Drug Development to Enable Precision Dosing

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Roche pRED

Disclosures

- I am an employee of and hold stock in F Hoffmann la Roche

Precision dosing in practice today

Clinical endpoint guided

- Many situations
- Individual MTD for cancer drugs

Biomarker guided

- Anti-hypertensives, cholesterol lowering, insulin and oral hypoglycaemics, warfarin, erythropoietin
- Generally biomarkers that are part of routine clinical care

PK guided

- “Classical” patient subgroups – ethnicity, organ failure, age, DDIs…
- Therapeutic Drug Monitoring

Pharmacogenetics

- 7% of approved drugs have actionable germ line pharmacogenetics (Relling & Evans, Nature, 2015)

- BUT Only implemented in highly selected cases or some tertiary care centres

Precision dosing in drug development today

Disease/Response guided dosing is unusual but has been done

Response guided

- IgG replacement (PK guided)
- Erythropoeitin and thrombopoeitin analogues (PD guided)

Disease-based

- omalizumab

Response guided dosing for immune globulin dosing

Gammagard liquid iv

Table 2.
Change in Weekly Dose of GAMMAGARD LIQUID for Intended IgG Trough Level Adjustment[a]

	Difference between Measured and Target IgG Trough Levels			
Body Weight	100 mg/dL	200 mg/dL	300 mg/dL	400 mg/dL
10 kg	2 mL	4 mL	6 mL	8 mL
20 kg	4 mL	8 mL	11 mL	15 mL
30 kg	6 mL	11 mL	17 mL	23 mL
40 kg	8 mL	15 mL	23 mL	30 mL
50 kg	9 mL	19 mL	28 mL	38 mL
60 kg	11 mL	23 mL	34 mL	45 mL
70 kg	13 mL	26 mL	40 mL	53 mL
80 kg	15 mL	30 mL	45 mL	60 mL
90 kg	17 mL	34 mL	51 mL	68 mL
100 kg	19 mL	38 mL	57 mL	75 mL
110 kg	21 mL	42 mL	62 mL	83 mL
120 kg	23 mL	45 mL	68 mL	91 mL
130 kg	25 mL	49 mL	74 mL	98 mL
140 kg	26 mL	53 mL	79 mL	106 mL

[a] Derived using a linear approximation to the nomogram method with a slope of 5.3 kg/dL.

Cuvitru sc

Table 1
Change in Volume to Be Administered Weekly/Biweekly for Intended IgG Trough Level Change[a]

		Body Weight				
Difference from Target Serum IgG Trough Levels	Dosing Frequency	30 kg	50 kg	70 kg	90 kg	110 kg
100 mg/dL	Weekly	3 mL	5 mL	7 mL	9 mL	11 mL
	Biweekly	6 mL	10 mL	13 mL	17 mL	21 mL
200 mg/dL	Weekly	6 mL	10 mL	13 mL	17 mL	21 mL
	Biweekly	12 mL	19 mL	27 mL	35 mL	42 mL
300 mg/dL	Weekly	9 mL	14 mL	20 mL	26 mL	32 mL
	Biweekly	17 mL	29 mL	40 mL	52 mL	63 mL

[a] Derived using a linear approximation of trough levels and weekly dose per kg body mass with a slope of 52.1 kg/dL.

Dose individualisation using baseline disease variability

Omalizumab dose varies with body weight and IgE level

Table 1. Subcutaneous XOLAIR Doses Every 2 or 4 Weeks* for Patients 12 Years of Age and Older with Asthma

Pretreatment Serum IgE (IU/mL)	Dosing Freq.	Body Weight			
		30–60 kg	>60–70 kg	>70–90 kg	>90–150 kg
		Dose (mg)			
≥30–100	Every 4 weeks	150	150	150	300
>100–200		300	300	300	225
>200–300		300	225	225	300
>300–400	Every 2 weeks	225	225	300	Insufficient Data to Recommend a Dose
>400–500		300	300	375	
>500–600		300	375	Insufficient Data to Recommend a Dose	
>600–700		375	Insufficient Data to Recommend a Dose		

*Dosing frequency:

- Subcutaneous doses to be administered every 4 weeks
- Subcutaneous doses to be administered every 2 weeks

