

Modelling the evolution of two biomarkers in Gaucher patients receiving enzyme replacement therapy

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CONTEXT

Gaucher disease (GD)

- Rare recessively inherited disorder due to deficiency of lysosomal enzyme glucocerebrosidase [1]
- Accumulation of glucosylceramide in macrophages
- This accumulation leads to the increase in several biomarkers: ferritin, chitotriosidase
- Patients suffer from bone events: bone infarcts, osteonecrosis, fractures

Enzyme Replacement Therapy (ERT)

- Imiglucerase (Alglucerase from 1991 to 1996)
- Normalized glucosylceramide
- No physiopathological model has been proposed to analyse the evolution of biomarkers during ERT [2,3]

OBJECTIVES

- To develop a drug-disease model explaining the response of biomarkers to ERT
- To analyze the influence of several covariates on their evolution

METHODS

Data

- Patients from the French Registry on GD [4] treated by ERT, N=238
- Evaluation of two biomarkers: serum ferritin and chitotriosidase activity
- All measurements since initiation of ERT to stop of ERT (more than 6 months) or end of follow-up

Structural Model

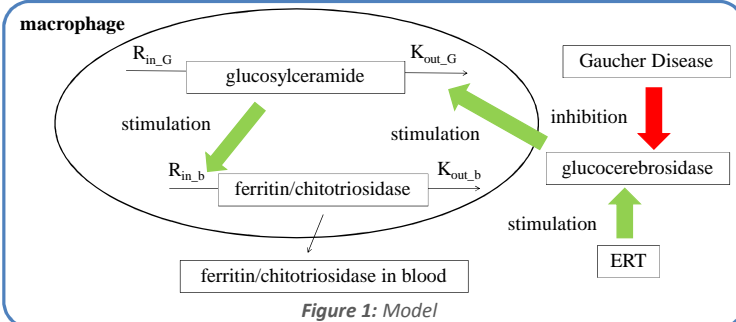


Figure 1: Model

- Half-life of biomarkers are very short compared to disease evolution, so they are neglected
- The model for ferritin (F) or chitotriosidase (C) is:

$$C(t) = C_0[r + (1 - r)\exp(-kt)]$$
 - where C_0 : initial concentration
 - r: amplitude of biomarkers decrease
 - k: rate constant of glucosylceramide normalisation under ERT

Model building

- Non linear mixed effect model
- Exponential model for random effect
- First step: separate analysis of each biomarker
- Second step: joint analysis, evaluation whether one or several parameters are correlated
- Selection of covariates on the joint model with backward selection: age at initiation of ERT, splenectomy before ERT, gender, genotype, dose at initiation of ERT, presence of bone events before ERT
- Estimation was performed with MONOLIX v4.2.0 [5]

RESULTS

Data

- N=176 patients with data on ferritin or chitotriosidase
- Patients are followed up during (median (min-max)): 7 (0-19) years after initiation of ERT
- 51 % are male, 18 % were <15 years at initiation of ERT, 11 % are homozygous for the mutation N370S
- 18 % had bone events or bone manifestations before ERT, 49% had splenectomy before ERT

ERT

- Infusion every 2 weeks
- Median (min-max) dose per month at initiation: 120 (29-240) UI/kg
- 80 % of the patient received 120 UI/kg/month

Model fitting and goodness-of-fit evaluation

Table 1: Study Population

	Ferritin (F)	Chitotriosidase (C)
N	138	155
Number of observation	602	624
Median (min-max) per patient	3 (1-22)	3 (1-24)

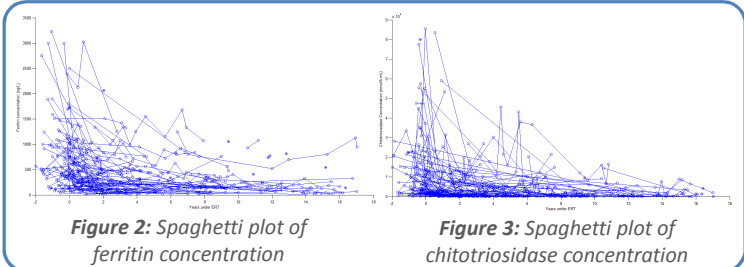


Figure 2: Spaghetti plot of ferritin concentration

Figure 3: Spaghetti plot of chitotriosidase concentration

- Best model with similar rate constant of glucosylceramide normalization

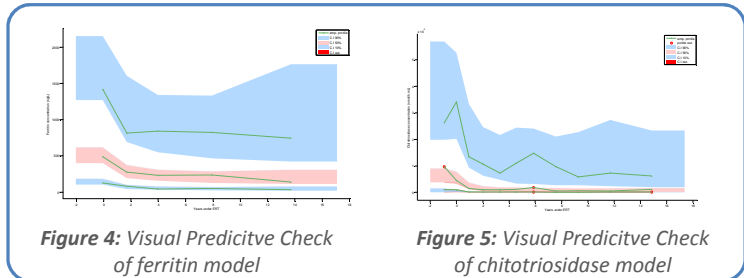


Figure 4: Visual Predictive Check of ferritin model

Figure 5: Visual Predictive Check of chitotriosidase model

- The model adequately describes evolution of both biomarkers

Parameter estimation and relative standard errors (RSE%)

Table 2: Values of fixed effects and variabilities

Fixed effects	Estimates	RSE (%)	Variabilities	Estimates	RSE (%)
k (years ⁻¹)	1.04	17	ω_k	1.25	14
C_{OF} (ng/L)	611	8	$\omega_{C_{OF}}$	0.86	7
C_{OC} (nmol/h.mL)	7.23 10 ³	11	$\omega_{C_{OC}}$	1.21	7
r_F	0.29	10	ω_{r_F}	0.74	10
r_C	0.08	16	ω_{r_C}	1.20	11
			b_F	0.29	4
			b_C	0.6	4

- Parameters are estimated with a good precision
- Half-life of glucosylceramide normalization under treatment: 0.67 years
- Asymptotic normalized ferritin value: 177 ng/L
- Asymptotic normalized chitotriosidase value: 578 nmol/h.mL

Covariate analysis

- 3 significant effects of covariates

Table 3: Effect of age at initiation of ERT

	<15 years	>15 years	p
C_{OF} (ng/L) (rse%)	193 (17%)	726 (8%)	<0.01
C_{OC} (nmol/h.mL) (rse%)	11300 (26%)	7080 (13%)	0.03

r_F : 0.16 (15%) if splenectomized women vs 0.47 (10%), p<0.01

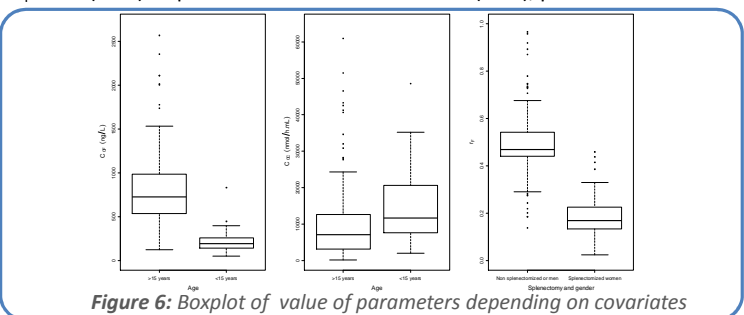


Figure 6: Boxplot of value of parameters depending on covariates

- No effect of ERT dose was found

CONCLUSION

- This is the first study of the evolution of biomarkers in GD using a dynamic model
- Perspectives:
 - Modelling evolution of haemoglobin and platelets
 - Studying the link with clinically relevant repeated bone events [4]