Integrated Dose-Exposure-Response Modeling and Use in Clinical Trial Simulation

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Novartis Pharmaceuticals

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Novartis

Mission ›

We want to discover, develop and successfully market innovative products to prevent and cure diseases, to ease suffering and to enhance the quality of life.

Businesses ›

Novartis offers a wide range of healthcare products through our Pharmaceuticals, Vaccines and Diagnostics, Sandoz and Consumer Health Divisions.

People ›

Nearly 100 000 people are working at Novartis to help save lives and improve quality of life.

Corporate citizenship ›

Corporate citizenship at Novartis rests on four pillars: patients, business conduct, people and communities, and environmental care.

Locations ›

We operate in 140 countries, with our global headquarters in Basel, Switzerland.

Company history ›

Novartis was created in 1996 through the merger of Ciba-Geigy and Sandoz.

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Novartis and the authors

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Research, Development, Marketing, …

Clinical Advanced Statistical Solutions

… takes the leadership to ensure availability, application and further development of methodological statistical expertise by collecting, creating and fostering new ideas in close cooperation with its customers in Novartis and the scientific community

Modeling and Simulation

For the optimal development and use of drugs, we integrate the principles of biology, pharmacology, and statistics to predict and explain the quantitative consequences of decisions.

Outline

- Dose-exposure-response modeling as an integrating principle for drug development
- Example: Certican for kidney transplantation

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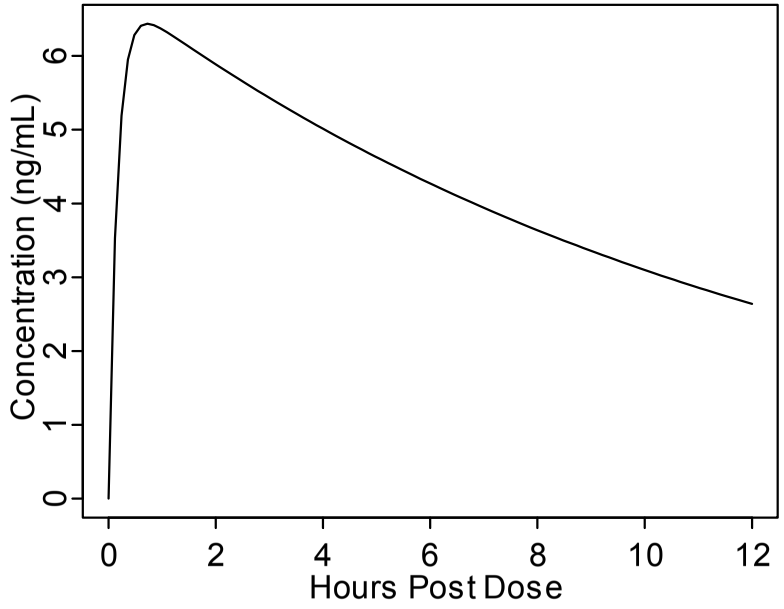
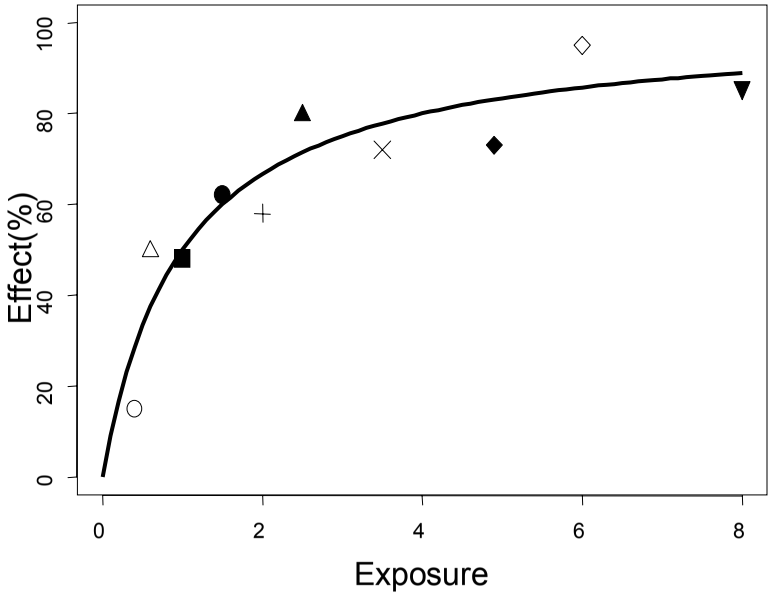
Dose-exposure-response modeling as an integrating principle for drug development

- Model: input → ouput

Dose, time → concentration



concentration → response



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Dose-exposure-response modeling as an integrating principle for drug development

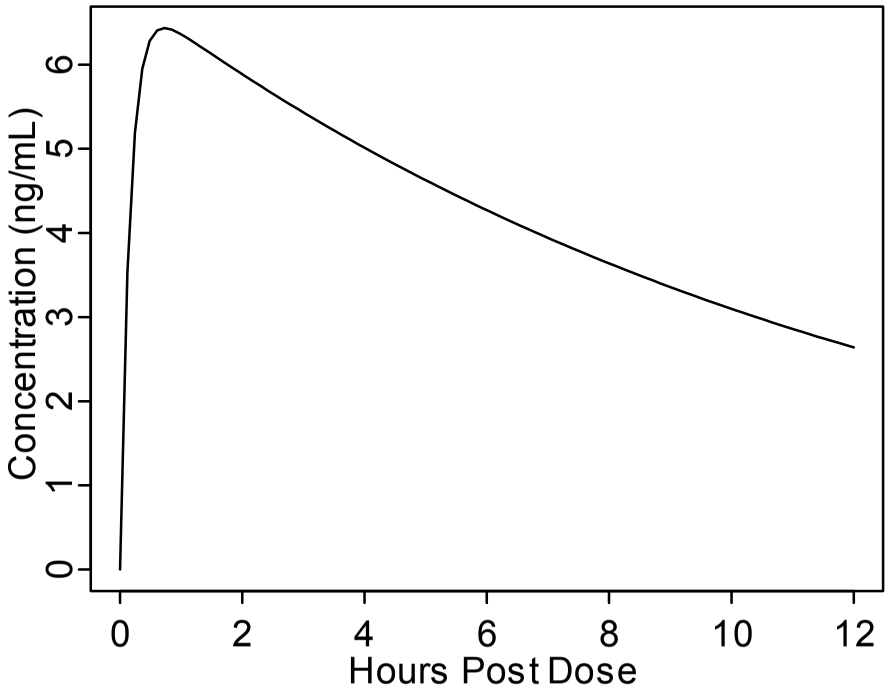
- Model: input → ouput
- Understanding, prediction, control, decision
  - What is the relationship between the input and the output?
  - What will happen if the input is changed?
  - What input will achieve a desired output?
  - Should a proposed action be taken?

