INVITED ARTICLE

TREATMENT STRATEGIES IN RHEUMATOID ARTHRITIS

M L Boey

ABSTRACT

Intervention therapies in rheumatoid arthritis (RA) are directed at the immune dysregulation and chronic inflammatory events in the joint. An ideal therapeutic program would rapidly control inflammation, prevent joint damage and preserve function. The various strategies of treatment involve the use of disease-modifying anti-rheumatic agents (DMARDs) either singly or in combination. Gold salts, penicillamine, sulphasalazine, methotrexate and hydroxychloroquine are used when NSAIDs fail to control inflammation. RA not only decreases the functional disability but the life-span of patients. The traditional pyramid strategy which uses single DMARDs consecutively has been found to be inadequate and slow in suppressing joint inflammation. Hence the race to find treatment regimes and strategies that will favourably alter the outcome of RA patients. Both the "step-down bridge" approach and saw-tooth strategy have been advocated in the attempt to break the progression of joint disease. None of the known regimes can be said to be most beneficial and least toxic.

Keywords: Rheumatoid arthritis, disease-modifying anti-rheumatic drugs DMARDs, strategies, combination DMARDs

SINGAPORE MED J 1992; Vol 33: 631-632

INTRODUCTION

Rheumatoid Arthritis (RA) is a chronic inflammatory disease accompanied by intense synovial inflammation. The principle of therapy is effective suppression of inflammation with protection of the joint. The non-steroidal anti-inflammatory drugs (NSAIDs) and second-line drugs alleviate symptoms and have been used extensively but none could satisfactorily reverse the events in the joint. New approaches to therapy are currently being developed and existing therapies re-evaluated.

PYRAMID STRATEGY

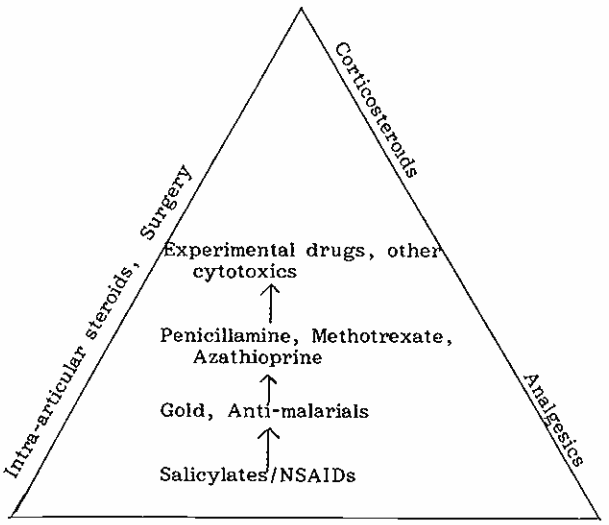
The conventional approach to the treatment of RA comprises use of a NSAID with a rapid onset of action. Joint inflammation confirmed by standard clinical and laboratory criteria (low Hb, thrombocytosis, elevated ESR and C-reactive protein) requires a NSAID unless contraindicated by peptic ulcer disease. When NSAIDs fail to control inflammation and there is evidence of erosive joint disease, a 'pyramid'[1] of other drugs are tried sequentially (Fig 1). These drugs are the second line drugs and are known as disease-modifying anti-rheumatic agents (DMARDs). At this point the family physician who may be less familiar with recent literature and less comfortable with the use of DMARDs should refer to a rheumatologist.

The second-line drugs are agents with different structures and modes of action. They have in common that they are slow acting and may modify the disease but rarely induce disease remission. They are reserved primarily for patients with disease characterized by persistent synovitis and/or erosive arthritis. Early intervention by the use of these drugs help suppress synovitis and alter the course of the disease (Table I). The DMARDs include parenteral gold compounds, oral gold (Auranofin), penicillamine, Salazopyrin, anti-malarials such as hydroxychloroquine and cytotoxic agents eg methotrexate, cyclophosphamide and azathioprine. Signs of improvement occur between 4 to 12 weeks of commencement of therapy. The choice of agent is personal. Adverse side-effects can occur and regular blood counts, urinalysis and liver function tests should be performed. All second-line drugs require a therapeutic trial of at least 4 months and auranofin at least 6 months.

