Drug Development to Enable Precision Dosing

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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>
<thead>
<tr>
<th>Body Weight</th>
<th>100 mg/dL</th>
<th>200 mg/dL</th>
<th>300 mg/dL</th>
<th>400 mg/dL</th>
</tr>
</thead>
<tbody>
<tr>
<td>10 kg</td>
<td>2 mL</td>
<td>4 mL</td>
<td>6 mL</td>
<td>8 mL</td>
</tr>
<tr>
<td>20 kg</td>
<td>4 mL</td>
<td>8 mL</td>
<td>11 mL</td>
<td>15 mL</td>
</tr>
<tr>
<td>30 kg</td>
<td>6 mL</td>
<td>11 mL</td>
<td>17 mL</td>
<td>23 mL</td>
</tr>
<tr>
<td>40 kg</td>
<td>8 mL</td>
<td>15 mL</td>
<td>23 mL</td>
<td>30 mL</td>
</tr>
<tr>
<td>50 kg</td>
<td>9 mL</td>
<td>19 mL</td>
<td>28 mL</td>
<td>38 mL</td>
</tr>
<tr>
<td>60 kg</td>
<td>11 mL</td>
<td>23 mL</td>
<td>34 mL</td>
<td>45 mL</td>
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<tr>
<td>70 kg</td>
<td>13 mL</td>
<td>26 mL</td>
<td>40 mL</td>
<td>53 mL</td>
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<tr>
<td>80 kg</td>
<td>15 mL</td>
<td>30 mL</td>
<td>45 mL</td>
<td>60 mL</td>
</tr>
<tr>
<td>90 kg</td>
<td>17 mL</td>
<td>34 mL</td>
<td>51 mL</td>
<td>68 mL</td>
</tr>
<tr>
<td>100 kg</td>
<td>19 mL</td>
<td>38 mL</td>
<td>57 mL</td>
<td>75 mL</td>
</tr>
<tr>
<td>110 kg</td>
<td>21 mL</td>
<td>42 mL</td>
<td>62 mL</td>
<td>83 mL</td>
</tr>
<tr>
<td>120 kg</td>
<td>23 mL</td>
<td>45 mL</td>
<td>68 mL</td>
<td>91 mL</td>
</tr>
<tr>
<td>130 kg</td>
<td>25 mL</td>
<td>49 mL</td>
<td>74 mL</td>
<td>98 mL</td>
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<tr>
<td>140 kg</td>
<td>26 mL</td>
<td>53 mL</td>
<td>79 mL</td>
<td>106 mL</td>
</tr>
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</table>

### Cuvitru sc

<table>
<thead>
<tr>
<th>Difference from Target Serum IgG Trough Levels</th>
<th>Dosing Frequency</th>
<th>30 kg</th>
<th>50 kg</th>
<th>70 kg</th>
<th>90 kg</th>
<th>110 kg</th>
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</thead>
<tbody>
<tr>
<td>100 mg/dL</td>
<td>Weekly</td>
<td>3 mL</td>
<td>5 mL</td>
<td>7 mL</td>
<td>9 mL</td>
<td>11 mL</td>
</tr>
<tr>
<td>200 mg/dL</td>
<td>Biweekly</td>
<td>6 mL</td>
<td>10 mL</td>
<td>13 mL</td>
<td>17 mL</td>
<td>21 mL</td>
</tr>
<tr>
<td>300 mg/dL</td>
<td>Weekly</td>
<td>9 mL</td>
<td>14 mL</td>
<td>20 mL</td>
<td>26 mL</td>
<td>32 mL</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Body Weight</th>
<th>Dosing Frequency</th>
<th>30 kg</th>
<th>50 kg</th>
<th>70 kg</th>
<th>90 kg</th>
<th>110 kg</th>
</tr>
</thead>
<tbody>
<tr>
<td>30 kg</td>
<td>Weekly</td>
<td>3 mL</td>
<td>5 mL</td>
<td>7 mL</td>
<td>9 mL</td>
<td>11 mL</td>
</tr>
<tr>
<td>50 kg</td>
<td>Biweekly</td>
<td>6 mL</td>
<td>10 mL</td>
<td>13 mL</td>
<td>17 mL</td>
<td>21 mL</td>
</tr>
<tr>
<td>70 kg</td>
<td>Weekly</td>
<td>9 mL</td>
<td>14 mL</td>
<td>20 mL</td>
<td>26 mL</td>
<td>32 mL</td>
</tr>
<tr>
<td>90 kg</td>
<td>Biweekly</td>
<td>12 mL</td>
<td>19 mL</td>
<td>27 mL</td>
<td>35 mL</td>
<td>42 mL</td>
</tr>
<tr>
<td>110 kg</td>
<td>Weekly</td>
<td>17 mL</td>
<td>29 mL</td>
<td>40 mL</td>
<td>52 mL</td>
<td>63 mL</td>
</tr>
</tbody>
</table>

<sup>a</sup> Derived using a linear approximation to the nomogram method with a slope of 5.3 mg/dL.

