Regulatory Aspects and Interpretation of Immunosuppression Adverse Events in Nonclinical Studies

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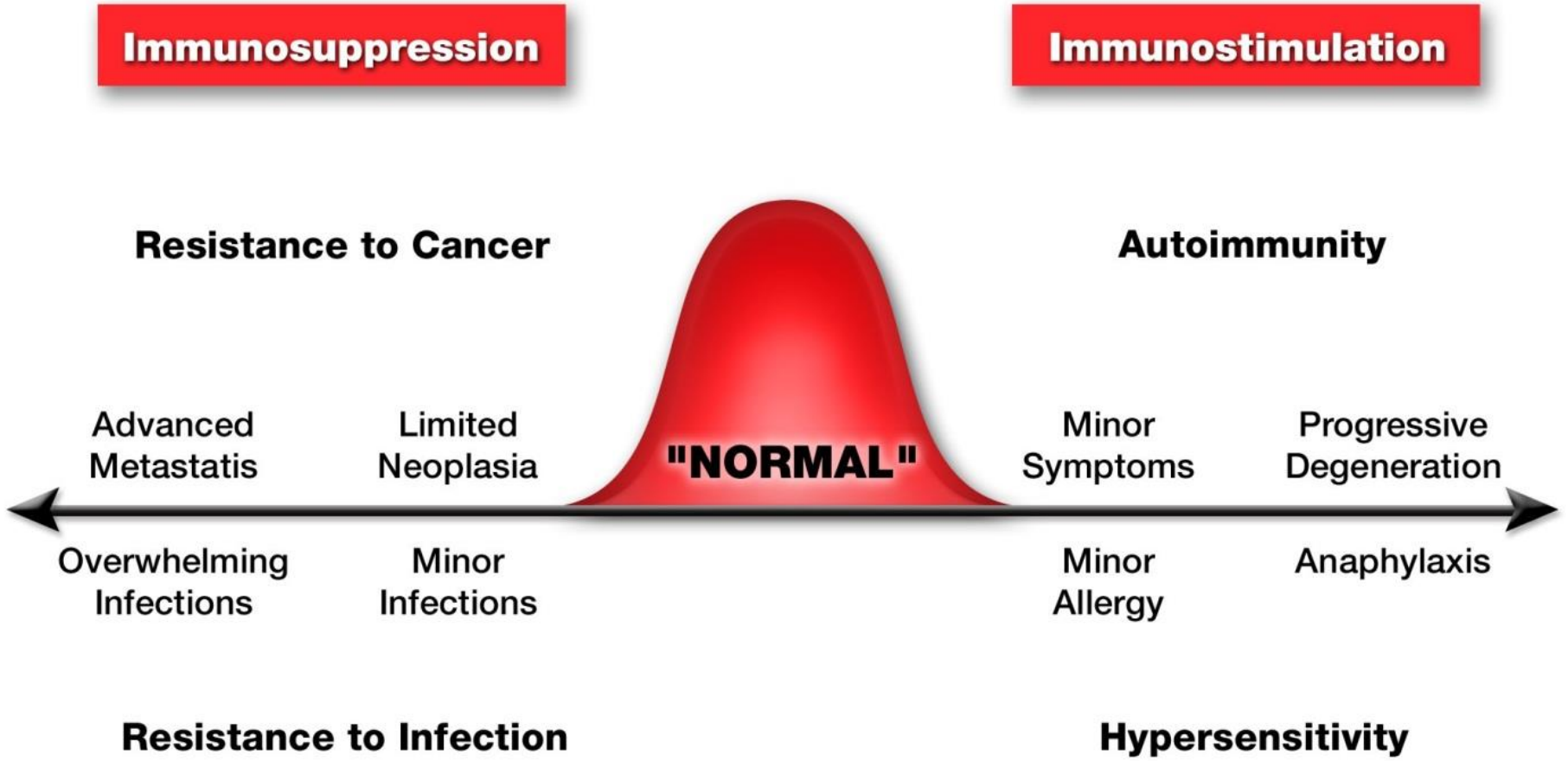
Types of Adverse Drug Reactions

