Azathioprine in Treatment of Bullous Pemphigoid

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Summary

Azathioprine was given to 11 patients with pemphigoid who had been on long-term maintenance therapy with prednisone or prednisolone. In nine of these prednisone therapy was withdrawn and all were maintained symptom-free on azathioprine alone, while in two the dose of prednisone was considerably reduced. One patient who had never received corticosteroids was controlled by azathioprine alone during the initial acute phase of the illness. Since azathioprine acts slowly, it is recommended that corticosteroids should be used together with azathioprine during the acute stage. Thus azathioprine is valuable in long-term management of pemphigoid, particularly in patients showing corticosteroid toxicity or in whom the minimum maintenance dose is dangerously high.

Introduction

Pemphigoid is a chronic disabling disease which, before the advent of corticosteroids, was fatal in about one-third of the cases (Sneddon, 1968). This mortality has been greatly reduced by systemic corticosteroid treatment, but though spontaneous remissions may occur most patients require permanent corticosteroid maintenance therapy (Church, 1960; Stevenson, 1960). Since pemphigoid mainly affects the elderly, side effects from this treatment are particularly severe.

The demonstration by Beutner *et al.* (1965) and Jordon *et al.* (1967) of circulating autoantibodies reactive with the cutaneous basement membrane zone in patients with pemphigoid raises the possibility that immunosuppressive therapy might provide an alternative to corticosteroid treatment. Azathioprine (Imuran) is an effective immunosuppressant (Corley *et al.*, 1966) with a higher therapeutic index than some other available immunosuppressants (*New England Journal of Medicine*, 1968; Bach *et al.*, 1969). We have recently found azathioprine to be effective in another putative autoimmune bullous disease, pemphigus vulgaris (Burton *et al.*, 1970). We have therefore given azathioprine to 12 patients with pemphigoid.

Patients and Methods

Twelve patients aged 47-79 years with pemphigoid were studied. The clinical diagnosis in all patients was confirmed by histological demonstration of subepidermal vesicle formation in biopsy material. Eleven patients had been on maintenance therapy with prednisone or prednisolone for months or years previously. The twelfth, who had never had corticosteroids, was treated during the initial acute phase of the illness by azathioprine alone.

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Before beginning azathioprine treatment an attempt was made to reduce the maintenance dosage of prednisone. Stepwise reduction of 2.5 mg was made at intervals of no less than one week. In all 11 patients evidence of relapse appeared on daily dosage of prednisone ranging from 0 to 50 mg. This dosage, designated the "relapse" dose, is a rough indication of the degree of activity of the disease at the time of the study and is detailed in the Table. Since all 11 patients relapsed on reduction of prednisone dosage it is highly unlikely that they were in spontaneous remission at the beginning of treatment with azathioprine.

Autoantibody determinations were carried out on the serum of nine patients before azathioprine treatment by the indirect immunofluorescent method (Jordon *et al.*, 1967). Two of the nine sera contained detectable basement membrane zone antibody (titre 1/40 and 1/1,250 respectively). The high proportion of negative results is probably due to the prednisone-induced remission of the disease in this group, since antibody titre is directly related to clinical disease activity (Jordon *et al.*, 1967).

Azathioprine was given in dosage 2.5 mg/kg body weight/day. Weekly or fortnightly white cell and platelet counts, liver function tests, and blood urea determinations were carried out before azathioprine was given and repeated at weekly or fortnightly intervals afterwards.

In the 11 patients who had been previously maintained on long-term prednisone treatment the following procedure was adopted. Azathioprine was added to the existing maintenance dose of prednisone. After a minimum of four weeks the dosage of prednisone was then reduced stepwise to zero or until evidence of relapse appeared.

Results

The results are summarized in the Table. In nine of the 11 patients who had been on long-term maintenance prednisone treatment it proved possible to withdraw prednisone entirely under azathioprine cover, and these patients have remained symptom-free on azathioprine alone for at least six weeks and in most cases for three to four months. In the remaining two considerable reduction in the previous maintenance dosage of prednisone has been achieved by using azathioprine.

