Acta Derm Venereol (Stockh) 1995; 75: 150–152

The Steroid-sparing Effect of Long-term Plasmapheresis in Pemphigus

K. SØNDERGAARD[1], J. CARSTENS[1], J. JØRGENSEN[2] and H. ZACHARIAE[1]

Departments of [1]Dermatology and [2]Clinical Immunology, Aarhus University Hospital, Aarhus, Denmark

Glucocorticoids and immunosuppressive agents can induce remission in most patients with pemphigus, but mortality remains at 5 to 15% due to complications from these drugs. We reviewed the adjunctive effect of long-term plasmapheresis in 8 patients with pemphigus. Four cases had been resistant to conventional therapy. One or two large-volume plasmapheresis treatments were given monthly for 5 to 73 months. All patients were in clinical remission within 2 months after the addition of plasmapheresis. Relapses of pemphigus seldom occurred, and the patients stayed in remission 90% (40–100%) (median and ranges) of the plasmapheresis period. In all cases the daily dose of glucocorticoid was reduced. The prednisone level could be decreased significantly from 38 (15–80) mg/day to 10 (5–35) mg/day ($p = 0.008$). The overall level of other immunosuppressive agents remained unchanged, except in one patient where cyclosporine was introduced. This first report of long-term plasmapheresis demonstrates clinical efficacy in pemphigus and a considerable steroid-sparing effect. ***Key words: pemphigus therapy; combined immunosuppressive therapy; autoimmune disease therapy; plasma exchange; bullous therapy.***

(Accepted October 12, 1994.)

Acta Derm Venereol (Stockh) 1995; 75: 150–152.

K. Søndergaard, Department of Dermatology, Marselisborg Hospital, University of Aarhus, P P Ørumsgade 11, DK-8000 Aarhus C, Denmark.

Glucocorticoids and immunosuppressive agents effectively induce clinical remission in most patients with pemphigus (1, 2). However, dosages are usually high and so are complication rates (3–5). The most serious complications from glucocorticoids are potentiation of infections, osteoporosis with multiple fractures of the spine and muscular atrophy, while bone marrow depression may occur with any of the cytotoxic agents and kidney toxicity is the most important side-effect of cyclosporine (6). Besides, we have to reckon with an increased incidence of malignancies after long-term use of immunosuppressive agents (7). Plasmapheresis (PP) has been suggested as a steroid-sparing procedure in pemphigus. PP was introduced in pemphigus by Roucco et al. (8) and by Cotterill et al. (9) in 1978 and later studied in case reports and small open studies (10–17). Roujeau et al. (13) reported in a small uncontrolled study about 3 to 20 plasma exchanges performed in periods ranging from one to 16 weeks. Only two controlled studies (18–19) have been done, and they were both short-term investigations with PP carried out in a maximum of 4 weeks. The role of long-term PP in pemphigus is unknown. For this reason we have found it important to present our data on 8 patients with pemphigus treated with PP from 5 to 73 months.

PATIENTS AND METHODS

Patients

Eight patients with pemphigus were reviewed, one woman (patient no. 7, Table I) and 7 men aged between 42 and 77 years. Seven patients had pemphigus vulgaris and one had pemphigus foliaceus (patient no. 4, Table I). Three patients had cutaneous blisters, 3 had cutaneous and mucosal blisters and 2 had only mucosal blisters. In the initial phase of the disease the patients received 30–120 mg prednisone/day (median 50 mg/day). All patients fulfilled the clinical, histopathological and immunofluorescent criteria for pemphigus, including acantholytic bullae and intercellular epidermal deposits of IgG and in some cases complement C3.

The disease activity was characterized as active disease, partial remission or total remission. Partial remission was defined as "few lesions", "solitary lesions" or < five lesions. Two patients were in total remission and 6 had active disease, when they entered PP therapy. In 3 cases PP was given as part of the initial therapy of the disease. The rest of the patients had suffered from pemphigus for 7 to 82 months before they entered PP. In 4 of these cases pemphigus had been resistant to previous therapy. At the onset of PP adjunctive immunosuppressive therapy included azathioprine, cyclophosphamide and cyclosporine. The patients were allowed to use topical treatment. We chose, as a general rule, to reduce glucocorticoid treatment prior to a reduction of other immunosuppressive agents. Doses and clinical data are listed in Table I.

