Mechanistic Understanding of the Differences and Similarities in PK/PD for Therapeutic Monoclonal Antibodies in Various Diseases

Chao Han, PhD
Scientific Director of Early Development, Pharmacokinetics & Pharmacodynamics Biologics Clinical Pharmacology

AAPS NBC, May 19th, 2014, San Diego
Level of Mechanistic Understanding for SMD

- Drug Concentration in Circulation
  - GI
  - Tissue
  - Kidney

- Disease ↔ PK
  - First-path

- Disease ↔ PK
  - Blood flow

- Tissue
  - Permeability
  - Transporters
  - Protein binding
  - Tissue metabolism

- Drug Concentration in Circulation
  - CYPs, MAO, ADH…
  - Phase II enzymes
  - P-gp, OATP…
  - Enterohepatic cycling

- Liver
  - P-gp, OATP, OCT…
  - CYPs, others…
  - Phase II enzymes
  - Filtration, size…

- Kidney

- May 19, 2014
Are Hepatic Impairment Studies Necessary for Therapeutic Proteins?

Jun Yang, PhD; Stacy Shord, PharmD; Hong Zhao, PhD; Yuxin Men, PhD; and Atiquir Rahman, PhD

Table I. Therapeutic proteins included in the survey for evaluating the effect of hepatic impairment on their pharmacokinetics.

<table>
<thead>
<tr>
<th>Category</th>
<th>Therapeutic Protein</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cytokines and growth factors (n=23)</td>
<td>Cytokines (12): aldesleukin, anakinra, denileukin difitox, interferon alfa-2a, interferon alfa-2b, interferon alfacon-1, interferon alfa-n3, interferon beta-1a, interferon beta-1b, interferon gamma-1b, peginterferon alfa-2a, peginterferon alfa-2b Growth factors (11): becaplermin, darbepeotin alfa, epoetin alfa, filgrastim, oprelvekin, pegzerepoitin alfa, palifermin, pegfilgrastim, romiplostim, sargramostim, tbo-filgrastim</td>
</tr>
<tr>
<td>Enzymes (n=23)</td>
<td>Agalsidase beta, alglucosidase alfa, alteplase, asparaginase, collagenase, dornase alfa, drotrecogin alfa, erwinaze, galsulfase, glucarpidase, idursulfase, laronidase, oripalense, repalase, streptokinase, velaglucerase alfa Adalimumab, ado-tra: bevacizumab, brentinolodendate, cetuximab, gemtuzumab ozogam, infliximab, ipilimumab, ofatumumab, omalizumab, ranibizumab, raxibacus, ustekinumab</td>
</tr>
<tr>
<td>Monoclonal antibodies (n=32)</td>
<td>Adalimumab, absciximab, brentinolodendate, cetuximab, gemtuzumab ozogam, infliximab, ipilimumab, ofatumumab, omalizumab, ranibizumab, raxibacus, ustekinumab</td>
</tr>
</tbody>
</table>

Table II. The impact of hepatic impairment on the pharmacokinetics (PK) of therapeutic proteins.

<table>
<thead>
<tr>
<th>Category</th>
<th>Name</th>
<th>Approved Indication</th>
<th>Study Analysis</th>
<th>Impact of Hepatic Impairment</th>
<th>Dose Adjustment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Enzyme</td>
<td>Rasburicase</td>
<td>Management of plasma uric acid levels in chemotherapy</td>
<td>PK subgroup analysis</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Drotrecogin alfa</td>
<td></td>
<td>Reduction of mortality associated with severe sepsis</td>
<td>PK subgroup analysis</td>
<td>Clearance decreased 24% - 27% in patients with elevated ALT or AST (≥3 x ULN)</td>
<td>No</td>
</tr>
<tr>
<td>Cetuximab</td>
<td></td>
<td>Squamous cell carcinoma of the head and neck; K-Ras mutation-negative, EGFR-expressing colorectal cancer</td>
<td>Population PK</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Panitumumab</td>
<td></td>
<td>EGFR-positive metastatic colorectal carcinoma</td>
<td>Population PK</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Ipalimomab</td>
<td></td>
<td>Melanoma</td>
<td>Population PK</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Cetolizumab</td>
<td></td>
<td>Crohn’s disease; rheumatoid arthritis</td>
<td>Population PK</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Ziv-afibrecpe</td>
<td></td>
<td>Metastatic colorectal cancer</td>
<td>Population PK</td>
<td>No</td>
<td>No</td>
</tr>
</tbody>
</table>

