Difficult Decisions

The use of disease modifying antirheumatic drugs in the management of rheumatoid arthritis

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Introduction

Lack of predictability in the clinical course of rheumatoid arthritis (RA) is but one of several factors that challenge our ability to treat this condition effectively. A further consideration is the aetio-pathogenesis of the disease which, for all practical purposes, remains obscure. While several strands of evidence point to an infectious agent as a likely mediator of joint inflammation, no specific micro-organisms have ever been unequivocally linked to the causation of RA.^{1,2} Immune mechanisms almost certainly play a role in the initiation and perpetuation of rheumatoid synovitis, but a convincing unifying hypothesis that accounts for all of the disparate elements of the process is still awaited.^{2,3}

The disease modifying antirheumatic drugs (DMARDs), or slow acting antirheumatic drugs, are so named because it is thought that they modify the progression of RA by (i) favourably altering the natural history of the disease, or (ii) slowing the development of joint erosions or joint destruction, as measured on joint radiographs.⁴ These agents are a diverse group of compounds that produce a common pattern of clinical response when used to treat RA. They can be broadly divided into two groups. In group 1 are such agents as the antimalarials, gold salts, D-penicillamine and sulphasalazine. Although these DMARDs do exert some effect on the immune response, the actual mechanism of their immunosuppressive action is poorly understood. The second group of DMARDs have a well documented capability for suppressing immunity, but they also have recognized cytotoxic properties. Medications in this group include methotrexate, azathioprine, cyclophosphamide and chlorambucil.

Before treating patients with a DMARD, it is important to appreciate the likely impact of these

agents on both the natural history of RA and the radiographic manifestations of joint destruction.

The impact of DMARD therapy on the natural history of rheumatoid arthritis

Because the natural history of RA is characteristically unpredictable, attempts at prognostication in individual patients are often difficult. However, some generalizations are possible. Disease remissions, should they occur, are most likely within a year of disease onset. Women tend to have more severe disease than men, and the presence of subcutaneous nodules or radiographic evidence of joint erosions at the time of diagnosis are recognized indications of a poor outcome.^{5,6} About 10% of patients with RA will experience an unrelenting and aggressively destructive polyarthritis that leads very rapidly to cartilage destruction, bone erosion, and unsightly deformities. For most of the remainder, cyclical exacerbations of active disease will be interspersed with variable periods of disease quiescence, though, eventually, a majority of patients will be considerably incapacitated by their disease.⁶ Moreover, several studies have demonstrated a higher death rate in patients with RA than in age and sex matched controls in the general population.

In perhaps the most comprehensive long term study of RA, Scott *et al.*⁷ found that patients tended to deteriorate more rapidly during the second decade of their disease than during the first 10 years following their diagnosis. All of the 112 patients who were entered into the study were aggressively treated with DMARDs. During the first 10 years, there was a significant fall in the number of patients with elevations of their erythrocyte sedimentation rate (ESR); initially 33% had an ESR of over 50 mm/h and by 10 years, only 12% had such high readings. In addition, the functional capacity of these patients showed a general improvement during the 10 year follow-up. Initially, only 23% of cases were in classes I and II for

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functional capacity (according to the Steinbrocker Criteria⁸), but by 10 years, 67% of cases were in these classes. As patients entered the second 10 year period of their disease, the acute phase reaction fell much less frequently and functional improvement was rarely seen, as the number of severely disabled cases rose.⁷ Seventeen deaths occurred during 1 to 10 years from presentation and 20 between 10 and 20 years. Deaths were due to infections (septicaemia/abscess/pneumonia) or renal failure in 13 patients. Many of the other deaths were attributed, at least in part, to rheumatoid disease. While none of the deaths was directly linked to the use of DMARDs, corticosteroids may have been a contributing factor in the mortalities associated with infection or coronary heart disease.

In other studies that have examined the prognosis of RA, Ragan and Farrington⁹ followed up 500 patients for up to 16 years. At entry, 82% were in Steinbrocker functional classes I and II, while at 16 years only 45% were in these categories. Similarly Rasker and Cosh¹⁰ found that, of 100 patients seen within one year of onset of RA, 35 were dead and 8 in Steinbrocker class IV at 15 years. Such declines were not only attributed to the progress of a pathological mechanism but were thought also to have been influenced by socio-economic factors. Pincus and Callahan,¹¹ in a study of 75 RA patients, showed that educational status influenced prognosis. Death or a 50% reduction in functional capacity occurred in 79% of patients educated only at grade school, in 43% who had attended high school, and in only 20% of those with a college education.