Plasmapheresis

The patients were initially given two large volume PP treatments every 4th week. There was one day between the two treatments. When the patients had been in remission for several months on an acceptable glucocorticoid level, the PP was reduced to one treatment every 4th week. The patients were given 5 to 89 (median 36) PP treatments.

Each procedure removed 1.5 to 3 l of the plasma volume. Five per cent human albumin, isotonic citrate ACD and isotonic NaCl were used as replacement, and the patients were given an oral supplement of calcium. Before each PP the blood erythrocyte volume, thrombocyte count and serum calcium were determined. The pemphigus antibody titers were not determined.

Statistical analysis

The signed rank test of Wilcoxon was applied in the comparison of daily doses of prednisone at the beginning and at the end of the PP treatment. Data are expressed as median values and ranges. The level of significance was $p < 0.05$.

RESULTS

By combining PP with the immunosuppressive therapy listed in Table I it was possible to reduce the daily dose of glucocorticoids in all cases. At onset of PP the glucocorticoid doses were from 15 to 80 mg/day, with a median level of 38 mg/day. At the end of PP the ranges of glucocorticoid doses were from 5 to 35 mg/day, with a median level of 10 mg/day. A pairing of individual values showed that the daily prednisone doses were significantly lower after than before the PP treatments, $p =$

 ISSN 0001-5555

Table I. *Clinical data*

PP: plasmapheresis; Cs: cyclosporine; Az: azathioprine; Cp: cyclophosphamide.

Pat. No.	Duration of disease Months	Onset of plasmapheresis Therapy (mg/day)		During plasmapheresis					End of plasmapheresis Therapy (mg/day)	
		Prednisone	Other	Months until 1. remission	Months of remission	No. of relapses	Months of PP	No. of PP	Prednisone	Other
1	1	50	Az: 100	0	5	0	5	5	35	Az: 100
2	82	15	Az: 50	2	2	1	5	13	10	Az: 100
3	8	25	Cp: 150	1	10	1	12	20	15	Cp: 100
4	41	75	–	2	62	1	71	62	5	–
5	23	40	Cp: 100	0.5	67	2	73	89	5	Cs: 200
6	1	35	–	2	39	2	61	64	10	Cs: 200
7	0.5	80	Cp: 100	1	30	1	32	51	20	Az: 50
8	7	25	–	0	10	0	10	19	5	–

0.008. Fig. 1 shows the clinical course of a case (patient no. 4) in relation to therapy. The duration of the treatment was from 5 to 73 months, with a median level of 22 months. Two patients received PP for only 5 months. One of them had achieved a lasting remission after 7 years of active disease. The other was excluded after two episodes of hypotension during the PP. Five patients (nos. 4 to 8) continue the PP.

Cyclosporine had been added in one case (200 mg/day). Other minor changes in adjunctive immunosuppressive therapy are presented in Table I. Two patients were kept in remission by PP therapy and a small prednisone dose alone (nos. 4 and 8). Discontinuation of PP has still not been attempted. At the onset of PP treatment 75% of the patients had active disease; after 2 months of combined PP and immunosuppressive therapy all patients were in remission. During the PP treatment the patients stayed in remission in 40–100% (median 90%) of the time. In the same period 2 patients had no relapses, 4 patients had one and 2 patients had two relapses. In 5 cases we were able to reduce PP therapy to one treatment every 4th week. This reduction was in one case (patient no. 7) followed by a relapse, which was managed by two monthly PP treatments and an increase of the prednisone dose from 10 to 20 mg/day.

