Combination DMARD treatment with parenteral gold and methotrexate

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ABSTRACT

Introduction

Both methotrexate (MTX) and gold sodium thiomalate (GSTM) have been shown to be very effective in the treatment of rheumatoid arthritis (RA) and to slow x-ray progression. The combination of both drugs could be useful because of their different and complimentary mechanisms of action. However, there is only one long-term study comparing this combination with MTX monotherapy.

Methods

In this prospective long-term observational study, all patients who started MTX treatment from 1980 to 1987 in one center were followed for 12-108 (mean 34.1) months. Ninety-seven patients were treated with MTX, while 126 patients received the combination MTX/GSTM, both drugs being given at the full dose. All patients had active disease, most of them long-lasting destructive RA not responsive to previous disease-modifying antirheumatic drug (DMARD) treatment.

Results

There were no significant differences in the demographic and baseline data between the two groups, with the exception of higher swollen joint counts (SJC) and C-reactive protein (CRP) in the combination group. In both groups the parameters of disease activity (erythrocyte sedimentation rate [ESR], CRP, SJC) improved significantly. A > 50% improvement in the SJC after 1 and 3 years was seen in 62% and 70% of patients in the MTX group, and in 55% and 85% of the patients in the combination group, respectively. A > 50% improvement in the ESR occurred in 54%/63% (MTX group) and in 49%/68% (combination group) for the same timepoints. There was no difference between the groups regarding the nature, frequency, or severity of side effects. A total of 20.6% (MTX) and 15.1% (combination) of patients were withdrawn for side effects. After 5 years, 54% of the patients in both groups were still being treated.

Conclusion

This long-term observational study shows that the combination MTX/GSTM is well tolerated and is at least as effective as MTX single treatment. Taking into account the higher disease activity at baseline and the greater x-ray progression before baseline among the patients in the combination group, one may conclude that combination treatment is superior to monotherapy.

Introduction

The primary objective of combining disease-modifying antirheumatic drugs (DMARDs) is to improve efficacy and in particular to prevent joint damage and subsequent disability. In recent years, we have seen multiple treatment regimens combining two or more DMARDs with conflicting results. This paper will focus on the combination of parenteral gold and methotrexate (MTX), two compounds that have demonstrated convincing effectiveness as individual agents in the treatment of rheumatoid arthritis (RA).

Parenteral gold has been the most widely used DMARD in the treatment of RA for decades, and it still remains one of the most effective traditional therapies (1, 2). Gold salts have been shown to inhibit radiographically visible joint destruction in two placebo-controlled trials (3, 4) and in longer observational studies comparing different doses of gold (5-8). These results have been confirmed in comparative studies with auranofin, which show a slower rate of progression with parenteral gold (9). In a quantitative microfocal radiographic study, Buckland-Wright (10) found a significant increase in the total erosion area during the first 6 months of parenteral gold treatment, no change during the second 6 months, and a decrease in the total erosion area during the third half year.

A shift to MTX as the most widely used

DMARD worldwide has occurred during the last 10 - 15 years. Although there are reports indicating that radiographic progression continues in spite of clinical improvement (11-13), two studies have shown a significant retardation of radiographic progression when x-ray progression during a pre-treatment period was compared with a period of MTX treatment (14, 15).

Several studies have compared the effectiveness of parenteral gold with that of MTX. Three trials, each conducted over a period of 6 months, demonstrated a significant improvement in all clinical parameters and in the erythrocyte sedimentation rate (ESR) without significant differences between the groups (16-18).

In a two-center, double-blind randomized trial involving 174 patients with early erosive RA (median disease duration 11 months), which compared 50 mg/week of gold sodium thiomalate (GSTM) with 15 mg/week of MTX given intramuscularly, a significant improvement of > 50% in all clinical parameters and in the acute phase reactants after one and three years was seen without significant differences between the groups. The intention-to-treat analysis showed marked improvement (> 50%) in 68% of the patients treated with MTX and in 76% of the patients treated with parenteral gold. There were more withdrawals due to side effects in the gold group (19, 20). However, many of these had entered into clinical remission by the time of withdrawal (21). In the same study, x-ray progression was comparable for both compounds with marginal advantages for parenteral gold. In both groups, the slope of the progression was significantly smaller during the second six months when compared with the first six months (22).