Impact of DMARD therapy on the radiographic manifestations of joint destruction

There has been ongoing debate over whether DMARDs actually slow the progression of joint erosions. Several studies have addressed this issue,^{12–16} but, to date, there has been little agreement on the impact of these drugs. Luukainen *et al.*¹⁷ have suggested that gold therapy is effective in slowing the rate of radiological deterioration, but their study groups were not comparable and the observed differences were small. Although other studies have suggested that disease severity, assessed clinically or by acute phase responses at a specified point in time, is related to the extent of radiological progression,^{12,18,19} they fail to show that such progression is favourably influenced by DMARDs over a period of time.

In a study by Sharp *et al.*²⁰ mean radiographic scores, when plotted against years after diagnosis of RA, showed no deviation from the straight line determined by a regression equation, implying that, when RA is fairly well established, progression of joint deterioration is irrevocable and inevitable. In another

recent study, 50 patients with RA were followed for a minimum of 10 years.²¹ In 48 cases the total joint score deteriorated (a mean increase in maximal damage of 13%), regardless of treatment. During the 10 year period, most progression occurred in the wrists, knees and metacarpophalangeal joints, but also there was a highly significant correlation between scores in these joints and those in all other joints.

Evidence supporting an improved outcome in shorter term studies has been similarly disappointing. Pullar *et al.* followed 47 patients on gold and D-penicillamine over a period of 24 months.¹⁵ Hand radiographs of all patients showed a statistically significant deterioration (when compared to controls) and, although there did appear to be a trend towards a slowing of the rate of erosions in the DMARD treated groups, healing of erosions was very unusual. In this study, it was demonstrated that radiological changes showed a steady progression, and that fewer than one third of patients did not progress by at least one (Steinbrocker) functional class. A detailed examination of radiographic progression showed that only 7 patients (8% of cases) did not have significant joint destruction by 10 years; of these 4 were consistently seronegative for rheumatoid factor and 3 of these never had a raised ESR. By implication this was an atypical group with mild disease who may not have warranted DMARD therapy in the first place. In more typical patients it was exceptional not to have radiological changes by 10 years.

Iannuzzi's review of controlled trials since 1960 came to the conclusion that gold and cyclophosphamide were the only agents where the weight of evidence indicated retardation of radiographic progression.⁴

An approach to the management of rheumatoid arthritis

When managing patients with RA, we are faced with a chronic, inflammatory, multisystem disorder in which causation, pathogenesis, course and outcome are incompletely understood. As a result treatment strategies have had to evolve empirically and have, for the most part, been directed at (i) pain relief, (ii) reduction or suppression of inflammation, (iii) preservation of muscle and joint function, (iv) minimization of drug side effects, and (v) return of the patient to a desirable and productive lifestyle.²²

When planning a treatment programme for patients with RA, it is essential to set specific objectives and prospective time limits for the various therapeutic options. This approach should be clearly explained to the patient. In pursuing a comprehensive, though prudently individualized protocol for the patients with RA, a stepped care or staged approach (e.g. Figure 1) has been advocated.^{23,24} The physician should never

Figure 1 The treatment pyramid: an example of the stepped care approach to managing rheumatoid arthritis. Modified from *Primer on the Rheumatic Diseases*.²² *Definitive position in sequence has yet to be determined.

rush to make a diagnosis of RA, and in many instances, the earliest stages of therapy may overlap with the diagnostic process. Competing diagnoses should be assiduously ruled out since the label of RA implies a lifelong commitment to sometimes aggressive treatment – and this should never be invoked without due consideration for the patient's physical and emotional well being. In addition, it is useful to advise the patient that the longer he or she goes without a specific diagnosis (while being comprehensively evaluated) the better his or her prognosis is.

Ancillary treatment, administered by physiotherapists and occupational therapists, should complement drug treatment from the earliest phases of diagnosis and should continue, whenever indicated, throughout the patient's course.

Drug management

The outcome variables that are most frequently used and have been shown to be sensitive and reliable in assessing disease activity in RA are: (i) the physician's global evaluation of disease activity, (ii) the patient's global evaluation of disease activity, (iii) a count of swollen and tender joints, and (iv) the patient's assessment of pain.²⁴

Aspirin and the other nonsteroidal anti-inflammatory drugs (NSAIDs)

It has been demonstrated in controlled trials, that treatment with aspirin and the other NSAIDs can lead to improvement in the various outcome measures that are used to assess disease activity.²³

Low dose glucocorticoids as bridge therapy

Low dose oral prednisone is often used as 'bridge' therapy between the time that the treatment with a DMARD is begun and the juncture at which the latter exerts its effect.²³ Also, if the DMARD does not work, longer therapy with the glucocorticoid is often appropriate.

