Comparative study of intramuscular gold and methotrexate in a rheumatoid arthritis population from a socially deprived area

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Abstract

***Objective*—To compare the risk-benefit ratio of intramuscular gold (gold sodium thiomalate (GST)) and methotrexate (MTX) in a population with rheumatoid arthritis (RA) from a deprived area.**

***Methods*—Patients with active RA were randomly assigned to open treatment with GST or MTX. Clinical and laboratory assessment was performed at 0, 12, 24, and 48 weeks. Results were analysed on an intention to treat basis.**

***Results*—141 patients were recruited—72 were randomly allocated to GST and 69 to MTX. There were no statistically significant differences found in either the clinical or demographic variables at baseline. At 48 weeks 31 (43%) patients continued to receive GST and 43 (62%) MTX. The median MTX dose achieved was 10 mg. Gold caused significantly more withdrawals for toxicity (43% GST *v* 19% MTX, p=0.0026, log rank test). Both groups experienced a significant improvement in erythrocyte sedimentation rate, C reactive protein, Ritchie Articular Index, and pain score by 24 weeks (p<0.001, Friedman test). Although a trend towards an improved Health Assessment Questionnaire (HAQ) score and global wellbeing was seen in both groups, this did not reach statistical significance. No differences in efficacy were found when the two groups were compared (Mann-Whitney).**

***Conclusion*—GST and low dose MTX showed equivalent efficacy, but toxicity was more common in patients treated with GST. GST, although more toxic, remains a useful alternative for patients in whom MTX is contraindicated.**

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Ranking available disease modifying antirheumatic drugs (DMARDs) for treatment of rheumatoid arthritis (RA) is notoriously difficult. Gold salts have been used in the treatment of RA since 1929 and, although considered more toxic,[1] have the advantage of ensuring compliance. Methotrexate (MTX) use in RA has gained popularity over the past 15 years, especially in the United States, where it has been shown to have sustained benefit (>2 years) in over 50% of patients. This is in contrast with the experience with hydroxychloroquine, D-penicillamine, parenteral gold, and azathioprine, where fewer than 20% of courses are maintained beyond five years.[2]

Nevertheless, several west of Scotland rheumatologists became aware of serious adverse events when using MTX in low doses for RA.[3] There was uncertainty as to whether these occurred more frequently with MTX than had been previously reported, or whether such observations might be linked to local lifestyle factors. Of those residing in Scotland's most deprived areas (as defined by Carstairs and Morris),[4] 50% live within the remit of the Greater Glasgow Health Board.[5] Health related behaviour, such as cigarette smoking, poor diet, alcohol consumption, and lack of exercise, are highest among the deprived.[5] Evidence that the adverse gastrointestinal effects of MTX can be reduced with folic acid supplementation without a significant decrease in efficacy[6] is likely to be of particular value in people whose diet is poor. Liver toxicity may be greater in patients with a history of alcohol excess,[7 8] and pulmonary adverse effects, such as pneumonitis, are more common in patients with pre-existing lung disease.[9 10] Conceivably, lifestyle factors may considerably modify the appropriate choice of DMARDs in treating RA. It has been shown that MTX is associated with increased levels of plasma homocysteine[11] and with increased mortality in patients with RA with pre-existing cardiovascular disease.[12] Such concerns are particularly relevant to the general applicability of DMARD trials performed in distinct genetic and environmental conditions. This study was performed to compare the risk-benefit ratio of MTX (most studied in the more affluent American population) with GST, which has been studied extensively in the more deprived west of Scotland cohort.

Patients and methods

PATIENT SELECTION

Recruitment was performed between 1993 and 1998. Patients with active RA (fulfilling the 1987 criteria)[13] were invited to participate. Active disease was defined as clinical evidence of synovitis (painful and swollen joints) and prolonged morning stiffness, with or without evidence of acute phase response.

EXCLUSION CRITERIA

Exclusion criteria were as follows: (*a*) previous treatment with intramuscular gold (gold sodium thiomalate (GST)), MTX, or auranofin; (*b*) previous treatment with more than three DMARDs; (*c*) previous treatment with cytotoxic drugs (including cyclosporin); (*d*) oral prednisolone dose >7.5 mg/day; (*e*) pulmonary fibrosis; (*f*) hepatic disease; (*g*) severe renal

impairment (creatinine >200 μmol/l); and (*h*) patients unwilling to abstain from alcohol.

