REVIEW ARTICLE

Remission-inducing drugs in rheumatoid arthritis

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The administration of certain drugs to patients with established rheumatoid arthritis frequently results in improvement that is slow to appear but persists for long periods, even after the drug is discontinued. The three main drugs with this effect, whose efficacy and toxicity are reviewed in this paper, are gold salts, D-penicillamine and chloroquine. The cytotoxic agents used to treat rheumatoid arthritis, which likely have nonspecific anti-inflammatory actions and have serious long-term side effects, are also briefly reviewed. A new drug, levamisole, is currently being tested in patients with rheumatoid arthritis.

It is suggested that the time for considering the introduction of a remission-inducing drug in patients with progressive rheumatoid arthritis is after an adequate trial of therapy with salicylates or other nonsteroidal anti-inflammatory agents, or both, and before the oral administration of steroids. It is difficult, however, on the basis of rigorous clinical comparisons, to recommend which of the three main remission-inducing drugs should be tried first, although gold salts have been used the most. Patients who have improved with 6 months of chrysotherapy may continue treatment for at least 3 years, during which time the frequency of mucocutaneous and renal toxic effects will steadily decrease. Some aspects of the medical economics of therapy with remission-inducing drugs for rheumatoid arthritis are discussed.

L'administration de certains médicaments à des patients souffrant de polyarthrite rhumatoïde établie entraîne fréquemment une amélioration qui est lente à apparaître mais qui persiste pendant de longues périodes, même après l'arrêt du médicament. Les trois principaux médicaments produisant cet effet, et dont l'efficacité et la toxicité sont revues dans cette publication, sont les sels d'or, la D-pénicillamine et la chloroquine. Les agents cytotoxiques utilisés pour traiter la polyarthrite rhumatoïde, qui sont susceptibles d'avoir des actions anti-inflammatoires non spécifiques et qui ont des effets secondaires sérieux à long terme, sont aussi brièvement revus. Un nouveau médicament, la lévamisole, est présentement mis à l'essai chez des patients atteints de polyarthrite rhumatoïde.

On suggère que le moment indiqué pour considérer l'introduction d'un médicament inducteur d'une rémission chez des patients souffrant de polyarthrite rhumatoïde évolutive se situe après un essai adéquat d'un traitement aux salicylates ou à d'autres agents anti-inflammatoires non stéroïdiens, ou à une association des deux, et avant l'administration de stéroïdes par voie orale. Il est difficile cependant de recommander, sur la foi de comparaisons cliniques rigoureuses, lequel des trois médicaments inducteurs d'une rémission devrait être essayé le premier, bien que les sels d'or aient été utilisés le plus souvent. Les patients qui se sont améliorés après 6 mois de chrysothérapie peuvent poursuivre ce traitement pendant au moins 3 ans, temps durant lequel la fréquence des effets toxiques cutanéomuqueux et rénaux diminuera constamment. Quelques aspects médicoéconomiques du traitement de la polyarthrite rhumatoïde avec des médicaments inducteurs d'une rémission sont discutés.

The administration of certain drugs to patients with progressive rheumatoid arthritis results in prolonged improvement more often than would be expected by chance alone and sometimes produces complete remission. Attempts to give these drugs a group name have generally been unsatisfactory, and they have been labelled as "specific" therapeutic agents for rheumatoid arthritis,[1] disease-"suppressive" agents[2] or "remittive" (remission-inducing) drugs.[3] There is no general agreement on what constitutes a remission in rheumatoid arthritis, which adds to the problems of terminology.

