DETERMINATION OF EFFECTIVE BLOOD CONCENTRATIONS OF CYCLOSPORINE IN PEDIATRIC SEVERE APLASTIC ANEMIA BASED ON TIME-TO-RESPONSE MODEL

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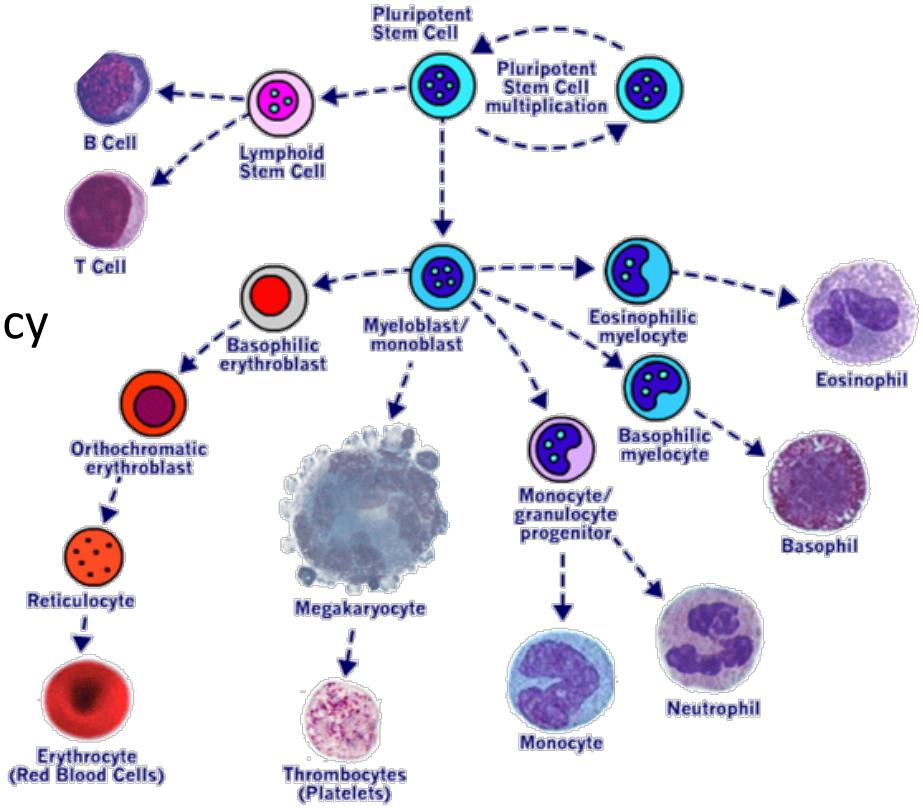
SEVERE APLASTIC ANEMIA

- Rare hematologic disease
  - Affecting 1-2 person per million population per year
  - Two incidence peaks: between 10 and 20 years old, over 60 years old

- Quantitative bone marrow insufficiency
  - Neutrophils < 0.5 G/L
  - Platelets < 20 G/L
  - Hemoglobin < 80 g/L



Camitta et al. Blood 1979

TREATMENT ALTERNATIVES

- Without treatment, the disease is fatal
  - Mainly from infectious diseases due to immunodepression
- **Bone marrow transplantation** from a matched sibling donor

  ⇒ 90% relapse-free survival
- **Immunosuppressive therapy (IST)**, if no geno-identical donor is available:
  - Anti-thymocyte globulin (ATG)
  - Cyclosporine (CsA)

  ⇒ 60-80% response at 6 months
  40% disease-free survival at 10 years
- If no response obtained within 6 months, **a pheno-identical allograft** from voluntary donors is considered

Kojima et al. Br J Hematol 2000; Kojima et al. Blood 2000; Führer et al. Blood 2005

CsA Therapeutic recommendations

- CsA has a narrow therapeutic margin and large variability in PK
  - Dose adaptation based on trough blood concentrations (TBC)

- No recommendation in SAA until 2006:
  - TBC Target arbitrarily chosen (within IHOP: 100-150 ng/mL)

- Since 2006, recommendations proposed:
  - TBC should be maintained between 200 and 400 ng/mL

CsA recommendations remain questionable

Not supported by any PK-PD data

Relationships between SAA physiopathology and CsA mechanism of action?

