Intravenous Immunoglobulin (IVIg) in Autoimmune Blistering Disease

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What is Immunoglobulin?

Immunoglobulins can also be called “antibodies”.

When they attack a pathogen (bacteria, fungus) they are good, but when they attack yourself, they are bad and are “autoantibodies”

- Pemphigus
- Pemphigoid
What Makes Immunoglobulins?

Stem cell  Pro-B cell  Pre-B cell  Immature B cell  Naive B cell  Mature B cell  Memory B cell

Bone marrow  Periphery

CD19 expression  CD20 expression

Respond to rituximab  Don’t respond to rituximab

Plasmablast  Plasma cell

Secreted IgG  IgM  IgD  IgG
Goals of treating autoimmunity

• Stop making “bad” antibodies
• Continue making good antibodies
• Selectively inhibit the immune response against self
• Do not affect the immune response against pathogen.
Strategies to treat autoimmunity

• Inhibit the inflammatory response to antibody
  – Works to a degree in pemphigoid, less in pemphigus

• Remove circulating antibodies from the blood
  – Works temporarily, but antibodies already on the skin cause disease. New antibodies will be made

• Decrease antibodies being released by plasma cells
  – Decreases all antibodies, not just “bad” antibodies

• Kill the plasma cells
  – We only indirectly kill plasma cells by killing their precursor and waiting for them to die
  – In long-standing disease, they can last 2-3 years!
What is IVIg

- Pooled from 1000s of donors
- IVIg preparations are routinely screened for hepatitis B, hepatitis C and HIV
- Different formulations vary by preservatives, subtle techniques
What is FcRn?

• FcRn binds to antibodies, “recycles” them and puts them back into circulation

• This makes the half-life of IgG ~3 weeks, in contrast to other antibodies of ~5 days
How does IVIg work?

Amber et al. Role of Intravenous Immunoglobulin in Dermatologic Disorders. Biologic and Systemic Agents in Dermatology
Where does IVIg come in?

• **Inhibit the inflammatory response to antibody**
  – To a small degree blocks autoantibody binding and immune response, can help cell-death in pemphigus.

• **Remove circulating antibodies from the blood**
  – “dilutes” autoantibodies, increasing the speed of digestion

• **Decrease antibodies being released by plasma cells**
  – Has some anti-inflammatory effect on B-cells

• **Kill the plasma cells**
  – Only affects precursors
How is IVIg Given?

- Intravenous
- Standard total dose of 2g/Kg
- Divided over 3-5 days depending on patient risk factors
- Can be infused by IV or Port.
- Subcutaneous is not possible as too much would be required
- Given monthly
What is the Rebound Phenomenon?

- B-cells “want” to make autoantibodies.
- They compensate to the loss of autoantibodies by making more.
- This can be prevented by using a second medication (rituximab, azathioprine, cyclophosphamide, mycophenolate).

Does IVIg Work?

- Beneficial in trials, but IVIg was only used for 1 month in trials
- Clinical trials are expensive
- Do we have any more applicable evidence
Does IVIg Work?

Retrospective analysis of a single-center clinical experience toward development of curative treatment of 123 pemphigus patients with a long-term follow-up: efficacy and safety of the multidrug protocol with the mitochondria

Long-Term Remissions in Recalcitrant Pemphigus Vulgaris

Sergei A Grando

A Razzaque Ahmed, Srin Kaveri, Zachary Spigelman

The mean duration of complete remission off drugs until relapse was 15.8 months. That until end of follow up was 48.4 months, with a minimum of 14 and a maximum of 91 months. The overall complete remission rate off all drugs was 100%, with 12% overall relapse rate. Most relapses, 8.1 vs. 3.3%, occurred during the time of treatment, compared to posttreatment. No patients had more than a single relapse. The duration of the posttreatment follow-up ranged from 9 to 97 months with a mean of 64.8 months, or 5.4 years. The total number of IVIg cycles ranged from 26 in patients without a relapse to 37 in patients with a relapse. The clinical outcome in patients that received IVIg with RTX or another ICD were found to be very similar.
Risks of IVIg

- Headache (particularly in patients with migraine)
- Blood clots (low risk but seemingly a bit higher in pemphigoids than pemphigus)
- Excessive fluid (swelling or blood pressure increases)
- Fatigue
- Time-intensive
Why IVIg?

• There is no one size fits all treatment for every patient.
• Not immunosuppressive: doesn’t increase the risk of infections
• Allows non-steroid maintenance therapy to induce long term remission
• Good long-term remission rates when used correctly
• Generally safe
Who is the “right” patient for IVIg? (in my opinion)

• I use IVIg over ~2 years to put the disease in remission. My goal is for the disease to never come back and to never require further treatment.
• Per the FDA protocol, rituximab relapse rates are >60% at 2 years
• Greater time investment in the beginning, greater reward in the long term
• Long standing disease
• Pregnancy
• Severe/hospitalization, etc requiring multiple therapies
Who is the “wrong” patient for IVIg? (in my opinion)

- Time limitations preclude 3-5 days infusion/month
- Poor prognosis/health status (is it worth treating heavily to induce long-term remission?)
- Patient goals?
  - Would you rather receive rituximab every couple of years, or be more aggressive to ideally not require further treatment?
Managing side effects

- Headaches: Change formulation, pre-hydration, aggressive Tylenol, migraine management, divided dosages, 2g/kg divided over more days.
- Swelling/High blood pressure: Less fluids/pre-hydration.
- Fatigue: Change formulation, divided dosages, 2g/kg divided over more days.
A word on flares and autoimmunity

• Why do vaccines work?
• Disease flares are like a “booster”
• The longer the body is not exposed to “yourself,” the better chance of it forgetting about autoimmunity (i.e. plasma cells die off)
Why IVIg for so long?

• Reactivation of disease “restarts” the process
• Long term inhibition of autoantibodies can reduce long term
• Taper every 6 months after remission of disease off prednisone
Will insurance cover IVIg?

• Yes! And often with the ability for home infusions so you don’t have to go into the office 3-5 days per month.

• Different manufacturer’s and infusion companies will offer assistance programs and manufacturer discounts.

• Not all infusion companies are the same
A few notes

• Not all dermatologists are trained on using IVIg in blistering disease. Because of this, it’s not always offered as an option.

• Protocols for long-term IVIg are not as well described in the literature.

• Goals of care are the absolute most important part of treating blistering disease in my opinion. IVIg is a good choice for some, and the wrong choice for others. It all depends on goals.
How do I use IVIg?

• 2g/kg/month divided over 3-5 doses
• Rarely given alone
  – Rituximab or Cellcept unless pregnant (Prevent rebound)
  – Doxycycline unless pregnant (Prevent mini-flares)
  – Steroids (Acutely control disease). IVIg makes it easier to come off the steroids
• Monthly infusions until off of steroids, and in remission
  – This can take several months and is the hard part.
• Monthly infusions continue for 6 months after disease is in remission
• Drop to every other month for 6 months if still in remission
• Drop to every 3 months for 6 months if still in remission
• Stop everything!
Questions?