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Research Article

Alternate-Day Corticosteroid Therapy in Pemphigus Vulgaris and Bullous Pemphigoid

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Abstract

Background: There are numerous therapeutic options for the treatment of autoimmune bullous skin diseases, but systemic corticosteroid is still the gold standard. The treatment of these diseases is based on empirical knowledge, and the guidelines are not uniform. In many centers the patients are treated according to local tradition. We use corticosteroid therapy as baseline therapy at the start of the treatment and gradually decrease the dose on alternate days. We use azathioprine as a steroid sparing agent. In our experience, a symptom-free status can be reached in most cases.

Objectives: We set out to analyse the efficacy and the prevalence of side-effects caused in our patients by this long term daily alternating corticosteroid therapy.

Methods: The data on 148 patients (70 with pemphigus vulgaris, 78 with bullous pemphigoid) from 2004 to 2015 were processed.

Results: With intermittent reduction of the corticosteroid dose and maintenance dose administration on every second day, the symptom-free status was maintained, relatively few side-effects were observed and the quality of life of the patients improved.

Conclusion: We recommend prednisolone as first-line treatment and for maintenance therapy. The maintenance dose can be reduced to a very low level but the permanent cessation of steroid is not suggested in most cases. A lifelong low dose corticosteroid is usually required for these patients to prevent recurrence of the disease.

Keywords: Systemic treatment; Autoimmune bullous diseases; Intermittent corticosteroid therapy; Maintenance dose; Side-effects

Introduction

Autoimmune blistering skin diseases are uncommon disorders characterized by the presence of autoantibodies directed against desmosomal proteins (in the pemphigus group), or against adhesion molecules of the dermal-epidermal junction (in pemphigoid diseases) [1].

The most frequent autoimmune bullous diseases are Pemphigus Vulgaris (PV) and Bullous Pemphigoid (BP), the incidences of which differ in the various geographical regions [2-10]. Pemphigus is less frequent, the incidence in central Europe ranging from 0.6 to 6.8 new patients/million/year (3,7). The proportion of the population with pemphigus is higher in South-east Europe, Iran, in the RomanianJewish population, and in the Mediterranean region [8-10]. BP has a reported incidence of 13.4-42 new patients/million people/year [3-6] with 150-190 new patients/million/year in the population aged 80 years and above [5,10].

The most common form of pemphigus, PV; accounts for 70% of all pemphigus cases [1]. PV is often life-threatening, without treatment its mortality is nearly 100% [12]. In the 1950s, before the use of oral corticosteroids (CSs), the mortality rate was 75% [13] Antibodies are directed against antigens (desmoglein (Dsg) 1 and 3) in the desmosomes linking keratinocytes.

The most frequent subepidermal bullous disease is BP. The two major target antigens have been identified in the hemidesmosomal proteins of the basal membrane, BP180 and BP230. Autoantibodies against these proteins mainly belong in the IgG class. BP is a much milder disease than PV, and lower doses of CSs are suggested for its treatment.

In both diseases the therapeutic management comprises mainly immunosuppression with CSs or CS-sparing agents. Specific treatment options include the therapeutic blockage of autoantibody production, cytokines or signaling pathways. A wide range of medication is used in the treatment, such as azathioprine, methotrexate, cyclophosphamide, mycophenolate mofetil, cyclosporine or dapsone. Intravenous immunoglobulin (Ig), immunoadsorption, plasmapheresis and rituximab can also be used [14-26].

Despite the numerous therapeutic choices, the gold standard in the systemic treatment of PV and BP is CS. A number of treatment guidelines have been put forward, but in many centers the patients are treated according to the local tradition. We treat autoimmune bullous skin diseases with CSs in an alternating daily dosage, which differs from literature recommendations, and we report here a retrospective analysis of the efficacy and the side-effects of this therapy.

Materials and Methods

Between January 2004 and January 2015, 70 patients with PV (mean age at onset 54.37 years) and 78 with BP (mean age at onset 73.39 years) were treated at our clinic. There were more female patients than male patients, in accordance with the literature experience (Table 1) .

2004-2014	PV	BP
No. of Patients	70	78
Male	32	34
Female	38	44
Age on Onset	27-82 years	49-99 years
Mean age at Onset	54.37 years	73.39 years

Table 1: Age and Gender Charateristics of patients followed up during the last 10 years.

