TEN, SJS, EM, BP, PV Pearls

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Disclosures

• I have served on Advisory Boards for:
  • Amgen
  • Janssen Biotech
  • Genentech
  • Medac
  • Ranbaxy
  • Pfizer
  • Promius
  • Castle Biosciences Inc.

• I have been a Consultant for:
  • Novartis

• My talk will contain off-label uses of most drugs mentioned.
Toxic Epidermal Necrolysis
TEN: natural history

- Mortality rate: 25-35%
- Fas-FasL → caspases → apoptosis
- TNF within lesional skin → activates apoptosis
- Healing within 3 weeks for untreated survivors
Current Therapeutic Options

• **STOP OFFENDING DRUG**
• **Supportive care**
  • wound dressings, ophthalmology, fluids/electrolyte balance, airway, renal function, nutrition, pain control, and prevention of infection
• **Cyclosporine** 3-5mg/kg/d p.o.
• **IVIg** 2g/kg i.v. over 3-5 days (data conflicting)
• **Infliximab** 5mg/kg i.v. once
• **Etanercept** 50mg s.c. once

• **Prednisone?**
  • Perhaps with liver involvement (DRESS)
• **NOT thalidomide**
Cyclosporine for TEN

- Open trial of ciclosporin treatment for Stevens-Johnson syndrome and toxic epidermal necrolysis.

7 TEN patients
Cyclosporine 3mg/kg x 10 days, then taper x 1 month
Re-epithelialization 7-25 days
IVIg for TEN

• High-dose intravenous immunoglobulin for severe drug reactions: efficacy in toxic epidermal necrolysis

• 10 TEN patients
• IVIg 400mg/kg qd x 5 days
• Re-epithelialization: 24-40 days, 1 death
• Other studies → equipoise as to its benefit
Infliximab for TEN

• Antitumour necrosis factor-alpha antibodies (infliximab) in the treatment of a patient with toxic epidermal necrolysis.

• Rapid resolution of toxic epidermal necrolysis with anti-TNF-alpha treatment.

• Each 1 case; infliximab 5mg/kg i.v. once; re-epithelialization in 5 days
Etanercept for TEN

• **Etanercept therapy for toxic epidermal necrolysis.**

• 10 TEN patients
  • Treated within 72 hours

• Etanercept 50mg s.c. once

• Re-epithelialization: 8.5 days (7-20 range)
Thalidomide **NOT** for TEN

- Randomised comparison of thalidomide versus placebo in toxic epidermal necrolysis.

- Thalidomide 400mg po qd x 5 days
- 10/12 patients died in active vs. 3/10 in placebo
Bonus: Etanercept for GVHD

- Etanercept for steroid-refractory acute graft versus host disease following allogeneic hematopoietic stem cell transplantation.

- 18 patients
- Etanercept 25mg s.c. b.i.w. x 4 weeks
- Partial responses for GVHD in skin and gut, but not liver
- 4 patients died of infections
Erythema Multiforme

Etiologies:
- Herpes simplex*
- Drug
- Mycoplasma
- Orf
- *Histoplasma capsulatum

*HAEM = herpes-associated EM
EM: Therapeutic Options

- Antivirals (valacyclovir, acyclovir, famciclovir)
- Prednisone
- Anti-TNF: Etanercept, Thalidomide, Adalimumab
- Cyclosporine
- Apremilast
- Dapsone, SSKI
- others
My approach:

• **First Episode:**
  • Prednisone ~1mg/kg taper
    • 60mg for 3d, taper by 10mg q2d

• **Recurrent:**
  1. Check HSV 1 and 2 IgG titers (sensitive, not specific for HAEM)
  2. Famciclovir
  3. Apremilast
  4. Thalidomide
  5. Etanercept

• **Maintenance:** famciclovir

• **Last resort:** cyclosporine
Famciclovir for EM

- Famciclovir for recurrent herpes-associated erythema multiforme: a series of three cases.
- Routt E\(^1\), Levitt J\(^2\).