The prolonged improvement brought about by remission-inducing drugs can be distinguished from the anti-inflammatory effects of salicylates, other nonsteroidal anti-inflammatory agents and the glucocorticoids. Improvement due to remission-inducing drugs has a striking latency period, occurring weeks or months after the initiation of therapy; the improvement often persists, usually for months or years, while therapy is continued, and it usually lasts for weeks or months after therapy has ceased. There is

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also evidence that some of the remission-inducing drugs may modify the natural course of rheumatoid arthritis by slowing the erosion of bone and cartilage. The clinical response to remission-inducing drugs contrasts sharply with that following therapy with salicylates, other nonsteroidal anti-inflammatory agents and glucocorticoids. When these are administered a response, if it occurs, is generally prompt, within hours or days, and on withdrawal of the medication deterioration is generally just as rapid. Furthermore, there is no convincing evidence that these anti-inflammatory agents favourably modify bone or cartilage damage.

The remission-inducing drugs that I will discuss are gold salts, D-penicillamine, chloroquine and some of its derivatives, and levamisole, a new drug undergoing testing.

At first the remission-inducing drugs were used to treat conditions other than rheumatoid arthritis, including those of unrelated cause such as parasitic infestations, tuberculosis and Wilson's disease. The remission-inducing drugs are chemically unrelated and have diverse mechanisms of action. However, the use of these drugs to treat inflammatory diseases of unknown cause has been largely confined to the management of rheumatoid arthritis, although chloroquine has been used to treat discoid and systemic lupus erythematosus. While none of the remission-inducing drugs were specifically designed for rheumatoid arthritis, there is a broad distinction between them and other potent anti-inflammatory agents, such as corticosteroids and cytotoxic drugs, that have been used in a wide variety of chronic inflammatory states and should not be considered as specific in their actions. I will discuss the cytotoxic (immunosuppressive) agents briefly since their place in the treatment of rheumatoid arthritis remains controversial, and several studies have compared them with remission-inducing drugs.

The main objects of this review are: to summarize the evidence for the efficacy of individual remission-inducing drugs; to present a balanced view of the risk of side effects with current dosage regimens and preparations; and to attempt to resolve questions about the choice and order of use of remission-inducing drugs, and about the length of therapy once a satisfactory clinical response has been achieved. No attempt will be made to cover the literature exhaustively, and mechanisms of action and pharmacokinetics will be mentioned only when they have direct relevance to the clinical use of the drug in question.

Gold salts

Among the remission-inducing drugs for progressive early rheumatoid arthritis gold salts are probably preferred by most North American rheumatologists. The historical use of gold salts exemplifies the empiricism that has prevailed in the use of remission-inducing drugs. Although Abu Moussa the Wise apparently recommended the use of gold as a panacea in the eighth century, it was not until 1890 that Robert Koch showed that gold cyanide inhibited the growth of tubercle bacilli; it was subsequently shown that several gold salts had similar effects in vitro. In 1924 Møllgaard[4] of Copenhagen showed that aurothiosulfate sodium was effective in the treatment of pulmonary tuberculosis. In the 1920s, largely by relating the chronic inflammation of tuberculosis to that of rheumatoid arthritis, several clinicians in Germany and Forrestier in France reported improvement in patients with rheumatoid arthritis treated with gold salts. Other encouraging reports soon followed.[5,6] Forrestier's visit to the United States in 1934 and the publication of his experience with 550 patients[7] seem to have stimulated considerable interest in the use of gold salts for rheumatoid arthritis in North America.[8]

Controlled studies

Several controlled studies in the 1940s clearly showed long-term benefit of the intramuscular administration of gold salts to patients with rheumatoid arthritis.[9-11] However, the enthusiasm that followed the introduction of glucocorticoids in 1949 and experience with gold-associated toxic reactions resulted in considerable uncertainty regarding the role of gold salts in the 1950s and early 1960s.[12] The most convincing proof of the benefits of chrysotherapy was a double-blind multicentre trial coordinated by the Empire Rheumatism Council in Great Britain.[13,14] In this large study it was unequivocally demonstrated that in most patients being given weekly intramuscular injections of 50 mg of sodium aurothiomalate there was progressive improvement in a number of objective variables, including the number of joints clinically inflamed, grip strength and the erythrocyte sedimentation rate. Furthermore, when treatment was discontinued after 20 weeks, each patient having received a total of 1 g of gold, the improvement persisted for up to a year in many patients. However, after a year there was a high relapse rate. These results were confirmed more recently by another double-blind multicentre trial by the American Rheumatism Association.[15]

