Hot Topics in Medical Dermatology
Dangerous Dermatoses: TEN, SJS, EM, BP, & PV Pearls

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DISCLOSURE OF RELATIONSHIPS WITH INDUSTRY

Jonathan Ungar, MD

S010 - Hot Topics in Medical Dermatology
Dangerous Dermatoses: TEN, SJS, EM, BP, & PV Pearls

DISCLOSURES

Janssen Pharmaceuticals, Inc – Advisory board - honorarium
Menlo Therapeutics – Advisory board – honorarium
UCB – Advisory board – honorarium
• I will discuss off-label uses of medications

• I will discuss treatments currently undergoing trials for FDA approval
SJS/TEN

SJS/TEN

History

- Stevens-Johnson Syndrome
  - First described in 1922
  - A.M. Stevens and F.C. Johnson
  - Two children with eruptive fever, stomatitis, and ophthalmia

- Toxic Epidermal Necrolysis
  - First coined in 1956
  - A. Lyell
  - Four patients presenting with “a toxic eruption which closely resembles scalding in its clinical appearance and in the sensations to which it gives rise in the patient”

SJS/TEN

• Severe cutaneous adverse drug reaction
  • Case series vary on most common causative agents

• Most common classes of implicated drugs
  • Anticonvulsants
  • Antibiotics

• Allopurinol

• High mortality: 25-35%
SJS/TEN

Mortality

• **SCORTEN**
  - Introduced in 2000 by Batsuji-Garin, et al
  - Seven mortality risk factors
  - Combined score to predict mortality risk

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**Table II. Independent prognosis factors of TEN.**

<table>
<thead>
<tr>
<th>Variables</th>
<th>Odds ratio (95% CI)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (≥ 40 y old)</td>
<td>2.7 (1.0–7.5)</td>
<td>0.05</td>
</tr>
<tr>
<td>Heart rate (≥ 120 per min)</td>
<td>2.7 (1.0–7.3)</td>
<td>0.04</td>
</tr>
<tr>
<td>Cancer/haematologic malignancy</td>
<td>4.4 (1.1–18.0)</td>
<td>0.04</td>
</tr>
<tr>
<td>BSA involved at day 1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt; 10%</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>10–30%</td>
<td>2.9 (0.9–8.8)</td>
<td>0.04</td>
</tr>
<tr>
<td>&gt; 30%</td>
<td>3.3 (1.2–9.6)</td>
<td></td>
</tr>
<tr>
<td>Serum urea level (&gt; 10 mmol per liter)</td>
<td>2.5 (0.9–7.3)</td>
<td>0.09</td>
</tr>
<tr>
<td>Serum bicarbonate level (&lt; 20 mmol per liter)</td>
<td>4.3 (1.1–16.0)</td>
<td>0.03</td>
</tr>
<tr>
<td>Serum glucose level (&gt; 14 mmol per liter)</td>
<td>5.3 (1.5–18.2)</td>
<td>&lt; 0.01</td>
</tr>
<tr>
<td>SCORTEN</td>
<td>2.45 (2.26–5.25)</td>
<td>&lt; 10⁻⁴</td>
</tr>
</tbody>
</table>

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SJS/TEN

Pathophysiology (proposed and simplified)

Drug or drug-peptide complexes recognized by MHC I receptors on T-cells

Activation and clonal expansion of CD8+ and NK cells in skin

Release of inflammatory cytokines and apoptotic mediators (granulysin*, granzyme b, perforin, FasL, etc)

Keratinocyte apoptosis

*likely “key mediator” of keratinocyte death; highly expressed in blister fluid; can induce SJS/TEN phenotype when injected into murine skin

SJS/TEN

Treatment Options

- **Non-Pharmacologic**
  - *Stop offending medication !!!*
  - **Supportive care**
    - Wound care
    - Fluid electrolyte balance / nutrition
    - Infection control / prevention
    - Ophthalmology / GYN / Urology
    - Pain control
    - Airway management

  - Transfer to appropriate center
    - Burn Unit, if possible

- **Pharmacologic**
  - Glucocorticosteroids
  - IVIg
  - Cyclosporine
  - TNF-inhibitors
  - Thalidomide
SJS/TEN

Treatment Options

• **Non-Pharmacologic**
  • Stop offending medication !!!

