

TREATMENT OF PEMPHIGUS VULGARIS AND PEMPHIGUS FOLIACEUS: EXPERIENCE WITH 71 PATIENTS OVER A 20 YEAR PERIOD*

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SUMMARY

Forty one cases of pemphigus vulgaris and thirty cases of pemphigus foliaceus were investigated at Hospital Universitário Clementino Fraga Filho from 1978 to 1999. They were divided into two treatment groups: one group received up to 100 mg of oral prednisone daily and the other group received >120 mg daily. The dose up to 100 mg provided good initial control of pemphigus vulgaris and pemphigus foliaceus and did not increase the mortality rate associated to disease. The dose >120 mg induced higher morbidity. These data allowed us to establish a regimen of oral prednisone (1–2 mg/kg/daily) with maximum of 120 mg daily in the treatment of pemphigus vulgaris and pemphigus foliaceus.

KEYWORDS: Pemphigus vulgaris; Pemphigus foliaceus; Treatment.

INTRODUCTION

Systemic corticosteroids are the most useful drugs for the treatment of pemphigus⁶. Some patients have mild disease manifested by only a few indolent lesions that can be controlled simply with low doses of corticosteroids. Others have fulminating disease that cannot be controlled even with massive doses. Efforts are rarely made to correlate therapeutic results with extent or activity of disease even though the severe cases require larger doses of corticosteroids and have a higher mortality. The terms activity, extent and severity are poorly defined; as a consequence, the evaluation of therapeutic results in published studies must be limited to an analysis of two basic variables: mortality and remission. The methodology used to define and study adverse effects is so wide and poorly described in most studies that no attempt have been made to analyze it^{1,4,6}.

We present a retrospective study of the clinical course of pemphigus vulgaris and pemphigus foliaceus treated with prednisone.

MATERIAL AND METHODS

41 cases of pemphigus vulgaris and 30 cases of pemphigus foliaceus were investigated at Hospital Universitário Clementino Fraga Filho, Rio de Janeiro, from 1978 to 1999¹² with the following criteria:

1. histological confirmation; the direct immunofluorescence was performed only in case of doubtful diagnosis; the indirect immunofluorescence test is not routinely performed in the follow up of pemphigus cases⁴.

2. therapy initiated with oral prednisone: a) 2mg/kg/daily in the extensive pemphigus vulgaris that is with involvement of the mucous membranes and skin⁹ or rapidly progressive skin disease; b) 2mg/kg/daily in the extensive pemphigus foliaceus that is rapidly progressive skin disease; c) 1 mg/kg/daily in pemphigus vulgaris when oral lesions were the only clinical manifestations; d) 1 mg/kg/daily in not extensive and progressive skin disease of pemphigus foliaceus⁸; e) 1mg/kg/daily for both pemphigus in the presence of relative contraindications to corticosteroids: peptic ulcer, diabetes, cataracts, osteoporosis, hypertension, tuberculosis, obesity, glaucoma, old age.
3. both groups were kept on prednisone for 4–6 weeks to achieve a state in which no new lesions were appearing and old lesions were healing (control phase); then it was gradually tapered (10 mg every ten days interval) until 20 mg daily was reached. From this stage on, the following schedule was employed: 20 mg (6 months); 10 mg (6 months); 5 mg (6 months); 2.5 mg (6 months). The drug could be stopped when a state of no new lesions were observed in the last twelve months.
4. the 20 cases submitted to a combined treatment schedule with azathioprine (pemphigus vulgaris), dapsone (pemphigus vulgaris) or chloroquine (pemphigus foliaceus) were not included in the present study; these situations were the following:
 - Patients who were not controlled to initial therapy with prednisone until 10 weeks⁴;

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- Patients being treated with prednisone in whom complications developed with its use (psychosis, aseptic necrosis of femur, emotional lability, severe hypertension, uncontrolled diabetes)⁴;
 - Patients in whom repeated attempts to taper corticosteroids was associated with recurrence of disease⁴.
5. in a 5-year-follow-up, all cases of pemphigus (vulgaris and foliaceus) were assessed on clinical development of prednisone side effects: infections (impetigo, septicemia, kidney infection, candidiasis, *tinea*, herpes simplex, zoster, molluscum), hypertension, diabetes, psychosis, Cushing syndrome, cataracts, aseptic necrosis of femur and peptic ulcer. The mortality rates were evaluated in pemphigus vulgaris and foliaceus (each one) considering that this variable depends also on the disease itself.
6. Chi-square (Yates) or Fisher exact test were used whenever appropriate.

