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Long term results of systemic chemotherapy for ocular cicatricial pemphigoid

C. STEPHEN FOSTER, RON NEUMANN & JOSEPH TAUBER
Immunology Service and the Hilles Immunology Laboratory, Massachusetts Eye and Ear Infirmary, Boston, Mass. USA

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Abstract. Ocular cicatricial pemphigoid (OCP) is a chronic, progressive, blinding, autoimmune disease that scars mucous membranes. We studied the long-term outcome in 104 consecutive patients (average follow-up: 4 years) to determine whether complete remission could be achieved following a course of treatment with immunosuppressive drugs. We found that prolonged periods of remission off therapy are maintained in about one third of OCP patients. Follow-up must be continued for life as relapse occurs in approximately one third of cases. Those who relapsed regained disease control readily upon reinstitution of therapy and did not deteriorate to more advanced cicatrization. Sex, age, initial degree of inflammation and the incidence of extraocular involvement did not bear a prognostic significance. The mechanism which underlies the differing responses to therapy is not yet known.

Abbreviations: BMZ – basement membrane zone; CP – cicatricial pemphigoid; OCP – ocular cicatricial pemphigoid; OD – right eye; OS – left eye

Introduction

Cicatricial Pemphigoid (CP), a systemic autoimmune disease produces a blistering rash and mucous membrane inflammatory lesions that typically cicatrize. This leads to irreversible damage to the mucous membranes, sometimes including strictures of the esophagus, trachea, anus or vagina. Esophageal and/or tracheal strictures may occasionally result in asphyxiation and death. About 70% of CP patients develop ocular manifestations [1] and are thus diagnosed as ocular cicatricial pemphigoid (OCP). The primary ocular involvement is conjunctival cicatrization. Untreated, OCP eventually destroys the lacrimal gland ductules and meibomian gland orifices impairing both the aqueous and the oily constituents of the tear film and resulting in xerosis. Eyelid malposition, symblephara formation and trichiasis eventually develop, contributing to keratopathy and reduced vision. Once the disease reaches advanced stages of cicatrization it may rapidly progress [2, 3]. OCP is characterized by deposition of immunoreactants (immunoglobulin or complement) in the conjunctival basement membrane zone (BMZ) [1].

Conjunctival scarring cannot be reversed. Control of inflammation and arrest of the cicatrizing process are, therefore, the goals of therapy in OCP. Previous studies of dermatologists and ophthalmologists caring for patients with CP have shown that it can be effectively treated with systemic immunosuppressive chemotherapy [1–8]. Two randomized, controlled clinical trials have established the efficacy and safety of chemotherapy for OCP and have allowed formation of recommended therapeutic guidelines [1]. To date, however, no study has evaluated the long term outcome of these treatments, particularly in regard to the prevalence of relapse, severity of the relapse, and ease or difficulty in bringing a relapse under control. In this study we address these topics summarizing an average of four years of follow-up of patients treated with immunosuppressive chemotherapy for OCP.

Subjects and methods

Over 200 patients have been treated over the past five years on the Immunology Service of the Massachusetts Eye and Ear Infirmary in Boston. We screened data on 184 of these patients, and found that 104 met the following criteria for inclusion in the present study: biopsy proven OCP (positive immunoreactant deposition in the BMZ demonstrated by immunofluorescence or, when immunofluorescence was negative, by the immunoperoxidase ABC method); apparent full compliance with our therapeutic instructions; and follow-up of at least five months in our care.

Most of the patients were treated according to our previously published guidelines [1, 8]. Briefly, for mild to moderate inflammation we prescribe diaminodiphenylsulfone (Dapsone), provided the patient is not glucose-6-phosphate dehydrogenase deficient. If the therapeutic response is unsatisfactory, or if the patient cannot tolerate Dapsone, we add or substitute azathioprine (Imuran). If inflammation is still not controlled, or if the eye is highly inflamed initially, cyclophosphamide (Cytoxan) is used sequentially or initially. In case of severe inflammation, we add systemic prednisone for a limited period (maximum three months). Cyclosporine and methotrexate were the other agents employed on occasion. In order to judge accurately whether a change of drug or dosage is justified, we carefully eliminate potentially confounding inflammatory stimuli such as exposure, trichiasis, lid abnormalities, meibomianitis and dry eye [1]. We also have emphasized the importance of drug management by an expert chemotherapist [1]. After full control of inflammation is achieved (inflammation score < 0.5) we continued therapy with the successful regimen for one year. Medication is then slowly tapered, and disease activity is carefully monitored. Since late exacerbation is possible, regular longitudinal evaluation is maintained indefinitely.

Each patient was placed in one of the following outcome groups arbitrarily defined, based on our familiarity with OCP: Group 1, total control of

disease activity, patient no longer receiving therapy; Group 2, total control of disease activity, patient still receiving therapy; Group 3, partial control of disease activity, patient still receiving therapy; Group 4, relapse following cessation of therapy; Group 5, no control of disease activity; Group 6, treatment discontinued due to adverse effects. Total control of disease activity was defined as residual inflammatory activity of 0.5 or less in the final examination and an inflammation decrement of at least 0.5 between initial and final examination. Partial control (Group 3) was defined as those patients in whom final disease activity was 1.0 or 1.5 and who had at least 0.5 decrement of disease activity between initial and final examination. Uncontrolled inflammation (Group 5) was defined as those patients whose final disease activity was above 1.5, or had no improvement between initial and final activity for inflammation score of 1.0 or higher.

