ANTIMALARIALS have been used to treat rheumatic diseases for more than a century [1]. In evaluating these medications over the last four decades, three clinical characteristics have become better understood: effectiveness, safety and an expanding number of conditions for which these drugs may be used. Although much work has been expended to elucidate mechanisms of action, those relevant to antimalarial effect on rheumatic diseases have not yet been confirmed.

Three antimalarials are now employed to treat connective tissue diseases: chloroquine, hydroxychloroquine and quinacrine. The latter drug is used present only for patients with lupus skin lesions who fail to respond to one of the other drugs or who cannot take them. Quinacrine is not used more often for long-term therapy because it imparts a yellowish discoloration to the skin.

COMPARISON OF ANTIMALARIALS

A comparison of chloroquine and hydroxychloroquine is difficult. The drugs are chemically similar. Each is a 4-aminoquinoline compound differing only by a replacement of an ethyl group in chloroquine with a hydroxylethyl group in hydroxychloroquine. The only direct comparisons of effectiveness and toxicity were made by Sherbel et al. [2]. These were not controlled. Still, chloroquine was definitely shown to be both more effective and more toxic on a milligram basis. What is not entirely clear are the relative ratios of effectiveness to toxicity for each compound. Furthermore, toxicity ratios may be based mainly on gastrointestinal symptoms which stop when the medication dose is decreased or when the drug is discontinued. They may cause patients to stop taking antimalarials, but are not associated with severe problems such as the gastric ulcer complications produced by non-steroidal anti-inflammatory drugs (NSAIDs).

The authors suggested that hydroxychloroquine was one-half to two-thirds as effective as chloroquine and one-half as toxic [2]. Chloroquine, however, appears to be much more retinotoxic (vide infra) and this probably accounts for the increasingly frequent use of hydroxychloroquine.

EFFECTIVENESS

Antimalarials are used extensively to treat two rheumatic diseases: lupus erythematosus and rheumatoid arthritis.

Lupus erythematosus

The skin lesions of both discoid lupus erythematosus and systemic lupus have been reported to respond to antimalarial medications since quinine was first used in the late nineteenth century [1]. Systemic manifestations, such as malaise, fever and arthritis, have been noted to respond, but it has only been recently that a well-controlled clinical study [3] has confirmed antimalarial benefit.

In this study, 47 patients who had responded to hydroxychloroquine were placed on either a placebo or continued on their antimalarial. Those on placebo flared significantly more frequently, usually with symptoms which had previously responded to the antimalarial. Of interest, severe flares occurred more often in the placebo group. This did not reach statistical significance, probably due to the relatively small number of patients studied. It must be borne in mind that this study did not assess the percentage of patients with systemic lupus erythematosus (SLE) who respond to antimalarials. We might expect up to 45% to respond, depending on disease manifestations, but those benefiting may not go into complete remission. Seventy-six per cent of patients treated with antimalarials in a community rheumatological practice remain on medication at 2 yr [4].

Rheumatoid arthritis

Antimalarials have been used to treat rheumatoid arthritis since the 1950s [5]. Early studies often used daily doses which are no longer considered safe [6]. However, three recent controlled studies now confirm that hydroxychloroquine in daily doses of 400 mg is effective [7–9]. These studies were mutually reinforcing, lasting from 6 months to 1 yr and utilizing patients with mild or more severe disease. In all studies, joint and global assessment improved, and side-effects were equal to placebo. One study assessed response by the rather stringent Pauling criteria and found significant differences between hydroxychloroquine and the placebo groups [9]. Although these three studies clearly show that hydroxychloroquine is effective, even in those patients who had more extensive disease activity, the duration of disease was <5 yr.

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Uncontrolled studies suggest that 60% of patients will show improvement on antimalarials [6] and we have observed patients who have complete disease remission, including loss of rheumatoid factor. However, after 2 yr of treatment, only ~46% of patients in a community rheumatological practice will remain on these medications [4].

Two of the primary considerations in judging the response to slow-acting anti-rheumatic drugs is whether these medications can improve patients’ ability to function and affect radiological manifestations of rheumatoid arthritis, particularly erosive changes.

Assessment of function has been studied in a reliable, valid and sensitive fashion during the past decade. Improvement recorded in some early studies [11] used less controlled assessments. The hydroxychloroquine in early rheumatoid arthritis (HERA) study [9] best documents benefits in patients’ functional ability. A physical function index incorporating the McMartien Toronto Arthritis Patient Disability Questionnaire (MACTAR), the Health Assessment Questionnaire (HAQ) and quality of life physical disability section of the Arthritis Impact Measurement Scales (AIMS). Even though the placebo group showed some significant improvement from baseline, the patients on hydroxychloroquine had significant improvement of the function index compared to the placebo group (P = 0.02) at the end of the 6 month trial.

