Management of pemphigus
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Chapter II

Therapy of pemphigus

Abstract

Systemic glucocorticoids are still the cornerstone in treatment of pemphigus, but constitute a considerable health risk when used long-term. New treatment strategies focus first on averting the use of systemic glucocorticoids by using topical glucocorticoids, nicotinamide and tetracyclins as initial treatment in milder cases. The second focus is on reducing the daily glucocorticoid dose by using steroid-sparing adjuvans, such as azathioprine, mycophenolate mofetil, glucocorticoids pulse therapy, methotrexate, and intravenous immunoglobulins. The aim is to lower the morbidity caused by the treatment of this autoimmune disease, which often follows a chronic course.
**Introduction**

Pemphigus is a severe chronic autoimmune blistering disease of skin and mucous membranes which was lethal until 1950s when glucocorticoids became available. Glucocorticoids are the cornerstone of treatment. However, the disease is still difficult to treat, and the long-term use of steroids leads to severe side-effects. Pemphigus is a rare disease with an annual incidence of approximately 0.1-0.42 per 100,000 (1-3). A peak incidence occurs in patients between the fourth and sixth decade. About 0.8% of all dermatological patients suffer from pemphigus (4). Pemphigus vulgaris (PV) is the most common subtype and comprises about 80% of patients with pemphigus (5). In about 50-70% (4;6) of the PV cases the disease begins with oral lesions, which may precede the cutaneous lesions by several months or be the major, if not only (4), manifestation in some patients. The mucous membranes are ultimately involved in most cases of PV.

In about 20% of the pemphigus patients, the subtype is pemphigus foliaceus (PF). In PF only skin is affected (7), and its course is less severe than in PV. PF patients are often treated with milder treatment modalities, although this subtype appears to be very chronic and sometimes refractory to therapy.

‘How to treat pemphigus?’, has always been a difficult question, since the disease may break through milder treatment modalities, whereas robust immunosuppressive modalities require careful monitoring of the patient. Choice of treatment, i.e. first and second line immunomodulators, depends on disease phase. For instance, in mild orally affected patients, glucocorticoid- or tetracycline mouthwashes can be started as first line therapy. Whereas the severe affected patient needs to be treated with robust immunosuppressive modalities. Bystryn and Steinman reported in reviews of pemphigus therapy that the available literature has to be interpreted carefully for several methodological flaws in the research approaches, which are inseparable linked to the low incidence of this bullous autoimmune disease (8;9).

ELISA is a new diagnostic tool that measures circulating autoantibodies against desmoglein 1 and 3. A positive correlation between ELISA values and IIF titers was found in 11 PV patients by Lenz et al. (10). Aoyama et al. suggested to use the ELISA titer for desmoglein 1 for determining the initial therapy for PF (11). PF patients with low
ELISA titre were treated with topical steroids, whereas those with high titres with high-dose glucocorticoid pulse therapy.

**Topical glucocorticoids**

Topical application of potent steroids can be considered in mild cases of pemphigus. Topical steroid therapy alone was considered to be insufficient for sustained disease control, since pemphigus is a systemic autoimmune disease, and as long as there are adequate amounts of circulating autoantibodies binding to the skin, lesions will continue to develop. Recent uncontrolled studies however report successful treatment of mild cases with bullous pemphigoid (12), and pemphigus (13). Clobetasol propionate 0.05% cream was applied twice daily on pemphigus lesions for 15 days. Skin lesions seemed to be controlled in all patients within this period. For mucosal lesions, in pemphigus vulgaris, it took at least one month. However, a trend to relapse, mostly in previous affected areas, was observed during tapering of the topical treatment. In our experience intralesional triamcinolon may be used successfully in cases with solitary erosions in the mouth or with localised pemphigus.

**Systemic glucocorticoids**

As mentioned before, systemic glucocorticoids are a major breakthrough in the treatment of pemphigus (9;14). Glucocorticoids transformed pemphigus from an almost invariably fatal disease into one whose mortality is now between 5 to 10% (9;15;16). At present, most patients who die of pemphigus do so through complications of therapy, especially when long-term daily glucocorticoids at high-dose are needed to sustain disease-control. Minimising the incidence and severity of glucocorticoid-related side effects requires carefully decreasing the dose; using disease-modifying immunosuppressive and anti-inflammatory agents as adjuvans; and taking general preventive measures (8;9).

