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J Rheumatol 2001;62;10-15
http://www.jrheum.org/content/62/10

Disease Modifying Antirheumatic Drugs: Longterm Safety Issues

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ABSTRACT. The trend for more aggressive management of rheumatoid arthritis includes earlier introduction of disease modifying antirheumatic drugs (DMARD). As patients may continue their therapy for several decades instead of several years, the evaluation of benefit versus risk of DMARD with particular emphasis on longterm safety is essential. Longterm safety assessment is difficult for a number of reasons: there are relatively few trials that have followed patients beyond 5 years and the use of a combination of DMARD therapy with nonsteroidal antiinflammatory drugs and corticosteroids complicates the assessment of an observed adverse event with a particular drug. This review of longterm studies incorporating DMARD provides insight into adverse events associated with currently available DMARD. (J Rheumatol 2001;28 Suppl 62:10–15)

Key Indexing Terms:
DMARD METHOTREXATE SULFASALAZINE
HYDROXYCHLOROQUINE RHEUMATOID ARTHRITIS

Information regarding safety of disease modifying antirheumatic drugs (DMARD) is vital if informed choices are to be made by patients and their physicians. Many patients express anxieties about taking any drug long term. Rheumatological cynics might consider that the recognized early termination of DMARD therapy renders longterm followup data irrelevant. Nevertheless, a proportion of patients do receive DMARD long term (30% at 5 years, 20% at 10 years). Furthermore, the availability of newer but inevitably more expensive agents does not necessarily indicate that more familiar DMARD will become redundant. Reporting of patient years may reflect individuals followed for a relatively short time. Although reassuring, this will not provide information about late toxicity due to prolonged exposure, an important aim in targeted therapy.

When weighing up efficacy and toxicity, it is important to emphasize that untreated rheumatoid arthritis (RA) is associated with morbidity and premature mortality[1,2]. Thus DMARD safety issues should be balanced against this background. Reduction in death rates from RA and its complications and better management of comorbidity have contributed to increased longevity and thereby increased relevance of longterm safety issues. It is also possible that late adverse events may become apparent from a therapy discontinued some years previously. DMARD Phase III studies in which patients participated, and which were subsequently withdrawn, are a further confounding factor.

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Identification of major unacceptable toxicity may not require large numbers; in a 10 year followup of total nodal irradiation, a high death rate and occurrence of B cell related malignancies was reported[3]. Ten patients had been exposed to treatment: 7 out of 10 died compared with 2 of 9 controls; 3 developed B cell malignancy compared to no controls. Thus longterm safety issues precluded further prescription of total nodal irradiation.

Factors that complicate longterm safety assessment. A greater choice of DMARD, the use of serial agents or combination regimens, and the co-prescription of nonsteroidal antiinflammatory drugs (NSAID) and corticosteroids in a significant proportion of patients make apportioning blame to a particular DMARD difficult. Concurrent prescriptions for co-morbidity increase complexity still further. On the other hand DMARD may have a beneficial effect on morbidity and mortality in RA by reducing requirements for systemic corticosteroids[4] and NSAID. Such an effect is difficult to quantify.

Patient perception of risk. There is some evidence relating to patient perception of risk[5]. It is of interest that a common longterm problem, eg., chrysiasis during gold therapy, seldom causes complaints whereas fear of eye toxicity with antimalarials, however uncommon, can be difficult to allay in some patients. Informing patients of possible risks, especially where there is uncertainty, is a difficult task.

Avoiding toxicity. Every possible option should be employed to avoid toxicity, including patient education about risks, monitoring and the need to be alert to side effects, use of folic acid in patients on methotrexate (MTX)[6] and in the future the possibility of targeting patients to avoid use of preparations in those genetically susceptible to toxic reactions[7].

Dearth of reliable prospective data. There is abundant

evidence about the early side effect profile of commonly used DMARD from comparative studies[8-10], the meta-analyses of Felson, *et al*[11,12], the derived toxicity index from Singh and Fries and co-workers[13,14] and a recent "strategy" study from The Netherlands[15]. Most of these adverse events reverse promptly on withdrawal of therapy. Of considerable concern is the detection of late, potentially cumulative or irreversible adverse events.