• **Supportive care**
  • Wound care
  • Fluid electrolyte balance / nutrition
  • Infection control/prevention
  • Ophthalmology / GYN / Urology
  • Pain control
  • Airway management

• Transfer to appropriate center
  • Burn Unit, if possible

All the studies and data agree that these are most important.
SJS/TEN

Treatment Options

• Non-Pharmacologic
  • Stop offending medication !!!
  • Supportive care
    • Wound care
    • Fluid electrolyte balance / nutrition
    • Infection control/prevention
    • Ophthalmology / GYN / Urology
    • Pain control

• Transfer to appropriate center
  • Burn Unit, if possible

Can we do anything to decrease mortality beyond these...?
SJS/TEN

Treatment Options

• **Pharmacologic**
  • Glucocorticosteroids
  • IVIg
  • Cyclosporine
  • TNF-inhibitors
  • Thalidomide
SJS/TEN

Treatment Options

• **Pharmacologic**
  • Glucocorticosteroids
  • IVIg
  • Cyclosporine
  • TNF-inhibitors
  • Thalidomide

Systemic Immunomodulating Therapies for Stevens-Johnson Syndrome and Toxic Epidermal Necrolysis: A Systematic Review and Meta-analysis


• **Supportive Care**
  • **Most important**
  • Glucocorticosteroids
    • Inconclusive
  • IVIg
    • Does not support use
  • Cyclosporine
    • Beneficial effect on mortality
SJS/TEN

Treatment Options

- **Pharmacologic**
  - Glucocorticosteroids
  - IVIg
  - Cyclosporine
  - TNF-inhibitors
  - Thalidomide

  **Supportive Care**
  - Most important
  - Glucocorticosteroids
    - No benefit over Supportive Care
  - IVIg
    - No benefit over Supportive Care
  - Cyclosporine
    - Probable beneficial effect on mortality
  - TNF inhibitors
    - Confer survival benefit
  - Thalidomide
    - Clinical trial showed increased mortality

Stevens-Johnson Syndrome and Toxic Epidermal Necrolysis: A Concise Review with a Comprehensive Summary of Therapeutic Interventions Emphasizing Supportive Measures

SJS/TEN

Treatment Options

• **Pharmacologic**
  - Cyclosporine
  - TNF-inhibitors
  - Glucocorticosteroids
  - IVIg
  - Thalidomide
SJS/TEN

Treatment Options

• **Pharmacologic**
  • Cyclosporine
  • TNF-inhibitors
  • Glucocorticosteroids
  • IVIg
  • Thalidomide
SJS/TEN

Treatment Options

- **Glucocorticosteroids**
  - Traditional mainstay therapy
  - EuroSCAR (2008) analysis shows no significant mortality benefit vs supportive care alone
    - case-controlled (n=379 included)
    - 6 countries (80% from France and Germany)
    - OR = 0.4 (95%CI 0.1-1.7) in France
    - OR = 0.3 (95%CI 0.1-1.1) in Germany

SJS/TEN

Treatment Options

- **IVIg**

  - Search for alternative to GCS led to IVIg (concern for increased mortality with GCS)\(^1\)

  - **Rationale:** Fas-FasL interaction – reversal of FasL-mediated keratinocyte apoptosis demonstrated with IVIg (Viand *et al.*, 1998)\(^1\)

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SJS/TEN

Treatment Options

• **IVIg**

  • EuroSCAR (2008) analysis shows **no significant mortality benefit** vs supportive care alone
    • case-controlled (n=379 included)
    • 6 countries (80% from France and Germany)
  
  • OR = 1.4 (95%CI 0.6-4.3) in France
  • OR = 1.5 (95%CI 0.5-4.4) in Germany

SJS/TEN

Treatment Options

• IVIg

The efficacy of intravenous immunoglobulin for the treatment of toxic epidermal necrolysis: a systematic review and meta-analysis.