Scheinberg et al. N Engl J Med 2011

LEARNING FROM CLINICAL EXPERIENCE

- Three children experiencing initial failure to IST (no response at 6 months)
  - Considered for an allograft while decreasing CsA exposure
  - Neutrophil response obtained within a couple of weeks

- Increase of treatment failure (allograft) since new recommendations
  - Logistic regression for the probability of treatment failure

    ⇒ higher probability when average TBC > 130 ng/mL

Clinical data suggest that CsA exposure should be lowered…

SAA Pathophysiology – CsA mechanism of action

- Aplastic anemia results from an auto-immune process
  - **Regulatory T-cells (Treg) are deficient**, either in count or in function
  - Recently, it has been shown that Treg counts are reduced at SAA diagnosis
  - Treg count have been suggested as a prognostic factor for response to IST.

- CsA appears to have a **dual effect on Treg *in vivo*** :
  - At low concentration, CsA stimulates the Treg proliferation
  - At higher concentration, CsA inhibits their development

CsA dual effect is not considered in the current recommendations

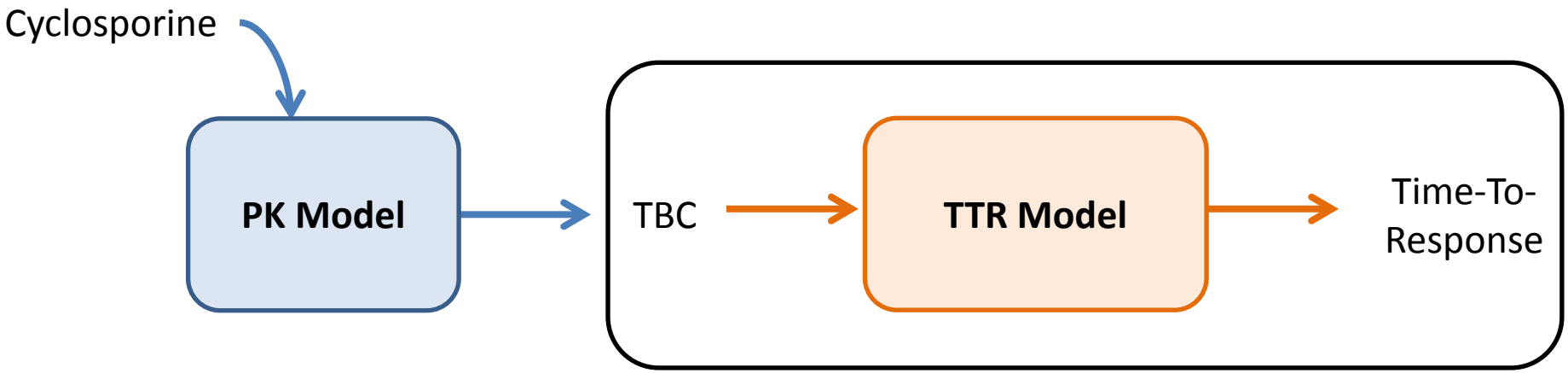
Motivation to explore PK-PD relationships

Solomou et al. Blood 2007; Sutton et al. Pediatr Blood Cancer 2013; Kordasti et al. Blood 2012

OBJECTIVES

Characterise the relationships between exposure to CsA and time-to-response

Determine the **effective range for CsA TBC** in children with SAA



Retrospective Analysis of 23 SAA Patients

- 23 SAA patients receiving CsA for up to 6 months
  - Treated in IHOP, Lyon, France, from 1998 to 2013
  - Aged 8.5 years (range: 8-15 years), weighting 34 kg (range: 9.8-72.3 kg)

- IST success = hematological response within 6 months
  IST failure = no hematological response at 6 months

  ⇒ considered for bone marrow transplantation

Time-to-Neutrophil response:

