Longterm Maintenance Therapy with Disease Modifying Antirheumatic Drugs

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ABSTRACT. Longterm safety and efficacy of disease modifying antirheumatic drugs (DMARD) have been challenging to assess. There are few studies that have evaluated patient outcome beyond 5 years. As patients may receive several DMARD over the course of their disease along with nonsteroidal antiinflammatory drugs, corticosteroids, and other drugs for comorbidities, it is difficult to design and implement a trial to define a specific drug's longterm effect. Based on the findings of several key studies, however, it does appear that DMARD are safe when taken longterm, and that they are more likely to be discontinued because of inefficacy than toxicity. Although DMARD are often discontinued because of lack of efficacy, 12 year data suggest that DMARD can provide benefit over this period. The toxicity profiles vary significantly between DMARD. In addition, the time during therapy when the majority of these adverse effects most frequently appear is DMARD-specific. Prospective studies are needed to further clarify longterm safety and efficacy of the newer DMARD. (J Rheumatol 2002;29 Suppl 66:38–43)

Key Indexing Terms:
DISEASE MODIFYING ANTIRHEUMATIC DRUGS RHEUMATOID ARTHRITIS
METHOTREXATE SULFASALAZINE HYDROXYCHLOROQUINE

INTRODUCTION

Disease modifying antirheumatic drugs (DMARD) have earned their place as a cornerstone of contemporary rheumatoid arthritis (RA) management. Both the rheumatology literature and clinical evidence support the benefit of early intervention with DMARD for controlling symptoms, reducing joint damage, and reducing morbidity and mortality associated with RA[1].

The call for earlier and more aggressive use of DMARD began once investigators realized that the traditional "pyramid" approach to RA care — the sequential administration of increasingly more potent drugs starting with nonsteroidal antiinflammatory drugs (NSAID) — did not utilize DMARD until 2 years or more after diagnosis of disease, by which time significant erosions had already developed. Rheumatologists are now more willing to initiate DMARD therapy as soon as the diagnosis of RA is confirmed.

Since RA is a chronic disease, any true assessment of a drug's efficacy and safety must withstand the rigors of longterm trials and years of clinical experience. Yet longterm data have been difficult to obtain, for several reasons. During the course of their disease, patients may be exposed to several DMARD sequentially (being switched to another DMARD due to lack of efficacy or toxicity) or in combination. Most patients taking DMARD are taking NSAID, corticosteroids, and/or other drugs for comorbidity, making it difficult to attribute an adverse event to the effect of a specific DMARD. RA is associated with early morbidity and mortality, and many patients are elderly; hence the issue of comorbidities and death further complicates the picture.

Longterm treatment with DMARD is essential if sustained suppression of disease activity is to be achieved. As with all drugs, a balance of efficacy and toxicity needs to be achieved, but given the available supply of drugs this can prove problematic. This review aims to highlight some evidence of longterm DMARD efficacy, comment on the timing of side effects, in particular in relation to commonly used drugs such as sulfasalazine (SSZ) and methotrexate (MTX), provide evidence about comparative data, and refer to selected areas such as elective joint surgery as well as conception, pregnancy and lactation.

CONTINUANCE RATES WITH DMARD

Evidence suggests that DMARD vary in their toxicity and adverse effect profiles. In many cases, these adverse events appear within the first months of treatment and thereafter are less of a problem. In other cases, adverse events may appear at any time during therapy or emerge with cumulative use. The issue of delayed effects is an important area that merits further exploration in longterm studies.

Several studies have examined treatment continuance rates with DMARD therapy. The continuance rate is generally considered to reflect drug efficacy, toxicity/tolerability, or both. This review will highlight only studies of 5 years' duration or longer.

Sulfasalazine monotherapy. Jones and colleagues[2] performed a 5 year followup study of 86 patients being

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treated with SSZ. They examined outcome, reasons for discontinuing treatment, and incidence/nature of adverse effects. All patients had active RA (from 1.5 to 49 yrs), and had been treated with 1 to 4 DMARD before starting SSZ. During regular followup visits, disease activity was measured and toxic effects were documented.