• Meta-analysis, 17 studies with at least 8 patients
  • IVIg showed no conclusive mortality benefit vs supportive care alone
    • Adults – High-dose (>2g/kg): OR=0.63 (95%CI 0.27-46.0, p=0.27)
    • Pooled Multivariate: OR=1.00 (95%CI 0.58-1.75, p=0.99)
  • High-dose IVIg (>2g/kg) vs low-dose IVIg (<2g/kg)
    • OR=0.494 (95%CI 0.106-2.300, p=0.369)
SJS/TEN

Treatment Options

- Pharmacologic
  - Cyclosporine
  - TNF-inhibitors
  - Glucocorticosteroids
  - IVIg
  - Thalidomide
SJS/TEN

Treatment Options

- **Cyclosporine**

  - **Rationale:**
    - Cytotoxic T-cells and NK cells implicated in keratinocytes apoptosis (like GVHD)
    - Cyclosporine interferes with T-cell signaling and function

SJS/TEN

Treatment Options

• **Cyclosporine**

  • Multiple case reports in the literature with positive results

A meta-analysis of cyclosporine treatment for Stevens-Johnson syndrome/toxic epidermal necrolysis.

Ng QX. *J Inflamm Res*. 2018 Mar 28;11:135-142

  • Examined 12 studies, n=357
  • Overall, showed mortality benefit vs supportive care alone
    • OR = 0.320 (95%CI 0.119-0.522, p=0.002)

  • Generally well-tolerated despite critically-ill patients
SJS/TEN

Treatment Options

• **Pharmacologic**
  
  • Cyclosporine
  • TNF-inhibitors
  • Glucocorticosteroids
  • IVIg
  • Thalidomide
SJS/TEN

Treatment Options

• **Etanercept**

  • **Rationale:**
    • High levels of TNF-α in blister fluid
      • Released by activated keratinocytes and macrophages
      • Potential mediator of keratinocyte apoptosis

SJS/TEN

Treatment Options

• **Etanercept**

Randomized, controlled trial of TNF-α antagonist in CTL-mediated severe cutaneous adverse reactions.


- Prospective, randomized (n=96)
  - Etanercept - 25mg SQ BIW (50mg if >65kg)
  - Corticosteroids – 1-1.5mg/kg/d prednisolone

- Etanercept **decreased SCORTEN-predicted mortality**: 8.3% vs 17.7%
- **Reduced time-to-skin-healing** in mod-to-sev compared to GCS: 14d vs 19d
SJS/TEN

So what should I do.........?

- **ALWAYS:**
  - Identify and **stop offending medication**
  - Appropriate **supportive care** (consider transfer to appropriate unit)

- **Consider:**
  - **Cyclosporine** and **etanercept** emerging as preferred treatments
    - Always consider contraindications
      - Cyclosporine: 3-5mg/kg/d split BID* (?taper after re-epithelialization)
      - Etanercept: 50mg SQ once*
  - **IVIg** if other options are contraindicated
    - IVIg 1-2g/kg split over 2-5 days

*No consensus on appropriate dosing
Bullous Pemphigoid
Bullous Pemphigoid

**History**
- Term first used by Lever in 1953
  - Bullous disease with subepidermal detachment
  - To distinguish from pemphigus
- Autoantibodies identified by Jordan and Beutner using DIF and IIF

**Epidemiology**
- Most common bullous disorder
  - Europe: 2.5-42.8 cases/million/year
  - Asia: 2.6-7.5 cases/million/year
- Mortality: ~23.5% (1-year mortality)

