Immunosuppressives in uveitis

A preliminary report of experience with chlorambucil

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Since the mid-1960s there has been a small but steady trickle of reports of patients with severe uveitis who have been treated with non-steroid immunosuppressive drugs. This has paralleled the use of these drugs in other non-malignant conditions.

In the past 2 years 14 patients at the Institute of Ophthalmology have been treated with chlorambucil. This report is concerned with the preliminary findings in this group of patients.

Chlorambucil was chosen for its relatively low toxic/therapeutic ratio, and its selective depression of lymphocytes (de Gruchy, 1970). The choice was encouraged by the experience of others who had used chlorambucil (Mamo and Azzam, 1970; Abdalla and Bahgat, 1973).

Rationale: evidence of an immunological disorder in uveitis

In attempting to explain the association of uveal disease with disorders of other tissues Perkins (1961, 1963) suggested an immunological disturbance based on common tissue antigens. He and others have demonstrated common tissue components, but without adducing firm evidence of their role in disease.

Support for the antigenic role of uveal pigment in sympathetic ophthalmitis and Vogt-Koyanagi-Harada disease was advanced by Hammer (1971) in his work on lymphocyte transformation in patients with these conditions. Feinberg, Shore, Leopold, and Henley (1972) demonstrated leucocyte migration inhibition by an aqueous extract of uveal tissue in 11 of 12 patients with uveitis, although Strandgaard and Braendstrup (1971) had previously failed to show this in 22 patients. Bonnet, Mouriquand, Jolbert, and Laurent (1971) demonstrated the failure of aqueous in patients with relapsing uveitis to activate their own lymphocytes, and inferred from this the existence of cellular autoantibodies.

Several studies show the existence of antimucosal antibodies in the serum of patients with Behçet's disease during relapses (Oshima, Shimizu, Yokohari, Matsumoto, Kano, Kagami, and Nagaya, 1963; Lehner, 1967). However, similar changes have been found in patients with aphthous ulcers alone. Shimizu, Katsuta, and Oshima (1965) showed increased reactivity in Behçet's disease to heat-aggregated human gamma-globulin, and their immunofluorescent studies showed responses with Behçet's sera similar to those seen in certain collagen diseases.

There are many points at which immunological mechanisms may play a part in the pathogenesis of ocular disease, but the subject is at present still highly speculative. Much of our thinking derives by analogy from advances made in the understanding of other diseases in which the eye may be involved.

Work on the role of immune complexes in producing vascular damage with subsequent inflammation proceeds apace in systemic medicine, but the importance of this in the eye is conjectural. Nor does the presence of such complexes prove their complicity, as was well shown by Parish (1971a, b) in his studies of cutaneous vasculitis. Parish found antigens of several bacteria in cutaneous vascular lesions, sometimes combined with immunoglobulin, indicating the formation of complexes, but in only one instance was the immunoglobulin demonstrated to be antibacterial antibody. Although there was indirect evidence of complex formation in these patients, specific antibacterial antibody commonly found in their sera rarely combined with the antigen in the lesion. In further studies on patients developing cutaneous vasculitis after streptococcal pharyngeal infections, Parish (1971b) found that antibodies formed to streptococcal antigens in these patients had no particular ability to form tissue-damaging complexes when compared with antibody from patients with similar infections who did not develop vasculitis.

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These patients also formed the subject of a paper presented at the Netherlands Ophthalmological Society meeting in November 1974 and of a short communication presented to the Section of Ophthalmology of the Royal Society of Medicine, London, in the same month

The drugs and their hazards

The drugs so far used fall into three groups:

Antifolates

The example of this group is methotrexate. Toxicity is high. Mouth ulcers, nausea and vomiting, bowel disorders, and liver damage are common. Severe bone-marrow depression, with particular effect on the platelets, alopecia, and dermatitis may occur; it also severely interferes with embryogenesis.