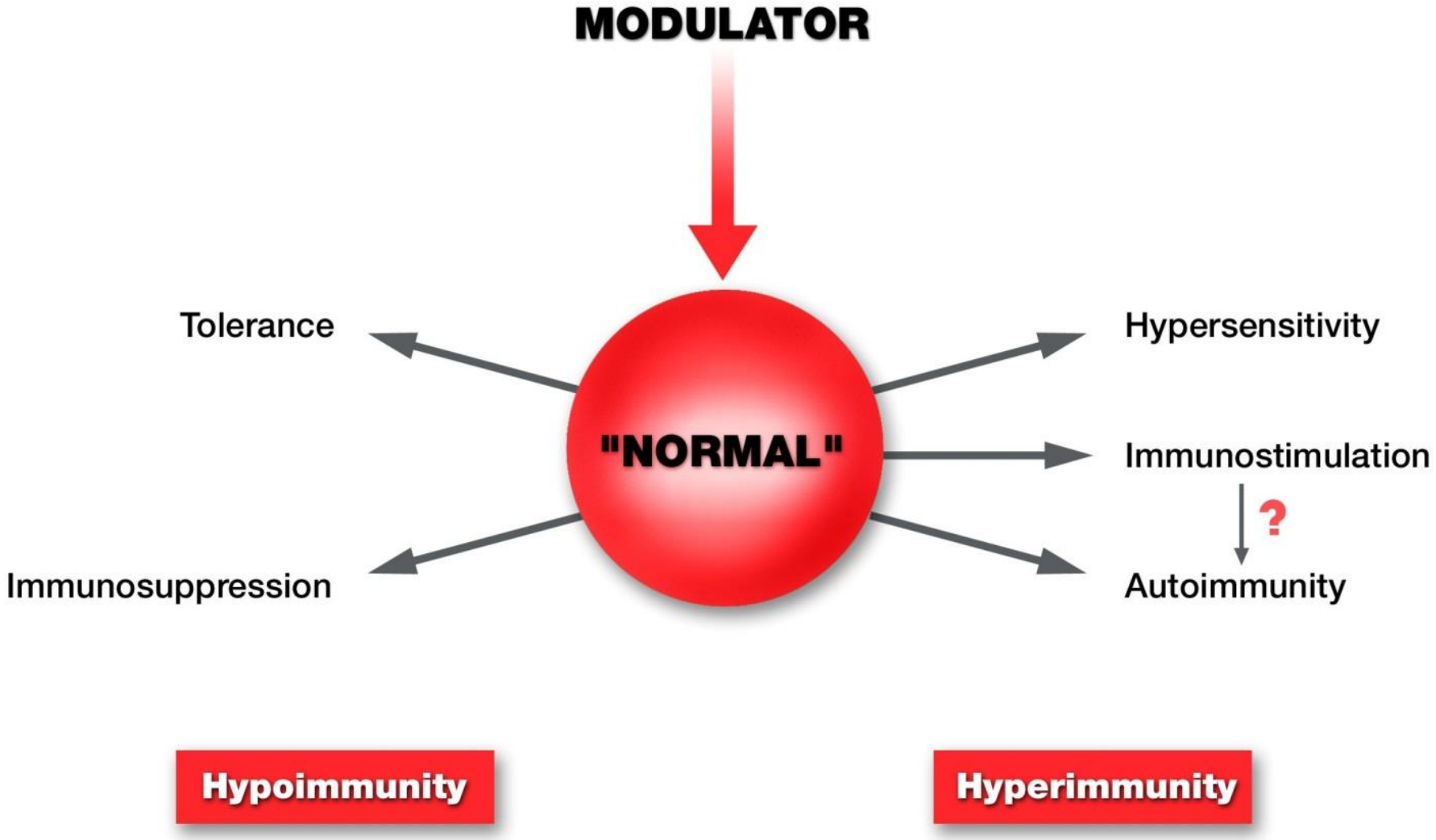
- Type A: dose-related, relatively predictable, and likely related to pharmacological action of the drug;
- Type B: not related to dose, not generally predictable, likely to have an immunological basis or related to a metabolic idiosyncrasy
- Type C: cumulative-dose related, likely associated with defect in clearance or other pharmacokinetic parameter
- Type D: time-related, such as chronic exposure resulting in drug-induced tumors
- Type E: withdrawal of drug resulting in adverse effects
- Type F: failure of efficacy.

Edwards and Aronson: *Lancet,* 356, 1255, 2000.


Immunosuppression
Immunostimulation
Resistance to Cancer
Autoimmunity
Advanced Metastatis
Limited Neoplasia
"NORMAL"
Minor Symptoms
Progressive Degeneration
Overwhelming Infections
Minor Infections
Minor Allergy
Anaphylaxis
Resistance to Infection
Hypersensitivity

But Is This Correct?