Although these data suggest that gold and MTX are nearly equivalent in their effects on RA, no attempts had yet been made when we started our MTX/GSTM study in 1987 to combine both drugs and compare the combination with single-drug treatment. Our study was an investigator-initiated trial with some administrative support (randomization, drug supply, statistics) from Lederle/Germany. It was not possible to organize a combination arm because there was no interest in such a study at that time. Therefore, a good chance to investigate the combination in comparison with the single drug was missed. I am not aware of any other double-blind study with a combination arm involving parenteral gold/MTX. In a review of the clinical pharmacology of combination DMARD treatment, Furst (23) considered this combination to be potentially useful because of the different and complementary mechanisms of action of the drugs, but also disadvantageous because both drugs are eliminated through the kidney and may have similar side effects (stomatitis, bone marrow depression, etc.).

We initiated a prospective long-term observational study including all patients who were begun on treatment with MTX in our department between January 1, 1980 and December 31, 1987. We monitored patients with long-lasting severe destructive disease who did not respond or who responded incompletely to previous DMARD treatment. In all of these patients the "new" drug MTX (the first American pilot studies on MTX appeared in 1980-1982) was introduced because the disease was very active in spite of current treatment with a DMARD, which was parenteral gold in the majority of cases.

In some of these patients the previous DMARD was stopped and replaced by MTX, but in most MTX was prescribed in addition to the previous DMARD. Thus, three groups of patients emerged. Of a total of 271 patients started on MTX, 97 were treated with MTX alone, 126 received the combination methotrexate plus parenteral gold, and 48 patients received a combination of methotrexate plus another DMARD (in general, D-penicillamine or chloroquine).

This paper will be restricted to a comparison of those patients who were treated with MTX alone and those treated with the combination of MTX plus parenteral gold, focusing on: (i) clinical and laboratory efficacy and toxicity parameters, as well as withdrawals, during an observation period lasting between 12 and 108 months (mean 31.4 ± 24.3), and (ii) an examination of the mortality data in both groups after a mean observation period of 10 years (range 8 - 15).

Patients and methods

Study design

The methodology of this long-term open observational study has been previously described in detail (24, 25). Therefore only a brief description will be given here.

Patients

All patients from our department with definite or classic RA (26) who started MTX between January 1, 1980 and December 31, 1987 were included in this observational trial. The reasons for starting MTX treatment were: (i) an insufficient response to the previous DMARD treatment, and (ii) active disease, defined as > 6 swollen joints and > 9 tender joints, and an ESR >20 mm/hr in men and > 30 mm/hr in women.

Treatment

MTX treatment was usually started by parenteral application [intravenous (i.v.) or intramuscular (i.m.)] in dosages between 15 mg/week and 25 and was continued as oral medication in most cases. Later, the dose was reduced or increased depending on efficacy and tolerability. MTX either replaced the previous DMARD or was added to the previous DMARD if this was regarded to be useful. The decision to treat a patient with MTX alone or in a combination therapy was based on the physician's judgement without strict previously defined criteria. In a small number of patients (< 5%) with very active disease and a short disease duration, the combination treatment was started from the outset.

For the combination therapy, each DMARD was administered in the full dosage usually applied in our department, i.e., 50 mg/week GSTM up to a total dosage of 2,000 mg, and thereafter 50 mg of GSTM every 2 weeks. In the case of decreasing efficacy, the dose was increased to 50 mg/week.

There was no regular folic acid supplementation. In the case of side effects, the serum level of folic acid was determined, and folic acid (5 mg/week) was added if the serum level was found to be below normal.

Clinical assessments

Standardized clinical evaluations were

Table I. Demographic and baseline data for both treatment groups.

	MTX	MTX + Gold
Number of patients	97	126
Mean age, years (SD)	59 (10.6)	57.2 (10)
Female (%)	84.5	77
Mean disease duration, years (SD)	9.6 (7.2)	7.7 (6.8)
Disease duration > 5 years, %	67	52.3
Rheumatoid-factor positive, %	80.4	88.1
Extraarticular manifestations, %	36.1	36.5
Steinbrocker anatomical stage, %		
Stage I	2.1	5.6
Stage II	25.8	36
Stage III	49.5	40.8
Stage IV	22.7	17.6
Oral corticosteroids, %	62.9	58.7
Mean prednisone dose, mg/day (SD)	7.8 (4.3)	7 (3.9)
Patients with intra-articular steroids, %	75.2	75.3
Therapy with NSAIDs, %	94.8	96
Mean erythrocyte sedimentation rate, mm/hr	55.1	56.7
Mean number of swollen joints, 0 - 32	16.8	19.3
Number pre-treated with		
Parenteral gold	93	126
D-penicillamine	42	28
Chloroquine	42	30
Other DMARD	37	13

MTX: methotrexate; SD: standard deviation; NSAIDs: nonsteroidal antiinflammatory drugs; DMARD: disease-modifying antirheumatic drugs.

performed at baseline, after 1, 3, 6, 9 and 12 months, and every 6 months thereafter, and the following variables were recorded: the number of swollen joints (0-32), grip strength (bar), and the patient's assessment of pain and mobility on a 5-point Likert scale. Side effects and their severity (mild - moderate - severe) (27), changes in medication, and the current and cumulative dose of MTX (and other DMARDs) were also recorded.

