Steroid responsiveness in connective tissue diseases

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SUMMARY Thirty-four patients with connective tissue diseases used dexamethasone drops 0.1% in one eye for 6 weeks. There was a higher incidence of positive steroid response than would be expected in a normal population. Most of the male patients were responders. Care should be exercised when prescribing local steroids for these patients. Males should be offered regular screening for glaucoma.

Eye involvement is a prominent feature of connective tissue diseases (CTD). Keratoconjunctivitis sicca (KCS) is the commonest complication, occurring in 11% of patients with rheumatoid arthritis (RA)¹ and sporadically in systemic lupus erythematosus (SLE), progressive systemic sclerosis (PSS), polymyositis, and psoriatic arthritis. Scleritis appears in 0.67% of RA patients and in other cases of CTD (e.g., ankylosing spondylitis and Behçet's disease) from time to time. Uveitis is of particular importance in juvenile rheumatoid arthritis, ankylosing spondylitis, and Reiter's syndrome. Conjunctivitis is one of the diagnostic criteria for Reiter's syndrome. Proptosis, diplopia due to extraocular myopathy, corneal disturbances, optic neuritis, and retinal vascular changes may occur in SLE and lid shortening and iris atrophy in PSS. Discolouration and oedema of the lids and extraocular muscle changes occur in polymyositis and dermatomyositis and retinal vasculitis in up to 20% of patients with polyarteritis nodosa.

The large host of ocular phenomena that are reported make it unlikely that the trabecular meshwork is exempt from autoimmune inflammatory processes, though glaucoma is not a recognised complication of CTD.

The intertrabecular spaces of the 'pore' area of the trabecular meshwork are lined by a layer of mucopolysaccharide.² If this layer is removed by hyaluronidase, resistance to aqueous outflow falls. Topical steroids increase outflow resistance. This may be due to increased production of mucopolysaccharide

from mast cells or to swelling of the mucopolysaccharide layer because of increased water binding capacity. Trapping of greater amounts of mucopolysaccharide by degenerate trabecular meshwork accounts for the increased dexamethasone effect on glaucomatous eyes.

The pressure response to steroids has been widely studied. Local steroids (dexamethasone or betamethasone) are instilled 4 times daily for 6 weeks. 4-5% of the normal population show a dramatic rise in intraocular pressure (IOP).^{3,4} Almost all individuals with primary open-angle glaucoma show a dramatic response to steroids.⁵ On the basis of genetic and family studies it has been postulated that a dramatic response to steroids identifies a predisposition to develop open-angle glaucoma.^{3,5} A positive corticosteroid provocative test is the result of trabecular damage.⁶

Following the observation of one of us (M.J.A.) that some patients with CTD showed a marked rise in IOP when treated with local steroids we felt that corticosteroid provocative testing might be used to determine whether patients with CTD do sustain damage to their trabecular meshwork.

Patients and methods

Thirty-four patients (11 male, 23 female) with connective tissue diseases (mainly RA) were entered in the study (Table 1). Patients with diabetes mellitus, thyroid disease, high myopia, a family history of glaucoma, Krukenberg's spindle, IOP greater than 22 mmHg at the start of the study, or other signs of

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Table 1 Data of 34 patients

Patient	Age	Sex	Diagnosis	HLA type				Response to steroids
1.	63	F	RA	A1	A25	B8	B18	None
2.	41	M	Seronegative polyarthritis					Dramatic
3.	50	F	Seronegative polyarthritis	A1	A35	BW44	B15	None
4.	61	F	Polyarthritis	A3	AW24	B8	B13	Intermediate
5.	64	M	RA	A3	A11	B7	B27	Intermediate
6.	59	F	RA	A2	A28	B27	BW48	None
7.	49	F	?SLE	A1	A11	B8	BW35	None
8.	65	F	Primary biliary cirrhosis/psoratic arthropathy	A2	AW31	BW44	BW35	None
9.	61	F	RA	A1	A3	B8	B40	None
10.	64	M	Seronegative polyarthritis	A2	AW32	B8	B18	Intermediate
11.	43	M	RA	A2	A28	B8	BW44	Intermediate
12.	53	M	RA	A2	A28	B8	BW44	Dramatic
13.	59	M	RA	A1	A26	B8	B27	None
14.	53	F	RA	A2		B40		None
15.	71	M	RA/ankylosing spondylitis	A11	AW24	B7	B27	Dramatic
16.	63	M	RA	A1	A11	B8	BW55	Dramatic
17.	61	F	RA	A3	A28	BW44	BW35	Intermediate
18.	57	F	RA	A2	AW24	B7	B27	None
19.	63	F	Polyarthritis	A3	A28	B27	BW35	None
20.	64	F	Seronegative polyarthritis	A1	AW31	B8	B27	None
21.	60	F	RA	A1	A26	B8	B27	None
22.	67	F	RA	A28		B5	B18	None
23.	55	M	RA	A2	A11		BW44	Dramatic
24.	35	F	RA		A28	B15	B40	None
25.	64	F	RA	A1	A3	B13	BW49	None
26.	20	F	RA	A1	A2	B8	BW44	None
27.	48	F	RA	A3	AW32	B14	B15	None
28.	69	F	RA	A11		B17	BW22	None
29.	78	F	RA	A2	A11	B5	BW44	None
30.	54	M	Seronegative polyarthritis	A1	A3	B8	B14	None
31.	61	F	RA	A2	AW31	BW44	BW49	None
32.	73	M	RA	A1	A3	B8	BW35	Intermediate
33.	53	F	RA	A2	AW30	B13	BW50	None
34.	54	F	RA	A2	AW32	B40	BUSV	Intermediate

glaucoma were excluded, as were those currently taking systemic steroids.

