Preclinical Development of Biologics: Case-by-case, so get off of my case!

Northeast Chapter SOT

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Biologic drugs have been around for over 20 years: why the controversy?

- Principles are the same, practices differ
  - Recommend initial safe starting dose and dose escalation scheme for phase 1.
  - Identify potential target organ(s) of toxicity
  - Identify appropriate parameters to monitor in the clinic/delayed effects/reversibility
  - Identify potentially “at risk” populations
Preclinical Safety Evaluation…What to consider

- Product Characteristics
- Related INDs or products
- Principal mechanism(s) of action
- Principal efficacy model and limitations
- Dose/exposure information
  - NOAEL
  - Maximum Toxicity (MTD)/(MFD)
Problem areas

- Selection of relevant species
- Immunogenicity assessment
- Duration of chronic studies
- Carcinogenicity testing
- Need for an MTD
- Reproductive toxicity
- Start dose
- This presentation will not answer all the questions!

Food and Drug Administration (FDA)
Species selection

- Studies should only be done in relevant species, i.e. species that demonstrate pharmacological effects.
- With biologics NHP are often the only relevant species. If so, one model is sufficient.
- If a second species is relevant, it should also be evaluated.
We can probably agree that some animals, no matter how similar to humans, should rarely be used in toxicology studies. Two examples are shown below.
Species selection, cont.

- Use of homologous material is appropriate if no relevant species can be identified. Since the clinical product has not been evaluated, clinical trials should proceed with caution.

- Use of homologous material may also be appropriate for studies which cannot be performed or easily performed in NHP: carcinogenicity and reproductive toxicity.
Are MTD studies always necessary?

- In general identification of an MTD and NOAEL is desirable.
- Toxicity associated with biologics is most often associated with exaggerated pharmacology.
- Eliciting an MTD may be difficult; MFD may be acceptable.
- Saturation of binding may represent an appropriate top dose.
- Limit dose? What is a reasonable margin of safety? 10X, 50X, 100X. Healthy volunteers or patients?
- Potency differences between test species and humans should be taken into account.
Carcinogenicity studies

- Traditional two-species, two-year carcinogenicity studies have not been routinely performed with biologics.
- This situation arose primarily because such studies could not be performed for practical reasons (ADA), early biologic products were for life threatening indications (oncology) and/or not for chronic use.
- Some biologics may raise a carcinogenicity concern, e.g., growth factors, immune suppressors.
Carcinogenicity studies, cont.

- Can these effects be managed in labeling? Will sponsors accept a carcinogenicity label if their product has never been tested? Do we need to understand the relative carcinogenic potency of products in the same class? Can we assume the relative potency for carcinogenicity is directly correlated to relative pharmacologic potency?
- Should chronic studies in primates be extended to one year as an indicator of potential carcinogenicity?
- If a homologue is available, should it be used for carcinogenicity testing?
- If a rat and mouse homologue are available, should both be tested?
Carcinogenicity testing, cont.

- Are growth promoting effects on tumor cells in vitro informative?
- When should similar studies be performed in xenographs in vivo?
- Should immune “modulators” (as opposed to suppressors) be tested for carcinogenicity?
Reproductive toxicology studies

- Do biologics need to be tested in two species in a manner analogous to small molecules?
- What if the only relevant species is a NHP?
- Are reproductive studies in monkeys using the clinical material more relevant than studies with the homologue?
Duration of chronic studies

- In general, 6 month studies are adequate to predict clinical toxicities (Clarke et al., Reg. Toxicol Pharmacol, 50:2-22, 2008).
- Out of 23 biologics examined, two exceptions were found where longer studies revealed new toxicities.
Role of immunogenicity testing

- Immunogenicity assessment aids in the interpretation of the animal toxicology data; not done to predict immunogenicity in people.
- Immunogenicity assessment may not be necessary if there is no change in PK/PD in the course of the study.
- Blood samples should be collected in the course of toxicology studies and stored in case information is needed.
Nonclinical Safety Study:
Multiple dose and/or Exposure > 7 days

Yes

Is a PD biomarker available?