Laboratory assessments

Laboratory assessments included ESR, the total blood count including the differential and platelet counts, liver function tests, creatinine, C-reactive protein (CRP), and rheumatoid factor (RF). Safety assessments were carried out at regular intervals, and in the case of side effects MTX was withheld or the dose was adjusted.

Statistical analysis

All data were analyzed by descriptive statistics. Disease variables were analyzed in terms of the difference in the group means between baseline and the different time points by two-tailed t-tests. The group means for other parameters, as well as the differences between the groups, were also compared using two-tailed t-tests. Life table analysis was performed to evaluate the probability of continuing treatment with MTX or combinations.

Results

Patients

Overall, 223 patients are included in this report, 97 of whom were given MTX alone, and 126 of whom received the combination of MTX and i.m. gold. There was no statistically significant difference between the groups with respect to the demographic data (Table I). The mean age of the patients was 58 years and the mean disease duration was 8.5 years. About 80% of the patients were female. Eighty percent of those on monotherapy and 88% of those on combination therapy were RF positive. Sixty-one percent of the patients received systemic corticosteroids (mean dosage of 7.4 mg/day), while 75% required intra-articular corticosteroid injections.

Although the differences were not significant, the single-therapy group had a slightly longer disease duration, more patients with a disease duration of more than 5 years, and more patients with advanced disease (72% Steinbrocker stages III and IV compared with 58% in the combination group). While the ESR was nearly the same in both groups, the number of swollen joints was significantly greater in the combination group ($P < 0.001$).

Treatment

MTXwas started by parenteral application (i.v. or i.m.) at dosages between 15 mg/week and 25 mg/week (mean 17 mg). After 2 months, 80% of the patients had switched to oral medication (15 mg in most cases). In some patients, the mode of application was changed to parenteral again to improve the efficacy or tolerability, and there were always between 10% and 20% who received MTX by the parenteral route. The mean dosage (oral or parenteral) was 12 mg/week in both groups, reaching a mean total cumulative dose of 2,800 mg in patients who were treated for over 48 months (Table II).

Efficacy

A statistically significant improvement in all of the clinical and laboratory parameters of disease activity - the swollen joint count, grip strength, ESR, CRP, and the patient's global assessment of pain and mobility - was observed at all time points during the study in both groups. This was accompanied by a reduction in the number of patients taking steroids and in the mean prednisone dose. The relative decrease in the number of swollen joints was greater in the combination group, which had registered significantly more swollen joints at baseline than the MTX group. In contrast, the decrease in the ESR was greater in the MTX group after 6 and 12 months.

CRP, determined in all 154 patients (63 MTX and 91 MTX+gold) recruited since January 1983, was more elevated in the combination group at baseline and decreased significantly in both groups. The differences between both groups were

Table II. Baseline and follow-up data on efficacy for the two patient groups, one treated with methotrexate (MTX) alone and the other treated with MTX plus gold. Data are expressed as mean values (SD) unless otherwise indicated.

