Treatment of Bullous Pemphigoid: from Evidence-Based Medicine Findings to Practical Situations -

Pascal JOLY
French Study Group on Autoimmune Blistering Diseases (Groupe Bulle)

Rouen University Hospital, France
DISCLOSURE OF RELEVANT RELATIONSHIPS WITH INDUSTRY

- **Consulting**: GSK, Genentech, Novartis, Roche

- Roche provided Rituximab for one study on BP from the French study group on AIBD
Introduction

• **Numerous treatments have been proposed for BP patients:**
  - High doses of oral CS (prednisone 1 mg/Kg/day)
  - Medium doses of oral CS (prednisone 0.5 mg/kg/day)
  - Conventional immunosuppressants (azathioprine, MMF)
  - Medium / low doses of methotrexate
  - Super potent topical CS (clobetasol propionate)
  - Tetracyclines
  - Omalizumab / anti-IgE mAbs
  - Rituximab

• So many treatments, usually means that none of them is completely satisfactory…
Which treatment must we choose?
What must we take into account from the literature for the management of BP patients?

1. Bullous pemphigoid occurs in elderly patients
   - mean age: 80 years

2. Many patients are in poor general condition

3. Frequent cardiovascular, neurological diseases, diabetes
   - Low Karnofsky score (1/3 patients bed-ridden)
   - Stroke, dementia, Parkinson’s disease, major risk factors for BP
   - major prognostic factors
Prognostic factors of BP

Prediction of survival of patients with BP

(Joly P et al – Arch Dermatol 2005)

• **Deleterious prognostic factors**
  - older age *
  - cardiac insufficiency
  - dementia
  - past history of stroke
  - poor general condition
  - Use of high doses of oral corticosteroids

NOT
  - extent of BP (+++),
  - number of daily new bullae
BP is NOT a benign disease
It is a severe condition with a poor prognosis

1. Age- and sex-adjusted mortality rate of BP patients is much higher than the general population

2. meta analysis: 2080 BP patients (15 studies)
   - One-year mortality between 20% to 41%
   - standardized mortality ratio (SMR) (age and sex adjusted)
     - Europe: SMR: 3.3 (1 year) to 3.8 (2 years)
     - USA: SMR=2.2 (1 year) to 3.9 (2 years)
What are the goals of BP treatment?

- 1 - Treat the skin eruption, reduce itch, prevent the risk of recurrences;
- 2 - Improve the quality of life for patients;
- 3 - **limit treatment side-effects**, particularly frequent in the elderly. 

Try to rapidly obtain: “Complete remission off therapy”

“Complete remission on minimal therapy”:

- $\leq 0.1\text{mg/kg/d}$ of prednisone or
- $\leq 20\text{ g/week}$ of topical CS
What are the therapeutic options?
Medium doses of oral CS: Prednisone 0.5 mg/kg/d

- poorly evaluated in the literature

  - 95% patients achieved disease control (Day 21)
  - 40% relapse
  - **40% severe treatment side effects +++**
    - (vs 90% with 1 mg/kg/d of prednisone)

- One RCT in the UK, prednisone 0.5 mg/kg/d versus tetracyclines (in press)
  - Disease control with prednisone ≈ 70%; **40% severe side effects +++**

- One prospective ongoing open study (200 patients with **all types** of BP):
  - *(Joly et al EADV AIBD task force)*
    - Disease control Day 21: **70%**
Topical corticosteroids

- **Most validated treatment** (more than 1000 patients reported)

- **clobetasol propionate**
  - 30 to 40g/day (extensive BP)
  - 20 to 30g/day (moderate BP)

- Initially in one (≤20g) or two applications per day (>20g),
- Over the entire body including blistering and erosions, but excluding the face

- **Efficacy:** 90-100% of cases (mean delay of disease control: 15 days)
  - (most effective treatment +++ )

- Initial doses can be reduced 15 days after disease control.
Topical corticosteroids in BP:
How to decrease topical CS doses?

• Initial dose (20 to 40g)
• - daily during the 1st month (initial treatment)
• - every 2 days the 2nd month;
• - x 2 times per week the 3rd month;
• - once a week the 4th month.

• - After the 4th month of treatment: 2 possibilities:
  • -stop treatment
  • -maintenance once a week until M9-12

Limitations of topical corticosteroids in BP

1. **Side effects**
   - Local side effects: skin atrophy, purpura
   - Some systemic effects: diabetes, pneumonia.

