Population Pharmacodynamics of Cladribine Tablets Therapy in Patients with Multiple Sclerosis: Relationship between Magnetic Resonance Imaging and Clinical Outcomes

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Relapsing forms of multiple sclerosis (MS) are characterized by:

- Unpredictable periods of remission
- Slow disease progression
- Substantial inter-patient variability
- Poorly-understood relationship with biomarkers (MRI)

Making it a challenge to quantify effects of therapies on disease progression dynamics
Aim

- We previously developed NLME models to characterize the effect of cladribine tablets on clinical outcomes in patients with relapsing–remitting multiple sclerosis\(^1\)–\(^2\)

- These models allow predictions of relapse rate dynamics and disability progression based on an individual’s disease activity, baseline characteristics, renal clearance and cladribine dose

AIM

- To integrate key MRI readouts into models relating cladribine exposure to clinical efficacy, and delineate the poorly-understood relationship between MRI and clinical markers of MS progression

NLME, nonlinear mixed-effects

1. Savic R et al. ECTRIMS 2010 (Poster P477);  
2. Savic R et al. ACoP 2011 (Poster M-9-5)
Data, clinical endpoints, biomarkers

- **Data**
  - (i) CLARITY trial (96 weeks)
    - 1,326 patients with relapsing–remitting MS
    - 3 arms (placebo or cladribine tablets at cumulative doses of 3.5 and 5.25 mg/kg over 96 weeks, given as 4 and 6 short 4–5-day courses)
  - (ii) OWIMS trial (48 weeks) and PRISMS trial (96 weeks)
    - Additional 287 placebo patients with relapsing–remitting MS

- **Clinical endpoints**
  - Expanded Disability Status Scale (EDSS) score
    - Categorical variable (0–10 scale, with 0.5-point increments)
  - Relapse rate
    - Repeated time-to-event variable (up to 6 relapses, over 96 weeks)

- **MRI Biomarkers**
  - I. T2 lesion volume – burden of disease (BOD) (continuous variable)
  - II. Combined unique (CU) lesion count (count variable)
Modeling strategy

(i) Develop population models for time course of biomarkers (with covariates)
   • CU model
   • BOD model

(ii) Link the time course of biomarkers with the time course of clinical endpoints

Final aim: establish predictive models for 2 major clinical endpoints:
1) Exposure – MRI BOD – EDSS
2) Exposure – MRI CU lesions – relapse rate (RR)
STEP I: MODEL DEVELOPMENT FOR BIOMARKERS
Raw data

Large variability, skewed baseline

Large variability in placebo group, variability decreased with cladribine
Modeling strategy

- Development of the placebo model
  - Constant vs time changes
  - CU lesions: choice of count data model (overdispersion)

<table>
<thead>
<tr>
<th>Count model</th>
<th>Data</th>
<th># of parameters</th>
<th>Parameters</th>
<th>OFV</th>
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<td>$\lambda$, IIV ($\lambda$), OVDP, IIV (OVDP)</td>
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</tbody>
</table>

- Development of the drug model

OVDP, overdispersion factor
General MRI model

\[ \text{Eff} = \frac{E_{\max} \times \text{Exps}}{\text{Exps}_{50} + \text{Exps}} \]

\[ \text{Exps} = \frac{\text{CD} \times CL_{CR\_median}}{CL_{CR}} \]

- \( E_{\max} \): maximum effect
- \( \text{Exps} \): exposure
- \( \text{Exps}_{50} \): exposure needed for half maximal effect
- \( \text{CD} \): cumulative dose
- \( k_{in} \): production rate constant
- \( k_{out} \): elimination rate constant
- \( CL_{CR} \): creatinine clearance
- \( CL_{CR\_median} \): median creatinine clearance
- \( \text{Eff} \): drug effect

\( \text{CdA} \), cladribine
**Covariate model for biomarkers**

**BOD**

1. Baseline EDSS, MSD and age on baseline BOD ($\Delta$OFV=95, 35 and 26)
   - BOD increases with greater baseline EDSS and duration of disease, and decreases with greater age

   \[ \text{BOD}_0 = \theta_1 \cdot (1 + 0.185 \cdot (\text{BASE} - 2.5)) \cdot (1 + 0.0364 \cdot (\text{MSD} - 6.22)) \cdot (1 - 0.15 \cdot (\text{Age} - 38)) \]

2. Age on Emax ($\Delta$OFV=22)
   - Emax decreases with greater age

   \[ \text{Emax} = \theta_2 \cdot (1 - 0.027 \cdot (\text{Age} - 38)) \]

**CU lesions**

1. AGE on mean count ($\Delta$OFV=110)

   \[ \lambda = \theta_1 \cdot (1 - 0.0348 \cdot (\text{Age} - 38)) \]

2. SEX on EC50 ($\Delta$OFV=8): lower EC50 in men

MSD, duration of disease
Diagnostics: visual predictive check (BOD)
STEP II: BIOMARKER – CLINICAL ENDPOINTS MODELS
Clinical endpoint I: EDSS disease progression model for MS

**DISEASE PROGRESSION MODEL**
- Linear model where baseline ($EDSS_0$) and disease progression rate ($SL$) are estimated from the data
- Strong correlation $EDSS_0 \sim SL$
- $EDSS_0$ related to patient age and disease duration