MTX	Baseline n = 97	6 mos. n = 58	12 mos. n = 58	24 mos. n = 54	36 mos. n = 27	48 mo. n = 18	48 mos. n = 65
Swollen joints, 0-32	16.8 (11.8)	9.6** (7.4)	8.1** (8.5)	7.1** (9.2)	5.8** (8.3)	5** (8.6)	7.7* (12.2)
Grip strength right hand, bar	0.26 (0.25)	0.36* (0.25)	0.40** (0.29)	0.37* (0.24)	0.40* (0.24)	0.48* (0.32)	0.35* (0.22)
Patient global pain, 0-4[1]	2.70 (0.55)	2.17** (0.86)	2.05** (0.93)	2.00** (0.90)	2.05** (0.90)	2.05** (0.92)	2.20** (0.85)
Patient global mobility, 0-4	2.54 (0.66)	2.14** (0.89)	1.98** (0.94)	1.93** (0.90)	1.86** (0.89)	1.85** (0.91)	2.26* (0.85)
Erythrocyte sedimentation rate, mm/hr	55.1 (30.2)	25.5** (24.4)	26.6** (27.4)	29.6** (24.1)	18.7** (27.3)	20.8** (28.6)	21.1** (23.0)
C-reactive protein, mg/dl	4.38 (3.8)	1.94** (1.9)	1.86** (2.0)	2.51** (1.7)	2.78* (4.0)	2.84* (1.5)	2.98* (2.0)
MTX dosage, mg/week	16.8 (6.1)	11.6** (5.1)	11.8** (4.5)	10.5** (4.4)	10.1** (3.9)	12.1* (4.0)	12.0** (3.3)
Total cumulative MTX dose		375 (107)	684 (174)	1196 (358)	1736 (443)	2319 (519)	2805 (709)
Daily prednisone dosage, mg	7.8	5.1	4.2	4.7	5	3.7	4
% of patients taking steroids	63	45	33	30	22	16	22
MTX + Gold	n = 126	n = 93	n = 90	n = 70	n = 38	n = 14	n = 56
Swollen joints, 0-32	19.3 (11.7)	9.3** (9.2)	9** (7.8)	8.5** (6.5)	6.6** (3.9)	7.3* (8.4)	12.5* (10.9)
Grip strength right hand, bar	0.29 (0.24)	0.41* (0.23)	0.39* (0.23)	0.36* (0.23)	0.34* (0.27)	0.32* (0.21)	0.28* (0.18)
Patient global pain, 0-4[1]	2.74 (0.47)	2.03** (0.91)	2.25* (0.91)	2.12** (0.86)	1.84** (0.92)	2.45* (0.78)	2.17* (0.82)
Patient global mobility, 0-4	2.58 (0.57)	1.88** (0.94)	2.19* (0.91)	2.02** (0.87)	1.88** (0.91)	2.45* (0.78)	2.09* (0.83)
Erythrocyte sedimentation rate, mm/hr	56.7 (32.4)	36.7** (29.6)	31.3** (21.7)	32** (22.9)	25.4* (20.2)	30.1* (19.3)	27.5** (18.0)
C-reactive protein, mg/dl	5.08 (3.5)	2.1** (2.1)	2.73* (2.1)	3.09* (2.9)	2.42* (3.6)	3.02* (2.1)	3.69* (2.6)
MTX dosage, mg/week	17.0 (5.6)	12.7** (4.4)	12.6** (4.5)	11.3** (5.5)	11.2** (4.1)	11.6* (6.1)	11.1** (4.9)
Total cumulative MTX dose		377 (92)	690 (168)	1216 (291)	1717 (539)	2119 (556)	2876 (671)
Daily prednisone dosage, mg	7	4.5	4.2	4.6	5.2	3.7	7.5
% of patients taking steroids	59	45	43	31	31	14	29

[1] The swollen joint count was significantly greater ($P < 0.001$) in the MTX + gold group.
Difference from baseline significant: * = $P < 0.001$, ** = $P < 0.0001$.

Table III. Reduction in the swollen joint count (% of patients).

Month	MTX		MTX + Gold	
	20 - 50%	≥ 50%	20 - 50%	≥ 50%
6	28	52	24	61
12	17	62	31	55
24	13	72	30	59
36	19	70	13	85
48	17	72	33	67
> 48	17	61	6	53

Table IV. Decrease in ESR (% of patients).

Month	MTX		MTX + Gold	
	20-50%	≥ 50%	20-50%	≥ 50%
6	27	53	28	44
12	20	54	35	49
24	33	46	33	53
36	22	63	23	68
48	22	56	7	79
> 48	11	72	35	59

not significant (Table II).
The percentages of patients in each group who achieved > 50% improvement and 20-50% improvement in the number of swollen joints and in the ESR, respectively, are shown in Tables III and IV. A marked improvement in the number of swollen joints was seen in 52% of those on monotherapy and in 61% of those on combination therapy after 6 months, and in 70% and 85% after 3 years (Table III). A similar improvement in the ESR was seen in 53% and 44% of the patients, respectively, after 6 months, and in 63% and 68% after 3 years (Table IV). After 1 year 35% and 28% of the patients, and after 3 years 67% and 48% of the patients had an ESR below 20 mm/hr compared with 3% and 4% at baseline.
Furthermore, the hemoglobin increased by at least 1 gm/dl in 48% and 55% of the patients in the MTX single-therapy and the combination-therapy groups, respectively.
A remission, defined as less than 2 swollen joints, ESR < 20 mm/hr, no morning stiffness, and no corticosteroids during the last 2 months was seen in 9% and 8% of the patients in the two groups after 1 year, and in 30% and 11% after 3 years.

