

Treatment of Behçet's disease with chlorambucil

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Behçet's disease is more common and widespread than was previously thought, especially in the Middle East, the Mediterranean countries, and Japan (Abdalla and Bahgat, 1973). Loss of visual acuity is one of the most frequent, as well as the most serious, of its varied manifestations. Total blindness is often inevitable and the rate of deterioration of sight may be used as a criterion for assessing the effectiveness of any treatment (Mamo, 1970).

Various kinds of treatment have been tried, but with disappointing results. Corticosteroid therapy usually gives transient improvement, but does not modify the relentless course of the disease nor its final outcome. Heavy doses of corticosteroids have only a mild delaying effect upon the onset of blindness (Mamo and Azzam, 1970). Interest was therefore aroused by reports of improvement after therapy with immunosuppressive drugs, especially chlorambucil (Abdalla and Bahgat, 1973; Buckley and Gills, 1969; François and Van Oye, 1973; Godfrey, Epstein, O'Connor, Kimura, Hogan, and Nozik, 1974; Mamo and Azzam, 1970; Pezzi, 1972; Rosselet, Saudan, and Zenklusen, 1968; Smulders and Oosterhuis, 1975; Wong, 1969).

Material and methods

Five patients with Behçet's disease were followed-up during a period of 2 years. Each patient showed at least the triad of uveitis, genital and oral lesions. Table I shows the main clinical findings before treatment was started; Table II summarizes their ocular findings. All the patients were receiving systemic steroids and some were also having subconjunctival or retrobulbar injections of 40 mg methylprednisolone (Depot Medrol) and atropine drops locally. In spite of such treatment recurrences of symptoms became more frequent and vision gradually deteriorated.

Three daily doses of chlorambucil (Leukeran) 6 to 8 mg were taken after meals for 3 months and for a further 3 months 6 mg were given on alternate days (Perkins, 1974). In the meantime the corticosteroids were gradually discontinued. The patients were seen weekly for 2 months and then monthly. White blood cell and platelet counts were made weekly. If the total

white cell count falls below $3,500/\text{mm}^3$ or the platelet count below $100,000/\text{mm}^3$ the drug should be discontinued. In none of our patients was this necessary.

Two of the patients (Cases 1 and 3) had previously been treated with azathioprine for 6 months without any effect.

Results

In all patients there was a remission of the ocular lesions and other manifestations of the disease. This remission started within a few weeks of the addition of chlorambucil to the treatment. In all patients it was possible to reduce gradually and to stop completely the regimen of orally-administered corticosteroids 2 months after starting chlorambucil. The regimen of atropine and corticosteroid drops or injections locally was also discontinued 2 to 3 weeks after starting therapy with chlorambucil.

In all cases the uveitis quietened down and the flare and cells in the anterior chamber disappeared. Remission was obtained in all cases of posterior uveitis and neuroretinitis. The vascular sheathing of the retina remained stationary, and no further ocular damage was recorded. In none of our patients did vision deteriorate even in the two who were followed-up for 2 years. In some the visual acuity improved (Tables III and IV).

In two patients (Cases 1 and 2) there were mild recurrences of posterior uveitis 8 to 10 months after the treatment with chlorambucil had stopped, but the inflammation soon disappeared with a small dose of corticosteroids and another chlorambucil regimen for 3 months. All patients showed a definite improvement of aphthous oral lesions, skin lesions, thrombophlebitis, and other manifestations. There were occasional recurrences of mucocutaneous lesions in some cases, but these were milder and less numerous than before treatment with chlorambucil.

The drug was well tolerated in all patients except one who complained of a mild epigastric burning and fatigue.

Discussion

Cytotoxic drugs are administered in inflammatory disease of uncertain cause because of their immunosuppressive properties. These drugs interrupt nucleic acid and protein synthesis, thereby inhibiting various immune responses at different stages (Steinberg, Plotz, Wolff, Wong, Agus, and Decker, 1972). The chemotherapeutic activity of chloram-

Table I *Clinical findings*

Case no.	Sex	Age (yr)	Duration of disease (mth)	Ocular findings	Oral ulcers	Scrotal lesions	Erythema nodosum	Thrombophlebitis	Arthropathy	CNS involvement
1	Male	41	78	+	+	+	+	+	+	-
2	Male	38	71	+	+	+	+	+	+	+
3	Male	49	82	+	+	+	-	-	-	+
4	Male	29	62	+	+	+	+	-	+	-
5	Male	28	26	+	+	+	-	-	-	-