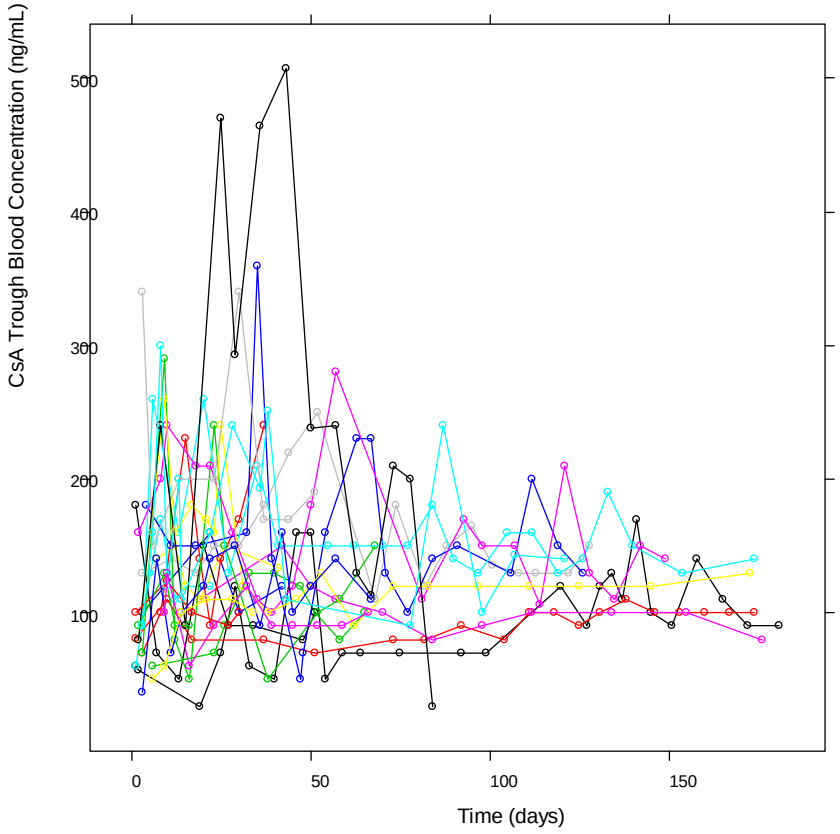
From CsA initiation…

… to 2 consecutive ANC observations above 0.5 x 10^9/L

ROUTINE CARE DATA FROM 23 SAA PATIENTS

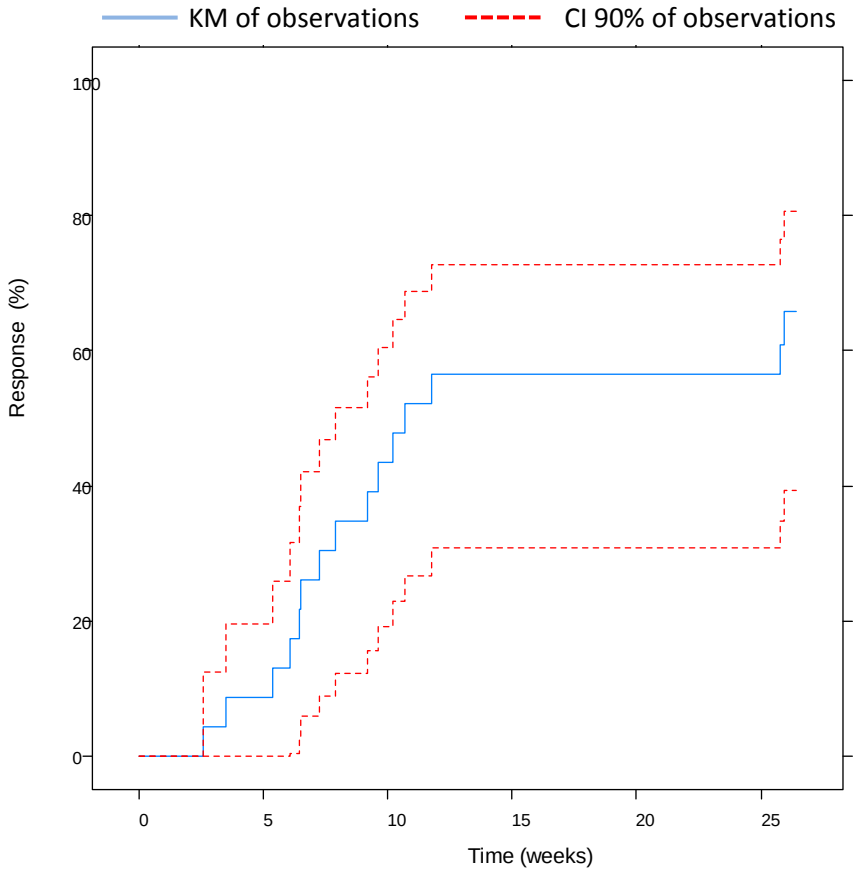
CSA TROUGH BLOOD CONCENTRATIONS

- CsA administered per os, every 12h
- 12 TBC (range 4-27) values per patient
- 96 days (range 19-183 days) follow-up



