



The Patient: Emerging Clinical Applications

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Off-label Use of IGIV Products

- The off-label use of IGIV products will be discussed in my presentation.

IGIV Applications

- Immune replacement
 - Repletion of missing antibody
 - Lower doses required for therapeutic benefit
- Autoimmune modulation
 - Multiple purported mechanisms
 - Higher doses required for therapeutic benefit

IGIV Applications: Immune Replacement

- Primary congenital hypogammaglobulinemia
 - X-linked agammaglobulinemia
 - Common variable immunodeficiency (CVID)
 - Immunodeficiency with hyper IgM
 - Severe combined immunodeficiency disease (SCID)
 - Wiskott-Aldrich syndrome
 - IgG subclass deficiency
- Secondary acquired antibody deficiency
 - Chronic lymphocytic leukemia (CLL)
 - Pediatric HIV infection
 - Acute parvovirus B19 infection
 - Allogeneic stem cell transplantation

IGIV Applications: Autoimmune Modulation

- Hematologic disorders
 - Immune thrombocytopenic purpura (ITP)
 - Autoimmune neutropenia
 - Autoimmune hemolytic anemia
 - Posttransfusion purpura
 - Neonatal alloimmune thrombocytopenia
 - Autoimmune von Willebrand's disease
 - Anti-factor VIII antibodies
- Vasculitic disorders
 - Kawasaki disease
 - Wegener's granulomatosis

IGIV Applications: Autoimmune Modulation

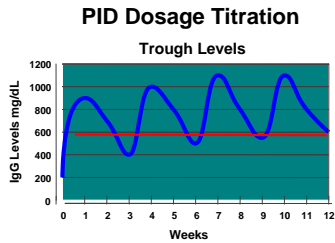
- Neurologic disorders
 - Polymyositis/dermatomyositis
 - Acute/chronic intermittent demyelinating polyneuropathies (A/CIDP)
 - Myasthenia gravis
- Transplantation
 - Reduction in panel reactive antibodies (PRA)
 - Humoral rejection
- Asthma
- Dermatologic/blistering diseases

IGIV Applications

- First description of benefit in autoimmune process described in 1981
- How and why does it work in such a variety of diseases?
 - Immune homeostasis mechanisms
 - Lack of specificity/understanding at the molecular level
 - Immunologic source of disease
 - Self vs non-self

Mechanisms of Action: Immune Replacement

- Dose response to 300–600 mg/kg q 3–4 weeks



Mechanisms of Action: Autoimmune Modulation

- Fc receptor blockade in macrophages
 - Prevention of phagocytosis of circulating blood cells
- Provision of anti-idiotypic antibodies
 - Neutralization of pathogenic auto-antibodies
- Complement absorption
- Down-regulation of immunoglobulin production
- Inhibition of lymphocyte proliferation
- Reduction in IL-1 production
- Enhancement of suppressor functions
- Direct virus neutralization
- Apoptosis induction
- Dendritic cell inhibition

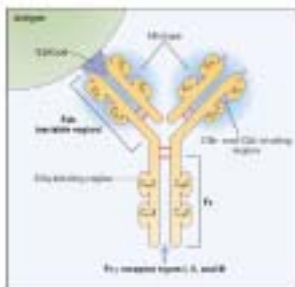
IGIV Mechanisms of Action



Mechanisms of Action

- Treatment of self-reactive autoantibodies
 - ITP, anti-factor VIII inhibitors, Hashimoto's thyroiditis
 - Occur early in ontogeny
 - Unknown origin
 - Natural vs pathological?
 - Functional Abs show no self Fc binding
 - Autoantibodies show lack of self-regulation
 - Altered self-reactivity seen in MDS
 - IGIV treatment may:
 - Block macrophage Fc receptors
 - Provide anti-idiotypic Abs
 - Promote clearance of pathologic Abs