Patients were randomly assigned to receive either oral MTX or GST. Patients, medical and metrology staff were unaware of the treatment allocation. Patients were subsequently reassessed by a trained metrologist in a routine DMARD monitoring clinic.

TREATMENT

MTX

MTX was started at 5 mg/week and increased in monthly increments of 2.5 mg/week according to clinical response to a maximum of 20 mg/week. All patients in the MTX group were asked to abstain from alcohol. Folic acid 5 mg weekly was prescribed four days after MTX ingestion.

GST

Initial test dose of 10 mg GST was followed by 50 mg/week for 20 weeks or until clinical response was achieved (whichever occurred earliest). Thereafter, the interval between injections was increased to two, three, and ultimately, four weeks.

Dose increments and discontinuation of treatment were decided by the attending doctor to achieve a setting as true to life as possible. MTX was discontinued if the white cell count (WCC) fell below 4×10^9/l, platelets $<150\times10^9$/l, lymphocytes $<0.5\times10^9$/l, hepatic enzymes greater than twice normal despite temporary discontinuation plus or minus dose reduction, intractable gastrointestinal upset despite appropriate anti-emetics, pneumonitis, recurrent or life threatening infection. GST was discontinued for significant skin rash or mouth ulcers, WCC $<4\times10^9$/l, platelets $<150\times10^9$/l, or proteinuria >250 mg albumin/24 h. When a drug was stopped for either lack of efficacy or toxicity, an alternative DMARD was substituted. Follow up was maintained in the original group on an intention to treat basis.

Non-steroidal anti-inflammatory drugs (NSAIDs)

Dose alterations to NSAIDs were allowed at the discretion of the attending doctor.

Oral steroid

Oral steroid was allowed up to 7.5 mg/day and was kept stable for three months before study entry. The dose was not changed within four weeks of assessment.

Intra-articular corticosteroid injections (triamcinolone acetonide or triamcinolone hexacetonide)

Intra-articular corticosteroid injections, 40 mg for a large joint or 5–10 mg for a small joint, were permitted, as required, to a maximum of 40 mg for a three month period.

CLINICAL MEASURES

All patients including those who withdrew from the study were assessed at baseline, 12, 24, and 48 weeks. Demographic details recorded at baseline included age, sex, disease duration. The level of social deprivation was ascertained for each patient using the Carstairs index.[4] This is a composite score derived using the postcode and based on overcrowding, male unemployment, social class, and car ownership. The most affluent areas are those listed as deprivation category 1, where 11% of the population have no car, 6% are unemployed, only 2% live in overcrowded conditions, and 2% of the population are in social class 4 or 5. The most deprived areas are listed as category 7 (72% of this population have no car, 35% are unemployed, 17% overcrowded, and 35% in social class 4 or 5). Clinical measures recorded were as follows: Ritchie Articular Index (RAI),[14] patient global wellbeing (1=very poor; 2=poor; 3=fair; 4=good; and 5=very good), duration of morning stiffness (min), visual analogue pain score (0=no pain; 100=worst pain imaginable), and the Health Assessment Questionnaire (HAQ) as modified for use by British patients[15] and were assessed at each visit. The presence or absence of nodules was also documented. Laboratory measures determined to measure efficacy included erythrocyte sedimentation rate (ESR) and C reactive protein.

Evaluation of response

Response to treatment was graded as follows: (*a*) inactivation/remission; (*b*) marked improvement; (*c*) improvement; (*d*) no change; (*e*) deterioration as defined by Menninger *et al* (see appendix 1).[16] In addition, a modified Paulus response was calculated.[17] For a 50% response three out of four of the following were present: (*a*) a 50% fall in RAI; (*b*) ESR normal as defined by <30 mm/1st h for women and <20 mm/1st h for men or a 50% fall; (*c*) early morning stiffness <30 minutes or 50% improved from baseline; and (*d*) an improvement in two or more grades in the global wellbeing score. For a 20% response three out of the following were present: (*a*) a 20% fall in RAI; (*b*) ESR normal as defined by <30 mm/1st h for women and <20 mm/1st h for men or a 20% fall; (*c*) early morning stiffness <30 minutes or 20% improved from baseline; and (*d*) an improvement of one grade in the global wellbeing score.

