Rheumatology 2005;44:61–66 doi:10.1093/rheumatology/keh512

The treatment of inflammatory arthritis with methotrexate in clinical practice: treatment duration and incidence of adverse drug reactions

A. J. Kinder, A. B. Hassell[1], J. Brand[1], A. Brownfield[1], M. Grove[1] and M. F. Shadforth[1]

Objective. **To identify the proportion of patients with inflammatory arthritis who remain on methotrexate in the medium to long term and the incidence of side-effects in clinical practice.**

Method. **The study population comprised all patients with inflammatory arthritis treated with methotrexate and monitored in clinics under the auspices of Staffordshire Rheumatology Centre. Two clinical auditors collected data retrospectively from the computer database used to support monitoring of patients on disease-modifying anti-rheumatic drugs. Information was collected on duration of treatments and reasons for stopping treatment. For patients identified as having potentially serious side-effects or who died whilst taking methotrexate, further information on their outcome was collected from patients' medical notes and where applicable post mortem reports and death registers.**

Results. **Between 1986 and 1999, 673 patients were treated with methotrexate, of whom 551 had a diagnosis of rheumatoid arthritis. From the Kaplan–Meier analysis, the probability of patients remaining on treatment 5 yr after starting methotrexate was 0.74. Three hundred and sixteen patients stopped methotrexate between 1986 and 1999. In 117 patients, the methotrexate was restarted. Seventy-two patients (10.7% of all patients) stopped because of inefficacy or patient choice or situation. Thirty-seven patients (5.5%) stopped methotrexate due to abnormal haematology (usually low neutrophils). Thirty-seven patients (5.5%) stopped methotrexate due to abnormalities in liver function tests. Life-threatening side-effects were identified in 12 patients (1.8%). These included six pneumonitis, five cytopenias and one disseminated varicella zoster. Two of these patients (0.3%) died, one from pneumonitis and one from disseminated varicella zoster. A total of 25 patients (3.7%) died while taking methotrexate and four died (0.6%) within 3 months of stopping methotrexate. One death (0.15%) was directly attributable to methotrexate (methotrexate pneumonitis).**

Conclusion. **This study has shown that methotrexate is well tolerated in clinical practice in the medium to long term. It has produced accurate data on the incidence of adverse effects of methotrexate in a local population in a non-research setting. It has identified the incidence of life-threatening side-effects to be 1.7% with one death (0.15%) directly due to methotrexate. This information should prove useful when recommending such treatment to patients with inflammatory arthritis.**

KEY WORDS: Methotrexate, Inflammatory arthritis.

Methotrexate is among the most commonly used drugs for the treatment of rheumatoid arthritis. It is equal or superior to other disease-modifying agents in rheumatoid arthritis in randomized controlled trials and is an effective treatment in the non-research setting [1–6]. As with other disease-modifying anti-rheumatic drugs (DMARDs), a major constraint on the use of methotrexate is the occurrence of adverse effects. Both 'major' (i.e. potentially life-threatening) and 'minor' side-effects may lead to termination of treatment even if the efficacy of the drug is satisfactory. The risk of side-effects with methotrexate is difficult to quantify from clinical trials because of issues such as relatively small numbers and short trial duration, with estimates of serious adverse drug reactions such as methotrexate pneumonitis varying from 0.3 to 7.5% [7]. Moreover, clinical trials do not necessarily reflect clinical practice. In particular, patient selection for clinical trials may exclude a significant number of patients who might be treated in clinical practice. In addition, the monitoring, support and follow-up of patients in clinical trials may differ from routine practice. Obtaining accurate information on side-effects and duration of therapy in clinical practice is extremely difficult, with few centres having this information available. Yet such information is invaluable in informing the decision to start methotrexate and in explaining to patients the risks of methotrexate treatment. Because our practice has been to monitor all patients on DMARDs, supported by a computer decision-support system which doubles as a clinical database, we are in a strong position to provide such information. We have previously reported an overview of our experience with patients on DMARDs [8]. In this study we aimed to identify the proportion of patients who stayed on methotrexate, the incidence of side-effects in clinical practice and details of any serious adverse events occurring in patients while they were being treated with methotrexate.

