The Role of the Patient in Human Pharmacology – A Changing Paradigm?

When are early-Phase Studies more appropriate in Patients as compared to Healthy Subjects

- Targeted Therapeutic Proteins exemplified through Monoclonal Antibodies -

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1. Lessons from FIM Guideline EMEA/CHMP/SWP/294648/07
2. Patients preferred due to study objective related aspects
3. Exceptions where healthy volunteers might be preferred
4. Phase I studies for biosimilars
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Protocol of a Tragedy

TGN1412 (Tegenero, Würzburg):
- MAb directed against CD28 on T-lymphocytes

Pharmacological Strategy
- Supra-agonistic activation of CD28-pos. T-lymphocytes

Target indication:
- Chronic Lymphatic Leukemia

First in Man Study on 13th March 2006 in London:
- 8 Healthy Volunteers (6 verum / 2 placebo)

Dose:
- SAD starting with 100 µg/kg

Side effects:
- Life threatening Cytokine Release Syndrome
After the TGN1412 Experience…
A new Standard for First in Man Clinical Studies

Transition from non-clinical to early clinical development

Applicable to all new chemical and biological investigational medicinal products (IMPs) except gene and cell therapy medicinal products

Risk assessment & risk classification for IMPs

* Date for coming into effect 1 September 2007
Risk Criterion 1: “Novel Mechanism of Action“

- Proposed mode of action connected to multiple signaling pathways or cascades?
  - Immune system
  - Cell proliferation
  - Angiogenesis
  - Blood coagulation system
  - Nervous system

- Antagonistic or agonistic effects?

- Depletion of soluble molecules or binding to cell membrane associated targets?
New type of structural format? = Are there any chemically or gene-technologically engineered modifications introduced to the molecule?

- Antibody fragments
- Immunotoxins
- Immunocytokines
- Fc-glyco-engineering
- PEGylation
- Soluble receptor fusion proteins
Risk Criterion 2: “Nature of the Target“

Specificity of “Magic Bullets“ = Cross-reactivity related side effects?
- Epitope expressed on non target tissues?
- Epitope member of a structurally highly similar family of proteins (e.g. EGF Receptor family)

Pharmacogenetics / Pharmacogenomics: Impact of polymorphisms on the pharmacological effects of the MAb?
- Polymorphisms of the epitope: Modulation of affinity and downstream effects?
- Polymorphisms of Fcγ receptors I-III: Modulation of effector functions?
Risk criterion 3: “Relevance of Animal Models”

Relevant animal toxicology model available, from which quantitative conclusions can be drawn for initial dose finding in humans?

A relevant species is one in which the test material is pharmacologically active due to the expression of the epitope!

Preclinical Safety Evaluation of Biotechnology derived Pharmaceuticals (ICH S6, CPMP/ICH/302/95)
Typical MAb-related side effects are explainable by exaggerated pharmacological activity

**Immunotoxicity**
- Cytokine Release Syndrome e.g. anti-CD 20
- Immunosuppression e.g. anti-TNFalpha
- Induction of Autoimmunity anti-CTLA4

**Cardiovascular adverse effects**
- Cardiotoxicity e.g. anti-HER2
- Gastrointestinal perforation e.g. anti-VEGF

**Skin rash e.g. anti- EGFR**

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The safety and side effects of monoclonal antibodies

Trevor T. Hansel*, Harald Kropshofer§, Thomas Singer§, Jane A. Mitchell§ and Andrew J. T. George†

Demonstration of Relevance:
A complex Approach needed…

Effector cells (e.g. macrophages, NK cells):
ADCC / phagocytosis?

PK in model and man identical?

Expression pattern of epitope?

CDC?

Humanized / fully human Fc-part

Immunogenicity:
masking of side effects?

Induction or blockade of signal transduction cascades?

Sequence homology of the epitope?

Affinity constants?

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<table>
<thead>
<tr>
<th>amino acid sequence</th>
<th>score</th>
</tr>
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<tbody>
<tr>
<td>NKLLYEQSPPLVATTWAQLSCXYSTNLPHSBRAISLQEHDLSAVHVVCYVSYNSQQLYQV</td>
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<td>YSNTPSCEDKXGLQHESVPTFLQKLTVKQTDYFCKIHYNTFPPYLANHSHOTIHYGEX</td>
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<td>121</td>
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<tr>
<td>HLCPSPFOPSHFP</td>
<td>134</td>
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</table>
After the TGN1412 experience it is rather difficult to convince Health Authorities of the relevance of any tox model for targeted therapies
Confirmation of at least one risk criterion is sufficient for the assumption of an increased safety risk in FIM clinical trials!