A total of 25 patients discontinued SSZ because of adverse effects. Most of these tolerance issues occurred within the first 3 months of treatment. No adverse effects occurred between 12 and 60 months. The most common problem was gastrointestinal (GI) intolerance (nausea, bloating, or vomiting). Two patients discontinued treatment because of drug induced fever, and 5 because of thrombocytopenia, mild hemolysis, and hematoma. Rash and elevation of liver enzymes occurred early but reversed once the drug was withdrawn.

Lack of efficacy caused 38 patients to discontinue SSZ. Six patients stopped treatment because of remission; their condition remained stable for 1 to 2 years. A group of 15 patients remained stable or improved, and had a 50% reduction in active joint count. Another 6 continued to have active controlled disease. Two patients died, but for reasons unrelated to SSZ.

Thus in this study 96% of adverse effects developed within the first 3 months of SSZ treatment. The risk of discontinuing SSZ was 64% at 5 years. Ninety percent of patients in whom SSZ was effective and well tolerated after 2 years continued treatment after 5 years.

Methotrexate monotherapy. Weinblatt and colleagues[3] followed 123 RA patients taking MTX for 5 years (maximum dose 20 mg/week). Among patients in this group 77% were seropositive. Seventy-nine patients (64%) completed the 60 months of study. Withdrawals were for lack of effect (7%), intercurrent illness (8%), lack of compliance/loss to followup (15%), and adverse events (7%). Most side effects occurred in months 0–6, but a significant proportion were observed between months 48 and 60, highlighting the need for continued vigilance. Unusually in this 5 year followup no deaths from intercurrent illness were documented. Three patients were withdrawn from the study because of hepatic abnormalities (one with a diagnosis of cirrhosis with ascites at 4 yrs was noted 10 months earlier to have recurrent elevations in serum transaminases of 1–2 times above normal). No MTX related pneumonitis was observed. A subsequent small series of patients (n = 26) with longer followup (11 yrs) showed that 10 patients (38%) were receiving therapy, and 16 had withdrawn (toxicity in 3 — 1 alopecia, 2 pneumonitis) at 11 years. Liver biopsies in 17 of these study patients over the followup period were reassuring[4].

In a cohort of 152 MTX treated patients from a tertiary care center continuation rates were found to be 30% at 10 years[5]. Toxicity was the most frequent cause of discontinuing MTX. A greater than expected number of deaths from infections was observed but the number of deaths from cancer and cardiovascular disease were within expected range.

Kremer followed a small series of patients for 7.5 years and found that toxic reactions were as common in the second half of followup as in the first[6]. This was also the finding of Galindo-Rodriguez, *et al*, who, in an observational study of 2296 patients taking DMARD, found that 50% of DMARD therapy was discontinued by 16 months and 75% by 4.5 years[7]. Although MTX had the highest probability of continuation within the first 5 years, differences between drugs decreased beyond 5 years.

COMPARATIVE STUDIES

Sulfasalazine vs Penicillamine, Sulfasalazine vs Auranofin

In 2 sequential studies from Glasgow[8,9] (patients enrolled between 1984 and 1986 and 1988 to 1989, 200 patients in each series) 29% of SSZ patients continued therapy at 5 years in the first cohort (comparator penicillamine) and 31% in the second cohort (comparator auranofin). The majority of these patients (86%) had been seropositive at the outset and initial Health Assessment Questionnaire (HAQ) scores were high.

Sulfasalazine vs penicillamine cohort. This cohort of 200 patients has been followed to 12 years[8]. Over this time no unexpected or late toxicities were observed. Reversible leukopenia occurred within the first 6 months in 3 patients taking SSZ. Seventeen patients receiving D-penicillamine developed significant proteinuria that resolved when the drug was withdrawn. In addition, there was a case of drug induced systemic lupus erythematosus, which presented late in a patient taking penicillamine.