Leicester Royal Infirmary and [1]Staffordshire Rheumatology Centre, Haywood Hospital, Burslem, Stoke on Trent, UK.

Submitted 3 September 2004; revised version accepted 7 November 2004.

Correspondence to: A. B. Hassell. E-mail: andyhassell@doctors.org.uk

Methods

Monitor clinics

Staffordshire Rheumatology Centre has five consultants serving a population of 550 000. Over 95% of patients treated with DMARDs are monitored by the department.

In a nurse-led clinic, patients are seen weekly for the first month following initiation of methotrexate and monthly thereafter unless there are drug-related problems that require more frequent monitoring. At each visit the patient is interviewed by a nurse with respect to drug-related side-effects and their blood is taken for a full blood count (FBC) and differential white cell count (WCC) and liver function tests. The nurse has access to a physician when there is uncertainty over patient management. Blood results and drug-related side-effects are later entered onto a monitor program and computer database. The monitor program has protocols for blood abnormalities to be identified. These were defined by consensus between the participating rheumatologists [9]. They are defined not only by absolute levels but also by the rates of change of results, allowing potential problems to be detected earlier. The program reads the current and previous two results when monitoring for abnormalities. Any results falling outside the monitoring program's parameter are highlighted on screen and generate a print out. The print outs are reviewed daily by a physician who takes appropriate action. If therapy is stopped, this is entered onto the program together with the reason for stopping which is chosen from a 'look-up' table.

All patients on methotrexate under the care of the rheumatology unit attended the drug surveillance clinic, with a few exceptions for whom monitoring is performed by the general practitioner.

Prescribing protocol

A prescribing protocol for methotrexate is generally followed with flexibility of dosage regimens according to efficacy and side-effects. Methotrexate is generally started at 7.5 mg weekly with folic acid 5 mg daily [10]. After 2–3 months, the dose is increased by 2.5 mg/week if clinical response is deemed inadequate. The maximum dose used is 25 mg/week.

Patients are educated to limit their alcohol consumption to only occasional alcohol ($\leq$10 units/week) and to avoid binge drinking. Methotrexate was not stopped routinely prior to surgery.

Data collection

Two clinical auditors collected data retrospectively from the rheumatology monitoring database using a scannable audit pro forma. Any data that were required for the audit but which were not directly recorded on the monitoring database were gleaned from the clinic letters. Data on blood results were also recorded from the hospital information support system (HISS) for 17 patients.

For patients identified as having potentially serious side-effects or who died whilst taking methotrexate or within 3 months of stopping, further information on their outcome following cessation of methotrexate was collected by a rheumatology nurse (AB) from patients' medical notes, post mortem reports and death registers.

All data were analysed by the clinical audit department using the statistical package SPSS.

Quality control

In order to check the accuracy of the data entered onto the monitor database, a random sample of 108 blood test results from the database were compared with results on the hospital information system.

Survival analysis

Statistical analysis used SPSS version 9.0. For the purpose of the Kaplan–Meier survival analysis, adverse drug reactions that led to hiatus in therapy of $\leq$3 months were ignored, the two courses being analysed as one course. Only the first courses of methotrexate were included.

Results

Between 1986 and 1999, 673 patients were treated with methotrexate, the equivalent of 1402 patient years of methotrexate treatment. Five hundred and fifty-one patients had rheumatoid arthritis. The characteristics of the patients treated with methotrexate are shown in Table 1.

Over this period, 316 patients (47%) stopped taking methotrexate, 206 of whom had rheumatoid arthritis. Seventy-two patients (10.7%) stopped because of inefficacy or patient choice/situation leaving 244 patients (36.3%) who stopped treatment because of some form of adverse event. The diagnosis in these 244 patients is given in Table 2. Table 3 identifies the reasons why these patients stopped treatment. Methotrexate was prescribed as monotherapy in 225 patients (92%) of the 244 who had an adverse reactions to it. In the remaining patients, it was prescribed in combination with azathioprine (two patients), penicillamine (two patients), hydroxychloroquine (four patients), sulphasalazine (six patients), parenteral gold (four patients) and ciclosporin (one patient).