Dose-exposure-response modeling as an integrating principle for drug development

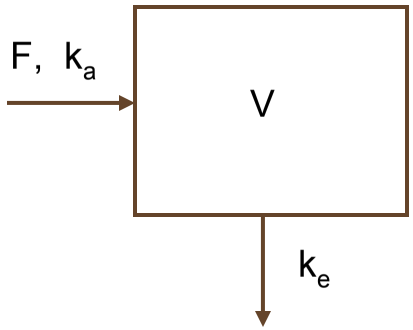
- Pharmacokinetic model

Dose, time → concentration

$$D, t \rightarrow \quad \frac{D * F * k_a}{V * (k_a - k_e)} (e^{-k_e * t} - e^{-k_a * t})$$



One-compartment model
Response to a single dose



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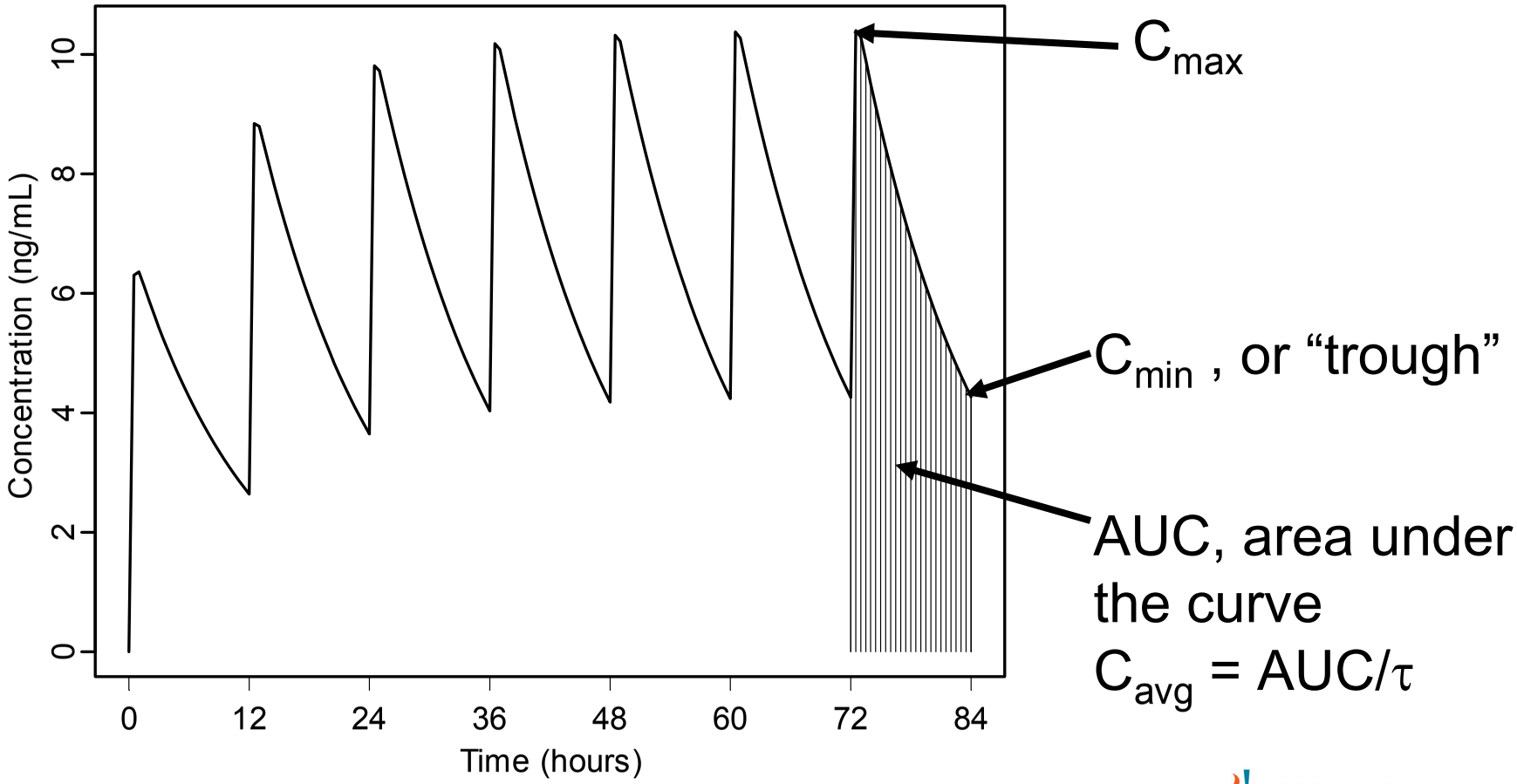
Dose-exposure-response modeling as an integrating principle for drug development

- For long-term treatment, steady-state summaries of exposure are most relevant



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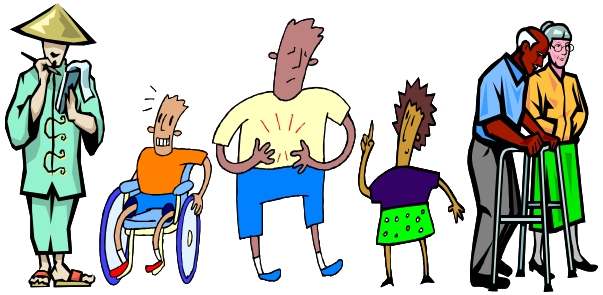
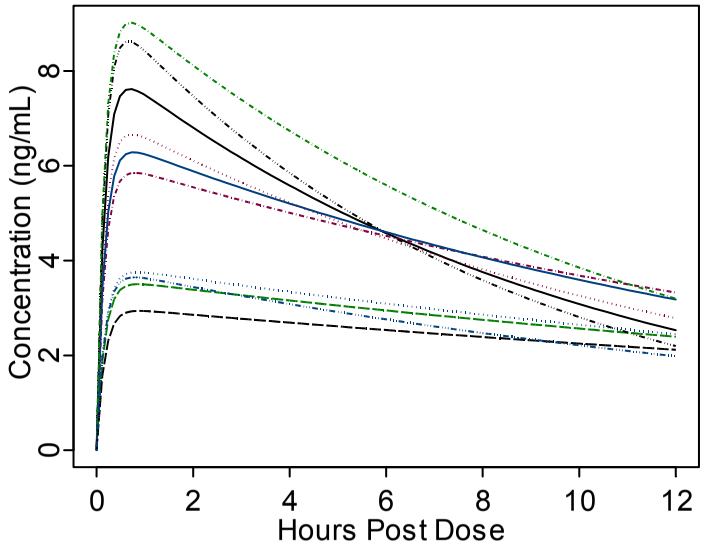
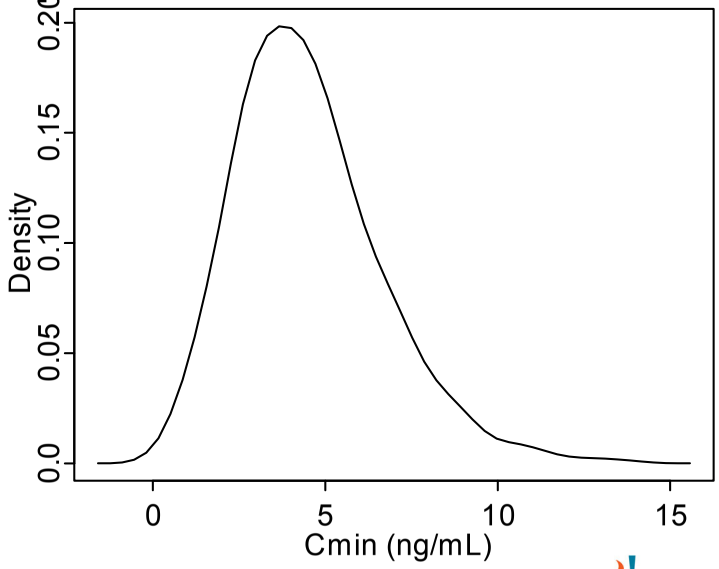
Dose-exposure-response modeling as an integrating principle for drug development

different patients



different exposures





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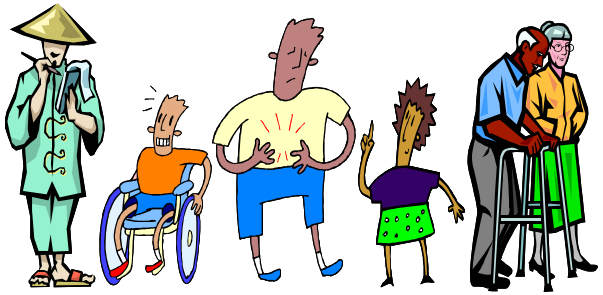
Dose-exposure-response modeling as an integrating principle for drug development