Table V. The number of patients with adverse clinical or laboratory events and the number of patients who withdrew because of side effects.

	MTX no. (%)		MTX + Gold no. (%)	
Number of patients*	97	(100)	126	(100)
Adverse clinical events				
Nausea/vomiting	49	(51)	65	(52)
Diarrhea	20	(21)	17	(14)
Stomatitis	22	(23)	30	(24)
Hair loss	27	(28)	36	(29)
Skin lesion	12	(12)	15	(12)
Pulmonary symptoms	7	(7)	4	(3)
CNS symptoms	3	(3)	3	(2)
Others	24	(25)	38	(30)
Total	78	(80)	104	(83)
Adverse laboratory events				
Leukopenia**	2	(2)	4	(3)
SGOT elevation	13	(13)	25	(20)
SGPT elevation	34	(35)	51	(40)
Alkaline phosphatase	16	(17)	27	(21)
Proteinuria	20	(21)	21	(17)
Thrombocytopenia***	3	(3)	2	(2)
Total	57	(59)	74	(59)
Withdrawals due to side effects				
Nausea/vomiting	10	(10)	8	(6)
Diarrhea	4	(4)	3	(2)
Stomatitis	6	(6)	6	(5)
Hair loss	4	(4)	4	(3)
Skin lesions	1	(1)	1	(1)
Pulmonary symptoms	1	(1)	2	(2)
Increased pain	1	(1)	2	(2)
Central nervous system symptoms	0	(0)	2	(2)
Others	3	(3)	5	(4)
Total	20	(21)	19	(15)

* The same patient may have had one or more side effects/reasons for withdrawal. ** = < 3,500/mm^3 , *** = 150,000/mm^3. MTX: methotrexate; SGOT: serum glutamic oxaloacetic transaminase; SGPT: serum glutamic pyruvic transaminase.

Tolerability

Seventy-eight patients (80.4%) in the MTX single-therapy group and 104 patients (82.5%) in the combination group reported side effects at some time during the study. A total of 364 side effects were observed; 59 were severe, 161 were moderate, and 144 were mild according to the World Health Organization classification (27). The severity of the side effects was equally distributed in both groups. Side effects regarded to be typical for MTX - i.e., nausea/vomiting, diarrhea/stomatitis, and hair loss - were the ones most frequently observed. Interestingly, rash and stomatitis did not occur more frequently in the combination group (Table V).
Pulmonary symptoms were somewhat

more frequent in the single therapy group and were due to bronchitis in most cases; alveolitis was diagnosed in only one patient in the MTX group. Central nervous system symptoms, including dizziness, concentration problems, forgetfulness, or headache occurred less frequently in the combination group (3.1% for MTX only versus 2.3% for MTX+gold). Other complaints were seen more frequently in the combination group and included an increased tendency to infection (primarily urinary tract infection or bronchitis), wound-healing disturbances, development of rheumatoid nodules, angina pectoris, and post-injection fever. In most cases, the side effects were mild and self-limited, and disappeared spontaneously after a reduction in the dose of MTX, discontinuation of MTX and/or the other DMARD for 1 or 2 weeks, or additional measures (folic acid supplementation or metoclopramide). In both groups, most of the adverse events were reported during the first months of treatment irrespective of the nature of the side effects: 52% of all side effects occurred during the first year.

Laboratory abnormalities were observed in 59% of the patients in both groups (Table V); the most frequent was a slight elevation of the serum glutamic pyruvic transaminase (SGPT) in one-third of the patients, which returned to normal after a change in the nonsteroidal antiinflammatory drug (NSAID) (i.e., from diclofenac to ibuprofen), a reduction in the dose of MTX, or folic acid supplementation. Proteinuria was not observed more frequently in the combination group. This might have been due to a protective effect of MTX against the renal toxicity of parenteral gold (28), or to the fact that the vast majority of these patients had tolerated gold treatment before the introduction of MTX.

Depression of the leukocyte or platelet count was rare in both treatment groups. Some hematologic side effects may have been due to concomitant treatment with sulfonamides or NSAIDs.

The withdrawal rate for side effects was somewhat greater in the single-therapy group (20.6%) than in the combination-treatment group (15.1%), although this difference was not statistically significant.