TABLE 1. Characteristics of all patients treated with methotrexate ($n = 673$)

Diagnosis	No of patients	No of females (%)	No of males (%)	Average age (±S.D.) (yr)	Average disease duration (±S.D.) (yr)
Polymyalgia rheumatica	4	4 (100%)	0 (0%)	72.8 (±3.5)	5.75 (±4.2)
Juvenile chronic arthritis	21	13 (62%)	8 (38%)	17.5 (±8.5)	11.7 (±12.7)
Systemic lupus erythematous	6	4 (67%)	2 (33%)	39.8 (±15.4)	6 (±3.6)
Scleroderma	4	2 (50%)	2 (50%)	53.3 (±6.2)	10.5 (±2.5)
Relapsing polychondritis	2	2 (100%)	0 (0%)	66.5 (±4.9)	2.5 (±2.1)
Primary Sjögren's	2	2 (100%)	0 (0%)	59 (±8)	2 (±2.8)
Polymyositis	5	2 (40%)	3 (60%)	63.8 (±7.5)	12 (±3.9)
Mixed connective tissue disease	1	1 (100%)	0 (0%)	31	N/A
Giant cell arthritis	3	3 (100%)	0 (0%)	73.7 (±6.4)	0.7 (±1.2)
Undifferentiated vasculitis	2	1 (50%)	1 (50%)	60.5 (±19.1)	4.5 (±4.9)
Reiter's syndrome	2	1 (50%)	1 (50%)	51.5 (±17.7)	6.5 (±0.7)
Ankylosing spondylitis	3	1 (33%)	2 (67%)	49.7 (±10.8)	20 (±12.7)
Psoriatic arthritis	54	30 (56%)	24 (44%)	50.2 (±15)	10.1 (±7.9)
Rheumatoid arthritis	551	382 (69%)	169 (31%)	63.5 (±11.7)	14.9 (±9.9)
Undifferentiated inflammatory arthritis	13	11 (85%)	2 (15%)	37.85 (±11.6)	7.9 (±3.9)

The commonest reasons for stopping treatment were gastrointestinal symptoms (10.8%) or abnormal liver function tests (5.5%), haematological abnormalities (5.5%), respiratory symptoms or signs (3%) and skin abnormalities (2.1%). For eight patients, we were unable to identify the reason for stopping treatment.

In 117 patients (17%), the methotrexate was restarted. The median time from stopping to restarting methotrexate was 28 days. Of the patients who restarted methotrexate, 62 patients stopped taking methotrexate for a second time. Some patients in the sample started and stopped methotrexate up to five times.

Figure 1 shows the Kaplan–Meier survival analysis for all patients for discontinuation of methotrexate due to either adverse drug reactions or inefficacy. Courses of methotrexate stopped for other reasons were censored. The probability of patients remaining on methotrexate 5 yr after starting treatment was 0.74. Figure 2 shows the same data for patients with rheumatoid arthritis only. For these analyses, courses interrupted for less than 3 months were treated as a single course.

One hundred and two patients (15.2%) were identified as having potentially serious side-effects from methotrexate. These included 37 (5.5%) due to abnormal liver function tests, 25 (3.7%) due to low white cell count, nine (1.3%) due to low platelets and two (0.3%) due to pancytopenias. Six patients (0.9%) were thought to have methotrexate pneumonitis on the basis of a respiratory illness with no pathogen identified, an abnormal chest X-ray, restrictive pulmonary function tests and hypoxia. Our approach was to manage the potential pneumonitis patients in conjunction with the local respiratory team, and where pneumonitis was suspected, high-dose steroids were used. Bronchopulmonary lavage and lung biopsies were not performed. One patient (0.15%) died from pneumonitis. Fourteen patients (2.1%) stopped because of other pulmonary adverse events (generally chest infections).

In 12 patients (1.8%), the side-effects were identified as life-threatening. These included the six (0.9%) with pneumonitis, five (0.7%) with cytopenias and one (0.15%) with disseminated varicella zoster. One of the patients with pneumonitis and the patient with disseminated varicella zoster died.

A total of 25 patients (3.7%) died while taking methotrexate and four (0.6%) died within 3 months of stopping methotrexate. The causes of death are shown in Table 4. Only one death (0.15%) (due to methotrexate pneumonitis) was directly attributable to the methotrexate. There were seven deaths (1%) from infection in which methotrexate may or may not have played a part. None of the seven patients had leucopenias.