Ninety-four (47.5%) patients died over the 12 year course of followup, 93 of these deaths were unrelated to DMARD. One patient who had been switched to MTX succumbed to sudden thrombocytopenia and pulmonary hemorrhage. Deaths were more common in patients who had a higher baseline HAQ score and who were of lower socioeconomic status, older, and underweight. At 10 and 12 year followup in the SSZ versus penicillamine cohort the median dose of SSZ was 2.5 g and that of penicillamine was 750 mg. Intention to treat analysis showed that sustained suppression of erythrocyte sedimentation rate (ESR) was achieved in those taking any DMARD (median ESR at outset 62 mm/h, at 10 years 31 mm/h; Wilcoxon $p < 0.001$). Efficacy results are shown in Table 1.

Of the 105 survivors in this cohort, 78 were taking a DMARD at 12 years. Overall, there were 25 patients (32%) taking SSZ, 16 (21%) intramuscular gold, 14 (18%) D-penicillamine, 12 (15%) MTX, 8 (11%) azathioprine, and 3 (3%) hydroxychloroquine (HCQ). Over the 12 years of the study, DMARD treatment duration was 0 to 36 months in 16 patients, 37 to 119 months in 27, and 120 to 144 months in 55 patients. There was no factor that predicted duration of DMARD therapy.

Table 1. Outcome Effects. Intention to treat analysis of patients taking DMARD at 12 years. From Capell H, *et al*[8].

	Sulfasalazine			D-penicillamine		
	Baseline	12 yr	p (W)	Baseline	12 yr	p (W)
Variable						
Morning stiffness (min)	90	30	0.0409	120	90	0.0626
HAQ	2.13	2.25	0.1147	2.08	2.5	0.02*
Hb (gm/dL)	11.7	12.1	0.2314	11.6	12.7	0.0158
Platelets (x 10^9/L)	419	283	0.0003	443	272	0.0001
ESR (mm/h)	62	39	0.0003	61	29	0.0001

* Deterioration.
HAQ: Health Assessment Questionnaire; Hb: hemoglobin; ESR: erythrocyte sedimentation rate. W: Wilcoxon matched pairs.

Thus a large proportion of patients were taking an alternative DMARD such as gold, MTX, azathioprine, or HCQ and not the original allocation. Elucidating the etiological agent is difficult in the event of late toxicities and all groups are likely to be contaminated by multiple DMARD.

Sulfasalazine vs auranofin. The efficacy and toxicity of SSZ and auranofin were compared in a 5 year, prospective randomized trial involving 200 patients with RA[8] (in an earlier study of the same patients, no differences between the 2 drugs were evident at 12 months[10]). Throughout the study, more patients continued SSZ therapy than auranofin; by 5 years, continuance rates were 31% and 15%, respectively. This finding held true even when patients previously treated with intramuscular gold were excluded from both groups. Patients treated with SSZ had improvement in ESR, C-reactive protein (CRP), articular index, and duration of morning stiffness; this was constant throughout the entire study. In the auranofin group, the ESR and duration of morning stiffness were not significantly improved at 5 years. Decreases in CRP and articular index were significant at 1 year, but not at 5 years.

By 5 years, 34 of the SSZ and 26 of the auranofin group had discontinued treatment because of diminished or absent efficacy. Twenty-four of the SSZ group and 49 of the auranofin group stopped their drug because of side effects (upper GI symptoms and rash for SSZ; diarrhea for auranofin). Hematologic side effects (leukopenia for both drugs, thrombocytopenia for auranofin) reversed when the drug was stopped. From this study, it appears that SSZ is more effective and likely to be taken longterm than auranofin.

Hydroxychloroquine, penicillamine, and gold. While MTX and SSZ are the most commonly prescribed DMARD for patients with RA, HCQ, D-penicillamine, and gold still play a role in treatment. These agents were compared by Jessop, *et al* in a 5 year randomized controlled trial in which the percentage of patients who continued the first DMARD for 5 years or who experienced remission were considered a reflection of drug efficacy[11]. Among this group of patients 82% were seropositive.

A total of 541 patients from one center were entered in the study. All patients had active RA inadequately controlled by NSAID; all were DMARD-naïve. In all, 76% were rheumatoid factor positive; most (82%) also had erosions in the hands and/or feet. Patients were randomized to receive HCQ, D-penicillamine, sodium aurothiomalate, or auranofin. Primary outcome measures were continuation of the original DMARD for 5 years and/or remission; withdrawal from the study; failure related to adverse effects; and failure related to inefficacy or death. Secondary outcome measures were changes in laboratory, functional, and radiographic measures of disease activity.