No

Is the PK assay sensitive to ADA?
*e.g. target binding design*

No/Unknown

ADA Screen

No

Yes

Is PK or PD altered?

No to all

Possible ADA-induced clinical observation?

Yes

No

Perform ADA Screen

ADA +

Quasi-Quantify ADA+ *(Titer or Relative Conc.)*

ADA -

Perform ADA characterization as warranted by risk or for study interpretation
CDER guidance on “start dose”


- Relevant for small molecule or biologic therapeutics

- Not intended to address dose-escalation or maximum clinical doses, or dosing in patient populations.

- Toxicity is to be avoided at the initial dose.

- Approaches other than that described may be used (e.g., PK/modeling); however, approach selected needs to be justified.

Food and Drug Administration (FDA)
FIM Dose Calculation

- Identification of NOAEL; often one species for biologics
- Conversion of NOAELs to Human Equivalent Doses (using body surface area conversion factor)
  - BSA-CF: converts mg/kg dose in animals to mg/m2 dose, then to mg/kg dose in human
- Selection of more sensitive species (i.e., lower HED when more than one species NOAEL available)
Safety Factor

- Application of safety factor
  - default is 10, but may not be adequate in all cases
  - Increase
    - Steep dose-response curve
    - Severe toxicity at doses above NOAEL
    - Non-monitorable toxicities
    - Toxicities with no premonitory signs
    - Irreversible toxicity
    - Unexplained death
    - Widely variable bioavailability in animals
    - Non-linear PK
    - Wide variability between species in doses or exposures eliciting toxicities
    - Less than optimal nonclinical study design/conduct
    - Novel therapeutic targets
    - Animal models with limited utility
Safety Factor, continued

- Default of 10, may be decreased if:
  - Drug is a member of a well-characterized class, is being given according to an established clinical dosing regimen, and has similar PK/ADME and toxicity profiles across species, including human.
  - Toxicities are easily predicted, monitored, and are reversible.
  - Dose-response for toxicity is not steep.
  - The NOAEL upon which the HED is based was determined in longer-term nonclinical studies; this assumes that toxicities are cumulative and were not observed early in the longer-term studies.
Changes in start dose

- It is always acceptable (from a safety perspective) to use a clinical start dose lower than the MRSD.

- Use of pharmacologically active dose (PAD)
  - May use if lower than MRSD
  - May be used to justify lowering the MRSD, e.g., in cases in which toxicity is due to exaggerated pharmacologic effects.
History of Safety

- Phase 1 clinical trials, especially in healthy subjects have a long history of safety.
- With the exception of a few instances, the paradigms we currently use for selecting safe starting and stopping doses have served us well.
- One glaring failure: TGN1412.
Balancing your Immune System

TeGenero is a biopharmaceutical company dedicated to the identification and development of innovative, highly effective and broadly applicable immunotherapeutics.

We strive to provide patients the means to regain a functional and balanced immune system.
Drug trial creates 'Elephant Man'

Thursday, March 16, 2000 Posted: 0951 GMT (1751 HKT)

LONDON, England -- Two men are in critical condition in a London hospital and four others are in serious condition after taking part in a clinical trial for a new drug.

One victim, whose head and neck were reported to have increased to three times normal size, was described by a friend as resembling "the Elephant Man."

The men were admitted late Monday to the intensive care unit from an independent medical research unit at Northwick Park Hospital after reacting badly to the drug, which is intended to treat chronic inflammatory conditions and leukemia.

The volunteers suffered extreme reactions while participating in a drug trial run by clinical research company Parexel International, based in Boston, Massachusetts.
Events in clinical trial

- TeGenero contracts with Parexcel for a first entry into man study of monoclonal antibody, TGN1412.
- Application received by MHRA on December 23, 2005, trial authorized on January 27th, IRB approved February 14th, trial begun on March 13th.
- Four single doses of 0.1, 0.5, 2.0 and 5.0 mg/kg were planned to be administered to 4 groups of 8 subjects.
- Six subjects given 0.1 mg/kg IV in the course of one hour. Two subjects given placebo.
Events in clinical trial