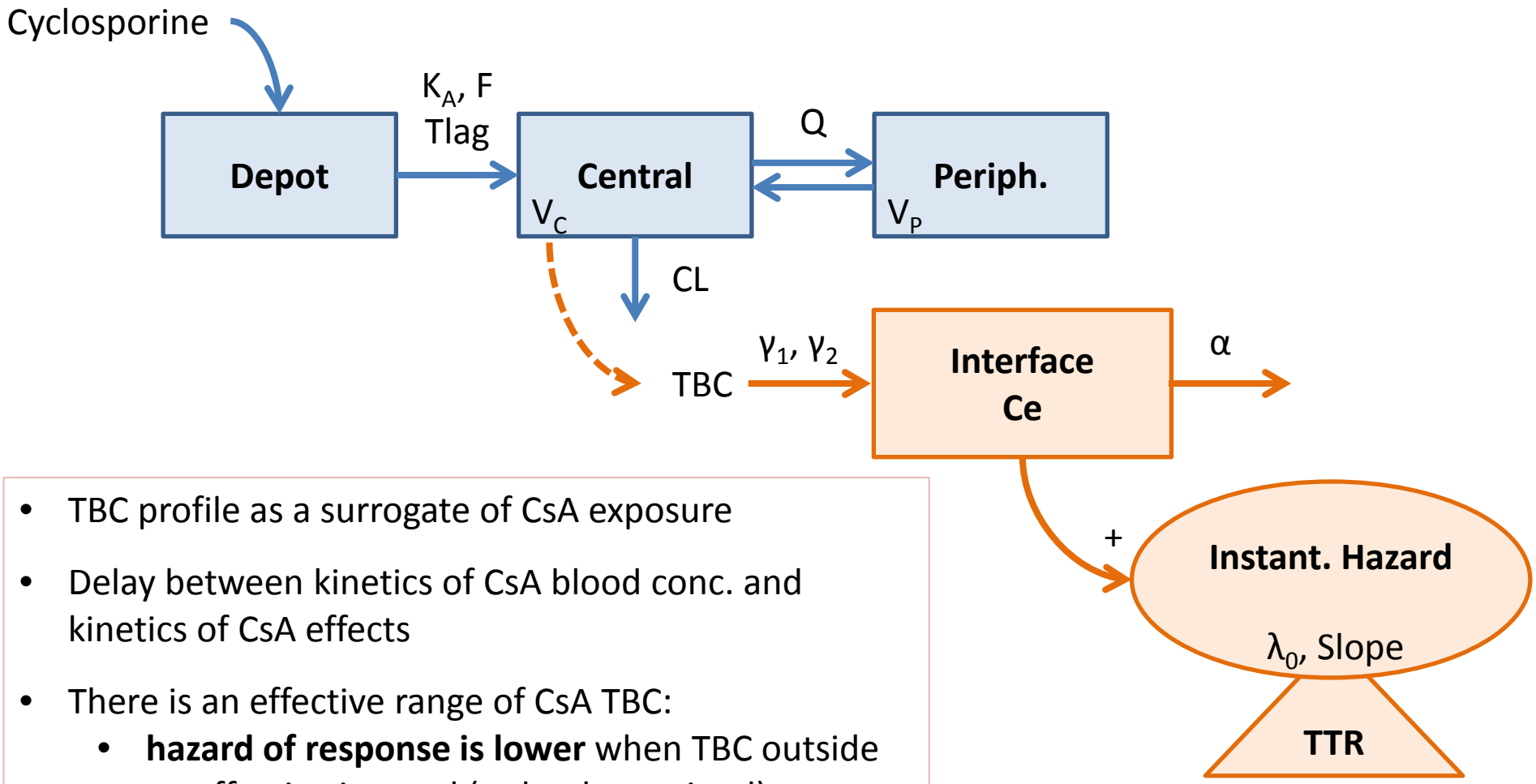
TIME-TO-NEUTROPHIL RESPONSE

- 15/23 patients (65%) responded at 6 months
- Median TTR: 69 days (range 19-182 days)