At the molecular level, glucocorticoids form complexes with their specific glucocorticoid-receptors that migrate to the nucleus where they interact with selective regulatory sites on the DNA; this results in direct positive and negative modulation of several genes critical in inflammatory and immune responses (17). A second molecular
mechanism of glucocorticoids was recently shown to induce the synthesis of IκB, thus antagonising NF-κB translocation to the nucleus and gene transcription (18;19). A prompt inhibition of the inflammatory response is effected, but also other cells like fibroblasts and keratinocytes are inhibited.

A recent study showed that in approximately 75% of the patients after 10 years systemic therapy can be safely discontinued without a flare in disease activity (20). Morbidity in pemphigus is mostly iatrogenic, especially when long-term high-dose steroids are needed to sustain disease control (9;21-23). Most relevant adverse effects of glucocorticoids are diabetes mellitus, hypertension, infection (cave masking of diverticulosis), ulcus pepticum (bleeding, perforation, cave masking), increased clotting tendency, osteoporosis, acne, and delayed wound healing (21).

Prednisolone is the preferable glucocorticoid for oral administration, since it is the active hydroxylated metabolite of prednisone after liver passage. We use the ester form of prednisolone, since the salt-formulation of prednisolone, prednisolone-metasulfbenzoate, is even less absorbed than the prodrug prednisone (24;25). If the prednisolone-ester is not available like in France, prednisone is advised (24). There is no consensus regarding the initial steroid dosage needed to induce remission and the effect of this on the subsequent course of the disease. The controlled trial of Ratnam et al. (26) demonstrated that moderate dose of prednisone, 60 mg/day was effective in controlling pemphigus.

In our experience low doses (below 60 mg / day) usually do not suffice to induce initial control, especially when skin is affected. We use 80 mg/day as starting dose in a clinical setting. If no initial control after one week, daily dose is increased according to the Lever regimen (27). This means that in case of a severe pemphigus daily dosage of 240 mg can be reached in two weeks to prevent new blister formation (table I). After initial control prednisolone is tapered weekly until 40 mg/day is reached. Subsequently the dose is tapered in 4 months until zero. In case of new blister formation, i.e. positive disease activity, go two steps back in the tapering schedule (table II), and keep for two weeks. It is also possible to taper from 10 mg on in 1-mg steps (use 1-mg prednisolone tablets). Most pemphigus patients do need maintenance schedule prednisolone varying
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from about 5-15 mg/day. Alternating daily doses for administration of steroids are well-known to cause less side-effects on the hypothalamic-pituitary-adrenal axis function (68). However on non-steroid days the patients may complain of a sensation of erythema, or itch. Standard we prescribe a H$_2$-blocker, ranitidine 150 mg, to prevent steroid-induced dyspepsia.

Table I: Oral prednisone schedule for initial control

<table>
<thead>
<tr>
<th>Week</th>
<th>Prednisolone (mg/day) schedule</th>
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<tr>
<td>1</td>
<td>80 80 80</td>
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<tr>
<td>2</td>
<td>60 120 120</td>
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<td>3</td>
<td>40 60 240</td>
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<td>4</td>
<td>40 120</td>
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<tr>
<td>5</td>
<td>60</td>
</tr>
<tr>
<td>6</td>
<td>40</td>
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Table II: Oral prednisone schedule for tapering of maintenance dose after tapering schedule table I

<table>
<thead>
<tr>
<th>Step</th>
<th>Period (number of weeks)</th>
<th>Daily schedule Prednisolone (mg/day)</th>
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<tbody>
<tr>
<td>7</td>
<td>2</td>
<td>30</td>
</tr>
<tr>
<td>8</td>
<td>2</td>
<td>20</td>
</tr>
<tr>
<td>9</td>
<td>2</td>
<td>15</td>
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<tr>
<td>10</td>
<td>2</td>
<td>12.5</td>
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<td>11</td>
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<td>13</td>
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<tr>
<td>14</td>
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<td>2.5</td>
</tr>
<tr>
<td>15</td>
<td>-</td>
<td>0</td>
</tr>
</tbody>
</table>