- Ninety-one (91) therapeutic proteins (TPs) approved by the FDA up to 2013 were reviewed
- No dedicated trials to assess PK for TPs in patients with hepatic impairment were conducted
- Subgroup (n=2) or population PK (n = 5) PK analyses were performed for 7 TPs
Renal elimination processes of peptides and Small proteins:

glomerular filtration followed by either
(a) intraluminal metabolism or
(b) tubular reabsorption with intracellular lysosomal metabolism or
(c) peritubular extraction with intracellular lysosomal metabolism

Tang and Meibohm 2006.
Renal Filtration Size Cutoff

• **FDA Draft Guidance:** Renal impairment studies are also recommended for therapeutic proteins ... with a MW less than **69 kDa**.

• **CHMP Guideline:** For larger protein (> **50 kDa**) molecules, elimination in other tissues and/or in target cells through e.g. receptor-mediated endocytosis followed by catabolism is more important relative to renal filtration.

• The size-selective cutoff for glomerular filtration is approximately **60 kDa**
  - Peptides and small proteins (<5 kDa): their glomerular filtration clearance approaches the glomerular filtration rate
  - For MW > **30 kDa**, the filtration rate falls off sharply

• **IgG** (MW: ~150 kDa), while not considered to be renally eliminated, may be eliminated through the kidneys of proteinuric patients

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rHuIL-10: Protein with MW <30 kDa

- The clearance of rHuIL-10 (MW: 18 kDa) is dependent on glomerular filtration
- Dose alteration may be needed for rHuIL-10 in subjects with chronic renal insufficiency

Anakinra: Protein with MW <30 KDa

- **Anakinra**, a rHuIL-1 receptor antagonist, has MW of 17.3 kDa
- Anakinra is predominantly cleared through the kidney in humans: its CL/F is reduced by **70%** and **75%** in severely impaired and end-stage renal disease (ESRD) groups, respectively
- A Dose or schedule adjustment is indicated for persons with several renal impairment or ESRD

Increased Total Clearance of Adalimumab in Nephrotic Patients

- Adalimumab total clearance in focal segmental glomerulosclerosis (FSGS) patients (n = 7) 2- to 5-fold higher than that in RA

- Renal CL of adalimumab only account for 0-13% of the dose.

- Non-renal (CL_{NR}) clearances contributed more to increased total clearance of adalimumab in FSGS patients.

Medicine is a science of uncertainty and an art of probability.

- Sir William Osler

As quoted in Computers in biomedical research (1965) by Ralph W. Stacy, p. 320
Presentation Overview

• Clearance Mechanisms for Biologics

• PK in Disease Populations - discussions
  – Diabetics
  – Inflammatory bowel disease
  – Membrane bound target – cancer
  – PK in Geriatrics
  – Racial/Ethnic and Body Weight

• More Discussions on Disease
The Role of FcRn and Fcγ in mAb Disposition

FcRn protects mAb from endosomal proteolysis. The binding affinities affect CL; but not fully explainable by the data alone. Plays a role in absorption and distribution too.

Fcγ receptors may play a role in mAb elimination: mAb-target complex as well as antidrug antibody-mAb complex.
Saturation of FcRn Leads to Faster Clearance

- Albumin: 3.4-5.0 g/dL (not compete with IgGs)
- Total globulin: 2.2-4.0 g/dL – 75% IgG - 66% IgG1
- Normal population average IgG conc is 1.1 g/dL (Gonzalez-Quintela 2007)
- At a 200 mg/kg dose of mAb the $C_{\text{max}}$ would be $\sim$0.5 g/dL.
Target Mediated Clearance/Disposition

Target-mediated clearance is a main cause of non-linear PK for biologics.
Immunogenicity (ADA)

- **Altered PK**
  - The impact could be either way
  - ADA may not accurately detectable depends on the assay and residual drug in the sample

- **Reduced efficacy**
  - Neutralizing and/or clearing ADA

- **Patient Safety**
  - Cross reactivity
  - Allergic reactions (e.g. PRCA)
  - Immune complexes

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**Staining of hIgG in immune complex deposits in the kidney in monkey**

Heyen et al. 2014

**Richter et al. 1999**
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• More Discussions on Disease
Diabetic Comorbidity on Ustekinumab PK in Psoriatic Patients

Primary analysis estimate and 90% CI

- 10.6% of psoriatic patients had diabetic comorbidity
- Diabetic comorbidity resulted in 28.7% higher CL/F
- Exact reasons are under investigation

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- Diabetic comorbidity resulted in 28.7% higher CL/F
- Exact reasons are under investigation
Several Plausible Mechanism(s) for the Diabetic Effect on Ustekinumab CL/F?