CSA TBC – TIME-TO-RESPONSE MODEL

CsA TBC – Time-To-Response Model



- TBC profile as a surrogate of CsA exposure
- Delay between kinetics of CsA blood conc. and kinetics of CsA effects
- There is an effective range of CsA TBC:
  - **hazard of response is lower** when TBC outside an effective interval (to be determined)
  - **hazard of response is maximal** for an optimal CsA TBC value (center of the interval)

EFFECTIVE CsA CONCENTRATION

Interface Model: non-linear effect compartment

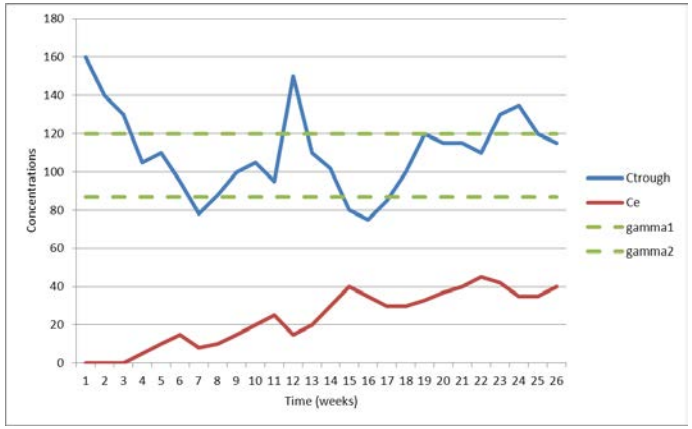
$$\frac{dC_e}{dt} = (TBC - \delta) \cdot \underbrace{H(TBC - \delta)}_{= 1 \quad if\ TBC > \delta \\ = 0 \quad otherwise} \quad - \underbrace{\alpha \cdot \exp(-\beta \times Ce) \cdot Ce}_{\text{linear elimination if } \beta=0}$$

Lower- (γ_1) and upper-bounds (γ_2) for the effective interval

$$\frac{dC_e}{dt} = \sqrt{(TBC - \gamma_1) \times (\gamma_2 - TBC) \cdot H1 \cdot H2} \quad - \alpha \cdot Ce$$

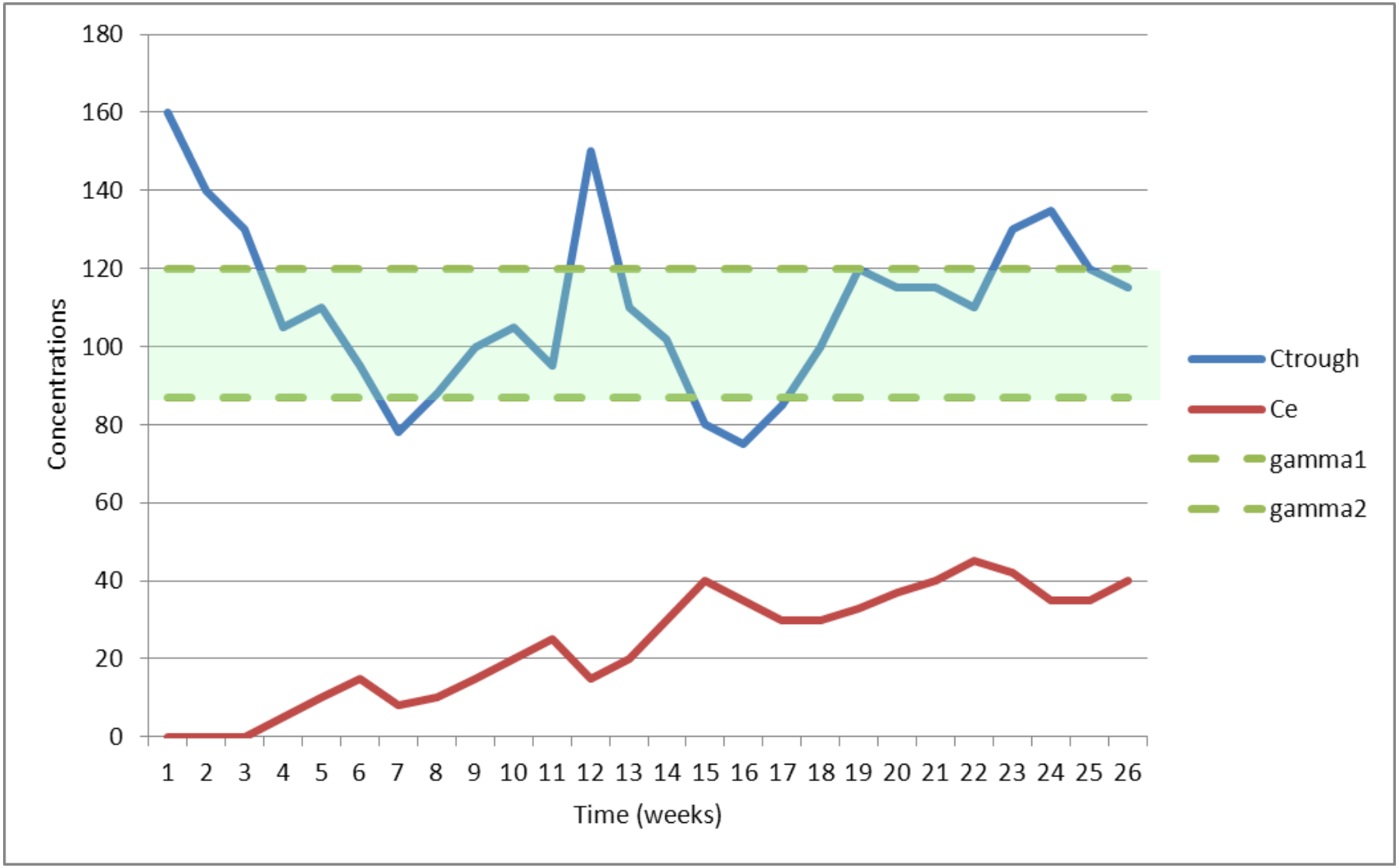
$$H1 = 1 \quad if\ TBC > \gamma_1 \\ = 0 \quad otherwise$$