At the end of 5 years, 210 patients (39%) had experienced remission or were still taking their original DMARD. Continuance rates were highest for penicillamine and lowest for HCQ (Table 2).

Patients who continued their first DMARD for 5 years showed improvement in all measures of disease activity. For each of the drugs, CRP, ESR, Ritchie Articular Index, and joint stiffness improved by 30% to 50%. In all treatment groups, the Larsen radiological score deteriorated by a similar amount.

In all, 126 patients (23%) stopped treatment because of adverse effects. Dermatologic effects were the most common problem in all DMARD tested. Other adverse reactions observed were nausea and vomiting (most common in the HCQ group), proteinuria (especially in penicillamine and sodium aurothiomalate groups), epigastric pain (penicillamine), and diarrhea (auranofin).

Inefficacy or death caused 173 patients (32%) to discontinue the study. Most treatment failures occurred within 18

Table 2. Percentage of patients still taking original DMARD after 5 years*.

DMARD	Percentage
Penicillamine	53
Sodium aurothiomalate	34
Auranofin	31
Hydroxychloroquine	30

* Total number of patients: 541.

months for HCQ, 2 years for gold, and at any time during the 5 years of the study for penicillamine. The percentages of patients not responding to treatment were 49% for HCQ, 36% for auranofin, 22% for sodium aurothiomalate, and 19% for penicillamine.

The continuance rates observed in this study for sodium aurothiomalate and HCQ were similar to those reported by other investigators[12,13]. Penicillamine had a higher longterm continuance rate than HCQ or auranofin, and caused less toxicity than injectable gold.

Late adverse effects included: visual field defect in one patient taking HCQ, pemphigus in one patient and myasthenia gravis in one patient taking D-penicillamine, and cholestatic jaundice in one patient taking intramuscular gold. In this group, 36% were taking their initial DMARD at 5 years; there were 16 deaths that included 6 cardiovascular, 3 infection, 6 tumor, and 1 pneumothorax.

MULTIPLE DMARD

Sokka and Hannonen[14] prospectively examined the effects of DMARD in a group of 135 patients with early RA followed for up to 15 years. Study participants were treated according to the "sawtooth" strategy, in which DMARD were taken early, continuously, and serially as needed. Of these patients, 79% were seropositive for rheumatoid factor. DMARD included in their study were HCQ, SSZ, D-penicillamine, azathioprine, MTX, intramuscular aurothiomalate, auranofin, cyclophosphamide, and chlorambucil. There were 2 study cohorts; patients in cohort 1 started treatment with intramuscular aurothiomalate, while those in cohort 2 initially took SSZ or placebo. Patients were switched to another DMARD or to combination therapy (COMBO) if clinical remission or significant improvement did not occur within 6 months. The interval from initiation to discontinuation of a DMARD or COMBO was defined as a DMARD period. Reasons for discontinuing a DMARD period were categorized as inefficacy (insufficient suppression of disease activity, loss of beneficial effect after primary response), remission, toxicity (cytopenia, proteinuria, GI, skin, respiratory, increase in blood pressure, etc.), and other reasons (pregnancy, drug cost, comorbidity, etc.).

During 1401 person-years of followup, the patients were challenged 606 times with a DMARD or COMBO, each period lasting an average of 10 months. The median number of DMARD periods was 6 in cohort 1 and 3 in cohort 2. No DMARD appeared to be superior to the others.

A total of 528 (87%) out of the 606 DMARD periods were abandoned. Reasons for withdrawal were inefficacy 170 (51%), adverse reactions 149 (28%), and other reasons 77 (15%). A DMARD period was stopped because of clinical remission in only 32 (6%) cases. Inefficacy was the leading reason for discontinuation of DMARD throughout the 15 years of followup.

