IMMUNOLOGICAL SAFETY ISSUES IN EARLY CLINICAL TRIALS: A translational approach

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Introduction

- Immunotoxicology ➔ "THE SCIENCE OF POISONS TO THE IMMUNE SYSTEM"
  - Quantitative changes = suppression or stimulation
  - Qualitative changes = hypersensitivity or autoimmunity

- Immunological changes VS. immunotoxic effects
  - Immunological changes often "toxicologically inconsequential"
  - Immunotoxic effects ➔ only those immunological changes capable or shown to trigger adverse clinical consequences

- Rather few implemented guidelines
  - Small molecules ➔ ICH S8 (2005)
  - Biologics ➔ ICH S6R1 (2011) - FDA and EMA guidances on the immunogenicity assessment of therapeutic proteins, or mAbs

- Dormant area for long, but clearly thriving today
  - Exponential development of biopharmaceuticals
  - Significant therapeutic progress of immuno-oncology products
  - And, therapeutic vaccines, innovative constructs (bispecific antibodies, antisense drugs, nanomedicines), cell/gene therapy
4 types of immunotoxic effects

- IMMUNOSUPPRESSION
- IMMUNOSTIMULATION
- HYPERSENSITIVITY
- AUTOIMUNITY

Markedly different clinical consequences (i.e. drug-induced adverse effects)

Focused preclinical strategy essential to predict and assess immunotoxic risk(s)
• 2 MAIN CLINICAL CONSEQUENCES
  o Infections/infectious complications
  o Virus-induced neoplasia

• INFECTIONS
  o Viral, bacterial, fungal, parasitic infections
  o Always more frequent +++ (➔ statistical evidence ?)
  o Also unremarkable clinically in quite a few instances
  o Often more severe, possibly life-threatening, or relapsing
  o If distinctively atypical ➔ IMMUNOTOXICITY WARNING

• VIRUS-INDUCED NEOPLASIA
  o Unlikely outcome during early clinical trials in contrast to Phase III trials (e.g. tacrolimus), and beyond
  o Primarily skin cancers (>30% of transplant patients), and B-lymphomas (with possible spontaneous recovery in case of cessation of the offending drug)
Current preclinical evaluation primarily aimed at detecting (unintended) immunosuppressive drugs (see ICH S8 guideline)

- **Standard toxicity studies**: identification of warning readouts including clinical signs (e.g. infections, even though SPF and barrier-protected animals often used); hematological changes (e.g. marked neutropenia), and histological examination of the main lymphoid organs (atrophy of the thymus and lymph nodes)

- **Weight of evidence review** encompassing all preclinical toxicity data, fully elucidated or putative mechanism of action, intended therapeutic indication(s), at-risk patients…

→ IMMUNOTOXICITY WARNING or NOT?

if YES → Additional immunotoxicity studies required
TRANSLATIONAL CONSIDERATIONS

- **Additional immunotoxicity studies**
  - *TDAR* (T-Dependent Antibody Response) assay: recommended first-line assay to assess immunocompetence globally in rodents as well as non-rodents (dogs, monkeys, minipigs)
  - *Lymphocyte subset immunotyping*, essentially as an attempt to better understand the mechanism of action, and related immunotoxic effects; or hopefully validate biomarkers of efficacy (including in man)
  - *NK cell activity*, a "historical" readout with limited, if any significant role in immunotoxicity assessment (alike NK cell numbers)
  - *Moreover*, assessment of cell-mediated immunity (DTH) and innate immunity (phagocytosis, macrophages), to cite but a few, in a long list of possible (often academic and ill-qualified) functional assays

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**IMMUNOSUPPRESSION ➤ TAKE-HOME MESSAGE**

- Careful clinical (time course and symptoms) and microbiological description of every infection **absolutely essential**
- Detailed diagnosis criteria and monitoring of any infection to be included in clinical trial protocols **at any phase** (+++)
4 types of immunotoxic effects

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**IMMUNOSTIMULATION**

- **4 MAIN CLINICAL CONSEQUENCES**
  - Cytokine release-mediated acute reactions
  - More frequent autoimmune diseases
  - More frequent reactions to unrelated allergens
  - Inhibition of CYP-450 biotransformation pathways

