Uses (and abuses) of IVIG in immunology, hematology, and rheumatology
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Learning objectives
• Where does IVIG come from?
• How is IVIG used in antibody deficiency?
• Why does IVIG work in ITP?
• How well does IVIG work in other autoimmune and inflammatory conditions?
• What are the drawbacks of IVIG therapy and what are some alternatives?

A brief synopsis of the illustrious history of antibodies and antibody therapy

Early years
• 1890s: Emil von Behring demonstrates adoptive transfer of immunity with serum; wins first Nobel Prize in Medicine 1901
• 1930: Arne Tiselius develops electrophoresis for analyzing and separating plasma proteins (Nobel Prize in Chemistry 1948)
• 1939: Tiselius & Elvin Kabat demonstrate plasma γ fraction contains antibodies
• 1946: E. J. Cohn develops method for large scale purification of plasma proteins
• 1952: Col. Ogden Bruton discovers agammaglobulinemia and demonstrates effectiveness of γ-globulin injections
Modern Era

- 1970s: Development of IVIG; first product approved by US FDA in 1984
- 1972: Gerald Edelman and Rodney Porter win Nobel Prize in Medicine for studies on antibody structure
- 1975: Cesar Milstein and Georges Kohler develop monoclonal antibodies (Nobel Prize in Medicine 1984, with N.K. Jerne)
- 1986: FDA approves OKT3 (anti-CD3) for treatment of transplant rejection

Serum protein electrophoresis (SPEP)

Antibody Structure

IgG does the heavy lifting

- Highest affinity
- Greatest specificity
- Fastest synthetic rate
- Longest half-life
- Placental transfer
- 96-99% of IVIG is IgG
**Regulation of IgG half-life**

[Diagram showing regulation of IgG half-life]

Roopenian & Akilesh, Nature 2007

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**IgG placental transfer**

[Diagram showing IgG placental transfer]

Roopenian & Akilesh, Nature 2007

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**Multiple Choice Test**

IVIG comes from:

a. The pharmacy  
b. Human plasma  
c. Animal plasma  
d. Recombinant DNA  
e. None of the above

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**Why is IVIG derived from human plasma?**

- Need for thousands/millions of specificities  
  - Reflects exposure of human populations
- Additional technical and cost hurdles for recombinant technology
- Avoidance of serum sickness from animal sources
Further purification of Cohn fractions II & III

- Biochemical purity
  - Enzyme treatment
  - Acid treatment
  - Caprylic acid treatment
  - Chromatography
- Eliminates trace components that may cause side effects
  - Complement
  - Kinins

- Viral safety
  - Solvent treatment
  - Detergent treatment
  - Ultrafiltration
- Further reduces risk of disease transmission
  - Enveloped viruses
  - Other viruses

How does IVIG “work”?

- Neutralization
- Agglutination
- Complement fixation
- Opsonization
Use of IVIG in antibody deficiency

- Replaces missing IgG
- Used prophylactically
- Functions by binding microbes and eliminating them by usual mechanisms

Nuts and Bolts

- Usual dose: 400-600 mg/kg once a month
- Infusion rate limited by side effects
- Some clinical improvement usually seen immediately
- Maximum improvement may take 4-6 months

IVIG side effects

- 10-20% of recipients
  - Subject and product variability
- Transfusion-like reactions
  - Fever, chills, myalgias, headache, nausea, vomiting (aseptic meningitis)
- Premedication
  - Acetaminophen
  - Antihistamines
  - Corticosteroids

IVIG safety

- Viral safety
  - HIV: no reported cases
  - HCV: no recent cases with latest generation products (1994)
- Rare side effects
  - Renal failure, thrombosis
  - Usually seen in critically ill and/or older patients
  - Sucrose and other stabilizers implicated
Choice of IVIG Brand

- Therapeutic equivalence
- Liquid vs. lyophilized
- Concentration and packaging
  - Stabilizers
  - Trace component profile
  - Individual patient variation

Current FDA approved indications

- Primary immune deficiencies
  - CLL with low IgG
- HIV infection in children
  - Allo-BMT
  - ITP
  - Kawasaki disease

Efficacy of IVIG in ITP

How Does IVIG Work in Immune Thrombocytopenia (ITP)?