Safety monitoring

Full blood count and differential WCC, urea and electrolytes, liver function and tests, and urine analysis were performed at each study visit and in between visits as indicated by local monitoring protocols (coincident with every injection for GST, monthly for MTX). Red cell folate levels were checked at baseline, 12, 24, and 48 weeks.

STATISTICAL ANALYSIS

All patients were analysed on an intention to treat basis. Baseline characteristics for both groups were compared with Mann-Whitney U tests for continuous variables and χ^2 tests (or Fisher's exact test, where appropriate) for categorical variables, on SPSS software. Within-group change over the 48 weeks was assessed with the Wilcoxon signed rank test for two variables and the Freidman test for more than two variables. Survival curves were generated

Table 1 Baseline demographics. No statistically significant differences were found when the groups were compared using a Mann-Whitney test or χ^2 test, where appropriate

	Gold (n=72)	Methotrexate (n=69)	p Value
Median age, years (IQ* range)	58 (49–67)	60 (51–67)	0.475
Median disease duration, years (IQ range)	6 (3–15)	6 (2–11)	0.778
Median previous DMARDs*, No (IQ range)	1 (1–1.5)	1 (1–1)	0.455
Female, No (%)	58 (81)	54 (78)	0.736
RF* positive, No (%)	46 (64)	43 (62)	0.345
ANF* positive	18	19	0.419
Carstairs 1, 2, or 3 (affluent areas)	18	21	
Carstairs 4 or 5	24	29	0.275
Carstairs 6 or 7 (deprived areas)	26	17	

*IQ = interquartile; DMARDs = disease modifying antirheumatic drugs; RF = rheumatoid factor; ANF = antinuclear factor.
No Carstairs code was available for six patients.

Table 2 Baseline laboratory and clinical parameters. Results are shown as median (interquartile range)

Parameter	Gold	Methotrexate	p Value*
CRP† (IU/l)	31 (11–77)	33 (14–59)	0.522
ESR† (mm/1st h)	39 (18–57)	46 (30–68)	0.283
Ritchie Articular Index	12 (6–18)	11 (6–16)	0.415
Pain score	62 (42–76)	71 (50–76)	0.175
Early morning stiffness (min)	60 (25–240)	60 (30–120)	0.672
HAQ†	2 (1.5–2.375)	2 (1.5–2.5)	0.864

*Mann-Whitney.
†CRP = C reactive protein; ESR = erythrocyte sedimentation rate; HAQ = Health Assessment Questionnaire.

by the Kaplan-Meier method. The log rank test was used to compare differences between the treatment groups.

Results

A total of 177 patients were invited to participate in the study—36 patients (20%) declined. The reasons for refusal were: did not want to reduce their alcohol intake (13), did not wish to receive either one of the study drugs (10), wanted to choose the drug (8), decided after reading information that they did not want a DMARD at all (2), and not documented (3). Thus 141 patients were recruited—72 were randomly allocated to GST and 69 to MTX. Eighty six (61%) patients were rheumatoid factor positive and 37 (26%) antinuclear antibody positive.

Tables 1 and 2 show the baseline characteristics for both groups. No statistically significant differences were found in either the clinical or demographic variables at baseline when the two groups were compared using a Mann-Whitney or χ^2 test/Fisher's exact test, where appropriate.

WITHDRAWALS

Significantly more patients withdrew from the GST group than from the MTX group (p=0.024, log rank test; fig 1). During the first six months of the study 23/72 (32%) of patients receiving GST withdrew as a result of toxicity compared with only 12/69 (17%) of those receiving methotrexate (p=0.05, χ^2). Of the remaining 49 patients receiving gold, a further 7/49 (14%) withdrew owing to toxicity in the second half of the study compared with only 1/57 (2%) of the patients continuing to receive methotrexate. The time of withdrawal was unavailable for one patient in the gold group (p=0.014).

