patients we had available with retrospective samples and data for analysis. Lyso-GL1 is our leading biomarker for assessing global disease burden and response to treatment, and it is disappointing we could not show a comparison of baseline lyso-GL1 and sMR.

Future work should prospectively evaluate the level of MR on treatment naïve patient tissue, assessing a broader range of tissue (spleen, bone marrow, liver) and seeing if sMR can be correlated not just to disease burden, but also perhaps to be able to predict response to therapy, particularly ERT which utilises MR to be delivered to the

lysosome. Comparing baseline sMR with lyso-GL1 will be important. Validation of our results with another centre with a similar or larger cohort would be beneficial.

5 | CONCLUSIONS

sMR was elevated in patients with Gaucher disease prior to therapy commencement and falls to the level of healthy controls after therapy. Further work is required to assess if sMR reflects overall disease burden and if it could be used to predict patients who may not respond as expected to ERT, and if it may help predict patients at risk of plasma cell dyscrasias or B cell malignancies.

AUTHOR CONTRIBUTIONS

Design of the work: B. B. *Acquisition of the data*: B. B. *Analysis of the data*: B. B., D. A. H. *Interpretation of the data*: B. B., D. A. H. *Drafting of the work*: B. B., D. A. H. *Final approval of the work to be published*: B. B., D. A. H. *Agreement of be accountable for all aspects of the work*: B. B., D. A. H.

ACKNOWLEDGEMENTS

We would like to acknowledge our patients and our healthy volunteers for providing blood samples; and the clinical staff at Royal Free NHS Trust London for their help with collecting and documenting clinical data throughout routine clinical work. Matthew Reed and Hatim Ibrahim are acknowledged for their support in the research laboratory.

FUNDING INFORMATION

This work was funded out of a discretionary research trust fund held by the Derralynn A Hughes laboratory at the Lysosomal Storage Disorder Unit of Royal Free Hospital NSH Trust and University College London.

CONFLICT OF INTEREST STATEMENT

D.A.H. has received consulting fees and fees for non-CME/CE services from Genzyme, Sanofi, and Takeda. B.B has no conflicts to declare.

DATA AVAILABILITY STATEMENT

The data for this study are not available from a public repository but can be requested for review and will be provided if complying with ethical and governance restrictions.