Antipurines

6-mercaptopurine, and its imidazole derivative azathioprine, have been used in uveitis. The latter has a better therapeutic/toxic ratio than 6-mercaptopurine.

Mason, Currey, Barnes, Dunne, Hazleman, and Strickland (1969) have found it useful in sparing steroid in rheumatoid arthritis, but its greatest use is in suppressing homograft rejection after transplant surgery. Its side-effects include bone-marrow depression and muscle atrophy. Although it is teratogenic, it does not appear to produce infertility.

Nitrogen mustards

Cyclophosphamide and chlorambucil have a fairly well established place in the management of the minimal-change nephrotic syndrome in childhood. Cyclophosphamide produces chromosomal damage and sterility (Fairley, Barrie, and Johnson, 1972; Uldall, Kerr, and Tacchi, 1972), as well as bone-marrow depression. Haemorrhagic cystitis is often troublesome.

Chlorambucil, on the other hand, rarely produces anaemia and thrombocytopenia and it depresses lymphocytes rather more than polymorphs. Chromosomal damage has been reported. The question of its effect on fertility is not settled. Although Jackson, Fox, and Craig (1959) and Fox and Fox (1967) found that the aryl-substituted mustards did not affect the fertility of male rats, Richter, Calamera, Morgenfeld, Kierszenbaum, Lavieri, and Mancini (1970) reported azoospermia in eight patients treated for malignant lymphoma. The daily dose was generally higher than that which has been used in uveitis, although the total dose was not necessarily so.

Besides those undesirable side-effects mentioned above, there are possible long-term hazards the importance of which is not yet fully assessed. The most serious is the risk of inducing tumours. Penn, Halgrinson, and Starzl (1971) reported an incidence of 6 per cent in 236 patients with renal transplants, and 0.058 per cent in a general population of similar age. All their patients were taking prednisolone and azathioprine. The recognition of the importance of immunological surveillance in tumour growth makes this finding less surprising—that is, if the drug is working as an immunosuppressive and not exerting its therapeutic action by some other means.

It is probable that many of these agents have a powerful anti-inflammatory effect, and previous workers have commented on the presence of a therapeutic effect without evidence of immunological depression (Newell and Krill, 1967; Hersh, Wong, and Freireich, 1966; Buckley and Gills, 1969).

Previous reports

Hersh and others (1966), writing on the inhibition of local inflammatory response by antimetabolites, mentioned 13 patients with uveitis who were having methotrexate. They recorded in detail their experience with six of these patients (Wong and Hersh, 1965), all with pars planitis. Despite improvement while on treatment, five of the six had a recurrence within 2 to 18 weeks of stopping the treatment. Two responded to a second full course. The mononuclear response was suppressed, but there was no effect on the secondary antigenic response. Four patients showed evidence of liver toxicity.

The first report of the use of azathioprine was made by Bignell and Mackay (1967), who were unable to draw any conclusions about its efficacy in 20 patients with chronic uveitis. Newell and Krill (1967) were more hopeful, and reported improvements lasting up to 1 year in patients with pars planitis. Toxic reactions were less than they had previously experienced with 6-mercaptopurine, and they were able to reduce steroid dosage.

Rosselet, Saudan, and Zenklusen (1968) used azathioprine in three patients with Behçet's disease, and the most satisfactory result was an improvement in extraocular symptoms.

Aoki, Fujioka, and Saito (1971) reported a similar impression with 25 patients with Behçet's disease treated with azathioprine. More than half this group showed no satisfactory improvement in ocular findings, and no alteration in the course of their disease. Another five patients were treated with 6-mercaptopurine, but treatment had to be stopped because of anorexia. François and Van Oye (1973) treated five patients with Behçet's disease with azathioprine and prednisolone. Two had no recurrence during treatment, and in one case there was no recurrence for a further 6 months after stopping treatment; another two had a milder recurrence.