Department of Rheumatology & Immunology
Tan Tock Seng Hospital
Moulmein Road
Singapore 1130

M L Boey, MBBS, M Med (Int Med)
Consultant Physician

Fig 1 - Pyramid treatment for RA



Recently, the pyramid strategy has been challenged. NSAIDs when used alone provide satisfactory control of joint inflammation in very few patients. The DMARDs have a delayed onset of action and tend to lose their effectiveness over time. They are seldom continued for long periods of time. Less than 20%[2,3] of patients who started on gold, penicillanine or sulfasalazine were on the drugs after 5 years.

Joint damage occurs maximally within the first 2 years of persistent, uncontrolled synovitis, the time needed to move through the pyramid. Methotrexate and cyclophosphamide are drugs most feared and reserved for the top of the pyramid. Such drugs are typically prescribed to patients who have substantial erosive disease and disability. The drugs are usually given too late, thus 'missing the boat'. The pyramidal approach is therefore too slow in suppressing joint inflammation and does not adequately prevent joint damage.

STEP-DOWN BRIDGE STRATEGY

Wilske and Healey[4] proposed a "step-down bridge" approach in therapy whereby these same agents are sequentially withdrawn from the patient. Prednisolone and NSAIDs are advocated for early control of inflammation. If the patient continues to have active disease after one month of treatment with NSAID or prednisolone, combination DMARD therapy should be started. Combination of drugs include choices like methotrexate, oral and injectable gold, chloroquine, hydroxychloroquine, penicillamine, sulfasalazine and azathioprine (Fig 2). Prednisolone and methotrexate can be

Table I - Second-line Therapy for RA

Indications :
Patients who fail to respond to analgesics and NSAIDs.

Dosage regimens

Intramascular gold :
10 mg initial dose; then 50 mg weekly to a total summated dose of 1000 mg and then 50 mg monthly thereafter.

Auranofin *(oral gold) :*
3 mg twice daily.

Penicillamine :
125 mg daily initial dose; increase by 125 mg daily every month to 750 mg daily.

Sulphasalazine (enteric-coated) :
500 mg daily initial dose; increase by 500 mg daily every week to 3g daily.

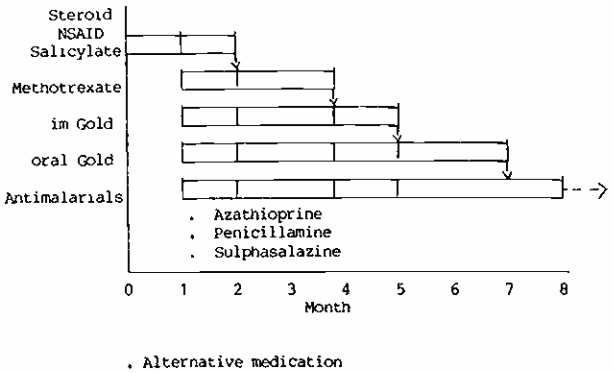
Hydroxychloroquine:
200-400 mg daily with ophthalmological review 6 monthly.

Methotrexate :
7.5 mg/week, increase by 5 mg/week to a maximum of 25 mg/week.

withdrawn as the injectable gold, then oral gold and finally the anti-malarial drug control the inflammation. The different drugs used have different mechanisms of action and they take effect after different time intervals. This combination of rapid acting anti-inflammatory medication and slower acting second line drugs provides early control of inflammation and a 'bridge' until the slower acting drugs take effect. The therapeutic program becomes progressively simplified.

The optimum combination of drugs in this "step-down bridge" therapy is still unknown and proponents of this strategy are unclear if this concept will ultimately prevent bone and