RESULTS

Twenty-eight females and 13 males aged 20 to 80 years had pemphigus vulgaris (Table 1). The initial dose did not influence the response to treatment ($p>0.05$) (Table 2) and mortality rate ($p>0.05$) (Table 3) in these cases.

Table 1
Distribution of cases according to age and sex

Age	PV sex		PF sex		Total
	Male	Female	Male	Female	
10 – 19	-	-	1	1	2
20 – 29	2	2	-	2	6
30 – 39	2	8	6	2	18
40 – 49	4	2	3	1	10
50 – 59	3	4	2	1	10
60 – 69	1	6	5	2	14
70 – 80	1	6	2	2	11
Total	13	28	19	11	71

HUCFF-UFRJ (1978-1999); PV – Pemphigus vulgaris; PF – Pemphigus foliaceus

Table 2
Distribution of cases (Pemphigus vulgaris), according to dosage of prednisone and response to treatment

Dose	Response		Total
	Yes	No	
80 – 100	9	3	12
> 120	21	8	29
Total	30	11	41

HUCFF-UFRJ (1978-1999); $p>0.05$

Nineteen males and eleven females aged 10 to 80 years had pemphigus foliaceus (Table 1). The initial dose did not influence the response to treatment ($p>0.05$) (Table 4) and mortality rate ($p>0.05$) (Table 5) in these cases. The side effects could be related to larger doses of prednisone ($p<0.05$) (Table 6) in both diseases.

DISCUSSION

In our retrospective study we grouped the patients according to the initial dose of prednisone as other investigators^{7,9}; the dose was determined by criteria of extension of skin disease (pemphigus vulgaris and pemphigus foliaceus) and mucous disease (pemphigus vulgaris). The dose higher than 120 mg daily was not more effective in the initial control of pemphigus vulgaris ($p>0.05$) [Table 2] and pemphigus foliaceus ($p>0.05$) [Table 4]. The dosage up to 100 mg daily provided good initial response in both pemphigus (control phase).

Table 3

Distribution of cases (pemphigus vulgaris) according to mortality

Dose	Mortality		Total
	Yes	No	
80 – 100	0	12	12
> 120	3 (10%)	26	29
Total	3	38	41

HUCFF-UFRJ (1978-1999); $p>0.05$

Table 4

Distribution of cases (Pemphigus foliaceus), according to dosage of prednisone and response to treatment

Dose	Response		Total
	Yes	No	
80 – 100	15	7	22
> 120	6	2	8
Total	21	9	30

HUCFF-UFRJ (1978-1999); $p>0.05$

Table 5

Distribution of cases (pemphigus foliaceus) according to mortality

Dose	Mortality		Total
	Yes	No	
80 – 100	2(9%)	20	22
> 120	1(12%)	7	8
Total	3	27	30

HUCFF-UFRJ (1978-1999); $p>0.05$

Table 6
Distribution of cases according to dosage of prednisone and side effects

Dose	Infections	Hypertension	Diabetes	Cushing syndrome	Psychosis	Cataracts	Aseptic necrosis of femur	Peptic ulcer	Total
80-100	16	5	6	2	-	-	1	1	31
> 120	48	7	4	3	2	2	-	-	66
Total	64	12	10	5	2	2	1	1	97

HUCFF-UFRJ (1978-1999); $p < 0.05$

There is no consensus regarding the initial dosage needed to induce remission in pemphigus vulgaris. Some consider that it should be 200 mg daily or even more^{6,7} because this is life – saving and contributes to long term remission. Other consider that a daily oral prednisone dose of 180 mg is an important cause of treatment related fatality². Many patients are treated with daily steroid doses of 40 – 80 mg^{8,12}. A lack of prospective studies and of well controlled trials contribute to the dilemma over the best initial dose and maintenance therapy^{1,3}.