Table 2. Diagnosis in 244 patients who stopped methotrexate because of an adverse event

Diagnosis	Number
Rheumatoid arthritis	206
Psoriatic arthritis	12
Juvenile chronic arthritis	8
Polymyositis	3
Systemic lupus erythematous	2
Reactive arthritis	2
Systemic sclerosis	2
Ankylosing spondylitis	1
Polymyalgia rheumatica	1
Inflammatory monoarthritis and acquired IgA deficiency	1
Churg–Strauss syndrome	1
Total	239[a]

[a]In five cases, this information was not recorded.

Table 3. Reasons for patients stopping methotrexate ($n=236$)[a]

Reason for stopping methotrexate	Number of patients ($n=673$)[a]	% of patients	Number of patients with RA ($n=551$)	% of patients with RA	Number of patients without RA ($n=122$)[b]	% of patients without RA
Haematology	37	5.5	29	5.3	7	5.7
Low neutrophils	23	3.4	16	2.9	6	4.9
Low platelets	9	1.3	8	1.4	1	0.8
Pancytopenia	2	0.3	2	0.4	0	0
Other (↑Eos., anaemia, abnormal blood results)	3	0.4	3	0.5	0	0
Gastrointestinal	73	10.8	61	11.1	12	9.8
LFT abnormalities	37	5.5	29	5.3	8	6.5
Mouth ulcers	13	1.9	12	2.2	1	0.8
Nausea and vomiting	11	1.6	10	1.8	1	0.8
Diarrhoea	8	1.2	8	1.4	0	0
Other (indigestion, abdominal pain, sore tongue or mouth, diverticular abscess)	4	0.6	2	0.4	2	1.6
Pulmonary	20	3.0	18	3.3	2	1.6
Pneumonitis	6	0.9	5	0.9	1	0.8
Shortness of breath	4	0.6	4	0.7	0	0
Chest infection	4	0.6	3	0.5	1	0.8
RA-related pulmonary fibrosis	1	0.1	1	0.2	0	0
Others (asthma 2, adverse reaction 1,chest problems 1, pleural effusion 1)	5	0.7	5	0.9	0	0
Skin	14	2.1	11	2.0	3	2.4
Rash	10	1.5	8	1.4	2	1.6
Itching	2	0.3	1	0.2	1	0.8
Alopecia	2	0.3	2	0.4	0	0
Intercurrent infection	30	4.4	22	3.9	7	5.7
Increase nodules	2	0.3	2	0.4	0	0

RA, rheumatoid arthritis; LFT, liver function test; Eos., eosinophils.
[a]For eight patients, the reasons for stopping methotrexate could not be found.
[b]The diagnosis was not known in one patient.

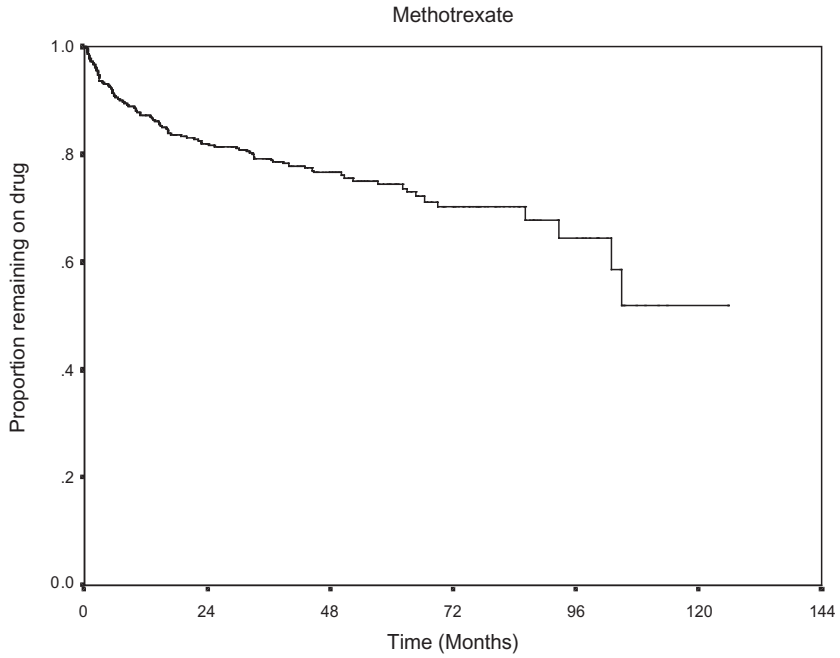

FIG. 1. Kaplan–Meier survival curve of patient continuation on methotrexate in months ($n = 673$).