Disease modifying antirheumatic drugs

When to treat?

While there is much conjecture about the role of DMARDs in both favourably modifying prognosis and slowing radiographic deterioration in patients with RA, these agents clearly have a role to play in the

comprehensive management of advancing disease. In those instances where NSAIDs alone have failed, DMARDs have been shown to suppress the clinical sequelae of disease activity and to have provided patients with symptomatic relief and an improved quality of life.

Thus, the 'difficult decision' for the physician treating RA is when to begin therapy with the DMARDs. There are no clearly defined rules, since our ability to measure progression of synovitis and destruction of cartilage is often inadequate. In general, physicians tend to underestimate the amount of joint destruction at any given time, and a case can therefore be made for starting DMARDs earlier than is usually done. In some countries, DMARDs are often started at the initial presentation of patients with a definite diagnosis of RA²³ but this practice is not universally accepted. Steinberg²⁵ has weighed up the relative advantages and disadvantages of early intervention with DMARDs, and has concluded that earlier, rather than later, introduction of these medications is inevitably in the patient's best interests.

Harris²³ has proposed a set of practical guidelines for the introduction of DMARDs. These are based on the following:

(i) *Impressions of the patient* The rheumatoid patient with active, progressive disease, almost always complains of tiredness, easy fatigability and loss of functional capacity. When such a patient gives up pleasurable activities, no matter what the excuse, disease is usually active. Patients with active disease usually sleep poorly and may even develop a fibromyalgia-like syndrome that can be partially attributed to their sleep deprivation.

(ii) *Examination of the patient* Joint destruction rarely occurs in the absence of significant soft tissue swelling in joints. Joint counts for simultaneous swelling and tenderness are useful quantitative measures. Signs of synovitis in a joint or set of joints not previously involved is a good indicator of progressive disease, as is enlargement of already existing rheumatoid nodules. Rarely, manifestations of rheumatoid vasculitis involving skin, peripheral nerves, or the gut may be evident relatively early in the disease and, when present, are predictors of poor prognosis. Warm joints and the prominence of superficial veins over involved joints are confirmation of continued, aggressive synovitis.

(iii) *Radiographic findings* Periarticular osteopenia can develop before joint space narrowing or erosions in subchondral intracapsular bone and reflects active inflammation and release by synovial cells of cytokines that mediate bone loss. Which joint should be examined for the earliest manifestations of disease?

Interestingly, in patients with polyarticular disease, the metatarsophalangeal and hallux interphalangeal joints show the earliest signs of involvement on radiographs.^{18,21} However, radiographs of the hands and wrists are a better measure of generalized disease activity.²¹ It has been demonstrated that radiographic changes are more likely to develop in the dominant hand or wrist.²⁶

(iv) *Laboratory tests* Several laboratory tests have been used in the ongoing assessments of patients with RA. The acute phase reactants are routinely measured to assess progression of disease activity. Sequential assessments of the ESR in a given patient can provide a useful index of disease intensity, while quantitation of the C-reactive protein (CRP), usually in combination with the ESR, may correlate with the development of erosive disease.¹⁸⁻²⁷ Some other routine laboratory tests are occasionally of value. A falling haemoglobin, thrombocytosis and eosinophilia often reflect an increase in disease activity in patients with RA. Synovial fluid analysis may be useful. A joint fluid leucocyte count greater than $50 \times 10^9/l$ in RA indicates a joint at risk for rapid destruction. More specialized tests on synovial fluids that correlate with disease activity include the measurement of synovial fluid complement levels.

What drug to use?

When introducing a DMARD, it is important not to decrease or withdraw NSAID therapy. The DMARDs act on inflammatory or proliferative pathways that are different from those affected by cyclo-oxygenase inhibitors.²³ While it might be anticipated that side effects would increase when additional drugs are administered, there are few well documented examples of synergistic toxicity between the NSAIDs and DMARDs.²³

It is usually prudent to begin with a DMARD that is known to have the least toxicity. The antimalarials (of which hydroxychloroquine is the most widely used) or sulphasalazine are the best examples.^{23,24} The usual oral dose of hydroxychloroquine is 200–400 mg/day. The drug is well absorbed and peak plasma levels are rapidly reached. Conversely, excretion is extremely slow and may continue for as long as 5 years after cessation of drug intake. The antimalarials, like most of the other DMARDs, can cause a host of adverse reactions.^{23,24,28,29} Gastrointestinal side effects are most frequent and sometimes may resemble those due to NSAIDs (e.g. nausea, vomiting, and epigastric pain). Anorexia, abdominal bloating, cramps and diarrhoea may be caused by reversibly depressed contractility of smooth muscle. Also, weight loss may be significant. These effects are usually benign, and may be at least partially offset by dividing the daily dosage.