$$H2 = 1 \quad if\ TBC < \gamma_2 \\ = 0 \quad otherwise$$



Meille et al., J Pharmacokinet Pharmacodyn, 2008

EFFECTIVE CSA CONCENTRATION



TIME-TO-NEUTROPHIL RESPONSE

- **Instantaneous hazard λ:** hazard of response to treatment at time t given that the patient had not responded at time t-dt (dt approaching 0)

$$\lambda(t) = \lambda_0 \cdot (1 + Slope \times Ce)$$

- **Survival function S**: probability that response had not occurred at time t, as a function of the cumulated hazard through time

$$\mathrm{S}(t) = exp\left(-\int_0^t \lambda(u)du\right)$$

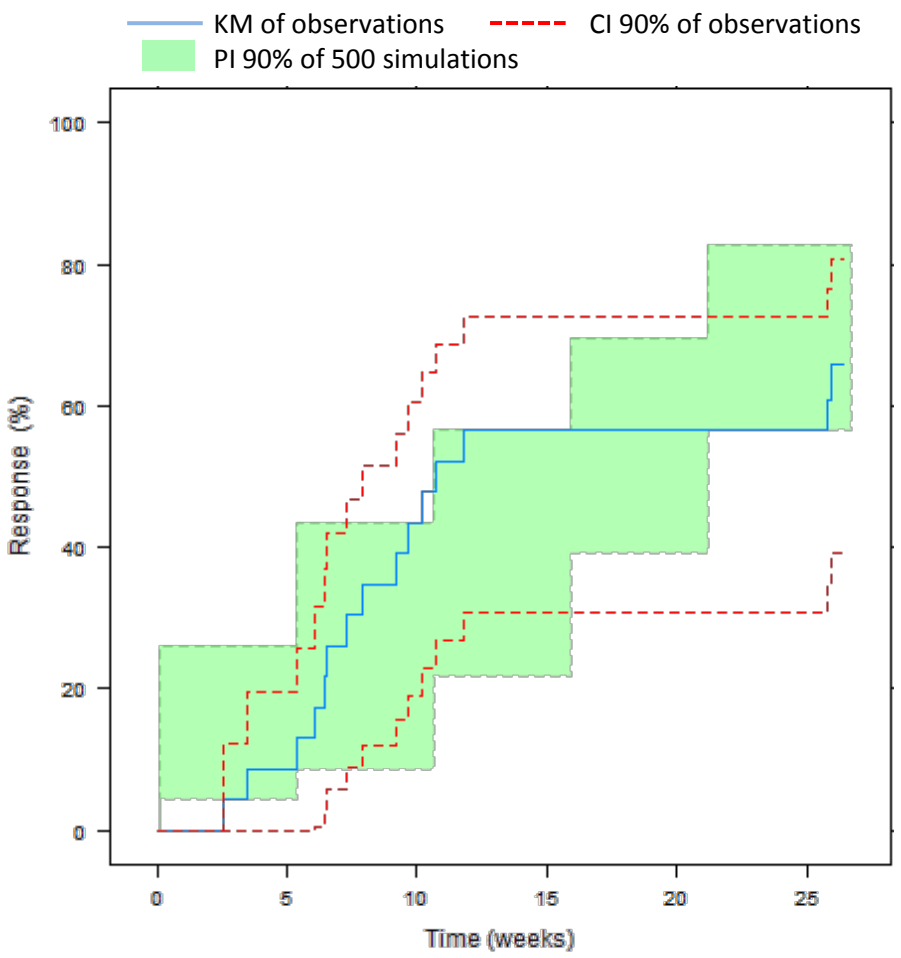
$$\mathrm{F}(t) = 1 - exp\left(-\int_0^t \lambda(u)du\right)$$

