Prediction of progressive joint damage in patients with rheumatoid arthritis receiving gold or D-penicillamine therapy

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SUMMARY   Seventy two patients with classical or definite rheumatoid arthritis (RA) were randomly allocated to receive gold or D-penicillamine therapy (DPA) in a prospective study designed to evaluate whether it is possible to predict which patients will show radiological progression despite therapy. Forty five patients completed 12 months' treatment. There were no significant demographic or clinical differences between them and the 27 drop outs. Twenty of the 45 patients showed no radiological progression between six and 12 months. These patients had less severe initial radiological damage, lower levels of serum aspartate transaminase (serum AST) and lactic dehydrogenase (LDH), but higher levels of serum cholesterol. Twenty five patients did show progression during the six to 12 month period. This group included all the men with nodules. Of the 43 pretreatment clinical and laboratory variables examined, however, the majority failed to predict whether or not progression would subsequently occur. This included the acute phase response and seropositivity.

Key words: radiological progression, SAARD therapy, serum AST, lactic dehydrogenase, cholesterol, nodules.

Rheumatoid arthritis runs a variable course with frequent exacerbations and remissions. Clinical and laboratory evidence of disease activity relate to progressive joint damage.[1–3] Although it is accepted that slow acting antirheumatic drugs (SAARDs) improve laboratory and clinical features of disease, it is not accepted that they may decrease the rate of radiological progression.[4 5] We have previously demonstrated that a group of patients with RA receiving SAARDs showed progressive radiological damage throughout the first 12 months of therapy but that a subgroup who achieved a good response to therapy at six months, maintained at 12 months, had less deterioration.[6 7] SAARD therapy is potentially toxic, so the risk-benefit ratio has to be estimated by the clinician for each individual patient. If, by definition of prognostic features, we

could identify patients whose disease is most likely to become well controlled we could improve this ratio. Furthermore, advanced recognition of poor prognostic features would indicate patients in whom more aggressive[8] or combination therapy[9] should be considered initially.

We have studied patients with active RA requiring gold or DPA therapy and grouped those completing 12 months' treatment according to the radiological progression during the six to 12 month period. Pretreatment characteristics of the groups have been compared in an attempt to identify any predictors of radiological response.

Patients and methods

PATIENTS
Seventy two patients with classical or definite RA (American Rheumatism Association (ARA) criteria) attending the Staffordshire Rheumatology Centre were randomly allocated to receive treatment with

gold or DPA. Exclusion criteria included administration of a SAARD within the previous three months and pregnancy. Admission criteria were failure to respond to non-steroidal anti-inflammatory drugs or antimalarial drugs and/or progression of disease as shown by increasing clinical, laboratory, or radiological features of disease. Mandatory entry criteria were (a) more than six painful joints and (b) erythrocyte sedimentation rate (ESR)>30 mm/1st h or C reactive protein>20 mg/l, or both. A standard dosage regimen for gold and DPA was used. Gold was started at 50 mg/week for 20 weeks and then 50 mg/2 weeks; DPA was started at 250 mg/day for one month, then 375 mg/day, and increased by not more than 125 mg/day each month thereafter according to response to a maximum of 750 mg/day. All the patients could have completed 12 months' therapy and 45 did so. The reason for withdrawal in the 27 drop outs is shown in Table 1. They appeared to have more severe disease initially, though only the ESR reached significance (Table 2).

CLINICAL MEASURES
Details recorded at initial examination included length of history, presence of nodules, and ARA criteria. Disease activity was assessed by clinical metrologists at the start of therapy. Functional assessment was on the Steinbrocker 1 to 5 scale. The number of painful joints was recorded (maximum 28), and the tenderness of each joint group was measured by the method of Ritchie with a maximum possible score of 84. A limited Ritchie index confined to the proximal interphalangeal (PIP) metacarpophalangeal (MCP), wrist, and metatarsophalangeal (MTP) joints was recorded with a maximum possible score of 24. Visual analogue pain score (VAS) was recorded on a 10 cm horizontal line and recorded in millimetres from no pain. Morning stiffness was recorded in minutes to a maximum of 720 min. Grip strength was measured by the standard technique. Synovial thickening was estimated for each finger PIP joint and thumb IP joint on a four point scale (maximum score 30).

LABORATORY MEASUREMENTS
Morning samples were taken the day treatment started. Routine haematology, biochemistry (SMAC), ESR (Westergren), C reactive protein (CRP), and antinuclear antibody estimations were carried out. Rheumatoid factor was assessed by a standard agglutination test (Ortho RA test). IgG and IgM rheumatoid factor (enzyme linked immunosorbent assay (ELISA)), immunoglobulins, and α_1 antitrypsin measurements were performed on sera stored at −70°C.

