THERAPEUTIC UPDATE

CLINICAL STRATEGY IN RHEUMATOID ARTHRITIS

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INTRODUCTION

It is estimated that some five to six million adults and 250,000 children in the U.S. suffer from rheumatoid arthritis (RA). In Singapore no prevalence study has been done but according to physicians and orthopaedic surgeons it is not an uncommon disease. Unfortunately the disease and indeed the subspeciality of rheumatology has been confined to the back-waters of medicine. Similarly the management of the disease has been far from satisfactory. It is the intention of this article to acquaint our doctors with the clinical strategy and modality of management of this condition.

DIAGNOSIS OF RA

Although the basic lesions of RA nearly always occur in the joints, especially the synovial membranes, it should be kept in mind that the disease itself is systemic. Many patients together with arthritis suffer systemic symptoms like fatigue, weakness, malaise, diffuse muscle stiffness or paraesthesia. Hence although the diagnosis of RA may present few problems in some patients, it can pose great difficulties in others, since many other diseases produce similar symptoms.

A set of 11 diagnostic criteria provided by a subcommittee of the American Rheumatism Association (ARA) is quite useful in clinical practice — Table 1. Seven of the criteria are required for diagnosis of classical RA, five for definite RA, three for probable RA. There are also 20 exclusions — Table 2 — any one of which, if present rules out RA.

MANAGEMENT OF RA

In the programme of management after RA is diagnosed, the first step is a conference between the physician, the patient and if possible other family members most likely to be concerned with the patient's problem. It is essential that the patient understands the nature of the disease and what the consequences of the disease process can be. The physician should know that in 5% to 10% of patients there will be one or two clinical episodes with almost no recurrences, whereas in about 25% of the disease it is intermittent with prolonged remissions and relapses. The vast majority however experience few or no real remissions and many exhibit progressive worsening of the disease over months or years.

Table 1 — Abridged Diagnostic Criteria for Rheumatoid Arthritis

At least 7 must be present for a diagnosis of classical RA, 5 for definite RA, 3 for probable and 2 for possible RA.

1 Morning stiffness
2 Pain on motion or tenderness in at least one joint*
3 Swelling (soft-tissue thickening or fluid, not just bony over-growth) in at least one joint*
4 Swelling in at least one other joint*
5 Symmetrical joint swelling* (not terminal phalangeal joints) with simultaneous involvement on both sides

The above signs and symptoms must be present continuously for at least six weeks.

6 Subcutaneous nodules*
7 Typical x-ray changes: at least localized bony decalcification, not just degenerative changes
8 Rheumatoid factor or positive strep agglutination test
9 Poor mucin precipitate from synovial fluid
10 Characteristic histologic changes in synovial membranes
11 Characteristic in histologic changes in nodules

*Observed by a physician

Table 2 — Findings That Exclude A Diagnosis Of RA

1. Butterfly rash of SLE
2. High concentration of LE cells
3. Histologic periarteritis nodosa
4. Dermatomyositis or its muscle symptoms
5. Definite scleroderma
6. Clinical rheumatic fever
7. Clinical gouty arthritis
8. Tophi
9. Clinical acute infectious arthritis
10. Joint tuberculosis or tubercle bacilli in the joints
11. Clinical Reiter's syndrome
12. Clinical shoulder-hand syndrome
13. Clinical hypertrophic pulmonary osteoarthropathy
14. Clinical neuroarthropathy
15. Urinary homogentisic acid
16. Histologic sarcoid or positive Kveim test
17. Multiple myeloma
18. Skin lesions of erythema nodosum
19. Leukemia or lymphoma
20. Agammaglobulinemia

Abridged from Primer on Rheumatic Diseases, page 137 et seq.

It is necessary to explain to the patient that the goals of therapy are to minimize pain and stiffness, suppressive active or progressive disease and preserve as much function as possible in the affected joints and soft tissues. Most patients already know that they cannot expect a cure, but many are optimistic that more effective therapy will be developed and that the physician can assist them in learning to live with whatever limitations RA may impose. A patient who understands the goals of therapy is much more likely to adhere to the therapeutic programme than one who does not.

(A) Non-drug Therapy

A programme of graded rest and activity should be initiated as early as possible so that joint and muscle function are stabilized and muscle strength improved if possible. In some instances mechanical devices for support like light aluminium or plaster cock-up splints may be extremely useful in patients with acute pain in the wrist. This physical programme is best worked out in conjunction with a physiotherapist, an orthopaedic surgeon or a rehabilitation physician.

(B) Drug Therapy

(i) Aspirin.

For decades the drug of choice in RA has been aspirin. The usual starting dose is 600 to 900 mgm (two or three tablets) four times a day. The aim is to achieve a serum salicylate level of 20 to 30 mgm/100 ml which should provide not only analgesia but also the necessary anti-inflammatory response. One should aim at an anti-inflammatory rather than an analgesic effect although less seems to "work" in some patients. Unfortunately side-effects like dyspepsia and blood loss from GIT are considerable although this can be minimized by taking the drug with milk, food or large quantities of water. Enteric-coated aspirin can also be tried. Antacids is known to interact with aspirin and can reduce its absorption.