- Model building and parameter estimations with **Monolix 4.3.2**

TIME-TO-NEUTROPHIL RESPONSE

- **Estimated interval for effective TBC: 87 – 120 ng/mL**
  - Current recommendations: 200 – 400 ng/mL !
- **CsA effect half-life is 25 days**
  - blood CsA half-life is about 3 hours

TTR VISUAL PREDICTIVE CHECKS

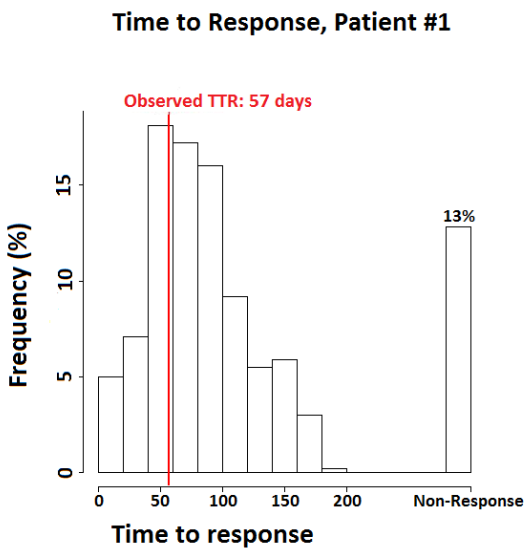


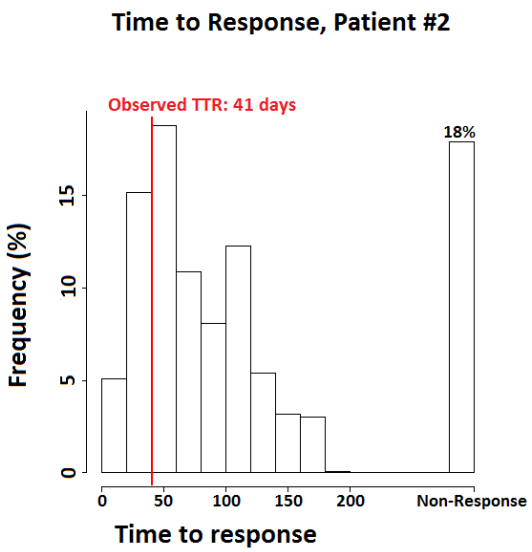
Application to new external patients

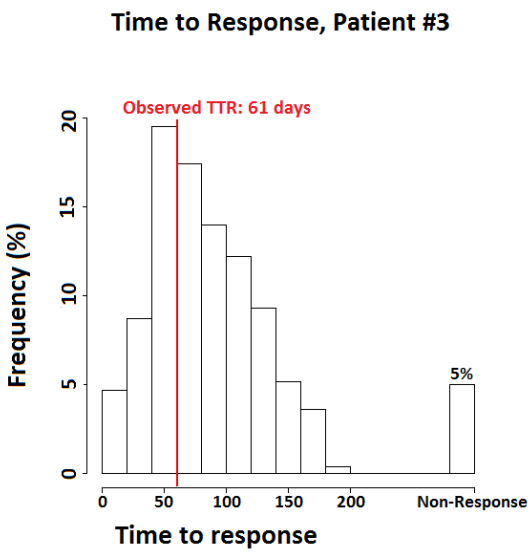
APPLICATION TO NEW PATIENTS

- 3 newly diagnosed patients with SAA
  - Not considered for model building
  - Target CsA TBC: 100 ng/mL
  - Observed TTR: 57, 41 and 61 days respectively

  - Observed TBC profile used as an input to the TTR model







DISCUSSION

DISCUSSION - LIMITATIONS

- SAA is a **rare and potentially fatal disease**
- Model-based approach for **the time-to-response in children with SAA**
  - Prospective external validation on 3 newly diagnosed patients

- Model building and evaluation limited by the **small number of patients**
  - Rarity of disease: 23 patients = 15-year data in Lyon Hospital
  - Need further validation on large prospective cohort