2. **Practical problems**
   - Need to apply the cream on the whole body
   - Requires the assistance of patient’s relatives or a nurse
   - Close management of patients to avoid problems of non adherence
     - mainly due to: lack of nurses in many nursing homes
     - frequent misunderstanding of nurses (stop treatment just after epithelialization is obtained)
Bullous pemphigoid and methotrexate

- **Review of the literature**  
  *Gürkan & Ahmed, BJD 2009*

  - Some open studies suggested efficacy in monotherapy or associated with topical CS
  - Rate and delay of improvement highly depends on MTX doses

  - Low doses (5 mg/week): well tolerated, but poorly effective: delay of disease control up to 6 months

  - Higher doses (15-25mg/w): more effective, but severe side effects: infections +++
Bullous pemphigoid and methotrexate

• French Study group on autoimmune bullous diseases

• Prospective RCT compared:
  - MTX (12.5 mg/w) + initial topical CS (1 month) versus Topical CS alone for 9 months

• 300 patients included. Study undergoing… BUT

• only 1/3 of BP patients screened have been included (restrictive inclusion criteria)

• high rate of MTX side effects: (infections favored by impaired renal function in elderly patients)
Bullous pemphigoid and methotrexate

- **Effective**, especially when combined with topical CS at the beginning of treatment

- **Convenient**, although risk of mistake in the elderly (dose, intake every day versus weekly)

- **NOT as safe as claimed in case reports and retrospective series ++++**
  - numerous contra indications in elderly,
  - **risk of side effect** with « effective » doses (10-15mg/w)
  - off-label treatment
  - **lower doses** (5-7.5 mg/d): safer, but poorly effective
Other Immunosuppressants in BP

- Immunosuppressive drugs often poorly tolerated in the elderly

1- RCT: Azathioprine versus CS alone (Guillaume JC et al 1993)
   - No clear benefit demonstrated over CS alone
   - Higher rate of severe treatment side effects

2- Other immunosuppressants:
   - RCT: MMF versus AZA (Beissert S et al V 2007)
     - Underpowered RCT
     - No demonstration of CS-sparing effect (no CS alone group)

Conclusion
- No demonstration AZA, MMF effective as first line treatment
- Usually used in relapsing BP (frequent), recalcitrant cases (rare)
Tetracyclines and nicotinamide

- Quite popular treatment in some countries (UK, Japan), whereas considered as poorly effective in other countries

- Oxytetracycline 2 g/d, doxycycline 200 mg/d + nicotinamide (2 g/d) ???
- Efficacy suggested by an initial small study UK: 14 patients

Data not really confirmed by other studies, single observations…

- Very often associated with topical CS…
Tetracyclines

RCT in the UK and Germany (in press, The Lancet):

- **Doxycycline** 200 mg/d + **topical CS**, 30g/week (potent class) versus
- prednisone 0.5 mg/kg/d

- After 6 weeks, investigators **allowed to switch patients from the tetracycline arm to the prednisone arm**, or an alternative treatment they considered appropriate …

- Efficacy at week 6 of the **strategy**: 75% mild BP; 65% severe BP
Tetracyclines

Personal interpretation:

- Association with topical CS likely over estimated the true efficacy of tetracyclines
- Assessment of disease at 6 weeks: rather long in clinical pratice
- Acceptable efficacy in mild BP, questionable efficacy in severe BP,

- **Useful in:**
  - mild BP,
  - patients in poor general condition,
  - as maintenance therapy in some relapsing cases, (especially in patients with topical /oral CS side effects … )

- Try and make your own experience!
Rituximab

- Case series and case reports suggested a dramatic efficacy, good tolerance
- Despite a rather young age of patients (65y): 20% rate of death, including one child...

Prospective study of the French Group:
- 17 patients with relapsing BP (2 previous relapses)
- Treatment: 2g Rituximab + 1 month topical CS

Results
- M24: 2/17 (12%) CT off therapy, 7/17 (41%) CR on minimal therapy
- 7 severe side effects (41%), including 5 deaths: 29%
- Much less dramatic efficacy in BP than in pemphigus
Omalizumab (anti IgE mAb)

- Only 10 cases reported in the literature
- Subcutaneous injections of 300 mg every 3 weeks
- Omalizumab added to many previous drugs
  - « Improvement » of patient condition…
  - Decrease of CS doses…
  - Well tolerated

- Rate and level of efficacy remain to be determined
IV Immune globulins

- One recently published RCT \((Amagai Met al. J Dermatol Sci 2017)\)
- 56 BP patients who showed no symptomatic improvement with prednisolone \((0.4 \, \text{mg/kg/day})\) \((\text{mean at Day0}=0.55 \, \text{mg/kg/d})\)
- \((\text{IVIG}; \, 400 \, \text{mg/kg/day for 5 days})\)
- patients with previous or existing cerebrovascular or cardiovascular disorder were excluded \(+++\)
- 15 patients \((28\%)\) withdrew \((\text{reasons not mentioned})\)
- **Primary end point**: difference in disease activity score \((\text{DAS})\) on day 15
  - IVIG group \(\text{baseline 46 pts to 20 pts (56\% improvement)}\)
  - placebo group \(\text{baseline 46 pts to 32 pts (30\% improvement)} \, (p=\, 0.09)\)
Which of these treatments should we choose in the most frequent practical situation?