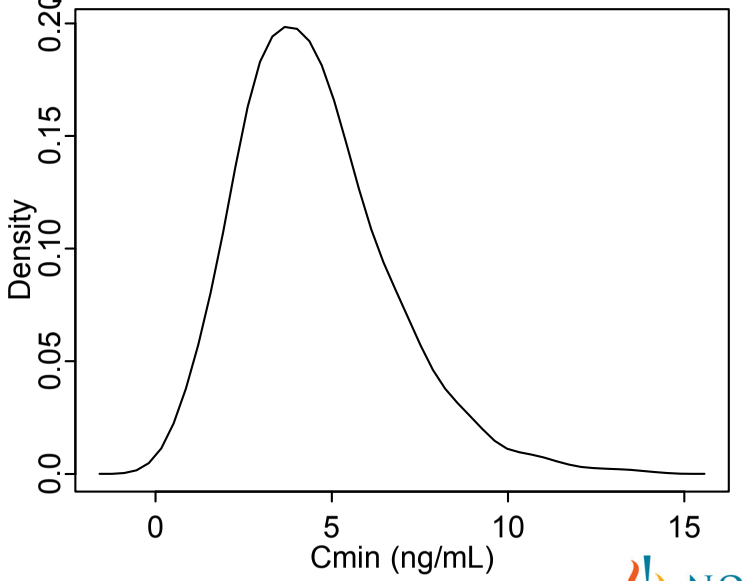
different patients



different exposures

$$\log(C_{min,i,j}) = \beta' \mathbf{x} + \delta_i + \varepsilon_{ij}$$

Mixed-effects models



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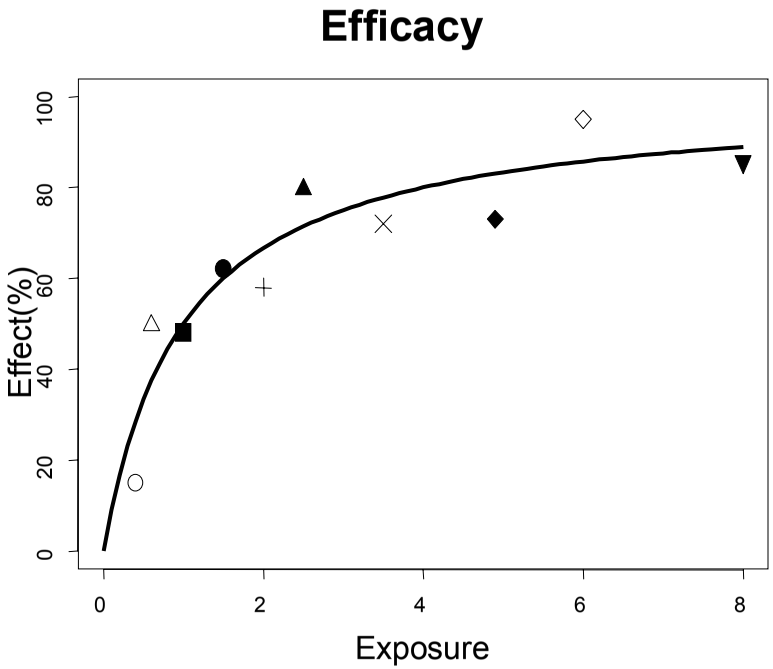
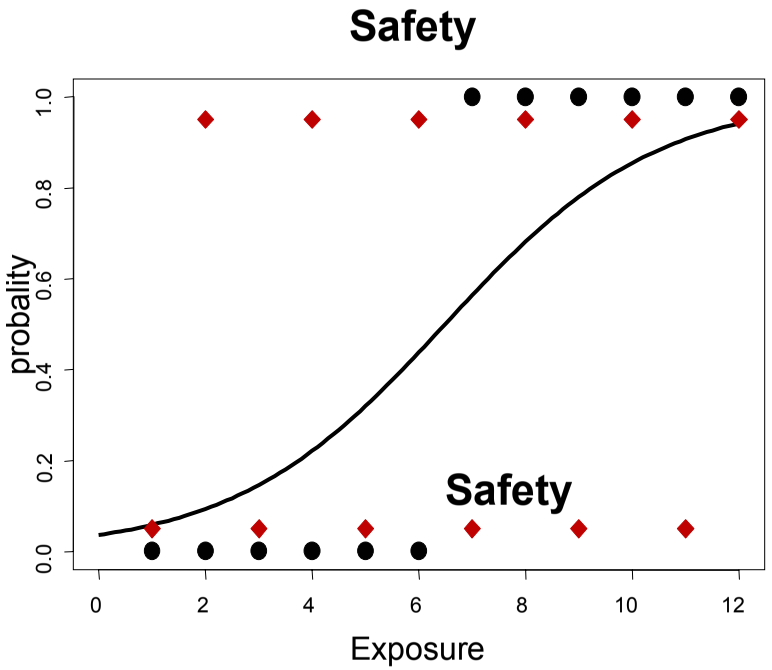
Dose-exposure-response modeling as an integrating principle for drug development

- Exposure → response





$$\text{Effect} = \frac{E_{max} C}{C_{50} + C}$$

$$\text{logit}(p) = \beta_0 + \beta_1 C$$

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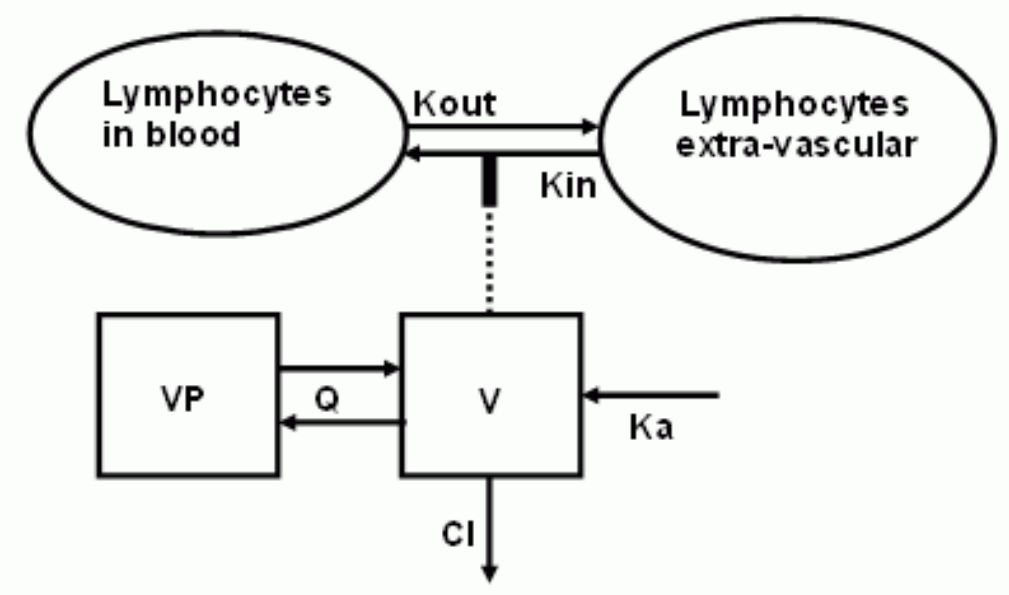
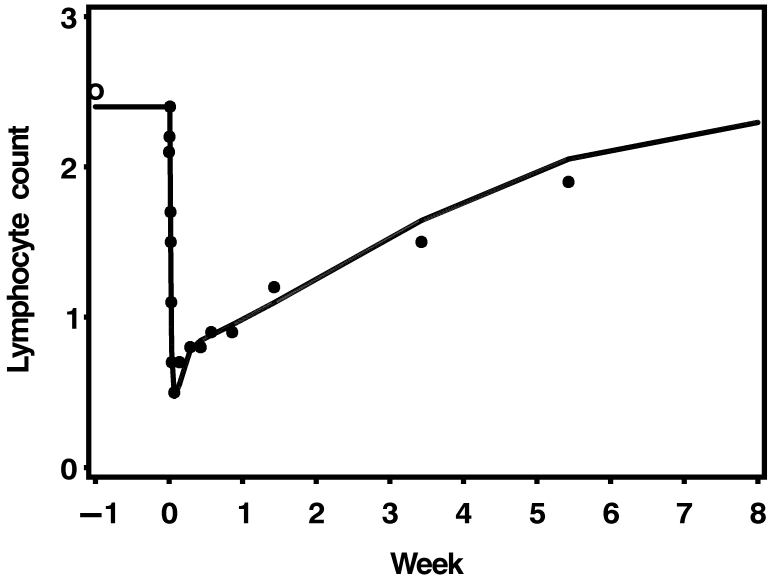
Dose-exposure-response modeling as an integrating principle for drug development