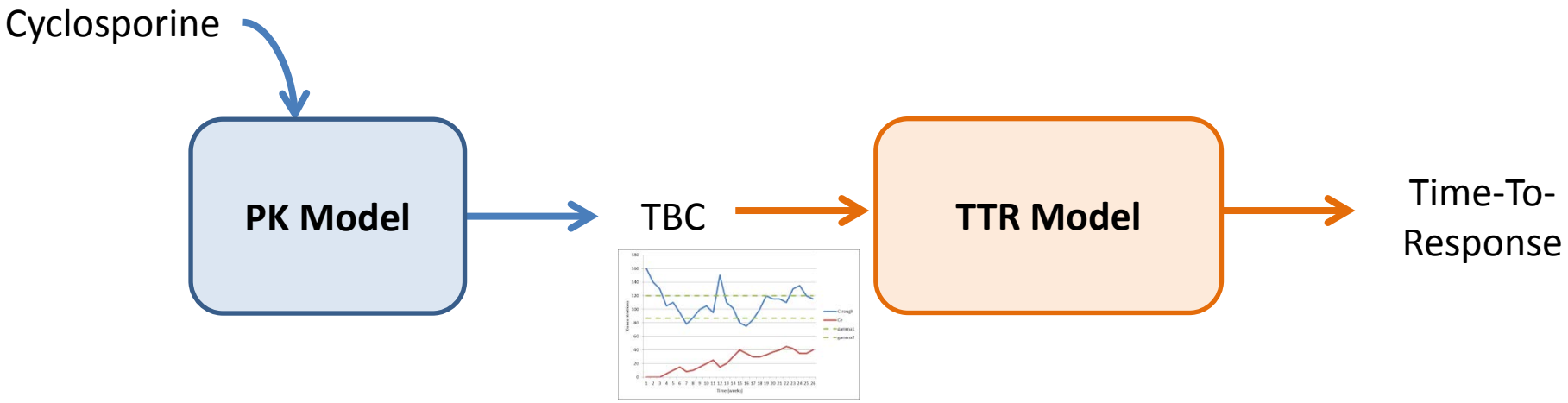
- Routine care data: **only trough blood concentrations** available
  - rude surrogate for CsA exposure
  - rich sampling was impossible in these children

DISCUSSION

- Time-To-Neutrophil Response linked to CsA TBC profile
  - **Effective range: 87-120 ng/mL** Current recommendations: 200-400 ng/mL
  - Lower doses and CsA exposure should be investigated in clinical studies

- Use of ANC as a response criterion
  while usual criteria include hemoglobin, platelets and ANC:
  - Neutrophil response allows patients' discharge from hospital
  - Red blood cells and hemoglobins can be supplemented
  - Neutrophil usually respond first!
    - Followed by red blood cell-, then platelet-response

CONCLUSIONS



- Determination of an effective range for CsA TBC: **87 – 120 ng/mL**
  - **Target for TDM around 100 ng/mL**

- Lower concentrations than those currently recommended may be associated with better response
  - 3/3 patients had neutrophil-response **within 2 months**
  - Expecting new SAA patients for further validation!!


Thank you for
your Attention!