Can Gold Therapy Be Used More Safely in Rheumatoid Arthritis? Adverse Drug Reactions Are More Likely in Patients with Nodular Disease, Independent of HLA-DR3 Status

PREETI SHAH, SIAN M. GRIFFITH, MICHAEL F. SHADFORTH, JUNE FISHER, PETER T. DAWES, KAY V. POULTON, WENDY THOMSON, WILLIAM E.R. OLLIER, and DEREK L. MATTEY

ABSTRACT. ***Objective***. To investigate whether features associated with severe rheumatoid arthritis (RA) are predictive of adverse drug reactions (ADR) to gold salts, independent of HLA-DR3 status.

Methods. A cohort of patients with RA (n = 41) who developed thrombocytopenia (platelets < 100 × 10^6/l) or proteinuria (> 1.0 g/24 h) upon treatment with gold sodium thiomalate was identified from patient records and matched for age, sex, and disease duration with 41 RA controls treated with gold without development of ADR. A second group of 161 random RA patients that had received gold therapy for at least as long without development of an ADR was also compared. All patients were typed for HLA-DRB1, and the presence of rheumatoid factor (RF), antinuclear antibodies (ANA), and nodules before initiation of therapy was recorded. Association of clinical or genetic factors with ADR was investigated using the McNemar test and logistic regression analysis.

Results. Patients with ADR were more likely to have nodular disease than their matched controls (51.3% vs 25.6%; odds ratio, OR = 3.0, p = 0.02) and more likely to be HLA-DR3 positive (41.2% vs 17.6%; OR = 3.0, p = 0.045). No difference between the groups was found for RF or ANA. Nodular disease was associated with development of ADR independently of HLA-DR3, although a combination of both factors significantly increased the likelihood of an ADR.

Conclusion. Our data suggest that nodular disease may be a predictor of gold-induced ADR independent of HLA-DR3. (J Rheumatol 2004;31:1903–5)

Key Indexing Terms:
RHEUMATOID ARTHRITIS GOLD THERAPY ADVERSE REACTIONS
HLA NODULES

Treatment of patients with rheumatoid arthritis (RA) with gold salts is associated with a high frequency of adverse drug reactions (ADR)[1]. Gold is now most likely to be used only for patients with severe and resistant disease, e.g., patients that have failed treatment with methotrexate and biologics such as anti-tumor necrosis factor. However, in such patients it is still important to identify those at risk of developing toxic reactions to the drug.

Several studies have demonstrated an association between HLA-DR3 and gold-induced proteinuria and/or thrombocytopenia[2-6]. Other studies have shown an association with extended HLA-DR3 haplotypes, or with HLA-DR5 and HLA –DQA1*0501[7,8]. Minimal data are available on whether any clinical variables are predictive of toxic reactions. We wished to determine whether variables associated with severe disease were predictive of developing ADR in response to gold. We examined the association of nodular disease, RF, and ANA with risk of gold-induced proteinuria and thrombocytopenia, and investigated whether these factors were independent of the influence of HLA-DR3 or other HLA-DR types.

MATERIALS AND METHODS

Patients with RA attending the Staffordshire Rheumatology Department between 1987 and 1997 and treated with intramuscular gold sodium thiomalate were identified using a computerized drug monitoring database. Those who had developed ADR were selected on the following basis: thrombocytopenia — platelet count < 100 × 10^6/l; proteinuria — 24 h urinary protein excretion > 1 g. Forty-one patients fulfilled the inclusion criteria: 39 were taking intramuscular gold, 50 mg/week, while 2 were taking 10 mg/week. Patients with coexisting renal disease or hematological conditions were excluded.

Each individual with an ADR was matched with a control that had not

From the Staffordshire Rheumatology Centre, University Hospital of North Staffordshire NHS Trust, The Haywood, Burslem, Stoke-on-Trent, Staffordshire; and the Centre for Integrated Genomic Medical Research, Manchester University Medical School, Oxford Road, Manchester, UK.

Supported by the Haywood Rheumatism Research and Development Foundation and the Arthritis Research Campaign.

P. Shah, MRCP; S.M. Griffith, FRCP; M.F. Shadforth, FRCP; J. Fisher, SRN; P.T. Dawes, FRCP, K.V. Poulton, PhD; W. Thomson, PhD, Staffordshire Rheumatology Centre; W.E.R. Ollier, PhD, Centre for Integrated Genomic Medical Research; D.L. Mattey, PhD, Staffordshire Rheumatology Centre.

Address reprint requests to Dr. D.L. Mattey, Department of Rheumatology, Staffordshire Rheumatology Centre, The Haywood, Burslem, Stoke-on-Trent, ST6 7AG, UK. E-mail: d.l.mattey@keele.ac.uk

Submitted November 24, 2003; revision accepted April 28, 2004.

developed an ADR. Matching was by sex, age, disease duration and onset, and gold treatment for at least the same duration as the case. Although 41 matched pairs were suitable, it was not possible to match every patient for each variable due to some missing results. A second group of patients available for comparison comprised 161 random patients treated with gold for at least as long as the cases without development of an ADR (Table 1).