Bullous Pemphigoid

Treatment Landscape

• **First Line**
  - High potency topical steroids
  - Systemic steroids

• **Second line**
  - Doxycycline +/- niacinamide
  - Dapsone
  - Methotrexate
  - Azathioprine
  - Mycophenolate mofetil
  - IVIg
  - Rituximab
  - Omalizumab
Bullous Pemphigoid

• **Dosing**
  - Systemic steroids -
    • 0.5-1mg/kg/d
  - Doxycycline +/- niacinamide
    • 100mg BID + 750mg BID
  - Dapsone
    • 100mg PO QD
  - Methotrexate
    • 15mg PO qWeek
  - Azathioprine
    • 0.5-2mg/kg PO QD
  - Mycophenolate mofetil
    • Up to 3g QD (split q12h)
  - IVIg
    • 2g/kg split over 5 days
  - Rituximab
    • 1g x 2 (two weeks apart)
    • 375mg/m² (4 weekly doses)
  - Omalizumab
    • 300mg SQ every 2-4 weeks
Bullous Pemphigoid

Doxycycline vs Systemic Steroids

Doxycycline versus prednisolone as an initial treatment strategy for bullous pemphigoid: a pragmatic, non-inferiority, randomised controlled trial.

- Multicenter, randomized trial
  - Arm 1: Doxycycline 200mg daily spilt into 2 doses (TCS for weeks 1-3)
  - Arm 2: Prednisolone 0.5 mg/kg daily (TCS for weeks 1-3)

- Doxycycline arm showed 74% of patients had fewer than 3 blisters at Wk 6
- Prednisolone arm showed 91% of patients had fewer than 3 blisters at Wk 6

- Results favor use of systemic steroids vs doxycycline
Bullous Pemphigoid

**Rituximab (!!!)**

First-line combination therapy with rituximab and corticosteroids provides a high complete remission rate in moderate-to-severe bullous pemphigoid.


- Rituximab – 500mg x 4 weekly doses + prednisolone 0.5 mg/kg/d (tapered rapidly after disease control)
  - n=13
- Control: prednisolone 0.5mg/kg/d
  - n=19

- 92% vs 53% of rituximab group achieved complete remission (p=0.02)

- **Should rituximab be first line for patients with severe disease?**
Bullous Pemphigoid

Don’t Forget Drugs

<table>
<thead>
<tr>
<th>Drug class</th>
<th>Examples</th>
<th>Study design</th>
<th>OR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dipeptidyl peptidase-IV (DPP-IV) inhibitors</td>
<td>Vildagliptin</td>
<td>Systematic review and meta-analysis including 3563 BP patients using DPP-IV inhibitors(^5)</td>
<td>Pooled 10.16</td>
</tr>
<tr>
<td></td>
<td>Linagliptin</td>
<td></td>
<td>Pooled 6.13</td>
</tr>
<tr>
<td>Diuretics</td>
<td>Furosemide</td>
<td>British case-control study including 86 patients with BP and 134 age and sex-matched controls(^5)</td>
<td>Adjusted 3.8</td>
</tr>
<tr>
<td></td>
<td>Spironolactone</td>
<td>French case-control study with 201 BP patients and 345 controls matched according to age, sex, place of residence and hospital(^5)</td>
<td>Adjusted 2.3</td>
</tr>
<tr>
<td>Antipsychotics</td>
<td>Phenothiazine aliphatic chain</td>
<td></td>
<td>Adjusted 3.7</td>
</tr>
<tr>
<td>Checkpoint inhibitors Anti-PD-1/PD-L1</td>
<td>Pembrolizumab, Nivolumab, Durvalumab</td>
<td>Review study including 21 case reports of BP induced by checkpoint inhibitors(^5)</td>
<td>Not applicable</td>
</tr>
</tbody>
</table>

Bullous Pemphigoid

Relationship to Malignancy

• Meta-analysis of 8 studies showed no association between BP and overall cancer\(^1\)
  • One cohort – association with lymphoid leukemia, kidney ca, laryngeal ca
  • Overall pooled of case-controlled showed no association