In case of gastric complaints we increase the ranitidine to 150 mg bd. or prescribe a protonpump-inhibitor, such as omeprazol 20 mg dd.. To prevent secondary osteoporosis and (spine) fractures calcium 1000 mg dd. is advised as co-medication. Daily prednisolone dosage of 7.5 mg or more is an indication for bone densitometry. In case of low bone density ($T$- or $Z$-score $\leq -1$), or in postmenopausal females bifosphonate is added (400 mg etidroinacid or 10 mg alendroinacid during 14 days every 3 months).
(28). Alternatively, you may recommend drinking 6 glasses milk per day and ad vitamin D, 400-800 IE colecalciferol per day, to the medication list. Further precautions are monitoring of blood pressure, and blood sugar. For patients having symptoms suggestive for nasal/pharyngeal involvement or ophtalmological side-effects, specialists are consulted. An adequate medical history should always detect suppurative infections in the immunosuppressed patient.

**High-dose glucocorticoid pulse therapy**

Pulse therapy, the ‘big shot’ (29), refers to discontinuous intravenous infusion of very high doses glucocorticoids over a short time. Pulse therapy is used as adjuvant in combination with maintenance schedule prednisolone and azathioprine, since reviewing the published cases no increased efficacy has been found with pulse glucocorticoid therapy alone (29). However in our experience, monthly glucocorticoid pulses are effective as monotherapy in patients with mild oral lesions in the early stage of pemphigus vulgaris. Noteworthy, in our experience pulse therapy alone does not induce Cushingoid side-effects, whereas even daily low-doses of prednisolone induce the Cushingoid habitus within 8 weeks. Contra-indications for pulse therapy are chronic or recurrent infections (diverticulitis, herpes simplex oculi), tuberculosis, cardial dysrhythmias (atrial fibrillation is no contra-indication), low serum potassium, morbus Cushing, and pregnancy. Be aware of psychosis or lability in patients with psychiatric medical history.

Doses of each pulse are not standardised, but are usually 500-1000 mg methylprednisolone or 100-200 mg dexamethasone. We have chosen dexamethasone, a fluoridated glucocorticoid, for pulse therapy. Dexamethasone is per mg about 6.7 stronger than prednisolone on the hypothalamic axis, the mineralocorticoid effect is neglectible, and is has a very low equipotent volume (21). In the literature a variation in choice of steroid, dosage of pulse and cycle repeat are mentioned. The aim of pulse therapy is getting quicker and stronger efficacy of glucocorticoid therapy and decreasing the need for long-term use of steroids. The paradox is that pulsed administration of high dose steroids is used to achieve the steroid-sparing effect.
The largest experience with pulse therapy has been reported in patients with pemphigus (30). Pasricha et al. described both a steroid-sparing effects and long-term remission up to 9 years (31). More than 300 pulses have been administered in our department. Side-effects are limited to facial flushing, and sleeping disturbances in the first night after administration.

The intravenous rather than the oral route is often chosen for administration of high-dose pulsed glucocorticoids, despite the lack of evidence to support the presumed necessity of intravenous administration. It is still unknown whether the effects of pulse therapy are due to the peak concentration or the time-dose effect of the high-dose steroid. We now pulse with 300 mg dexamethasone per os in stead of 1000 mg methylprednisolone or 200 mg dexamethasone intravenously. The first results, although not placebo-controlled, are promising, and will be published separately.

**Azathioprine**

Azathioprine is a purine-antagonist, used as first choice adjuvant immunosuppressive agent in treating pemphigus (33). The metabolism of azathioprine and 6-mercaptopurin have been more clearly defined and a mechanism for acute toxicity is identified (34). The purine antagonist azathioprine, is rapidly absorbed and methylated in the intestine to 6-mercaptopurine (6-MP), which is then metabolized in the liver and erythrocytes via three competitive pathways. The hypoxanthine phosphoribosyl transferase pathway produces several metabolites including 6-thioguanine nucleotides (6-TGNs), which are responsible for suppression of *de novo* purine synthesis and cytotoxicity. The thiopurine methyltransferase (TPMT) activity and xanthine oxidase pathways produce inactive metabolites which are excreted in the urine. TPMT shows wide interindividual variation, but xanthine oxidase does not. The TPMT pathway thus determines the drug clearance.

The drug has well-documented toxic effects on hematopoietic cells that may be acute or chronic, including: macrocytosis, anemia, trombocytopenia, leukopenia, pancytopenia, and acute bone marrow failure.