The following variables were obtained from case records and the computerized database: (1) presence of subcutaneous rheumatoid nodules; (2) RF titer: a concentration > 60 IU/ml was considered positive; and (3) ANA [determined by indirect immunofluorescence on rat kidney substrate (until 1991) or on HEp 2 cells (after 1991): a reaction at a dilution > 1:40 was considered positive].

HLA-DRB1 typing was performed as described[9].

Statistical analysis. Associations of clinical or genetic factors with ADR were examined using the McNemar test for matched pairs. Logistic regression analysis was used to establish whether the associations of clinical or genetic factors with ADR were independent of each other. Analyses were carried out using the Number Cruncher statistical package for Windows (NCSS 2000).

RESULTS

Comparison with a matched group. Patients with ADR to gold were more likely to have nodular disease than matched controls [51.3% vs 25.6%; OR = 3.0 (95% CI 1.03–10.6), p = 0.02]. They were also more likely to carry HLA-DR3 [41.2 vs 17.6%; OR = 3.0 (95% CI 1.4–8.0), p = 0.045] (Table 1). The combination of nodular disease and HLA-DR3 was found only in the ADR group. No significant difference between groups was found for RF or ANA.

Comparison with a random cohort. As above, the ADR group was more likely to have nodules and HLA-DR3 than the random group (Table 1). Multivariate logistic regression analysis showed that nodules and HLA-DR3 were independently associated with development of ADR (Table 2). There was no association with RF or ANA or other HLA-DR types.

Investigation of thrombocytopenia and proteinuria separately revealed a significant association of nodular disease with both types of ADR. HLA-DR3 was significantly associated with thrombocytopenia only [OR = 3.3 (95% CI 1.1–9.7), p = 0.03], which was independent of nodular disease [OR = 3.9 (95% CI 1.3–11.7), p = 0.01]. In the case of proteinuria we also looked specifically at HLA-DR5, since there was previous evidence that this was associated with gold-induced proteinuria[8]. A weak association with HLA-DR5 was found [OR = 4.5 (95% CI 1.0–20.7) p = 0.05], independent of HLA-DR3 [OR 2.4 (95% CI 0.8–6.7) p = 0.1].

Overall, thrombocytopenia was far more likely in patients with nodular disease and HLA-DR3 than in those without nodules and DR3, or with DR3 only (Table 3).

DISCUSSION

Our data indicate that nodular disease in RA is associated with increased risk of gold-induced ADR. This appears to be independent of the previously described association of HLA-DR3 with ADR[2-6]. A combination of nodular disease and carriage of HLA-DR3 significantly increased the likelihood of developing an ADR, compared to either factor alone.

This is the first study to use a control group matched for severity, sex, and duration of treatment on gold. Using this type of control group we found that the risk of developing an ADR in patients with HLA-DR3 or nodules was similar to that determined by comparison with a random control group. Although there is a potential problem with multiple comparisons, the use of a second control population reinforces the results of the first set of comparisons and provides some confidence in a real association.

Development of nodular disease in RA has been associated with certain HLA-DRB1 alleles, particularly the HLA-DRB1*0401 allele[10-12]. However, an association with DRB1*0401 is unlikely to explain the association of

Table 1. Characteristics of patient groups and comparison of clinical variables and HLA-DR3 frequencies. Age and disease duration are at the start of gold therapy.

	ADR Group, n = 41	Matched Group, n = 41	Random Group, n = 161
Male:female	7:34	7:34	47:114
Age, yrs, mean (SD)	53.7 (12.4)	52.7 (10.7)	54.0 (10.4)
Age of onset, yrs, mean (SD)	44.0 (12.4)	44.1 (11.4)	45.5 (11.3)
Disease duration, yrs, mean (SD)	9.7 (8.2)	8.6 (5.8)	8.5 (5.2)
Months taking gold, median (IQR)	6.0 (4–18.5)	62.0 (26–130)	30.0 (4–90)
Nodules	20/39*	10/39	28/161
RF+	30/37	27/37	108/160
ANA ever	11/24	11/24	41/98
HLA-DR3+	14/35†	6/35	32/161
HLA-DR3+ plus nodules	9/35††	0/35	8/161

IQR: interquartile range; ADR: adverse drug reaction; RF: rheumatoid factor; ANA: antinuclear antibody. ADR group vs matched controls (McNemar test for matched pairs). * Odds ratio (OR) 3.0 (1.03–10.6) p = 0.02; † OR 3.0 (0.9–12.8) p = 0.045; †† OR 19.0, p = 0.008 (continuity corrected). ADR group vs random group (Fisher's exact test). * OR 4.9 (2.3–10.3) p < 0.0001; † OR 2.7 (1.2–5.8) p = 0.015; ††OR 6.8 (2.5–18.7) p = 0.0004.