A single observer (CSF) had graded the degree of disease activity (conjunctival inflammation) using a scale of zero to four in increments of 0.5 upon each patient's examination. Because OCP is sometimes asymmetric, each patient was grouped according to the eye with further advanced disease or higher degree of inflammation.

Additional data for each patient including sex, age at time of diagnosis, disease stage (as previously published [1], drugs given and time schedule of each drug used, disease-free period (when relevant) and reasons for changing or stopping medications.

Results

The distribution of patients over the six groups is shown in Table 1. The average age at diagnosis (68 years, range 27–91 years) was essentially the same for the six study groups (Table 2). A female preponderance was obvious (71 women, 33 men).

Group 1 and Group 4 combined (37 patients), were all patients whose inflammation was completely controlled and who were off medication at some point. Eight (Group 4) eventually relapsed, representing a cure rate of 35% with a relapse rate of 27%.

In Group 1 an average of 28 months (range 3–110 months) of treatment

Table 1. Distribution of 104 patients over groups defining response of therapy

Group/Definition	Number of patients	Average age at diagnosis
1 Total control of inflammation, off therapy	29	65
2 Total control of inflammation, on therapy	33	71
3 Partial control of inflammation, on therapy	19	68
4 Relapse, following cessation of therapy	8	68
5 No control of inflammation	10	67
6 Treatment discontinued due to adverse effects	5	77

Table 2. Average age, initial and final inflammatory activity in Groups 1–5

Patient group	Age at diagnosis	Initial inflammatory activity		Final inflammatory activity	
		OD	OS	OD	OS
1	65	1.3	1.7	0.3	0.2
2	71	1.6	1.8	0.2	0.2
3	68	1.7	1.6	0.9	0.9
4	68	1.4	1.6	0.4	0.6
5	67	1.7	1.9	1.6	1.7

elapsed before treatment was stopped. Total remission, without medication was maintained for an average of 34 months (range 2–75 months); 22 of the 29 patients (76%) in total remission remained free of disease activity while off medication for more than one year. Patients in Group 4 enjoyed an average of 19 months (range 2–43 months) off medication and free of inflammation before relapse. One of these patients remained off medication for 3.5 years before reactivation occurred.

Ninety-four percent of the patients had advanced cicatrizing disease with symblepharon formation at the time of their first visit with us. The average disease stage was the same (3.0) at the initial visit and at the last visit. Apart from two patients in whom the disease regressed to stage 2, i.e. disappearance of symplephara, treatment did not markedly change the degree of cicatrization. The average degree of inflammation in each group before initiation of therapy and at the final examination is presented in Table 2. There was not significant difference between the groups in the level of average initial inflammation (1.3–1.9). Final average inflammation differed markedly between the groups according to their definitions. In groups with controlled inflammation (Groups 1 & 2) the average final score was low (0.2–0.5), while in Groups 3 & 5, defined as having controlled or partially controlled inflammation, final inflammation scores were 0.9–1.7. The average final disease activity in Group 4 (patients who had suffered relapse) was relatively low, 0.4 OD and 0.6 OS. Patient distribution in the groups (Table 1) combined with the average final inflammatory activities (Table 2) confirms the clinical impressions on which the grouping was based.

Tables 3 and 4 illustrate different patterns of treatment in the five groups of patients able to tolerate immunosuppressive drugs. Table 3 presents the average follow-up period for each group and the duration of treatment with each immunosuppressive medication. Dapsone was the most commonly used drug followed by Imuran and Cytoxan. Cyclosporine was prescribed for 15 patients (5 mg/kg/day). The results of cyclosporine usage were grossly disappointing, with only one patient benefitting from it. Table 4 presents the number of patients treated in each group with a specific drug. As might be

Table 3. Average duration (months) of treatments and of complete follow-up periods per patient group*

Patient group	Follow-up	Cytoxan	Prednisone	Imuran	Dapsone	Cyclosporine
1	62	6 (10)	6 (10)	8 (13)	8 (13)	
2	41	4 (10)	10 (24)	10 (24)	22 (54)	
3	42	6 (14)	13 (30)	9 (21)	30 (71)	1 (2)
4	81	18 (22)	7 (9)	2 (<1)	30 (37)	
5	38	2 (5)	24 (63)	12 (32)	16 (42)	5 (13)

* Percentage of total average follow-up to drug is noted in parentheses.