Consequently nearly every FIM study for MAbs is expected to be associated with potentially unpredictable risks

What does this mean for the responsible choice of the study population?
The paramount factors should always be the safety, rights and well-being of the volunteers, whether patients or healthy individuals.

Neither HVs nor patients are not expected to derive any individual benefit from a FIM trial.

Responsible specification of initial dose (MABEL) and dose escalation strategy: Healthy volunteers are not generally excluded from MAb FIM studies.

An indirect recommendation in favour of patients: Value of what can be learned from the clinical trial.
1. Lessons from FIM Guideline EMEA/CHMP/SWP/294648/07

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4. Phase I studies for biosimilars
Safety evaluation in a relevant population: 
Character and intensity of side effects are functions of target expression

*Incidence and severity of adverse events during the first infusion of anti-CD 20 Rituximab in patients with CLL are dependent on the number of circulating CD20+ tumor cells*


Some MAbs are associated with severe side effects, when given at clinically relevant dose levels

anti-CTLA4 Ipilimumab (YERVOY®)

Some MAbs induce severe Type 1 hypersensitivity incl. anaphylaxis

Ethical dimension:
Patients serve for the group benefit due to altruistic motives
(group of patients suffering from disease)
Antibodies that are directed against cell-surface antigens often exhibit nonlinear PK behavior

Total clearance:
- Specific, saturable antigen-related pathway
- Nonspecific linear clearance pathway (reticuloendothelial system, RES: Fcγ/FcRns receptors)

PK evaluation in a relevant population:
Cell receptor density and number of receptor-positive cells (tumor burden) as crucial covariates

anti-EGFR Matuzumab: Dependence of total CL on concentration (C) of the MAb

Patients preferred due to Study Objective related Aspects

**Pharmacokinetics**

- Multiple dose steady state PK evaluation for MAbs intended for chronical use (e.g. TNFalpha antagonists in AIIDs)

- PK evaluation in a relevant population: Impact of immunogenicity, itself affected by
  - Immunestatus of patients
    (healthy volunteers < patients with autoimmune diseases)
  - Concomitant immunosuppressive or immuno-stimulatory medication

- Ethical dimension:
  - Today’s healthy subject might develop a disease, where the tested MAb is indicated for treatment
  - Anti-drug immune-response provoked during clinical trial participation could negatively influence therapy


**Pharmacokinetics of Infliximab in RA patients treated with infliximab at 1, 3, or 10 mg/kg with ☐ or without ☪ MTX**
GL EMEA/CHMP/SWP/294648/07 encourages to make use of qualified pharmacodynamic biomarkers, suitable to monitor therapy induced changes, which are correlated with clinical outcome.

In oncology (e.g. PSA for Prostate Cancer; AFP: Testicular Tumors, B cell count: CLL), as well as in AllIDs (e.g. CRP) a number of markers are identified and qualified.

For MAb-based therapies the target itself is often a surrogate marker (e.g. VEGF in CRC, TNFalpha in RA).

PD evaluation in a relevant population:
Pathophysiological expression of markers normally restricted to patients.

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Exceptions where healthy volunteers might be preferred
Criteria for making HVs attractive

Safety:

• Even at target saturation, no DLT expected (clinical experience with comparable MAbs !)

• Fully human MAb: Risk for infusion reactions low

PK:

• Linear PK expected (soluble target, no target mediated clearance)
  Exploratory (Phase 0) trials for PK based candidate selection at low dose

• Intended duration of treatment short: SS PK not essential for Phase I

PD:

No qualified marker of interest identified
Exceptions where healthy volunteers might be preferred

Advantages of HVs

- Homogenous population with respect to age, health status, physiological parameters and reactions

  Reduced variability of PK parameters like Cmax or AUC
  Facilitated PK analysis and interpretation for even very low doses (MABEL)