• Japanese study with 1,113 BP patients\(^2\)
  • 5.8% malignancies
    • Lymphomas, gastric, colorectal, lung, prostate, and uterine cancers
  • Higher than the expected for age-matched controls

Bullous Pemphigoid

Upcoming Potential Therapies

• Bertilimumab
  • Human, monoclonal antibody targeting Eotaxin-1
  • Granted fast-track status in 9/2018¹
  • Phase 2 complete¹ (ClinicalTrials.gov Identifier: NCT02226146)
    • Safe and efficacious
    • Decline in BPDAI of 81% (p=0.015) at day 84

• BIVV009 (formerly TNT009)
  • Humanized, monoclonal antibody targeting complement component 1s
  • Phase 1 trial recruiting (ClinicalTrials.gov Identifier: NCT02502903)

Pemphigus
Pemphigus

Epidemiology

- Rare disease classification by NIH
  - <200,000 cases in US

- ~ 0.76-5 new cases/1mm/year in US\(^1\)
- Ashkenazi Jews: up to 32/1mm/year\(^1\)

- Mortality rate: 5-25\(^2\)

- HLA-DR4 haplotype DRB1*0402 and HLA-DQB1*0503\(^3\)

Pemphigus

Pathophysiology

• Autoantibodies against desmosome cadherins (Dsg 1 and Dsg 3)

Image source: Stevens NE. Front Immunol. May 2019
Pemphigus

Treatment Landscape

• **Immunosuppression**
  • Corticosteroids
  • Mycophenolate mofetil
    • Orphan Drug Status (2006)
  • Azathioprine
  • Dapsone

• **Biologics**
  • Rituximab

• **Other**
  • Plasmapheresis
  • IVIg +/- cyclophosphamide
Pemphigus

**Rituximab**

- Approved for PV by FDA 6/2018
- Human chimeric anti-CD20 monoclonal antibody
- First reported use in 2002

**Mechanism**
- Depletes CD20+ via complement-mediated cytotoxic cell death

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FIGURE 1 | Dual mechanisms of B cell depletion: 1: elimination of autoreactive B cells; 2: induction of regulatory B cells.

Image adapted from: Musette P. Front Immunol. Apr 2018
Pemphigus

Rituximab

First-line rituximab combined with short-term prednisone versus prednisone alone for the treatment of pemphigus (Ritux 3): a prospective, multicentre, parallel-group, open-label randomised trial


• Study Design
  • Prospective, multicenter, parallel-group, open-label, randomized
  • Treatment naïve
  • Arms:
    • Prednisone alone: (n=44) 1-1.5mg/kg (12-28 month taper)
    • Rituximab + prednisone: (n=46) rituximab 1g x 2 doses (2 weeks apart) + pred 0.5-1mg/kg (3-6 month taper)
Pemphigus

**Rituximab**

First-line rituximab combined with short-term prednisone versus prednisone alone for the treatment of pemphigus (Ritux 3): a prospective, multicentre, parallel-group, open-label randomised trial


- **Results**
  - At 24 months:
    - Rxn + pred: 41/46 (89%) complete remission off therapy
    - Prednisone alone: 15/44 (34%) complete remission off therapy
  - **AE**: Worse in prednisone only group (corticosteroid-related)

- **Take Away**: Rituximab with short prednisone taper MORE EFFECTIVE than prednisone alone
Pemphigus

Rituximab: Dosing

- **High Dose**
  - Lymphoma Protocol
    - 375mg/m$^2$ → 4 doses → 1 week apart
  - RA Protocol
    - 1g → 2 doses → 14 days apart
  - Initial clinical response comparable
  - RA has higher relapse rate (65% vs 41%) in 16-17 mo

- **Low Dose**
  - RA Protocol
    - 500mg → 2 doses → 14 days apart
  - Comparable clinical response to high dose with lower AE

Pemphigus

**Rituximab: Time to initial treatment**

An assessment of treatment history and its association with clinical outcomes and relapse in 155 pemphigus patients with response to a single cycle of rituximab.