The diagnoses of the autoimmune bullous diseases were based on the clinical features and routine histological and immunohistological examinations (Direct Immunofluorescence (DIF), Indirect Immunofluorescence (IIF), and Salt Split Skin Technique (SSS) as described previously [27-30]. In PV, DIF demonstrates the binding of IgG and/or C3 to the Intercellular Cement Substance (ICS). IIF with the use of epidermal substrate (monkey or rabbit esophagus) identifies the presence of anti-ICS antibody with IgG and C3. The recombinant ectodomains of Dsg1 and Dsg3 have been utilized to develop highly sensitive and specific ELISA assays. The different types of pemphigus (such as PV, pemphigus foliaceus and paraneoplastic pemphigus) were also distinguished by the detection of circulating autoantibodies by Western blotting.

In BP, linear basement membrane zone deposits of IgG and C3 are seen in DIF. In IIF with SSS technique the circulating IgG antibodies bind to the epidermal side of the SSS (lamina lucida). We earlier used our "home-made" ELISA tests for the detection of circulating autoantibodies in order to achieve a more accurate diagnosis [28,29], hereas in the last 6 years we have applied commercially available ELISA tests to detect the main autoantibody entities (MESACUP BP180 and BP230 tests, Dsg1 and Dsg3 tests; MBL Medical and Biological Laboratories, Nagoya, Japan) [28]. In some patients the presence of BP230 and BP180 autoantibodies were also demonstrated by means of Western blotting, which helped to establish the diagnosis of BP.

Before the treatment of our patients was started, the blood glucose level, full blood count and differential, electrolytes, liver and kidney function tests and blood pressure were measured and urinalysis was performed. During the treatment osteoporosis was controlled with DEXA scan in every second year.

Results

During the last 10 years, we have not lost any patients in the consolidation phase of either PV or BP, and we have succeeded in stabilizing and achieving a symptom-free status in almost 100% of the cases. The alternated-day CS therapy that we applied differed from the treatment guidelines for autoimmune bullous skin diseases. (Table 2).

2004-2014	PV	BP
No. of Patients	70	78
Follow-up time	1.5-10 years	1.5-10 years
Mean Follow-up time (years)	6.93 years	3.45 years
Steroid Maintenance Dose	5-40mg/every second day	5-30mg/every second day
Mean Steroid Maintenance Dose	16.64 mg/ecery second day	15.67 mg/ecery second day

Table 2: Steriod Therapy in Patients.

Presents data on patients followed up for at least 1 year and in whom the CS dose given every second day reached a level which could be administered as long-term maintenance therapy.

During the follow-up period, 12 PV patients and 29 BP patients died. The cause of death was pulmonary embolism in 2 PV and 1 BP patients, different kinds of tumors (breast cancer and lung cancer) in 2 PV patients and 2 BP patients, and cardiac or respiratory failure in 3 PV patients and 6 BP patients. We could not find information as to the exact cause of death of 4 PV patients and 20

BP patients in the computer database at our department. The mean age at death in PV was 71.9 years, and in BP was 81.3 years.

The therapy of PV and BP

Our first choice of therapy was CS. The initial dose was selected with regard to the severity of the disease, the general status of the patient, and incidental co-morbidities (Diabetes Mellitus (DM), hypertension, anticoagulant treatment and cardiac diseases). In PV we administered a higher dose of CS, generally 100 mg (1.2 mg±0.2 mg/kg body weight/day), and in BP a lower dose, generally 50 mg (0.6±0.1 mg/kg body weight/day). The CS was always given in a single daily dose, in the morning. The CS was generally oral prednisolone, but methylprednisolone was administered intravenously to patients with severe oral erosions or who experienced intense pain on swallowing many tablets or who presented extensive clinical symptoms. In the course of the dose reduction methylprednisolone was changed for prednisolone as soon as possible; methylprednisolone treatment was given throughout the follow-up period in 4 PV and 4 BP patients.