About 1 of 300 patients are homozygous for the inactive TPMT allele (35). Azathioprine should not be prescribed to such patients that will otherwise develop acute myelosuppression. TPMT as measured in erythrocytes also discloses patients with an
high TPMT activity. On standard dosage of 100-150 mg azathioprine per day, patients with a high azathioprine metabolism would be not optimal treated, and should receive more azathioprine.

We recommend to start azathioprine with a test dose of 50 mg for 3 days so that the drug can be withdrawn at early stage if gastro-intestinal complaints occur. The adequate therapeutic dosage is 1.5 or 3 mg/kg per day dependant on the TPMT-enzyme activity level of less or more than 15 U/ml. Azathioprine is continued for a period varying between 3-12 months after prednisolone is tapered to zero. Tapering azathioprine is not necessary. Daily dosage azathioprine should be halved in case of leukopenia of less than $4 \times 10^9$ /L or of if the liver enzymes increase. Azathioprine is stopped when leukopenia less than $2 \times 10^9$ /L, or when trombocytopenia is less than $100 \times 10^9$ /L.

The study of Guillaume and co-workers (36), in which 100 and 150 mg azathioprine was administered in bullous pemphigoid patients did not claim a steroid-sparing effect. TPMT was not monitored and the dose of 150 mg might have been inadequate in a number of patients. The controlled trial of Burton in 1979 (37) cumulates prednisone dosage for three years follow-up in 25 in BP patients on tapering schedule prednisone with either azathioprine (2.5 mg/kg/day), or prednisone alone. Prednisone was however “dosed on command” by the physician. Total dose of glucocorticoids was however significantly lower in the group also given azathioprine, and therefore suggests a steroid-sparing effect. Well designed placebo-controlled studies evaluating the steroid-sparing effect of azathioprine in autoimmune bullous dermatosis are lacking. Nevertheless, there is a communis opinio that azathioprine is first choice adjuvant because the low range of side-effects, compared to other immunosuppressive agents, which may have a strong efficacy but major side-effects.

**Mycophenolate mofetyl**

Mycophenolate mofetyl is a new immunosuppressive agent and like azathioprine, a purin-antagonist. Mycophenolate mofetyl is the semisynthetic ester of mycophenolic acid. Mycophenolic acid, the active metabolite, interferes with de novo synthesis of purine by inhibiting type II inosine monophosphate dehydrogenase, an enzyme expressed in proliferating of T- and B-lymphocytes.
Since mycophenolate mofetyl is less hepatotoxic than azathioprine, it might be preferable in patients with liver function abnormalities. The daily dose of 2000 mg mycophenolate mofetyl is about five times more expensive than that of 200 mg azathioprine. Enk and Knop (38;39) treated 11 of 12 PV patients successfully after first relapse on tapering schedule oral glucocorticoids with azathioprine. These patients did not relapse for a median period of 12 months. Introduction of mycophenolate mofetyl was unfortunately coinced with an increase of maintenance dose prednisolone up to 2 mg/kg, so these spectacular effects are difficult to interpret (40). In another small open study, 4 pemphigus vulgaris, and 1 pemphigus foliaceus were successfully treated with adjuvant mycophenolate mofetyl (41). In 4 patients mycophenolate mofetyl was introduced after initial treatment with azathioprine (up to 250 mg/day). Also use of mycophenolate mofetyl was demonstrated to be successfully as monotherapy in a patient with recalcitrant PV (42). Complete remission was achieved in six weeks with 2 grams per day mycophenolate mofetyl. Since long-term (side-) effects of mycophenolate mofetyl are unknown the value of this promising immunosuppressive has to be demonstrated.

Cyclophosphamide

Cyclophosphamide is an alkylating agent that disrupt cell growth and mitotic activity by cross-linking DNA. It is appears to be highly effective in maintaining remission in pemphigus. Pasricha used cyclophosphamide 500 mg i.v. (only on the first day) in conjunction with high-dose glucocorticoid pulse therapy. Besides daily 50 mg oral cyclophosphamide was administered (43). The main concern of cyclophosphamide in non-oncologic doses are hemorrhagic cystitis in particular after daily administration and increased risk of malignancy after prolonged use. Therefore pulsed cyclophosphamide was introduced for improving efficacy in combination with low-rate of side-effects. Fleischli et al. used intravenous cyclophosphamide pulses of 500 mg in nine patients, of which four responded partially and two achieved remission of skin lesions (44). However, most patients experienced severe side-effects. All patients were also on daily dosage cyclophosphamide 50 mg per day and prednisolone.
Chapter II