ORCID

Brendan Beaton https://orcid.org/0000-0002-9260-720X

REFERENCES

1. Stein M, Keshav K, Harris N, Gordon S. Interleukin 4 potently enhances murine macrophage mannose receptor activity: a marker of alternative immunological macrophage activation. *J Exp Med*. 1992; 176(1):287-292.
2. Linehan SA, Marinez-Pomares L, Stahl PD, Gordon S. Mannose receptor and its putative ligands in normal murine lymphoid and nonlymphoid organs: in situ expression of mannose receptor by selected macrophages, endothelial cells, perivascular microglia, and mesangial cells, but not dendritic cells. *J Exp Med*. 1999;189(12):1961-1972.
3. Engering AJ, Cella M, Fluitsma DM, Hoefsmit EC, Lanzavecchia A, Pieters J. Mannose receptor mediated antigen uptake and presentation in human dendritic cells. *Adv Exp Med Biol*. 1997;417:183-187.
4. Martinez-Pomares L, Mahoney JA, Kaposzta R, Linehan SA, Stahl PD, Gordon S. A functional soluble form of the murine mannose receptor is produced by macrophages in vitro and is present in mouse serum. *J Biol Chem*. 1998;273(36):23376-23380.
5. Rodgaard-Hansen S, Rafique A, Christensen PA, et al. A soluble form of the macrophage-related mannose receptor (MR/CD206) is present in human serum and elevated in critical illness. *Clin Chem Lab Med*. 2014;52(3):453-461.
6. Andersen MN, Andersen NF, Rodgaard-Hansen S, Hokland M, Abildgaard N, Moller HJ. The novel biomarker of alternative macrophage activation, soluble mannose receptor (sMR/sCD206): implications in multiple myeloma. *Leuk Res*. 2015;39(9):971-975.
7. Clemmesen JO, Moller S, Jensen JS, Bendtsen F, Gronbaek H. The soluble mannose receptor is released from the liver in cirrhotic patients, but is not associated with bacterial translocation. *Liver Int*. 2017;37(4):569-575.
8. De Vlieger G, Vanhorebeek I, Wouters PJ, et al. The soluble mannose receptor (sMR/sCD206) in critically ill patients with invasive fungal infections, bacterial infections or non-infectious inflammation: a secondary analysis of the EPaNIC RCT. *Crit Care*. 2019;23(1):270.
9. Tsuchiya K, Suzuki Y, Yoshimura K, et al. Macrophage mannose receptor CD206 predicts prognosis in community-acquired pneumonia. *Sci Rep*. 2019;9(1):18750.
10. Reuken PA, Brozat JF, Quickert S, et al. Soluble mannose receptor CD206 and von Willebrand factor are early biomarkers to identify patients at risk for severe or necrotizing acute pancreatitis. *J Intensive Care*. 2022;10(1):28.
11. Embgenbroich M, van der Zande HJP, Hussaarts L, et al. Soluble mannose receptor induces proinflammatory macrophage activation and metaflammation. *Proc Natl Acad Sci U S A*. 2021;118(31): e2103304118.
12. Van der Zande HJP, Nitsche D, Schlautmann L, Guigas B, Burgdorf S. The mannose receptor: from endocytic receptor and biomarker to regulator of (meta)inflammation. *Front Immunol*. 2021;12:7655034.
13. Beutler E, Kuhl W, Trinidad F, Teplitz R, Nadler H. Detection of Gaucher's disease and its carrier state from fibroblast cultures. *Lancet*. 1970;286:369.
14. Ho MW, O'Brien JS. Gaucher's disease: deficiency of 'acid' beta-glucosidase and reconstitution of enzyme activity in vitro. *Proc Natl Acad Sci U S A*. 1971;68(11):2810-2813.
15. Devine EA, Smith M, Arrendondo-Vega FX, Shafit-Zagardo B, Desnick RJ. Chromosomal localization of the gene for Gaucher disease. *Prog Clin Biol Res*. 1982;95:511-534.
16. Grabowski GA. Gaucher disease: gene frequencies and genotype/phenotype correlations. *Genet Test*. 1997;1(1):5-12.
17. Davidson BA, Hassan S, Garcia EJ, Tayebi N, Sidransky E. Exploring genetic modifiers of Gaucher disease: the next horizon. *Hum Mutat*. 2018;39(12):1739-1751.
18. Thomas AS, Mehta A, Hughes DA. Gaucher disease: haematological presentations and complications. *Br J Haematol*. 2014;165(4): 427-440.
19. Vieira SRL, Schapira AHV. Glucocerebrosidase mutations and Parkinson disease. *J Neural Transm*. 2022;129(9):1105-1117.
20. Barton NW, Furbish FS, Murray GJ, Garfield M, Brady RO. Therapeutic response to intravenous infusions of glucocerebrosidase in a patient with Gaucher disease. *Proc Natl Acad Sci U S A*. 1990;87(5): 1913-1916.