At 48 weeks 31 (43%) patients continued to receive GST and 43 (62%) MTX. Where

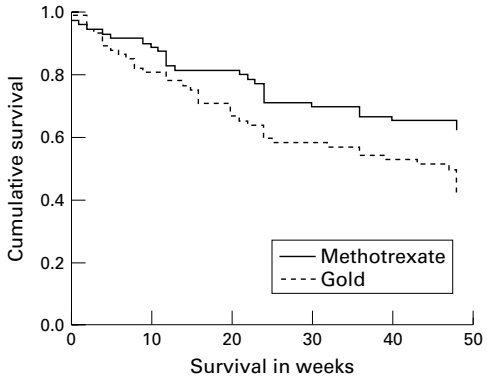

Figure 1 Cumulative survival on gold or methotrexate over 48 weeks.

withdrawal was for toxicity or lack of effect the patients continued follow up in their original groups. Five deaths unrelated to treatment (two GST, three MTX) occurred. Forty four patients were withdrawn because of toxicity (31 GST, 13 MTX), 10 for lack/loss of effect (seven GST, three MTX), three patients were lost to follow up (MTX group), four patients in the MTX group wished to withdraw, and one other in the GST group.

DRUG DOSAGE

In the group who continued to receive MTX treatment until week 48 the median weekly dose was 10 mg (range 2.5–20). GST recipients, in contrast, achieved a median cumulative dose of 1460 mg (range 810–2610).

Steroid treatment

There were no statistically significant differences in the number of intramuscular or intra-articular steroid injections given during the study (median 1 injection (range 0–10), for intra-articular injections and median dose 0 mg (range 0–160) for intramuscular triamcinolone acetonide). Only 2/141 (1%) patients were receiving oral prednisolone 5 mg at baseline. This continued unchanged in one patient and was stopped by week 12 in the other. One patient required the addition of prednisolone 7.5 mg at week 12, which was continued unchanged during the remainder of the study.

Additional DMARDs

No patient required the addition of a second DMARD.

NSAIDs

Ten patients in the GST group and five patients in the MTX group were able to stop their NSAID by week 48.

EFFICACY

Significant within-group improvement in most measures of efficacy occurred in patients treated with GST by 12 weeks, and in MTX treated patients by 24 weeks (table 3). Despite this, between-group comparison showed more rapid improvement only in the ESR in the GST group (p<0.05, Mann-Whitney; table 3). From week 12, no differences in efficacy were found

Table 3 Response to treatment over 48 weeks

	Baseline Median (IQ† range)	*12 Weeks Median (IQ range)*	*24 Weeks Median (IQ range)*	*48 Weeks Median (IQ range)*
Gold (n=72)				
ESR† (mm/1st h)	39 (18–57)	22 (12–44)	28 (10–41)	24 (9–52)**
CRP† (IU/l)	31 (11–77)	14 (10–37)	10 (9–33)	16 (9–40)**
RAI†	12 (6–18)	6 (3–12)	5 (2–9)	4 (1–10)**
Pain score	62 (42–76)	54 (31–76)	42 (24–65)	50 (15–75)**
HAQ†	2.0 (1.5–2.375)	2.0 (1.261–2.5)	1.875 (1.375–2.375)	1.937 (1.3–2.5)
EMS† (min)	60 (25–240)	45 (10–120)	60 (10–105)	45 (2–90)**
GWB†, No (%) good or v good	26 (36)	21 (29)	23 (32)	24 (33)
Methotrexate (n=69)				
ESR (mm/1st h)	46 (30–68)	40 (20–62)	31 (18–51)	24 (16–44) **
CRP (IU/l)	33 (14–59)	18 (10–36)	18 (10–37)	10 (9–25) **
RAI	11 (6–16)	7 (4–13)	6 (3–10)	5 (2–10)**
Pain score	71 (50–76)	50 (46–70)	50 (35–65)	50 (29–70)**
HAQ	2 (1.5–2.5)	2 (1.562–2.25)	1.875 (1.562–2.375)	1.875 (1.25–2.25)
EMS (min)	60 (30–120)	60 (30–90)	30 (15–60)	30 (10–60)
GWB, No (%) good or v good	20 (29)	14 (20)	27 (39)	24 (35)

*p<0.05, **p<0.01.
†IQ = interquartile range; CRP = C reactive protein; RAI = Ritchie Articular Index; PS = pain score; HAQ = Health Assessment Questionnaire; EMS = early morning stiffness; GWB = global wellbeing.

between groups (Mann-Whitney). Improvements were maintained up to 48 weeks. No improvement in HAQ or in global wellbeing scores was detected in either group.