Methotrexate

Methotrexate as adjuvant therapy was initially recommended in treatment of pemphigus (27), however concerns about severe toxic effects after often required high-dosage (up to 150 mg / week) has lead to preferences for other treatment modalities (8;9). A recent study showed remission induction in six of nine chronic vulgaris patients (45), in which prednisone could not be tapered without flare-up. Disease flared-up after about 3 weeks when administration of methotrexate was discontinued. In a contrary review study, MTX was found not the reduced mortality or change the rate of remission (46).

Gold

In cases with mild or moderate pemphigus, gold compounds, sometimes used as monotherapy, can be effective. The mechanisms of action remains unexplained. Because a delayed onset of action, patients often require oral glucocorticoids for initial disease control. Usually therapy is started with 50 mg aurothioglucoce i.m. once a week (after try-out dose of 10 mg). Frequence of administration is decreased to monthly injections after cumulative dose of one gram aurothioglucose. Monitor for proteinuria (nephritis) and eosinophilia.

Pandya et al. (47) reviewed 22 patients treated with gold and prednisone, and 4 with gold alone over a period of 10 years. The average duration of gold therapy was 12 months. Twenty patients achieved remission, lasting for an average of 8 months.

Tetracyclins and nicotinamide

In case of mild disease, first a combination of nicotinamide (1500 mg/day) and tetracyclins (2 gr/day) can be tested for a period of four weeks. Primary advantage nicotinamide and tetracyclins offer over corticosteroids (and other immunosuppressives agents) is a broader safety profile. The most common side-effect is gastrointestinal upset.

Tetracyclins have an inhibitoir effect on chemotaxis of neutrophilic and eosinophilic granulocytes. Besides tetracyclins possible improve the strength of the dermo-epidermal layer. Long-term use (>1 year) causes little chance for drug-induced LE (especially in woman), autoimmune hepatitis, and hypersensitivity syndrome or DRESS (“drug rash
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with eosinophilia and systemic symptoms) (48). Minocycline more than tetracyclines seems at risk for DRESS, which might have a delayed onset (49).

Nicotinamide (niacinamide, vitamin B3) has a stabilizing effect on leukocytes and mast cells, probably by increasing adenosine 3,5 cyclic-phosphate. Advised dose is 1500 mg/day. Since the maximal dosage in one capsule goes up to 50 mg, the capsules have to be hand made by the pharmacist.

A recent study showed that only a combination of nicotinamide and tetracyclins used as only oral agent in combination with topical steroids could control two of six cases of pemphigus vulgaris (50). In the other PV patients the combination appeared to be steroid sparing. The benefits has been demonstrated for tetracyclins used as only adjuvans only in the controlled trial of Calebotta et al (51), besides low toxicity and good safety profile were demonstrated. In case of mild oral affected patients we favor mouth washes tetracycline suspension 5% FNA (taste corrected) four times a day (52).

Human intravenous immunoglobulins (HIVIG)

Encouraging results have been reported with the use of adjuvant high dose intravenous immunoglobulins (IVIG) for treatment of patients with recalcitrant autoimmune bullous disease (53-57). Therapy consists of 400 mg/kg/day IVIG in courses of 3 to 5 consecutive days per month used as adjuvant therapy in combination with maintenance schedule prednisolone and azathioprine. In pemphigus, both therapeutic successes and failures have been reported (53). Human normal immunoglobulins are expensive: 30 grams used for a single intravenous infusion costs about $1000. Two recent case reports, confirm that low dose IVIG (40 mg/kg/day) appeared to be effective in a patient with epidermolysis bullosa aquisita (58), and a patient with recalcitrant pemphigus foliaceus (59), thereby reducing the costs of this expensive treatment considerably. The amount of intravascular IgG approximates 60 g. Infusion of 3 g instead of 30 g immunoglobulins, given a standard patient with a body weight of 75 kg, seemed to be sufficient modulating the humoral immune system in our patient. The improved cost-effectiveness of low dose IVIG therapy may push this modality forward as preferable adjuvant in pemphigus (53). However, the effect of HIVIG is transient and it is recommended for rapid action in severe cases (56).
Cyclosporine

