Safety and efficacy of a 0.5 mg/kg/day dose of prednisone as initial treatment of bullous pemphigoid

Validation of the EADV/EDF guideline therapeutic ladder

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Background

Bullous pemphigoid (BP) is the most frequent autoimmune blistering disease of the skin. BP mainly affects the elderly. Importantly, a significant proportion of these elderly BP patients are in poor general condition, with a high prevalence of neurological and cardiovascular disorders. Old age and poor general condition have been demonstrated to be major deleterious prognostic factors of BP.

High doses of systemic corticosteroids (CS) have been considered the standard treatment for BP patients for many years. Then a large controlled clinical trial demonstrated that high doses of super-potent topical CS increased survival of patients with extensive BP, and dramatically decreased the rate of severe treatment side effects as compared with oral prednisone 1mg/kg/day. Moreover, topical CS have been shown to be more effective than oral prednisone, as the rate of disease control obtained with topical treatment was 100 and 99% in patients with moderate and extensive BP, as compared with 95% and 91% with oral prednisone, respectively. Another randomised controlled trial (RCT) and a retrospective study have then confirmed the extremely high efficacy of super-potent topical CS in both limited and extensive BP.

However, the application of topical CS over a long period is inconvenient for elderly patients, since it often needs the assistance of nurses who are not available in all European countries. Therapeutic alternatives are limited. Tetracyclines have been recently tested with rather poor results even in mild/moderate pemphigoid. Methotrexate has a higher efficacy but many elderly BP patients have contraindications to this drug.

Thus, EADV guidelines have proposed the use of medium doses or oral CS (prednisone, 0.5 mg/kg/day) as an alternative to topical CS in the treatment of BP.

The main reasons for this recommendation were the following:

1. Proposing an alternative treatment to topical CS in countries in which the practical management of topical treatment is difficult.
2. Avoiding high doses or oral CS due to their well-demonstrated deleterious side effect profile.
3. Avoiding low doses 0.3 mg/kg/d of prednisone, which have been demonstrated to be ineffective.

Objectives

The primary objective of this study is to assess the safety and efficacy of a first-line treatment with prednisone 0.5 mg/kg/day in BP patients, namely in terms of rate of disease control and one-year survival.

Secondary objectives are: i) to evaluate the characteristics of BP patients treated with prednisone 0.5 mg/kg/day in clinical practice, in order to assess the external validity of this study; ii) to assess other markers of treatment efficacy (delay of control, rate of CR off therapy, and rate of CR on minimal therapy), and safety (rate of severe side effects); and (iii) to identify prognostic factors of treatment success.

Methods

We are currently undertaking a European

observational non-interventional study enrolling 200 newly-diagnosed BP sufferers who are followed for 2 years. Patients with localised BP have been excluded, since there is a consensus in clinical practice to treat these patients with topical CS, rather than oral CS.

According to the EADV guidelines, it was proposed that patients could be treated with an initial prednisone dose of 0.5 mg/kg/day. According to the recommendations of the guidelines, patients not achieving disease control within 1-3 weeks with 0.5 mg/kg prednisone, should be treated by increasing the prednisone dose up to 0.75 mg/kg/day or 1 mg/kg/day. Then, the EADV guidelines proposed that the initial dose will be tapered gradually with the aim to stop treatment or to maintain minimal therapy (0.1 mg/kg/day) within 6 months from initiation of treatment. However, investigators were free to decide the optimal time for stopping CS treatment even if EADV treatment guidelines recommended discontinuation in patients free of symptoms for at least 3 to 6 months under minimal therapy with oral prednisone (0.1 mg/kg/day).

After starting treatment, investigators were free to treat their patients as they think best. However, the addition of any treatment potentially effective on BP or increase of oral prednisone doses were considered as "failure of the therapeutic strategy ".

Preliminary Results

311 patients were screened and 111 excluded (1/3). 200 patients have been included. The main reasons for non-inclusion were: associated disorders, poor general condition (n=65), too extensive NP (n=15); localised BP (n=16).

Patients excluded had a lower Karnowsky Index (69 vs 59; P<0.01), were older (82 versus 80 years; p=0.07) than patients who were included. Most patients excluded were treated by topical CS.

Only 100 patients had completed a 12-month follow-up. A preliminary analysis on the first 100 patients included showed that the rate of disease control by day 21 was 58/69 (84%) in patients with moderate BP versus 15/31 (48%) in patients with extensive BP (p<0.01), and the rate of disease control at any time during the study was 62/69 (90%) in patients with moderate BP and 18/31 (58%) in patients with moderate BP.

These preliminary data suggest that the 0.5 mg/Kg/day dose of prednisone recommended in the EDF/EADV guidelines is not an adequate treatment for patients with extensive BP.

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