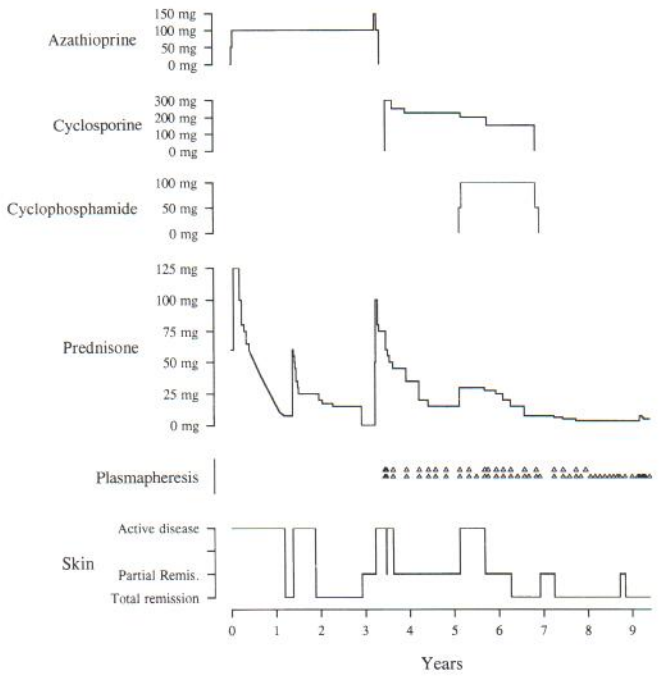

Fig. 1. The clinical course of patient no. 4 in relation to therapy.

Side-effects were rare. Complications occurred in 6 of 323 PP treatments. Most had little or no clinical significance. They were all transient and included nausea, dizziness, fever and leg muscle spasm. However, one patient with arrhythmia perpetua was excluded from the treatment after having had two episodes of hypotension. No complication occurred in 5 patients.

DISCUSSION

Prior to the use of glucocorticoid therapy, significant morbidity and mortality were associated with patients having pemphigus. Today, mortality has been reduced and remains at 5–15% due to drug-associated complications (1–3). This uncontrolled retrospective study of long-term PP in combination with immunosuppressive agents demonstrates a clinical efficacy and a considerable steroid-sparing effect. This is the first report of long-term PP in pemphigus.

We did not study circulating levels of pemphigus antibodies. But it is known from the literature (19) that PP in combination with immunosuppressive drugs more rapidly reduces the levels of antibodies than immunosuppressive drugs alone. Case reports and short-term open studies have shown that the best clinical results were obtained in steroid-resistant cases of pemphigus when PP was added to a previously ineffective therapeutic regimen (13, 15, 17). Optimal control of disease activity has been achieved with PP in association with both glucocorticoids and other immunosuppressive agents (16).

In our study 4 patients had prolonged disease activity resistant to conventional therapy with prednisone and different immunosuppressive agents. One to three PP treatments added every 4th week resulted in clinical remission in all 4 patients within a couple of months. The plasma exchanges continued monthly (5 to 73 months), with little changes in other immunosuppressive agents, while the prednisone doses were gradually decreased and all stayed in remission with the exception of one to two brief relapses. Our data suggest that long-term PP with one to two

treatments every month may be effective as a steroid-sparing therapy.

Whether PP has a role in the initial treatment of pemphigus is uncertain. In the controlled study of Guillaume et al. (18), patients with no previous treatment of their pemphigus had no clinical benefit of PP in the treatment of pemphigus, as PP was performed in combination with low doses of prednisolone. In 2 of our patients PP was used in the initial treatment with prednisone in moderate to high doses and other immunosuppressive agents. Within 2 months the disease was in remission in both patients without drug increase. Plasma exchanges were continued, and prednisone doses could be gradually reduced in subsequent months. One of these patients had a minor relapse after 30 months of treatment, while the other had a more prolonged relapse, which was successfully treated by temporarily increasing the doses of immunosuppressive drugs.

In 2 patients with pemphigus already in remission, a steroid-sparing effect was obtained during the long-term PP treatment. Neither had symptoms of relapse.

In conclusion, our observations in all of the 8 patients indicate that long-term PP in association with glucocorticoids and other immunosuppressive agents is effective in pemphigus, although the results should be interpreted with caution due to the small number of patients. It should also be noted that the optimal method of performing PP has not yet been established. An increase of infectious and haematologic complications has been reported in patients with pemphigus treated with PP (18, 20, 21). However, in our study, only a few transient side-effects occurred in more than three hundred PP treatments. It is therefore our opinion that long-term PP, once or twice a month, could be a relatively safe and effective procedure. A controlled and randomized study to evaluate the clinical benefit of long-term PP would be useful.

