A 48-week, randomized, double-blind, double-observer, placebo-controlled multicenter trial of combination methotrexate and intramuscular gold therapy in rheumatoid arthritis: results of the METGO study

Lehman A J, Esdaile J M, Klinkhoff A V, Grant E, Fitzgerald A, Canvin J

Record Status
This is a critical abstract of an economic evaluation that meets the criteria for inclusion on NHS EED. Each abstract contains a brief summary of the methods, the results and conclusions followed by a detailed critical assessment on the reliability of the study and the conclusions drawn.

Health technology
The study examined the effect of adding intramuscular (IM) gold to the same standard dose of methotrexate (MTX) that patients were prescribed prior to this trial, in patients with rheumatoid arthritis (RA) with suboptimal response to MTX. This drug is one of the disease-modifying antirheumatic drugs (DMARDs) that are used in the treatment of RA to avert long-term disability and premature death.

Type of intervention
Treatment.

Economic study type
Cost-effectiveness analysis.

Study population
The study population comprised patients with RA diagnosed, according to the American College of Rheumatology (ACR), with suboptimal response to at least 12 weeks of MTX therapy. Suboptimal control was defined as 4 or more swollen joints, 5 or more tender joints, and an erythrocyte sedimentation rate of at least 25 mm/hour or morning stiffness for 30 minutes or longer. MTX therapy at a dose of 15 mg/week or more was necessary for inclusion in the study (unless toxicity necessitated a lower dose). Other inclusion criteria were RA disease duration of between 4 months and 10 years, age 19 years or older, and provision of informed consent. The exclusion criteria were:

- prior treatment with auranofin or IM gold (aurothiomalate or aurothioglucose);
- treatment with any DMARD other than MTX or MTX-HCQ or other experimental drug within 3 months of entry;
- confined to bed or a wheelchair;
- platelet count <140,000 per mm3, white blood cell (WBC) count <3,500 per mm3, serum creatine >140 micromoles/L, proteinuria +/+ on dipstick (or >250 mg/day), or levels of aspartame aminotransferase or alanine aminotransferase greater than twice the upper limit of normal;
- intent to become pregnant;
- unwillingness to continue with contraceptive practices;
- major surgery within 3 months;
- severe co-morbid condition likely to compromise survival or study participation; or
- unwillingness or other inability to cooperate.
Setting
The setting was both tertiary care and secondary care. The study was conducted in Canada.

Dates to which data relate
The clinical and resource use data referred to patients enrolled between May 1999 and March 2002, who were followed a 48-week trial period. The price year was 2002.

Source of effectiveness data
The effectiveness data were derived from a single study.

Link between effectiveness and cost data
The costing was undertaken on the same patient sample as that used in the effectiveness study.

Study sample
"The sample size was originally calculated to provide a power of 80%, with a 2-tailed alpha level of 0.05, to detect a 20% improvement in responder rate for the MTX-IM gold group over the MTX-placebo group". Eighty-two patients were initially assessed for eligibility but 17 did not meet the criteria. Thus, the study contained data on 65 patients (38 in the treatment group and 27 in the placebo group). The model hypothesised an expected response in the treatment and placebo groups of 36% and 16%, respectively, and withdrawal rates of 35% and 10%. These results were hypothesised because there were too few patients for the study sample: there were other competing industry trials requiring participants with suboptimal response to MTX.

Study design
This study was a blinded, randomised, placebo-controlled trial that lasted 48 weeks. The trial was conducted in 13 centres in Canada, using a treatment protocol that was developed by consensus of all the investigators. The block randomisation was stratified by study centre and generated from a random-number table with variable-sized blocks. The study attempted to maintain blinding of the outcome assessment by using external assessors, who were unaware of the treatment, to assess outcomes at 12-weekly visits over the 48 weeks of the trial. Three patients in the placebo group and two patients in the gold group were lost to follow-up.

Analysis of effectiveness
The analysis of the clinical study was conducted on an intention to treat basis. The primary health outcome was "the percentage of patients who met the ACR 20% improvement (ACR20) criteria at week 48". This improvement is measured after an examination of the tenderness of 50 joints and an assessment of the swelling of 26 joints. The pain level and the RA activity were also assessed using a visual analogue scale. Physical functioning was assessed using the Health Assessment Questionnaire for physical function index. Other secondary outcomes included:

- the ACR50 and ACR 70, the individual criteria that make up the primary outcome;
- the results of laboratory tests;
- the number of dose of intraarticular corticosteroids;
- the daily dose of prednisone;
- the duration of morning stiffness;
- grip strength;
- adverse events; and
quality of life, as assessed by the EuroQol.

