Eosinophilia in D-penicillamine therapy

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SUMMARY Cross-sectional and longitudinal studies have been carried out to determine the incidence and clinical significance of eosinophilia in patients taking penicillamine for rheumatoid arthritis. In a cross-sectional study of 204 patients eosinophilia was found with equal frequency during treatment with penicillamine, gold, and nonsteroidal anti-inflammatory drugs. A longitudinal study of 89 patients treated with penicillamine showed no consistent relationship between eosinophilia and adverse reactions to the drug. It is concluded that routine monitoring of eosinophil counts is unlikely to be of value in the management of patients taking penicillamine.

Eosinophilia is considered to be a frequent finding in patients with rheumatoid arthritis (RA).¹ It has been related to severe disease with nodules, extra-articular manifestations, and immunological changes,^{2,3} although not all studies support this view.⁴

Davis and Hughes⁵ studied the relationship of eosinophilia to gold therapy and suggested that there was an important association between an eosinophilia and the development of adverse reactions, especially cutaneous. Their results imply that sequential eosinophil counts might be useful when monitoring gold therapy. In contrast Jessop *et al.*⁶ found this relationship to be less clear. Nevertheless a number of centres routinely monitor eosinophil counts during gold therapy.

Eosinophilia has been observed in patients treated with penicillamine,^{7,8} but its clinical importance has not been clearly determined. The case notes of 25 patients attending rheumatology clinics in Coventry between 1974 and 1980 and whose penicillamine therapy was discontinued were studied. In a few patients there appeared to be a temporal relationship between the development of an adverse reaction and eosinophilia (Table 1). We now report cross-sectional and longitudinal studies to establish the relationship of eosinophilia to penicillamine therapy and to determine its frequency and significance.

Patients and methods

In a cross-sectional survey the total and differential white cell count was measured in 204 consecutive

Table 1 Review of 25 patients in whom penicillamine therapy was stopped

Indication for stopping therapy	Number of patients	Number with an eosinophilia within 1 month of adverse reaction
Mouth ulcers	5	1
Haematuria	4	2
Dyspepsia	2	0
Rash	1	0
Myopathy	1	1
Myasthenia	1	0
Vasculitis	1	1
Renal impairment	1	0
Proteinuria	1	0
Thrombocytopenia	1	0
Neutrophilia	1	0
No benefit or poor compliance	6	—

patients with definite or classical RA (by the criteria of the American Rheumatism Association) attending rheumatology outpatient clinics in Coventry and Birmingham. Details of drug therapy were recorded.

In a longitudinal study 89 patients currently attending a rheumatology clinic in Coventry and receiving penicillamine were reviewed. All had definite or classical RA. The results of full blood counts, total white cell counts, and platelet and differential white cell counts prior to the start of treatment with penicillamine, and at 2- or 4-weekly intervals during treatment, were noted, together with the results of urine examination for blood and protein on the same occasions. All patients were questioned at each attendance about adverse reactions. Penicillamine

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Table 2 Incidence of eosinophilia in cross-sectional study

Drug therapy	Penicillamine	Gold	Sulphasalazine	Dapsone	NSAID alone
Number of patients	63	64	18	3	56
Number with eosinophilia	9 (14%)	7 (11%)	2 (11%)	2 (66%)	5 (8.9%)
Mean eosinophil count (range) $\times 10^9/l$ in patients with eosinophilia	0.63 (0.43–0.85)	0.59 (0.41–0.88)	0.70 (0.60–0.80)	0.85 (0.60–1.1)	0.74 (0.44–1.63)

Table 3 Adverse occurring within 1 month of an eosinophilia during longitudinal study

Type of reaction	Number	M/F ratio	Further details	(Number of patients)	Mean duration of therapy in months (range)	Outcome of therapy	(Number of patients)
Cutaneous	10	5:5	Eczematous	(8)	10	Continued	(5)
			Erythematous	(1)	(1–36)	Suspended*	(5)
			Perniosis	(1)		Stopped	(0)
Urinary	4	4:0	Haematuria	(3)	11	Continued	(0)
			Proteinuria	(1)	(6–16)	Suspended*	(3)
						Stopped	(1)
Haematological	4	1:3	Thrombocytopenia	(4)	12	Continued	(0)
					(1–30)	Suspended*	(4)
						Stopped	(0)

*Treatment discontinued but later resumed.

dosage ranged from 125 to 750 mg daily, in accordance with a flexible response-related regimen.⁹

Blood counts, including total white cell counts, were measured by a Coulter Counter Senior. Differential white cell counts and platelet counts were performed manually by standard laboratory methods.¹⁰ An eosinophilia was defined for the purposes of this study as a total eosinophil count of greater than $0.4 \times 10^9/l$.