Cyclophosphamide was used by Buckley and Gills (1969) in nine cases of peripheral uveitis, and they reported a clinically significant suppression of inflammation. Follow-up was short, and their best results were gained when the drug was combined with steroids. Firat (in press) reported encouraging results with a series of 30 patients with Behçet's disease treated with combined cyclophosphamide, azathioprine, and steroids.

The first reported use of chlorambucil was that of Mamam and Azzam (1970) who obtained encouraging

results in 11 patients with Behçet's disease. Abdalla and Bahgat (1973) obtained complete remission for 10 months in four of 14 patients with Behçet's disease and a similar experience with Behçet's disease has also been reported by Godfrey, Epstein, O'Connor, Kimura, Hogan, and Nozik (1974) in a large series of cases treated over 10 years. Unquestionably, the most hopeful results have been with Behçet's disease, and the findings of Godfrey and others (1974) also point to sympathetic ophthalmitis as another condition where this form of treatment might be useful. Newell, Krill, and Thomson (1966) reported a favourable result from 6-mercaptopurine in one patient with presumed sympathetic ophthalmitis.

Material and methods

Fourteen patients were treated. One of these was under the care of Mr J.R.S. Barton of Taunton who has kindly allowed us to include his patient in this series.

All patients had disease not responding to steroids, or they were suffering from unacceptable steroid side-effects. They were all instructed to report any worsening of their ocular or general condition, if possible by telephone, for immediate advice. Full blood counts were performed at intervals of 2 to 3 weeks.

In the early part of the trial three patients (3, 11, and 12) were given chlorambucil 10 mg daily, but subsequently dosage started at 5 mg daily and was reduced to 5 mg every other day after several months. Concomitant attempts were made to reduce the amount of steroid the patients were taking. Treatment was given for about 9 months, except for two patients on 10 mg daily who took it for only 4 months.

A beneficial result was recorded if the ocular or the general condition improved, or if a substantial reduction in steroid dose could be made.

Results

In Table I the findings are summarized; in Table II they are presented in detail.

Table I Results

Diagnosis	Total	Improved	No change	Worse
Chronic generalized uveitis	3	2	1	
Uveitis with retinal vasculitis	3	1	1	1
Behçet's disease	5	3	2	
Vogt-Koyanagi-Harada disease	1	1 (temporary)		
Sympathetic ophthalmitis	1	1 (probably)		
Pars planitis	1			1

CHRONIC GENERALIZED UVEITIS

All three patients had suffered a steady decline in vision with recurrent exacerbations of inflammation.

Patient 1 had appalling steroid side-effects. His vision improved a little, and he is now on a minimal dose of steroids. His Cushingoid features have almost disappeared. He had one mild flare-up during his first course of treatment, and a second 4½ months after stopping. A second, shorter course was then given.

Patient 2 had suffered more severe visual deterioration than the other patients, and he had secondary glaucoma. No visual change occurred, although some reduction in steroid dosage was achieved.

Patient 3 has also had a slight visual improvement, and was able to stop steroids after giving up chlorambucil. She had one mild flare-up of inflammation 13 months after stopping both drugs, but this responded to treatment with drops only. She feels much better generally.

UVEITIS WITH RETINAL VASCULITIS

Two patients, with vision already reduced to 6/60 or less, derived no benefit at all. One of these, Patient 5, had a severe vitreous haemorrhage while on treatment. However, the third, Patient 4, had quite a dramatic improvement. Vision improved; he had three mild attacks of inflammation during the course of treatment; he was able to abandon steroids except for an occasional tablet when he felt a flare-up might be impending.

BEHÇET'S DISEASE

Vision in all five patients had been very poor for several years.

Patient 8 had a dramatic cessation of cutaneous phlebitis and mucosal ulceration immediately after he began treatment. At the end of his course he was able to discontinue steroids and has remained well for 4 months after treatment.

Patient 10 had a similar cessation of mucosal ulceration. He had three flare-ups of ocular inflammation early in the course of treatment. He now feels better than he has for some time, but only a slight reduction in steroid dose has yet been made.