Table II *Main ocular findings before treatment*

Case no.	Eye	Iridocyclitis		Posterior uveitis	Posterior subcapsular cataract	Neuroretinitis	Vascular sheathing	Retinal haemorrhages	Visual acuity
		With hypopyon	Without hypopyon						
1	Right	-	+	+	+	+	+	+	0.1
	Left	-	+	+	-	+	+	+	0.4
2	Right	-	+	+	+	+	+	+	0.2
	Left	-	+	+	-	+	+	+	0.6
3	Right	+	-	+	+	+	+	+	CF
	Left	+	-	+	+	+	+	+	PL
4	Right	+	-	+	+	Fundus not seen			HM
	Left	+	-	+	+				
5	Right	-	+	+	-	+	+	+	0.5
	Left	-	+	+	-	+	+	+	0.8

CF = Counting fingers HM = Hand movements PL = Perception of light

bucil is attributed to the formation of electrophilic carbonium ions that alkylate or form covalent linkages with neutrophilic substances. The specific activity of chlorambucil is influenced by the electron-withdrawing capacity of the aromatic ring which reduces the rate of carbonium ion formation. This permits oral administration and distribution to sites of action, before it reacts with neutrophilic substances (Godfrey and others, 1974). Immunosuppressive drugs have been shown to be potentially useful adjuncts in the short-term therapy of ocular inflammation (Wong, 1969). Results of experimental studies with mercaptopurine in allergic uveitis in rabbits (Wirosko and Halbert, 1962) support this clinical finding.

There are several reports on the treatment of corticosteroid-resistant uveal tract inflammations with various immunosuppressive drugs. Clinically favourable results have been reported in some cases using azathioprine, methotrexate, and cyclophosphamide but in others no change was observed (Newell, Krill, and Thomson, 1966; Newell and Krill, 1967; Buckley and Gills, 1969; François and Van Oye, 1973; Godfrey and others, 1974; Laatikainen and Erkkida, 1974; Moore, 1968; Rosselet and others, 1968; Wong, 1969).

Favourable reports on chlorambucil in the treatment of Behçet's disease have been published recently (Abdalla and Bahgat, 1973; Godfrey and others, 1974; Mamo and Azzam, 1970; Pezzi, 1972; Smulders and Oosterhuis, 1975).

Our results confirm those of other authors, although the protocol in some studies was different. In our work there was no control group, each patient serving as his own control. The assessment of the effect of the drug was made individually by comparing the course of the disease before and after treatment.

As has been shown (Mamo, 1970), loss of visual acuity occurs on average after 3 to 6 years of onset of ocular symptoms. The steroids have only a mild delaying effect upon the rate of visual loss, so this information acts as a base line in the assessment of a new treatment.

All patients who were treated with chlorambucil in our study improved. They all had a long-lasting remission without serious toxic reactions or side-effects of the drug. Two patients suffered benign relapses of posterior uveitis 8 to 10 months after the treatment had been stopped.

In Behçet's disease the damage to the ocular tissues and especially to the retina is essentially

Table III Effect of treatment with chlorambucil and corticosteroids

Type of eye lesion	No. of cases	Remission	Partial improvement	No change	Deterioration
Iridocyclitis	5	3	2	0	0
Posterior uveitis	5	3	2	0	0
Neuroretinitis	4	2	2	0	0
Retinal vasculitis	4	0	0	4	0

Table IV Effect of treatment upon visual acuity

Case no.	Eye	Visual acuity		Duration of treatment (mth)
		Before treatment	During treatment	
1	Right	0.1	0.1	24
	Left	0.4	0.6	
2	Right	0.2	0.2	23
	Left	0.6	0.6	
3	Right	CF	0.1	18
	Left	PL	PL	
4	Right	HM	HM	14
	Left	PL	PL	
5	Right	0.5	0.8	10
	Left	0.8	1.0	

CF = Counting fingers HM = Hand movements PL = Perception of light

irreversible, so that a complete cure is impossible. The utmost that can be hoped for is arrest of the disease. Thus far, it seems that this goal may have been attained, although a much longer follow-up period is needed.

Summary

Five patients with Behçet's disease in the active

and progressive stages were treated with chlorambucil (Leukeran). In all patients a long-lasting remission was obtained, the ocular lesions did not progress and the vision did not deteriorate. Follow-up varied between 10 and 24 months. Results were encouraging and the form of treatment with chlorambucil and small doses of corticosteroids was superior to other forms of therapy.

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