(ii) Non-steroidal anti-inflammatory drug (NSAID).

If the adverse effects of salicylate are too great or if they fail, one should switch over to NSAID. Indeed recent trend is to start off with NSAID since the side effects of aspirin are so common. There have been three major advances in the field of non-steroidal anti-inflammatory analgesics. Firstly, there are now many more compounds from which to choose from. Secondly, we recognise that differences between patients are more important than differences between drugs so that there is a best drug for an individual patient. Thirdly, the new generation of NSAID have fewer side-effects and hence an increasing number of patients are able to continue treatment. The art in using drugs of this type is to find the right drug for the right patient with the right disease. There are two possible approaches to the use of this group of fairly similar drugs. First, one can select a drug one is most familiar with. This usually means selecting a drug that "has been around for a long time."

Unfortunately these "early" drugs like phenylbutazone and indomethacin usually possess the most severe side effects. Second way is to select from a group of drugs that is safer with regard to side effects but still provide the necessary analgesic and anti-inflammatory potential. Such a group are propionic acid derivatives and there are four to choose from namely naproxen, fenoprofen, ibuprofen and ketoprofen. They now represent the first line treatment for the non-specific relief of rheumatic symptoms.

Whichever drug one uses first there will be at the end of two to four weeks a group of patients who are better and another group who are not. In the responders, one should keep the dose to the minimum which continues to achieve symptomatic relief, review from time to time the need for continuation of therapy, stop it when it is no longer needed and keep a sharp lookout for adverse reactions.

For the group of patients who fail to achieve adequate symptomatic relief on the first drug, one must move on to another. However before one does this, one should give up to the optimal dose recomended. It is worth trying all 4 propionic acid derivatives in order to find the best for a particular patient and at the end of such an exercise about 60% of patients with RA will have achieved adequate symptomatic relief. The remainder must move to other classes of drugs like Tolmetin, Sulindac, Diclofenac Sodium, Meclomen and Piroxicam.

Contraindications

The following are considered significant contraindications to the use of NSAID: aspirin sensitivity, pregnancy (prostaglandins play an important role in uterine contraction which may be reduced by the NSAID) lactation, active ulcer disease. Here aspirin, indomethacin and phenylbutazone are absolutely contraindicated. The propionic acid derivatives and the new generation NSAID could be used with careful monitoring. Indomethacin or naproxyn suppositories could also be used.

Important drug interactions of the NSAID are with the coumarin-type anticoagulant agents and oral hypoglycaemic agents.

(iii) Second Line Drugs — Gold or Penicillamine.

At the end of six months one should critically reassess the patient. Patients who fail to respond to NSAID or those who have further progressed either clinically or radiologically are candidates for gold or penicillamine therapy. Exactly why these two drugs work is unknown but there is some evidence to suggest that they can halt the destructive process of the disease. Hence these two drugs are also known as remittive drugs and recent trend is to start these drugs early especially in patients where the disease is obviously active and progressive inspite of optimal therapy with NSAID. Physicians must be fairly experienced in the use of these two drugs.

Their onset of effect is slow, usually about three months, and the drugs are associated with a number of dangerous side effects such as proteinuria, thrombocytopenia and leukopenia.

Experience in Singapore suggest that more RA patients could benefit from these drugs rather than allowing them to go on with NSAID for years with no real success. Initiation of therapy with gold or penicillamine should best be done in a hospital setting and by someone well-versed in the finer points of their usuage.

(iv) Immunosuppressives.

In the event that none of the drugs mentioned above provides the control sought and that the disease appears to be leading quickly to crippling, then immunosuppressive agents must be considered. Drugs used in this group are cyclophosphamide, azathioprine, chlorambucil and methotrexate. Adverse effects are however common and they include mouth ulcers,