Table 2. Subcutaneous XOLAIR Doses Every 2 or 4 Weeks* for Pediatric Patients with Asthma Who Begin XOLAIR Between the Ages of 6 to <12 Years

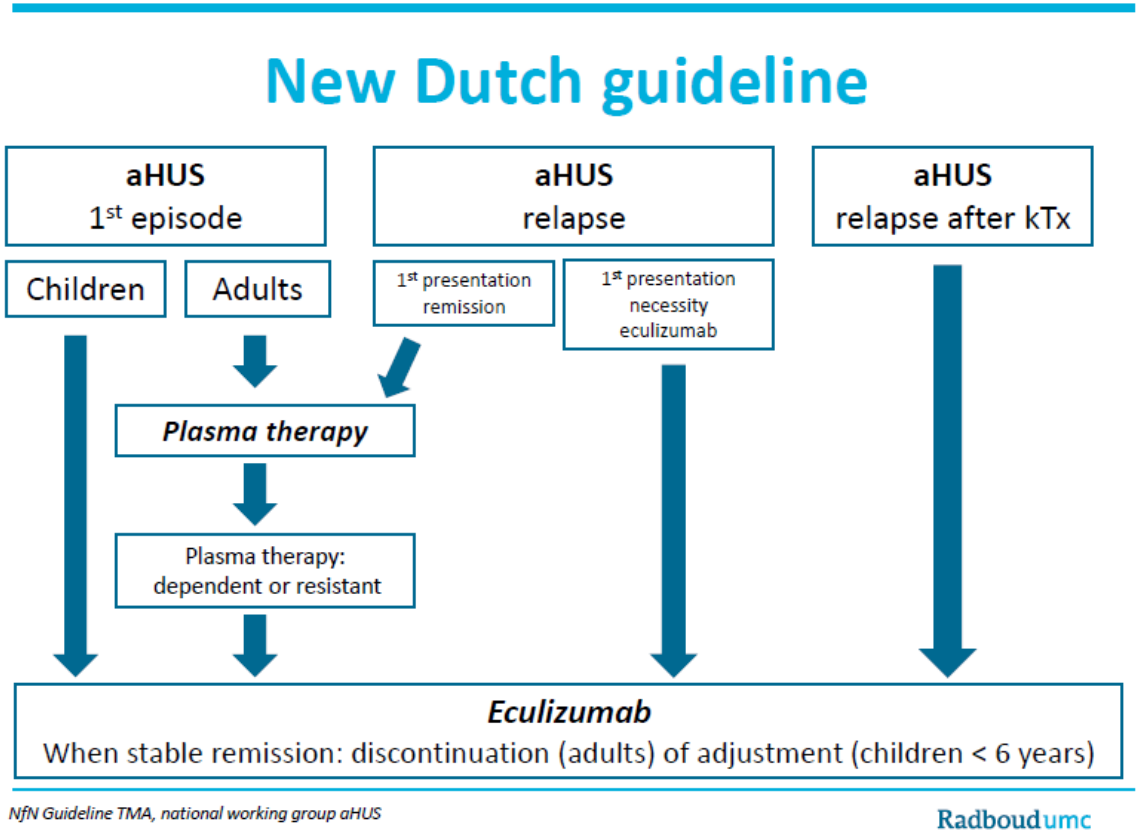
Pre-treatment Serum IgE (IU/mL)	Dosing Freq.	Body Weight									
		20-25 kg	>25-30 kg	>30-40 kg	>40-50 kg	>50-60 kg	>60-70 kg	>70-80 kg	>80-90 kg	>90-125 kg	>125-150 kg
		Dose (mg)									
30-100	Every 4 weeks	75	75	75	150	150	150	150	150	300	300
>100-200		150	150	150	300	300	300	300	300	225	300
>200-300		150	150	225	300	300	225	225	225	300	375
>300-400		225	225	300	225	225	225	300	300	Insufficient Data to Recommend a Dose	
>400-500		225	300	225	225	300	300	375	375		
>500-600		300	300	225	300	300	375	Insufficient Data to Recommend a Dose			
>600-700		300	225	225	300	375	Insufficient Data to Recommend a Dose				
>700-800	Every 2 weeks	225	225	300	375	Insufficient Data to Recommend a Dose					
>800-900		225	225	300	375						
>900-1000		225	300	375	Insufficient Data to Recommend a Dose						
>1000-1100		225	300	375							
>1100-1200		300	300	Insufficient Data to Recommend a Dose							
>1200-1300		300	375								

