A Semi-mechanistic Model of Lymphocyte Dynamics in Patients with Multiple Sclerosis Treated with Cladribine Tablets

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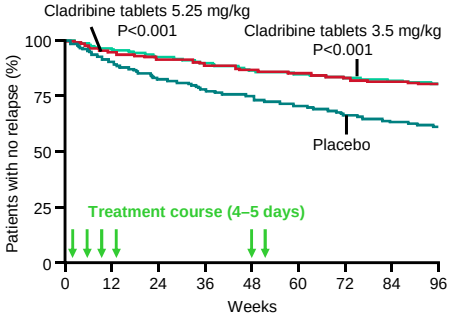
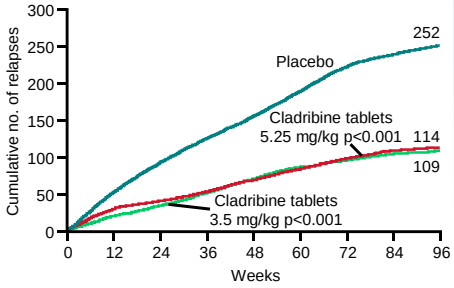
Cladribine tablets: effective in multiple sclerosis (MS)

- Cladribine selectively reduces peripheral lymphocyte counts
- Evaluated in the 96-week, parallel group, double-blind phase III CLARITY trial (1,326 patients)
  - Placebo
  - Cumulative dose 3.5 mg/kg ➔ 4 courses (Weeks 1, 5, 48 and 52)
  - Cumulative dose 5.25 mg/kg ➔ 6 courses (Weeks 1, 5, 9, 13, 48 and 52)





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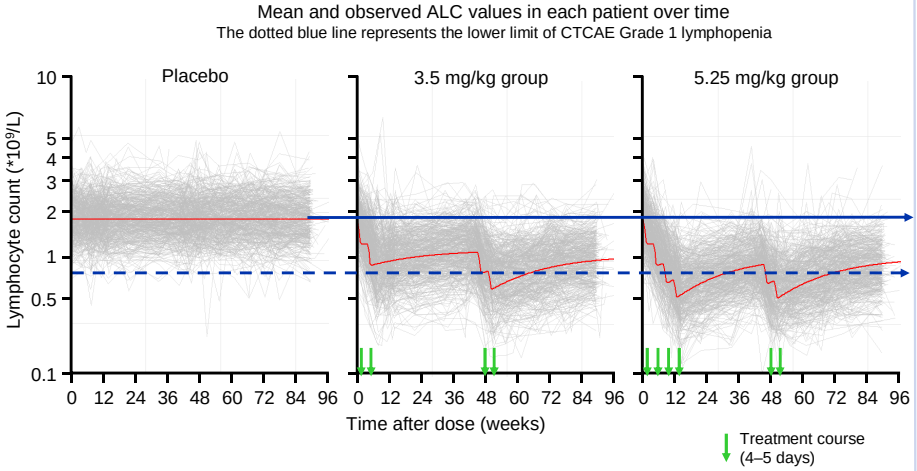
Giovannoni G, *et al. N Engl J Med* 2010;362(5):416–26

Most common adverse event: lymphocytopenia

- Lymphocytopenia was mostly graded as mild or moderate
- Infection rates may increase with severe lymphocytopenia (below CTCAE Grade 2)



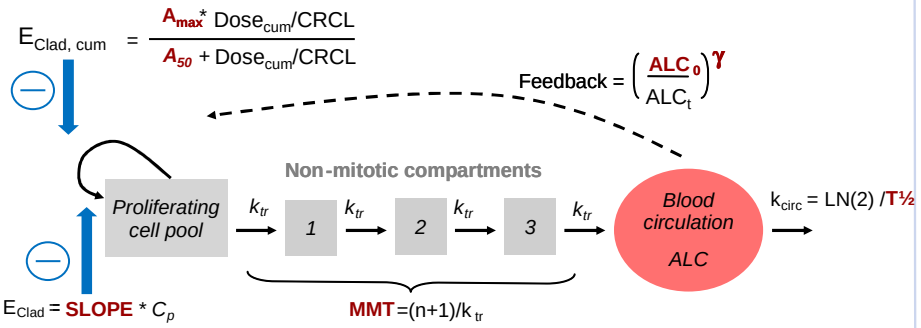
ALC, absolute lymphocyte count; CTCAE, Common Terminology Criteria for Adverse Events

Rationale and objectives of ALC model and simulator

- Treatment delay may be necessary in a few cases to allow recovery of ALC to above CTCAE Grade 2 and prevent the development of severe lymphopenia
  - Need for a tool to evaluate the potential impact of treatment delay
- Identify a predictive model for ALC
- Build a simulator for evaluation of
  - Lymphocyte dynamics in the rare cases of patients requiring treatment delay
  - Proportion of patients showing Grade 2 and over, and their recovery time
  - Percentage of patient completing treatments

