Nonclinical Allergenicity of Biologics

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What is Drug Allergy?

*Drug allergy* is an adverse drug reaction (ADR) that *seems* to have an immunological basis. Another, more accurate term, is Immune-Mediated Drug Hypersensitivity Reaction (IDHR). Some ADRs *appear* to be drug allergy, are not immune-mediated.
Sensitization

Induction Phase

challenge

Effector Phase

Allergen

Exposure to Allergen → Sensitization → Symptoms
What are the types of drug allergy?

Spectrum of pathologies is daunting
Range from allergic contact dermatitis associated with topical exposure and maculopapular (morbilliform) skin reactions following oral administration to life-threatening reactions such as anaphylaxis and toxic epidermal necrolysis/Stevens-Johnson syndrome
Immunogenicity of Biologic Drugs

Proteins: inherently immunogenic

Minor alterations in protein structure can enhance immunogenicity

Immune responses (antibodies, T cells) can alter PK and PD: esp. important in toxicology studies (false negatives for adverse reactions)

Anti-drug antibodies (ADA) associated with hypersensitivity, other types of immunopathies

Induction of human ADA (HADA) may not be predicted by nonclinical studies

Can be basis for autoimmune reactions (esp. if intended as replacement for endogenous protein)
Intended Immunogenicity

Vaccines: intended to induce *specific* immune response

Prophylaxis → traditional vaccines for communicable disease

Therapeutic vaccines → induce immune response to tumor antigens

Allergy therapeutics → induce immune tolerance

“Passive immunotherapy” → anti-venoms, post-exposure prophylaxis
**Unintended Immunogenicity**

Drug allergy → immune response resulting in variety of immunopathies (e.g. anaphylaxis, organ-specific immunopathology, autoimmune reactions, systemic hypersensitivity)

Deleterious effects on drug pharmacodynamics (e.g. neutralizing antibodies, alterations in pharmacokinetics)

Product quality → immune responses to altered proteins, process contaminants
Immunopathy: The Gell & Coombs Categories

Current classification system was proposed Gell and Coombs (G&C) in the 1960s

Categories:
- Type I: immediate hypersensitivity
  - Respiratory
  - Urticaria
  - Systemic
- Type II: antibody-mediated
  - Antibody-mediated cytotoxicity
  - Antibody-dependent cell-mediated cytotoxicity (ADCC)
- Type III: immune complex-mediated reactions
- Type IV: delayed hypersensitivity
  - Dermal
  - Respiratory
  - Systemic
In humans, mediated by IgE

In some rodents, IgG may be mediator

Three general subtypes:
- Respiratory (asthma)
- Urticaria (hives)
- Systemic (anaphylaxis)
Mouse Anaphylaxis

Finkelman, J Allergy Clin Immunol 2007;120:506-15
Human Anaphylaxis

- Allergen
- MHC class II molecule
- TCR
- T_{reg} cell
- T_{eff} cell
- T_{H1} cell
- T_{H2} cell
- APC
- IL-10
- IL-5
- IL-4
- IL-13
- IL-9
- TNF-α
- INF-γ
- IL-17
- IL-22
- TNF-β
- IgE
- Mast cell
- Release of soluble mediators:
  - Histamine
  - Cysteinyl leukotrienes
  - Prostaglandins
  - Cytokines
- Epithelial cell
- Mucus
- Smooth muscle cell
- Blood vessel
<table>
<thead>
<tr>
<th><strong>Anaphylaxis or Anaphylactoid?</strong></th>
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<tbody>
<tr>
<td>IgE-mediated</td>
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<td>Previous exposure to antigen</td>
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<td>Rarely modeled in animals</td>
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<td><em>May</em> be able to diagnose with skin tests, RAST, or ELISA</td>
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Contaminated Heparin Associated with Adverse Clinical Events and Activation of the Contact System

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Contaminated Heparin: Anaphylaxis or Anaphylactoid?

Patients demonstrated signs consistent with anaphylaxis, but unusual for heparin.

Most common immune-mediated adverse reaction observed with heparin: thrombocytopenia (HIT).

Ability to model reaction in animals (pigs) suggested the reaction was anaphylactoid.

Analysis of suspect heparin products demonstrated unusual contaminant – oversulfated chondroitin sulfate, which has significant anti-coagulant activity.

