Evidence Based Management of Bullous Pemphigoid

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Disclosure of relevant relationships with industry
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“Evidence based Management of Bullous Pemphigoid”

- Genentech Roche
- Syntimmune
- Bioverativ
- Immune Pharmaceuticals
- Principia
- NIH Research Grant
- Note: Off Label uses of drugs will be discussed
BULLOUS PEMPHIGOID
Evaluation of Clinical Evidence

- **Definition of Disease and Subjects**
  - Possible inclusion of EBA in older studies
  - Extent and duration of disease before trial
  - Co-morbidities and existing conditions

- **Definitions of success**
  - Complete remission of skin disease
  - QOL measures (itching, new lesions)
  - Survival
  - Duration of remissions
  - Total dosage of prednisone therapy
  - Complications of disease and/or therapy
  - Laboratory markers (antibody titers etc)
Current Treatments Utilized

- Topical corticosteroids
- Non-steroidal anti-inflammatory drugs
  - Tetracyclines
- Systemic Corticosteroids
- “Steroid sparing” agents
  - Dapsone
  - Cyclophosphamide
  - Azathioprine
  - Mycophenolate mofetil
  - IVIG
  - Plasmaphersis
  - Methotrexate
Questions that remain to be answered

- What is the optimal dosage and mode of administration of corticosteroids for the management of newly diagnosed patients with BP?
- What population of BP patients should be treated with systemic corticosteroids vs topical corticosteroids vs non-steroidal drugs?
- Are ‘steroid sparing’ agents needed or effective?
Systemic Corticosteroids
What is the right dose?

- 0.75 mg/kg/day of prednisolone show equal disease control to 1.25 mg/kg/day at 51 days
  - Randomized
  - Diagnosis based on DIF only
  - Control defined as no new blisters day 21 – 51
  - 24 and 22 patients in each group
  - More adverse effects with higher dose

Morel P, Guillaume JC; Treatment of bullous pemphigoid with prednisolone only: 0.75 mg/kg/day versus 1.25 mg/kg/day. A multicenter randomized study, Ann Dermatol Venereol, 1984
Systemic Corticosteroids
What is the right formulation?

- No significant difference between patients treated with methylprednisolone vs prednisolone
  - Randomized, multi-center
  - Evaluated treatment response 5 and 10 days post treatment
  - Dosage of 1 – 1.5 mg/kg/day
  - No difference in erythema or blister formation; pruritus control better with methylprednisolone

Systemic Corticosteroids

- Generally thought to be effective
- Optimal dosage and optimal formulation have not been established in well controlled, randomized studies
- Long term outcomes and morbidity have not been carefully addressed in randomized, well controlled studies
Topical Corticosteroids

Are high potency topical corticosteroids effective in the treatment of BP compared to systemic corticosteroids?

- Multi-Center, prospective, randomized, non-blinded study comparing topical clobetasol (40 gram/day) or oral prednisone (0.5 mg/kg/day to 1.0 mg/kg/day)

- Patients with newly diagnosed disease, with positive DIF and c/w BP
- Stratified for mild vs severe disease
- Survival at 1 year primary outcome
Topical Corticosteroids for BP

- 188 patients with severe BP studied
  - Survival rate: 76% survival with topical therapy vs 58% with systemic therapy
  - Disease control at 3 weeks: 99% with topical treatment, 91% with systemic therapy
  - Severe Complications: 29% with topical therapy, 54% with systemic therapy

- 153 patients with moderate BP studied
  - No differences in survival, disease control or severe complications noted

Topical Corticosteroids for BP

“Topical corticosteroid therapy is effective for both moderate and severe bullous pemphigoid and is superior to oral corticosteroids for extensive disease”

Topical Corticosteroids for BP
Comparison of Different Dosages

312 BP patients randomized to:
- 40 gm/day clobetasol until 15 days after disease control with taper over 12 months (BID dosage)

OR
- 20 -30 gm/day clobetasol until 15 days after disease control with taper over 4 months (BID dosage)

312 BP patients randomized
- 178 Severe disease (> 10 new bullae/day)
- 134 Moderate disease (< 10 new bullae/day)

Median cumulative dose of clobetasol
- Standard: 2880 grams
- Mild: 435 grams

All patients treated with 40 gm/day achieved control of disease by day 21

156/159 (98%) of patients treated with ‘mild’ regimen achieved control by day 21

Topical Corticosteroids for BP
Comparison of Different Dosage

- **Time to disease control**
  - ‘Standard’ 7.9 days (cost 21 days = $1,008)
  - ‘Mild’ 8.2 days (cost 21 days = $504)

- **No difference in deaths or severe side effects**

- **No evidence of adrenal axis suppression**

- **Adjusting for age and Karnofsky score**
  strong beneficial effect in moderate BP treated with ‘mild’ therapy with increased event free survival

- **Joly et al.** J Invest Dermatol 129:1681,2009
Rates of Survival in patients with BP