When progression ceased and no new blisters appeared, the initial dose was begun to be gradually reduced. In PV this generally took 2 or 3 weeks, while in BP 1 or 2 weeks was needed to reach the symptom-free state. The initial CS dose was then decreased alternately, every second day. The treatment was supplemented with azathioprine at 100−150 mg daily in 18 PV patients (25.7%), especially who had oral mucosa involvement, due to its steroid-sparing feature. In 13 cases of BP (16.6%), where the clinical lesions were widespreador the status of the patients did not improve sufficiently, the therapy was similarly supplemented with azathioprine. Before the start of azathioprine therapy, measurement of thiopurine methyl transferase activity is suggested in order to examine the risk of drug-induced Bone Marrow Toxicity (BMT). Since there is no technical possibility to use this test in Hungary, we closely monitored the patients for BMT. The patients who received azathioprine treatment exhibited no other risk factors or other suspected clinical or laboratory signs of myelosuppression.

Besides the immunosuppresssant therapy, gastroprotective medication (generally an H2 receptor inhibitor) and potassium and calcium replacement were given with vitamin D3 to the prevent osteoporosis.

An example of the alternating steroid therapy decrease in a representative BP case is presented in (Table 3).

Treatment Time	Prednisolone Dosage
0 weeks	60mg everyday
2 weeks	60mg-30mg alternated
4 weeks	30mg-15mg alternated
6 weeks	30mg-10mg alternated
8 weeks	30mg-5mg alternated
10 weeks	30mg every second day
14 weeks	25mg every second day
26 weeks	20mg every second day
50 weeks	15mg every second day

Table 3: Reduction of prednisolone dosage in BP.

This demonstrates how the CS dosage was reduced in an alternating manner.

We start to reduce the dose on every other day by half. Then, in line with the patient's clinical symptoms, we continue the reduction of the corticosteroid dose, usually at weekly intervals, maintaining the situation that the higher dose is always alternated with a dose that is 50% lower. When the higher dose has reached 30 mg/day, we reduce the lower dose in 5 mg steps to zero. The rate of dose reduction and the final dose can depend on the patient's status; the severity and the extent of the disease slower in pemphigus, and faster in pemphigoid during a period of some months or even years, until the definitive maintenance dose is reached. Finally, the maintenance corticosteroid dose (in PV 25-30 mg CS and in BP generally 15-20 mg,) is administered only every second day. Thus the difference in the mode of reduction of the doses from the literature recommendations is that we reduce the corticosteroid dose by alternating between a lower and a higher corticosteroid dose, together with progressive dose reductions. The achieved maintenance dose may be reduced very cautiously during months or years, but its permanent omission is usually not possible. The interval required for the reduction was longer in PV than in BP, but the final dose was always defined by the actual status of the patient or the energence of new symptoms. In patients with DM, we strived to reduce the CS dose and the azathioprine therapy as fast as possible.

In our practice, CS treatment combined with azathioprine was generally sufficient.

Complications

The complications of long-term systemic CSs are well known: DM, iatrogenic Cushing's syndrome, infections, osteoporosis, hypertension, gastrointestinal ulcers, and a loss of calcium and potassium. The side-effects that occurred among our patients are listed in (Table 4).

Side-effects		PV (n=70)	BP (n=78)
Infection	Herpes Zoster	4	2
	Erysipelas	2	2
	Pneumonia	8	4
	and other inf.		
	Total	14	8

		20%	10.20%
DM	Worsening of existing DM	9	4
		12.80%	5.13%
Iatrogenic Cushing's sy.		5	1
		7.10%	1.30%
Osteoporosis		9	1
Blood Pressure spike		3	2
Steroid acne		2	0
Gastric complaint		1	0

Table 4: Side-effects of corticosteroid treatment.

Infection was detected in 16 patients with PV, and in 8 with BP. Herpes zoster, erysipelas and pneumonia infections were most frequent.

Previously existing DM worsened in 9 patients with PV, and in 3 with BP. New DM emerged in 3 patients in each group. 5 PV and 4 BP patients with long-standing DM needed correction of their antidiabetic therapy after the implementation of CS. In 3 DM PV patients transient and in 1 permanent insulin therapy was needed after the CS therapy. Iatrogenic Cushing's syndrome developed in 5 patients with PV and in 1 with BP.

Osteoporosis (proved by DEXA scan) developed in 9 PV patients. At the beginning of high-dose CS therapy, blood pressure spikes were observed in 3 patients with PV, and in 2 with BP. Only 1 patient suffered a serious gastrointestinal complaint during CS treatment (but no hemorrhagic ulcer).

During the treatment with azathioprine, the liver function levels increased in 5 PV and 3 BP patients, but in all 8 cases normalized after a decrease of the dose of azathioprine or after a transient or permanent cessation of azathioprine therapy.