Randomized controlled trials are often inadequate since relatively few cohorts have been followed beyond 5 years, contamination of groups is inevitable in the long term, and numbers enrolled are relatively small. Databases such as Arthritis, Rheumatism, and Aging Medical Information Systems (ARAMIS) have the advantage of dealing with large numbers of patients but cannot provide firm comparative evidence since patients are not randomly allocated to DMARD. Ensuring 100% followup with adequate documentation of death certificates and drug related morbidity is an expensive and demanding task, particularly when required over a number of years.

Areas of particular concern. Unraveling background events from drug induced toxicity is difficult. Lymphoproliferative disorders are known to be more common in patients with RA and deaths from infection are increased[1,2]. Some patients with RA will go on to develop an overlap with connective tissue disorders, and lung and liver disease are recognized extraarticular manifestations in RA. Changing patterns of co-morbidity and disease management require constant reevaluation of any available data including that generated by Wolfe, *et al* in 1994[2] relating to the observed to expected ratios for deaths attributable to infection (pneumonia 5.3, others 6.2:1), lymphoma (8.0:1), gastrointestinal disease (1.5:1) and RA itself (12.8:1). There is also premature mortality from circulatory causes.

Available longterm studies. For the purpose of this discussion, studies of DMARD duration 5 years or more published in the last decade will receive particular emphasis. These are listed in Table 1. Given the very large number of patients treated with DMARD, the pooled information is relatively sparse.

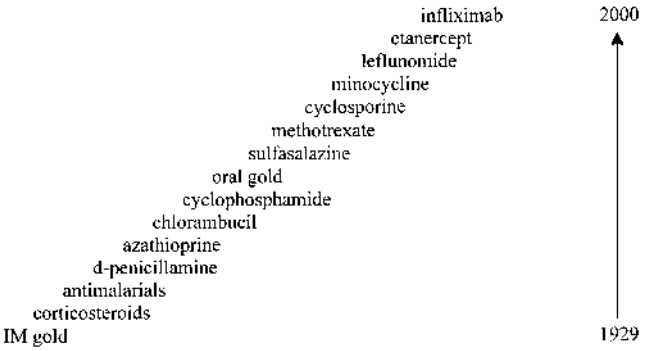
Evidence relating to late harm is patchy and incomplete. Knowledge of the denominator relating to drug use is vital when reporting toxicity. The range of available DMARD has increased markedly since the introduction of gold in 1929 (Table 2), highlighting the need for coherent DMARD monitoring in the future.

Table 1. Longterm safety issues with DMARD in the treatment of RA.

Year	Author	n	Drugs	Years
1990	Wolfe[24]	671	Multiple	14
1991	Capell[33]	123	GOLD, PEN, LEV	10
1991	Jones[22]	86	SASP	55
1992	Kremer[26]	29	MTX	7.5
1995	Alarcon[27]	152	MTX	10
1995	Boerbooms[28]	80	MTX, AZA	4–6
1996	McEntegart[18]	200	SASP/AUR	5
1996	Möttönen[35]	142	SAARD	6.2
1997	Levy[17]	1,207	HCQ	3–4
1998	Capell[19]	200	SASP, PEN	12
1998	Jessop[10]	541	Multiple	5
1998	Weinblatt[25]	26	MTX	11
1999	Sokka[34]	135	Multiple	15
2000	Landewe[31]	623	Multiple	10–12

PEN: penicillamine; LEV: levamisole; AZA: azathioprine; SAARD: slow acting antirheumatic drugs; AUR: auranofin; SASP: sulfasalazine.

Table 2. Disease modifying antirheumatic drugs that have become available to patients with rheumatoid arthritis, according to year of introduction.