While the antimalarials are also associated with various dermatological, neurological, and haematological side effects, their ophthalmological toxicity is usually the cause of greatest concern among physicians who regularly prescribe them.^{23,24,28,29} Although it is recognized that high concentrations of these compounds are found in the pigment layers of the retina and may lead to retinal damage with destruction of rods and cones and migration of pigment to the nuclear layers, it needs to be acknowledged that a decrease in visual acuity rarely occurs in patients taking no more than 400 mg/day of hydroxychloroquine. Nonetheless, patients on these drugs should be examined carefully by an ophthalmologist every 3 to 6 months. Even if the patient is asymptomatic, the drug should be withdrawn at the first sign of retinal toxicity, since worsening retinal damage may occur even after the agent has been discontinued.

Sulphasalazine^{23,24,30-34} was initially introduced for the treatment of RA in 1941, but it subsequently fell into disuse for about 25 years, and it is only very recently that its efficacy in the rheumatic diseases has been re-established. For RA, the usual dosage is 500 mg of enteric coated sulphasalazine four times a day. If this dose is well tolerated but is of no clinical benefit, the dosage may be increased to 1 gram three times a day after 3 to 6 months of treatment. About 20% of patients with RA stop sulphasalazine because of nausea, vomiting, or dyspepsia. Skin rashes occur in about 1–5% of patients and haematological toxicity, though rare, has also been reported.²⁴ An advantage of sulphasalazine (or sulphapyridine, its probable active metabolite) is that blood levels are available at reasonable cost and access.²³ Although fewer patients will derive unequivocal benefit from either hydroxychloroquine or sulphasalazine compared with gold salts, the toxicity of these agents is less than that among patients taking gold, and thus patient drop out because of adverse side effects is also less common.^{23,35}

If an antimalarial or sulphasalazine is not effective, one of the gold preparations should be considered the next line of treatment.^{23,36} Aurothiomalate and aurothioglucose are usually given intramuscularly in a dosage of 50 mg weekly, after test doses of 10 mg and 25 mg have been administered to establish tolerance. The oil based suspension of aurothioglucose is less rapidly absorbed than the aqueous solution of aurothiomalate.²⁴

Toxicity to injectable gold preparations occurs in 30% to 50% of patients. In responsive patients who do not experience drug side effects, the intervals between gold injections can be increased, initially to every second week and then progressing to every third or fourth week. Important side effects include skin rashes (which occur in 15–25% of patients), proteinuria due to an immune complex mediated membranous

glomerulonephritis (which occurs in 10–20% of patients), stomatitis (occurring in 5–10% of patients), and haematological abnormalities (which occur in 1–2% of patients).²⁴

An oral gold compound, auranofin,^{23,24,37-40} has recently been introduced and provides an alternative to the more traditionally used injectable preparations. Auranofin is usually administered in a dosage of 6 mg/day. While it is generally less toxic than the injectable preparations, auranofin is also less efficacious than intramuscular gold.³⁸ Diarrhoea is a common and troublesome side effect of oral gold, and abdominal cramps, anorexia, dyspepsia and serious colitis have also been reported.²⁴ It has been suggested that auranofin-induced diarrhoea may be partially prevented by beginning therapy at 3 mg/day and then increasing to the full dose of 6 mg after one month or more.²³

If a patient taking auranofin goes into a relative remission, it may be less expensive and just as effective to maintain this by giving him/her monthly (or bi-weekly) injectable gold salts rather than continuing the more expensive oral programme.²³ The converse, however, does not seem to apply: patients achieving remission on injectable gold, rarely maintain such control when changed to the oral preparation.