Patient 9 should also perhaps be included in the 'improved' category. He had hypopyon 1 month after beginning treatment, but has had no flare-up in the subsequent 13 months. He feels much better than he has for many years. He has been off chlorambucil for only 3 months, and steroids have been reduced only a little although they are continuing to be gradually reduced so far without ill-effect. However, in the past he has gone up to 1 year without ocular or systemic flare-up of his disease.

Patient 7 is in the middle of her course. She feels her vision is less misty, and we have reduced her steroid dose substantially, but it is too soon to draw a conclusion except to say that the response is favourable so far.

Table II *Clinical details and response to treatment with chlorambucil*

No.	Age	Sex	Diagnosis	Duration of disease (yrs)	Pre-treatment course, and visual acuity	Duration of treatment (mths)	Attack rate on treatment	Visual change and acuity after treatment
1	23	M	Chronic generalized uveitis	3	Chronic bilateral inflammation with several severe exacerbations each year despite high steroid dose Severe Cushingoid features 6/18 6/12	10+5	1 minor flare-up after 6/12 Second flare-up 4½/12 after stopping treatment Second course no flare-up	Slight improvement 6/9 6/12
2	49	F	Chronic generalized uveitis	9	Chronic uveitis never completely settled Occasional severe flare-up Secondary glaucoma from iris bombé * PL 6/60	4	Nil	Nil
3	38	F	Chronic generalized uveitis	10	Steady decline in vision with exacerbations of inflammation 1-2 times a year 6/18 6/12	4	Nil	6/12 6/12
4	36	M	Uveitis with retinal vasculitis	11	Recurrent attacks, most severe in left eye 6/9 **CF	9	3 mild attacks	Improved 6/9 6/18
5	46	M	Uveitis with retinal vasculitis	13/12	Steady decline Yearly flare-ups with severe vitreous haemorrhages Perforated gastric ulcer from steroids 6/60 ***NPL	5	Severe vitreous haemorrhage	Worse CF NPL
6	36	M	Uveitis with retinal vasculitis	3	Steady decline on steroid treatment Frequent flare-ups NPL CF	3	One	Nil
7	19	F	Behçet's disease	6	Steady decline High steroid dosage CF CF	5	Nil	'Less misty'
8	34	M	Behçet's disease	3	Steady decline despite steroid treatment Recurrent phlebitis and pustules in skin with buccal ulcers and ocular flare-up every 6 weeks CF CF	9	Nil	Nil
9	26	M	Behçet's disease	3½	Yearly hypopyon uveitis with steady visual decline 3 short courses of cyclophosphamide 2 yr before without success, and with skin infections, alopecia, purpura, and cystitis 6/60 NPL	12	Hypopyon 1 month after beginning	Nil
10	27	M	Behçet's disease	10	Treated with prednisolone and ACTH Steady decline with yearly exacerbations Frequent hospital admissions Frequent mucosal ulcers 6/60 NPL	9	2 flare-ups after 1/12 and a third after 3/12 when attempting to reduce ACTH	Nil
11	46	M	Behçet's disease	11	Steady decline despite high steroid dosage Persistently severe inflammation with frequent hypopyon Secondary glaucoma and cataract Doubtful PL CF	13	Nil	Nil
12	44	M	Vogt-Koyanagi-Harada disease	14	Steady worsening Attacks every few months 6/60 PL	3.5	Nil	Improved on treatment 6/36 ****HM
13	26	M	Sympathetic ophthalmitis	16	On prednisolone and ACTH from age of 9 Dwarfed in stature Several flare-ups each year Secondary cataract 6/60	9	Nil	Uneventful lens aspiration while on treatment 6/18
14	58	F	Pars planitis	11/12	Progressive worsening of vision in left eye despite high dose systemic steroids 6/9 6/60	7	Activity continued	Initially worsened

* PL = Perception of light
** CF = Counting fingers

*** NPL = No perception of light
**** HM = Hand movements

Patient 11 had no ocular flare-up during 13 months of treatment, and for 10 months afterwards, when he had a small hypopyon. He is taking the lowest steroid dose since he began steroids 11 years ago. The recent hypopyon settled rapidly when the steroids were increased for 2 weeks.