- Dose, time → exposure, time → response





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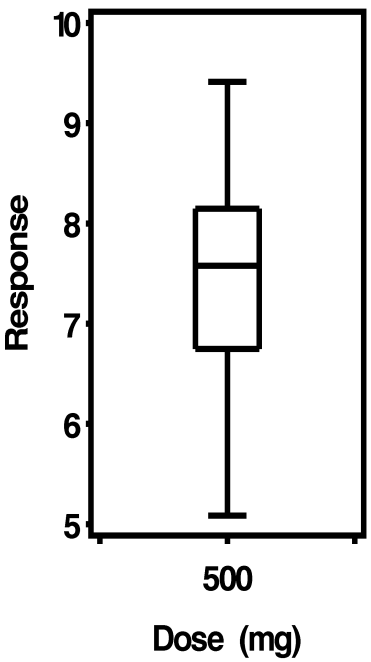
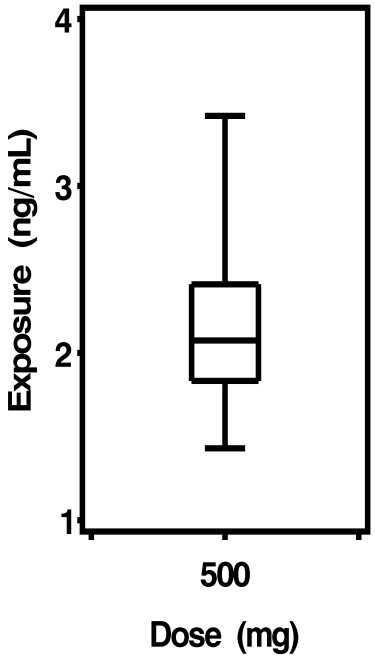
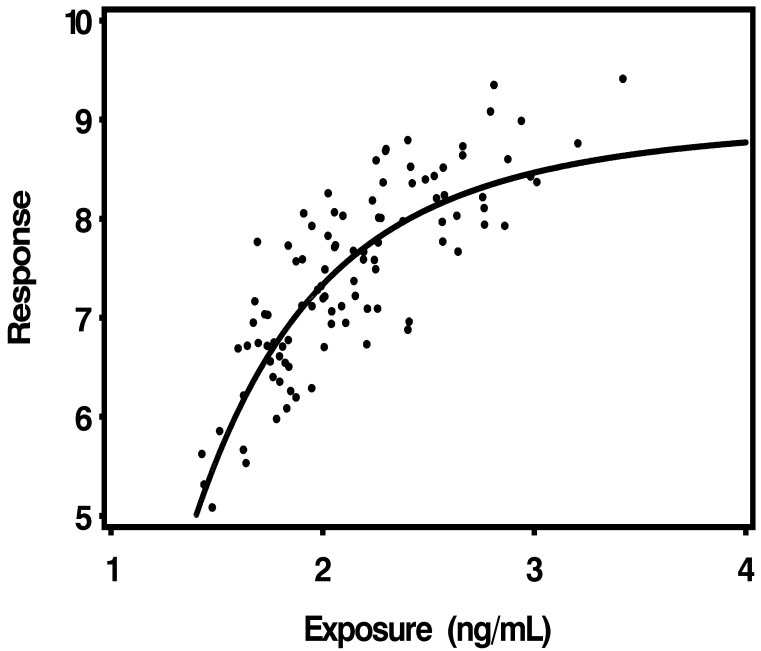
Dose-exposure-response modeling as an integrating principle for drug development

Dose-Response Dose-Exposure Exposure-Response

$$p(R \mid D) = \int dE \; p(E \mid D) \cdot p(R \mid E)$$







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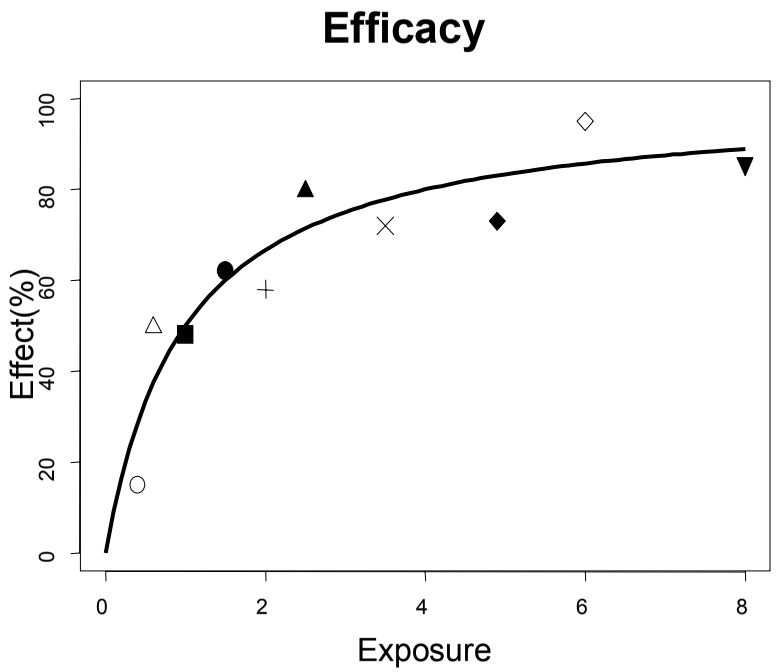
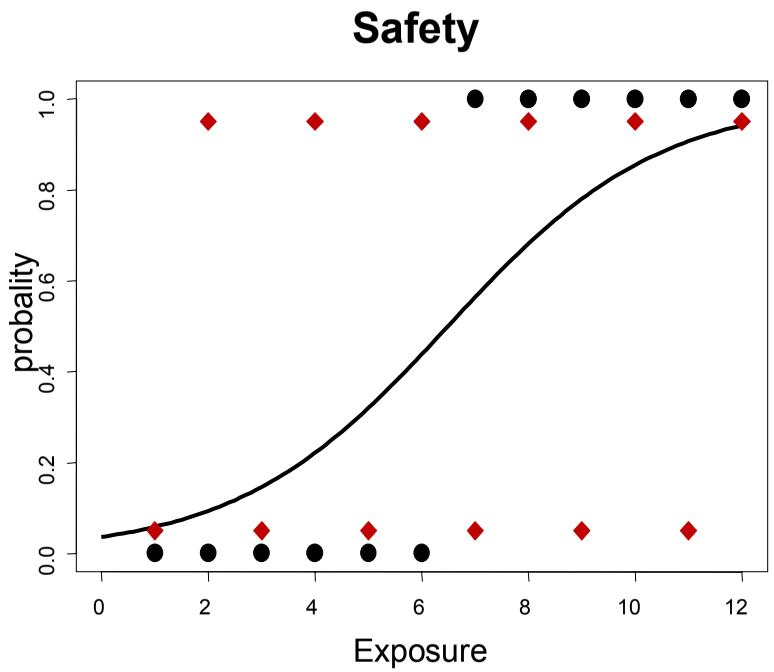
Dose-exposure-response modeling as an integrating principle for drug development