Anti-platelet antibody
**IVIG in ITP: Hypotheses**

- Elimination of environmental antigen
  - Binding, opsonization, etc.
- FcR blockade of phagocytosis (passive)
- FcR signalling (active)
  - Down regulation of antibody production
  - Increased elimination via FcRn

**Mechanisms of action 2010**

**Different FcR mediate macrophage activation vs. inhibition**

**Recent Translational Studies**

- Anti-inflammatory activity of IVIG mediated by signaling through macrophage FcγRIIb
- Anti-inflammatory activity of IVIG due to sialylation of IgG Fc region
  - Kaneko, Nimmerjan, Ravetch, Science 2006
- Dr. Ravetch elected to US National Academy of Sciences 2006
IVIG in ITP and inflammatory disorders

- 400 mg/kg/d x 4 days
  - alternatively
- 1 g/kg/d x 2 days
- “Lather, rinse, repeat”

What is the evidence supporting the use of IVIG in other immune-mediated diseases?

Cochrane EBM Reviews

- MG
  - Acute: no significant difference between IVIG and oral methylprednisolone
  - Chronic: insufficient evidence to determine whether intravenous immunoglobulin is efficacious
- MS
  - some evidence to support use of intravenous immunoglobulins as a preventative treatment for relapses in relapsing remitting MS
- Preterm infants
  - IVIG does not have any significant effect on mortality from any cause
- Sepsis
  - Polyclonal IVIG significantly reduced mortality and is a promising adjuvant in the treatment of sepsis and septic shock

AAAAI Work Group report 2004

- Defined four categories:
  - Definitely beneficial
  - Probably beneficial
  - May provide benefit
  - Unlikely to be beneficial
Definitely beneficial

- Existing FDA indications
- Graves ophthalmopathy
- Demyelinating polyneuropathies

Probably beneficial

- Dermatomyositis and polymyositis
- Myasthenia gravis and Eaton-Lambert myasthenia
- Established bacterial sepsis
- TEN/Stevens-Johnson syndrome

May provide benefit

- Prevent neonatal sepsis
- Autoimmune cytopenias
- SLE
- APL and ANCA syndromes
- Severe, steroid-dependent asthma
- Intractable childhood epilepsy
- PANDAS

Unlikely to be beneficial

- Inclusion body myositis
- Non steroid-dependent asthma
- Atopic dermatitis
- Chronic fatigue syndrome
- Autism disorders
Drawbacks of IVIG Therapy

- Safety
  - Not currently a critical issue
- Method of administration and need for monitoring
- Supply
- Cost

IVIG cost and access

Issues

- Limited supply
- Increase in demand, particularly off-label
- Increase in production costs
  - Source plasma testing
  - Post production safety treatments
- Adverse Medicaid reimbursement decision

IVIG acquisition costs

Average Hospital Price for IVIG

IDF survey 2006
Cost to the patient

- Acquisition cost of IVIG $48 to $60/g
- A single infusion of IVIg may cost about $3000 for a child to $10,000 for adult
- If you have insurance you will see the cost of infusion may go to $100,000.

IVIG in Alzheimer's Disease !!

Alternatives to IVIG

- Primary immune deficiencies
  - Subcutaneous Ig infusion
- Other indications
  - Corticosteroids and other immunosuppressive agents
  - Anti-D for ITP
  - Recombinant mAbs, Fc fragment
  - Other specific therapies

Subcutaneous IG (Vivaglobin™)

- Weekly subcutaneous infusion vs. monthly intravenous infusion
- Less peak-to-trough variation in serum IgG levels
  - Clinical benefit?
- Patient satisfaction seems to correlate with home infusion regardless of route
Thank you!

Questions?

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