Because of its varied and unpredictable toxicity, D-penicillamine^{23,24,41-43} should probably be used only after a trial of gold has failed or when, for other reasons, gold salts are not appropriate therapy.²⁸ The starting dose of D-penicillamine is usually 250 mg/day which is increased by 125–250 mg at 2 to 3 month intervals until clinical improvement is detected or a total daily dose of 750–1000 mg is reached.²⁴ The dose may be reduced slightly for maintenance, but the drug is continued indefinitely, unless there is toxicity or a loss of efficacy. The major side effects of D-penicillamine include: dermatitis (in 12–25% of patients), anorexia, nausea, vomiting, and diarrhoea (in 12–20% of patients), dose dependent thrombocytopenia (in 5–10% of patients), and proteinuria due to reversible immune complex mediated glomerulonephritis (in 10–20% of patients).²⁴ Autoimmune syndromes such as myasthenia gravis, polymyositis,⁴⁴ Goodpasture's syndrome and systemic lupus erythematosus⁴⁵ have also been reported. D-penicillamine is probably more efficacious though more toxic, than auranofin in RA,⁴⁶ and with similar magnitude of benefit as injectable gold.²³

As more studies are published demonstrating that methotrexate is efficacious in the short and long term therapy of RA, a more general acceptance of its use is emerging.^{22,24,47-51} The true place of methotrexate in the staged approach to the management of RA has yet to be firmly established. Some rheumatologists use the drug early, after gold has failed and before D-penicillamine is started. Trials are currently in pro-

gress comparing it to gold before any of the other DMARDs are used. It has also been used instead of gold in patients with proteinuria or thrombocytopenia.²⁴

Methotrexate is usually administered weekly, either in a single dose or in three divided doses separated by 8–12 hours. Typical dosages range from 7.5 to 15 mg/week (but dosages up to 40 mg/week or 0.7 mg/kg/week have been used).²⁴ The drug can be administered either intramuscularly or orally, but, irrespective of the mode of administration, total doses should be lowered in patients with renal insufficiency. Curiously, the onset of action of the drug appears to occur much earlier than with gold salts or D-penicillamine, often within 3–4 weeks after therapy is started.²³ Toxicity from methotrexate includes bone marrow suppression with leucopenia and thrombocytopenia, ulcerative stomatitis, diarrhoea from loss of intestinal epithelium, nausea and vomiting, dermatitis, alopecia, and cirrhosis. It is thought that the liver toxicity may be reduced by carefully avoiding potential liver toxins; and alcohol consumption is therefore strictly prohibited in patients receiving the drug.²⁴ Pulmonary fibrosis and bronchiolitis obliterans have also been reported⁵² and may be life threatening.

Managing intractable disease: the use of cytotoxic agents

In cases where RA remains active and joint deformities are progressing, despite adequate trials of gold, D-penicillamine, and methotrexate, a trial of one of the immunoregulatory drugs (other than methotrexate) should be considered. The purine analogue, azathioprine, and alkylating agents such as cyclophosphamide and chlorambucil, have all been used in the management of progressive, resistant, RA.

The beneficial effect of azathioprine in RA has been supported by a number of controlled trials. Typically doses are 50–250 mg/day (0.8–4.0 mg/kg/day).^{24,53,54} Cyclophosphamide may be given orally or intravenously.^{24,53,54} The usual oral dose is 50–150 mg/day (0.7–3.0 mg/kg/day), but under some circumstances it is possible to substitute the less toxic regimen of

boluses of intravenous drug (0.5–1.0 g/m² body surface area) every 3 to 4 weeks. This regimen puts the patient at risk for toxicities for only a short period of time each month instead of continuously, as with daily drug therapy. While there are several reports of the successful use of chlorambucil in RA, there have been few controlled trials to substantiate these.^{24,55} The drug has a plasma half-life of 90 minutes and is given in doses of 4–12 mg/day (0.1–0.2 mg/kg/day).²³

A major problem with all of the immunoregulatory drugs (with the possible exception of methotrexate) is their propensity for very severe toxicity, including their well documented association with carcinogenesis. In general, the administration of drugs to patients with RA is an exercise in risk benefit assessment, but for these drugs, in particular, extra caution is mandatory, if potentially disastrous side effects are to be avoided. Cyclosporine is effective in reducing joint inflammation but further trials comparing it with other active agents, and more data on its nephrotoxicity, are needed before recommendations can be made on its place in the therapeutic pyramid.^{56–58}

Conclusion

Recommendations on the optimal pharmacological management of patients with RA are changing as more information is published on the use of sulphasalazine, auranofin, methotrexate, low dose glucocorticoids and new drugs such as cyclosporine. There is increasing variation in the sequences that guide administration of the different DMARDs. This may be appropriate since it allows the management of RA to be tailored to (i) the individual patient's preference for oral versus parenteral preparations, (ii) frequency of follow-up and (iii) the patient's own concern for different types of potential toxicities (e.g. some may worry more about ocular toxicity from hydroxychloroquine than liver toxicity from methotrexate). The complexity of selecting appropriate DMARDs for patients with RA requires that clinicians keep up to date with the latest comparative trials of the different agents. Familiarity with risk estimates for toxicities of these drugs is also mandatory.

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