Pharmacodynamic model of the evolution of biomarkers and analysis of repeated bone events in Gaucher Disease patients

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Gaucher Disease (GD)

- Rare recessive inherited disorder due to deficiency of lysosomal enzyme glucocerebrosidase
- Accumulation of glucosylceramide in macrophage
- Leads to abnormal concentrations of different biomarkers
- Patients suffer from bone events: bone infarcts, osteonecrosis, fractures...
- French Registry on GD\(^1\): 562 patients

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Treatment

- Enzyme Replacement Therapy (ERT): imiglucerase
- Normalized glucosylceramide
- Normalized biomarkers under ERT
  - Serum ferritin
  - Chitotriosidase activity
- Cohort of treated patients in the French Registry
  - Repeated measurements of biomarkers
  - Presence of bone events

$\Rightarrow$ No physiological model has been proposed to analyze the evolution of biomarkers$^2$

Objectives

1. To develop a drug-disease model explaining the response of two biomarkers to ERT

2. To analyze the occurrence of repeated bone events
   ⇒ Analysis of response to ERT and of effect of several covariates
Patients characteristics

- 176 patients with data on ferritin or chitotriosidase under ERT
- ERT: infusion every 2 weeks
- Patients are followed during: 7 (0-19) years after initiation of ERT
- Analysis of all measurements since initiation of ERT until stop of ERT/end of follow-up
- Covariates
  - Sexe: 51% are male
  - Age: 18% were under 15 years old at ERT initiation
  - Genotype: 11% are homozygotous for the mutation N370S
  - Splenectomy: 49% had a splenectomy before ERT
  - Dose of ERT: 120 (29-240) UI/kg
  - Dose of ERT greater than 120 UI/kg: 80%
Deficiency of lysosomal enzyme glucocerebrosidase
- Accumulation of glucosylceramide
- Leads to the increase of biomarkers
Non linear mixed effect models

For i = 1,...,N patients, $y_{ij}$ concentration of biomarker of individual i at time j (j = 1,...,$n_i$)

$$y_{ij} = f(t_{ij}, \psi_i)(1 + \varepsilon_{ij})$$

- $f$: structural model
- $\psi_i$: individual parameters

$$\psi_i = \mu \exp(\eta_i)$$

- $\mu$: fixed effects
- $\eta_i$: random effect, $\eta_i \sim N(0, \Omega)$
  - $\Omega$: variance-covariance matrix
- $\varepsilon_{ij}$: random variable of error model, $\varepsilon_{ij} \sim N(0, \sigma^2)$
Model building

Half-life of biomarkers are very short compared to disease evolution, and are neglected

\[ f(t_{ij}, \psi_i) = C(t) = C_0[r + (1 - r) \exp(-kt)] \]

- \( C_0 \): initial concentration
- \( r \): amplitude of biomarkers decrease
- \( k \): rate constant of glucosylceramide normalization under ERT

Vector of parameters: 
\((C_0, r, k)\)
Model building (2)

- Separate analyses of each biomarker
  - Choose the best model
  - Compare models using BIC
- Joint analysis of the two biomarkers
  - Evaluation whether one or several parameters are correlated
  - Selection of covariates with LRT
- Estimation were performed with SAEM algorithm in MONOLIX$^3$
v4.2.0 and likelihood computed with Importance Sampling

## Data

<table>
<thead>
<tr>
<th></th>
<th>Ferritin</th>
<th>Chitotriosidase</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>138</td>
<td>155</td>
</tr>
<tr>
<td>Number of observations</td>
<td>602</td>
<td>624</td>
</tr>
<tr>
<td>Median per patient</td>
<td>3 (1-22)</td>
<td>3 (1-24)</td>
</tr>
</tbody>
</table>

Serum ferritin

Chitotriosidase activity
### Parameters estimation

- **Best model with similar rate constant of glucosylceramide normalization** (BIC= 19018 vs. 19034)