- Signs of infection – indicating immunosuppression – may be confused with signs of immunostimulation
- This is especially true for inflammation: when observed, is this hypersensitivity/autoimmunity, or the immune system functioning as designed?
- Chronic inflammation can result from persistent viral infection – inability to demonstrate an infectious agent does not mean that what is observed is a form of drug allergy


MODULATOR
Tolerance
"NORMAL"
Hypersensitivity
Immunostimulation
?
Autoimmunity
Immunosuppression
Hypoimmunity
Hyperimmunity

Immunosuppression Associated with Two Therapeutic Types

Test article intended to modulate immune function for therapeutic purposes (e.g. to prevent organ transplant rejection, anti-inflammatory drugs) where *adverse* immunosuppression can be considered exaggerated pharmacodynamics

Test article not intended to affect immune function but causes immunosuppression due, for instance, to bone marrow toxicity or interaction with cellular receptors shared by both target tissues and non-target immune system cells

Immunosuppressant Drugs

- Cytotoxic cancer chemotherapeutics (e.g. cyclophosphamide, 5-fluorouracil, vincristine, rituximab)
- Transplant drugs (e.g. azathioprine, cyclosporine, tacrolimus, rapamycin, mycophenolate mofetil)
- Anti-inflammatory drugs (prednisone, methotrexate, natalizumab, anti-TNFα mAbs)

Immunomodulatory mAbs

- Natalizumab → α4-subunit of integrins
- Basiliximab → IL-2 receptor
- Daclizumab → CD25 (IL-2 receptor)
- Rituximab → CD20
- Infliximab, etanercept, adalimumab → TNFα
- Omalizumab → IgE
- Ipilimumab → CTLA-4
- Nivolumab → PD-1
- Avelumab → PD-L1

Guidance for Industry

S6 Addendum to Preclinical Safety Evaluation of Biotechnology-Derived Pharmaceuticals

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)

May 2012
ICH

Guidance for Industry

Immunotoxicology Evaluation of Investigational New Drugs

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)

October 2002
Pharmacology and Toxicology

Guidance for Industry

S8 Immunotoxicity Studies for Human Pharmaceuticals

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)

April 2006
ICH

Guidance for Industry

Immunogenicity Assessment for Therapeutic Protein Products

DRAFT GUIDANCE

This guidance document is being distributed for comment purposes only.

Comments and suggestions regarding this draft document should be submitted within 60 days of publication in the *Federal Register* of the notice announcing the availability of the draft guidance. Submit comments to the Division of Dockets Management (HFA-305), Food and Drug Administration, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852. All comments should be identified with the docket number listed in the notice of availability that publishes in the *Federal Register*.

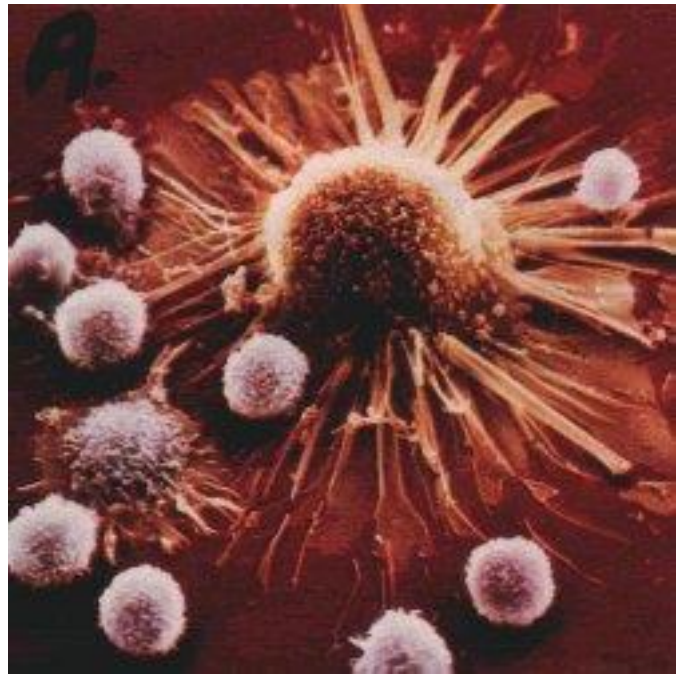
For questions regarding this draft document contact (CDER) Amy Rosenberg 301-827-1790 or (CBER) Office of Communication, Outreach, and Development at 1-800-835-4709 or 301-827-1800.

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)

February 2013
Clinical/Medical

ICH S8

- Guidance on a weight-of-evidence decision making approach for immunotoxicity
- Recommendations on nonclinical testing approaches to identify compounds which have the potential to be immunotoxic
- Immunotoxicity defined as suppression or enhancement of immune response



Types of Immunotoxicity

- Immunosuppression: Effects on the immune system that result in decreased immune function
- Immunogenicity
- Hypersensitivity: *Adverse* immunogenicity
- Autoimmunity: Immune reactions to self-antigens
- Adverse Immunostimulation: Non-antigen specific activation of the immune system

ICH S8 and Biologics

- Specifically states that guidance not intended for biologics
- However, general guidance on *unintended* immunosuppression
- Really, any of the signs of immunotoxicity can be associated with biologics
- Difference between *unintended* immunosuppression and pharmacodynamic immunosuppression: hazard identification and risk assessment