Termination of treatment

Ninety-six patients (43%) stopped treatment during the follow-up, 43 (44%) in the MTX group and 53 (42%) in the combination group. More patients were withdrawn for side effects in the MTX group than in the combination group (47% and 38% of all withdrawals, respectively); 3 and 6 patients stopped treatment because of remission (no swollen joints, ESR < 20 mm/hr, no steroid intake for 2 months), 1 and 4 patients, respectively, stopped for inefficacy, 6 and 9 for non-compliance, 3 and 3 patients were lost to follow up, and 3 and 2 stopped for other reasons, including intercurrent disease or skepticism regarding the MTX treatment. Seven and 8 patients, respectively, from the two treatment groups died during this observation period, 7 due to myocardial infarction or heart failure, 2 due to stroke, 3 with malignancies, and one patient each due to ulcer perforation, suicide, and atypical pneumonia.

The number of patients who continued treatment was the same in both groups: 72% and 79% after one year, 70% and 74% after 2 years, and 54% and 54% after 5 years. According to our life-table analysis, the probability of remaining on therapy with MTX or combination therapy after 5 years was 60%.

Discussion

The disadvantages of a non-randomised non-blinded study may have been compensated for in our case by various factors: the fact that all the patients who started MTX in our department were included without strict inclusion and exclusion criteria; the large number of patients monitored in one center; the long observation period; and the similarity of the study conditions to the situation in actual clinical practice. It is possible that these conditions may overcome some of the limitations of randomized controlled clinical trials, the results of which may not be applicable to long-term therapy (29).

This unique observational study with a follow-up period of between 12 and 108 months (mean 31.4) confirms the superb results of MTX treatment even in patients with severe progressive RA who are not sufficiently responsive to previous treatment with other DMARDs.

In other clinical combination treatment trials, the drugs within the combination tended to be prescribed at the minimal effective dose, yet more patients from the combination group were withdrawn for toxicity (30). In contrast, we treated our patients in both groups with the full dose used for the individual drug (thus, the mean MTX dose was not different between the MTX monotherapy and the combination groups). Despite this fact we did not find any differences between the groups with respect to the frequency and nature of the side effects and, surprisingly, the withdrawal rate was somewhat lower in the combination group. In contrast to other studies (31-33), we did not observe different or more severe clinical or laboratory side effects with the combination therapy.

Since this study was not designed to be a randomized trial, the comparability of the two groups is a critical point. There were no differences between the groups regarding age, sex, RF positivity, extra-articular manifestations, steroid treatment, or ESR. Disease activity as measured by the number of swollen joints and the CRP was greater in the MTX/GSTM combination group. On the other hand, there was a trend toward a longer disease duration, more advanced disease (Steinbrocker stages III and IV) and multiple DMARD pre-treatment in the group with MTX single therapy. The evaluation of disease in an individual patient by the physician is a complex process which must take into consideration the patient's history, disease activity, drug tolerability, personality, and other factors, and possible differences between groups are not always reflected in their demographic data.

After publishing the results of the first part of this study, the x-ray progression in both groups during the last year before baseline was evaluated. This analysis showed a mean increase in the Ratingen score of 4.4 per patient in the MTX group and of 9.3 in the combination group, which corresponds to 2.6% and 4.9% of the maximum score. The total score at baseline was 35.6 in the MTX group and 42.6 in the combination group, corresponding to 18.7% and 22.4% of the maximum score. These data indicate

that, in addition to a higher number of swollen joints and higher CRP levels, the combination group had greater progression and more destructive disease, as indicated by the radiographic score, than the MTX group.

Knowing the greater radiographic progression before baseline, the comparable efficacy seen in both groups could be interpreted as the superiority of the combination treatment over single therapy with MTX, since patients in the combination treatment group had more severe and aggressive disease at baseline. This impression may have contributed to the physicians' decision to combine both drugs in these patients.

Comparison of mortality in patients treated with MTX or with combination MTX/parenteral gold: An outlook

In 1995 and 1996, an attempt was made to re-investigate all of the patients in this study who were still alive and to determine the date and the reason of death in deceased patients. Some of the patients were still being seen in our outpatient clinic on a regular basis, others were invited to return for re-examination, and patients unable to travel were visited at home.

The outcome at 8 - 15 years (mean 10 years) from baseline in 94% of the patients from both groups could be determined - 91 of 97 patients from the MTX group and 118 of 126 from the combination group. Thirty-seven patients from the MTX group and 39 from the combination group had died before 1996, which corresponds to a mortality rate of 38% and 31%, respectively. This high mortality rate was due to the long disease duration (18.5 years) at the time of re-investigation (the mean age of these patients at disease onset was 52 years). In other studies, a clearly increased mortality rate among RA patients compared with a normal population could be detected only after a disease duration of over 10 years (34).