- Use of mortality as indicator requires knowledge of survival rates for BP patients
  - France: Roujeau et al (Arch Derm, 1998)
    - 59% survival at one year
    - 89% survival at one year
    - 77% survival at one year
Use of non-steroids in treatment of BP

Doxycyline vs Prednisolone

- 200 mg/day doxycycline (132 patients) vs 0.5 mg/kg/d prednisolone (121 patients)
- Pragmatic, non-inferiority design
  - Positive result if doxycycline was no more than 37% less effective than prednisolone in frequency of severe adverse events at 52 weeks
- Response success was 3 or fewer lesions at 6 weeks

Results

- 74% of patients with doxycycline had 3 or fewer lesions at 6 weeks (Prednisolone 91%)
- Severe adverse events at 52 weeks
  - Doxycycline 18%
  - Prednisolone 36%

Williams et al  Lancet 389: 1630-1638, 2017
Are ‘steroid sparing’ drugs effective in treatment of BP?

- Intravenous immunoglobulin (IVIG) treatment of patients with Bullous pemphigoid
  - Patients with no symptomatic improvement with prednisolone (> 0.4 mg/kg/day) for 10 – 21 days
  - Randomized 6 weeks Prednisolone + IVIG (400mg/kg/d for 5 days) vs. Prednisone + placebo

- Results
  - Reduction in disease activity score in IVIG group at 15 days
  - Higher prednisolone dose in the placebo group at day 15
  - Results not statistically significant

Amagai et al, J Dermatol Sci 85:77-84, 2017
Are ‘steroid sparing’ drugs effective in treatment of BP?

- Azathioprine is an effective steroid sparing drug
  - After 1 week of prednisone therapy consultant determined if patients qualified
  - Patients (25) randomized to Prednisone alone or Prednisone plus 2.5 mg/kg azathioprine
  - 3 years of follow up
  - Patients treated with azathioprine decreased total steroid dose by 45% with no increase in serious side effects

Are ‘steroid sparing’ drugs effective in treatment of BP?

- Azathioprine is NOT an effective steroid sparing drug
  - Randomized, multi-center, not blinded trial
    - Prednisolone (1 mg/kg/day) alone, or
    - Prednisolone with azathioprine (100-150 mg/day) or
    - Prednisolone with plasma exchange
  - 100 patients randomized and evaluated at 28 days
  - No significant difference in disease remission in the three groups, more complications in Azathioprine group

What is the best ‘steroid sparing’ drug for the treatment of BP?

Comparison of methylprednisolone plus mycophenolate mofetil vs methylprednisolone plus azathioprine in the treatment of BP

- Prospective, multi-centered, randomized, non-blinded
- 73 patients randomized (blister roof antibody deposition)
- Assessed total cumulative steroid dose and rates of remission
- Both treatment arms showed similar efficacy and cumulative corticosteroid dose

Mycophenolate mofetil group showed lower liver toxicity

Evidence Based Management of Bullous Pemphigoid

- Small numbers of true randomized trials
- Criteria for diagnosis have changed over the decades making precise comparison between older studies difficult
- Agreement in outcome measures makes comparison between studies difficult
- Significant variability in disease severity in clinical practice
Evidence Based Management of Bullous Pemphigoid

- Evaluation of study populations critical for comparisons
  - Different survival rates in different countries
  - Co-morbid conditions need clear identification (diabetes, hypertension etc.)
  - Natural history of disease remains a confounder (role of duration of disease, extent of disease, laboratory markers)
How is BP actually Treated?

- Treatment of BP by German dermatologist 2009 survey
  - 50% use systemic corticosteroids as first line therapy (< 1.0 mg/kg/day)
  - 27% use clobetasol propionate as first line therapy
  - 69% use azathioprine as first line adjuvant therapy

Hofmann SC et al, JDDG, 2009
Questions that remain to be answered

- What is the optimal dosage and mode of administration of corticosteroids for the management of newly diagnosed patients with BP?
- What population of BP patients should be treated with systemic corticosteroids vs topical corticosteroids vs non-steroidal drugs?
- Are ‘steroid sparing’ agents needed or effective?
Conclusions:

- Very potent topical steroids are effective and safe treatments for bullous pemphigoid; their use in extensive disease may be limited by side effects and practical factors.

- Starting doses of prednisolone greater than 0.75 mg/kg/day do not seem to give additional benefit for disease control.

- Antibiotic therapy with doxycycline may be effective in some patients with BP as primary or adjunctive therapy.
Current State of Knowledge

Conclusions:

- The effectiveness of the use of azathioprine, mycophenolate, dapsone, IVIG, plasma exchange have not been clearly established but studies suggest they may be effective in some patients.

- Understanding the severity of the disease, the patients other health issues and patient desired outcomes are very important in choosing treatment.
Current State of Knowledge

A systematic review of treatments for bullous pemphigoid.

Guidelines for the management of bullous pemphigoid

Interventions for bullous pemphigoid
Khumalo NP, et al, *Cochrane Database of Systematic Reviews* 2005