Altered renal excretion?

Increased glycation?

and/or

FcRn affinity or receptor density difference in diabetics?

...
Increased Renal Clearance: - Unlikely a Major Cause ...

<table>
<thead>
<tr>
<th>Populations</th>
<th>CLcr (mL/min)</th>
</tr>
</thead>
<tbody>
<tr>
<td>With Diabetes (n = 206)</td>
<td>136 ± 48</td>
</tr>
<tr>
<td>Without Diabetes (n = 1731)</td>
<td>128 ± 41</td>
</tr>
</tbody>
</table>

Non-diabetic

Diabetic

May 19, 2014
Increased Glycation May Account for Enhanced Clearance in Diabetes

Fig. 1. The amount of radioactivity per mg of whole blood over time, up to 48 h after injection. The values are expressed as a percentage of the \( t=0 \) values for both glycated (●) and unglycated IgG (○). Points shown are obtained from the mean of six animals and bars show ±1 s.e.m.

Kaneshige H. Diabetes 1987

Elevated Serum IgG Level in Diabetic Patients

**Graph:**
- **IgG concentration (mg/dL):**
  - Normal Population: N=349
  - ~117 Glucose (mg/dL) Diabetic Patients: N=27
  - ~221 Glucose (mg/dL) Diabetic Patients: N=34
  - ≤9% HbA1c Chronic Periodontitis Patients: N=35
  - >9% HbA1c Chronic Periodontitis Patients: N=35

- **Normal CL:**
- **Diabetic Conc:**
- **Range of IVIG:**

A ~20% increase in CL would be expected for the diabetics due to elevated circulating IgG concentrations.

**References:**
Exploration of the Diabetic Effect on Ustekinumab Apparent Clearance (CL/F)

- A notable diabetic effect (↑CL/F: 28%) in two pivotal psoriasis studies has been confirmed by other ustekinumab studies in psoriasis

- Less of a diabetic effect was observed for two other in-house mAbs or ustekinumab in another indication (↑CL/F: 10~13%)

- **Future work:**
  - analyze glycation/glycoform patterns of ustekinumab in psoriatic subjects with and without diabetes;
  - experimental confirmation of glycation’s effect on CL;
  - collect circulating IgG level for PK/PD analysis.

Zhu Y et al JCP 2009
## History of Infliximab Clinical Development

### Approved Indications

<table>
<thead>
<tr>
<th>CD: Acute treatment for luminal CD</th>
<th>1998</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acute treatment for fistulizing CD</td>
<td></td>
</tr>
<tr>
<td>RA (MTX-Failure): Reducing signs and symptoms</td>
<td>1999</td>
</tr>
<tr>
<td>RA (MTX-Failure): Inhibiting progression of structural damage</td>
<td>2000</td>
</tr>
<tr>
<td></td>
<td>2001</td>
</tr>
<tr>
<td>RA (MTX-Failure): Improving physical function</td>
<td>2002</td>
</tr>
<tr>
<td>CD: Maintenance therapy for luminal CD</td>
<td></td>
</tr>
<tr>
<td>CD: Maintenance therapy for fistulizing CD</td>
<td>2003</td>
</tr>
<tr>
<td>RA (MTX-Naïve): All claims for MTX-failures</td>
<td>2004</td>
</tr>
<tr>
<td>AS: Reducing signs and symptoms</td>
<td></td>
</tr>
<tr>
<td>PsA: Reducing signs and symptoms</td>
<td>2005</td>
</tr>
<tr>
<td>UC: Reducing signs and symptoms; Inducing and maintaining mucosal healing; Eliminating corticosteroid use</td>
<td></td>
</tr>
<tr>
<td>PedCD: Reducing signs and symptoms</td>
<td>2006</td>
</tr>
<tr>
<td>Inducing and maintaining clinical remission</td>
<td></td>
</tr>
<tr>
<td>PsA: Inhibiting progression of structural damage</td>
<td></td>
</tr>
<tr>
<td>Improving physical function</td>
<td></td>
</tr>
<tr>
<td>PsO: Severe disease with needs for systemic therapy</td>
<td></td>
</tr>
<tr>
<td>UC: Maintaining clinical remission and mucosal healing</td>
<td>2007</td>
</tr>
<tr>
<td>PedUC: Reducing signs and symptoms</td>
<td>2008</td>
</tr>
<tr>
<td>Inducing and maintaining clinical remission</td>
<td>2009</td>
</tr>
<tr>
<td></td>
<td>2010</td>
</tr>
<tr>
<td></td>
<td>2011</td>
</tr>
</tbody>
</table>
### Differential Infliximab Clearance In Various Patient Populations