Initial model for ALC

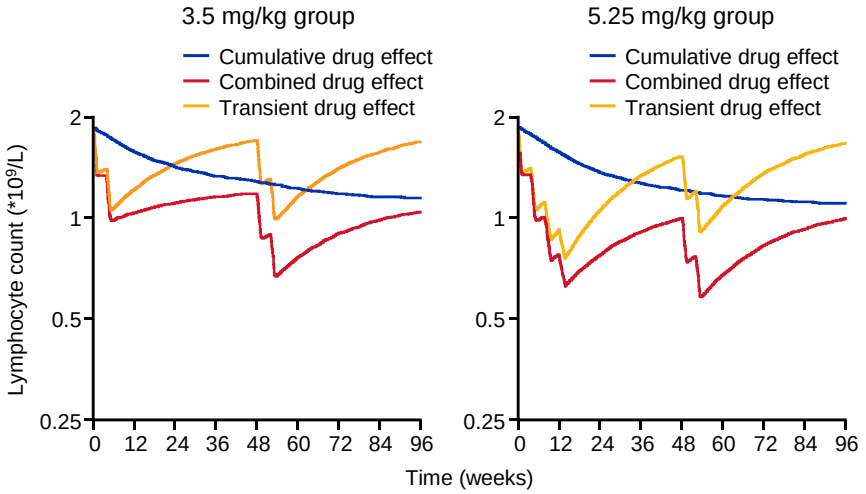
- Based on myelosuppression model[1]
  - Cladribine myelosuppression reversible effect
  - + Cumulative cladribine non-reversible effect
  - + Gender, body weight and creatinine clearance (CRCL) covariate influence



1. Friberg LE, *et al. J Clin Oncol* 2002;20:4713–21

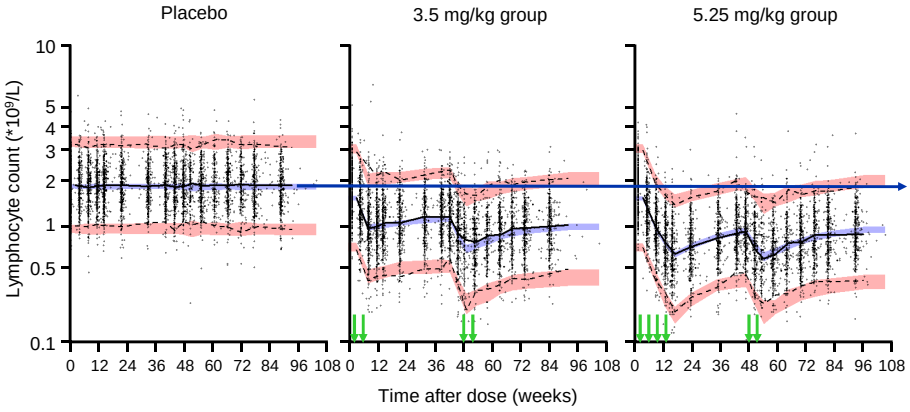
Typical prediction ALC versus time

(typical 67 kg female)



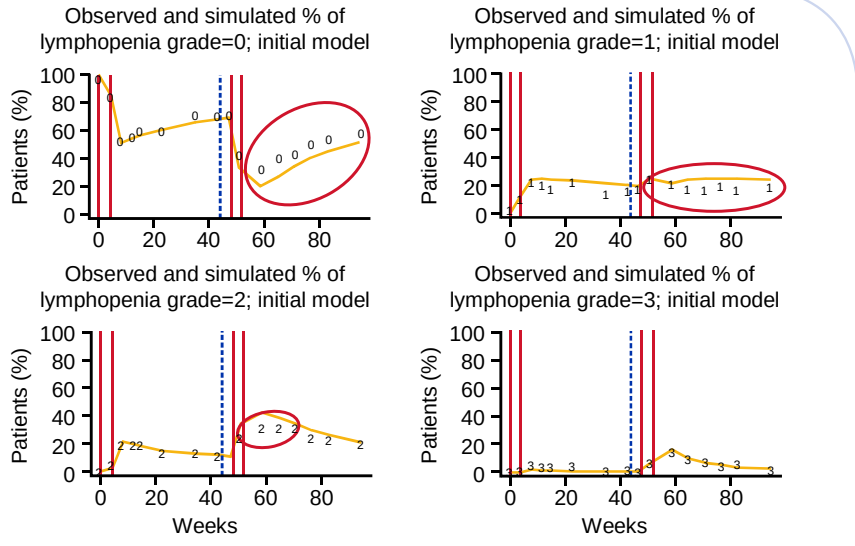
VPC looks OK ...