The groups were comparable at baseline as there were no statistically significant differences in the demographic variables between the groups (compared using Student's t-test or chi-squared tests).

**Effectiveness results**

Sixty-one per cent of patients receiving gold and 30% of those receiving placebo achieved an ACR20 response (chi-squared 6.04, p=0.014; logistic regression odds ratio 3.64, 95% confidence interval, CI: 1.3 - 10.4; p=0.016). Twenty-six per cent of patients receiving gold and 4% of those receiving placebo achieved an ACR50 response, (p=0.0017), while 21% of patients receiving gold achieved an ACR70 response compared with 0% of patients receiving placebo, (p=0.011).

Patients receiving gold were significantly more likely to have an improvement in tender joint count, erythrocyte sedimentation rate and physician's rating of disease. In addition, there was a trend in favour of an improved swollen joint count.

For physician's assessment of disease severity (scale of 0 - 100), the change score was -49 (+/- 6) and -49 (+/- 7) in the gold group at weeks 24 and 48, and -16 (+/- 9) and -16 (+/- 16) in the placebo group at weeks 24 and 48.

For pain severity (scale of 0 - 100), the difference in change at 48 weeks was 16 (+/- 22) (95% CI: -28 - 59; p=0.476).

For patient's assessment of disease severity (scale of 0 - 100), the difference in change at 48 weeks was 11 (+/- 17) (95% CI: -23 - 44; p=0.537).

**Clinical conclusions**

In patients with RA and suboptimal control response to MTX, the addition of weekly gold is significantly more effective than the addition of placebo in increasing the percentage of ACR20 responders.

**Measure of benefits used in the economic analysis**

No summary measure of health benefits was reported. In effect, a cost-consequences analysis was performed. In addition to clinical outcomes, patient preferences for health states were valued using EQ-5D health states.

**Direct costs**

The health service direct costs were evaluated. These included physician services, non-physician services, technical and professional components, medication costs, hospitalisations and outpatient surgery costs, and emergency room visits and assistive devices. The costing for physician services was based on an average of data from Quebec and Ontario. The costs and resource use were not reported separately. For non-physician services, the costs were based on fee data provided by professional associations in Quebec and Ontario. The costs were not discounted as the time horizon was too short. The study reported the average costs for the previous 24 weeks at weeks 0, 24 and 48 of the study. Essentially, the authors took the costs of the previous 24 weeks at week zero to be the cost of MTX alone, and then calculated the incremental costs (referred to as marginal costs in the paper) of MTX-IM gold and MTX-placebo compared with MTX alone and of MTX-IM gold compared with MTX-placebo. The price year was 2002.

**Statistical analysis of costs**

The study presented mean or median values, ranges and interquartile ranges for the direct costs and productivity values for both groups, at weeks 0, 24 and 48. In addition, the incremental costs comparing the groups were calculated with the mean and standard deviation, and the 95% CI, according to the intention to treat analysis and the analysis of patients completing 48 weeks.
Indirect Costs
The difference in productivity values between the alternative interventions was estimated, which the authors quantified as the value of time spent at work by the patient less the cost of time spent by others providing care for the patient. The value of time was the average age and gender-matched wages of Canadians. The authors derived incremental costs as described under 'Direct Costs'. The price data referred to year 2002. No discounting of the costs was performed.

Currency
US dollars ($). The cost calculations were originally conducted in Canadian dollars, but were converted into US dollars using the purchasing power parity.

Sensitivity analysis
No sensitivity analysis was performed in this study.

Estimated benefits used in the economic analysis
The authors did not determine a summary benefit measure. See the 'Effectiveness Results' section. However, some quality of life data were reported: at both weeks 24 and 48, the patients had higher scores (35 +/- 7 and 33 +/- 7) in the gold group than in the placebo group (-7 +/- 5 and -6 +/- 5), (p<0.001).

Cost results
In the intention to treat analysis, the incremental total cost of MTX-IM gold compared with MTX alone was -$2,471 (+/- 13,527). The incremental total cost of MTX-placebo compared with MTX alone was -$2,024 (+/- 15,196).