*Dosing frequency:

- Subcutaneous doses to be administered every 4 weeks
- Subcutaneous doses to be administered every 2 weeks

Eculizumab for aHUS in The Netherlands
Individualized dosing to manage costs and maintain reimbursement

- Eculizumab not cost effective at approved dose in aHUS
- EMA Approved dose produces exposures 3-9 fold above target
- Less frequent maintenance dosing and cessation of therapy in stable patients maintains clinical benefit
- Reduced drug costs (↓ > 50%)
- Reimbursed in The Netherlands for aHUS with new dosing guideline.
- Prospective observational study ongoing – CUREiHUS

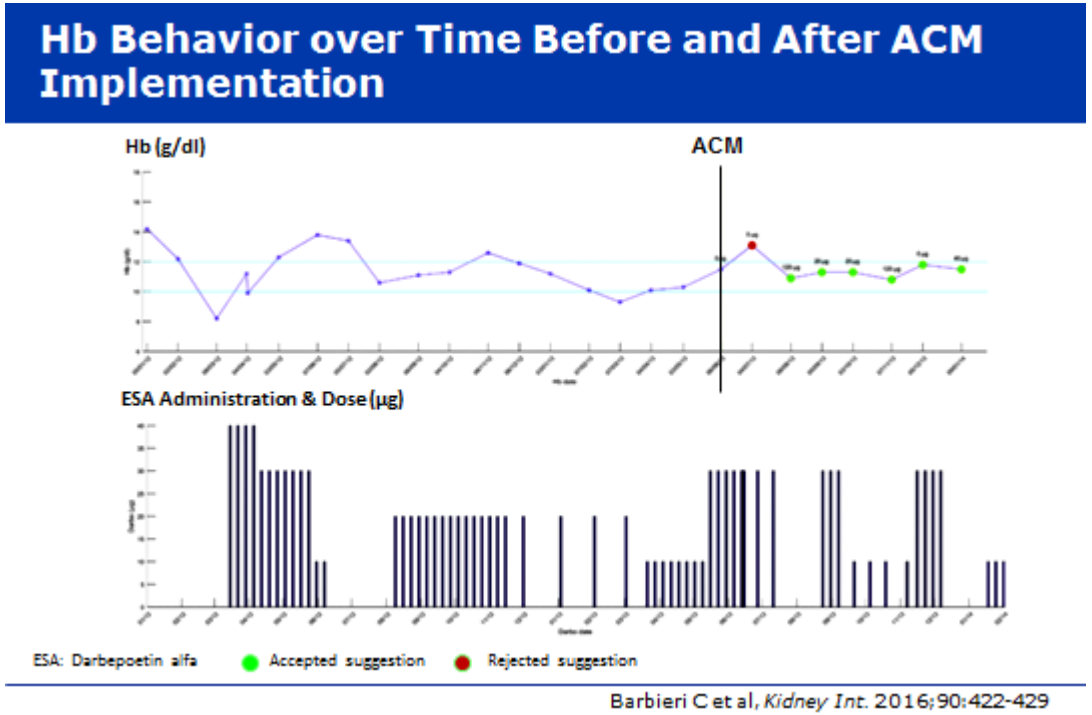


Volokhina et al. CPT, 2017;102:671-678

Wijnsma et al. Nephrol Dial Transplant, 2017;126:2085-96

Artificial Intelligence (AI) based renal anaemia management system improves outcomes with individualised dosing

	Pre ACM	Using ACM	when ACM believed
In range Hb (%)	70.6	76.6	83.2
Median darbopoetin dose (µg/kg/month)	40	30	20
CV events (/1000 patient years)	517	440	
Transfusion events (/1000 patient years)	152	92	



Barbieri C. Kidney Int. 2016 Aug;90(2):422-9.