SPECIFIC DRUG ISSUES

Hydroxychloroquine

Hydroxychloroquine (HCQ) is widely used as initial therapy in RA and in some combination regimens. Two longterm studies have addressed the issue of hydroxychloroquine retinal toxicity[16,17]. In addition, data are available from Jessop's 5 year followup report[10]. The study published by Mavrikakis, *et al* in 1996 reported retinal toxicity in 2 young patients, one with RA and one with systemic lupus erythematosus (SLE), from a cohort of 360 patients followed prospectively. These 2 instances occurred with cumulative doses of 700 and 730 g and a duration of treatment of 6.5 and 8 years, respectively. Both patients were noted to have permanent paracentral scotomata. A subsequent publication from Levy, *et al* in 1997[17] evaluated a cohort of 1,207 patients from California who had filled HCQ prescriptions between 1991 and 93. The authors undertook a retrospective chart review and identified 21 individuals (1.7%) with possible HCQ toxicity. Only one definite retinal toxicity was identified. In their followup, no patient had substantial visual loss. They recommended annual ophthalmic screening only if the daily dose exceeds 6.5 mg/kg or if HCQ is taken continuously for more than 10 years. They do however comment that the rarity of this side effect makes study difficult. The Mavrikakis study data suggest that the caution zone should be sooner than 10 years since in the

Greek patients toxicity had occurred at 6.5 and 8 years. Information is also available from Jessop *et al*[10] over 5 years who reported that one patient (of a cohort of 173 patients with RA) taking HCQ was noted to have a visual field defect, but this was subsequently considered to be a preexisting problem.

Sulfasalazine

Commonly used in Europe as initial DMARD therapy for RA, an enteric coated formulation of sulfasalazine has relatively recently been introduced in North America. (Sulfasalazine plain tablets had been available in North America for ulcerative colitis.) Studies comparing sulfasalazine with leflunomide[8] documented early toxicity and expected efficacy. Five and 12 year studies (randomized open label) from Glasgow compared sulfasalazine and auranofin and sulfasalazine and pencillamine (200 patients each). No unexpected late toxicity was identified in either sulfasalazine cohort[18,19]. Enteric coated tablets were used in the trials to reduce the likelihood of adverse GI effects.

Drug induced SLE. Sulfasalazine has been shown to be associated with drug induced SLE and in a small series in 1997, Gunnarsson, *et al* reported that slow acetylators and patients with disease of longer duration and higher cumulative dose of sulfasalazine appeared most at risk[20]. In our sulfasalazine versus auranofin cohort, Gordon, *et al* specifically addressed the issue of sulfasalazine induced SLE and no cases were identified[21]. Of patients who were antinuclear antibody (ANA) negative at the outset, 14 of 72 taking sulfasalazine (19%) became strongly ANA positive compared with 11 (14%) of the 80 taking auranofin. ANA positive patients at baseline or those who became positive were no more likely to develop drug toxicity or withdraw from treatment. Thus no case of drug induced SLE was seen over 5 years even though ANA positivity was frequent. Similarly, no case of drug induced SLE was identified in the 12 year followup of 102 taking sulfasalazine (although one patient with drug induced SLE was seen in the penicillamine cohort)[19]. These findings have been confirmed by a study of 86 patients from Halifax (Canada). Ninety-six percent of adverse events of sulfasalazine were seen in the first 3 months and no unexpected longterm difficulties were documented over 5 years[22].

Immunodeficiency. Immunodeficiency, in particular hypogammaglobulinemia, has been described with sulfasalazine (and other DMARD). Measurements of serum immunoglobulins in patients taking sulfasalazine for RA and other indications for up to 10 years showed a fall in immunoglobulins[23]. The level fell below normal in 10% of patients (transient in one third). Two patients had recurrent chest infections but cessation of therapy was not necessary. The authors' advice was that sulfasalazine need not be discontinued in the face of low immunoglobulins unless infections are a problem.

MTX

MTX has been the most widely used DMARD in North America over the past decade, and is being increasingly prescribed in Europe and elsewhere. In his study utilizing the ARAMIS database, Wolfe reported on 671 patients (mainly middle class Caucasians attending private clinics)[24]. He measured time to termination of therapy of a number of drugs including intramuscular (IM) and oral gold, HCQ, penicillamine and MTX over 14 years. MTX retention was better than the other drugs but no detailed information about deaths or late morbidity in this cohort was included. Both Weinblatt[25] and Kremer[26] have also provided longterm followup in 26 and 29 patients receiving MTX over 11 and 7.5 years, respectively. In Weinblatt's study, 38% were on treatment at 11 years and liver biopsies in 17 patients showed no abnormality. Kremer, *et al* reported that MTX toxic reactions were as common in the second half of followup as in the early years.