When an intention to treat analysis was used, although eight patients from the GST treated group and 15 from the MTX group achieved a modified Paulus 50% response and 19 gold and 27 methotrexate treated patients reached a modified Paulus 20% response, this did not reach significance (p=0.069, χ^2, 50% response and p=0.069, χ^2, 20% response). Similarly, no significant difference was detected when completers only were compared (p=0.099 for 50% response and p=0.474 for 20% response).

By 48 weeks 18% of GST treated patients compared with 6% of MTX treated patients achieved inactivation (see appendix 1 for definition). This was not statistically significant. Of interest, by week 48, 3/41 (7%) of the GST treated group who had been withdrawn from GST treatment remained in remission, and 11 (27%) continued to show either a marked improvement or improvement from baseline. In contrast, none of the MTX withdrawals were in remission, but 5/26 (19%) continued to have either improvement or marked improvement in comparison with baseline.

Table 4 Percentage of patients experiencing each adverse event

	Gold No (%)	*Methotrexate No (%)*
Nausea/anorexia	0	13 (19)
Abdominal pain	1 (1)	2 (3)
Diarrhoea	3 (4)	5 (7)
Proteinuria >250 mg/24 h	11 (15)	1 (1)
Proteinuria <250 mg/24 h	8 (11)	1 (1)
Haematuria	1 (1)	1 (1)
Skin rash	12 (17)	7 (10)
Pruritis	4 (6)	2 (3)
Hair loss/alopecia	2 (3)	0
Mouth ulcers/stomatitis	11 (15)	10 (14)
Vasovagal	1 (1)	0
Leucopenia <4×10^9/l	5 (7)	3 (4)
Thrombocytopenia <150×10^9/l	4 (6)	0
Increased transaminases <2×normal	3 (4)	4 (6)
Increased transaminases >2×normal	2 (3)	8 (12)
Hypogammaglobulinaemia	0	0
Pulmonary toxicity	0	0
Breathlessness (pneumonitis not proved)	1 (1)	1 (1)
Infection	4 (6)	11 (16)
Life threatening infection	0	1 (1)
Increased nodules	1 (1)	3 (4)
New nodules (previously none)	0	4 (6)
Haematological neoplasm	0	0
Neoplasm	0	1 (1)

DRUG TOXICITY

Overall, 51 (74%) of the MTX group experienced some form of toxicity, but this led to withdrawal in only 13 patients (19%). By contrast 51 (71%) of the GST treated group experienced toxicity, leading to withdrawal of treatment in 31 (43% of patients overall). The commonest adverse events in the MTX group were nausea (19%) (median dose 5 mg, range 5–7.5; median time to onset 12 weeks, range 2–48), stomatitis (14%) (median dose 7.5 mg, range 2.5–12.5; median time to onset 17.5 weeks, range 10–48), and infection 16% (median dose 7.5 mg, range 2.5–15; median time to onset 24 weeks, range 3–48). In the GST group 15% experienced significant proteinuria (median cumulative dose 660 mg, range 10–1310; median time to onset 22 weeks, range 2–48), 15% mouth ulcers and stomatitis (median cumulative dose 560 mg, range 560–1150; median time to onset 12 weeks, range 12–24), and 18% skin rash (median dose 560 mg, range 10–1510; median time to onset 12 weeks, range 2–48). Table 4 shows all the toxicities. GST was found to cause significantly more withdrawals for toxicity (p=0.0026, log rank test; fig 2).

Significantly more patients in the MTX group had episodes of infection (as defined by the need for antibiotic treatment or significant viral infection such as herpes zoster) (p=0.034, Fisher's exact test), but discontinuation of MTX was required in only three patients. At the assessment closest to the infective episode the median lymphocyte count was 1.98×10^9/l (range 0.7–3.19×10^9/l) in MTX treated patients compared with a median lymphocyte count of 1.6×10^9/l (range 0.13–4.2×10^9/l) in those who did not develop infection. Table 5 shows the toxicities leading to withdrawal.