Chrysotherapy appears to improve the natural history of rheumatoid arthritis in addition to suppressing inflammation. A 30-month, well controlled trial showed that patients who received 50 mg of gold salts weekly for 20 weeks initially, followed by maintenance therapy, had fewer bone erosions and less joint space narrowing than a control group of patients who received a placebo.[16] The favourable effect of gold salts on bone and cartilage erosions has been confirmed by Scandinavian researchers.[17] They also found that the effects of chrysotherapy after 5 or 6 years were better in patients that had received a total of nearly 2 g of gold than in those that had received much less because of gold's toxicity.[18]

Preparations, dosages and pharmacokinetics

The weekly administration of 50 mg of gold sodium thiomalate (usually following initial injections of 10 and 25 mg) is based primarily on clinical experience and remains the standard regimen. Recent studies have shown that giving 150 mg per week of gold sodium thiomalate has no additional therapeutic benefit and is more toxic;[19] however, giving 25 mg weekly[20] or less[21] may be as effective as giving 50 mg weekly.

Other organic salts of gold (e.g.,

aurothioglucose and aurothiosulfate) seem to be no more effective than aurothiomalate for intramuscular injection. However, it is possible that the associated organic anions may modify some of the toxic effects. An orally administered gold preparation (auranofin) has recently been developed; from preliminary reports it appears to be clinically effective.[22] However, it also has potent effects on humoral immunity and cellular processes, and its clinical toxicity has not yet been carefully evaluated.

The usefulness of monitoring blood levels of gold as a guide to therapy and toxicity remains controversial. While some studies have suggested that serum gold levels maintained at about 300 μg/dl (as measured by atomic absorption spectrophotometry) produce better clinical effects,[23] other data do not support this.[24-27] Most clinics do not routinely estimate serum gold levels and simply rely on an empiric dosage schedule.

After an intramuscular injection of gold the serum concentration peaks after a few hours. Clearance from the plasma is slow, however, with half the gold being excreted in about 5 to 6 days.[24,26,28] Most (70%) of the gold is eliminated in the urine and the remainder in the feces. If chrysotherapy is stopped a small and decreasing proportion of the administered gold is excreted for many weeks. A significant proportion of the administered gold is retained in the body for many months.[29] This partly explains why there appears to be little loss in efficacy when an injection is missed from a series of weekly gold injections. When a questionable abnormality is noted (e.g., a borderline platelet count) the general rule should be: If uncertain do not give. There is little advantage and possible harm in giving the weekly injection in these circumstances.

Toxic reactions and their relation to long-term chrysotherapy

The main types of toxic reactions associated with gold therapy are well known and include mucocutaneous reactions and renal and hematologic side effects.[7,8,13-15] According to a British review[30] aurothiomalate headed the list of drugs associated with death (on the basis of number of deaths per prescription), but this conclusion is open to criticism. For example, the duration of drug administration, the total amount prescribed, the follow-up of patients and, indeed, the accuracy of reporting were not at all clear. It was also suggested in the British review that certain drug reactions were reported much more often because the doctors were more familiar with the hazards of those drugs. Gumpel,[31] in a recent reassessment of the same data, concluded that, as the use of gold salts has increased, the number of deaths to which gold may have contributed has greatly decreased, probably because of better follow-up. Most reports of large studies in which toxicity has been carefully monitored have cited no deaths associated with chrysotherapy.[7,8,13-15,32] However, about 35% of patients receiving 20 weeks of chrysotherapy might be expected to have toxic reactions, compared with about 16% of a control population receiving placebo therapy.[8] If patients who respond to chrysotherapy are given this therapy beyond 20 weeks the total number of toxic reactions might be expected to increase. In the experience at our chrysotherapy clinic with 100 patients who received a total of 134 patient-years of chrysotherapy the numbers of toxic reactions of sufficient severity to necessitate withdrawal of gold therapy were as follows: rash 24, mouth ulcers 11, proteinuria 10, thrombocytopenia 4, immediate allergic reaction 2, low leukocyte count 1 and jaundice 1.[32]