The model seems to adequately describe the data and its variability:
2.5, 50 and 97.5 percentiles of observed data and their model-derived 95% CI



CI, confidence interval; VPC, Visual Predictive Check

But NPC revealed over-estimation of lymphopenia after 1 year



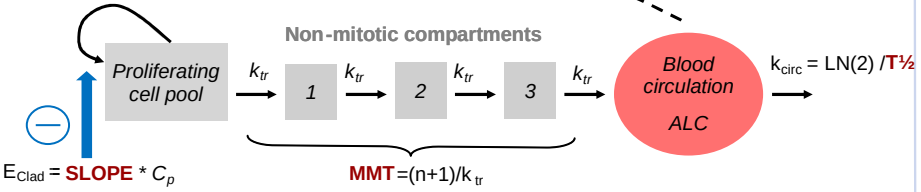
NPC, Numerical Predictive Check

Model update for ALC

- Cladribine myelosuppression reversible effect
- + Cumulative cladribine (formerly non-reversible) effect
- + Gender, body weight and CRCL covariate influence
- + Recovery on cumulative effect

$$E_{Clad,\,cum} = \frac{A_{max}^{*}\ \Sigma[Dose_{cum}/CRCL * e^{-K(t-Tdose)}]}{A_{50} + \Sigma[Dose_{cum}/CRCL * e^{-K(t-Tdose)}]}$$

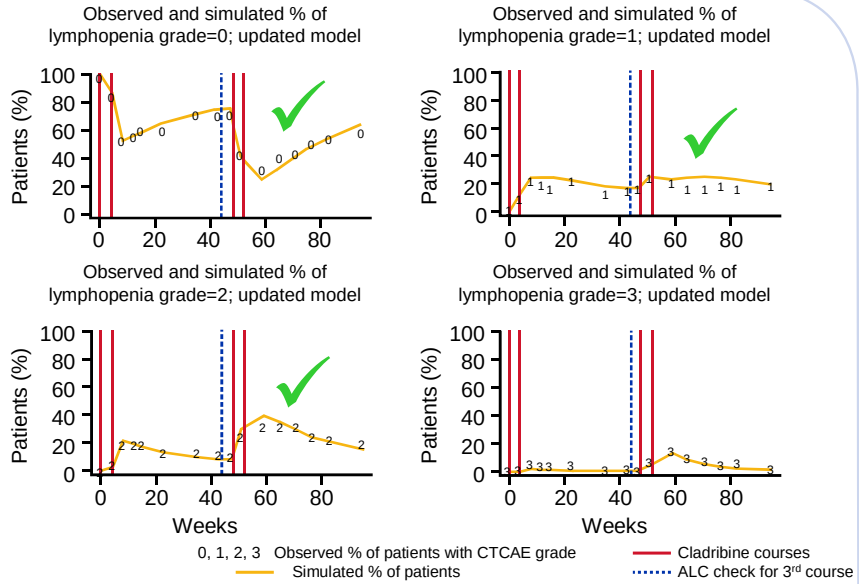
Feedback = $\left(\frac{ALC_0}{ALC_t}\right)^{\gamma}$



E_{Clad} = **SLOPE** * C_p

MMT =(n+1)/k_{tr}

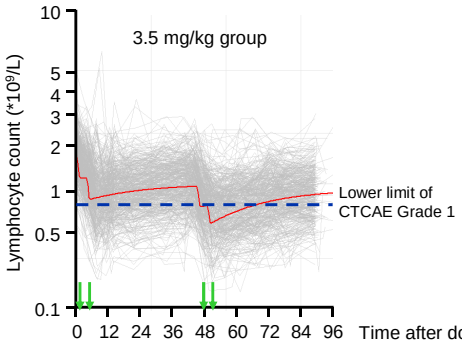
Model validation: with cumulative AUC recovery



Simulation of ALC model*

- Patients may in rare cases need to delay additional courses while their ALC recovers

Mean and observed ALC values in each patient over time



- **10,000 patients resampled from CLARITY study database for** gender, body weight, creatinine clearance and baseline ALC
- One course of treatment = 5 days of body-weight, dose-adjusted cladribine tablets
- No more than 4 courses of treatment per 48 weeks