Discussion

Since PV is an autoimmune disease, the most common mode of treatment is CS and other immunosuppressant agents. After CSs became available from the 1950s, the mortality of PV fell from 73% to 29% and then to 5.9% following the introductionof adjuvant therapy [31]. The cornerstone of therapy is still CS, as both initial and maintenance therapy. The management guidelines of PV published in 2015 by the European Dermatology Forum in cooperation with the European Academy of Dermatology and Venereology recommend CS therapy at a daily dose of 0.5-1.5 mg/kg daily dose for both PV and BP [32]. If the patient's clinical status does not improve within 2 weeks, a higher dose (up to 2 mg/kg/day) is suggested. Steroid pulse therapy is recommended in refractory cases. After 2-3 weeks of prednisolone therapy, the blisters are usually healing, and new lesions do not appear, and the CS dose may then be cautiously decreased. The latest guidelines suggest the tapering of prednisolone in bi-weekly 25% reduction steps. For adjuvant treatment, azathioprine, cyclophosphamide, mycophenolate mofetil, gold, methotrexate, cyclosporine and dapsone are available. The dose of azathioprine (most frequently used) is 1-3 mg/kg daily. In our 10-year study period there were 3 PV cases where CS administration could be stopped, but these patients are currently receiving azathioprine.

There have been no large randomized controlled clinical trials to determine the most effective treatment for PV. In severe or certain special cases, other forms of medication or therapy may be suggested, e.g intravenous Ig or plasmapheresis. Rituximab, an anti-CD20 monoclonal antibody, has recently proven to be highly effective in severe and refractory patients [33].

The best-established initial therapy for BP is systemic CS. In localized or mild BP, topical CSs alone may be successful. The BP management guidelines, published in 2012 by the British Association of Dermatologists, suggest 0.3, 0.5 and 0.75-1 mg/kg prednisolone daily for the mild or localized, the moderate, and the severe cases respectively [34].

In the treatment of PV and BP, we use similar doses during the initial therapy as suggested in the latest guidelines, but during the reduction of the prednisolone dosage we prefer to reduce the CS dose on alternate days rather than daily, and for maintenance therapy the patients receive CS only every other day. In the last 10 years we have treated and followed up 70 patients with PV and 78 patients with BP by using this CS regimen, combined with azathioprine (100 to 150 mg /day) if needed, and a symptom-free status could be attained in most cases. We usually set the initial dose somewhat high, the reason being that when the initial CS dose was not effective in preventing new symptoms within a few days, it was more difficult to reach a symptom-free state and higher doses of CS with additional immunosuppressant therapy were needed. We had only 2 cases where intravenous Ig was required. We had no need for other therapies.

Table 4 reveals that the alternate-day CS therapy that we used was accompanied by more side-effects in PV than in BP. This can be explained by the higher dose and the slower CS reduction in PV. The most frequent side-effects were infections, found in 16 PV patients (20.1%) and 8 BP patients (9%). In a literature cohort of more than 1200 PV patients, infections were also the most frequent complications, in 19% of the cases [35]. The infection rate seems similar for the alternate and the daily usage of CS.

Osteoporosis was demonstrated by the DEXA scan in 13% of the PV patients, but its close association with the CS treatment could notbe proved in every case as it can otherwise occur in el-

derly patients.

CS-induced DM is also well known to develop during long-term daily CS therapy via the development of insulin resistance. The use of CS increases the risk of new DM 2−4- fold [36]. A Brazilian study found that the incidence of DM and glucose intolerance among PV patients treated daily with CS was 22.5% among females and 26.67% among males [37]. With alternating CS treatment we observed a lower incidence: 13 cases with DM-related side-effects, i.e 15.5% of the PV patients.

Iatrogenic Cushing's syndrome occurred in 7.1% of the PV and 1.3% of the BP cases. Hydrocortisone at a dosage of 20 mg/day was earlier reported to decrease the function of the hypothalamic-pituitary system. Prednisolone at 5 mg/day can promote the formation of Cushing's syndrome. However, if CS is given every second day, this side-effect occurs only if the dose of prednisolone reaches 40 mg [38,39].

In a view of these results and our own experience, the relatively rare occurrence of Cushing's syndrome can be explained by the use of prednisolone instead of methylprednisolone and alternate-day steroid therapy.