How long should chrysotherapy be continued for patients that initially respond? This question may be approached by examining the frequency of toxic reactions during successive periods of long-term therapy. As can be seen from Table I the frequency of rash, mouth ulcers and proteinuria decreases progressively in successive periods of continued chrysotherapy. Interestingly, this progressive decrease cannot be accounted for simply by natural selection of patients that would not have toxic reactions, since many of the patients that received between 2 and 5 years of therapy had rashes early in their therapy. However, these reactions were generally mild, did not necessitate discontinuation of therapy and did not recur. Similar decreases in the frequency of thrombocytopenia with progressive chrysotherapy were not observed, and episodes of low platelet counts occurred anytime. However, we have not seen clinically significant thrombocytopenia in the 75% of our patients that received complete follow-up (all the necessary blood analyses and injections) in an organized gold therapy clinic. Our general policy in the gold clinic has been to discontinue, at least temporarily, treatment with gold when the platelet count drops below 200×10^9/l, and to re-evaluate the situation when the platelet count falls, even to levels above 200×10^9/l. A proper form for monitoring laboratory variables and dosage, a reliable laboratory and fresh blood specimens are indispensable if a trend toward toxicity is to be recognized. Most

Table I—Duration of chrysotherapy in relation to the frequency of certain toxic reactions*

Period of treatment (mo)	No. of patients	Total no. of treatment months	Toxic reaction; no. of episodes† (and frequency)		
			Rash	Mouth ulcers	Proteinuria‡
0–3	100	274	27 (9.9)	11 (4.0)	5/2 (1.8)
3–6	77	450	12 (3.5)	4 (1.1)	4/2 (1.2)
6–12	60	694	8 (1.9)	5 (1.2)	3/1 (0.7)
12–24	45	937	9 (2.1)	2 (0.4)	3/0 (0.7)
24–36	22	745	1 (0.6)	1 (0.6)	1/0 (0.6)
36–48	13	573	1 (1.3)	0 0	0 0
48–60	6	342	1 (4.9)	0 0	0 0
60–72	2	133	0 0	0 0	0 0

*Data adapted from Kean and Anastassiades.[32]
†Number of episodes per 100 patients per treatment month during a given period of chrysotherapy.
‡Second figure indicates number of episodes of the nephrotic syndrome (24-hour urinary excretion of protein greater than 3 g).

patients with clinically important thrombocytopenia recover, usually with the aid of glucocorticoid therapy.[32,33] The data in Table I, therefore, suggest that patients who improve within 6 months may receive chrysotherapy for up to 3 years at least, with an increasing margin of safety against mucocutaneous and renal toxic effects. However, regular adequate hematologic monitoring is essential.

Other toxic reactions associated with gold therapy are much less common. Leukopenia occurred in 0% to 3% of the patients in most of the large studies I have quoted, and bone marrow aplasia was rare. The frequency of acute reactions after injection has varied and may be decreased by substituting aurothioglucose for aurothiomalate.[34] Gold-salt-associated enterocolitis,[35] diffuse pulmonary injury[36] and hepatic involvement[37] are rare complications that have recently been reported. In the management of toxic reactions associated with chrysotherapy it is important to keep in mind that the metal cation is not necessarily the offending agent[34] and, indeed, the persistence of the thiomalate anion has been demonstrated experimentally.[38] Thus, the use of organic anion chelating agents to reverse a toxic reaction may not be soundly based.