VOGT-KOYANAGI-HARADA DISEASE

This patient's vision improved on treatment, but one year after stopping treatment it gradually fell back to pre-treatment levels. No change in his steroid dose was made.

Table II continued

Systemic change	Steroid treatment	Lowest white cell count on treatment		Follow-up after treatment (mths)	Complications
		Total	Lymphocytes (per mm ³)		
Greatly improved Cushingoid features almost disappeared	Greatly reduced	4000	660	3	Skin infection after 5/12 Drug dose reduced Leucopenia
Nil	Reduced	4000	800	3	Leucopenia
Felt subjectively better	Halved while on treatment Stopped after coming off chlorambucil	1700	493	15 One mild flare-up 13 after stopping Cleared with local treatment	Hordeolum Leucopenia (treatment stopped)
Felt well and very enthusiastic about the treatment	Reduced 'Occasional' tablet of steroid taken	No information		7	Nil
Nil	No change	8000	2080	10 No improvement	Nil
Nil	No change	10 000	2100	14 1 very severe flare-up	Nil
	Greatly reduced	11 000	1430	Treatment continuing	Nil
Greatly improved 1 attack of phlebitis after 3/12, while temporarily off treatment	Rapidly tailed off when chlorambucil stopped	2600	900	4 Transient slight flare in right eye	Thrombocytopenia (responded to suspension of treatment) Leucopenia Leucopenia
Feels generally better than he has for many years	Small reduction	4000	360	3	
Some weight reduction No ulcers at all Feels generally better	Unchanged	5000	160	3	? Purpura Haematological investigations normal
Nil	Reduced—maintained while off chlorambucil on the lowest dose he has ever had	5000	440	11 Hypopyon after 10 settled with increased systemic steroids	Nil
Nil	Unchanged	7000	1610	1 year Vision back to 6/60 HM****	Nausea Felt depressed and stopped the drug
Nil	Small reduction	9000	900	2	Nil
Nil	Small reduction	4000	280	8	Leucopenia

SYMPATHETIC OPHTHALMITIS

In Patient 13 conclusions are difficult to draw. From the age of 9 years he had been taking prednisolone and adrenocorticotrophic hormone, and 16 years later he is quite dwarfed. His uveitis, before chlorambucil was begun, flared up two or three times each year, but has been quiet for more than 11 months. A successful lens aspiration while on the drug has

produced a great visual improvement. His steroids have also been reduced a little. He has not been off treatment for very long, but if the condition remains quiet the improvement will be confirmed.

PARS PLANITIS

The vision of Patient 14 slowly deteriorated while on treatment.

In summary, the most impressive results were in Behçet's disease, and two of three patients with chronic generalized uveitis benefited largely in the reduction in steroid dosage that was possible. The patients with Behçet's disease became almost completely free of vascular and ulcerative lesions. Visual improvement in these patients was hardly to be expected, as their acuities had deteriorated to such low levels long before the drug was begun.

Toxicity

Anaemia was not encountered. In only two patients did the white cell count fall below $4000/\text{mm}^3$. In four others it was reduced to $4000/\text{mm}^3$.

One patient developed thrombocytopenia (less than $100\,000$ platelets/ mm^3) but responded to temporary withdrawal of treatment. Another patient complained of bruising, but this was due to mechanical trauma. A thorough investigation of his bleeding and clotting function was normal.

In one man with severe rheumatoid sclero-uveitis (who was under treatment elsewhere and is not included in this series), thrombocytopenia developed within 3 weeks of beginning treatment. He had had unexplained thrombocytopenia in the past and it was not felt that treatment with chlorambucil should be reintroduced.