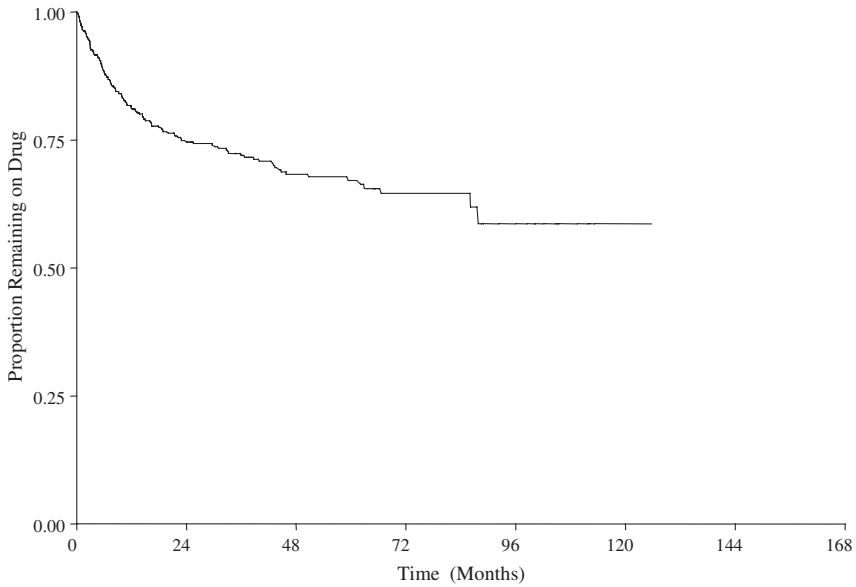

FIG. 2. Kaplan–Meier survival curve of continuation on methotrexate (in months) for patients with rheumatoid arthritis ($n = 551$).

In the patients who stopped methotrexate due to adverse reactions, 166 patients (68%) were documented as taking folic acid 5 mg daily. This percentage may be an underestimate due to a lack of documentation in the notes rather than prescription. In the patients who had adverse reactions to methotrexate, 44 patients (19%) were also on low-dose prednisolone and 118 patients (48%) were on a non-steroidal anti-inflammatory drug. The average dose on stopping methotrexate was 10.7 mg (range 2.5–25 mg).

Data quality

One hundred and eight blood results on the computer database were compared with results on the hospital information system. In all cases results had been entered correctly.

Discussion

We have previously reported an overview of our experience with patients on DMARDs [8]. That study was based solely on information available via the computer monitor database. In common with other groups, we found that patients stayed on methotrexate significantly longer than on other DMARDs, including sulphasalazine, Myocrisin and D-penicillamine. This reflected a combination of fewer side-effects and greater efficacy. In the current study, we have investigated methotrexate toxicity in clinical practice in an inception cohort of patients, with investigation of all patients stopping methotrexate for reasons other than efficacy. The study has shown the likelihood of patients remaining on methotrexate 5 yr after starting treatment was 0.74. It has produced accurate data on the incidence of adverse drug reactions

TABLE 4. The causes of death of patients who died while being treated with methotrexate

Cause of death	Total number ($n=29$)[a]	Number with rheumatoid arthritis ($n=24$)	Number without rheumatoid arthritis ($n=4$)	Methotrexate status at death
Cardiac				
Left ventricular failure/congestive cardiac failure	6	5	1	On methotrexate
Ischaemic heart disease	4	4	0	Two on methotrexate. Two within 3 months of stopping
Myocardial infarction	3	3	0	On methotrexate
Pulmonary oedema	1	1	0	On methotrexate
Cardiogenic shock	1	0	1	On methotrexate
Infections				
Bronchopneumonia	5	4	0	On methotrexate
Septicaemia (due to cellulitis)	1	1	0	On methotrexate
Disseminated herpes zoster	1	1	0	On methotrexate
Tumours				
Bronchial carcinoma	3	3	0	On methotrexate
Pancreatic carcinoma	1	1	0	On methotrexate
Other				
Chronic renal failure	1	0	1	On methotrexate
Methotrexate pneumonitis	1	1	0	Within 3 months of stopping