In the analysis of patients completing 48 weeks, the incremental total cost of MTX-IM gold compared with MTX alone was -$1,993 (+/- 11,774). The incremental total cost of MTX-placebo compared with MTX alone was $3,094 (+/- 13,850).

The incremental total cost of MTX-IM gold compared with MTX-placebo for the intention to treat analysis was -$447 (95% CI: -7,759 - 6,866). For the treatment completers analysis it was -$5,088 (95% CI: -13,649 - 3,473).

Synthesis of costs and benefits
The costs and benefits were not combined because, according to the authors, the intervention was a dominant strategy from both clinical and cost-effectiveness perspectives.

Authors' conclusions
The addition of weekly intramuscular (IM) gold to methotrexate (MTX) caused significant clinical improvement and also led to cost-savings. The authors therefore stated that the study had demonstrated the clinical effectiveness and cost-effectiveness of the combination MTX-IM gold.

CRD COMMENTARY - Selection of comparators
The authors explicitly compared the addition of IM gold with MTX, which is the most commonly prescribed DMARD. The rationale for this comparison was that the authors wished to assess whether IM gold, although an old therapy, might be an ideal step-up strategy in combination with MTX. The authors chose placebo as a comparator for the intervention drug, and this allowed the active value of the treatment to be evaluated.

Validity of estimate of measure of effectiveness
The effectiveness measures were obtained from a randomised, placebo-controlled, double-blind, double-observer trial, which was appropriate for the study question. The analysis was conducted both on an intention to treat basis and by
treatment completers only. The study sample was representative of the study population and, as it was a randomised study, confounders were controlled for. In addition, the patient groups were shown to be comparable at baseline. Details about many aspects of the study (such as the side effect monitoring, laboratory monitoring) were provided in the paper. This added-value information gives credibility to the quality of the methodology and the effectiveness results. The authors also provided information about the adverse events in each group, and the reasons for loss-to-follow up or discontinuations in each group.

**Validity of estimate of measure of benefit**
No summary measure of benefit was used. The study was, in effect, a cost-consequences analysis. However, the authors did derive patient utility values using EuroQoL estimates.

**Validity of estimate of costs**
All the categories of costs relevant to the study perspective were included in the study. The unit costs and resource use were not reported separately. The authors did not report the resource use in each group, nor provide any statistical analysis about this point. The authors detailed the source of all the relevant unit costs. They also reported the date to which the prices related and the currency conversions made, but only the total direct and indirect costs were reported and not each component. However, the total costs results were presented in a very detailed manner, with both direct and indirect costs and mean, median, range and marginal costs reported. The authors used the word “marginal” although the reader may better understand this to mean incremental.

**Other issues**
This study was important as it was the first reported randomised, placebo-controlled trial investigating the combination of MTX-IM gold for the treatment of RA. The effectiveness results were similar to those found in other studies (Marcus and Sebba, 1994; Brawer, 1988; Rau and Karger, 1989; see ‘Other Publications of Related Interest( for bibliographic details). However, this paper is more important because it assessed the resource use of IM gold and the costs derived, showing it to be a cost-effective treatment strategy. The authors did not report the results selectively and their conclusions matched the scope of the analysis.

**Implications of the study**
IM gold added to MTX is a treatment strategy that should be considered. It is important to note that some DMARDs are very expensive, so accurate evaluations of therapies such as IM gold are very important in obtaining the most cost-effective treatments for RA.

**Source of funding**
Supported by the Canadian Institutes of Health Research, the Arthritis Society of Canada, the Edmonton Arthritis Association, the Royal Alexandra Hospital Foundation, and the Penticton Regional Hospital Research Fund.

**Bibliographic details**

**PubMedID**
15880810

**DOI**
10.1002/art.21018

**Other publications of related interest**


Indexing Status
Subject indexing assigned by NLM

MeSH
Antirheumatic Agents /administration & dosage /adverse effects; Arthritis, Rheumatoid /drug therapy; Double-Blind Method; Drug Therapy, Combination; Female; Gold /administration & dosage /adverse effects; Humans; Injections, Intramuscular; Male; Methotrexate /administration & dosage /adverse effects; Middle Aged; Time Factors

AccessionNumber
22005000942

Date bibliographic record published
31/05/2006

Date abstract record published
31/05/2006