- All failed valacyclovir but responded to famciclovir
50 year old female with bullous erythema multiforme, + HSV2 IgG
Things she tried over 15 years with HAEM

- Mycophenolate mofetil
- Cyclosporine
- Long term prednisone → Cushingoid and osteoporosis
- Methotrexate
- Adalimumab
- IVIg
- **Acyclovir**
- **Valacyclovir**
- Doxycycline
- Hydroxychloroquine
- Oxycodone
- Hydroxyzine
Patient cleared after....

- **Famciclovir** 500mg po tid
- Now maintenance of Famciclovir 500mg po qd
Apremilast for HAEM

- Apremilast for treatment of recurrent erythema multiforme.
- *Dermatol Online J.* 2017 Jan 15;23(1).
- Chen T¹, Levitt J, Geller L.
Refactory Recurrent Erythema Multiforme Major

Failed:
- Prednisone
- IVIg
- Cyclosporine
Apremilast 45mg/day helped a lot!!! 😊
21 y.o. AA F, recurrent erosions x 10 years

• Diagnosed as Behçet’s, probably was HAEM
Within ONE WEEK of apremilast 30mg po bid!

I didn’t dose titrate – just go for it full dose and it works when you get to 1mg/kg-ish; she requires maintenance 30mg po bid
HAEM before therapy
Four days after apremilast 30mg po bid (no up-titration)
Another patient: Weaned off several years of prednisone, s/p rituximab and IVIg for presumed pemphigus:
Resolved with:

**famciclovir** → helped but recurred;

**etanercept** → helped but recurred;

**thalidomide** 50mg po qd → cleared her 😊

Then wanted to get pregnant...off thalidomide flared.... 😞
Apremilast worked!

**Cyclosporine**
5mg/kg/d also worked while trying to get pregnant, tapered to 2-3mg/kg/d
Hypothesis!

- Could Apremilast work for SJS/TEN?
- How could we test ethically?
Bullous Pemphigoid:
some diagnostic and therapeutic points
Do you screen for cancer in BP?

- early-onset pemphigoid
- former oncological history
- signs and symptoms of neoplasm
- BP refractory to common immunosuppressive therapy

BP: do we need to biopsy?

- Sensitivity and specificity of BP180 NC16A enzyme-linked immunosorbent assay for the diagnosis of pemphigoid gestationis
  - Al Saif F¹, Jouen F², Hebert V¹, Chiavelli H², Darwish B³, Duvert-Lehembre S¹, Joly P⁴; French Study Group on Autoimmune Bullous Skin Diseases.

  - 97% sensitive
  - 100% specific
  - Can avoid biopsy when ruling out PUPPP vs. PG
Must we biopsy an elderly patient with blisters with (+) BP180 or BP230 serology?

- If serology is (-), biopsy for BP or LABD or EBA or MMP (among others)
- If serology is (+), treat for BP
  - Specificity is 98.9%
  
  - BP180 ELISA using bacterial recombinant NC16a protein as a diagnostic and monitoring tool for bullous pemphigoid.
  
  
BP Therapy

• Prednisone taper 60mg x 3d, taper by 10mg q2d
• Doxycycline 100mg bid + niacinamide 750mg bid
• Clobetasol ointment bid to lesions

• If that fails and it’s extensive....
BP Therapy: don’t exclude rituximab!

• Think about rituximab early
  • 1g on Week 0 & 2

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


Cho YT, Chu CY, Wang LF.
Pemphigus vulgaris
Pemphigus vulgaris: what’s new?

• FDA granted breakthrough therapy status to rituximab for PV March 23, 2017

• **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.


• **At month 24**, 41/46 (89%) R + P vs. 15/44 (34%) P alone
  • Prednisone 1mg/kg x 3-6 months
  • Side effects in both groups relate to steroids: diabetes, myopathy, bone disorders
Rituximab dosing choices

- 1g at week 0 and 2 = **2.0g total**

- 375mg/m² x 4 doses = **2.8g total***

*For 70kg male, 5’10”, BSA = 1.87m²: 375mg/m² x 1.87m² = 701.25mg x 4 = 2.8g

  - Du Bois formula: BSA = 0.007184 × W^{0.425} × H^{0.725}

PV: what I do when Rituximab 1g wk 0 and 2 fails

First line for me:
• Rituximab 1g Week 0 & 2 plus Prednisone 60mg qd x 3d, taper by 10mg q2d (truly rapid taper)

If this fails:
• Repeat rapid prednisone taper +/- keep patient on 10mg until resolution
• Add IVIg 2g/kg/month

If this fails:
• Add mycophenolate mofetil 2g/d
• Prednisone 60mg for one week, taper by 10mg per week

If this fails:
• Repeat Rituximab (sometimes early at month 4) and do 375mg/m² q week x 4 weeks
What’s in the Pemphigus Pipeline?