- Retrospective
- Single cycle of rituximab

Failure to achieve remission correlated to longer time of disease activity prior to receiving treatment
Pemphigus

Rituximab + Azathioprine

Maintenance therapy with azathioprine prolonged duration of remission for pemphigus patients who received rituximab as first-line or add-on therapy.


- Retrospective (2008-2015)
- 78 patients with at least 1yr follow up s/p rituximab

- 71/78 (91%) achieved complete remission after 1 cycle of rituximab
- Repeated cycles of rituximab after relapse trended towards shorter times to complete remission
- Remission duration longer in patients put on AZA (1-2mg/kg/d) therapy after rituximab
  - 21.98 +/- 16.24 vs 9.98 +/- 7.93 months (*p=0.0232*)
Pemphigus

Rituximab is great, but what else is there.....?
Pemphigus

Treatment Pipeline

• Anti-CD20
• Vaccination
• Anti-BAFF
• BTK Inhibition
• Neonatal FcR Antagonism
• CAAR
Pemphigus

Treatment Pipeline

• Anti-CD20
• Vaccination
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• CAAR
Pemphigus

Treatment Pipeline – anti-CD20

• Type I
  • Rituximab, ofatumumab, veltuzumab, ocrelizumab (approved for MS)
  • B cell depletion via complement-dependent cytotoxicity$^1$

• Type II
  • Obinutuzumab, tositumomab
  • B cell depletion via signaling-dependent cell death (little complement dependent)$^1$
    • May be more efficient at depleting organ resident B cells$^2$

Pemphigus

Treatment Pipeline – anti-CD20

• Type I – Ofatumumab
  • Fully human, high affinity for CD20
  • Safe and effective in other autoimmune disorders
  • 40mg SQ at week 0 and week 4, then 20mg SQ every 4 weeks through week 56
  • Phase III trial terminated (drug acquired by new company, not safety)
    • ClinicalTrials.gov Identifier: NCT01920477

• Type I – Veltuzumab
  • Humanized; greater binding affinity and CDC compared to rituximab
  • Two 320mg SQ injections at week 0 and week 2
  • One patient – 22mo CR, subsequent cycle yielded 9mo CR

Pemphigus

Treatment Pipeline

• Anti-CD20
• Vaccination
• Anti-BAFF
• BTK Inhibition
• Neonatal FcR Antagonism
• CAAR
Pemphigus

Treatment Pipeline – Vaccination

- PI-0824
  - Synthetic Dsg3 peptide
    - AA residues 186-204

  - The idea: binding receptors without costimulatory signals leads to selective suppression of anti-Dsg3 autoantibodies

- Phase I/II Studies
  - No SAE
    - 2/17 pts experienced disease flare 1-5 months post-treatment

- No further studies at this time

- ClinicalTrials.gov Identifier: NCT00063752

Pemphigus

Treatment Pipeline

• Anti-CD20
• Vaccination
• Anti-BAFF
• BTK Inhibition
• Neonatal FcR Antagonism
• CAAR
Pemphigus

Treatment Pipeline – anti-BAFF

- BAFF = B-cell Activating Factor
  - TNF superfamily cytokine
  - Plays role in B-cell differentiation
  - Binding to receptor (BAFF-R) prevents apoptosis

- The idea: inhibition of BAFF/BAFF-R interaction will lead to apoptosis of autoantibody producing B-cells

- BAFF activity correlated in RA and SLE
  - NOT in PV

Pemphigus

Treatment Pipeline – anti-BAFF

• Belimumab
  • Human monoclonal antibody targeting BAFF
    • approved for SLE
    • not effective in RA

• VAY736
  • defucosylated, human IgG1 monoclonal antibody targeting BAFF-R
    • enhanced antibody-dependent cellular cytotoxicity-mediated depletion of B cells
    • blockade of BAFF