<table>
<thead>
<tr>
<th>Population</th>
<th>Mean Infliximab CL (L/day)</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rheumatoid Arthritis (RA)</td>
<td>0.264</td>
<td>Kavanaugh, et al., J Rheumatol 2000, 27: 841-50</td>
</tr>
<tr>
<td>Crohn’s Disease (CD)</td>
<td>0.383</td>
<td>Fasanmade, et al., Clin Ther 2011, 33:946-64</td>
</tr>
</tbody>
</table>

- Would the observed 40~50% higher clearance in inflammatory bowel disease (IBD), i.e., UC and CD, be caused by diseases or other factors (e.g., inter-study or assay variability, concomitant medications, etc.)?
Protein-Losing Enteropathy (PLE) in IBD

- Protein clearances show statistically significant correlation with the length of radiographically abnormal gastrointestinal segment ($r = 0.76$)

- Increases in intestinal clearances of IgG and IgA are closely related to the severity of the intestinal lesions


Fig. 1. Relationship between intestinal protein loss and the extent of Crohn’s disease.
Systemic lupus erythematosus (SLE) patients have marked increase in IgG turnover and decrease in $t_{1/2}$.

PLE often happened in patients with severe SLE.

Zheng et al. found that all SLE patients had severe hypoalbuminemia, and had albumin leaking to the intestinal lumen; $\sim$36% of SLE patients had significant decrease in serum IgG level.

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**PLE Is Also Observed in Lupus ...**

<table>
<thead>
<tr>
<th>Subject</th>
<th>Serum IgG Conc. (mg/L)</th>
<th>IgG $t_{1/2}$ (day)</th>
<th>Total Body IgG Catabolized/day (%)</th>
<th>IgG Absolute Synthetic Rate (mg/kg/day)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Healthy</td>
<td>10.7</td>
<td>18.0</td>
<td>3.9</td>
<td>34.5</td>
</tr>
<tr>
<td>SLE</td>
<td>18.3</td>
<td>8.2</td>
<td>10.7</td>
<td>127.5</td>
</tr>
</tbody>
</table>

Metabolic Studies of $^{125}$I- IgG, IgM, and Albumin in a Patient with SLE

Investigation of the IBD Effect on Infliximab PK

- Lack of cross-indication PK data from other mAbs are available for confirmation
- Variable immune-based assay and/or inter-study comparison may confound reliable PK comparison among diseases
- Other covariates perplexed the analyses
- Protein-losing enteropathy (PLE) may be one of the plausible mechanisms for the higher CL in IBD patients
For mAbs against membrane-bound receptors (e.g., rituximab), the apparent differences observed in PK might be related to the differential receptor expression (e.g., CD20)

MAbs Against Membrane-Bound Receptor – Rituximab Example

- Biphasic PKs of rituximab. The model shows high clearance by specific binding to CD20 which, after saturation, leads to low clearance through non-specific catabolism

Golay et al., mAbs 5:5, 826–837; September/October 2013
Predicting Efficacy of Rituximab Combination Chemotherapy in Non-Hodgkin’s Lymphoma