For pemphigus foliaceus, the Brazilian authors state oral prednisone (1 – 1.5 mg/kg/daily)⁸ or oral triamcinolone (48 mg/daily)¹¹. It is quite impossible to compare our figures because several data are lacking in these papers^{10,11}.

In our sample the mortality rate could not be related to the initial maximum dose of prednisone required to induce control in the cases of pemphigus vulgaris ($p > 0.05$) (Table 3) and pemphigus foliaceus ($p > 0.05$) (Table 5).

The literature contains contradictory reports about the relationship between the initial-dose of prednisone and mortality as well as the effect of initial dosage on the subsequent course of pemphigus vulgaris and foliaceus. These discrepancies are, in part, due to differences in data presentation.

The mortality rates in our cases are in accordance with literature data both for pemphigus vulgaris¹¹ (10%) (Table 3) and pemphigus foliaceus^{5,10,11} (9% to 12%) (Table 5). Prior to the use of glucocorticoid therapy, significant mortality was associated with patients having pemphigus; most of the deaths used to occur during the first 2–3 months of therapy⁷. Today it is due to drug associated complications¹².

In our sample increased morbidity was associated with statistical significance to > 120 mg prednisone ($p < 0.05$) (Table 6). As the mentioned side effects are complications of therapy, we analyzed both pemphigus together. The infections, hypertension and diabetes were the most frequent complications and could be (one or more) present in the same patient. The two cases of psychosis² and one case of aseptic necrosis of femur were not switched to adjuvant therapy (azathioprine, chloroquine, dapsone) for contraindications (renal impairment, retinopathy and glucose 6 – phosphate dehydrogenase deficiency).

Several authors believe that doses over 120 mg or 180 mg greatly increase treatment related morbidity^{2,12}. It seems that it is not merely a

high daily dose but the duration for which it is given that is important^{2,6}.

Mortality, morbidity and the length of clinical remission remain for some authors¹² the best measures of the efficacy of a therapeutic regimen. We decided not to evaluate the length of clinical remission because the patient's compliance intervenes with relapse rates.

It is probable that immediate high dose treatment in every case of pemphigus does not seem absolutely essential anymore¹⁴. It seems to be possible to try a mild therapy in patients with only a few lesions and slow progression¹⁴.

CONCLUSIONS

Our retrospective study indicates that an initial dose up to 100 mg daily of prednisone during 4–6 weeks provides good initial control of pemphigus vulgaris and pemphigus foliaceus; this dosage, besides, does not increase mortality rate associated to disease. On the other hand, higher doses than 120 mg are related to increased morbidity. These results allowed us to establish a regimen of oral prednisone (1–2 mg/kg/daily) with maximum of 120 mg daily in the treatment of pemphigus vulgaris and pemphigus foliaceus.

RESUMO

Tratamento do pênfigo vulgar e pênfigo foliáceo: experiência com 71 pacientes no período de 20 anos

Quarenta e um casos de pênfigo vulgar e trinta casos de pênfigo foliáceo foram investigados no Hospital Universitário Clementino Fraga Filho, no período 1978–1999. Os pacientes foram divididos em dois grupos de tratamento: um recebendo até 100 mg/dia de prednisona e o outro grupo > 120 mg diariamente. Com o primeiro esquema, houve bom controle inicial dos pênfigos sem aumento da taxa de mortalidade associada às doenças. A dose acima de 120 mg induziu maior morbidade. Os resultados permitiram estabelecer um esquema de prednisona (1–2 mg/kg/dia) com dose máxima de 120 mg diários no tratamento dos pênfigos vulgar e foliáceo.

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