Pharmacokinetic and Pharmacodynamic Considerations in the Development of Macromolecules

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OUTLINE OF LECTURE TOPICS

Macromolecules
Interspecies Scaling
Pharmacokinetic Characteristics
  ▪ Scientific Issues
Pharmacodynamics
Monoclonal Antibodies
<table>
<thead>
<tr>
<th>Macromolecule</th>
<th>Trade Name</th>
</tr>
</thead>
<tbody>
<tr>
<td>Erythropoietin</td>
<td>Epogen (Amgen)</td>
</tr>
<tr>
<td>Growth Hormone</td>
<td>Nutropin (Genentech)</td>
</tr>
<tr>
<td>G-CSF</td>
<td>Neupogen (Amgen)</td>
</tr>
<tr>
<td>IL-2</td>
<td>Proleukin (Chiron)</td>
</tr>
<tr>
<td>IL-11</td>
<td>Neumega (GI)</td>
</tr>
<tr>
<td>Factor IX</td>
<td>BeneFIX (GI)</td>
</tr>
<tr>
<td>rt-PA</td>
<td>Alteplase (Genentech)</td>
</tr>
</tbody>
</table>
### APPROVED MONOCLONAL ANTIBODIES

<table>
<thead>
<tr>
<th>Name</th>
<th>Approval</th>
<th>Indication</th>
</tr>
</thead>
<tbody>
<tr>
<td>Avastin Bevacizumab</td>
<td>Feb, 2004</td>
<td>First line (with 5-FU) in metastatic colon CA</td>
</tr>
<tr>
<td>Erbitux Cefuximab</td>
<td>Feb, 2004</td>
<td>Alone or in combination in metastatic colon CA</td>
</tr>
<tr>
<td>Raptiva Efalizumab</td>
<td>Oct, 2003</td>
<td>Moderate to severe psoriasis</td>
</tr>
<tr>
<td>Xolair Omalizumab</td>
<td>June, 2003</td>
<td>Asthma</td>
</tr>
<tr>
<td>Humira Adalimumab</td>
<td>Dec, 2002</td>
<td>Prophylaxis of acute organ rejection</td>
</tr>
<tr>
<td>Campath Alemtuzumab</td>
<td>May, 2001</td>
<td>Second line treatment of β-cell CLL in patients</td>
</tr>
</tbody>
</table>
ASSAYS FOR MACROMOLECULES

Immunoassays
- ECL (Electrochemiluminescence immunoassay)
- ELISA (Enzyme-Linked Immuno-sorbent Assay)
- RIA (Radioimmunoassay)
- IRMA (Immunoradiometric Assay)
- RRA (Radioreceptor Assay)
INTERSPECIES SCALING OF MACROMOLECULES

Factors to Consider
- Species specificity
- Glycosylation and sialation
- Binding proteins
- Size, shape and charge
- Relative abundance of tissue receptors
ALLOMETRIC EQUATIONS FOR
SOME MACROMOLECULES

table
INITIAL COMPARTMENT VOLUME
PREDICTED BY ALLOMETRIC SCALING COMPARED
WITH OBSERVED $V_1$

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ELIMINATION CLEARANCE
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COMPARED WITH OBSERVED CL

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ALLOMETRIC EQUATIONS for
EGF Mab PK PARAMETERS
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COMPARISON BETWEEN the PREDICTED EGF PK PARAMETERS and OBSERVED PK PARAMETERS

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PHARMACOKINETIC CHARACTERISTIC OF MACROMOLECULES

- Endogenous concentrations
- Absorption
- Distribution
- Metabolism
- Elimination
THE PROBLEM OF ENDOGENOUS CONCENTRATIONS OF MACROMOLECULES

- Endogenous concentrations - What do you do with them?
- Two examples
  Erythropoietin
ERYTHROPOIETIN

Scatter plot graph
ABSORPTION OF MACROMOLECULES

Flip-flop model
Site of administration
RELATIONSHIP BETWEEN MW AND LYMPHATIC ABSORPTION OF WATER SOLUBLE COMPOUNDS

Relationship between MW and Lymphatic Absorption of Water Soluble Compounds

COMPARISON OF ABSORPTION AND ELIMINATION RATE CONSTANTS

Chart comparison
SITE OF INJECTION EFFECTS
ON EPO ABSORPTION

2 line graphs

Subcutaneous Injection Site Effects on Golimumab Pharmacokinetics

ANOVA analysis except for Tmax which was Kruskal Wallis test
DISTRIBUTION OF MACROMOLECULES

Volume of Distribution
Binding Proteins
DISTRIBUTION VOLUMES
OF REPRESENTATIVE MACROMOLECULES

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PHARMACOKINETICS of MARKETED MONOCLONAL ANTIBODIES

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EFFECTS & RELEVANCE OF MACROMOLECULE BINDING TO $\alpha_2$-MACROGLOBULIN
METABOLIC EFFECTS OF MACROMOLECULES

Effects on P450 Enzymes
EFFECTS OF MACROMOLECULES
ON P450 CYP ENZYMES

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EXCRETION OF MACROMOLECULES

Contributions of kidney and liver
CHO vs E. Coli produced
Receptor mediated clearance
RELATIONSHIP BETWEEN MOLECULAR WEIGHT AND ELIMINATION CLEARANCE

table
LIVER CELL SURFACE RECEPTORS FOR CLEARANCE OF CARBOHYDRATES & MONOSACCHARIDES

table
DIFFERENCES BETWEEN rhEPO AND NESP (NOVEL ERYTHROPOIESIS-STIMULATING PROTEIN)

rhEPO
- 165 normal amino acid sequence
- Up to 40% carbohydrate
- 3 N-linked sugar chains
- Up to 14 sialic acids
- 30.4 Kd
- Plasma T\(_{1/2}\) = 4-8 hrs