Infection. Alarcon and her colleagues[27] observed 27 deaths in a cohort of 152 patients receiving MTX followed for 10 years (compared with 14 expected). A greater number of deaths from infection were noted.

The problem of infections in association with MTX compared with other DMARD has been reviewed by Boerbooms, *et al*[28]. In this overview, common infections tended to occur in the first 18 months of therapy whereas opportunistic infections occurred at any time. Their literature search in 1995 yielded 15 reports considered evaluable. Opportunistic infections occurred in a total of 30 patients after a mean of 20 months (range 0.9-84 or more). Of these patients, 63% were taking concomitant corticosteroids. Infections included herpes zoster, varicella, pneumocystis carinii, cryptococcus, listeria, nocardia, aspergillus, histoplasmosis and cytomegalovirus. No tuberculosis was reported in the series. Opportunistic infections are reported during cyclophosphamide and chlorambucil therapy but are relatively rare during azathioprine treatment for RA. They are not a feature of the gold, penicillamine, sulfasalazine or HCQ literature.

Malignancy. Epstein Barr virus-positive lymphomas have been observed during MTX therapy, which may reverse on MTX withdrawal. In a review by Beauparlant, *et al*[29], the authors concluded that the overall risk of malignancy was relatively low and in patients with severe disease the risks may be outweighed by the potential benefits of therapy.

Uncertainties in relation to MTX: cardiovascular (CVS) comorbidity and osteopenia. The possibility of accelerated atherosclerosis has arisen because homocysteine concentrations are higher in RA; these may be further increased by longterm low dose MTX[30]. Thus risk of cardiovascular disease may be increased. In one study, the effect on homocysteine levels observed during MTX treatment was not seen during sulfasalazine therapy[30]. Recent data from

Landewe, *et al*[31] suggest that MTX may have an adverse effect on CVS outcome in patients with RA with prior cardiovascular co-morbidity (central or peripheral vascular disease or hypertension). In this retrospective cohort study of 672 patients with RA, 82% were rheumatoid factor positive, 71% were female, the median age was 56 years (20-74 years), and median disease duration 4.5 years (range 0.2-4 years). Analysis was according to initial DMARD prescribed between 1984 and 90: followup was censored at December 1995 or at the time of death. Seventy-three patients died during followup. The relative risk for death if MTX was the index DMARD was 3.4. (This compares with the relative risk if patients were diabetic of 3.9). By contrast, the relative risk of death if penicillamine was used as the index DMARD was 0.38. Biases in initial prescription cannot be excluded. Clearly there are unanswered questions in this report, particularly relating to concomitant use of folic acid and in view of known premature CVS deaths in RA these issues require resolution.

MTX is known to be associated with osteopenia and lower osteocalcin levels in rats. Osteopenia, bone pain and fractures have been reported with high dose MTX in children (indication malignancy). There have been observations about MTX and severe osteoporosis in adults with RA and with psoriasis. A 3 year followup of 133 adults with RA found that treatment with prednisolone > 5 mg/day and MTX combined was associated with greater loss of bone density at lumbar spine than treatment with prednisolone without MTX[32].

Other longterm DMARD cohorts. Jessop, *et al* studied oral IM gold, HCQ, and penicillamine in a cohort of 541 patients, 82% of whom were seropositive[6]. As noted above, one patient in the HCQ group (n = 173) developed a visual field defect probably not related to HCQ treatment. Of the penicillamine group (n = 179), 2 patients developed late complications (1 pemphigus, 1 myasthenia gravis) and one patient in the IM gold group (n=119) developed cholestatic jaundice. No deaths were attributed to RA or treatment.

In a study of 123 patients from Glasgow recruited between 1977 and 79 (89% seropositive), initially allocated randomly to gold, penicillamine or levamisole, no late side effects were observed at 10 years and there were no DMARD related deaths[33]. Serial single DMARD were used. Unpublished data for the ongoing 20 year followup revealed 2 late complications of penicillamine (1 myasthenia gravis, 1 myeloperoxidase positive vasculitis). A median of 3 DMARD were used over 10 years (4 over 20 years). Eighteen percent of those alive remained on original DMARD at 20 years.