Signs of Immunosuppression

- Myelosuppression: e.g. pancytopenia, thrombocytopenia, anemia, leukopenia, lymphopenia
- Gross pathology findings (e.g. thymic atrophy, lymph node necrosis)
- Alterations in immune system organ weights and/or histology: hypocellularity/hypercellularity of immune system tissues
- Increased incidence of infections (esp. unusual pathogens)
- Increased incidence of tumors (esp. viral associated)
- Decreased serum immunoglobulin levels

Cancer in Transplant Patients

- Impaired immune surveillance
- Activation of oncogenic viruses (EBV)
- Lifetime risk of cancer in transplant patients approaches 70%; risk of cancer (excluding skin malignancies) might be as high as 100 X general population
- Skin (esp. lip and squamous cell carcinoma) and non-Hodgkin's lymphoma most prevalent
- Rare tumors also more common (e.g. Kaposi's sarcoma)
- Some (esp. lymphomas) may regress with cessation of immunosuppressant therapy

Nonclinical Assessment of Cancer Risk with mAbs

- Two year rodent bioassays not recommended
- Immunogenicity → false negative
- Immunosuppression-associated tumors likely due to viral activation
- Various host resistance models have been proposed, none validated
- Risk statements tend to be assumptions based on *theoretical* risk
- Clinical/epidemiological evidence of risk associated with chronic immunosuppression

Therapeutic Monoclonal Antibodies

- Immunogenicity: altered PK, PD, immunopathy/hypersensitivity/autoimmune reactions
- Exaggerated pharmacodynamics (e.g. tumor lysis syndrome)
- Type of mAb (IgG1: retains activity such as complement fixation, target cytolysis, neutralizing antibody; IgG4: does not fix complement, anaphylactoid reactions)
- Paradoxical effects (e.g. unintended agonist effects)
- Antibody-drug conjugates: off target toxicity due to unstable conjugation, toxicity of linker molecules
- Bispecific mAbs: immune complexes can be observed, uncertain if adverse
- Pegylation: altered PK, decreased immunogenicity, unexpected histologic findings (cell vacuolation: e.g. choroid plexus)

Tissue Cross-reactivity

- Limited usefulness
- Pattern consistent with pharmacology?
- Endogenous target (cytokines, checkpoint inhibitors)
- Exogenous target (microbial, tumor)
- False positive (non-specific binding)
- False negative (test article poor immunohistochemical reagent)

mAb Adverse Effects

- Infusion site reactions
- Rash
- Immunogenicity/hypersensitivity/ autoimmunity
- Types II and III immunopathies (e.g. serum sickness)
- Anaphylaxis/anaphylactoid reactions
- Cytopenias/ intravascular hemolysis
- Immunosuppression/infections/ malignancies
- Lymphoproliferative disorders
- Organ toxicities (liver, heart, lung, kidney)
- Capillary leak syndrome
- Complement activation-related pseudo-allergy (CARPA)
- Cytokine release syndrome
- Sterile sepsis

Unintended Immunogenicity

- Can be adverse effect associated with biologic drugs
- Proteins, polypeptides: inherently immunogenic
- Threshold: > 5,000
- 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)

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

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?

Xenobiotic-induced Autoimmunity

- Impairment of immune tolerance → xenobiotic damage to T_{REGs}
- No standard methods for evaluating autoimmunity
- Glomerulonephritis, lupus-like syndrome, hemolytic anemia, vasculitis, loss of tissue architecture with lymphocytic infiltrates
- Screening for autoantibodies has been used with limited success
- Replication-impaired virus → expression of viral antigen
- IL-17/IL-17r, IL-22, IL-23 polymorphisms

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

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 pseudo-allergy
- Cytokine release syndrome (CRS)
- Systemic inflammatory response syndrome (SIRS)
- Complement activation-related pseudo-allergy (CARPA)
- Sterile sepsis (“cytokine storm”)
- Tegenero (agonist anti-CD28 IgG_4 mAb)

MABEL

- Minimal Anticipated Biological Effect Level
- *In vitro* assay(s) using human cells (usually PBMCs), either plate bound or soluble (flow cytometry)
- Assessment of immune activation, cytokine release, ligand/receptor blockade
- Hazard identification for cytokine release syndrome → can be used to determine safe starting dose in clinical trials (risk assessment)

Conclusion

- Anti-inflammatory mAbs → therapeutic immunotoxicity
- Impairment of normal immune function → prevention of transplanted organ or tissue rejection
- Non-clinical studies demonstrate signs of immunosuppression
- Tissue cross reactivity studies → limited usefulness
- Rodent carcinogenicity bioassays not useful
- May be useful in determination of safe dose and duration of exposure
- Also, hazard identification (e.g. potential adverse effects of unintended immunogenicity)
- Non-clinical studies may be useful to distinguish immunopathy (drug allergy) from pseudo-allergy