- A framework for combining data from multiple studies of different designs, doses, patients
- A framework for combining risk and benefit





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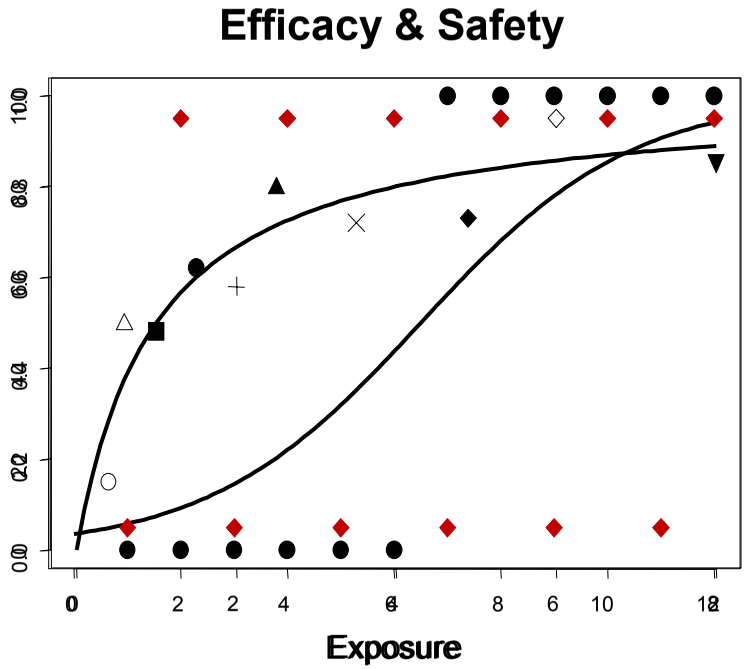
Dose-exposure-response modeling as an integrating principle for drug development

- A framework for combining risk and benefit



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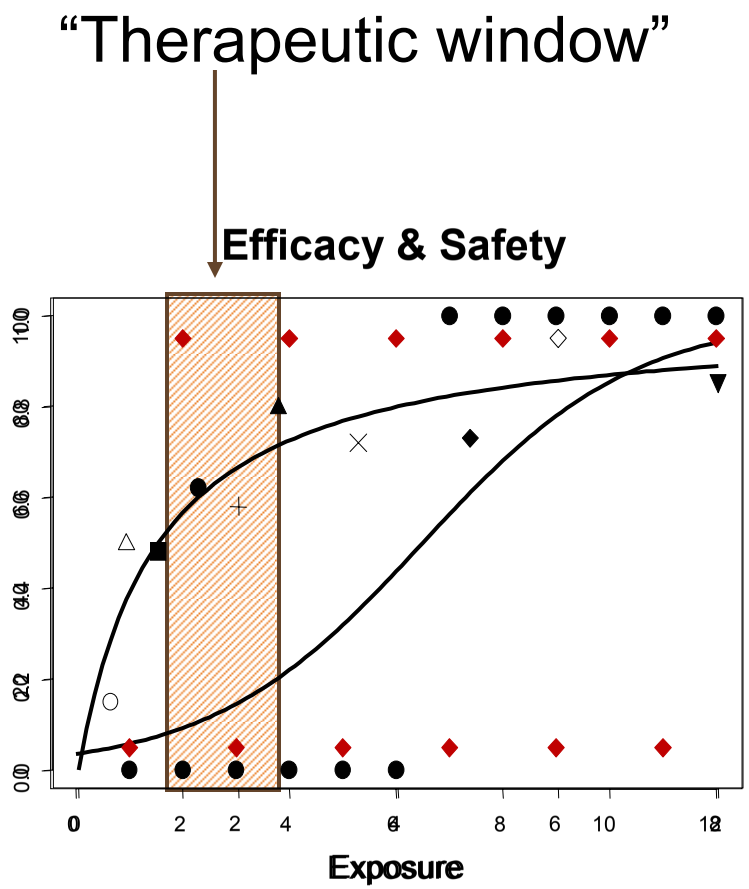
Dose-exposure-response modeling as an integrating principle for drug development



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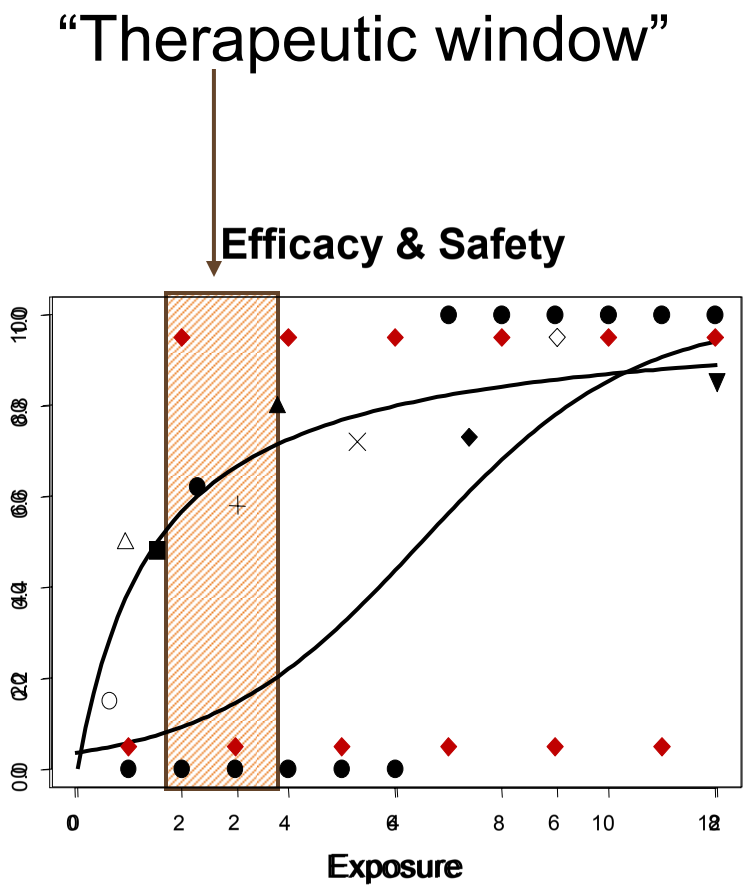

Therapeutic drug monitoring (TDM):

Adjust the dose to keep exposure in the therapeutic window.