Body Size + Disease Burden (IgE): Omalizumab Example

Table 4. Dose and Frequency Nomogram

<table>
<thead>
<tr>
<th>Baseline total IgE (IU/mL)</th>
<th>Weight (kg)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>30–60</td>
</tr>
<tr>
<td>≥30–100</td>
<td>150 mg</td>
</tr>
<tr>
<td>&gt;100–200</td>
<td>300 mg</td>
</tr>
<tr>
<td>&gt;200–300</td>
<td>300 mg</td>
</tr>
<tr>
<td>&gt;300–400</td>
<td></td>
</tr>
<tr>
<td>Every 2-wk dosing</td>
<td></td>
</tr>
<tr>
<td>≥30–100</td>
<td></td>
</tr>
<tr>
<td>&gt;100–200</td>
<td>see 4-wk dosing</td>
</tr>
<tr>
<td>&gt;200–300</td>
<td>225 mg</td>
</tr>
<tr>
<td>&gt;300–400</td>
<td>300 mg</td>
</tr>
<tr>
<td>&gt;400–500</td>
<td>300 mg</td>
</tr>
<tr>
<td>&gt;500–600</td>
<td>300 mg</td>
</tr>
<tr>
<td>&gt;600–700</td>
<td>375 mg</td>
</tr>
</tbody>
</table>

IgE = immunoglobulin E.

How About mAbs’ Clearance in Elderly?

- Upon inspection of around 30 FDA-approved mAbs, their PK in elderly were not altered to a magnitude that warrants dose adjustment
  - No significant effect of age on PK for most of the mAbs
  - Few cases:
    - **Adalimumab**: lower CL with increasing age in 40 to >75 yrs
    - **Belimumab**: higher CLcr and proteinuria (>2 g/day) resulted in higher CL

- Age-related decline in renal function in elderly subjects: ~1 mL/min/1.73 m²/year decrease in GFR

Frassetto LA et al. Am J Physiology 1996; FDA USPIs for all approved mAbs.
Molecular size, elimination rate and tissue/tumor uptake of therapeutic molecules

**Factor affect tissue uptake** | **Tissue uptake**
--- | ---
Size of mol | ↓
Capillary surface area | ↑
Conc. Gradient ($t_{1/2}$) | ↑
Binding affinity | ↑
CL* | ↓

* CL includes two components: catabolism and target mediated disposition

Wittrup et al. 2012, Schmidt and Wittrup 2009
Possible Sources for Ethnic Differences in ADME?

- **Absorption:** no evidence has suggested any ethnic difference in absorption parameters (i.e., lymphatic flow rate, transit time from lymph systems to systemic circulation, elimination rate during lymphatic transport)

- **Distribution:**
  - **Paracellular movement:** no reports describing ethnic difference observed in paracellular movements of mAbs

- **Elimination:**
  - **Nonspecific pathway (non-saturable)**
    * **FcRn:** ethnic differences in genetic polymorphism of FCGRT
    * **FcγR:** ethnic differences in the frequencies of variants of FcγRIIa, FcγRIIb, FcγRIIIa, and FcγRIIIb
  - **Target-mediated (saturable)**
    * **Target (antigen) level:** possible ethnic differences, however, confounded by heterogeneous disease conditions

FCGRT Genetic Polymorphism on mAb PK: Cetuximab Example

- A significantly slower distribution clearance ($Q$) for the homozygote group than the heterozygote group ($p = 0.021$), but not for elimination clearance
- Its clinical relevance is yet to be demonstrated

Lack of Ethnic Effect on mAb PK: Japanese vs. Non-Japanese Subjects


* Underlined mAbs: target cell surface antigens.
Similar mAb Dosing Regimens Despite Body Weight (BW) Difference

<table>
<thead>
<tr>
<th>Table 1: Approved Therapeutic Monoclonal Antibodies in Both Japan and the United States</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>United States</strong></td>
</tr>
<tr>
<td><strong>Generic Name</strong></td>
</tr>
<tr>
<td>Fixed dosing</td>
</tr>
<tr>
<td>Adalimumab</td>
</tr>
<tr>
<td>Omalizumab&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>Ustekinumab</td>
</tr>
<tr>
<td>Basiliximab</td>
</tr>
</tbody>
</table>