Table 4. Number of patients in each group and number treated with each drug*

Patient group	Number of patients	Cytoxan	Prednisone	Imuran	Dapsone	Cyclosporine
1	29	10 (34)	10 (34)	12 (41)	19 (65)	1 (3)
2	33	9 (27)	11 (33)	12 (36)	31 (94)	3 (9)
3	19	9 (47)	7 (37)	10 (53)	18 (95)	1 (5)
4	8	6 (75)	5 (62)	2 (25)	6 (75)	1 (20)
5	10	7 (70)	7 (70)	9 (90)	8 (70)	2 (20)

* Percentage of group is noted in parentheses.

expected, Group 5 was treated most extensively, both in terms of number of patients treated with each drug and the average duration of treatment. Notable also is the extensive use of steroids in Group 5.

Thirty-two of our patients experienced chemotherapy-related side effects that warranted a change in drug dosage. Dose reduction, increased fluid intake and change in time of administration to fit individual patient's schedules typically resulted in reversal of leukopenia and/or microscopic hematuria related to Cytoxan. Dapsone was associated primarily with low-grade red blood cell hemolysis and gastrointestinal complaints. Azathioprine was associated primarily with leukopenia and arthralgia, while cyclophosphamide was also associated with three instances of interstitial pneumonitis. Only five patients (Group 6) could not tolerate any chemotherapeutic combination involving immunosuppressive drugs. Further details depicting our experience of immunosuppressive chemotherapy for OCP had been previously published [1, 7, 8].

Extraocular involvement (Table 5) was noted in approximately half of the patients in each group, except Group 2. The most frequently involved extraocular site was the mouth, followed by the nose, vagina, trachea, pharynx and sinuses. These manifestations were primarily manageable with the same immunosuppressive strategy employed for the eyes.

Table 5. Incidence of extraocular involvement in OCP

Patient group	Number of patients	Number with extraocular involvement*
1	29	12 (41)
2	33	5 (15)
3	19	9 (47)
4	8	3 (37)
5	10	5 (50)

* Percentage of group is noted in parentheses

Discussion

Slightly more than one-third of our patients responded to therapy and remained free of inflammation, at least temporarily, following cessation of therapy. Another third (33/104) was free of disease activity, but continued to receive therapy because their disease had been controlled for only a short time (less than one year) or because they had a history of relapse while on therapy. Nearly one-third of our patients responded only partially to treatment. Inability to control inflammation and stop progression of cicatrization was seen in only a few individuals, usually in association with corneal ulcers and repeated conjunctival infections.

Our findings show that careful follow-up must be maintained for 'cured' patients (free of inflammation while off medication) as reactivation of inflammation (which occurred in 27% of our patients off medication) is usually slow to develop. Our follow-up period did not allow for a definition of a 'safe' period of OCP control while off medication that would insure against (future) reactivation. We were encouraged by the final low average level of inflammation in Group 4, which indicated that reestablishment of control was readily achieved upon reinstitution of therapy for those who relapsed. Indeed, effective treatment to control relapse can usually be less aggressive than the treatment used initially. Therefore, we conclude that cessation of therapy with proper follow-up does not carry a substantial risk of uncontrolled OCP progression in the event of relapse.

Tolerance for chemotherapy was considerably higher in this series of patients than in our previous publication [7], or in those of others [3]. We credit this higher tolerance level to the introduction of Dapsone, not used in the previous studies, and possibly to drug combinations that were not reported before. As previously emphasized, the role of a chemotherapist is of paramount importance in the follow-up of patients on immunosuppressive drugs [1, 3].

In our experience and in the reported experience of others [9], chronic prednisone usage for OCP is unacceptable; adverse disabling side effects, such as aseptic hip necrosis, pathologic fractures, uncontrolled diabetes mellitus and hypertension are common in patients who use prednisone for prolonged periods. Moreover, in previous studies we have shown that prednisone alone is less effective than immunosuppressive drugs in halting

the scarring ocular process [1]. Therefore, it is our policy to reserve steroid use for severely inflamed eyes that do not readily respond to immunosuppression alone and to taper it as soon as effective immunosuppression is achieved. The extensive prednisone usage in Group 5 reflects the difficulties we had in achieving a reasonable response to therapy in that group. Patients in Groups 1 and 2 usually responded readily, enabling us to avoid or shorten steroid use. This observation implies that, although initial inflammatory activity as shown in Table 2 was approximately the same for all groups, early response to chemotherapy was substantially better in Groups 1 and 2. Therefore, we consider early response to chemotherapeutic drugs as the best prognostic sign available.

We were not successful in our effort to define other prognostic parameters. No correlation could be drawn between the response to therapy and age, sex or initial degree of inflammation; nor could we demonstrate a significant difference between our study groups in the incidence of systemic involvement. Our observation of distinct response patterns, however, creates interest in further study of the mechanisms underlying the diversity in response to therapy. As previously published [1], we regard BMZ immunoreactant deposition as the gold standard criterion for diagnosis, provided appropriate techniques and controls have been employed. Now we are examining whether discrete therapeutic responses might be related to distinct types of immunoglobulin or complement derivative deposition on the conjunctival basement membrane zone.

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Address for correspondence: Dr C. Stephen Foster, MD, FACS, Immunology Service & the Hilles Immunology Laboratory, Massachusetts Eye and Ear Infirmary, 243 Charles Street, Boston, MA 02114, USA.
Phone: (617) 573 3591; Fax: (617) 573 3181.