D-penicillamine

Penicillamine is a structural analogue of the amino acid cysteine. It was first described in 1942 as an important component of the penicillin molecule exposed to acid hydrolysis.[39] Only the D isomer is used clinically, since the L form and the D,L mixture are much more toxic. It was noted in 1953 that penicillamine extracted from the urine of patients treated with penicillin caused increased copper excretion,[40] and penicillamine began to be used to treat Wilson's disease. Interest in penicillamine therapy for rheumatoid arthritis probably began in 1957 with the observation that human macroglobulins could be dissociated in vitro with sulfhydryl-reducing agents such as penicillamine.[41] The subsequent tentative experimental use of D-penicillamine in rheumatoid arthritis is an intriguing story in drug development.[42]

Several controlled studies have shown that penicillamine ingestion initiates a slow but sustained improvement in patients with rheumatoid arthritis.[43-45] In the study of a British multicentre trial group[43] 1.5 g of penicillamine per day was used and improvement was noted in all variables tested except for roentgenographically observed changes in joints.

Toxic reactions

The frequency of toxic reactions to D-penicillamine treatment is considerable. The problems include gastrointestinal, dermatologic, hematologic and renal involvement.[43-49] Taste impairment may be so severe that the patient requests discontinuation of the drug. This problem may respond to a lowering of the dose, and it has been suggested[49] that zinc or nickel supplements may be useful, but dysgeusia may also improve spontaneously. Explosive and intractable vomiting has been reported. Dermatologic complications are common and include morbiliform rashes that may progress to exfoliation and occasionally pemphigoid eruptions. A skin lesion, elastosis perforans serpiginosa, has been described in patients with Wilson's disease that were ingesting large doses of penicillamine.[50]

Hematologic side effects are probably the most serious potential toxic reactions, and fatal bone marrow aplasia has been reported by a number of investigators. We have seen apparently rapid agranulocytosis develop with the only forewarning being a change in the differential leukocyte count, and the very sudden development of bone marrow aplasia has been emphasized elsewhere.[48,49] Thrombocytopenia is common and has been reported in over 10% of patients;[43] although it may be the earliest forewarning of bone marrow aplasia it is more commonly transient, self-limiting or responsive to a reduction in dose. Proteinuria is also common, occurring in about 20% of patients in some series, but if moderate (the daily excretion of protein being less than 2 g) may respond to a reduction in dose; however, the possibility of long-lasting or irreversible renal lesions has been suggested by the persistence of proteinuria after the drug has been discontinued.[51] Many authorities recommend that a complete leukocyte count, a platelet count and a test for proteinuria be done every 2 weeks during the first 6 months of therapy and every month thereafter. A penicillamine monitoring sheet is also extremely useful. It appears that the true frequency (the number of episodes of toxic reactions per treatment month per 100 patients) of the more common complications decreases as penicillamine therapy proceeds past 6 months,[52] just as those of gold therapy do.

Less common complications include the so-called autoimmune syndromes and the detection of associated antibodies in the serum and tissues. Lupus-like disease[53] and autoantibodies[54] have been described, as have polymyositis,[55] a myasthenia-gravis-like syndrome,[56] Goodpasture's syndrome[57] and obliterative bronchiolitis.[58] Mammary gigantism[59] and fetal abnormalities have been reported.[60] Pregnancy probably constitutes a contraindication to therapy with penicillamine for rheumatoid arthritis, although this may not apply in Wilson's disease.[61] Some clinicians feel that penicillamine should not be given if there is a history of allergy to penicillin,[49,62] a view not shared by more enthusiastic advocates of the drug.[46] If there is a history of true penicillin hypersensitivity, penicillamine therapy should probably only be commenced with inpatient supervision.