Visual acuity determination, direct ophthalmoscopy, slit-lamp microscopy, and applanation tonometry were performed on both eyes at the first visit. Patients were asked to instill dexamethasone drops 0.1% in the right eye (RE) 4 times daily for 6 weeks. Both eyes were re-examined 3 and 6 weeks later at the same time of day. The same tonometer was used at each visit. All measurements were performed by one observer (H.G.). Patients were asked to reattend if they experienced discomfort, blurring, or haloes. The trial was discontinued immediately a dramatic rise in IOP occurred. Full HLA typing was carried out on all patients.

We classified patients' response to dexamethasone as follows: (1) dramatic: a rise in IOP (RE) to 32

mmHg or more; (2) intermediate: IOP (RE) at 6 weeks between 25 and 31 mmHg; (3) nonresponse: IOP (RE) at 6 weeks 24 mmHg or less. The pressures in the left eye acted as a control to ensure that changes in IOP (RE) were due to dexamethasone alone.

Results (Table 2)

Five patients (15% of the total) were dramatic responders. They were all male. Seven patients (20%) were intermediate responders; 4 (57%) were male and 3 were female. Twenty-two patients (65%) were nonresponders; 2 (9%) were male and 20 were female.

There was no correlation between the steroid responsiveness of the patients and their ESR, sheep cell agglutination titre, or the duration of their

Table 2 Steroid response of 34 patients with connective tissue disease

	Nonresponders		Intermediate		Dramatic		Total	
	No.	%	No.	%	No.	%	No.	%
Male	2	9	4	57	5	100	11	32
Female	20	91	3	43	0	0	23	68
Total	22	100	7	100	5	100	34	100

disease. The HLA types of the 34 patients did not differ significantly from those of a normal control panel.

The chi-square test⁷ was used to show that the percentage of dramatic responders in the patient group (15%) was significantly greater than that in normal population studies (4%³–5%⁴): $\chi^2=6.04$, DF=1, $p<0.02$. The test for trend in proportions⁸ was used to show that with increasing response to steroids there was an increasing proportion of males: $\chi^2_T=17.84$, DF=1, $p<0.001$.

Discussion

Bernstein and Schwartz⁹ found that 48 patients taking oral steroids for RA, skin diseases, and collagen diseases had a higher IOP than age- and sex-matched controls not taking steroids. They attributed this to the effect of systemic steroids, but none of the controls had RA or collagen diseases. In contrast Belousna¹⁰ found that 60 patients taking systemic steroids for collagen diseases had a lower IOP than normal. No studies have been reported on the IOP of patients with collagen diseases who were not taking systemic steroids.

Becker³ and Armaly⁴ have shown that 4–5% of the normal population show a dramatic response to local steroids, and they appear to be more at risk of developing open-angle glaucoma. 15% of our patients had a dramatic response to steroids, which is a significant difference. We used similar methods and entry criteria to their studies so that our figures and theirs should be roughly comparable. The use of age- and sex-matched controls, though theoretically desirable, would have exposed more individuals to the inherent risks of local steroids.

Five of our patients were dramatic responders. They were all male. One had seronegative polyarthritis. The other 4 had rheumatoid arthritis. One of these (patient 15) had both RA (typical clinical changes in, for instance, the hands and sheep cell agglutination test (SCAT) positive) and ankylosing spondylitis (stiff back, bilateral erosive changes in the sacroiliac joints, HLA B27 positive). This is a combination which is rare but has been described.^{11 12} He did not have rheumatoid nodules, but the

peripheral arthritis of ankylosing spondylitis is not associated with rheumatoid factor.

Seven of our patients were intermediate responders, and 4 (57%) of these were males. Five had RA; the other 2 had negative or insignificant SCAT titres.

The remaining 22 patients were nonresponders. Only 2 (9%) of these were male.

Thus there was a striking trend for dramatic or intermediate response in the males with CTD, whereas a sex difference in steroid responsiveness has not been recorded in the other studies.

We conclude that damage to the trabecular meshwork may be yet another possible ocular complication of CTD, and glaucoma may result from it. Certainly local steroids should be given with great circumspection in males with CTD, as they are likely to develop ocular hypertension after a few weeks' treatment. This is particularly relevant because many of the other ocular complications of CTD are treated with steroids.

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