Although we have reported here only our experience with alternating CS therapy during the last 10 years, we have been using this therapeutic approach for 40 years. During this period we have gained considerable experience with the treatment and the follow-up of patients with autoimmune bullous diseases: 463 patients with BP and 282 with PV have been diagnosed and treated at our clinic since the 1970s. Some of our early patients gave up the maintenance CS treatment arbitrarily, because they felt fully recovered. Moreover, the therapy was sometimes also stopped at the suggestion of the general practitioner because of the development of other medical problems. In these cases, the disease generally recurred within several months, or at most 1 or 2 years. Hence, as the recurring disease is less responsive to treatment, we consider that a very low sustaining dose of CS is necessary virtually lifelong for most patients. Most of our patients have in fact continued with the maintenanance therapy. We do not have exact data as to how many patients stopped the CS therapy arbitrarily during the treatment, but we are aware of 2 PV and 3 BP patients who have been without therapy for 1.5 and 3 years and in whom the disease has not recurred yet. This draws attention to the recommendation of the latest guidelines advising that, without clinical symptoms, discontinuation of the treatment should be considered if the Dsg ELISA results and/or IIF findings are negative.

In the 1970's and 80's some reports were published about the beneficial effect of alternate-day CS therapy, but its use in the daily routine has not spread. Fauci et al found that prednisone given in a single dose on alternate days in the morning did not interfere with the normal ACTH-cortisol cycle, nor would it expose the tissue to sustained levels of hormone throughout the day, which would-have been the situation if the CS was given daily [40]. Gallant reported normal neutrophilic accumulation in patients receiving alternate-day therapy but decreased numbers of it in patients getting daily-dosage regimen. Monocyte accumulation was normal on the alternate day and a little bit reduced on the prednisolone day. This accumulation in patients receiving daily prednisone was persistently suppressed [41].

Only a few reports are available concerning the benefits of alternating versus daily CS treatment in autoimmune diseases. Uchino et al. reported the same efficacy of alternating and daily-dose prednisolone therapy in patients with myositis, the incidence of side-effects proving lower in the former. The incidence of diabetes was found to be significantly higher in the daily therapy group. They additionally found a difference in the 20-year survival rate, which was significantly higher (68%) in the alternating group than in the daily group (37%) [42]. In a retrospective cohort study carried out in Germany on 369 patients diagnosed with BP and given CSs daily, 209 patients (57%) died during the 10-year follow-up (from 1987 until 1997) [43]. The 10-year survival rate in the BP group among our patients was 37% [29 -78]. Although the German and Hungarian patient groups are not directly comparable, it is possible that our better survival rate may be related to the alternating CS dosage that we used.

Alternating CS therapy is used in other autoimmune diseases (lupus nephritis, myeloma multiplex, Crohn's disease, myasthenia gravis, IgA nephropathy and membranoproliferative glomerulonephritis). Berenson et al. observed that alternate-day CS (50 mg/every second day) as maintenance therapy improved the survival of myeloma multiplex patients [44]. A retrospective analysis of Crohn's disease patients concluded that alternate-day prednisone may even reduce the symptomatic flares [45]. Greek experts successfully used the combination of azathioprine and the alternate-day 40 mg prednisone in patients with oral involvement of PV to achieve effective control of the illness. [46].

Our results and the literature references lead us to recommend alternate-day CS treatment in the therapy of autoimmune bullous skin diseases.

Conclusions

Our 10-year statistical data and our experience of more than 40 years with the treatment of autoimmune bullous disease patients indicate that alternated-day CS treatment is adequately effective without causing side-effects. In both PV and BP it is probable better to "overshoot" than down-dose the CS at the beginning, but bearing in mind that the subsequently given increased dose is not always effective, especially in PV.

Alternating CS therapy causes relatively few side-effects,

the patients can reach and maintain a symptom-free condition, and the maintenance CS dose can be decreasedto a very low level.

We have experienced that a very low dose of CS dose should generally be prescribed almost lifelong for these patients. A very low dose of CS given virtually lifelong may result in fewer side-effects than when an elevated re-dosage is required because of recrudescence of the disease after the total cessation of CS. Very rarely, we have encountered patients with autoimmune bullous diseases in long-term equilibrium without CS therapy. In certain cases, following the ELISA measurement of anti Dsg1 and/or Dsg3 IgG and with negative direct IF results, the CS therapy might possibly be discontinued. Further investigations are called for to clarify this question.

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