Mucocutaneous and GI effects were the most common adverse reactions causing patients to stop DMARD. Serious adverse effects were rare, and there were no deaths attributable to DMARD during the 15 years of followup. The results of this study support the safety of DMARD when taken alone or in combination for a prolonged period. Patients taking longterm DMARD are most likely to discontinue treatment because of drug inefficacy, rather than toxicity or adverse events.

A retrospective review of 1132 patient case records provided evidence of continuance rates of longterm DMARD therapy[7]. In analyzing 2296 DMARD therapies, Galindo-Rodriguez, *et al* found that antimalarial drugs, followed by parenteral gold, were most widely used. MTX was seldom a first choice. Other DMARD included azathioprine, cyclophosphamide, and cyclosporine.

Half of all DMARD treatments had been discontinued by 16 months. By 4.5 years, the discontinuation rate had escalated to 75%. The most common reasons were lack of efficacy (25% of all prescriptions and 46% of all discontinuations), followed by toxicity (20% of all prescriptions and 37% of all discontinuations). The reasons for discontinuation of treatment, categorized by DMARD, are listed in Table 3. After 3 years, continuance rates were 50% for MTX, 33% for HCQ and intramuscular gold, 30% for D-penicillamine, 25% for SSZ, and 18% for oral gold. After 6 years, only 20% of initial treatments continued and the DMARD did not differ significantly when compared.

Rashes and GI effects were the most common adverse effects. Side effects were least common in persons taking antimalarial drugs and MTX. MTX related toxicity occurred throughout the length of the study. Toxicity from gold compounds occurred within the first 18 months of treatment and stabilized after that.

20 year followup. In a 20 year followup of 123 patients allocated to their first DMARD in 1977 to 1978, no DMARD related deaths were observed[15].

Deaths attributed to antirheumatic medication. In a followup of 1666 patients with RA in Finland, 47 (2.8%) were noted to have died in relation to antirheumatic medication. The denominator for drug usage is not clear in this study; however, there were 30 NSAID related deaths, 11 attributed to corticosteroids and 6 to DMARD (1 HCQ, 2 SSZ, 2 MTX, and 1 azathioprine)[16].

Mortality as an outcome measure. It is, however, important to note that for longterm mortality outcomes in a study conducted by Symmons, *et al* from Birmingham, England (a cohort of 448 patients enrolled in 1964 to 1978), the patients who presented early for treatment did better than others. Overall there was an excess death rate from cardiovascular disease, infection, and renal failure, but patients treated early had a better outcome. These authors concluded that RA should be referred early and monitored for evidence of infection and renal failure[17].

A study suggesting that DMARD therapy might be asso-

Table 3. Reasons for discontinuing DMARD therapy*. From Galindo-Rodriguez G, *et al*[7].

DMARD	n in study	Toxicity	Inefficacy	Both	Other	Unknown	Total
Antimalarials	583	84 (14)	147 (25)	10 (2)	53 (9)	16 (3)	290 (50)
IM gold	579	153 (26)	125 (22)	9 (2)	37 (6)	24 (4)	330 (57)
SSZ	427	72 (17)	153 (36)	11 (3)	25 (6)	22 (5)	261 (61)
MTX	348	48 (14)	31 (9)	8 (2)	38 (11)	9 (3)	118 (34)
Oral gold	164	38 (23)	61 (37)	2 (1)	9 (5)	9 (5)	115 (70)
D-Pen	162	55 (34)	38 (23)	6 (4)	6 (4)	11 (7)	104 (64)
Other	33	7 (21)	12 (36)	3 (9)	3 (9)	2 (6)	21 (62)
Total	2296	457 (20)	567 (25)	49 (2)	171 (7)	93 (4)	1239 (54)

* Percentages, in parentheses, are calculated over total number of treatments (n). injectable gold, antimalarials; IM: intramuscular; SSZ: sulfasalazine; MTX: methotrexate; D-pen: D-penicillamine.

ciated with high survival rate was reported in 1991 from Finland, where 573 RA patients were followed from 1989. Forty-four percent had died by that time, but gold was associated with a high survival rate and certainly not with premature death[18].