Recent data suggest that radiographic lesions start during the first 2 yr of rheumatoid disease activity. Antimalarials have not been proven to affect radiological changes. It is possible that this is related to the lack of long-term studies of early disease.

Two studies compared radiographic abnormalities for patients treated with chloroquine or placebo [10, 11]. In each, a majority of patients had active disease for >2 yr. One showed no difference in radiographic changes compared to patients treated with placebo when reassessed after 3–24 months on treatment [10], while the other suggested more deterioration in the group on placebo after 1 yr [11]. A recent study of patients taking hydroxychloroquine noted only a trend toward radiographic improvement in the hydroxychloroquine group [9].

In one study comparing hydroxychloroquine and sulphasalazine, fewer new erosions were noted after 2 yr on sulphasalazine [12]. Patients on hydroxychloroquine had disease for a mean of 15.6 months and were treated with 200 mg/day for the first 6 months. Those taking sulphasalazine had disease for 12.8 months and were treated with 2 g daily.

**Comparison to other slow-acting anti-rheumatic drugs (SAARDs).** Felson et al. [13] analysed 117 treatment groups on various SAARDs in 66 trials by meta-analysis. They found antimalarials to be as effective as methotrexate and other SAARDs except for D-penicillamine. In personal experience, however, methotrexate is more effective in most patients. On the other hand, antimalarials lead to remission in a small percentage of patients, while methotrexate does not [14].

Many studies comparing antimalarials to various SAARDs have been unblinded [6], but some were controlled. Hydroxychloroquine and sulphasalazine were clinically equivalent in a double-blinded study [15], but patients who were started on sulphasalazine responded more rapidly and had fewer radiographic changes at 48 weeks [12]. In other controlled studies, D-penicillamine was more effective at 6 and 12 months, but equivalent at 24 months [16]. Chloroquine was more effective than dapsone [17] and equivalent to cyclosporine [18].

**Combination therapy.** Antimalarials are an attractive agent for combination treatment because their mechanism of action appears to differ from that of other medications and they have a high safety profile. Unfortunately, the results of studies are mixed and an improved safety record for combination therapy has not definitely been established.

There is no consensus on i.m. gold and antimalarials. Older studies [6] suggested that gold conferred therapeutic advantage when added to antimalarials, but in a controlled study, when hydroxychloroquine was added to gold, both efficacy and toxicity increased [19]. A more recent controlled study showed neither improvement nor increased toxicity when hydroxychloroquine at 400 mg/day was added to gold [20]. One hundred and forty-two patients who still had significant disease after a full course of gold were analysed in this placebo-controlled study.

Antimalarials confer no additional benefit to oral gold [21], nor does addition of an antimalarial to D-penicillamine produce improvement [16].

The combination of methotrexate and chloroquine was more effective than methotrexate and placebo in a study of 88 patients [22]. All parameters assessed except pain showed more improvement with combination therapy, with the difference statistically significant for the joint count, grip strength and functional ability. Adverse events were also greater in the combination group, but this was not statistically significant. Elevations of liver enzymes to less than twice normal occurred in 11 patients on combination treatment compared to one on methotrexate alone. Another study [23], which was a 38 week multicentre study, suggested that fewer flare-ups of disease occurred compared to methotrexate and placebo. This study was not conclusive.

An important study showed that hydroxychloroquine, sulphasalazine and methotrexate were significantly more effective than either methotrexate or hydroxychloroquine plus azulfidine [24]. One hundred and two patients who had failed a second-line drug were placed on one of these three regimens using an intention-to-treat protocol lasting 2 yr. Seventy-seven per cent of 31 patients on three drugs, 40% of 35 patients on two drugs and 33% of 36 patients on methotrexate alone improved by at least 50% of their pre-treatment status.

Seven patients on methotrexate discontinued treatment for toxicity compared with three in each of the other groups. Although sulphasalazine and hydroxychloroquine appeared to be equal in efficacy to
methotrexate, it is possible that more patients in the methotrexate group were discontinued for toxicity than would have been in non-proto1cal patient care. A separate study showed no benefit in combining hydroxychloroquine and sulphasalazine [25].

Antimalarials may decrease toxicity when used in combination. Two studies on lipid levels in patients who were taking corticosteroids have been published. In one study, cholesterol and low-density lipoprotein were lower in patients also receiving hydroxychloroquine [26]. Cholesterol levels remained constant in the other study, but triglycerides and the associated protein apolipoprotein C were decreased [27]. In distinction to the clinical study cited above [22], liver function tests in patients in the ARAMIS data base [28] treated with methotrexate and antimalarials showed fewer abnormal tests than with methotrexate alone.

Other rheumatic diseases
Antimalarials may be effective in other rheumatic diseases, but placebo-controlled studies have not been performed.

