IVIG in Pemphigus

Animesh A. Sinha, MD, PhD

Professor
Department of Dermatology
University at Buffalo

No conflicts

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Learning Objectives

1. Review the role of autoantibodies in pemphigus

2. Overview of therapeutic approaches in pemphigus

3. Immunoglobulin focused therapies – IVIG

4. Newer approaches
Autoimmune Blistering Disorders

**Pemphigus group**
- Pemphigus vulgaris (PV)
- IgA pemphigus
- Paraneoplastic pemphigus (PNP)
- Pemphigus foliaceus (PF)

**Pemphigoid group**
- Bullous pemphigoid (BP)
- Cicatricial pemphigoid (CP)
- Herpes gestationis (HG)
- Linear IgA disease (LAD)

Intra-epidermal

Sub-epidermal
Pemphigus Vulgaris

Pathology is linked to the presence of autoantibodies that target certain epidermal proteins.
Pemphigus – Disease Roadmap

- Th2
- AutoAbs
- Dsg3/Dsg1
- IgG4
- Keratinocyte
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Pemphigus – Disease Roadmap

General immunosuppression

Th2

AutoAbs

Dsg3/Dsg1

IgG4

Keratinocyte

Self/Foreign Antigen

Class II MHC

T Cell Receptor

Antigen Presenting Cell

T Cell

Therapy Cell

CD4

Self Agglutinin

General immunosuppression
Systemic Steroids

Initial dosing: prednisone – 1-1.5 mg / kg / day
  o higher doses are more effective, but side effects increase disproportionately
  o maintain at 60mg/d for 1-3 months
  o taper 25-50% q2-4wks
  o anticipate 5-10 mg q.o.d. in 9-12 months
  • Flare: 2 steps back in taper schedule

Mechanism of Action
   interaction with cytoplasmic corticosteroid receptor
   up-regulation of anti-inflammatory proteins, down-regulation of pro-inflammatory proteins
   inhibition of transcription factors key to inflammatory response (cAMP, NF-kB, AP-1)
   inhibition of IL-2 responses (esp important in B cell medicated diseases)

Side Effects (significant and known)
Non-steroidal Immunosuppressives

Add **second line adjunctive agent** if unable to taper steroids without flares, if serious steroids side effects occur, or in rapidly progressive disease

1. mycophenolate mofetil (CellCept) 500 - 1500 mg/d p.o. *
2. azothioprine (Imuran) 1-3 mg/kg, 50 - 200 mg/d p.o.; check TPMT *
3. cyclophosphamide (Cytoxan) 2 mg/kg/d p.o.
4. methotrexate 10 - 50 mg/wk p.o.
5. dapsone 50 - 200 mg/d p.o.
6. cyclosporin 3-5 mg/kg/d p.o.
7. gold 50 mg/wk i.m.
# Treatment of Pemphigus

<table>
<thead>
<tr>
<th>Category</th>
<th>Mortality Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>pre-steroids (1950s)</td>
<td>50% mortality at 2 years; &gt;85% mortality at 5 years</td>
</tr>
<tr>
<td>steroids</td>
<td>50% mortality at 5 years (mostly from steroid complications)</td>
</tr>
<tr>
<td>now</td>
<td>5-10% mortality at 5 years</td>
</tr>
</tbody>
</table>
Pemphigus – Disease Roadmap

General immunosuppression

Th2

Immunoglobulin focused therapy

AutoAbs

Dsg3/Dsg1

Keratinocyte

IgG4

AutAbs focused therapy
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Arc of Treatment – *Immunoglobulin Focused Therapy*

- IVIG *
- FcRn blockade
- Plasmaphoresis
Intravenous Immunoglobulin (IVIg)

- Purified immunoglobulins (IG) from plasma of blood donation of more than 10,000 donors

- Multi-step procedure to lower risk of pathogen transmission
  - strict donor screening
  - filtration
  - treated with caprylate, and other viral inactivation methods

- Various manufacturers — some variation in terms of sugars, salt content (relevant in certain patients with diabetes, renal disease, hypertension and cardiovascular disease, etc)

- Costs

- Global availability
Intravenous Immunoglobulin (IVIg)

Mechanisms of Action

- accelerated catabolism (destruction) of circulating antibodies
- functional blockade of FcRn receptors
- reduction of circulating antibodies via anti-idiotypic antibodies
- down-regulation of antibody production by B-lymphocytes, B cell function
- inhibition of complement-mediated damage
- neutralization of toxins which trigger autoantibody production, inflammatory cytokines
- immune complex mediated inhibition of reticuloendothelial system
- blocking of Fas (CD95) mediated keratinocyte death by inhibiting Fas-FasL interactions
- Inhibition of Th17 pathway
- expansion of T regulatory cells
Intravenous Immunoglobulin (IVIg)

- usually given **2 grams/kilogram divided over 2-5 days/cycle**, monthly until clinical improvement (depending on volume required/comorbid conditions)

**IV infusion**
- infusion center
- home infusion
- delivered over several hours
- monitor for urine production, blood pressure, infusion reaction

• **i.m.** painful
• **s.c.** local discomfort; not practical for large doses

*Pre-screen pts for IgA deficiency*
Intravenous Immunoglobulin (IVIg)

Side Effects (generally well tolerated)

more common (10%)
- nausea
- headache
- fatigue
- neutropenia
- hemolysis

serious
- thrombosis/embolism
- pulmonary edema
- renal failure (osmotic nephrosis)
- aseptic meningitis
- severe anaphylactic reaction
Intravenous Immunoglobulin (IVIg)

Clinical Data

<table>
<thead>
<tr>
<th>Study</th>
<th>Study Type</th>
<th>Participants</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Svecova, et al (2015)</td>
<td>case series</td>
<td>10 pts</td>
<td>PDAI reduced 98% at 12 mo, 90% reduction of steroid dose</td>
</tr>
</tbody>
</table>
Intravenous Immunoglobulin (IVIg)

**Indications**

2\(^{nd}\) or 3\(^{rd}\) line treatment

1\(^{st}\) line – foudroyant, rapidly evolving disease

Recalcitrant disease
Neonatal Crystallizable Fragment Receptor (FcRn) Blockade

**FcRn** – protection and transport of IgG and IgG circulating immune complexes

**SYNT001** Humanized monoclonal that disrupts interaction of FcRn and IgG

**Mechanism of action**
- Blocks FcRn–mediated recycling and retention of IgG
- enables IgG degradation
- decreases Ag presentation?

**Syntimmune (Alexion) Phase 1b trial** – *positive results reported in 2018*
Plasma Exchange/Plasmapheresis/Immunoadsorption

- Non-specific removal of plasma proteins / Removal of circulating immunoglobulins
- Reserve for recalcitrant, rapidly evolving, severe disease
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Pemphigus Treatment - *enhanced specificity*

- **Immune regulation**
  - T regulatory cells
  - Cytokine targets

- **Immunoglobulin focused therapy**
  - B cell targeted
    - Rituximab
    - CAAR-T cells
  - IgG4
  - Dsg3/Dsg1/non Dsg

**General immunosuppression**

**Blockade of autoimmune induction**
Treatment of Pemphigus

Major Challenges

• no universally accepted treatment algorithm
• multiple treatments are available, none are universally effective in all patients
• clinical course and treatment response is variable among patients
• treatment varies between individuals - variation in dosage plan and combinations of drugs used
Thank you!!

And remember to donate BLOOD!

Patients
Family members

University at Buffalo The State University of New York