REFERENCES

1. Rosenberg FR, Sanders S, Nelson CT. Pemphigus: a 20-year review of 107 patients treated with corticosteroids. Arch Dermatol 1976; 112: 962–970.
2. Sanders SL, Brodey M, Nelson CT. Corticosteroid treatment of pemphigus: experience with fifty cases over a period of ten years. Arch Dermatol 1960; 82: 717–724.
3. Lever WF, White H. Treatment of pemphigus with corticosteroids. Results obtained in 46 patients over a period of 11 years. Arch Dermatol 1963; 87: 12–26.
4. Savin JA. The events leading to the death of patients with pemphigus and pemphigoid. Br J Dermatol 1979; 101: 521–534.
5. Ahmed AR, Moy R. Death in pemphigus. J Am Acad Dermatol 1982; 7: 221–228.
6. Penn I. Tumor incidence in human allograft recipients. Transplant Proc 1979; 11: 1047–1051.
7. Barthelemy H, Frappaz A, Cambazard F, Manduit G, Rouchouse B, Kanitakis J, et al. Treatment of nine cases of pemphigus vulgaris with cyclosporin. J Am Acad Dermatol 1988; 18: 1262–1266.
8. Ruocco V, Rossi A, Argenziano G, Aatarita C, Alviggi L, Farzati B, et al. Pathogenicity of the intercellular antibodies of pemphigus and their periodic removal from the circulation by plasmapheresis. Br J Dermatol 1978; 98: 237–241.
9. Cotterill JA, Barker DJ, Millard LG. Plasma exchange in the treatment of pemphigus vulgaris. Br J Dermatol 1978; 98: 243.
10. Auerbach R, Bystryn JC. Plasmapheresis and immunosuppressive therapy. Arch Dermatol 1979; 115: 728–730.
11. Swanson DL, Dahl MV. Pemphigus vulgaris and plasma exchange: clinical and serologic studies. J Am Acad Dermatol 1981; 4: 325–328.
12. Roujeau JC, Kalis B, Lauret P, Flechet ML, Joneau Fabre M, André C, et al. Plasma exchange in corticosteroid-resistant pemphigus. Br J Dermatol 1982; 106: 103–104.
13. Roujeau JC, André C, Joneau Fabre M, Lauret P, Flechet ML, Kales B, et al. Plasma exchange in pemphigus: uncontrolled study in ten patients. Arch Dermatol 1983; 119: 215–221.
14. Ruocco V, Astarita C, Pisani M. Plasmapheresis as an alternative or adjunctive therapy in problem cases of pemphigus. Dermatologica 1984; 168: 219–223.
15. Walton S, Keczkes K, Robinson AE. A case of penicillamine-induced pemphigus, successfully treated by plasma exchange. Clin Exp Dermatol 1987; 12: 275–276.
16. Euler HH, Löffler H, Christophers E. Synchronization of plasmapheresis and pulse cyclophosphamide therapy in pemphigus vulgaris. Arch Dermatol 1987; 123: 1205–1210.
17. Fine JD, Appell ML, Green LK, Sams WMJ. Pemphigus vulgaris. Combined treatment with intravenous corticosteroid pulse therapy, plasmapheresis and azathioprine. Arch Dermatol 1988; 124: 236–239.
18. Guillaume JC, Roujeau JC, Morel P, Doutre MS, Guillot B, Lambert D, et al. Controlled study of plasma exchange in pemphigus. Arch Dermatol 1988; 124: 1659–1663.
19. Tan-Lim R, Bystryn JC. Effect of plasmapheresis therapy on circulating levels of pemphigus antibodies. J Am Acad Dermatol 1990; 22: 35–40.
20. Shumak KH, Rock GA. Therapeutic plasma exchange. N Engl J Med 1984; 310: 762–771.
21. Huestis DW. Mortality in therapeutic haemapheresis. Lancet 1983; 1: 1043.