Modification of dosage schedules has led to decreased toxicity without loss of efficacy. In British[63] and French[64] trials a low-dose regimen (500 to 600 mg/d) was compared with a high-dose regimen (1000 to 1200 mg/d). The two regimens were equally effective and superior to the placebo. However, adverse reactions that required termination of treatment occurred in 26% of the patients receiving 600 mg of penicillamine daily and in 40% of the patients receiving 1200 mg daily.[63] The current "go slow, go low" regimen consists of 250 mg daily at first, with an increase of 250 mg in the daily dose every 3 months to a maximum daily dose of 750 mg

until either a clinical response is observed or toxic effects develop.[65] However, even with these doses 40% of patients may require discontinuation of the drug owing to toxic reactions,[66] and fatal bone marrow aplasia has been reported.[67] Currently the question of optimal dosage is being investigated in a collaborative United States–Soviet Union trial and in a United States trial in which 125 to 750 mg of penicillamine is being given daily. Although considerable experience has been derived from the European and American trials and although the general clinical use of D-penicillamine seems to be rapidly increasing, this drug is not yet approved for use in treating rheumatoid arthritis in Canada. However, it has recently been approved in the United States.

Chloroquine

Since the initial report in 1951 that chloroquine was effective in the treatment of lupus erythematosus with arthritis[68] controlled studies have clearly indicated that both chloroquine therapy (500 mg/d initially and a maintenance dose of 250 mg/d)[69] and hydroxychloroquine therapy (200 mg/d)[70] are effective in the treatment of rheumatoid arthritis. The antirheumatic effect generally takes about 2 months to appear; once the effect is noted it often becomes progressively more marked with time, and clinical improvement is generally accompanied by a decrease in the erythrocyte sedimentation rate and in the rheumatoid factor titre.[69] More recent studies have indicated that chloroquine therapy is about as effective as therapy with gold salts or azathioprine.[71]

Toxic reactions

In spite of chloroquine's efficacy its use has probably decreased because of the risk of retinopathy, which may be irreversible. However, the retinal abnormalities, which have been described in detail,[72,73] depend on the total amount of chloroquine given;[73] the average "threshold" dose usually is 500 g.[74] Retinopathy rarely, if ever, occurs with daily doses of less than 250 mg of chloroquine, even with very prolonged administration.[74] Furthermore, retinopathy has not been reported in thousands of persons receiving about 500 mg of chloroquine per week as a long-term antimalarial drug.[75] Other ocular side effects have included corneal deposits and cataracts, which are thought to be often reversible.[76] The risks and benefits of chloroquine therapy at 2 mg/lb (4.4 mg/kg) body weight have been reviewed.[77]

It has been our practice to give 250 mg of chloroquine a day for 3 to 4 months and then to decrease the daily dose to 125 mg. Although this regimen appears to be effective in many patients and we have never observed chloroquine retinopathy, the efficacy of this low daily dose has not been evaluated in controlled studies. Some clinicians advocate intermittent therapy with 250 mg/d, but adequately controlled studies are lacking.

Other side effects that have received much less attention than ocular reactions and are rare include leukopenia and peripheral neuropathy,[78] myopathy[79] and blanching of the hair and skin.[80] These unusual side effects have generally been reported with large doses of chloroquine given over long periods. A variety of rashes have been reported; they have generally disappeared when the dose was reduced. Patients receiving chloroquine therapy should protect their eyes from excessive sunlight,[77] and children and persons with psoriasis should probably not receive the drug.[81]

Summary

Chloroquine provides a relatively inexpensive, effective therapy for rheumatoid arthritis. Toxic reactions are infrequent if chloroquine is given in a dose of less than 250 mg/d. There is a feeling among many rheumatologists that its efficacy may be less than that of gold salts or penicillamine, but rigorously controlled studies are lacking on this point. It may be that gold salts and penicillamine have relatively greater placebo effects, in part because of the required close supervision of the patient. A carefully controlled study of low-dose penicillamine and low-dose chloroquine therapy is required to place these drugs in a proper perspective of relative efficacy, safety and cost.