<sup>b</sup> Derived using a linear approximation of trough levels and weekly dose per kg body mass with a slope of 52.1 mg/kg.
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

<table>
<thead>
<tr>
<th>Pretreatment Serum IgE (IU/mL)</th>
<th>Dosing Freq.</th>
<th>Body Weight</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>30–60 kg</td>
</tr>
<tr>
<td>≥30–100</td>
<td>Every 4 weeks</td>
<td>150</td>
</tr>
<tr>
<td>&gt;100–200</td>
<td></td>
<td>300</td>
</tr>
<tr>
<td>&gt;200–300</td>
<td></td>
<td>300</td>
</tr>
<tr>
<td>&gt;300–400</td>
<td>Every 2 weeks</td>
<td>225</td>
</tr>
<tr>
<td>&gt;400–500</td>
<td></td>
<td>300</td>
</tr>
<tr>
<td>&gt;500–600</td>
<td></td>
<td>375</td>
</tr>
<tr>
<td>&gt;600–700</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*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

<table>
<thead>
<tr>
<th>Pretreatment Serum IgE (IU/mL)</th>
<th>Dosing Freq.</th>
<th>Body Weight</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>20–25 kg</td>
</tr>
<tr>
<td>≥30–100</td>
<td>Every 4 weeks</td>
<td>75</td>
</tr>
<tr>
<td>&gt;100–200</td>
<td></td>
<td>150</td>
</tr>
<tr>
<td>&gt;200–300</td>
<td></td>
<td>150</td>
</tr>
<tr>
<td>&gt;300–400</td>
<td>Every 4 weeks</td>
<td>225</td>
</tr>
<tr>
<td>&gt;400–500</td>
<td></td>
<td>225</td>
</tr>
<tr>
<td>&gt;500–600</td>
<td></td>
<td>300</td>
</tr>
<tr>
<td>&gt;600–700</td>
<td></td>
<td>375</td>
</tr>
<tr>
<td>≥700–800</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt;800–900</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt;900–1000</td>
<td></td>
<td></td>
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<tr>
<td>&gt;1000–1100</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt;1100–1200</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt;1200–1300</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Dosing frequency:*
- Subcutaneous doses to be administered every 4 weeks
- Subcutaneous doses to be administered every 2 weeks

Insufficient Data to Recommend a Dose
Eculizumab for aHUS in The Netherlands

Indi
d

vidualized 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

<table>
<thead>
<tr>
<th></th>
<th>Pre ACM</th>
<th>Using ACM</th>
<th>when ACM believed</th>
</tr>
</thead>
<tbody>
<tr>
<td>In range Hb (%)</td>
<td>70.6</td>
<td>76.6</td>
<td>83.2</td>
</tr>
<tr>
<td>Median darbopoetin dose</td>
<td>40</td>
<td>30</td>
<td>20</td>
</tr>
<tr>
<td>CV events (/1000 patient years)</td>
<td>517</td>
<td>440</td>
<td></td>
</tr>
<tr>
<td>Transfusion events</td>
<td>152</td>
<td>92</td>
<td></td>
</tr>
</tbody>
</table>
Machine learning enabling individualised dosing

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

Gregory Yosuey
Pratik Shah*
Media Lab
Massachusetts Institute of Technology
Cambridge, MA, USA

Source of PKPD data, n=45

Cancer Therapy: Clinical

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

Benjamin Ribba1, Gerlind Kaloshii, Mathieu Peyre1, Damien Ricard, Vincent Calvez2, Michel Todd2, Branka Cajavec-Bernard1, Ahmed Iqbal6, Dimitri Psimaros, Linda Dainese5, Johan Pallud1, Stephanie Cartiaux-Care1, Jean-Yves Delattre1, Jerome Honnorat1,4,2, Emmanuel Grenier1, and Francois Ducay1,4,6

(a) (b) (c) (d)
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

Scenario simulated

Dose = 10 mg

$ED_{50\text{Eff}} = 5.5 \, \text{mg}$

$ED_{50\text{Tox}} = 24.5 \, \text{mg}$

$TI = 2 = \frac{ED_{30\text{Tox}}}{ED_{60\text{Eff}}}$

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

Sunitinib (6 fold range to achieve target exposures)

Allopurinol (14 fold)

No correlation between efficacy and toxicity

50% correlation

100% correlation

5-FU

axitinib

Warfarin (10-20 fold)
The benefit from dose-individualisation falls as therapeutic index increases.

There is still significant opportunity for “moderate” TI drugs.

**Example Calculations**

- **Dose = 10 mg**
- $ED_{50\text{Eff}} = 5.5 \text{ mg}$
- $ED_{50\text{Tox}} = 24.5 \text{ mg}$
- $TI = \frac{ED_{50\text{Tox}}}{ED_{50\text{Eff}}} = 2.0$

- **Dose = 10 mg**
- $ED_{50\text{Eff}} = 5.5 \text{ mg}$
- $ED_{50\text{Tox}} = 40.3 \text{ mg}$
- $TI = \frac{ED_{50\text{Tox}}}{ED_{50\text{Eff}}} = 3.2$

- **Dose = 10 mg**
- $ED_{50\text{Eff}} = 5.5 \text{ mg}$
- $ED_{50\text{Tox}} = 66.5 \text{ mg}$
- $TI = \frac{ED_{50\text{Tox}}}{ED_{50\text{Eff}}} = 5.3$
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

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