NESP
- 5 amino acid exchanges
- Up to 52% carbohydrate
- 5 N-linked sugar chains
- Up to 22 sialic acids
- 38.5 Kd
- Plasma T\(_{1/2}\) = 24 hrs
METABOLIC FATE OF EPO

*Extracellular deglycosylation and proteolytic cleavage*

Hepatocytic galactose receptor mediated uptake -> Intracellular degradation
Renal Filtration -> Tubular reabsorption and degradation
EPO receptor mediated uptake -> Intracellular degradation
SERUM CONCENTRATION-TIME PROFILES
FOR CHO VS. E. Coli PRODUCED GM-CSF

SERUM CONCENTRATION-TIME PROFILES FOR NON-GLYCOSYLATED VS. GLYCOSYLATED G-CSF

table

RELATIONSHIP BETWEEN G-CSF CLEARANCE AND ABSOLUTE NEUTROPHIL COUNT

Graph

CHARACTERISTICS THAT AFFECT THE PHARMACOKINETICS OF MACROMOLECULES

- Physical characteristics (charge)
- Post-translational modification
- Binding
  - Binding affinity to FcRn for Mabs
- Route of administration
- Duration of administration
- Frequency of administration
PATIENT CHARACTERISTICS THAT AFFECT PHARMACOKINETICS OF MACROMOLECULES

Age
Gender
Disease
Concurrent drugs
Patient Characteristics Affecting PK of Macromolecules

Gender

- Daily rhGH dose/kg required to normalize IGF-1 response in GH deficient women is higher than in men
- Estrogen replacement also significantly increases rhGH dose requirement

Disease

- In RA patients requiring a statin, the administration of tocilizumab (an IL-6 Mab), reduced the AUC of simvastatin by 50%
Drug-Drug Interactions

The Journal of Clinical Pharmacology
Points to Consider for DDIs of Biologics

In vitro or in vivo animal studies have limited value in predicting clinical interactions.

Evaluating drug-drug interactions is particularly important when the therapeutic index is narrow.

Not all interactions between biologics and small molecule drugs are due to CYP or transporter modulation.

If the biologic is a cytokine modulator, there is compelling evidence that cytokine modulation affects the CYP 450 enzyme system.
Types of DDI Studies Used During Drug Development of Biologics

Huang SM, Zhao H, Lee JI et al. CPT 2010;87:497-503
PHARMACODYNAMICS
OF MACROMOLECULES

Important considerations
- Regimen dependency
- Endpoints
- Models
REGIMEN DEPENDENCY OF IL-12 PHARMACOKINETICS AND IFN-γ STIMULATION

PHARMACODYNAMIC ENDPOINTS

Easy - replacement proteins
  - rFIX

Difficult - casade of events
  - IGF-1
RELATIONSHIP BETWEEN rFIX CONCENTRATION AND ACTIVITY

Schaub et al. Seminars in Hematology 1998; 35:28-32
PK-PD MODEL OF rhGH WITH
MEASURED VS. PREDICTED [IGF-1] AFTER SINGLE AND
DAILY SC rhGH INJECTIONS

graphs

Sun YN et al. JPET 1999; 289:1523-1532
Pharmacokinetic and Pharmacodynamic Models Used to Predict Dosing Regimens of Mabs
MONOCLONAL ANTIBODIES
HUMAN IgG

Scanned image
IgG and SINGLE-CHAIN Fv

image
MONOCLONAL ANTIBODY PRODUCTION

images
CONCEPT OF ANTIBODIES

Images
Murine, Chimaeric, Humanised, Human
DESIGN OF ANTIBODIES

Molecules that can be attached (ADCs):

- Enzymes
- Toxins
- Viruses
- Cationic tails
- Biosensors
PROPOSED HUMAN PLASMA CLEARANCE of DIFFERENT ANTIBODY MOLECULES
Development of Mabs

- General biologic standards [21 CFR Part 610]
- Comparability of manufacture processes (changes over the development program)
Advantages of mAbs

- High specificity
- Long half-life
- Improved benefit-risk ratio (in most therapeutic areas)
Risks of mAbs

- Immune reactions
  - Signs and symptoms
    - Infusion site reactions
    - Fever
    - Influenza syndrome
    - Acute anaphlaxis
    - Systemic inflammatory responses

- Infection
  - Reactivation of latent bacteria or virus
Risks of mAbs (continued)

- Platelet and thrombotic disorders
  - Thrombo- and hematopoietic toxicity
- Auto-immune disease
  - Cutaneous or systemic vasculitis
  - Nephritis
  - Colitis
- Cancer
Risk Assessment for
Cytokine Release Syndrome

In vitro assessments (cellular targets should be from patient population)
- Cellular inhibition or activation
- CDC or ADCC
- Cytokine and proliferation assays

Assess function and activity of Mab targets

Evaluate proposed clinical dose with other Mabs targeting same or similar antigens
Summary

Use scientific judgement and good sense in the interpretation of PK/PD results with macromolecules

Application of PK principles that have been developed work with macromolecules

Difficult to select the most appropriate pharmacodynamic endpoint
Acknowledgements

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Dr. Joyce Mordenti
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