Machine learning enabling individualised dosing

Proceedings of Machine Learning Research 85 2018 Machine Learning for Healthcare

Reinforcement Learning with Action-Derived Rewards for Chemotherapy and Clinical Trial Dosing Regimen Selection

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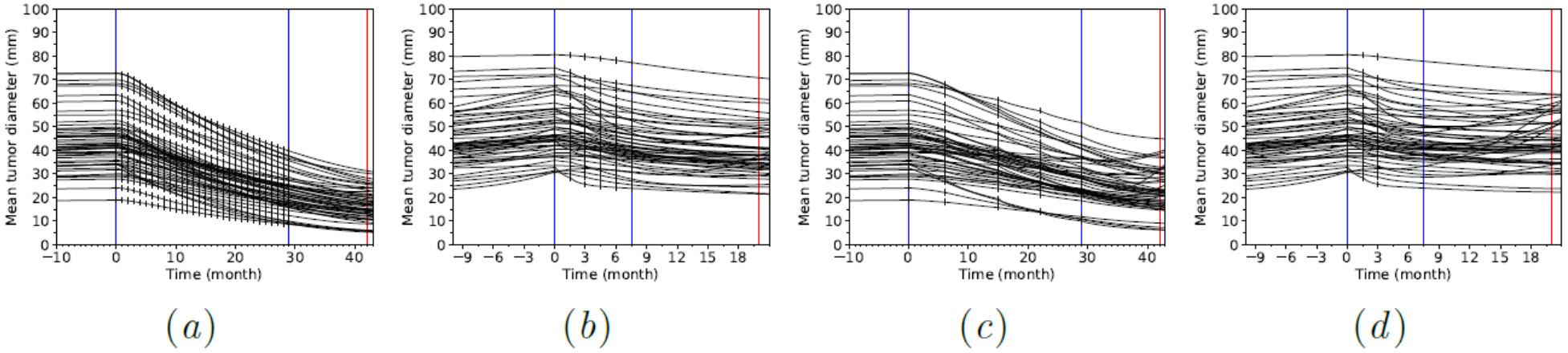
Source of PKPD data, n= 45

Cancer Therapy: Clinical

Clinical Cancer Research

A Tumor Growth Inhibition Model for Low-Grade Glioma Treated with Chemotherapy or Radiotherapy

Benjamin Ribba[1], Gentian Kaloshi[6], Mathieu Peyre[2], Damien Ricard[7], Vincent Calvez[1], Michel Tod[3,4], Branka Čajavec-Bernard[1], Ahmed Idbaih[6], Dimitri Psimaras[6], Linda Dainese[8], Johan Pallud[9], Stéphanie Cartalat-Carel[2], Jean-Yves Delattre[6], Jérôme Honnorat[2,4,5], Emmanuel Grenier[1], and François Ducray[2,4,5]



Lessons from drugs developed for precision dosing

Precision dosing is approvable after inclusion in pre-approval trials

Clinical development for precision dosing not fundamentally different from “one size fits all” dosing

Precision dosing needs a clearly defined target (or target range)

Precision dosing can be based on efficacy or safety or both

Current examples adjust dose based on single parameters

For low therapeutic index drugs, dose individualisation will benefit many patients

Methotrexate, tenoposide, cytarabine (3 fold dose range to achieve target exposures)

Sunitinib (6 fold range to achieve target exposures)

Allopurinol (14 fold)

Scenario simulated

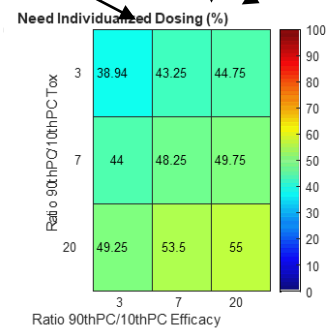
Dose= 10 mg

ED_{50Eff} = 5.5 mg

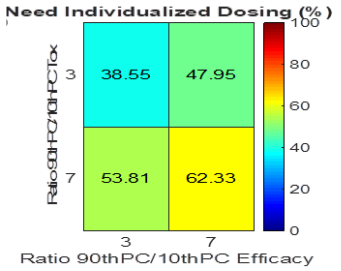
ED_{50Tox} = 24.5 mg

TI = 2 = ED_{30Tox}/ED_{60Eff}

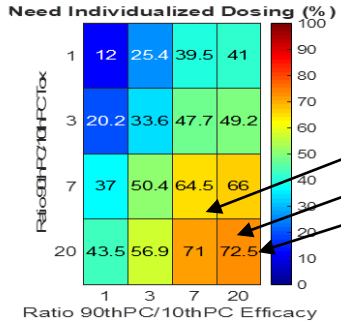
No correlation between efficacy and toxicity