One patient had a crop of boils, which cleared when the drug was withdrawn. Another developed a hordeolum when her white cell count was $4000/\text{mm}^3$.

One patient complained that the drug made him feel nauseated and depressed. He was taking 10 mg daily.

Lymphocyte changes

Most patients had a marked reduction in the total white cell count and lymphocyte count. The percentage of lymphocytes in the total white cell count was reduced in about half (Table III).

Table III *Lymphocyte changes (twelve patients)*

<i>Lymphocytes</i>	<i>Patients</i>
Total count reduced to less than half pre-treatment level	8
Fall in percentage of white cell count of one-third or more	5

Of the 12 patients to whom the Table applies, five are considered to have benefited from treatment, and we are reserving judgement in two. Four of the former (three of whom had Behçet's disease) and one of the latter (also with Behçet's disease) had lympho-

cyte counts reduced to less than half the pre-treatment levels.

These figures are presented simply for comparison with the findings of others. They illustrate the tendency of chlorambucil to produce relatively more lymphopenia than neutropenia.

Cytogenetic effects

Lymphocyte cultures after treatment were studied by Dr Sylvia Lawler of the Department of Immunology and Cytogenetics at the Royal Marsden Hospital. Chromosomal changes of doubtful significance were found in two of 10 patients. One of these had had 10 mg daily and the other had been unsuccessfully treated 2 years before with cyclophosphamide. Snaith, Holt, Oliver, Dunnill, Halley, and Stephenson (1973) reported findings in patients with systemic lupus erythematosus and nephritis. Of 10 patients treated with chlorambucil, none showed chromosomal damage, whereas damage was evident in five out of 10 patients treated with cyclophosphamide.

Discussion

The status of immunosuppressives in non-malignant conditions has been reviewed by Lessof (1973). When drugs so potentially toxic as these are used, it is essential to define the type of case likely to benefit from treatment. Despite wide experience with large numbers of patients, physicians are largely undecided about the part these drugs should play in the treatment of conditions in which immunological mechanisms may be disordered. Their experience should make us doubly cautious in drawing conclusions from the small number of cases so far treated for eye disease.

Only in the case of Behçet's disease does a clearer role appear to be emerging, but one cannot yet say that treatment will make a permanent impression on the course of the disease. The improvement in systemic symptoms noted by some of our patients has also been commented on by Mamo and Azzam (1970) and Rosselet and others (1968). Our preliminary findings with chronic generalized uveitis, and uveitis with vasculitis, are also mildly encouraging. It is intended to make a further report on this group of patients in 18 months' time. Ideally, double-blind trials might be attempted, but the practical difficulties of doing this are overwhelming.

Chlorambucil is probably one of the least dangerous of these agents. However, our ignorance about long-term side-effects, together with the inconclusiveness of published therapeutic findings, would deter one from using it indefinitely, or in repeated courses, in any one patient.

Serious short-term side-effects were uncommon in our patients. Leucopenia of less than $4000/\text{mm}^3$ was

encountered in only two patients, one of whom was on a higher dose than we subsequently used, as was the patient who stopped his treatment because of nausea and depression. Although thrombocytopenia is uncommon, its occurrence in one patient highlights the importance of including platelet counts in the regular blood examination.

Until the incidence of long-term side-effects is better understood, we should limit the duration of treatment. Six months would probably have been adequate at the dose level used in most of our patients.

In Behçet's disease we should be prepared to give the drug early in the disease, rather than to await the inexorable decline. All our patients had suffered visual

deterioration to 6/60 or less before they began taking chlorambucil.

In conclusion we should remind ourselves that these drugs have only recently masqueraded under the title of 'immunosuppressives'. They were once known as antimetabolites and cytotoxic agents. They have not changed by acquiring a new name.

Nevertheless, a continuing cautious approach to their use in serious uveitis where other means of treatment have failed would appear to be justified by the experience so far obtained with them.

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