Cytotoxic drugs

A number of cytotoxic drugs used primarily in cancer patients and renal transplant recipients have also been used in clinical trials for the treatment of rheumatoid arthritis.[82] Although some of these drugs have been called immunosuppressive, it is likely that the dosage regimens usually used in rheumatoid arthritis are effective on the inflammatory response in general rather than specifically on immunologic processes.[83,84] A variety of cytotoxic drugs have been used, including busulfan, 5-fluorouracil, 6-mercaptopurine (a metabolite of azathioprine) and methotrexate. However, the most attention has been paid to cyclophosphamide[85-89] and azathioprine.[71,90-92] The effective daily dose of cyclophosphamide is 2.0 to 2.5 mg/kg, and daily doses of less than 1.0 mg/kg have not been effective.[88] Azathioprine has a disease-suppressive effect at daily doses of 2.0 to 3.0 mg/kg but is also effective at lower daily doses, about 1 mg/kg.[91] A comprehensive review of the relative effects of cyclophosphamide and azathioprine has been published.[93]

The wisdom of administering cytotoxic agents to a person with a chronic, generally nonfatal disease can be questioned on the basis of the severe short-term and long-term side effects. Bone marrow suppression, increased susceptibility to infections (including those by opportunistic organisms) and mucocutaneous reactions are well known and can occur relatively frequently with any of the cytotoxic agents.[94-97] Certain cytotoxic drugs produce characteristic patterns of toxic reactions — for example, hemorrhagic cystitis, hair loss, azoospermia and anovulation, which occur frequently with cyclophosphamide therapy,[98,99] and liver cirrhosis, which has been observed with methotrexate treatment.[100] Also of considerable concern is the growing number of reports of acute leukemia,[101,102] solid malignant tumours[103,104] and chromosomal aberrations[92] in patients with rheumatoid arthritis who have been treated with cytotoxic drugs. Al-

though cytotoxic drugs are used by some clinicians in cases of progressive rheumatoid arthritis unresponsive to other forms of therapy, their use for rheumatoid arthritis does not have federal government approval.

Levamisole

This antihelmintic drug was first reported to be effective in the management of rheumatoid arthritis in 1975.[105] Under certain conditions levamisole stimulates some of the cellular elements of the immune response, but its mechanism of action in rheumatoid arthritis is not known. It has now undergone extensive testing by the European League Against Rheumatism and has been found to be an effective remission-inducing drug in the long-term management of rheumatoid arthritis.[106,107] The most serious and second most common side effect (after skin rashes) is agranulocytosis, which often appears suddenly and occurs in about 5% of patients.[108] The currently recommended dose is 150 mg once a week; a leukocyte count should be performed 10 hours after the dose is taken.

Some of levamisole's more enthusiastic proponents have recommended that it be used when gold salt or penicillamine therapy has failed,[109] but there is uncertainty about the long-term complications of treatment with levamisole. It is not approved for use in humans in Canada and can be obtained only with special permission as an experimental drug.

Discussion

There is little disagreement about the use of salicylates as the initial anti-inflammatory agent in patients with rheumatoid arthritis that can tolerate them, or that salicylates must be given in adequate doses to suppress inflammation in rheumatoid arthritis. Failure of salicylate therapy is ill defined, and the definition has been made more nebulous by the ever increasing offerings of new, attractively promoted nonsteroidal anti-inflammatory drugs. Indeed, it may well be that the ability of the physician to evaluate the compliance of the patient in taking the prescribed dose of a salicylate or to critically evaluate symptoms of drug intolerance has been further eroded by the ready availability of the many anti-inflammatory agents.