Psoriatic arthritis. Psoriatic arthritis has been successfully treated with antimalarials for a number of years [29] despite the possibility of severe exfoliative reaction of the skin lesions [6].

Palindromic rheumatism. Palindromic rheumatism may respond to antimalarials with a reduction in the frequency and duration of attacks [30].

Eosinophilic fasciitis. Antimalarials appear to be attractive agents for eosinophilic fasciitis with 25% showing complete resolution and 38% a partial response in one small series of patients [31].

Dermatomyositis. Skin lesions in dermatomyositis have been reported to respond to antimalarials [32], but data for muscle improvement are more tenuous [33].

Sjögren’s syndrome. Sjögren’s syndrome is often extremely difficult to treat. Antimalarials have improved laboratory abnormalities [34], but have not yet definitely been shown to have clinical benefit [35].

Juvenile chronic arthritis. Antimalarials have been reported to be effective in treating juvenile chronic arthritis [6], but the only double-blinded controlled study using a placebo group was a Russian–American collaboration [36]. NSAIDs plus placebo were as effective as NSAIDs plus hydroxychloroquine or d-penicillamine. One problem was the extraordinary response to continuation of NSAIDs alone of at least 50%. When antimalarials are given to children, they may be very sensitive to them. Death has occurred with as little as 1 g of chloroquine [37]. Children should take no more than 7 mg/kg/day of hydroxychloroquine or 4 mg/kg/day of chloroquine [38].

Other arthritides. Data about the effect of antimalarials on other diseases, such as erosive osteoarthritis [39] and calcium pyrophosphate crystal deposition disease [40], are even more tenuous.

MECHANISM OF ACTION
Similar to most anti-rheumatic drugs, antimalarials have a multitude of actions [6] and the one(s) responsible for disease improvement have not been established. A reasonable explanation for the predominant action must account for the facts that antimalarials help many different rheumatic diseases and that there is a delay in onset of benefit, often by 1–3 months, after the drug is begun.

Antimalarials have at least one unique action among anti-rheumatic drugs. They interfere with cellular function in compartments with acid microenvironments, such as lysosomes. This ‘lysosomotropic’ action occurs because antimalarials are weak bases which enter acidic subcellular areas, are protonated and raise the pH, thus interfering with physiological function which depends on an acidic pH [41]. This may have a variety of effects, such as interference with receptor function [42], inhibition of intracellular processing and secretion of proteins [43], possible interference with autoantibody production [44], decreased lymphocyte proliferation [45], interference with natural killer cell activity [46] and decreased cytokine production [47–49].

The effect of decreased cytokine production may be of particular importance in rheumatoid arthritis. For example, treatment with monoclonal antibodies against tumour necrosis factor alpha (TNF-α) has improved rheumatoid arthritis. In vitro studies show that antimalarials decrease production of TNF-α by human macrophages [49]. On the other hand, Sperber et al. showed that antimalarials induced no fall in TNF-α [47]. Other actions may also be important. For example, skin lesions in lupus may be inhibited by antimalarials by a photoprotective mechanism [50, 51].

TOXICITY
Despite a large number of potential side-effects [6], antimalarials have an impressive safety record. Meta-analysis confirms this. Reviewing 71 drug–placebo studies, Felson et al. [13] found fewer drug withdrawals for toxicity compared to other SAARDs. This reached statistical significance for comparison with i.m. gold, sulphasalazine and D-penicillamine.

The most common problem is gastrointestinal (GI) upset, manifested by cramps or nausea. This is probably due to antimalarial action on bowel muscle. Although antimalarials have some effect on prostaglandin formation [52], they cause no GI ulcer formation. Histamine H2 receptor antagonists do not help the bowel motility changes symptomatically in distinction to their action on NSAID-induced GI symptoms. The antimalarial GI upset can sometimes be avoided by starting with a very small daily dose and gradually increasing to full doses. However, patients may not tolerate the GI symptoms and then must discontinue the antimalarials.

Skin rash and mild central nervous system (CNS) disturbances are also common. Skin lesions may be of almost any type, although pruritic, morbilliform rashes are common. CNS side-effects are usually not significant. They are often reversible with lower daily drug doses and even remit spontaneously after several weeks [2]. Most
It should be noted that other lesions, such as retinal degeneration, may at first appear similar to antimalarial retinopathy. If the two conditions can be distinguished, antimalarials may be restarted.

Patients often complain of difficulty focusing when antimalarial treatment is started. This is probably related to drug effect on eye muscle and does not progress or threaten vision [6]. It usually regresses with continued drug use. Antimalarial corneal deposition depends on dose, but does not presage retinal disease. It is not a reason to discontinue treatment.