Mechanism: unusual combination of C3a and C5a generation and kallikrein activation producing profound hypotension.
Animal Model of Anaphylactoid Reaction

IgE-mediated reactions difficult to model in animals (PCA, ASA works with some allergens, but not predictive or useful in forensic setting)

Anaphylactoid reactions can be modeled, however

Contaminated heparin, OSCS direct activation of kinin-kallikrien system with generation of vasoactive bradykinin in human plasma

Concurrent generation of C3a and C5a, potent anaphylatoxins

Both effects linked to activation of factor XII

Effect modeled in swine
CARPA

Complement activation-related pseudo-allergy

Seen with certain liposomal formulations and other lipid excipients

Generally mild cardiovascular signs, typically infusion-rate and dose related

Modelled in pigs
Types II and III

Tend to occur simultaneously

Commonly associated with systemic or organ system immunopathy

IgG and/or IgM reactions to drugs or drug metabolites

Pathology due to ADC, ADCC (Type II), and/or immune complex formation (Type III)
Eprex and Pure Red-Cell Aplasia

1988 – 2004: 175 cases of PRCA reported in Europe and Canada associated with Eprex (~ 500 cases world-wide)

18/100,000 patient/years with Eprex without human albumin excipient

Human albumin removed due to concern for transmission of Creutzfeldt-Jacob disease

Organic compounds from rubber plungers and silicone may have acted as adjuvants

Antibodies inhibited bone marrow erythroid-colony formation

Changes in manufacturing led to 80% decrease in incidence
Type IV

T-cell mediated

Most commonly occur as DTH skin reactions (allergic contact dermatitis - ACD)

Photoallergy

Perhaps most common type (~ 30% of population have nickel allergy)

Some very severe reactions (Toxic Epidermal Necrolysis, Stevens-Johnson Syndrome) may be, at least in part, Type IV
Type IV Subtypes

Type IVa: activation and recruitment of monocytes
Type IVb: eosinophils
Type IVc: CD4 or CD8 T cells
Type IVd: neutrophils
Murine Local Lymph Node Assay
Adverse Immunostimulation

Antigen-nonspecific, inappropriate, or unintended activation of some component of the immune system

Chronic inflammation (probably more of an issue with vaccines, medical devices)

In some cases, overlaps with pseudoallergy

Cytokine release syndrome

No specific recommendations
**Tegenero**

Humanized agonistic anti-CD28 IgG4 mAb

Initial indication: rheumatoid arthritis

Therapeutic rationale: anti-inflammation by induction of regulatory cytokines/chemokines

Induce cytokine storm, massive release of pro-inflammatory mediators

New concept: “Sterile Sepsis”

Continuum of effects: activation of immune effector function without specific immunogen/antigen

mAb infusion and “anaphyalxis”
Hypersensitivity Cases Associated With Drug-Eluting Coronary Stents
A Review of Available Cases From the Research on Adverse Drug Events and Reports (RADAR) Project

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Salt Lake City, Utah; Chicago, Illinois; San Antonio, Texas; Albuquerque, New Mexico; Bethesda, Maryland; and New Haven, Connecticut
Figure 2. Photomicrograph of the non-stented coronary artery of Patient #2 just proximal to the stent showing severe stenosis and non-occlusive luminal thrombus (th) (A). In B is shown the proximal stented artery with marked inflammatory reaction around stent struts; high-power magnification of the boxed areas in B is shown in C and D, note that there is severe granulomatous reaction consisting of macrophages (arrowheads) and giant cells (arrows). In between the stent struts, there is severe eosinophilic and T-cell infiltration (high-power E) with only rare spindle-shaped cells seen close to the lumen. There is absence of endothelium in D; instead there is a surface thrombus.
Skin Rash and Viral Activation

Have we been looking in the wrong place?

Drug allergy model might be missing the obvious: skin rash has often been described as “viral exanthema”

Maybe that’s exactly what it is: activation of “cryptic” viral infection (e.g. HHV-8)

Problem: how to model?

Unrecognized use of host-resistance model

What is “viral activation”: a type of immunosuppression?
Conclusions

Allergenicity complex problem

Implications of unintended immunogenicity broader than Ig-mediated hypersensitivity

When is “hypersensitivity” really something else?