In this study we attempted to relate the mortality rate to the patients' response to treatment. Response to treatment was defined as the response after one year. It is well known that the maximum effect of MTX is reached after 6 - 12 months, and that there is not much change with continuing treatment thereafter. Moreover, we had a complete set of data on the patients after one year, since the shortest follow-up in the study was exactly 12 months.

When the patients from the two groups were divided into responders (patients with moderate or marked improvement after one year) and non-responders (no improvement or improvement of less than 20%), the responders in both groups had a significantly lower mortality rate than the non-responders. Moreover, the overall mortality rate in the combination treatment group was essentially the same as that of the MTX single-treatment group. Details cannot be given in this overview since the data have not yet been published.

Conclusions

In conclusion, our non-randomized and non-blinded study cannot provide a definite answer to the question as to whether combination therapy with parenteral gold and MTX is more efficacious than therapy with MTX alone. Taking into account the higher disease activity at baseline and greater x-ray progression before baseline among the patients in the combination group, one might come to the conclusion that combination treatment is superior to monotherapy. In addition, this study clearly showed that there is no increased toxicity with combination treatment.

The study also shows that there is no increased mortality in patients treated with combined MTX and parenteral gold. However, in patients continuing this treatment and responding to it - as with those on successful MTX treatment - the standardized mortality rate is dramatically decreased compared with patients not responding to or discontinuing this treatment.

References

1. FRIES JF, WILLIAMS CA, RAMEY D, BLOCH DA: The relative toxicity of disease modifying antirheumatic drugs. *Arthritis Rheum* 1993; 36: 297-306.
2. FELSON DT, ANDERSON JJ, MEENAN R: The comparative efficacy and toxicity of second-line drugs in rheumatoid arthritis. *Arthritis Rheum* 1990; 33: 1449-61.
3. Cooperation Clinics Committee of the American Rheumatism Association: A controlled trial of gold salt therapy in rheumatoid arthritis. *Arthritis Rheum* 1973; 353-8.
4. SIGLER JW, BLUHM GB, DUNCAN H, *et al*.: Gold salts in the treatment of rheumatoid arthritis. *Ann Intern Med* 1974; 60: 21-6.
5. CATS A: A multicenter controlled trial of the effects of different dosage of gold therapy, followed by a maintenance dosage. *Agents Actions* 1976; 6: 355-65.
6. LUUKKAINEN R, ISOMÄKI H, KAJANDER A: Effect of gold treatment on the progression of erosions in RA patients. *Scand J Rheumatol* 1977; 6: 123-7.
7. LUUKKAINEN R, ISOMÄKI H, KAJANDER A: Effect of gold on progression of erosions in rheumatoid arthritis. Better results with early treatment. *Scand J Rheumatol* 1977; 6:189-92.
8. LUUKKAINEN R: Chrysotherapy in rheumatoid arthritis with particular emphasis on the effect on radiographical changes and on the optimal time of initiation of therapy. *Scand J Rheumatol* 1980; 34: 1.
9. LARSEN A, HORTON J, HOWLAND C: The effects of auranofin and parenteral gold in the treatment of rheumatoid arthritis: An x-ray analysis. *Clin Rheumatol* 1984; 3 (Suppl. 1): 97-104.
10. BUCKLAND-WRIGHT JC, CLARKE GS, CHIKANZA IC, GRAHAME R: Quantitative microfocal radiography detects changes in erosion area in patients with early rheumatoid arthritis treated with myocrisine. *J Rheumatol* 1993; 20: 243-7.
11. SANY J, KALISKI S, COURET M, *et al*.: Radiologic progression during intramuscular methotrexate treatment of rheumatoid arthritis. *J Rheumatol* 1990; 17: 1636-41.
12. DROSOS AA, KARANTANAS AH, PSYCHOS D, *et al*.: Can treatment with methotrexate influence the radiological progression of rheumatoid arthritis? *Clin Rheumatol* 1990; 9: 342-5.
13. NORDSTROM DM, WEST SG, ANDERSEN PA, SHARP JT: Pulse methotrexate therapy in rheumatoid arthritis. A controlled prospective roentgenographic study. *Ann Intern Med* 1987; 107: 797-801.
14. REYKDAL S, STEINSSON K, SIGURJONSSON K, BREKKAN A: Methotrexate treatment of rheumatoid arthritis: Effects on radiological progression. *Scand J Rheumatol* 1989; 18: 221-6.
15. RAU R, HERBORN G, KARGER T, WERDIER D: Retardation of radiologic progression in rheumatoid arthritis with methotrexate therapy. *Arthritis Rheum* 1991; 10: 1236-44.
16. MORRASUT T, GOLDSTEIN R, CYR M, *et al.*: Gold-sodium-thiomalat compared to low-dose methotrexate in the treatment of rheumatoid arthritis - A randomised double-blind 26-week trial. *J Rheumatol* 1989; 16: 302-6.
17. SUAREZ-ALMAZOR ME, FITZGERALD A, GRACE M, RUSSELL AS: A randomised controlled trial of parenteral methotrexate compared with sodium aurothiomalate. *J Rheumatol* 1988; 15: 753-6.
18. RAU R, HERBORN G, KARGER T, BLECHSCHMIDT J: A double blind randomised parallel trial of intramuscular methotrexate and gold sodium thiomalate in early erosive rheumatoid arthritis. *J Rheumatol* 1991; 18: 328-33.