Examples of drugs:

- Aminoglycoside antibiotics (gentamicin)
- Antiepileptics (carbamazepine, phenytoin)
- Mood stablizers (lithium citrate)
- Antipsychotics (pimozide, clozapine)

http://en.wikipedia.org/wiki/Therapeutic_drug_monitoring

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Dose-exposure-response modeling as an integrating principle for drug development

- Design decisions for clinical trials:
  - What kind of patients?
  - How many patients?
  - What dose and dose regimen?
  - What observations and when?
- Using dose-exposure-response models, computer simulations can assess predicted performance of proposed designs

Outline

- Dose-exposure-response modeling as an integrating principle for drug development
- Example: Certican for kidney transplantation

Transplant rejection

- When the immune system of the recipient attacks the transplanted organ
- Acute:
  - Caused by T-cells, which take time to differentiate
  - Hence can begin only a few days after transplant, but may occur months to years later
  - Damage to tissues of transplanted organ
  - Ultimate diagnosis involves biopsy
  - Can be treated by immuno-suppressive therapy
  - A surrogate for chronic rejection
- Chronic:
  - Irreversible loss of viability of the transplanted organ
  - Only treatment is re-transplantation

Example: Certican for kidney transplantation

Prophylaxis of acute organ rejection in renal transplant recipients.

Triple therapy immunosuppression:

1. Everolimus (Certican®)
2. Cyclosporine
3. Corticosteroids (prednisolone)

Two phase-3 studies

Primary objective	**Certican vs. mycophenolate mofetil (MMF) control: prevention of acute allograft rejection, graft loss, or death within 6 & 12 months after transplantation**
Design	**Randomized, double-blind, 3 parallel groups, Phase 3**
Location	**Study 251: Americas** **Study 201: Europe, Australia, South Africa**
Dosage	**Certican 1.5 or 3 mg/day (0.75 or 1.5 mg bid) fixed-dose vs. MMF 2 g** **Patients also received full dose cyclosporine (CsA) and corticosteroids)**
Treatment	**1 year double-blind + 2 years open follow-up**
Numbers	**Study 251: 583 patients** **Study 201: 588 patients**

12 month study results

	Everolimus		
	1.5mg	3.0mg	MMF
***Efficacy**: freedom from acute rejection*			
B201	77%	80%	76%
B251	81%	78%	76%
***Renal function**: median creatinine [µmol/L]*			
B201	149	163	146
B251	150	159	133

Good efficacy, unsatisfactory renal function

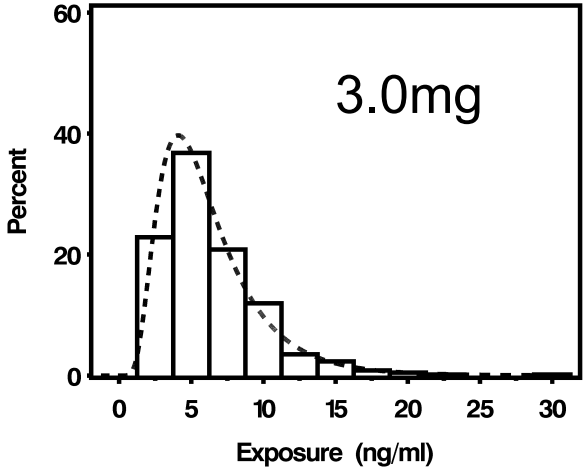
Vitko et al.(2004) Transplantation. Lorber et al. (2005) Transplantation.

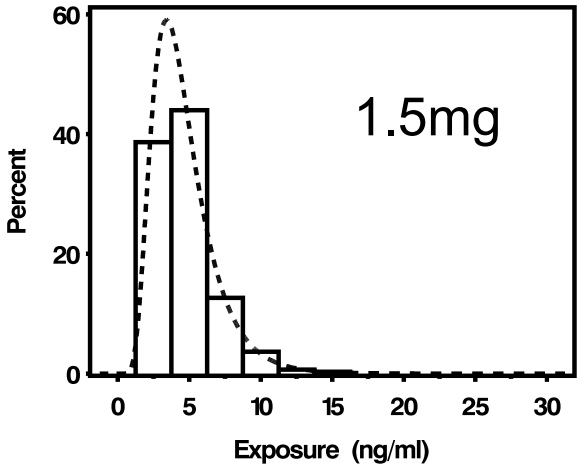
Challenge: Improve safety, retain efficacy

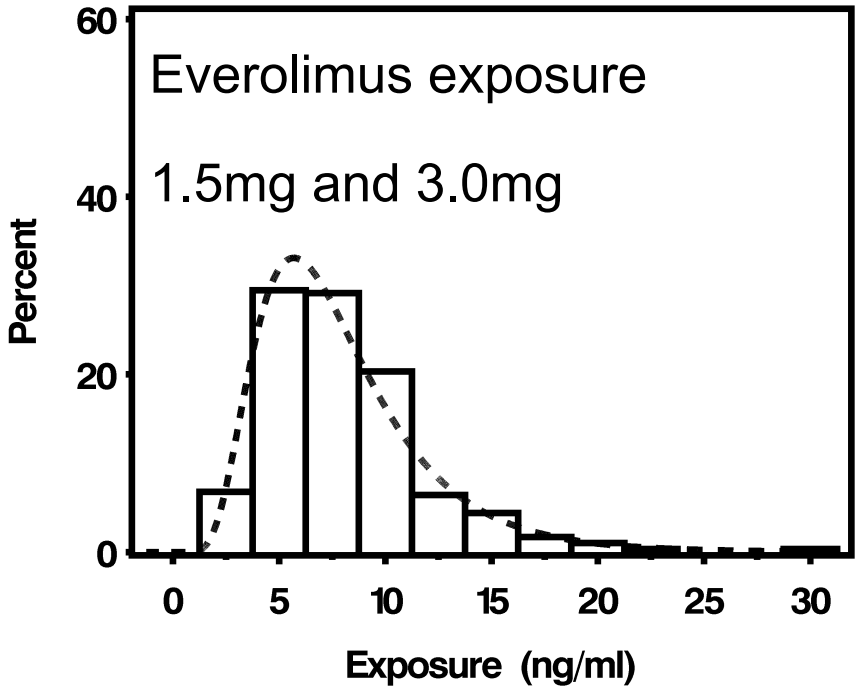
- Model dose-exposure-response
- Understand major influences on exposure, safety, and efficacy
- Determine a dose regimen to control risk/benefit balance
- Decide on design of follow-up study

Dose-Exposure

- Objective: to understand variability in exposure







5260 everolimus concentration records in 673 patients

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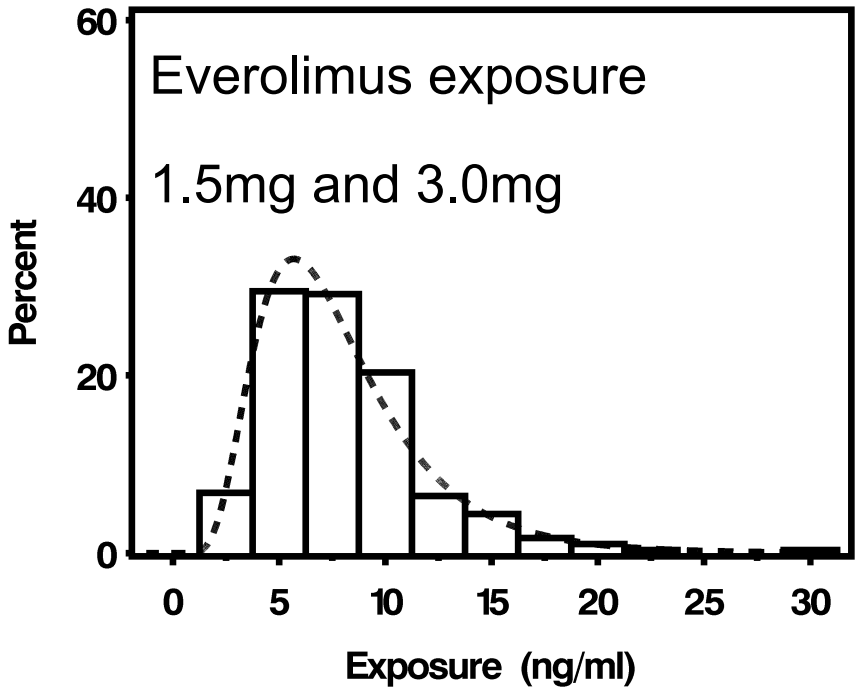
Dose-Exposure