DMARD THERAPY IN PATIENTS REQUIRING ORTHOPEDIC SURGERY

Many RA patients require surgery in the course of their disease. Should DMARD therapy be continued in RA patients undergoing elective orthopedic surgery? Grennan and colleagues[19] studied 388 patients in whom such surgery was planned. Patients who were receiving MTX were randomly allocated to either continue therapy (n = 88) or discontinue treatment for 2 weeks before and after surgery (n = 72). The complication rates in these 2 groups were also compared with those of 228 patients with RA who were not receiving MTX and who underwent surgery. Findings in this study indicated that MTX (continued or not) did not increase the early complication rate in patients with RA.

Thus this important prospective study has shown that since MTX does not increase the risks of early postoperative complications of elective orthopedic surgery in RA, it should therefore be continued in patients whose disease is controlled by the drug prior to surgery. If treatment is interrupted unnecessarily, the resultant flare of disease activity would lead to impaired rehabilitation postoperatively.

It is noteworthy that this study also confirmed clinical impression that comorbidities such as diabetes, bronchiectasis, hypertension, ischemic heart disease, and asthma are associated with increased postoperative morbidity.

DMARD AND FERTILITY, CONCEPTION, PREGNANCY, LACTATION

Sustained DMARD therapy initiated early in the disease is becoming the treatment approach for all patients with RA. This longterm exposure to DMARD presents a particular dilemma in younger patients. When initiating DMARD therapy in this population, plans for pregnancy should be considered in the selection of a drug and discussed at the outset with the patient.

Although the median age of patients receiving DMARD is 50 to 55 years, a significant proportion will be in child-bearing years; thus the influence of DMARD on conception, pregnancy, fetal development, and lactation is of relevance. These important aspects have been reviewed by Jaansen, *et al*[20].

Conception. In terms of conception, there have been no reports of problems with SSZ, azathioprine, or gold, but it is essential to discontinue MTX or penicillamine 3 months prior to conception. In the case of leflunomide the period is 2 years; if pregnancy is contemplated sooner than that an elimination procedure would be required.

Pregnancy. Janssen and Genta in their review of the effect of immunosuppressive and antiinflammatory medications on fertility, pregnancy, and lactation recommended SSZ as the drug of first choice in women of child-bearing age[20].

The US Food and Drug Administration categories suggest that there is no risk in humans with SSZ. Risk is probably low but cannot be ruled out with HCQ, gold, or cyclosporine. There is possible evidence of risk with azathioprine. MTX and leflunomide are contraindicated in pregnancy. D-penicillamine should not be used when the indication for treatment is RA.

Lactation. During lactation SSZ, HCQ, or prednisolone may be continued with close surveillance.

CONCLUSION

As with any chronic disease requiring sustained pharmacological treatment, the longterm safety and efficacy profiles of DMARD for RA are critical factors in patient management. Our knowledge base of longterm therapy with DMARD has been complicated by numerous confounding variables. However, available studies of longterm followup have shown that most patients who discontinue a DMARD do so more frequently because of loss of efficacy than toxicity. The adverse effects, profiles, and timing of these effects are different between DMARD. While the adverse effects

associated with SSZ are observed early during treatment (within the first year), discontinuation of MTX and penicillamine due to toxicity continues throughout the course of therapy.

It is reassuring that studies have demonstrated that sustained suppression of disease activity can be achieved over 5 to 10 years in terms of symptoms and signs of inflammatory disease and laboratory markers such as ESR and CRP, and that suppression of these markers in the early years of treatment probably reduces the need for orthopedic surgical intervention[15]. The availability of newer therapies and anticipated requirements of DMARD therapy for decades instead of years challenge the capacity of the rheumatological fraternity to continue surveillance of each drug's efficacy and safety profile. The increasing use of these agents in combination therapy is likely to lead to difficulty in elucidating which drug is responsible for a toxic event[20,21].

Patient registries have been instituted in many countries as a means of monitoring adverse events that may not have been evident in highly selected clinical trial populations. These programs are intended to increase awareness of any potential problems as soon as possible. Ideally such registries should become routine so that accurate longterm data are generated and facilitate optimum treatment of RA.

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