19. RAU R, HERBORN G, MENNINGER H, BLECHSCHMIDT J: Comparison of intramuscular methotrexate and gold sodium thiomalate in the treatment of early erosive rheumatoid arthritis: 12-month data of a double-blind parallel study of 174 patients. *Br J Rheumatol* 1997; 36: 345-52.
20. MENNINGER H, HERBORN G, BLECHSCHMIDT J, RAU R: A 36-month comparative trial of methotrexate and gold sodium thiomalate in the treatment of early active and erosive rheumatoid arthritis. *Br J Rheumatol* 1998; 37: 1060-8.
21. SANDER O, HERBORN G, BOCK E, RAU R: Prospective six-year follow-up of patients withdrawn from a randomised study comparing parenteral gold salt and methotrexate. *Ann Rheum Dis* 1999; 58: 281-7.
22. RAU R, HERBORN G, MENNINGER H, SANGHA O: Progression in early erosive rheumatoid arthritis: 12-month results from a randomised controlled trial comparing methotrexate and gold sodium thiomalate. *Br J Rheumatol* 1998; 37: 1220-6.
23. FURST DE: Clinical pharmacology of combination DMARD therapy in rheumatoid arthritis. *J Rheumatol* 1996; 23 (Suppl. 44): 86-90.
24. RAU R, SCHLEUSSER B, HERBORN G, KARGER T: Long term treatment of destructive rheumatoid arthritis with methotrexate. *J Rheumatol* 1997; 24: 1881-9.
25. RAU R, SCHLEUSSER B, HERBORN G, KARGER T: Long-term combination therapy of refractory and destructive rheumatoid arthritis with methotrexate (MTX) and intramuscular gold or other disease modifying antirheumatic drugs compared to MTX monotherapy. *J Rheumatol* 1998; 25: 1485-92.
26. ROPES WN, BENNETT GA, COBB S, JACOX R, JESSAR RA: 1958 revision of diagnostic criteria for rheumatoid arthritis. *Bull Rheum Dis* 1958; 9: 175-6.
27. *WHO Handbook for Reporting Results of Cancer Treatment*. World Health Organization, Geneva, 1979.
28. RAU R, WASSENBERG S, HERBORN G: Can methotrexate reduce the renal toxicity of parenteral gold? *J Rheumatol* 1993; 20: 759-61.
29. PINCUS T, STEIN M: What is the best source of useful data on the treatment of rheumatoid arthritis: Clinical trials, clinical observations, or clinical protocols ? *J Rheumatol* 1995; 22: 1611-7.
30. FELSON DT, ANDERSON JJ, MEENAN RF: The efficacy and toxicity of combination therapy in rheumatoid arthritis. *Arthritis Rheum* 1994; 37: 1487-91.
31. DAWES PT, TUNN EJ, FOWLER PD, SCOTT DL: Combination therapy in rheumatoid arthritis. *Br J Rheumatol* 1984; 41: 28-35.
32. KLIPPEL JH: Winning the battle, losing the war? Another editorial about rheumatoid arthritis (Editorial). *J Rheumatol* 1990; 17: 1118-22.
33. BOERS M, RAMSDEN M: Long-acting drug combinations in rheumatoid arthritis: A formal overview. *J Rheumatol* 1991; 18: 316-24.
34. SCOTT DL, SYMMONS DPM, COULTON BL, POPERT AJ: Long-term outcome of treating rheumatoid arthritis: Results after 20 years. *Lancet* 1987; 337; 1108-11.