Clinical trials in pemphigoid

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Conflicts of Interest

- Co-founder, Cabaletta Bio
- Inventor on licensed patents, Cabaletta Bio, Novartis
- Past consultant, Syntimmune
- Past grants, Sanofi
- Will be discussing off-label use of drugs (not FDA-approved for pemphigoid)
Pemphigoid (and Pemphigus) 101

<table>
<thead>
<tr>
<th>Disease</th>
<th>Structure</th>
<th>Protein targeted by antibodies</th>
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</thead>
<tbody>
<tr>
<td>Pemphigus</td>
<td>Desmosome</td>
<td>Desmoglein 3 +/- 1</td>
</tr>
<tr>
<td>Bullous pemphigoid</td>
<td>Hemidesmosome</td>
<td>BP180 and/or BP230</td>
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</table>

- **stratum corneum** ("dead" layer of skin)
- **basement membrane zone** ("velcro")
Bullous pemphigoid: pathophysiology

BP180 IgG or IgE binds to the basement membrane zone

- Complement activation
- Release of chemoattractants

- Recruitment/activation of eosinophils, mast cells +/- neutrophils

- Release of destructive enzymes

- Basement membrane zone damage and dermal-epidermal separation

Bullous pemphigoid: pathophysiology

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Rituximab: NCT00525616

Sutimlimab: NCT02502903

nomacopan: NCT04035733

Bertilimumab: NCT02226146

Mepolizumab: NCT01705795; DF2156A: NCT01571895

Omalizumab: NCT00472030

QGE031: NCT01688882

Ixekizumab: NCT03099538

Sutimlimab: NCT00525616

Omalizumab: NCT00472030

QGE031: NCT01688882

Ixekizumab: NCT03099538


Blocking IgE in pemphigoid

IgE: friend AND foe
- A type of antibody (IgM, IgA, IgG, IgE)
- Helpful for killing parasites
- Causes allergies and anaphylaxis
- Contributes to itch/inflammation in pemphigoid

Omalizumab
QGE031

Blocking IgE in pemphigoid

**Omalizumab, Xolair™**

- FDA-approved for asthma and chronic hives
- Dose based on weight/IgE level: 300-375 mg every 2-4 weeks
- 5/6 BP patients at least transiently symptom free off prednisone
- In trials, 2 patients treated:
  - 1 flare after OMZ stopped; refractory to OMZ re-treatment
  - 1 flare of COPD requiring prednisone

**Ligelizumab; QGE031**

- Similar to omalizumab, binds stronger to IgE
- Randomized, blinded trial in pemphigoid
- 8/13 pts treated with QGE031 (61.5%) compared to 2/7 (28.6%) placebo had “marked improvement” of disease
- 6/13 (46.2%) had serious adverse events compared to 2/7 placebo (28.6%)
- Heart attack, heart failure, arrhythmia
- Liver failure
- GI bleed

**Take home:** No active trials currently, sometimes prescribed off-label; not as immunosuppressive; when it works, it works relatively fast
Blocking complement in pemphigoid

- Bullous pemphigoid antibody binds to base of skin
- Complement “cascade” is activated
  - Sutimlimab: NCT02502903
  - Nomacopan: NCT04035733

- Recruitment/activation of inflammatory cells
- Release of destructive enzymes
- BLISTERS
- HIVES
- ITCH
- PAIN

Bullous pemphigoid antibody binds complement
Blocking complement in pemphigoid

**Sutimlimab: NCT02502903**
- Phase 1 “basket” trial: pemphigoid and other complement-mediated autoimmune diseases
- Infusions well tolerated
- Preliminary efficacy in autoimmune anemias
- Promising data in pemphigoid mouse models; currently has orphan designation for pemphigoid
- True North > Bioverativ > Sanofi

**Nomacopan: NCT04035733**
- Blocks two “SOS” signals called C5a and LTB4
- Promising data in pemphigoid mouse models
- Subcutaneous injection (daily)
- Phase 2 enrolling in Europe
- Data from first 3 patients are “encouraging”

➤ *Take home: No active trials in the US currently, stay tuned*

Blocking inflammation in pemphigoid

- Bullous pemphigoid antibody binds to base of skin
- Bullous pemphigoid antibody binds complement
- Complement “cascade” is activated
- Cascade creates SOS signals

**Targeting neutrophils**
- DF2156A: NCT01571895
- Ixekizumab (anti-IL-17): NCT03099538

**Targeting eosinophils and mast cells**
- Mepolizumab: NCT01705795
- Bertilimumab: NCT02226146

[Links]
- https://www.shutterstock.com/search/neutrophil
Blocking inflammation in pemphigoid

DF2156A: NCT01571895

Ixekizumab: NCT03099538

• Target neutrophils through CXCL8 and IL-17A
• Ixekizumab is FDA-approved for psoriasis
• Lack of IL-17A protects against disease in mouse pemphigoid models
• DF2156A trial: stopped early due to limited efficacy
• Ixekizumab trial: 6 patients, study results pending

Mepolizumab: NCT01705795

Bertilimumab: NCT02226146

• Target eosinophils/mast cells through IL-5 and eotaxin
• Randomized, double-blind trial of mepolizumab, 30 BP patients
• No improvement in disease or skin inflammation but eosinophils in blood decreased
• Phase 2a trial of bertilimumab in 9 patients
  ➢ Average disease activity score improved
  ➢ Cumulative prednisone dose decreased
  ➢ Generally well tolerated
  ➢ Received orphan drug status for BP
• Immune Pharma filed for bankruptcy in Feb 2019

➢ Take home: No active trials currently

Summary

• Despite trials and tribulations in pemphigoid, there are more companies initiating clinical trials in pemphigoid than ever before

• There are promising strategies to block antibody-mediated inflammation in pemphigoid

➢ Stay tuned with IPPF for updates on future clinical trials in pemphigoid
Thank you

Pemphigus and Pemphigoid patients

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