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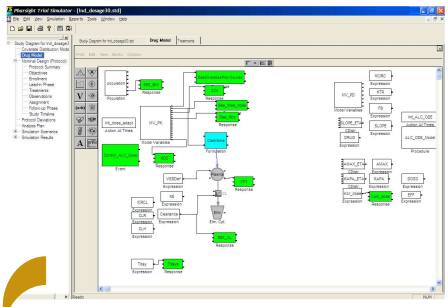
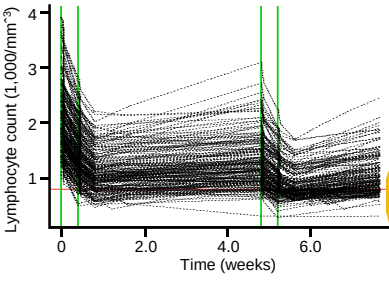
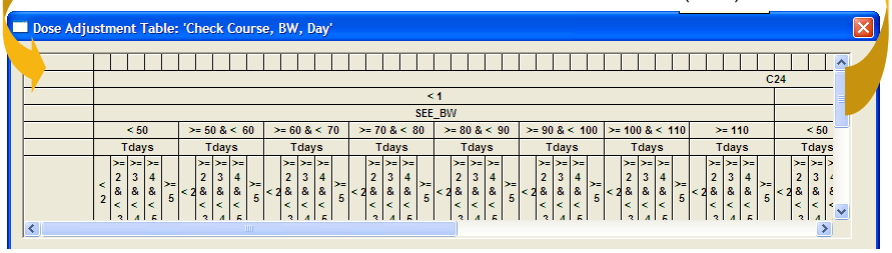
*TS2 (Pharsight, under Windows XP)

Model + patient resampling in TS2



200 simulated patients and nominal dose timings





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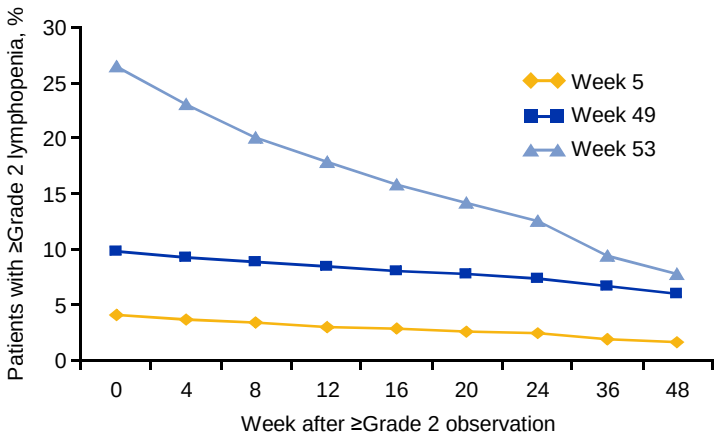
Simulation to estimate percentage of patients in CTCAE Grade 2 at start of courses 2 to 4, and their time to recovery



NB This simulation assumes that if ALC <800 / mm^3 at starting of 2nd, 3rd or 4th course, corresponding to weeks 5, 49 and 53, respectively, no more treatment is given

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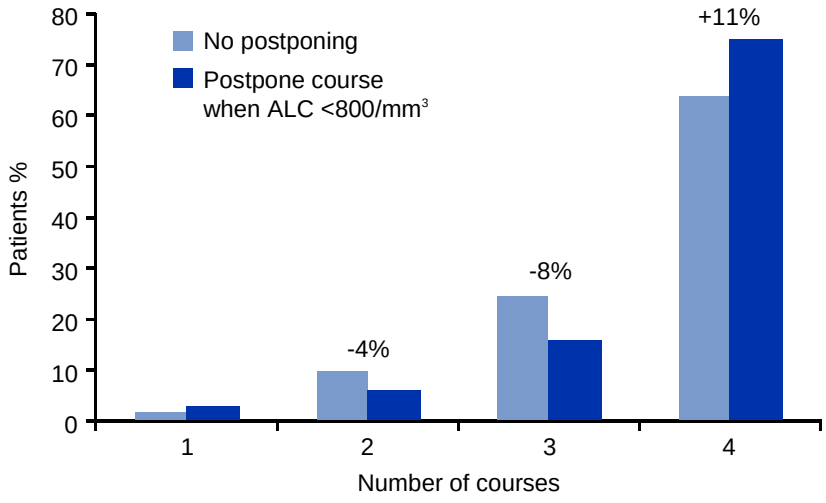
Proportion of patients achieving 1 to 4 courses (simulated data)



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Conclusions

- A model has been developed of lymphocyte dynamics with transient and slowly-recovering effect in patients with multiple sclerosis receiving cladribine tablets treatment
- The proposed model can be used to predict ALC dynamics in patients receiving cladribine tablets in a clinical trial or real-life setting
- Simulations allow exploration of
  - % of patients recovering to CTCAE Grade 1 and their recovery time
  - % of patients completing the full treatment (4 courses over 96 weeks)
- The ALC model is being coupled with an efficacy model
- It will be further refined with longer observation data

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- M Karlsson is a paid consultant for Merck Serono S.A.*
- A Munafo and P Girard are employees 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

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