- **CYTOKINE RELEASE-MEDIATED REACTIONS**
  - Continuum from flu-like reaction to acute cytokine syndrome
  - *Flu-like reaction*: quite ordinary reaction (e.g. vaccine boosting injection in children) with moderate fever, malaise, myalgias, quick and often spontaneous recovery
  - *Acute cytokine syndrome*: severe reaction with marked hyperthermia (>40°C), cardiovascular and/or neurological disturbances; often dose- or treatment limiting; symptomatic therapeutic measures required
  - *Cytokine storm*: (inappropriate hype from N Eng J Med) term associated for long with avian flu and septic shock (hence markedly different from TGN1412 accident)
• **MORE FREQUENT AUTOIMMUNE DISEASES**
  o Closely similar to spontaneous autoimmune diseases, only more frequent (and globally not more severe)
  o Wide array of autoimmune diseases possibly described
  o No reliable diagnostic criteria ➔ only statistical evidence, or suspicion

• **MORE FREQUENT REACTIONS TO UNRELATED ALLERGENS**
  o To be unequivocally differentiated from "drug allergy"
  o More frequent and/or more severe attacks of pre-existing asthma, urticaria, eczema, hay fever…
  o Often ignored, but reported with "old immunomodulating agents" (e.g. levamisole) as well as new nanomedicines

• **INHIBITION OF CYP450 BIOTRANSFORMATION PATHWAYS**
  o Convincingly shown to exquisitely involve IL-6 mediated inhibition of CYP450-related gene expression
  o Risk of drug interactions still poorly evaluated in the clinical setting
TRANSLATIONAL CONSIDERATIONS

- Cytokine release-mediated reactions
  - *Limited value*, if any of in vivo animal studies (especially in monkeys)
  - CRA (*Cytokine Release Assay*) using human whole blood or PBMCs: recommended assay, although still poorly standardized, but results of an international interlaboratory study to be published next fall
    - Subjective answer "yes or no" ➜ no agreed clinically significant threshold
    - Essential cytokines to be measured include pro-inflammatory cytokines (IL-1β, TNF-α, IL-6…), but importantly also IL-2 and IFN-γ
    - Results contributory to hazard characterization ➜ typically used to decide whether the first human starting dose should be based on the MABEL (Minimal Anticipated Biological Effect Level) or NOAEL (No Observable Adverse Effect Level) approach

**CYTOKINE RELEASE ➤ TAKE-HOME MESSAGE**
- Only in vitro CRA results *worth of consideration* for risk prediction
- No proven efficacy of any premedication scheme (acetaminophen, corticosteroids and/or antihistamine drugs)
TRANSLATIONAL CONSIDERATIONS

- More frequent autoimmune diseases
  - No relevant animal model or in vitro assay to evaluate risk

- More frequent reactions to unrelated allergens
  - Mouse or rat models to identify potential for enhanced sensitization to reference allergens (e.g. ovalbumin) by the dermal or respiratory route
    → identification of hazard
  - Risk characterization still problematic

- Inhibition of CYP450 biotransformation pathways
  - Wealth of in vitro assays, experimental models and pharmacokinetics data (including in humans) to evaluate risk

 IMMUNOSTIMULATION ➤ TAKE-HOME MESSAGE

- The times they are a 'changing'
- Hazard identification and risk evaluation expected to evolve quickly
4 types of immunotoxic effects

• IMMUNOSUPPRESSION
• IMMUNOSTIMULATION
• HYPERSENSITIVITY
• AUTOIMMUNITY
• BACKGROUND
  
  o HYPERSENSITIVITY = term to be preferred to replace the misleading and worn-out concept of "allergy"
  
  o Gell and Coombs' classification (1963): largely obsolete and often misleading → should be abandoned

• TWO CONTRASTING SITUATIONS

  o IMMUNE-MEDIATED hypersensitivity reactions (formerly known as immuno-allergic reactions)
  
  o NON IMMUNE-MEDIATED hypersensitivity reactions (or pseudo-allergic reactions)
    
    ***
    
    o No reliable detailed epidemiological data available
    
    o Hypersensitivity reactions commonly estimated to account for up to 10% of all drug-induced ADRs
    
    o Incidence of immune-mediated and non immune-mediated hypersensitivity reactions often thought to be comparable (namely ≈50%)
• IMMUNE-MEDIATED HYPERSENSITIVITY