• Immunosuppressants
• Anti-CD20 molecules
• Novel immune targets
• CAAR T cell approach
Sirolimus for acute pemphigus vulgaris

- Sirolimus 2mg/d (after 6mg loading dose) and IVIg 2g/kg/months x 8 months

- Sirolimus for acute pemphigus vulgaris: A case report and discussion of dualistic action providing for both immunosuppression and keratinocyte protection.
Anti-CD 20 monoclonal antibodies
(repurposing leukemia/lymphoma drugs)

• **Veltuzumab**: Two 320-mg subcutaneous doses 2 weeks apart; more potent than rituximab in non-Hodgkin’s lymphoma (one patient)

• **Ofatumumab**: anti-CD20 mAb, 40mg sc q month, Phase III in PV ongoing

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• **Obinutuzumab (GA-101)**: engineered anti-CD20 mAb with 50-fold higher binding affinity and resultant 10- to 100-fold efficacy against target B cells than nonmodified antibodies

• **Ocaratuzumab (AME-133v)**: anti-CD20 mAb

• **PRO131921**: anti-CD20 mAb
Novel Immune Targets
(initially for RA, lupus)

- **Naïve B cell → plasma cell**
  - **Belimumab** (GSK): anti-BAFF
    - Blocks the cytokine
    - BAFF = B cell activation factor; aka B Lymphocyte Stimulator (BLYS)
  - **VAY-736** (MorphoSys; Novartis): anti-BAFF-R
    - Blocks the receptor
    - BAFF-R = B cell activation factor receptor; aka B Lymphocyte Stimulator) mAb

- **Block B cell receptor signaling**
  - **PRN1008** (Principia Biopharma): oral, reversible covalent Bruton’s Tyrosine Kinase (BTK) inhibitor
    - Involved in B cell receptor signaling during normal B-cell development and activation

- **Block FcRn function**
  - **SYNT001** (Syntimmune): blocks neonatal Fc receptor (FcRn) function
    - FcRn prolongs half-lives of IgG
    - Allows accelerated catabolism of pathogenic anti-dsg IgG
BAFF / BAFF-R inhibition

- Apoptosis of autoreactive B cells
- ↓ B cell differentiation
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Bruton’s Tyrosine Kinase (BTK) inhibitor

- Block BCR signaling
- Induce B-cell apoptosis

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Neonatal Fc receptor (FcRn) Prevents Degradation of IgG:

- Found in endothelial cell membranes
- Responsible for IgG recycling
- Binds Fc portion of
  - Anti Dsg 3 IgG
  - IVIG
Competitive binding at FcRn

Pemphigus autoantibodies

Anti-Dsg3 Ab

IVIg or SYNT001
Chimeric Antigen Receptor T cells (CAR T Cells)

• Reengineering chimeric antigen receptor T cells for targeted therapy of autoimmune disease.
• Science. 2016 Jul 8;353(6295):179-84.
• Ellebrecht CT¹, Bhoj VG², Nace A¹, Choi EJ¹, Mao X¹, Cho MJ¹, Di Zendo G³, Lanzavecchia A⁴, Seykora JT¹, Cotsarelis G¹, Milone MC⁵, Payne AS⁶.

• Manipulate T cells that kill B cells
• Engineered human T cells to express a chimeric autoantibody receptor (CAAR)
  • Dsg 3 fused to CD137-CD3ζ signaling domains
• Dsg3 CAAR-T cells kill cells expressing anti-Dsg3 B-cell receptors
CAAR T cells for PV

Chimeric Antigen Receptor (CAR)

Chimeric Auto-Antibody Receptor (CAAR)
His Name is Hazel 😊