- Objective: to understand variability in exposure

$$\log(C_{min,i,j}) = \beta_0 + \beta_1 Dose_i + \beta_2 DGF_i + \delta_i + \varepsilon_{ij}$$

DGF = Delayed Graft Function



5260 everolimus concentration records in 673 patients

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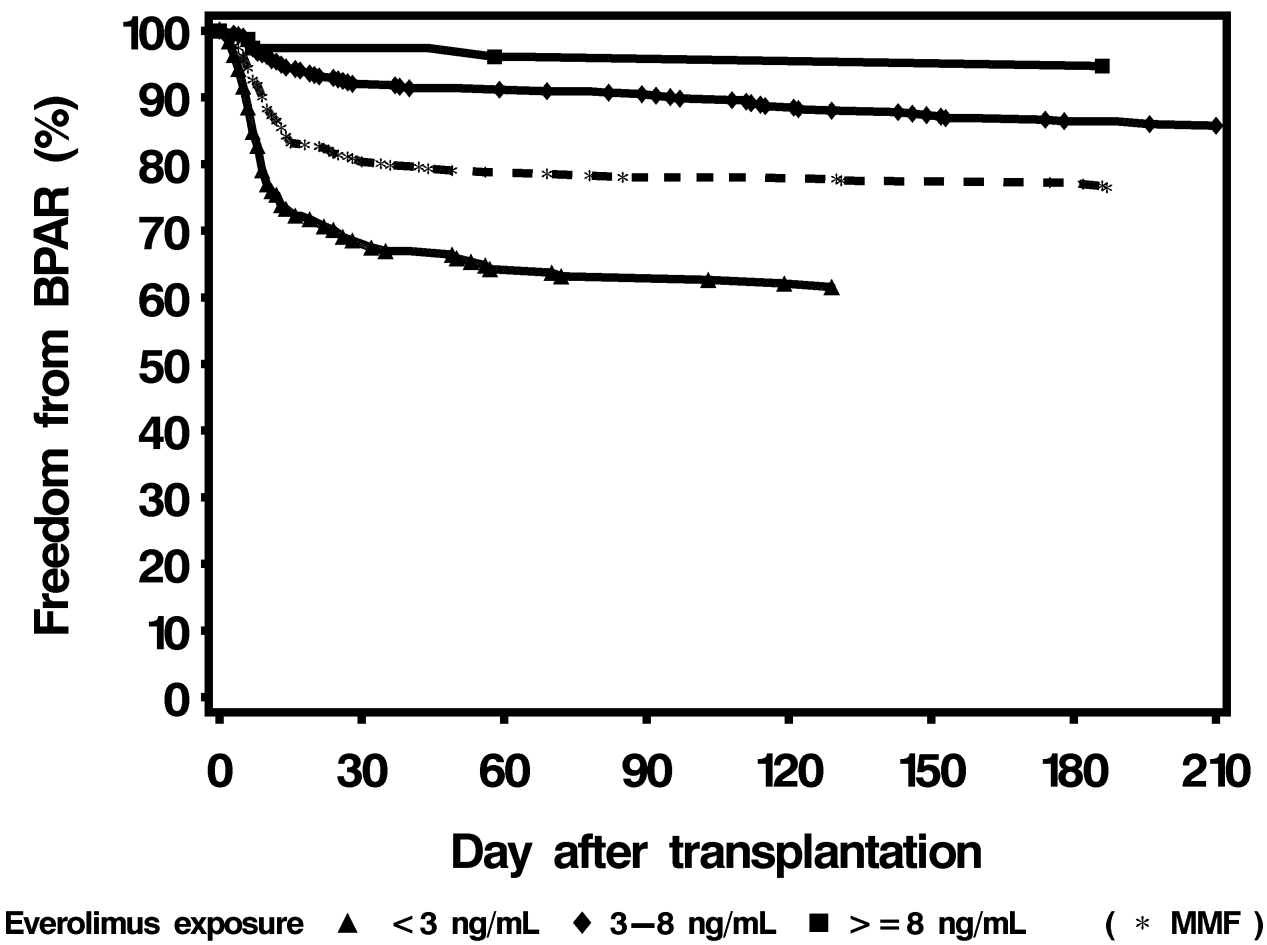
Exposure-Efficacy and Exposure-Safety

- Objective: to quantify joint effects of everolimus and cyclosporine exposures
- Efficacy: Cox proportional hazards model for Biopsy Proven Acute Rejection (BPAR) up to day 225.
  - Log-transformed everolimus and cyclosporine geometric mean troughs up to the time of event or censoring at day 225
  - Binary covariate: Delayed Graft Function (DGF)
- Safety: Cox proportional hazards model for “renal event”
  - Renal event: serum creatinine ≥ 200μmol/L
  - Log-transformed everolimus and cyclosporine geometric mean troughs up to the time of event or censoring at day 225
  - Binary covariate: gender

Exposure-Efficacy



Kaplan-Meier: everolimus exposure levels

Lorber et al. (2005) Transplantation.

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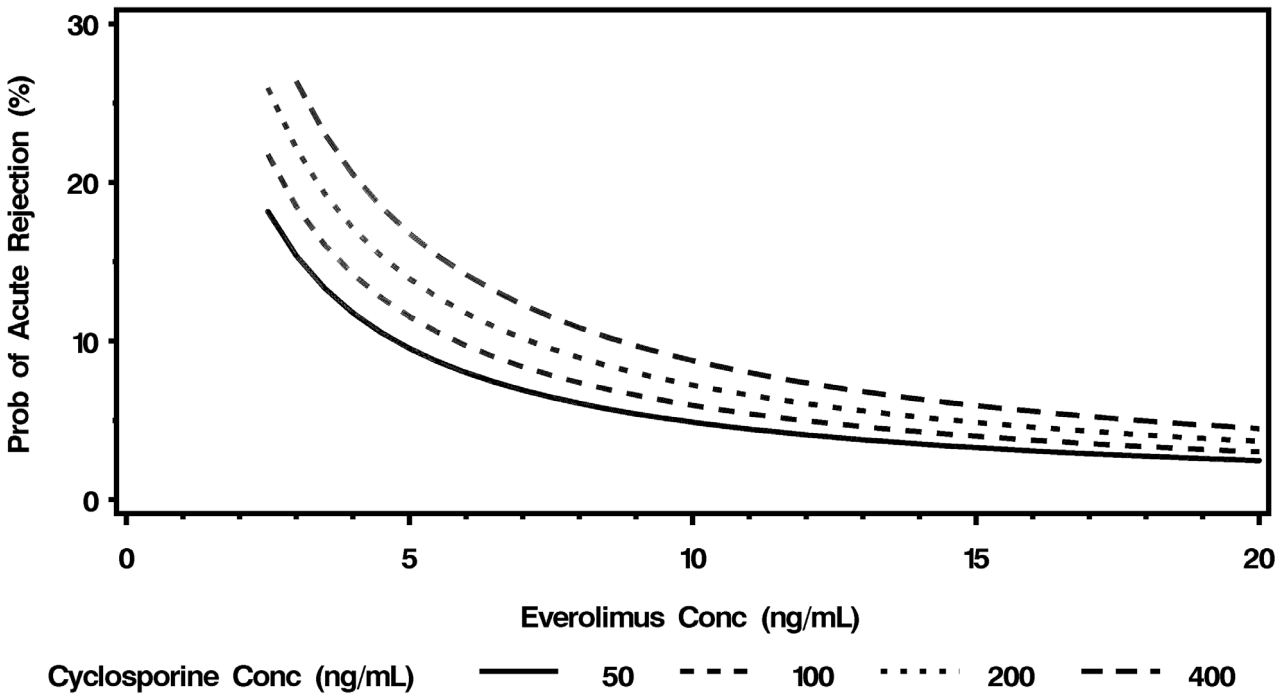
Exposure-Efficacy: Cox regression results



everolimus (p<0.0001)

cyclosporine (p=0.11)

Lorber et al. (2005) Transplantation.