21. Oh DB. Glyco-engineering strategies for the development of therapeutic enzyme with improved efficacy for the treatment of lysosomal storage diseases. *BMB Rep*. 2015;48(8):438-444.
22. Hughes DA, Mikosch P, Belmatoug N, et al. Gaucher disease in bone: from pathophysiology to practice. *J Bone Miner Res*. 2019;34(6):996-1013.
23. Stirnemann J, Vigan M, Hamroun D, et al. The French Gaucher's disease registry: clinical characteristics, complications and treatment of 562 patients. *Orphanet J Rare Dis*. 2012;7:77.
24. Giraldo P, Perez-Lopez J, Nunez R, et al. Patients with type 1 Gaucher disease in Spain: a cross-sectional evaluation of health status. *Blood Cel Mol Dis*. 2016;56:23-30.
25. Boven LA, van Meurs M, Boot RG, et al. Gaucher cells demonstrate a distinct macrophage phenotype and resemble alternatively activated macrophages. *Am J Clin Pathol*. 2004;122(3):359-369.
26. Lecourt S, Mouly E, Freida D, et al. A prospective study of bone marrow hematopoietic and mesenchymal stem cells in type 1 Gaucher disease patients. *PLoS One*. 2013;8(7):e69293.
27. Reed M, Schiffer C, Heales S, Mehta AB, Hughes DA. Impact of sphingolipids on osteoblast and osteoclast activity in Gaucher disease. *Mol Genet Metab*. 2018;124(4):278-286.
28. Nair S, Boddupalli CS, Verma R, et al. Type II NKT-TFH cells against Gaucher lipids regulate B-cell immunity and inflammation. *Blood*. 2015;125(8):1256-1271.
29. Pastores GM, Hughes DA. Lysosomal storage disorders and malignancy. *Diseases*. 2017;5(1):8.
30. Boot RG, Renkema GH, Strijland A, van Zonnerveld AJ, Aerts JM. Cloning of a cDNA encoding chitotriosidase, a human chitinase produced by macrophages. *J Biol Chem*. 1995;270(44):26252-26256.
31. Murugesan V, Chuang W, Liu J, et al. Glucosylsphingosine is a key biomarker of Gaucher disease. *Am J Hematol*. 2016;91(11):1082-1089.
32. Boot RG, Verhoek M, de Fost M, et al. Marked elevation of the chemokine CCL18/PARC in Gaucher disease: a novel surrogate marker for assessing therapeutic intervention. *Blood*. 2004;103(1):33-39.
33. Van Breemen MJ, de Fost M, Voerman JSA, et al. Increased plasma macrophage inflammatory protein (MIP)-1alpha and MIP-1beta levels in type 1 Gaucher disease. *Biochim Biophys Acta*. 2007;1772(7):788-796.
34. Jian J, Zhao S, Tian QY, et al. Association between progranulin and Gaucher disease. *EBioMedicine*. 2016;11:127-137.
35. Casal JA, Lacerda L, Perez LF, Pinto RA, Miranda MCS, Tutor JC. Relationships between serum markers of monocyte/macrophage activation in type 1 Gaucher disease. *Clin Chem Lab Med*. 2002;40(1):52-55.
36. Morgan MA, Hoffbrand AV, Laulict M, Luck W, Knowles S. Serum ferritin concentration in Gaucher's disease. *Br Med J (Clin Res Ed)*. 1983;286(6381):1864.
37. Kramer G, Wegdam W, Donker-Koopman W, et al. Elevation of glycoprotein non-metastatic melanoma protein B in type 1 Gaucher disease patients and mouse models. *FEBS Open Bio*. 2016;6(9):902-913.
38. Prassopoulos P, Daskalogiannaki M, Raissaki M, Hatjidakis A, Goutsoyiannis N. Determination of normal splenic volume on computer tomography in relation to age, gender and body habitus. *Eur Radiol*. 1997;7(2):246-248.
39. Muggli D, Muller MA, Karlo C, Fornaro J, Marincek B, Frauenfelder T. A simple method to approximate liver size on cross-sectional images using liver models. *Clin Radiol*. 2009;64(7):682-689.
40. Hassuna NA, Elgezawy E, Mousa SO, et al. Diagnostic value of monocyte chemoattractant Protein-1, soluble mannose receptor, Presepsin, and Procalcitonin in critically ill children admitted with suspected sepsis. *BMC Pediatr*. 2021;21(1):458.
41. Relster MM, Gaini S, Moller HJ, Johansen IS, Pedersen C. The macrophage activation marker sMR as a diagnostic and prognostic marker in patients with acute infectious disease with or without sepsis. *Scand J Clin Lab Invest*. 2018;78(3):180-186.
42. Hagert C, Sareila O, Kelkka T, Jalkanen S, Holmdahl R. The macrophage mannose receptor regulate mannan-induced psoriasis, psoriatic arthritis and rheumatoid arthritis-like disease models. *Front Immunol*. 2018;9:114.
43. Tentolouris A, Ntanasis-Stathopoulos I, Terpos E. Obesity and multiple myeloma: emerging mechanisms and perspectives. *Semin Cancer Biol*. 2023;92:45-60.
44. Zhang XS, Brondyk W, Lydon JT, Thurberg BL, Piepenhagen PA. Biotherapeutic target or sink: analysis of the macrophage mannose receptor tissue distribution in murine models of lysosomal storage diseases. *J Inherit Metab Dis*. 2011;34:795-809.

How to cite this article: Beaton B, Hughes DA. Soluble mannose receptor: A potential biomarker in Gaucher disease. *Eur J Haematol*. 2024;1-8. doi:10.1111/ejh.14171.