50% correlation



100% correlation



axitinib

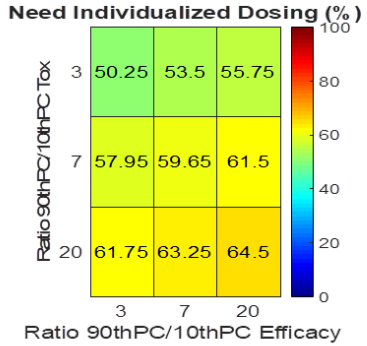
Warfarin (10-20 fold)

5-FU

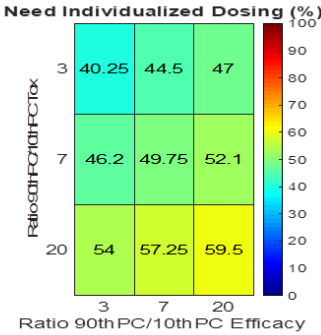
The benefit from dose-individualisation falls as therapeutic index increases

There is still significant opportunity for "moderate" TI drugs

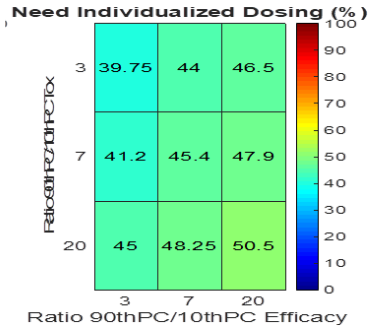
Dose = 10 mg
ED_{50Eff} = 5.5 mg
ED_{50Tox} = 24.5 mg
TI = ED_{30Tox}/ED_{60Eff}
TI = 2.0



Dose = 10 mg
ED_{50Eff} = 5.5 mg
ED_{50Tox} = 40.3 mg
TI = ED_{30Tox}/ED_{60Eff}
TI = 3.2



Dose = 10 mg
ED_{50Eff} = 5.5 mg
ED_{50Tox} = 66.5 mg
TI = ED_{30Tox}/ED_{60Eff}
TI = 5.3



To be useful, Precision Dosing must significantly improve benefit:risk

Improved benefit:risk most likely in the following situations

- Narrow therapeutic index
- Mechanism based adverse events
- Severe/irreversible adverse effects
- Irreversible consequences of inadequate dosing
- Difficult routes of administration
- Use in vulnerable populations
- Combination therapy

Challenges and barriers to precision dosing in drug development

Culture & beliefs

- Stick with what we know – “one size fits all” dosing
- Regulators don’t need or want it

Complexity

- Complexity is uncompetitive
- Patient monitoring/tests
- Interpreting the results
- Formulation complexity

Unclear development path

Unclear regulatory path for associated tools

Unclear reimbursement

Enabling precision dosing during clinical development

Population → Univariate Sub-Population → Additional and/or Multivariate Sub-Populations → Individual

Explore dose-exposure-response early

Understand & incorporate impact of PD and Disease variability on response

Use exposure-response from phase 1/2 to compare precision and fixed dosing and support pivotal trial simulations

- Identify/confirm target ranges

Dose “adaptive” clinical trials

- PK guided (Concentration-controlled)
- PD guided (Clinical response or biomarker-controlled)

Wider range of patients in clinical trials at all stages

- Phase 3 representative of real world patients

Companion CDS tool development

Formulation development to allow dose flexibility

Publish trials and models

Incentives to encourage precision dosing in drug development

It's the right thing to do

Higher development success rates

Outcomes based pricing

Patient, prescriber, provider and payer pressure – and post-approval action

Regulation

- Start by amending concepts such as "Recommended phase 2 dose" to " …dose range"
- Post approval commitments

Diagnostics developers

- Easy to use, new biomarkers
- Development and availability of clinical decision support tools

Doing now what patients need next