RADIOLOGICAL MEASUREMENTS
Hand and feet radiographs were taken before treatment and at six and 12 months. They were read 'blind' by a single observer and scored using the standard radiographs of Larsen *et al*.[10] Patients were subgrouped into two according to the change in the Larsen score during the six to 12 month period: group I having a maximum score increase of one group II having a score increase of more than one.

STATISTICS
Analysis of results between groups was by analysis of variance when the variables were normally distributed. Between group analysis for variables not normally distributed was by the Mann-Whitney U test. Comparison between groups was also made by the χ^2 test and Fisher's exact test when appropriate. As 43 variables were compared there is a risk of a type I error and therefore only a p value of less than 0·02 was regarded as significant.

Results

RADIOLOGICAL
Patients were divided into two groups as described Group I patients had a significantly lower Larsen

Table 1 *Reason for withdrawal in the 27 patients not completing 12 months' therapy*

	Gold	D-*Penicillamine*
Adverse reaction	13	5
Deteriorating disease	1	3
Non-compliance	2	3

Table 2 *Comparison of pretreatment results for patients completing 12 months' therapy and withdrawals*

	12 Month Completers	Non-completers	p Value
No	45	27	
Mean age (years)	54·4	56·6	0·19
No of men	24 (53%)	12 (44%)	0·62
Mean length of history (months)	74·2	81	0·29
No seropositive (1/80)	28 (62%)	21 (77%)	0·26
No with nodules	16 (35%)	11 (40%)	0·85
Median hand and feet x ray score (Larsen)	64	64	0·07
Median Ritchie index	16	18	0·21
Median morning stiffness (min)	120	170	0·31
Mean C reactive protein (mg/l)	70·1	88·3	0·06
Mean ESR (mm/1st h)	67·8	81·1	0·03

Table 3 *The Larsen index score for group I and II patients at 0, 6, and 12 months and the mean change*

	Group I (n=20)	95% Confidence limits	Group II (n=25)	95% Confidence limits	p Value
Mean Larsen index (0 months)	49·1	8·1	62·8	8·5	0·01
Mean Larsen index (6 months)	54	8·8	67·4	9·1	0·02
Mean change (6–0)	+4·9	1·2	+4·6	1·4	0·7
Mean Larsen index (12 months)	53·6	8·9	71·6	9·6	0·004
Mean change (12–6)	−0·4	0·6	+4·2	1·0	0·009

Table 4 *Comparison of pretreatment clinical variables*

	Group I (n=20)	95% Confidence limits	Group II (n=25)	95% Confidence limits	p Value
Gold:DPA	9:11		12:13		
Mean age (years)	52·3	5·4	56·2	3·8	0·24
Mean length of history (months)	62	20·6	84	21·2	0·09
No of men	8		16		0·14
No with nodules	4		12		0·045
Mean ARA criteria	6·9	0·33	7·1	0·27	0·16
Mean Steinbrocker scale	2·15	0·29	2·0	0·3	0·3
Mean No of painful joints	9·7	2·1	11·0	2·4	0·42
Mean VAS pain score (mm)	57·4	9·4	56·4	9·8	0·89
Mean morning stiffness (min)	161	89	81	27	0·07
Mean grip strength (mmHg)	125	25	123	21	0·92
Mean Ritchie articular index	14·5	3·5	17·2	4·1	0·33
Mean Ritchie index (hands and feet only)	5·7	1·7	6·2	1·3	0·69
Mean PIP synovitis score	9·4	2·5	11·2	3·1	0·4

Table 5 *Comparison of pretreatment variables*

	Group I (n=20)	95% Confidence limits	Group II (n=25)	95% Confidence limits	p Value
Mean values					
Haemoglobin (g/dl)*	11·4	0·61	11·5	0·51	0·91
Platelets×10^{-9}/l	532	53	505	53	0·49
ESR (mm/1st h)	62	11	73	10	0·18
C reactive protein (mg/l)	62	12	77	17	0·19
α_1 Antitrypsin (U/l)	214	27	185	19	0·08
Albumin (g/l)	39·1	1·1	37·6	1·1	0·08
Globulin (g/l)	37·7	2·7	41·0	2·4	0·08
Alkaline phosphatase (U/l)	118	14	127	17	0·47
Serum AST (U/l)	11·7	1·7	15·3	1·9	0·01
Lactic dehydrogenase (U/l)	192	15	235	23	0·005
Cholesterol (mmol/l)	5·1	0·4	4·5	0·23	0·008
IgM rheumatoid factor (ELISA U/l)	0·47	0·19	0·45	0·16	0·49
IgG rheumatoid factor (ELISA, U/l)	0·66	0·17	0·61	0·12	0·6
No of patients					
Seropositive (Titre ⩾ 1/80)	12		16		0·97
ANF positive† (Titre ⩾ 1/32)	8		8		0·29

