The Influence of Drug Therapy on Serum Immunoglobulin Profiles in Rheumatoid Arthritis

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Changes in the immunoglobulin levels in patients with rheumatoid arthritis receiving penicillamine have been measured by various authors (Zuckner *et al.* 1970, Bluestone & Goldberg 1973, Berry & Huskisson 1974). Correlation of immunoglobulin levels with drug action (Bluestone & Goldberg 1973) and disease activity (Zuckner *et al.* 1970, Berry & Huskisson 1974) have been attempted, but the results have been equivocal. Our studies would indicate that this is because the genetic control of the individual patient's immunoglobulin levels has not been considered.

The levels of immunoglobulin in any individual represent the balance of a dynamic equilibrium between synthetic and catabolic rates and the distribution between vascular and extravascular pools. In addition, there are numerous factors, both environmental and hereditary, which influence the actual levels so that they vary from one individual to another.

In normal health the plasma IgG, IgA and IgM concentrations are essentially constant and almost certainly phenotypic for the individual. Variations occur as changes around a median plasma concentration (Pettingale & Watkins 1973). Even in chronic disease states the relative proportions of IgG, IgA and IgM are maintained and the levels remain 'in phase' (Watkins *et al.* 1976).

Our previously reported data on immunoglobulin levels (Watkins *et al.* 1976), measured on a random group of 104 patients with rheumatoid arthritis receiving various types of therapy and with varying degrees of disease activity, indicated that only half the patients had significantly raised immunoglobulin levels (Table 1). This latter group we have come to regard as 'collagenosis-type' for diagnostic purposes. In general the 'collagenosis-type' patients showed more obvious fluctuations in their immunoglobulins, particularly IgA, than the other rheumatoid arthritic patients who had 'normal' immunoglobulin levels.

Table 1

Immunoglobulin levels in 104 random patients with rheumatoid arthritis

	No. of patients	*Seropositive*	*Seronegative*
Immunoglobulin levels normal	50	32	18
IgG alone raised	20	11	9
IgA alone raised	19	16	3
IgA, IgG and/or IgM raised	15	13	2

In order to discover whether penicillamine affected the immunoglobulin levels of patients with rheumatoid arthritis a small study was undertaken to compare the immunoglobulin status of penicillamine-treated patients with those receiving nonsteroidal anti-inflammatory agents alone.

A total of 30 patients diagnosed as suffering from rheumatoid arthritis by the American Rheumatism Association criteria (Ropes *et al.* 1958) were studied. Thirteen were receiving penicillamine and 17 were receiving nonsteroidal anti-inflammatory agents. Blood samples were taken at the start of the penicillamine therapy and at intervals of three to four weeks during treatment. The dosage of penicillamine was 125 mg daily for the first month, increased by 125 mg daily at monthly intervals, until therapeutic control occurred or a daily dose of 750 mg was reached. All patients were followed for periods in excess of three months. Measurements in the group receiving nonsteroidal anti-inflammatory agents were made at similar time intervals.

The levels of immunoglobulins IgG, IgA and IgM were measured in serum by automated immunoprecipitin technique using a Technicon Autoanalyzer System II. Rheumatoid factor titres were measured using the standardized hæmagglutination test kits supplied by Fujizoki, Japan. The normal ranges for immunoglobulins are those established at the Protein Reference Unit, Hallamshire Hospital, Sheffield (IgG 5.0–16.0 g/l, IgA 1.0–4.0 g/l, IgM 0.5–1.7 g/l).

The distribution of patients with 'normal' and those with 'collagenosis-type' levels of immunoglobulin in this smaller series of patients seemed to resemble the distribution found in our earlier random sample series of 104 patients (Table 2).

Although 'normal range' patients showed some elevation of their immunoglobulin levels in active disease, the protein levels nevertheless remained within the normal range and 'in phase'. Indeed, a number of these patients had immunoglobulin levels, particularly IgA, which were low.

Table 2

Distribution of patients in present series

	No. of patients	*Sero-positive*	*Sero-negative*
Normal profiles			
Immunoglobulin levels normal at all times	12	8	4
'Normal' but IgG elevated in active disease	6	4	2
Total	18	12	6
Collagenosis-type profiles			
IgG alone raised	2	1	1
IgA alone raised	8	7	1
IgA, IgG and/or IgM raised	2	2	0
Total	12	10	2

Table 3

Changes in clinical activity after three months

	Total patients	*Unchanged or worse*	*Improved*	*Much improved*
Normal immunoglobulin profiles	18(5)	4(2)	6(3)	8
Collagenosis-type profiles	12(8)	8(6)	2(2)	2

Parentheses indicate penicillamine-treated patients

Most of the patients with normal levels were either seronegative or had low titres of rheumatoid factor irrespective of disease activity.

Among the 'collagenosis-type' patients a significantly raised IgA with levels of 6.0–8.0 g/l was a frequent observation. These patients exhibited high rheumatoid factor titres and, unlike the normal patients, showed good correlations between IgA level, rheumatoid factor titre and clinical activity. The reason why IgA should be so elevated is obscure, but has been previously reported (Vey & Claessens 1968). Whether IgA levels correlate with disease activity in rheumatoid arthritis is at present not clear according to Farr *et al.* (1976), who have suggested that C-reactive protein most accurately reflects disease activity.

A clinical grading based on articular index and functional state strongly indicated a better response from the patients exhibiting 'normal' rather than 'collagenosis-type' immunoglobulin profiles, irrespective of variations in the mean immunoglobulin levels (Table 3). This difference in response between the 'normal' and the 'collagenosis-type' of immunoglobulin profile seemed also to be independent of the type of drug therapy (Table 3).

In our experience only patients exhibiting 'collagenosis-type' immunoglobulin profiles show significant level changes apparently correlating with changes in clinical activity. These changes are of course not limited to patients on penicillamine therapy (Watkins *et al.* 1976), and conclusions about the immunosuppressive action of penicillamine based on measurement of immunoglobulin changes in patients with rheumatoid arthritis must be treated with caution.

REFERENCES

Berry H & Huskisson E C
(1974) *Postgraduate Medical Journal* **50**, August Suppl., p 61
Bluestone R & Goldberg L S
(1973) *Annals of the Rheumatic Diseases* **32**, 50
Farr M, Kendall M J, Young D W, Meynell M J & Hawkins C F
(1976) *Annals of the Rheumatic Diseases* **35**, 163
Pettingale K W & Watkins J
(1973) In: Protides of the Biological Fluids. Ed H Peeters. Pergamon Press, Oxford; p 267
Ropes M W, Bennet G A, Cobb S, Jacox R & Jessar R A
(1958) *Bulletin on Rheumatic Diseases* **9**, 175
Vey E M & Claessens H E
(1968) *Annals of the Rheumatic Diseases* **27**, 431
Watkins J, Milford Ward A, White P A E & Swannell A J
(1976) In: Protides of the Biological Fluids. Ed. H Peeters. Pergamon Press, Oxford; p 455
Zuckner J, Ramsay R H, Dorner R W & Gantner G E
(1970) *Arthritis and Rheumatism* **13**, 131