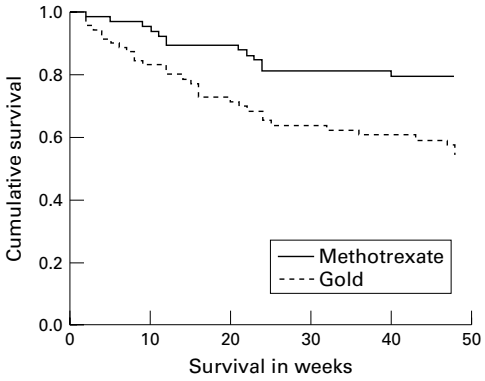

Figure 2 Cumulative survival before withdrawal for toxicity over 48 weeks

FOLIC ACID LEVEL AND TOXICITY IN MTX TREATED GROUP

Median red cell folate level was 275 ng/ml (IQ range 215–372 ng/ml), normal range 180–613 ng/ml at baseline. There were no statistically significant differences found in the median folate level (Mann-Whitney) when those experiencing toxicity (all causes), nausea/anorexia and stomatitis only, or infection only were compared with those free from such adverse events. Patients with a normal folate level were as likely to experience toxicity as those with a low red cell folate. These results should be treated with caution as the numbers with subnormal red cell folate were small—8 (12%) at baseline, 4(6%) at week 12, 6 (9%) at week 24, and 3 (4%) at week 48.

RESPONSE TO TREATMENT AND SOCIAL DEPRIVATION

Four of 21 (19%) patients within Carstairs groups 1, 2 or 3 (affluent areas), 7/29 (24%) of those in Carstairs group 4 and 5, and 2/17 (12%) of those within Carstairs groups 6 and 7 (deprived areas) withdrew from MTX treatment as a result of toxicity. This was not significant p=0.574, Fisher's exact test. By comparison 6/18 (33%) of those from Carstairs 1, 2, or 3, 12/24 (50%) from groups 4 and 5, and 9/17 (53%) of those from the most deprived areas withdrew from gold treatment (p=0.383, χ^2).

Discussion

This study set out to compare the efficacy and tolerability of MTX and GST. Intramuscular GST and low dose MTX exhibited equivalent efficacy, but toxicity was more common in GST treated patients. This is consistent with previous studies.[16 18–20] The number of remissions in the GST treated group was higher, though this did not achieve statistical significance; the study was, however, not powered to address onset of remission. Improvement was also sustained at 48 weeks in 14/41 (34%) of the GST withdrawals compared with 5/26 (19%) of those withdrawn from MTX treatment, reflecting the previously noted phenomenon of GST toxicity occurring simultaneously with symptomatic improvement.[21 22] This confirms the finding by Sander *et al* that patients with early RA stopping gold because of side effects show almost the same sustained improvement as patients continuing to receive gold or methotrexate.[23] Clinical improvement was not as dramatic in either group as that described by Menninger *et al*.[16] The reasons for this are not clear, but may reflect the lower median dose of MTX (10 mg orally *v* 14 mg intramuscularly—equivalent to approximately 22.5 mg orally[16]) and the lower proportion of oral prednisolone use in our cohort. The cumulative GST dose in the Menninger study was also higher and the median disease duration shorter. The slower onset of the MTX effect probably reflects the low dose escalating protocol for MTX treated patients, such that even by 48 weeks, the median dose remained only 10 mg (range 2.5–20). The slow escalation was selected because of anecdotal toxicities reported in the west of Scotland population. All patients with a suboptimal effect were, however, encouraged to increase the MTX dose to the maximum tolerated, up to 25 mg weekly. However, this was often limited by patient intolerance of adverse effects, such as gastrointestinal disturbance. It is also likely that owing to the previous adverse experiences with methotrexate, medical staff were more reluctant to increase the dose. The lack of improvement in the HAQ was disappointing but may simply reflect pre-existing joint damage with a limited capacity for improvement.

More patients withdrew from GST treatment. Reasons for withdrawal were similar to those reported elsewhere. However, more patients withdrew from the GST cohort than had been our previous experience obtained in several carefully controlled clinical studies.[24–28] That only 31/72 (43%) continued to receive GST in the current study compared with 59% in an earlier cohort[24] perhaps indicates that patients are now less likely to persevere with symptoms such as skin rash or mouth ulcers when alternative DMARD choices are available. Withdrawals for proteinuria in this GST treated group were higher than those reported elsewhere,[29 30] and more patients experienced leucopenia than expected. The reason for these discrepancies is also unclear. The skin rash and mucositis seen were similar to previous reports.[31] Nevertheless, even if this study has overestimated the potential toxicity of GST, our data are broadly consistent with those obtained previously, indicating that MTX is better tolerated than GST.[16 20]