* SI conversion: haemoglobin g/dl×10=g/l.
† ANF=antinuclear factor.
Total differential white cell count (neutrophils, lymphocytes, monocytes, eosinophils), blood creatinine, urea, γ-glutamyltransferase, conjugated and unconjugated bilirubin and uric acid, IgA, IgM, and IgG were also analysed and showed minimal differences between the two groups — the lowest p value being >0·21. The median RA factor titre (1/160) and ANF titre (1/80) was the same in each group.

score before the start of treatment (Table 3). Both groups showed progressive changes during the first six months of therapy, and the rate of change was similar. During the second six months no significant deterioration occurred in group I and the mean score in group II increased by 4·2.

CLINICAL

The number of patients having gold and DPA was similar in the two groups. Of the 13 clinical variables analysed (Table 4) on subgroup analysis, one feature, men with nodules, showed a significant relation with the x ray progression (p=0·017).

LABORATORY

Comparison between the groups was made for all the haematological, biochemical, acute phase response, and immunological features. These are shown in Table 5. The only differences established were significantly higher mean levels of serum AST and LDH in group II and cholesterol in group I. In particular, there was no relation between outcome and (a) seropositivity by the titre and the ELISA technique; (b) levels of immunoglobulin; (c) clinical variables such as morning stiffness and the degree of joint swelling and pain; and (d) the initial acute phase response.

Discussion

There is disagreement about the effect of SAARD therapy on the rate of radiological progression.[4 5 11] RA is not a static disease,[12] and the different opinions may be because SAARDs are effective only in certain phases. Furthermore, RA is a heterogeneous disease, in which subgroups may show differing responses. One feature may be the presence of rheumatoid factor,[13] which has been related to the pattern of radiological progression.[14 15] Patients with low levels of ESR and CRP, irrespective of therapy, have less radiological progression.[3]

All the patients in our study had failed to respond to various treatments and were showing progression of disease so that, by definition, patients with early disease or minimal radiological damage were unlikely to be included. A high proportion did not continue treatment and so did not have the appropriate 12 month radiological examination. Their progress could thus not be compared with those who completed.

All our patients had high ESR or CRP levels, or both, at the outset of the study, and it was therefore expected that without adequate disease control they would continue to show progression of the radiological changes. Despite the problem in scoring routine x rays[16] we were able to define two groups —those who did and those who did not show progression in the six to 12 month period of treatment.

Previous studies have shown that high seropositivity and nodule formation are bad prognostic pointers[17] particularly in early disease.[18] We had hoped to recognise other prognostic features, particularly in relation to progression of radiological changes. We found no relation with rheumatoid factor, but all men with nodules continued to show radiological deterioration. (There were no men with nodules in group I compared with eight in group II.) We did identify higher group mean levels of LDH, serum AST, or initial x ray score and lower serum cholesterol as poor prognostic features. The higher levels of serum AST are probably due to the hepatic dysfunction in active RA,[19] though none of our patients had abnormal levels. Although raised levels of LDH have not been previously noted in RA, there was a striking difference in means between the two groups. Seven of the patients in group II had levels above the normal, whereas there were none in group I. This could relate to hepatic dysfunction, or possibly represent an enzyme release from polymorphs within joints.[20]

Joint damage in RA as measured by radiological changes has two causes: continuing cartilage damage by inflammatory pannus and secondary damage by use of joints with incongruous or misaligned articulating surfaces following inflammatory damage. Suppressive drugs will control the inflammatory aspects of the disease, so that it is not surprising that they have been shown to be more effective when used early.[21] Our group I patients had a significantly lower initial x ray damage score.

It would be of great clinical and economic value if we could predict the likely outcome of SAARD therapy in individual patients. Some important factors such as immune complexes[22] and cellular immune response[23] were not considered in this study and facilities were not available for genetic studies. Although we have recognised that certain particular high or low group mean levels indicate poor prognosis, these are insufficiently precise to apply to individual patients, though certain pointers such as men with nodules, high levels of LDH and serum AST with low cholesterol indicate the need for early aggressive therapy.

Our study does not imply the impossibility of identifying precise prognosticators but indicates the difficulty in separating the inflammatory and mechanical features of the disease. A similar study limited to patients with active inflammatory disease but minimal though definite radiological damage would have much greater likelihood of success.

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