- The choice depends on:
- **Extent** of BP: localized vs mild/ moderate vs extensive.
- **Clinical type**: blisters (70%-80%), non blistering type: eczematous/prurigo-like, urticaria
- **Associated medical conditions**: neurological, cardiovascular
- **Availability of nurses** (or patients’relatives) for topical treatment
- **Cost**
## Costs

<table>
<thead>
<tr>
<th>Drug</th>
<th>Cost (per month)</th>
<th>Efficacy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Methotrexate 12.5 mg/ week</td>
<td>4 €….</td>
<td>++</td>
</tr>
<tr>
<td>Prednisone 0.5 mg/kg/d</td>
<td>6 €</td>
<td>++</td>
</tr>
<tr>
<td>Doxycycline 200 mg/d</td>
<td>12 €</td>
<td>+</td>
</tr>
<tr>
<td>Topical CS 20g/d</td>
<td>84 €</td>
<td>++</td>
</tr>
<tr>
<td>Topical CS 30g/d</td>
<td>126 €</td>
<td>+++</td>
</tr>
<tr>
<td>MMF 2g/d</td>
<td>140 €</td>
<td>? (no RCT)</td>
</tr>
<tr>
<td>Rituximab (2g)</td>
<td>5640 €</td>
<td>? (no RCT)</td>
</tr>
<tr>
<td>IVIG (2g)</td>
<td>12410 €</td>
<td>±</td>
</tr>
</tbody>
</table>
Which one of these treatments should we choose in the most frequent practical situation?

- Proposals of the French study group on AIBD
  - Only opinion +++
  - From evidenced based
  - From our experience

- Currently discussed by international panel of experts
Extensive / Severe BP

- **Start with:**
  - Super potent topical CS; **clobetasol propionate:** 30-40g/d (>90% efficacy)
  - Medium dose prednisone 0.5 mg/kg/d  (60%-70% efficacy)

- **Maintenance:**
  - Methotrexate 10-15 mg/w
  - MMF ??
Mild / moderate (not localized) BP (< 10 blisters/d)

- **Start with:**
  - Super potent topical CS; clobetasol propionate: 20 g/d
  - Tetracyclines + topical CS
  - ± Medium dose prednisone 0.5 mg/Kg/d

- **Maintenance:**
  - Rapidly decrease topical / oral CS (4 months)
  - Tetracyclines
Few blisters but extensive urticarial lesions

- **Start with:**
  - Medium dose prednisone 0.5 mg/Kg/d
  - Topical CS
  - Tetracyclines + topical CS

- **Maintenance:**
  - Tetracyclines
  - Methotrexate
  - MMF (in case of inefficacy of tetracyclines or CI to MTX)
Few blisters but extensive eczematous lesions

- **Start with:**
  - Super potent / potent topical CS

- **Maintenance:**
  - Low doses of MTX, 5-7.5 mg/week
  - Alternatively: topical CS
  - Tetracyclines: might be an option for patients with poor tolerance of MTX
BP in demented / bed ridden patients

- The most difficult to treat cases +++
- Often severe BP (dementia: both a risk and prognostic factor)

- Start with:
  - Topical CS (poor practicability +++)
  - Medium dose oral CS (poor tolerance +++)

- Maintenance:
  - MTX > tetracyclines (severity of BP)
BP in patients with cardiovascular disorders

- **Start with:**
  - Topical CS alone
  - Avoid oral CS +++

- **Maintenance:**
  - MTX / tetracyclines (depending on severity of BP)
BP in rather « young » patients ( <70-75y)

- **Start with:**
  - Medium doses of oral CS
  - Topical CS

- **Maintenance:**
  - MTX > tetracyclines
Treatment of BP; Key points

1. Consider patient’s age and co-morbidities
2. Avoid high doses of oral corticosteroids +++

3. Topical corticosteroids are the most validated treatment with an extremely high efficacy, but not always practical

4. Even medium doses or oral CS can induce serious adverse effects

5. Methotrexate (10 mg/w) or tetracyclines can be considered as maintenance therapy depending on BP severity
Thanks for your attention!