Fig 2 – "Step-down bridge" treatment for RA



. Alternative medication

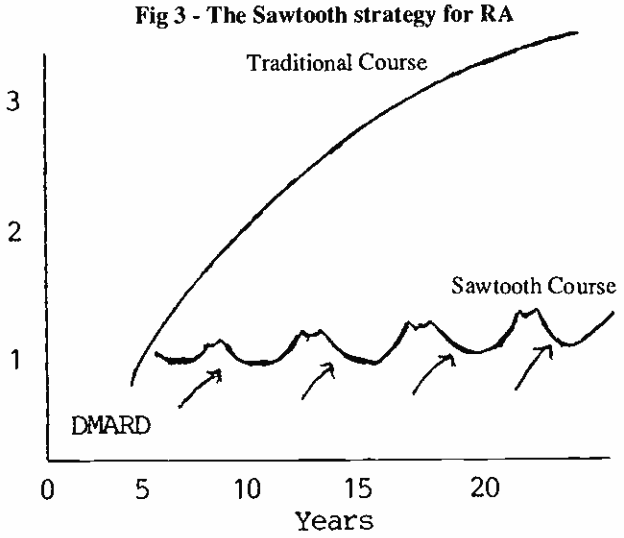
joint damage. In addition, daily oral prednisolone tends to dominate and remain in complex regimens of DMARDs which may be withdrawn due to toxicity, lack of efficacy or non-compliance. Studies on the complex combination of DMARDs have not been done. The "step-down" strategy deals largely with the first 12 months of a disease that affects most patients for more than 20 years. Whether this therapeutic approach can effect complete remission of disease is yet unknown.

SAW-TOOTH STRATEGY

Because RA is a chronic, progressive disease, Fries[5] proposed the use of multiple courses of DMARDs over many years to cause a "sawtooth-like" break in the progression of disease. DMARDs are begun early in the disease before substantial damage occurs in the joints.

DMARD therapy can be serially changed as the therapeutic benefit of earlier drugs is lost and they can be used continually throughout the disease course (Fig 3). This strategy appears to have a greater therapeutic potential. However, the question remains as to which DMARD is to be deployed first in the early stages of the disease. Currently, this is dependent on the preference of the rheumatologist. Which combination of DMARDs[6,7] should we utilise? Which is most effective and which least toxic? These questions need to be answered. Because RA is a heterogenous disease, treatment is influenced by the unpredictable course of the disease, which may wax and wane, progress aggressively or remit. Therefore, no drug regimen will be standard or strictly adhered to. Many patients require treatment for more than 10 years. Unnecessary medications must be avoided and constant monitoring of therapy is vital. The decision to change therapy for the patient is dependent on assessment of the disability level of the patient. This requires long-term follow-up and compliance by the patient. Patients are often referred to rheumatologists, many years into the disease. They are often managed by others with only NSAIDs, prednisolone and physical therapy. The role of DMARDs in damaged, deformed joints is limited. Second line therapies are unlikely to make lasting differences in this setting.

Fig 3 - The Sawtooth strategy for RA



CONCLUSION

Advances in therapy breakthrough can only come about through the unravelling of the pathogenesis of joint destruction in RA. Failure to identify the initiating agent for RA results in therapeutic regimes that are directed at interrupting the immunological reaction which produces the chronic inflammatory infiltrate in the synovium. This suppression of rheumatoid inflammation requires early use of DMARDs before substantial damage to the joints. One or multiple DMARDs could be used throughout the entire disease course. Well-designed, randomised, controlled trials on combination chemotherapy will determine which, if any, combinations and dosage schedules are most beneficial and least toxic.

REFERENCES

1. Schumacher HR, ed. Primer on the Rheumatic Diseases 9th Ed. Atlanta : Arthritis Foundation, 1988: 93.
2. Kushres I. Does aggressive therapy of rheumatoid arthritis affect outcome? J Rheumatol 1989; 16: 1-4.
3. Situnayake RD, Grindulis KA, Mc Conkey B. Long term treatment of rheumatoid arthritis with sulphasalazine, gold or penicillamine: a comparison using life-table methods. Ann Rheum Dis 1987; 46: 177-83.
4. Wilske KR, Healy LA. Remodelling the pyramid - a concept whose time has come. J Rheumatol 1989; 16: 5-7.
5. Fries JF. Re-evaluating the therepeutic approach to rheumatoid arthritis: the "Sawtooth" Strategy. J Rheum 1990 (Supp 22); 17: 12-5
6. Paulus HE. The use of combinations of disease-modifying anti-rheumatic agents in rheumatoid arthritis. Arthritis Rheum 1990; 33: 113-20.
7. Rau R, Herlorn G, Kruger T, Menninger H, Elhardt D, Schmitt J. A double blind randomised parallel trial of intramascular methotrexate and gold sodium thromalate in early erosive rheumatoid arthritis. J Rheum 1991; 18: 328-33.