Mechanisms of Action: Complement Inhibition



Mechanisms of Action

- Complement inhibition
 - Antiinflammatory effects through prevention of membrane attack complexes
 - Applications: dermatomyositis, Kawaski's disease
- Apoptosis induction
 - In vitro T and B cell apoptosis via Fas ligand
 - Caspase activation
 - Application: toxic epidermal necrolysis (Lyell's syndrome)

Mechanisms of Action

- Enhancement of suppressor functions
 - Applications: rheumatoid arthritis, lupus
 - Ratio of IgG Fc γ RII to RIII dictates response to inflammatory cytokines
 - Upregulation of the inhibitory Fc γ RII receptors by IGIV leads to reduction in inflammation

Enhancement of Suppressor Functions

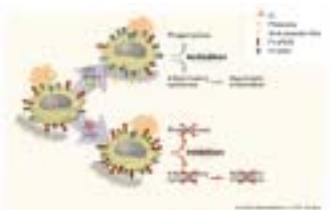
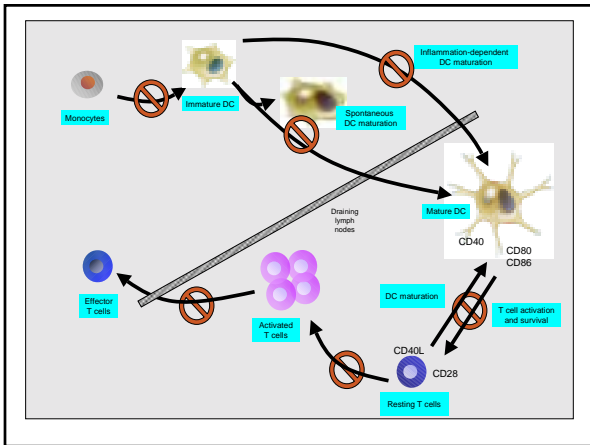
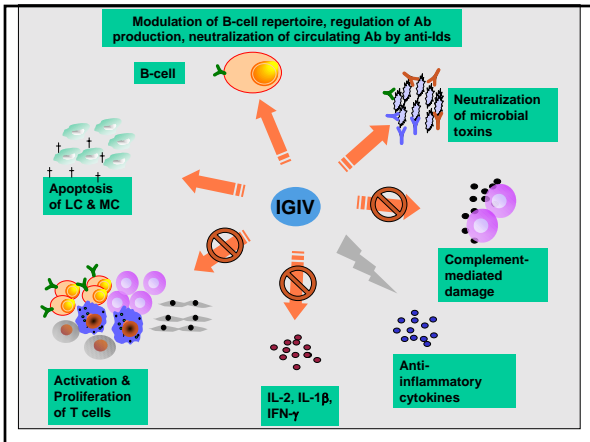


Figure 2
Regulatory T cells (Tregs) suppress T helper cell (Th) activity through various mechanisms. Tregs express inhibitory receptors (CTLA-4, BTLA-1, VISTA, HVEM, GITR, TIGIT) that bind to costimulatory molecules on Th cells, leading to suppression of their activity.

Mechanisms of Action

- Dendritic cell (DC) inhibition
 - IGIV inhibition of T cell proliferation and cytokine production described
 - Primary effect on T cells or earlier?
 - Bayry J, et al. *Blood*. 2003;101:758-765.
 - IGIV inhibits DC differentiation and maturation
 - Inhibits mature DC release of IL-12
 - Enhances DC release of IL-10





Novel Applications

- Level of evidence
 - Proven efficacy
 - Approved indications
 - Possible/probable efficacy
 - Well-designed studies, small patient numbers
 - Experimental
 - Theoretical basis for efficacy

Novel Applications: Renal Transplantation

- Expected that patient numbers on the waiting list will exceed 100,000 by 2006
- Approximately 30% have pre-formed antibodies to human leukocyte antigens (HLA)
- Antibodies exogenously obtained
- Historically, IgG positive T-cell crossmatch (CMX) testing precludes transplantation

Novel Applications: Renal Transplantation

- Panel reactive antibody (PRA) assay
 - Patient T cells incubated with 50 donors
 - Cytotoxicity measured as percentage of remaining viable cells
- PRA positivity means:
 - Increased rejection episodes and reduced allograft survival if transplanted
 - Longer waiting time on dialysis
- Can patients allosensitization be reduced to allow for transplantation?