[a]Cause of death is not known for one patient. Diagnosis is not known for one patient.

to methotrexate treatment from unselected patients seen in everyday clinical practice. Most studies of DMARD toxicity are short term and undertaken in selected patients under drug trial protocol. We have identified the incidence of life-threatening side-effects to be 1.7% (12 patients) with one death (0.15%) directly attributable to methotrexate. It is known that methotrexate is effective in reducing morbidity in rheumatoid arthritis and a recent paper has suggested that it is associated with decreased mortality [11].

These data are extremely useful to both physicians and patients. In contrast to clinical trials, continuing the drug in practice depends upon both physicians' and patients' perceptions of acceptability of disease control and significance of adverse effects. Fraenkel *et al*. [12] interviewed 100 patients with rheumatoid arthritis and found they had strong preferences for full disclosure of the risks of medication as well as treatment alternatives. The availability of accurate data is useful for explaining to patients the risks of methotrexate therapy and aids both acceptance of therapy and compliance.

The contribution of methotrexate to the seven deaths from infection (five bronchopneumonias, one septicaemia and one disseminated varicella zoster) is difficult to quantify, with both rheumatoid arthritis and steroids increasing the risk of infections in addition to methotrexate [13].

In this study, 36% of patients initially withdrew due to side-effects. However, 48% of this group of patients restarted methotrexate. The incidence of initial side-effects is higher than that found by the Cochrane Review of trials comparing methotrexate against placebo in patients with rheumatoid arthritis. This review found 22% of people on methotrexate had adverse drug reactions [1] compared with 7% on placebo. However, comparison of cessation rates for observational studies versus clinical trials should be interpreted cautiously as the latter will depend upon protocol criteria rather than patient and/or physician preferences.

A meta-analysis of treatment withdrawal rates reported in observational studies and randomized controlled trials between 1966 and 1986 showed that 36% of patients stayed on methotrexate for 60 months with only 23% remaining on parenteral gold and 22% on sulphasalazine [14]. The main problem limiting long-term therapy with sulphasalazine alone is inefficacy [8, 14]. The main limitation of parenteral gold therapy is the higher incidence of side-effects compared with methotrexate with efficacy similar between the two treatments [13–17].

Few centres have the ability to evaluate treatment on large numbers of patients in the routine clinical setting. In our case, this is facilitated both by the fact that the Staffordshire Rheumatology Centre performs almost all monitoring of its patients and by the computerized monitor system which also functions as a database. One of the strengths of this study is that data were collected prospectively to assist with monitoring of DMARD therapy in clinical practice and not as part of a research trial. One potential source of bias in this study is that methotrexate discontinuation is on the judgement of the supervising clinician in a clinical context and does not imply that thresholds for cell counts or liver function tests have been exceeded. The patient may not have been rechallenged with the methotrexate to ensure this had been responsible for the side-effects in patients on multiple medications. The study also does not take separate account of patients being on combination DMARDs or having further second-line therapy added in. Other co-morbid conditions or medications predisposing to certain side-effects of methotrexate are not considered.

Our approach obviously relies on the quality of data put into the monitor program, which in our study was shown to be accurate with 100% of the blood results sampled entered correctly.

This study has confirmed that methotrexate is well tolerated in clinical practice in the medium to long term. This supports the study from Melbourne of 460 patients with rheumatoid arthritis on methotrexate that showed that more than 50% of patients remained on treatment 12 yr later [18]. It would be useful to continue to follow up our group of patients to establish how many still remain on treatment in 15 to 20 yr.

Conclusion

This study has shown methotrexate is well tolerated in clinical practice, with the probability of patients remaining on methotrexate 5 yr after starting treatment being 0.74. It has identified the incidence of life-threatening side-effects to be 1.7% (12 patients) with one death (0.15%) directly attributable to methotrexate.

The authors have declared no conflicts of interest.

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