In the 12 year penicillamine *vs* sulfasalazine study from Glasgow, one drug related death occurred in a patient taking low dose MTX (5 mg weekly) who had sudden onset of thrombocytopenia and developed pulmonary hemorrhage[19].

No deaths related to DMARD occurred in the followup from Finland where 135 patients (79% seropositive rheumatoid factor) were studied. Serious adverse events were rare with individual or combination DMARD over 15 years. MTX was found to be comparable to the other DMARD[34]. Another Finnish study of sawtooth strategy in 142 patients over 6.2 years found many more problems with inefficacy rather than toxicity[35].

In all longterm followup studies, some patients are inevitably lost to followup and data are thus incomplete.

LONG TERM MORTALITY OUTCOMES

The benefits of DMARD therapy have been conclusively demonstrated and may well provide an important counterbalance to the morbidity discussed above. There is accumulating evidence that RA should be treated early, and some longterm evidence that early presenters continue to do well when followed for up to 27 years[36]. In this cohort of 440 patients from Birmingham in England enrolled between 1964 and 78, excess deaths from cardiovascular disease, infection, and renal failure were documented but no detailed drug information was presented[1]. The conclusions of these authors were that RA should be referred earlier and monitored for evidence of infection and renal failure. A study of 573 patients in Finland[37] recorded high survival rate in patients taking longterm gold. A similar effect has been shown in a 10-15 year followup of patients treated with MTX in Germany[38].

The review by Beauparlant, *et al* concluded that the relative risk of lymphoma in RA compared with the general population was two-fold; azathioprine is associated with the development of lymphoma and cyclophosphamide has been associated with the development of cancers, especially bladder cancer[29]. Data on gold, MTX, and cyclosporine are considered inconclusive. In this study too, it is considered that the risks of cancer may well outweigh the benefits of treatment.

Fries, *et al* reported fewer deaths from malignancy on gold and Scandinavian co-workers have suggested that gold is associated with lower mortality than expected[32]. Tumors in patients treated with cyclosporine are dose related and therefore more likely in transplant recipients. Azathioprine may require a cumulative dose of 600 g or more to pose a significant risk.

Mortality rates from DMARD remain difficult to ascertain. In a Finnish study, 47 deaths attributable to antirheumatic medication occurred in 1666 patients with RA: 30 deaths were attributed to NSAID, 11 to corticosteroids and 6 to DMARD (1 HCQ, 2 sulfasalazine, 2 MTX, and 1 azathioprine)[39]. The denominator for drug usage is not clear nor are the monitoring requirements and achievements. Certainly DMARD may have a beneficial effect on morbidity and mortality by reducing requirements for systemic corticosteroids and NSAID. By contrast, total lymphoid irradiation was unacceptably toxic when followed for 10 years[3].

FUTURE CHALLENGES

In many of the studies discussed above, 30% of patients remain on therapy for 5 years and 20% for 10 years. Databases directed at existing DMARD are of importance and require meticulous attention to detail over prolonged periods.

A metaanalysis of combination DMARD therapy[40] found evidence of increased toxicity highly relevant if more combination therapy is to be used in the future. Not all combination trials have reported more toxicity on combination DMARD[41,42].

Newer therapies such as infliximab and etanercept introduce concerns relating to increased propensity to develop infection and tumor. Clearly rheumatologists face considerable challenge if anxieties about longterm safety issues are to be addressed. These aspects have been recently addressed in 2 leading articles[43,44]. Of importance is the realization that matched patients may not reflect a true disease population[44] and a skewed database would be a cause for concern if restricted to the affluent. Socially disadvantaged patients are known to have poorer function and higher mortality rates[19,45]. Controlling for these variables is essential if meaningful information is to be obtained.

ACKNOWLEDGMENT

I wish to acknowledge the valuable contribution of colleagues in West of Scotland in relation to Glasgow studies, in particular Drs. R. Madhok, J.A. Hunter, D. Porter and metrologists E.A. Thomson and R. Hampson. Thanks to Ann Tierney for typing the manuscript.

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