**EXPOSURE – RESPONSE MODEL**
- Dual effect: disease-modifying and symptomatic

$$EDSS_t = EDSS_0 + (1 - EffP) \times SL \times \frac{10 - EDSS_0}{2 \times 365} \times TIME \times (1 - EffS)$$

$$EffS = \frac{E_{max} \times Exps_i}{Exps_{50} + Exps_i}$$

$$Exps = \frac{CumDose \times CL_{CR,median}}{CL_{CR}}$$
Exploratory analysis

Observed EDSS vs predicted BOD

<table>
<thead>
<tr>
<th>Placebo</th>
<th>3.5 mg/kg</th>
<th>5.25 mg/kg</th>
</tr>
</thead>
</table>

EDSS score vs BOD (model prediction)
Joint MRI burden of disease – EDSS model

\[ \text{Eff} = \frac{E_{\text{max}} \times \text{Exps}}{\text{Exps}_{50} + \text{Exps}} \]

\[ \text{Exps} = \frac{CD \times CL_{\text{CR,median}}}{CL_{\text{CR}}} \]

\[ \text{EDSS}_t = \left[ \text{EDSS}_0 \times S\text{0MRI} + (1 - \text{EffP}) \times \frac{SL \times (10 - \text{EDSS}_0) \times \text{TIME}}{2 \times 365} \right] \times (1 - \text{EffS}) \]

\[ S\text{0MRI} = 1 + \text{LNK} \times \left[ \ln(\text{BOD}) - 9.21 \right] \]

CdA, cladribine; MSD, duration of disease
## Overview of key models

The overview of likelihood comparison for some of the tested models

<table>
<thead>
<tr>
<th>Model</th>
<th>-2*log(likelihood)</th>
</tr>
</thead>
<tbody>
<tr>
<td>EDSS model, with drug exposure</td>
<td>5961</td>
</tr>
<tr>
<td>EDSS model, with BOD</td>
<td>5929</td>
</tr>
<tr>
<td>EDSS model, with BOD and drug exposure</td>
<td>5878</td>
</tr>
</tbody>
</table>
Disease progression model with BOD and drug effect

- Placebo
- Cladribine tablets 3.5 mg/kg
- Cladribine tablets 5.25 mg/kg

EDSS score vs. Time (days)
Clinical endpoint II: relapse rate

Baseline hazard (placebo model with covariate effect)

\[ HZ_t = HZ_0 \times COVH \times \gamma \times (HZ_0 \times t)^\gamma^{-1} \]

\[ COVH = 1 + SI \times (EXBN - EXBN_{median}) \]

- \( HZ_0 \) = baseline hazard
- \( HZ_t \) = instantaneous hazard at time \( t \)
- \( \gamma \) = shape factor
- \( SI \) = slope of \( EXBN - HZ_t \) relationship
- \( EXBN \) = # relapses in the year prior to study

Baseline disease activity = # relapses one year prior to study
Joint MRI CU lesions – relapse rate model

\[ HZ_t = HZ_0 \times COVH \times BIOM \times (1 - Eff_{rr}) \times \gamma \times (HZ_0 \times t)^{\gamma-1} \]

\[ Eff_{cu} = \frac{E_{max} \times Exps_{cu}}{Exps_{cu50} + Exps_{cu}} \]

\[ Exps_{cu} = \frac{CD \times CL_{CR\_median}}{CL_{CR}} \]

\[ BiOM = 1 + LNK1 \times (CU_{lesion} - CU_{lesion\_median}) \]

\[ CD \] = cumulative dose
\[ Exps \] = exposure
\[ k_{in} \] = production rate constant
\[ k_{out} \] = elimination rate constant
\[ CL_{CR} \] = creatinine clearance
\[ CL_{CR\_median} \] = median creatinine clearance
\[ Eff \] = drug effect
\[ Exps_{50} \] = exposure needed for half maximal effect
\[ LNK1 \] = coefficient of CU – RR relationship
\[ HZ_0 \] = baseline hazard
\[ HZ_t \] = instantaneous hazard at time \( t \)
\[ \gamma \] = shape factor

CdA, cladribine
## Overview of key final RR and CU models

<table>
<thead>
<tr>
<th>Model</th>
<th>-2*log(likelihood)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Final RR model, without CU lesions</td>
<td>7816</td>
</tr>
<tr>
<td>Final CU lesion model</td>
<td>7070</td>
</tr>
<tr>
<td>Joint CU and RR model with link</td>
<td>14850 &lt;7070 + 7816 = 14886</td>
</tr>
</tbody>
</table>
Visual predictive check: joint CU and RR model

The blue line represents the observed Kaplan-Meier curve; the orange shaded area displays 90% prediction intervals derived from model simulations. Probability relapse-free is defined as percentage of patients not experiencing 1 (upper), 2 (middle), or 3 (lower) relapses.
Conclusions

- Despite major technical challenges and poor mechanistic understanding about MRI–clinical outcome relationships, links between MRI lesion dynamics and clinical endpoints were established.

- The proposed exposure–biomarker–clinical endpoints models integrate a significant amount of knowledge and data, representing a useful platform for quantitative understanding of the MS time course.
Disclosures and acknowledgments

- This study was funded by Merck Serono S.A. – Geneva, Switzerland*

- R Savic and M Karlsson are paid consultants for Merck Serono S.A.*

- A Munafo is an employee of Merck Serono S.A.*

- Cladribine tablets treatment is not approved in the USA. Marketing authorization for the use of cladribine tablets in patients with RRMS has been granted in Russia and Australia (2010). Please refer to full prescribing information for further details on use.

*An affiliate of Merck KGaA, Darmstadt, Germany
BOD predictions w/ and w/o EDSS0 as covariate