Results

An eosinophilia was present in 12% of the 204 patients in the cross-sectional study. The eosinophil counts in these patients ranged from 0.41 to $1.63 \times 10^9/l$. Eosinophilia was as common in patients taking nonsteroidal anti-inflammatory drugs alone as in patients taking gold or penicillamine in addition (Table 2). A comparison of patients taking penicillamine with those taking nonsteroidal anti-inflammatory drugs alone showed no significant differences either in the numbers of patients with an eosinophilia ($\chi^2 = 2.2$, DF = 1, $p > 0.10$) or in the eosinophil counts themselves ($t = -0.33$, $p > 0.10$). The other groups of patients gave similar comparisons.

In the longitudinal study 47 patients out of 89 (53%) developed an eosinophilia on one or more occasions during penicillamine therapy. There were

no differences in age or sex between those patients who developed an eosinophilia and those who did not, nor was there a difference in the number of patients who had previously received gold. Eighteen of the patients had an adverse reaction within 1 month of developing an eosinophilia, and details are given in Table 3. Penicillamine therapy was continued unchanged in 5 patients, suspended and thereafter restarted at a lower dose in 12 patients, and stopped in only 1 patient. There was no indication that the development of an eosinophilia heralded the onset of a severe adverse reaction.

Discussion

Our results confirm that eosinophilia is common during penicillamine therapy. It occurs with equal frequency in patients taking gold or nonsteroidal anti-inflammatory drugs alone and is therefore not specific to penicillamine.

Eosinophilia occurred in association with adverse reactions in some patients included in the longitudinal study, but this was not invariable. Such adverse reactions were generally mild and the drug was continued or resumed after a suspension of treatment in all but one case.

The review of 25 patients who had stopped penicillamine (Table 1) showed that in 5 patients a serious

adverse reaction was preceded by an eosinophilia. However, further analysis qualifies this finding. One of these patients had developed repeated episodes of eosinophilia over several years, including an episode prior to penicillamine therapy. Another patient developed eosinophilia in association with cutaneous vasculitis and high titres of circulating immune complexes, suggesting that a change in the disease process³ rather than a drug reaction was involved.

We conclude that eosinophilia is common during penicillamine therapy and other forms of drug treatment for RA. There is no evidence that eosinophilia presages adverse reactions to penicillamine, and routine monitoring of eosinophil counts is unlikely to be of clinical value in the management of patients taking this drug.

References

- 1 Short C L, Bauer W, Reynolds W E. *Rheumatoid arthritis*. Cambridge, Massachusetts: Harvard University Press, 1957.
- 2 Winchester R J, Litwin S D, Koffler D, Kunkel H G. Observations on the eosinophilia of certain patients with rheumatoid arthritis. *Arthritis Rheum* 1971; **14**: 650-65.
- 3 Panush R S, Franco A E, Schur P H. Rheumatoid arthritis associated with eosinophilia. *Ann Intern Med* 1971; **75**: 199-205.
- 4 Sylvester R A, Pinals R S. Eosinophilia in rheumatoid arthritis. *Ann Allergy* 1970; **28**: 565-8.
- 5 Davis P, Hughes G R V. Significance of eosinophilia during gold therapy. *Arthritis Rheum* 1974; **17**: 964-8.
- 6 Jessop J D, Dippy J, Turnbull A, Bright M. Eosinophilia during gold therapy. *Rheumatol Rehabil* 1974; **13**: 75-9.
- 7 Jaffe I A. The effect of penicillamine on the laboratory parameters in rheumatoid arthritis. *Arthritis Rheum* 1965; **8**: 1064-79.
- 8 Camus J P, Crouzet J, Guillien P, Benichou C, Lievre J-A. Cent cas de polyarthrite rhumatoïde commune traités par la D-pénicillamine. *Ann Med Interne (Paris)* 1974; **125**: 9-28.
- 9 Hill H F H, Hill A G S, Day A T, Brown R M, Golding J R, Lyle W H. Maintenance dose of penicillamine in rheumatoid arthritis: a comparison between a standard and a response-related flexible regime. *Ann Rheum Dis* 1979; **38**: 429-33.
- 10 Dacie J V, Lewis S M. *Practical haematology*. London: Churchill Livingstone, 1975.