• Phase II trial is actively recruiting

• ClinicalTrials.gov Identifier: NCT01930175

Pemphigus

Treatment Pipeline

• Anti-CD20
• Vaccination
• Anti-BAFF
• BTK Inhibition
• Neonatal FcR Antagonism
• CAAR
Pemphigus

Treatment Pipeline – BTK Inhibition

• Bruton’s Tyrosine Kinase
  • Intracellular, essential enzyme for B-cell development and maturation
  • Inhibition could:
    • Block autoantibody production via B-cell receptor-mediated pathway
    • Dampen inflammation by inhibiting B-cell activation and FcR-induced cytokine release

Pemphigus

Treatment Pipeline – BTK Inhibition

• Ibrutinib
  • Small molecule that irreversibly binds BTK
  • Approved for:
    • Previously treated chronic GVHD
    • Previously treated mantle cell lymphoma
    • Waldenstrom’s Magrooglobulinemia
    • Previously treated marginal zone lymphoma

Pemphigus

Treatment Pipeline – BTK Inhibition

• PRN1008
  • Oral, small molecule, reversible BTK inhibitor
  • Granted orphan status in 2017

• Phase 1¹
  • No SAE
  • Main AE were GI-related; no discontinuations

• Phase 2²
  • Data pending, but press release from the company (11/2018):
    • Achieved primary endpoint (>50% attained disease control within 4 weeks)
    • Achieved secondary endpoint (sustained clinical efficacy at 12 weeks of therapy)

• Phase 3 – PEGASUS study
  • Currently recruiting
  • ClinicalTrials.gov Identifier: NCT03762265

Pemphigus

Treatment Pipeline

• Anti-CD20
• Vaccination
• Anti-BAFF
• BTK Inhibition
• Neonatal FcR Antagonism
• CAAR
Pemphigus

**Treatment Pipeline – neonatal FcR antagonism**

- Neonatal FcR
  - Receptor found predominantly on endothelial cells
  - Extends half-life of IgG by decreasing lysosomal degradation (inc. IgG recycling)

Pemphigus

Treatment Pipeline – neonatal FcR antagonism

- SYNT001
  - Humanized, monoclonal IgG4
  - Blocks interaction of FcRn and Fc portion of IgG4
  - Increased autoantibody lysosomal degradation
  - Granted orphan status 9/2018

- Phase 1b/2
  - Ongoing
  - Rapid lowering of circulating IgG
    - Well-tolerated
    - 5/7 pts showed reduction of disease activity at day 42

- ClinicalTrials.gov Identifier: NCT03075904

Pemphigus

Treatment Pipeline

- Anti-CD20
- Vaccination
- Anti-BAFF
- BTK Inhibition
- Neonatal FcR Antagonism
- CAAR
Pemphigus

Treatment Pipeline – CAAR

- **Chimeric Autoantibody Receptor T-cells**
  - CAR (Chimeric Antibody Receptor T-cells)
    - Shown to be effective in B-cell leukemia
    - Antibody structure fused to CD3 signaling domain on T-cells engineered to recognize tumor-associated antigens
    - Proliferate and expand *in vivo*

Pemphigus

Treatment Pipeline – CAAR

- **Chimeric Autoantibody Receptor T-cells**
  - CAR (Chimeric Antibody Receptor T-cells)
    - Shown to be effective in B-cell leukemia
    - Antibody structure fused to CD3 signaling domain on T-cells engineered to recognize tumor-associated antigens
    - Proliferate and expand *in vivo*

- CAAR
  - Truncated fragments of Dsg3 extracellular domain fused to CD137/CD3 signaling domains
  - Recognized autoantibodies to Dsg3 fixed on B-cell membrane
  - Efficacy in murine models and *in vitro*

Pemphigus

Treatment Pipeline – CAAR

FIGURE 2 | Chimeric auto antibody receptor (CAAR) T cell.

image from: Musette P. Front Immunol. Apr 2018
Thank you for your attention!

jonathan.ungar@mountsinai.org