A somewhat analogous situation is developing with respect to the more toxic drugs I have described. One cannot but be concerned about the possibility of a therapeutic hydra, with a decline in popularity of one remission-inducing drug because of serious side effects serving as an impetus for the evaluation of many other agents, whose significant toxicity might be appreciated only gradually. Nevertheless, the focus on the role of remission-inducing drugs has been sharpened by the growing reluctance of most rheumatologists to use oral steroid therapy in the routine management of rheumatoid arthritis. This reluctance is well founded in the almost invariable occurrence of side effects with even very low doses of glucocorticoids, the difficulty of ridding patients of corticosteroid dependence, the early realization that corticosteroids are no more effective than salicylates in altering the course of rheumatoid arthritis,[110,111] and the recent recognition of the increased bone and cartilage deterioration[112,113] that may, in part, be brought about by direct biochemical effects on connective tissue metabolism.[114,115]

It appears, therefore, that the best time for considering the introduction of a remission-inducing drug in most patients with steadily progressive disease is after an adequate trial of a salicylate or another nonsteroidal anti-inflammatory agent, or both, and before consideration of oral corticosteroid therapy. I usually consider, and often introduce, a remission-inducing drug after 4 to 6 months of definitely progressive disease. However, patients' apparent compliance with and tolerance of "first-line" anti-inflammatory medication as well as their reliability and attitudes are important factors in the decision to use remission-inducing drugs.

It is difficult to make a firm recommendation on the order or preference of use of the three main remission-inducing drugs (gold salts, D-penicillamine and chloroquine) on the basis of rigorous evidence from clinical trials. "Clinical experience", usually a euphemism for the personal prejudice of the clinician, is often invoked in this therapeutic dilemma and is sometimes colourfully reflected even in standard rheumatology textbooks.[3,8,49,116] There is no doubt that the longest and the most reported clinical experience has been with gold salt therapy. In addition, with chrysotherapy the progress of erosive changes may be decreased in many patients,[16-18] and some clinicians feel that the proportion of patients with complete remission, though small,[32] may be higher than that seen with chloroquine or penicillamine therapy. On the other hand, the claims that penicillamine favourably affects joint erosions are conflicting,[1,43] and the effect of chloroquine on the progress of erosions is not at all clear. Strict comparisons of efficacy and toxicity between injectable gold salts and orally administered penicillamine tablets are often difficult to interpret,[45] and some clinical trials of penicillamine have been restricted to patients that failed to respond to or tolerate gold salt therapy.[117] Chloroquine, administered in daily doses of less than 250 mg, appears to be considerably less toxic than either gold salts or penicillamine, but a strict comparison of the toxic effects of low-dose chloroquine and low-dose penicillamine therapy has not been carried out. My initial choice of a remission-inducing drug for active, rapidly progressing rheumatoid arthritis is usually gold sodium thiomalate. However, the choice often depends on a number of practical factors. For example, if the patient lives some distance from the clinic penicillamine may be more practical as the initial remission-inducing drug. I consider the use of chloroquine in less active or slowly progressing rheumatoid arthritis, and occasionally when frequent monitoring of the patient is not feasible.

Musculoskeletal diseases are the most prevalent cause of chronic disability.[118] In view of the high cost of treating rheumatoid arthritis, which probably has a prevalence of at least 1% in the general population,[119,120] attention is being paid to

not only the safety but also the cost of administering remission-inducing drugs that require monitoring.[121] In the United States 1.2 million injections of gold salts were given in 1974; the cost was about US$44 million. Thus, different strategies for monitoring toxic reactions were suggested.[122] Penicillamine, which also requires close monitoring, may be expected to have similar high costs for the health care system, and it is an expensive medication. On the other hand, chloroquine therapy is relatively inexpensive for the patient and for the health care system, assuming that frequent ophthalmologic assessments are not required with low-dose therapy. An organized clinic for gold salt and penicillamine therapy allows toxic reactions to be systematically monitored, overall costs and benefits to be assessed more accurately and, perhaps, the cost per patient receiving remission-inducing drugs to be kept down.

There is no question that the development of new drugs is expensive and that side effects may not become apparent in the initial stages of clinical use. A serious challenge must be met by clinical investigators in this field; they will have to decide whether to concentrate on developing more remission-inducing drugs or to attempt to answer the simple but important questions that remain unanswered about the drugs that are already available.

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This list is an acknowledgement of books received. It does not preclude review at a later date.

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