To show that azathioprine was exerting a suppressive effect, and that the disease was not in spontaneous remission, it was withdrawn in six patients. Relapse, confirmed histologically, occurred in four of these after one week to three months. In each case the relapse was controlled by beginning azathioprine treatment again. In the other two

Azathioprine in Corticosteroid-suppressed Pemphigoid

Case No.	Prednisone (mg./day)		Relapse after Azathioprine Withdrawal
	Relapse Dose	During Azathioprine	
1	5	0	—
2	5	0	+
3	50	0	+
4	17.5	0	—
5	2.5	0	+
6	30	2.5	+
7	0	0	Not done
8	10	0	" "
9	20	12.5	" "
10	5	0	" "
11	15	0	" "

patients no relapse has occurred after periods of one month and seven months, respectively.

Because of these encouraging results an attempt was made to treat one new patient with acute pemphigoid of limited extent with azathioprine alone, prednisone being withheld. This patient had bullae confined to the trunk, and after three months' treatment with azathioprine these had almost completely healed.

Side effects of azathioprine treatment of pemphigoid were noted in six patients. Four developed leucopenia, with a total white cell count below 4,000/mm³ at some stage during treatment. This was reversed by stopping the azathioprine. It was then possible to recontinue azathioprine at a reduced dosage. Nausea, vomiting, and diarrhoea occurred in two patients.

Discussion

The evidence from the present study that azathioprine is an effective treatment for pemphigoid may be summarized as follows: (1) By giving azathioprine it proved possible to withdraw maintenance prednisone therapy in nine out of 11 patients, who were then maintained symptom-free on azathioprine alone. In the remaining two it was possible to reduce considerably the dosage of prednisone. (2) Withdrawal of azathioprine in six patients, five of whom had been maintained on azathioprine alone, resulted in relapse in four which was reversed by restarting azathioprine. (3) In one patient the pemphigoid was controlled during the acute initial stage by using azathioprine alone. These results cannot be explained solely on the basis of spontaneous remissions.

We are not aware of any published reports of the effect of azathioprine in pemphigoid, though azathioprine has been used with success in pemphigus vulgaris (Wolff and Schreiner, 1969; Burton *et al.*, 1970).

Lever (1970) reported a favourable response to the immunosuppressant methotrexate in five patients with pemphigoid. In four of them the response was rapid, and in two of these the disease relapsed on ceasing methotrexate, becoming suppressed again on reintroducing it. In the fifth patient the response was more gradual. Lever's conclusion, however, that methotrexate is the treatment of choice in most cases of bullous pemphigoid is open to criticism. There have been several disquieting reports (O'Rourke and Eckert, 1964; Ryan and Vickers, 1966; Coe and Bull, 1968; Muller *et al.*, 1969) of renal and hepatic damage after methotrexate therapy in psoriasis. Results of histological examination of liver biopsy material from patients with psoriasis given methotrex-

ate in conventional dosage suggest that about 50% of patients who have had methotrexate for three years will have cirrhosis or some degree of hepatic fibrosis (M. G. C. Dahl, M. M. Gregory, and P. J. Scheuer, 1970, personal communication).

Though we have studied the speed of action of azathioprine in only one patient it seems likely, both from this patient and from our own (Burton *et al.*, 1970) and other observations (Lever and Goldberg, 1969; Wolff and Schreiner, 1969) in pemphigus, that this is likely to be slow. Thus we do not suggest that azathioprine should be used alone during the acute initial stage of pemphigoid. In this situation systemic corticosteroids remain the standard treatment because of their effectiveness and rapidity of action. Our results do, however, indicate that azathioprine is valuable in the long-term management of pemphigoid, particularly where evidence of corticosteroid toxicity has appeared or where the minimum maintenance dosage of corticosteroids is dangerously high. In these patients it is possible, by giving azathioprine, to maintain control of the disease either without corticosteroids or with a considerably reduced corticosteroid dosage.

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