<table>
<thead>
<tr>
<th>Fixed effects</th>
<th>Estimates</th>
<th>RSE (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>$k \ (\text{years}^{-1})$</td>
<td>1.04</td>
<td>17</td>
</tr>
<tr>
<td>$C_{0F} \ (\text{ng/L})$</td>
<td>611</td>
<td>8</td>
</tr>
<tr>
<td>$C_{0C} \ (\text{nmol/h.mL})$</td>
<td>$7.23 \times 10^3$</td>
<td>11</td>
</tr>
<tr>
<td>$r_F$</td>
<td>0.29</td>
<td>10</td>
</tr>
<tr>
<td>$r_C$</td>
<td>0.08</td>
<td>6</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Variabilities</th>
<th>Estimates</th>
<th>RSE (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>$\omega_k$</td>
<td>1.25</td>
<td>14</td>
</tr>
<tr>
<td>$\omega_{C_{0F}}$</td>
<td>0.86</td>
<td>7</td>
</tr>
<tr>
<td>$\omega_{C_{0C}}$</td>
<td>1.21</td>
<td>7</td>
</tr>
<tr>
<td>$\omega_{r_F}$</td>
<td>0.74</td>
<td>10</td>
</tr>
<tr>
<td>$\omega_{r_C}$</td>
<td>1.20</td>
<td>11</td>
</tr>
<tr>
<td>$\sigma_F$</td>
<td>0.29</td>
<td>4</td>
</tr>
<tr>
<td>$\sigma_C$</td>
<td>0.6</td>
<td>4</td>
</tr>
</tbody>
</table>

- **Half-life of glucosylceramide normalization under ERT**: 0.67 year
- **Normalized ferritin value**: 177 ng/L
- **Normalized chitotriiosidase value**: 578 nmol/h.mL
Individually fits

Serum ferritin

Chitotriosidase activity
Individual weighted residuals

Serum ferritin

Chitotriosidase activity
Visual Predictive Check

Serum ferritin

Chitotriosidase activity
## Covariate analysis

- **3 significant effects**

<table>
<thead>
<tr>
<th></th>
<th>&lt; 15 years</th>
<th>&gt; 15 years</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>$C_{0F}$ (rse %)</td>
<td>193 (17%)</td>
<td>726 (8%)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>$C_{0C}$ (rse %)</td>
<td>11300 (26%)</td>
<td>7080 (13%)</td>
<td>0.03</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Splenectomized women</th>
<th>Non splenectomized or men</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>$r_F$ (rse %)</td>
<td>0.16 (15%)</td>
<td>0.47 (10%)</td>
</tr>
</tbody>
</table>

![Box plots](image1.png)  
![Box plots](image2.png)  
![Box plots](image3.png)
Frailty model

For i=1,...,N patients

$T_{ij}$ time of $j^{th}$ events (j=1,...,$n_i$)

$T_{in}$ censure

- $\lambda(t_{ij})$ parametric hazard function

$$\lambda(t_{ij}) = \lambda_0(t_{ij}) \exp(b_i + \beta Z_i)$$

- $b_i$: random effect $\sim N(0, \omega^2)$
- $Z_i$: covariate vector
- $\beta$: vector of regression parameter

$\Rightarrow$ Exponential model $\lambda_0(t_{ij}) = \lambda$
Model building

- Studied of covariates
  - Similar covariates as before
  - Estimated individual random effects of ferritin and chitotriosidase from biomarkers modelling: $C_0, r, k$

- Selection using LRT

- SAEM algorithm in MONOLIX has already been evaluated for frailty models\textsuperscript{4}

- Estimation were performed using SAEM algorithm in MONOLIX v4.2.0 and likelihood computed with Importance Sampling

\textsuperscript{4} Vigan M et al., \textit{44\textsuperscript{ème} Journées de Statistiques}, mai 2012.
176 patients: 33 patients with bone events, total number 48 median number per patient: 0 (0-4)
Estimated parameters

- Without covariate

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Estimates</th>
<th>RSE (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>$\lambda$ years$^{-1}$</td>
<td>0.016</td>
<td>25</td>
</tr>
<tr>
<td>$\omega$</td>
<td>1.02</td>
<td>16</td>
</tr>
</tbody>
</table>

Probability of an event during the first 10 years: 14.8 %
Covariate analysis

- 2 significant effects

<table>
<thead>
<tr>
<th>Covariate</th>
<th>HR</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age &lt; 15 years vs. &gt; 15 years</td>
<td>9</td>
<td>0.007</td>
</tr>
<tr>
<td>Chitotriosidase increase of 10 nmol/h.mL</td>
<td>100</td>
<td>0.013</td>
</tr>
</tbody>
</table>

![Graph showing lambda vs. eta_C_OC (ng/L) with two clusters: one for >15 years and another for <15 years.]
Conclusion

- First study of the biomarkers evolution in GD using a dynamic model
- Similar rate constant of glucosylceramide normalization
- Effect of age below 15 years at initiation of ERT
- Perspectives
  - Modelling evolution of haemoglobin and platelets
  - Joint modelling of biomarkers and repeated bone events
Thank you for your attention!

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