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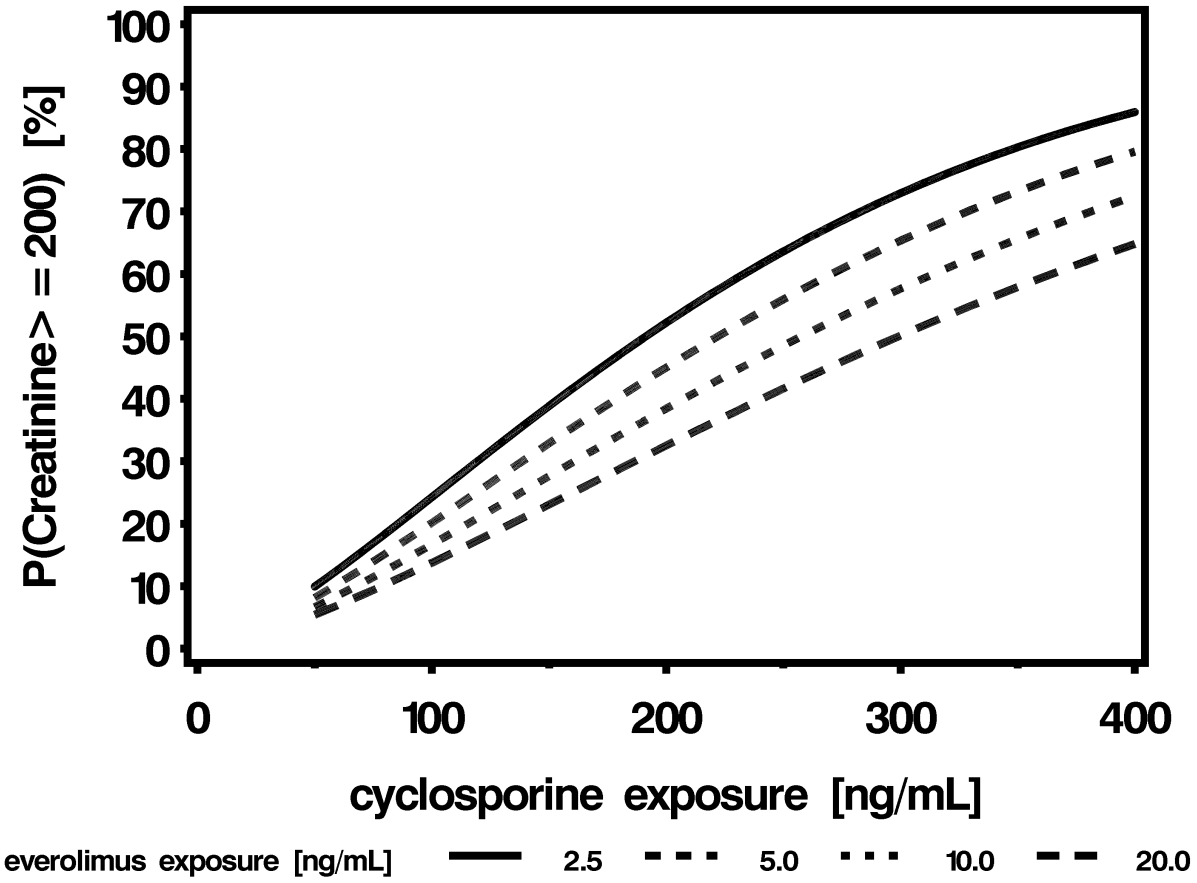
Exposure-renal function: Cox regression results

everolimus
(p=0.051)

cyclosporine
(p<0.0001)

Robustness checked by using different creatinine threshold values, time periods, and covariates. Cyclosporine effect robust. Everolimus effect small and positive or negative depending on the model.



Lorber et al. (2005) Transplantation.

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Understandings

Efficacy

- Reduced risk of acute rejection if everolimus exposure ≥3ng/mL
- No evidence for cyclosporine effect within observed exposures

Renal function

- Risk of renal event lower if cyclosporine exposure low
- No evidence for everolimus effect on renal function

Lorber et al. (2005) Clinical transplantation.

Controls

Efficacy

- Reduced risk of acute rejection if everolimus exposure ≥3ng/mL
- Suggests use everolimus therapeutic drug monitoring

Renal function

- Risk of renal event lower if cyclosporine exposure low
- Suggests reducing cyclosporine dose

Lorber et al. (2005) Clinical transplantation.

Decisions

Should a trial be conducted to test TDM?

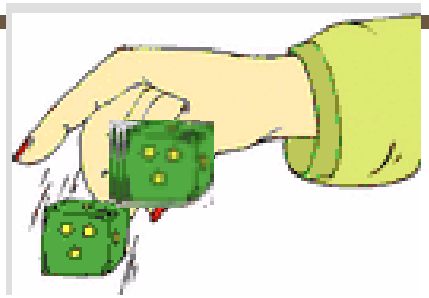
- Is logistically simple TDM capable of maintaining adequate exposure?
- Is acceptable efficacy likely?

Test a proposed TDM trial by clinical trial simulation.

Conservative TDM modeling proposal:

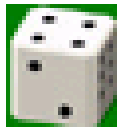
Start with 1.5mg, thereafter 2x TDM to ensure that troughs > 3 ng/mL

Design decision via cinical trial simulation

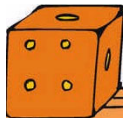


Simulation per patient

TDM modeling assumptions



patient type



trough level via dose-exposure model

acute rejection via exposure-response model

overall expected acute rejections

Design decision via cinical trial simulation

Results of simulations:

- 95% of patients have average everolimus exposure ≥ 3 ng/mL
- Expected freedom from BPAR (6 mo): 83%

Confirmatory study

Study A2306: study with 2 arms (n≈120/arm)

Everolimus starting dose of 1.5 mg or 3.0 mg

- Everolimus dose adjustment with therapeutic drug monitoring (TDM) to achieve an everolimus exposure of $\geq$3 ng/mL
- Reduced doses of cyclosporine after 3 months and C2 monitoring

6 month study results

	Everolimus (A2306) 1.5mg	Everolimus (A2306) 3.0mg	MMF (B201/B251)
***Efficacy**: freedom from acute rejection*			
	75%	85%	77%,77%
***Renal function**: median creatinine [µmol/L]*			
	133	132	140,133

Comparable efficacy and renal function

98% of patients everolimus ≥ 3 ng/mL (from mo 1)

Vitko et al.(2004) Am J Transpl. Kovarik et al.(2004) Ther Drug Monit

Conclusions

- Dose-Exposure-Response models integrate knowledge of drug properties
- Model based clinical trial simulation supports decisions about the design of clinical trials

Acknowledgements: H.Mayer, J.Kovarik, Y.Li, R. Fisch