- Pivotal role of both immunological recognition and memory → previous sensitization contact required in the vast majority of cases
- If very first contact, 7-10 days of treatment prior to clinical reaction onset
  (extremely rarely, possible cross-sensitization, e.g. cetuximab, or direct interaction with distinctive HLA, e.g. abacavir)
- If subsequent contact (not necessarily second contact), **rechallenge inconsistently positive** and delay of onset dependent on administration route (typically IV [min.] < IM / SC < oral [hrs])
- Reactions involving drug-specific antibodies: IgE (anaphylaxis), IgM or IgG (primarily immune-mediated cytopenias), immune complexes (classical serum sickness, or rare vasculitides)
- Reactions involving T lymphocytes: cell-mediated immune reactions (contact hypersensitivity ≠ delayed-type hypersensitivity)
• **NON IMMUNE-MEDIATED HYPERSENSITIVITY**

  o No involvement of any antigen-specific mechanism ➔ instead, release of some mediators involved in some immune-mediated reactions, but via a strictly pharmaco-toxicological process

  o Main differences
    - Adverse clinical reactions recorded even immediately after first contact
    - Clearly dose- or concentration-dependent ➔ more frequent above a threshold
    - Undebated role of administration route (IV), injection speed (bolus vs. infusion), few pharmaceutical solvents (e.g. Cremophor EL° and Tween 80)
    - Mitigation risk measures decisively applicable up to marketing authorization

  o Main mechanisms
    - Direct (i.e. non antigen-specific) histamine release ➔ flush, redness of skin, cough or shortness of breath, abdominal pain, malaise (e.g. vancomycin-induced red man syndrome)
    - Direct complement activation ➔ ≈ same as above, plus more severe respiratory disorders and inconsistent cardiovascular changes (hypotension, tachycardia)
    - **NSAIDs intolerance** ➔ asthma involving pharmacological disturbances of prostaglandins/leukotrienes biotransformation
    - **ICE-induced angioedema** ➔ directly linked to pharmacological mechanism = inhibition of converting enzyme leads to blockade of bradyklinin degradation
    - **Cytokine release** (?) Most often non-antigen specific mechanism
TRANSLATIONAL CONSIDERATIONS

- **Immune-mediated hypersensitivity**
  - Qualified animal models/in vitro assays available only to evaluate risk linked to some delayed-type hypersensitivity (e.g. contact dermatitis)
  - No relevance of animal immunogenicity studies → too many false negative (small molecules) or false positive results (biopharmaceuticals)

- **Non immune-mediated hypersensitivity**
  - More and more qualified animal models/in vitro assays to investigate mechanisms, to evaluate risk of non immune-mediated reactions, and to design animal studies intended to mitigate risk (e.g. role of speed or route of injection)

HYPERSENSITIVITY ➔ TAKE-HOME MESSAGE

- Careful description and time course of clinical symptoms absolutely crucial → erroneous diagnosis far too frequent
- Risk of drug-induced immune-mediated hypersensitivity reactions unpredictable in sharp contrast to non immune-mediated reactions
One "illustrative" situation: ACUTE INFUSION REACTIONS

- **Acute infusion reaction**: commonly used, although medically irrelevant term → clearly superficial, uninformative and misleading

- **Differential diagnosis**
  - **Anaphylactic reaction** → possible, but actually extremely uncommon during first infusion, as previous contact with suspected offending drug normally required (despite extremely rare exceptions to the rule)
    
    **NB In sharp contrast to the published literature, including high impact medical journals**
  
    - **Acute cytokine syndrome** → contribution of CRA results, but sequential cytokine measurements and correlation with clinical symptoms absolutely critical
  
    - **Direct histamine release** → decisive role of serial histamine blood levels and correlation with clinical symptoms
  
    - **Direct complement activation** → decisive role of complement activation blood levels (C3a, C5a, SC5b-9, Bb...), and needed correlation with clinical symptoms

**ACUTE INFUSION REACTION ➤ TAKE-HOME MESSAGE**
- Careful description and time course of clinical events crucial
- Several mechanisms possibly involved ➤ value of laboratory findings
4 types of immunotoxic effects

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- Autoimmune reactions ≠ more frequent diseases (related to immunostimulation)
- Generally, one particular reaction characteristic of one given medicinal product
- Autoimmune reactions closely mimicking or not at all spontaneous disease counterparts
- Late onset usually ➔ rarely to be expected during early clinical trials
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