Table 2. Logistic regression analysis to investigate the independent association of nodular disease and HLA-DR3 with adverse drug reactions (ADR) in RA patients treated with gold. Logistic regression analysis with presence or absence of an ADR as the dependent variable. The model was corrected for disease duration at the start of gold treatment by including this covariate with the independent variables [nodules, HLA-DR3, rheumatoid factor (RF), antinuclear antigen (ANA)]. ANA has been removed from the model because it had no association with ADR, and inclusion of ANA had no effect on the coefficients of other variables in the model. For a similar reason other HLA-DR types have not been included in the final model. The p values represent the significance of each variable compared with individuals negative for that variable. Chi-square for the model with 4 degrees of freedom = 21.6 ($p < 0.0001$).

Variable	Regression Coefficient	Standard Error	OR (95% CI)	p
Constant	–2.570	0.332		
Nodules	1.452	0.435	4.3 (1.8–10.0)	0.0008
HLA-DR3	1.279	0.433	3.6 (1.5–8.4)	0.003
RF	0.704	0.448	2.0 (0.8–4.9)	0.1

Table 3. Combined effect of nodular disease and HLA-DR3 on the likelihood of developing thrombocytopenia in RA patients treated with gold. In HLA-DR3+ patients the chance of thrombocytopenia was 4.5 times greater in those who had nodular disease ($p = 0.002$).

Variables	ADR Positive n	ADR Negative n	OR (95% CI)
Nodules–/HLA-DR3–	5	109	1.0 (reference)
Nodules–/HLA-DR3+	3	24	2.8 (0.5–14.4)
Nodules+/HLA-DR3–	3	20	3.4 (0.6–17.6)
Nodules+/HLA-DR3+	5	8	12.8 (2.7–72.4)*

* $p = 0.0009$ (compared with nodules–/HLA-DR3–).

nodules with ADR, since DRB1*0401 was not associated with ADR in this study.

Similarly, an association between nodular RA and RF[12] does not explain the association of nodules with gold-induced ADR. There was a trend towards a higher frequency of RF positive patients in those developing ADR, but this was not statistically significant. Our analysis indicated that the association of nodular disease with ADR was independent of RF.

We confirmed the association of HLA-DR3 with gold-induced ADR, and an association between HLA-DR5 and gold-induced proteinuria. However, the mechanism by which these alleles are involved in development of ADR remains to be elucidated.

It is likely that, for the foreseeable future, gold will have a reduced but more focused use in RA. Although patients prescribed gold are carefully monitored, our findings suggest that there is a need to be especially aware of a possible increased risk of developing thrombocytopenia in those with nodular disease.

REFERENCES

1. Husain Z, Runge LA. Treatment complications of rheumatoid arthritis with gold, hydroxychloroquine, D-penicillamine and levamisole in patients with rheumatoid arthritis. J Rheumatol 1980;7:825-30.
2. Panayi GS, Wooley P, Batchelor JR. Genetic basis of rheumatoid disease: HLA antigens, disease manifestations, and toxic reactions to drugs. BMJ 1978;2:1326-8.
3. Wooley PH, Griffin J, Panayi GS, Batchelor JR, Welsh KI, Gibson TJ. HLA-DR antigens and toxic reaction to sodium aurothiomalate and d-penicillamine in patients with rheumatoid arthritis. N Engl J Med 1980;303:300-2.
4. Gran TJ, Husby G, Thorsby E. HLA antigens and gold toxicity. Ann Rheum Dis 1983;42:63-6.
5. van Riel PLCM, Reekers P, van Putte LBA, Gribnau FWJ. Association of HLA antigens, toxic reactions and therapeutic response to auranofin and aurothioglucose in patients with rheumatoid arthritis. Tissue Antigens 1983;22:194-9.
6. Scherak O, Smolen JS, Mayr WR, Mayrhofer F, Kolarz G, Thumb NJ. HLA antigens and toxicity to gold and penicillamine in rheumatoid arthritis. J Rheumatol 1984;11:610-4.
7. Singal DP, Reid B, Green D, D'Souza M, Bensen WG, Buchanan WW. Polymorphism of major histocompatibility complex extended haplotypes bearing HLA-DR3 in patients with rheumatoid arthritis and gold-induced thrombocytopenia or proteinuria. Ann Rheum Dis 1990;49:582-6.
8. Sakkas LI, Chikanza IC, Vaughan RW, Welsh KI, Panayi GS. Gold induced nephropathy in rheumatoid arthritis. Ann Rheum Dis 1993;52:300-1.
9. Mattey DL, Dawes PT, Gonzalez-Gay MA, et al. HLA-DRB1 alleles encoding an aspartic acid at position 70 protect against development of rheumatoid arthritis. J Rheumatol 2001;28;232-9.
10. Weyand CM, Xie C, Goronzy JJ. Homozygosity for the HLA-DRB1 allele selects for extraarticular manifestations in rheumatoid arthritis. J Clin Invest 1992;89:2033-9.
11. Perdriger A, Chales G, Semana G, et al. Role of HLA-DR-DR and DR-DQ associations in the expression of extraarticular manifestations and rheumatoid factor in rheumatoid arthritis. J Rheumatol 1997;24:1272-6.
12. Mattey DL, Dawes PT, Fisher J, et al. Nodular disease in rheumatoid arthritis: Association with cigarette smoking and HLA-DRB1/TNF gene interaction. J Rheumatol 2002;29:2313-8.