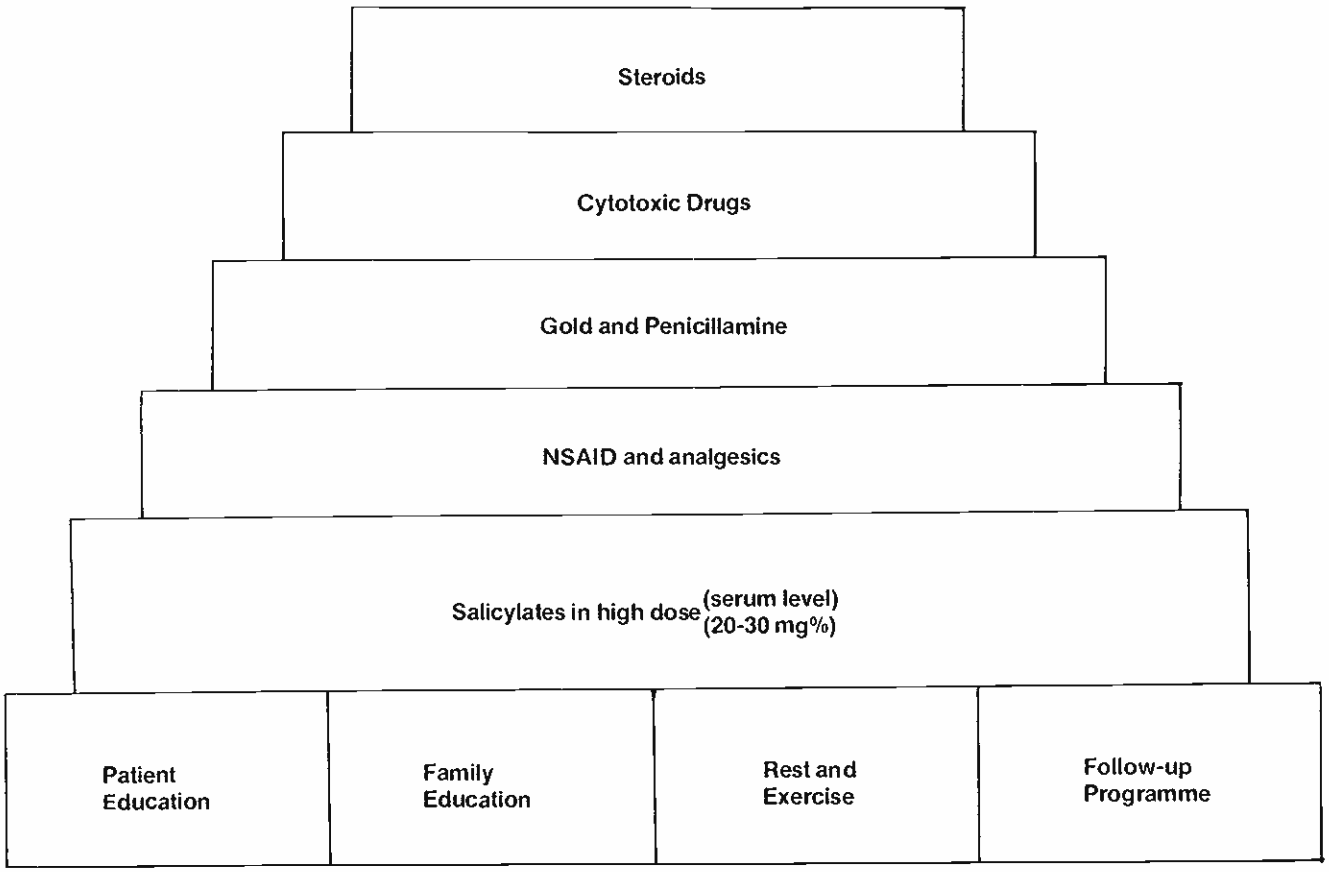

Fig 1 Pyramidal progression of treatment for Rheumatoid Arthritis

marrow depression, nausea, vomiting, sterility and induction of neoplasia.

All in all, the risks associated with all these drugs should restrict their use to rapidly progressive RA or to RA associated with life-threatening complications such as diffuse vasculitis.

(v) Corticosteroids

Probably the most potent anti-inflammatory agents for RA therapy are the corticosteroids. Their well-known adverse effects greatly limit their use especially for long term therapy for which they probably should be viewed as drugs of last resort. Physicians must not fall into the easy trap of using corticosteroids after a trial of NSAIDs without trying the other classes of drugs. Steroids however are indicated in eye complications of RA which may lead to blindness, severe systemic vasculitis, polyserositis and other potential life threatening complications.

They should be tapered off as soon as possible and use of 1 mgm tablets are useful in this regard. Some patients can be maintained on as little as 4 to 6 mgm/day. Alternate day therapy would be desirable but many patients cannot stand the pain during the off day.

(c) Experimental Therapies

Two new forms of treatment tried in recent years deserve mention. They are total lymphoid irradiation and plasmapheresis. However both are expensive, high technology modalities and only few centres in the world are geared to handle them.

Various drugs and their order of use are summarized in Fig 1.

CONCLUSION

Although the aetiology of RA is at present unknown, rheumatoid joint inflammation is currently conceptualized as an intra-articular immune-complex disease. It is also an infinitely variable disease which may last a few days or a lifetime; may persist unremittingly or come and go every few days or weeks. Hence treatment must be individualized. Although we have concentrated on medical management this is but only one facet in the total management of the rheumatoid patient. Other forms of therapy like surgery and rehabilitation are equally important. Like all other chronic illnesses, the patient must be the main actor and central figure on the stage in the rheumatoid drama.

Treatment, in the final analysis, is the patient's management of his own condition at home and at work under the advice and guidance of the family physician with, in the background, the rheumatologist and other members of the therapeutic team. This includes the physiotherapist, occupational therapist, surgeon, nurse, social worker, psychiatrist and often others. Success depends not only on progress of this unpredictable disease. Rheumatoid arthritis is not a disease the patient can suffer alone and unaided. Herein lies the therapeutic challenge for physicians, patients and family doctors.

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