- Headache and nausea onset within one hour of dosing and subjects (now patients) admitted to intensive care 10 hours after dosing.
- Subjects suffered multisystem failure and required pulmonary and renal support.
- All subjects recovered but may experience sequelae.
CD28 Monoclonal Trial in UK

- No evidence of contamination of the product.
- Conduct of the trial appeared to have followed the protocol, e.g., no dosing errors.
- Nothing in the preclinical data predicted the overwhelming systemic reaction to the antibody. Findings of lymph node enlargement in the monkeys, but the monkeys did not demonstrate the toxicological response seen in humans.
- Dose in humans was 1/160 of the NOAEL in monkeys, so it was well within accepted safety margins.
- Adverse reaction considered to be a "cytokine" storm that was triggered by the antibody and not predicted by the animal testing.
Preclinical toxicology studies

- Pivotal study was 28 day repeated dose study in cynomolgus monkeys (n=26). Four weekly doses given by infusion. Two male and two females sacrificed on day 28 and remaining animals used in recovery/observation period of 6 weeks.
  - No mortality
  - No clinical signs
  - No effect on body weight or food consumption
  - No ECG changes
  - Clinical chemistries and hematology normal
  - No findings at necropsy
  - No significant histological findings
  - 4 out of 16 animals had titres of anti-TGN1412
  - Mean half-life of approximately 8 days was calculated
Could this toxicity have been predicted?

- Hindsight is always 20/20.
- Limited amount of time in which to make safety decisions.
- There were some clues.
Initial dose 0.1 mg/kg would achieve plasma level of ~16nM compared with binding affinity of 2nM. 8X the binding affinity of “super agonist” might result in 90% CD28 receptor binding on first dose.

This occupancy ok for antagonist but too high for FIH with agonist. If starting dose was established using pharmacological principles, might have started 100X lower.
Other clues

- OKT3, murine monoclonal antibody used to suppress rejection of organ transplants.
- Adverse reactions include “cytokine release syndrome.”
- Clinical dose is approximately 70 micrograms/kg.
Cytokine Changes

Table 68: Mean peak serum concentrations in each dosing group after administration of TGN1412 in cynomologus monkeys

<table>
<thead>
<tr>
<th>Cytokine</th>
<th>Mean peak cytokine level (range) pg/ml</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>Control group (0 mg/kg)</td>
</tr>
<tr>
<td>IL-2</td>
<td>37 (20-60)</td>
</tr>
<tr>
<td>IL-4</td>
<td>12 (0-18)</td>
</tr>
<tr>
<td>IL-5</td>
<td>6 (3-7)</td>
</tr>
<tr>
<td>IL-6</td>
<td>7 (0-22)</td>
</tr>
<tr>
<td>TNF-alpha</td>
<td>20 (11-26)</td>
</tr>
<tr>
<td>IFN-gamma</td>
<td>18 (0-35)</td>
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</tbody>
</table>
Reaction to Tegenero Incident

- Final Guideline, July 2007
- Guideline on Strategies to Identify and Mitigate Risks for First-in-Human Clinical Trials with Investigational Medicinal Products.
- Initially defined “High Risk Drug”—omitted in final guideline
Mode of Action

- Nature and intensity (extent, amplification, duration, reversibility) of the effect of the drug on the target
- Shape of dose-response curve
- e.g. mechanism that bypasses physiological control mechanisms, CD3 or CD28 (supra-) agonists.
MABEL Approach

- “Minimal Anticipated Biological Effect (MABEL).
- The anticipated dose level leading to a minimal biological effect in *humans*.
  - Receptor binding and receptor occupancy studies in vitro in target cells from human and the relevant animal(s) species and in vivo in the relevant animal species.
  - Concentration-response curves in vitro in target cells from human and the relevant animal(s) species and dose response in vivo in the relevant animal species.
  - Exposure at pharmacological doses in the relevant species.
MABEL Approach

- What would have constituted the MABEL dose in the Tegenero studies?
- Not clear what effect would serve as the basis for the start dose.
On its face, this guidance does not appear to significantly change our current practices.

Even without this guidance, any sponsor proposing to test an immune system agonist and any regulatory reviewer is going to exercise extreme caution.
Thank you for your attention!