Withdrawals from MTX were similar to those reported elsewhere,[16 20 32] but occurred at a lower median dose and with earlier onset. In

Table 5 Toxicity leading to withdrawal

	Gold No (%)	*Methotrexate No (%)*
Gastrointestinal disturbance	2 (3)	5 (7)
Proteinuria	12 (17)	1 (1)
Pruritis	1 (1)	
Skin rash	6 (8)	
Mouth ulcers/stomatitis	3 (4)	1 (1)
Vasovagal	1 (1)	—
Leucopenia <4×10^9/l	4 (6)	—
Thrombocytopenia <150×10^9/l	2 (3)	—
Raised AST/ALT* >2×normal	—	3 (4)
Infection	—	3 (4)

*AST/ALT = serum aspartate transaminase/serum alanine transaminase.

particular, rates of gastrointestinal disturbance, stomatitis, and liver function abnormality were equivalent to the rates of toxicity normally seen in patients not receiving folate supplementation.[33] This could not be explained on the basis of non-compliance with folate because the median red cell folate level in the MTX group increased rather than fell over time. Nor could toxicity be linked to baseline folate level. An alternative explanation may lie in the social class demographic of the study cohort. We have previously shown that RA disease activity (HAQ) and mortality are altered in Carstairs groups 6 and 7.[34 35] Although subgroup analysis of drug withdrawals by Carstairs score showed neither significant change nor trends for any particular group, the study did not have sufficient numbers to deal with this issue.

More patients treated with MTX had episodes of infection, but these resulted in drug withdrawal in only three patients. Infection was not related to lymphocyte levels monitored throughout the study. Contrary to our perception at study outset, serious infective complications of MTX were rare provided that patients discontinued MTX during an infective episode. Appropriate immunisation may further decrease this complication of MTX treatment, though definitive data are awaited. We saw no episodes of pneumonitis during the first 48 weeks of the study despite the high incidence of patients who were smokers or ex-smokers within the study cohort (100/141 (71%)). This is commensurate with the findings by Alarcon *et al*, who found no relation between urban residence, smoking, and MTX pneumonitis.[36] Previous estimates of MTX induced pneumonitis suggest a frequency of between 1 and 7%.[37] However, only 50% of MTX lung toxicity occurs within the first 32 weeks of treatment, and further follow up in our cohort will be necessary.[38]

A unique feature of this study included documentation of the 36 patients refusing study entry, who represented one fifth of the patients invited to participate. Thirteen (7%) overall did not wish to reduce their alcohol intake. When the study protocol was written available guidelines recommended a ban on alcohol in all MTX treated patients.[39] Since then at least one study[40] has found no link between moderate alcohol consumption and MTX induced hepatotoxicity in patients with RA. Although we would still consider MTX to be contraindicated in heavy drinkers, we now allow moderate alcohol consumption. We presume that this will increase MTX acceptability within our RA population.

In conclusion, MTX proved a relatively safe and effective treatment for RA even when used in a population from a socially deprived area. GST is more toxic than MTX but it remains an effective alternative in patients in whom MTX may not be tolerated, including patients with heavy alcohol consumption, or pre-existing lung disease in whom MTX is contraindicated.

Appendix 1 Definitions

Inactivation: RAI = 0, ESR <20 mm/1st h for men and <30 mm/1st h for women and absence of systemic or intra-articular treatment with corticosteroids within the past four weeks.

Marked improvement: Reduction of RAI and of ESR to ⩽50% compared with the baseline value and absence of systemic or intra-articular treatment with corticosteroids within the past four weeks.

Improvement: RAI and ESR between 51 and 80% compared with baseline value and absence of systemic or intra-articular treatment with corticosteroids within the past four weeks.

No change: Joint count 81–120% compared with baseline.

Deterioration: Joint count >120% of baseline value.

Where their was a difference of two or more groups between the percentage change in ESR and RAI the mean group was always chosen unless the baseline and ESR and subsequent ESR were normal and the baseline joint count was greater than 6, under which circumstances the RAI was used. In the unusual circumstances that intramuscular or intra-articular steroid had been given within four weeks of an assessment the patient was excluded from the analysis.

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