Novel Applications: Renal Transplantation

- Cedars-Sinai desensitization protocol:
 - PRA-positive patient sera incubated 1:1 with IGIV
 - Donor plasma added, cytotoxicity of donor cells measured after complement added
 - Complete protection in vitro predicts in vivo response
 - Mechanism: anti-idiotypic antibodies

Novel Applications: Renal Transplantation

- Jordan SC, et al. Evaluation of IGIV as an agent to lower allosensitization and improve transplantation in highly-sensitized adult patients: report of the NIH IG02 trial (abstract). *Am J Transpl.* 2003;3:551.
 - Patients with PRA > 50% treated with IGIV 2 g/kg (max 140 g) monthly x 4 versus placebo
 - N=101
 - Assessment – reduction in PRA/anti-HLA antibodies, time to transplant

Novel Applications: Renal Transplantation

- Results: 35% reduction in PRA significantly different ($P = 0.004$)
- Time to transplant: IGIV 4.8 years, placebo 10.3 years ($P=0.02$)
- Superior allograft survival at 3 years
- Remaining questions
 - Role of plasmapheresis?
 - Role of rituximab?
 - Combination therapy?

Novel Applications: Renal Transplantation

- Humoral rejection
 - Antibody presence predates rejection (96% of 826 rejection episodes. Terasaki PI. *Am J Trans.* 2003;3:665-673.)
 - Responsible for hyperacute rejection and chronic rejection
 - Future strategies
 - IGIV?
 - Rituximab?
 - Additive immunosuppression?

Novel Applications: Neurologic Disorders

- Guillain-Barre syndrome (AIDP), myasthenia gravis
- IGIV 400 mg/kg qd x 5 equivalent to plasmapheresis in ventilation rates, functional grade improvements
- Mechanism: anti-idiotypic antibody inhibition
- CIDP: improvement versus placebo in muscle strength, disability scores
- Multifocal motor neuropathy: small trial showed improvement in grip strength, time to disease progression
- Multiple sclerosis: debatable benefits

Novel Applications: Infectious Diseases

- Recurrent bacterial infections
 - Neonatal sepsis
 - Rotavirus
 - Respiratory syncytial virus
 - Recurrent otitis media
 - Refractory autoimmune neutropenia
 - Gastroenteritis (oral)
 - Adjunct to antiviral therapy in cytomegaloviral disease

Novel Applications: Dermatologic Disorders

- Bullous pemphigoid
- Burn patients – ineffective for preventing infections, sepsis
- Polyarteritis nodosa
- Epidermolysis bullosa
- Stevens-Johnson syndrome/toxic epidermal necrolysis

Novel Applications: Hematology

- Acquired fVIII, vWF inhibitors
 - Rapid reduction in titers leading to fewer bleeding events
- Posttransfusion purpura
 - Treatment of choice
- Refractory autoimmune hemolytic anemia?
- Alloimmune thrombocytopenia?

Novel Applications

- Asthma
 - Corticosteroid-dependent asthma patients
 - Reduction in IgE production and corticosteroid potentiation
 - Suppression of IL-2 and IL-4 secretion from T cells
 - Small studies suggest reduction in corticosteroid needs, improved pulmonary function testing, and reduced hospitalizations with monthly dosing
- Systemic lupus erythematosus (SLE)
 - Severe active disease after failure of other therapies

Issues to Consider in IGIV Use

- Alternative therapy
 - Efficacy
 - Adverse reactions
 - Cost
- Therapeutic endpoints
- Dosage and duration of IGIV
- Quality of life
- Related costs (eg, hospitalization time)