- Most of all: Easy recruitment, accelerating pathway to Phase II/III
<table>
<thead>
<tr>
<th>Epitope</th>
<th>Indication</th>
<th>Potential side effects</th>
<th>Dosage</th>
<th>Trial Location</th>
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</thead>
<tbody>
<tr>
<td>TGN1412</td>
<td>CD28</td>
<td>cytokine storm</td>
<td>i.v 7.5 mg (single dose)</td>
<td>UK, (Germany)</td>
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<tr>
<td>(Tegenero)</td>
<td>CLL, RA</td>
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<tr>
<td>BT061</td>
<td>CD4</td>
<td>immunosuppression, cytokine storm</td>
<td>i.v 0.0035 – 0.500 mg (single dose)</td>
<td>Germany</td>
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<td>(Biotest)</td>
<td>psoriasis, RA</td>
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<tr>
<td>DI-17E6</td>
<td>integrins αvβ3 / αvβ5</td>
<td>cross reactivity to α4-integrins: immunosuppression,</td>
<td>i.v. 35-1500 mg (single dose)</td>
<td>Germany</td>
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<tr>
<td>(Merck</td>
<td>solid tumors</td>
<td>impairment of wound healing, bleedings</td>
<td></td>
<td></td>
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<tr>
<td>Serono)</td>
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<tr>
<td>GSK249320</td>
<td>MAG (myelin associated</td>
<td>impairment of neuronal function</td>
<td>i.v. 0.04-25 mg/kg (single dose)</td>
<td>US, Australia, Germany</td>
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<tr>
<td>(GSK)</td>
<td>glycoprotein)</td>
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<tr>
<td>TB-402</td>
<td>factor VIII</td>
<td>thrombosis</td>
<td>i.v. 0.000015-1.8 mg/kg (single dose)</td>
<td>Denmark</td>
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<tr>
<td>(ThromboGenics)</td>
<td></td>
<td>bleedings</td>
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<tr>
<td>MEDI-528</td>
<td>IL-9</td>
<td>immunosuppression</td>
<td>s. c. 0.3 – 9 mg/kg (single dose)</td>
<td>US</td>
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<td>(MedImmune)</td>
<td>asthma</td>
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<td>GSK182771</td>
<td>IL-1R</td>
<td>immunosuppression</td>
<td>?</td>
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<tr>
<td>(GSK)</td>
<td>RA</td>
<td></td>
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Exceptions where healthy volunteers might be preferred HVs as subjects in MAb FIM clinical trials after TGN1412

source: clinicaltrial.gov
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4. Phase I studies for biosimilars
Biosimilar Phase I studies bases on the knowledge of the originator’s PK, efficacy and safety profiles

• Demonstration of bioequivalence as primary goal
• Starting directly with the approved posology
• Including comparative safety as secondary endpoint

Guideline on similar biological medicinal products containing monoclonal antibodies
Draft
Pros

- HVs constitute a sensitive and homogeneous study population for PK analyses
- HVs are easily to recruit
  (Recruitment of patients for biosimilar studies can be very challenging due to the lack of incentives for investigators and patients)
- Europe: Guideline EMA/CHMP/BMWP/403543/2010 explicitly endorses the option of HV PK studies for biosimilar MAbs
- Outside Europe: Recently some countries have approved HV PK studies for MAbs or MAb-like biosimilars (China, Korea, NewZealand)

Cons

- HV studies with MAbs are normally restricted to single dose administration: Likely that at least for MA steady state PK will be requested
- Missing possibility to investigate treatment-induced effects on MoA-related PD/biomarkers, which could support extrapolation of indications
<table>
<thead>
<tr>
<th><strong>MAb</strong></th>
<th><strong>Condition</strong></th>
<th><strong>Phase</strong></th>
<th><strong>Study design</strong></th>
<th><strong>Avtive comparator</strong></th>
<th><strong>Dosing</strong></th>
<th><strong>Enrollment</strong></th>
<th><strong>Outcomes</strong></th>
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<td></td>
<td>Rheumatoid Arthritis</td>
<td>Phase I/II (NCT01123070)</td>
<td>Randomized, double-blind, parallel arm</td>
<td>MabThera®</td>
<td>Approved posology of MabThera®: 2 x of 1000 mg i.v. 2 wks apart</td>
<td>48 RA patients</td>
<td>Primary (1 year): Compare PK</td>
<td>Czech Republic, Hungary, Italy, Spain, UK</td>
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<td></td>
<td>Healthy Volunteers</td>
<td>Phase I (NCT01505491)</td>
<td>Randomized, open-label, single dose, parallel arm</td>
<td>Humira®</td>
<td>Approved posology of Humira®: 40 mg s.c</td>
<td>180 HVs</td>
<td>Primary (72 days): Compare Cmax, AUC</td>
<td>New Zealand</td>
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</tbody>
</table>

**Source:** Clinicaltrials.gov
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Vielen Dank für Ihre Aufmerksamkeit!