One toxic manifestation which may be difficult to assess is neuromuscular disease. Neuropathy and/or myopathy are frequent manifestations of many connective tissue diseases. Corticosteroids may also cause myopathy. Antimalarial neuromyotoxicity has been noted for over three decades. Creatine phosphokinases remain normal [59] and this may separate antimalarial toxicity from inflammatory myositis. Histological changes may also help. Electron microscopy findings of myeloid bodies and curvilinear bodies closely associated with secondary lysosomes in myocytes have been reported to indicate antimalarial toxicity [60]. However, it is difficult to be certain that this is pathognomic of toxicity, but could possibly be present in the muscle of patients receiving 4-aminoquinolone antimalarials who do not have myotoxicity, perhaps related to their effect on recycling of cell constituents. Vacuolar myopathic changes which have been noted by light microscopy in patients with antimalarial toxicity are also found in patients with SLE not receiving antimalarials [61]. It is, therefore, important to review clinical aspects of neuromuscular toxicity and to determine whether medication withdrawal improves findings.

**PREGNANCY AND ANTIMALARIALS**

4-Aminoquinolone antimalarials have not been recommended for use during pregnancy. This warning is primarily based on one article which described a woman intermittently treated with chloroquine at 500 mg/day [62]. She had six children. The three born when she took chloroquine had deafness, ataxia and/or vestibular paresis.

It is possible that the drug dose, and not simply use of the drug, may contribute to fetal abnormalities. Chloroquine remains in patients for over 5 yr [63]. Any patient who was recently receiving antimalarials will have some drug remaining in her system during subsequent pregnancy even if she stopped the drug several years before becoming pregnant. Furthermore, the patient who delivered babies with abnormalities was taking a high daily dose [62].

Ann Parke and colleagues [64] have described normal children of mothers with SLE receiving hydroxychloroquine during pregnancy. They suggest that continuing antimalarials in SLE patients who are pregnant may be of benefit in controlling disease and preventing fetal wastage due to disease flares. Because rheumatoid arthritis often goes into remission during pregnancy, antimalarials may be discontinued in these patients.
HOW TO USE ANTIMALARIALS IN RHEUMATIC DISEASES

Lupus erythematosus

Antimalarials may be tried in all patients with either discoid or systemic lupus. If a clinical response occurs, the antimalarial medication should probably be continued indefinitely on the basis of the Canadian study [3], assuming there is no toxicity. If there is no clinical response, the medication may be stopped. To date, there is no compelling evidence that antimalarials are effective in controlling disease affecting the kidneys or brain, or prolonging life, although the Canadian study raises the possibility that major flares may be prevented [3]. Further controlled studies are needed.

Rheumatoid arthritis

The role of antimalarials is moderately well defined in rheumatoid arthritis. If disease is mild, it may be worthwhile trying these medications for 6 months to determine whether remission is induced or disease is well controlled. With aggressive disease, methotrexate is more likely to be effective. Antimalarials are excellent candidates for a role in combination therapy. The combined use of antimalarials with methotrexate is not unreasonable even with aggressive disease. The antimalarial may reduce liver function abnormalities [28], although this is not certain [22]. If effective, it may allow methotrexate to be tapered and temporarily or permanently discontinued. Data to date suggest that the combination of hydroxychloroquine, methotrexate and azulfidine may be the most effective combination therapy [24].

Azulfidine and hydroxychloroquine may be equivalent to methotrexate [24].

Other rheumatic diseases

Antimalarials are worth a trial in treating dermatomyositis, which responds insufficiently to prednisone, in palindromic rheumatism and in eosinophilic fasciitis. It is not unreasonable to treat Sjögren’s syndrome with antimalarials. Data on juvenile chronic arthritis are not conclusive [6], despite a controlled study showing no benefit [36].

Monitoring toxicity

Antimalarials are generally safe. Knowledge of potential side-effects enables the practitioner to be aware of potential serious problems which must be clinically recognized. Routine laboratory monitoring is not needed.

The only potential side-effect which must be carefully monitored is retinopathy. It is not clear how often ophthalmological examinations are needed. For obvious reasons, patients taking antimalarials who develop any retinal lesion, which has been previously reported to occur with these medications, have the drug stopped. Progression to visual loss, therefore, has not been reported. Furthermore, we have restarted hydroxychloroquine in two patients after early changes regressed [58]. On the other hand, true retinopathy has developed in patients taking what are now considered to be safe daily doses [54]. In addition, the only prospective study has shown that patients receiving an ophthalmological examination every 6 months did not develop loss of vision [58].

On balance, therefore, we believe that patients taking antimalarials should be tested every 6 months using the protocol listed in Table I. Assessment of visual acuity, fundus pigmentation and visual fields appears sufficient to prevent retinopathy.

The relatively high efficacy to toxicity ratio justifies antimalarials as attractive medications to treat a variety of rheumatological diseases.

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