Cyclosporine plays a minor role in the treatment of pemphigus. Both beneficial effects and therapy failures have been reported in the literature (60). Even cyclosporine mouthwash (5 ml, 500 mg cyclosporine, t.d.s. for 15 mins) was shown to have beneficial effect in orally affected patients in an anecdotal report (61). The recent randomized controlled trial of Ioannides et al. (62) (33 pemphigus patients) showed no advantage of cyclosporine, 5 mg/kg/day, in addition to daily dose prednisolone equivalent 1 mg/day. Complications were even more common in the cyclosporine group.

Plasmapheresis, immunoapheresis and photopheresis

Plasmapheresis, or plasma exchange, has been experienced-based used successfully in the treatment of pemphigus. Blood plasma is exchanged for isotonic albumen solution. It is generally recommended to combine plasmapheresis with an immunosuppressive agent to prevent rebound production of IgG. This time-consuming treatment has to be repeated in short time intervals.

The controlled clinical trial of Guillaume et al., in which 19 bullous-pemphigoid patients were treated by prednisolone and ten plasma exchanges over four weeks compared to 15 patients treated only by prednisolone, suggest that plasma exchange had no additional beneficial effect above low dose steroid use (63).

Immunoapheresis is a new more specific therapeutic option, in which only the pathogenic IgG is depleted in the patients plasma. IgG autoantibodies are adsorbed on anti-human IgG affinity agarose column. It was successfully used in a patient with paraneoplastic pemphigus (64). Resynthesis of IgG autoantibodies was inhibited by postapheresis intravenous immunoglobulins (IVIG), therefore the additional effect of immunoapheresis is difficult to observe since IVIG also has an immunomodulatory potency. Immunoapheresis is even more expensive than plasmapheresis.

Photopheresis is ex-vivo radiation of leukocytes with UVA-light in conjunction with a psoralen. Among leukocytes, B-cell clones that produce IgG autoantibodies are inhibited. It has successfully been performed in a patient with recalcitrant pemphigus (65,66).
Evidence-based medicine analysis of treatment efficacy

The Cochrane Controlled Trials Register and PubMed database were used to collect drug treatment studies in pemphigus. Key words used were “pemphigus” and “trial”. There were only 4 randomized clinical trials (RCT) with a Sacket level of evidence of at least II (Table III) (66). No systematic reviews were available. It is extremely difficult to compare the results, since different criteria were used for therapeutic definitions. Meta-analysis was therefore impossible.
### Table III: Randomized clinical trials for pemphigus.

<table>
<thead>
<tr>
<th>Study</th>
<th>Indication</th>
<th>Drugs studied</th>
<th>Experimental group (n)</th>
<th>Control group (n)</th>
<th>Endpoint</th>
<th>Outcome +/-/=</th>
<th>Level of evidence</th>
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<tr>
<td>• Guillaume, et al. 1988 [36].</td>
<td>PV+PF</td>
<td>pred.* vs. pred. and plasma exchange</td>
<td>19</td>
<td>15</td>
<td>4 weeks</td>
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<td>Controlled study of plasma exchange in pemphigus</td>
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<td>• Ratnam, et al. 1990 [26].</td>
<td>PV+PF</td>
<td>pred. 120 mg vs. 60 mg per day</td>
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<td>11</td>
<td>5 years</td>
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<td>Pemphigus therapy with oral prednisolone regimen. A 5-year study</td>
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<td>• Chrysomallis, et al. 1994 [6].</td>
<td>oral PV</td>
<td>pred. vs. pred and cyclophosphamide vs. pred and cyclosporine</td>
<td>10</td>
<td>10</td>
<td>5 years</td>
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<td>Treatment of oral pemphigus vulgaris</td>
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<td>• Ioannides, et al. 2000 [61].</td>
<td>PV+PF</td>
<td>pred. and cyclosporine vs. pred.</td>
<td>17</td>
<td>16</td>
<td>12</td>
<td>=</td>
<td>II</td>
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<td>Ineffectiveness of cyclosporine as an adjuvant to corticosteroids in the treatment of pemphigus</td>
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*Legend:* *pred.* = prednisolone or prednisone, *PV* = pemphigus vulgaris, *PF* = pemphigus foliaceus
References

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