Body size–based dosing

<table>
<thead>
<tr>
<th><strong>Generic Name</strong></th>
<th><strong>Approval Date</strong></th>
<th><strong>Approved Dosage</strong></th>
<th><strong>Approval Date</strong></th>
<th><strong>Approved Dosage</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>Bevacizumab&lt;sup&gt;b&lt;/sup&gt;</td>
<td>February 2004</td>
<td>5 mg/kg or 10 mg/kg every 2 wk</td>
<td>April 2007</td>
<td>5 mg/kg or 10 mg/kg every 2 wk</td>
</tr>
<tr>
<td>Celecoxib&lt;sup&gt;b&lt;/sup&gt;</td>
<td>February 2004</td>
<td>400 mg/m², then 250 mg/m² weekly</td>
<td>July 2008</td>
<td>400 mg/m², then 250 mg/m² weekly</td>
</tr>
<tr>
<td>Gemtuzumab&lt;sup&gt;b&lt;/sup&gt;</td>
<td>May 2000</td>
<td>9 mg/m² × 2 (14 d apart)</td>
<td>July 2005</td>
<td>9 mg/m² × 2 (14 d apart)</td>
</tr>
<tr>
<td>Infliximab&lt;sup&gt;b&lt;/sup&gt;</td>
<td>August 1998</td>
<td>3 mg/kg at wk 0, 2, and 6, then up to 10 mg/kg every 8 or 4 wk&lt;sup&gt;c&lt;/sup&gt;, or 5 mg/kg at wk 0, 2, and 6, then 10 mg/kg every 8 wk&lt;sup&gt;c&lt;/sup&gt;</td>
<td>January 2002</td>
<td>3 mg/kg at wk 0, 2, and 6, then up to 10 mg/kg every 8 wk or 6 mg/kg every 4 wk&lt;sup&gt;c&lt;/sup&gt;; or 5 mg/kg at wk 0, 2, and 6 and every 8 wk&lt;sup&gt;c&lt;/sup&gt;</td>
</tr>
<tr>
<td>Palivizumab&lt;sup&gt;b&lt;/sup&gt;</td>
<td>June 1998</td>
<td>15 mg/kg monthly</td>
<td>January 2002</td>
<td>15 mg/kg monthly</td>
</tr>
<tr>
<td>Rituximab&lt;sup&gt;b&lt;/sup&gt;</td>
<td>November 1997</td>
<td>375 mg/m² weekly for 4 or 8 wk or 250 mg/m² with concomitant Indium-111</td>
<td>June 2001</td>
<td>375 mg/m² weekly (up to 8 wk) or 250 mg/m² with concomitant Indium-111</td>
</tr>
<tr>
<td>Trastuzumab</td>
<td>September 1998</td>
<td>4 mg/kg, then 2 mg/kg weekly&lt;sup&gt;d&lt;/sup&gt; or 8 mg/kg, then 6 mg/kg every 3 wk</td>
<td>April 2001</td>
<td>4 mg/kg, then 2 mg/kg weekly&lt;sup&gt;d&lt;/sup&gt; or 8 mg/kg, then 6 mg/kg every 3 wk</td>
</tr>
<tr>
<td>Tocilizumab</td>
<td>January 2010</td>
<td>4 mg/kg, then 8 mg/kg every 4 wk&lt;sup&gt;e&lt;/sup&gt;</td>
<td>April 2005</td>
<td>8 mg/kg every 4 wk&lt;sup&gt;f&lt;/sup&gt; or 8 mg/kg every 2 wk&lt;sup&gt;g&lt;/sup&gt;</td>
</tr>
</tbody>
</table>

Observed Ethnicity Differences in PK: Body Weight (BW)

For mAbs against soluble antigens (e.g., ustekinumab), the apparent differences observed in PK are most likely due to the differences in BW

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- Renal CL of adalimumab only account for 0-13% of the dose.

- Non-renal (CL_{NR}) clearances contributed more to increased total clearance of adalimumab in FSGS patients.

Possible Preexisting Immunologic Cross-reactivity?

- Etiology and diagnosis of FSGS
- Immune complex-induced glomerulonephritis and FSGS
- Possible preexisting anti IgG antibody in adalimumab case?
  - nephrotic syndrome after bevacizumab may be related to renal disposition of ADA-drug complex. (George et al. 2007)
  - Similar path finding in animals developed ADA (Heyen et al. 2014)

- ADA was not evaluated in the adalimumab study!

Figure 2. Adalimumab concentration-versus-time curves after single dose. Note that drug concentrations are provided as ng/mL to enhance the clarity of the graphs.

Mechanistic understanding of the PK/PD in disease or special populations for biologics is quickly developing.

Conventional pathways (hepatic and renal) do not cover all the covariates for biologic therapeutics, such as mAb.

Better unstinting of the “ADME” of biologics will help to build the framework for an additional set of information to be collected.

Implementation of the knowledge in clinical practice and collection of relevant information are critical and urgent.

Properly incorporating relevant covariates is vital for modeling.
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