Evolving Concepts in the Treatment of Rheumatoid Arthritis

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Introduction

Overview of Current Therapies for Rheumatoid Arthritis

HISTORICAL

Historically, disease modifying antirheumatic drugs (DMARD) were viewed as toxic drugs to be introduced only if absolutely necessary. The alternative name for DMARD was second line therapy, implying that other therapies [analgesics, nonsteroidal antiinflammatory drugs (NSAID)] had to have failed before they were justified. Given that at that time there was little evidence that DMARD worked and there was a great deal of evidence that they were toxic, this was not an unreasonable approach.

In addition to the late introduction of these drugs in the disease progression, most patients did not stay on them long term. With their high discontinuation rate due to toxicity, (approximately 50% at 12 months), gold and penicillamine were difficult drugs to administer[1]. As a consequence of this late introduction and short period of treatment, it is estimated patients spent as little as 10% of their disease career on therapy.

What has changed? Several related phenomena have occurred. First, there has been better use of existing DMARD; second, new DMARD have been introduced; and third, evidence of the impact of DMARD therapy on the rheumatoid arthritis (RA) disease process has been established. As a result, better cost to benefit ratios have been achieved with the newer DMARD such as sulfasalazine and methotrexate (MTX). This in turn has led to a higher retention of patients receiving therapy. Effectiveness studies show that approximately 75% of the patients stay on one of these drugs after one year. Physicians have been encouraged to support their use because of data from a variety of sources indicating that DMARD are effective in the treatment of RA including the following: (1) studies that show that the patients with a delay in introduction of DMARD do worse[2]; (2) controlled studies in which patients receiving placebo demonstrated worsening of symptoms and deterioration of function[3]; (3) strong evidence that inflammation is harmful and is suppressed by disease modifying drugs[4] using reduction in C-reactive protein (CRP), which is the hallmark of the impact of DMARD, to correlate with deterioration in structure and function and the development of osteoporosis[5]; and (4) new developments: DMARD use in early disease, patient compliance on longterm DMARD, and evidence of DMARD efficacy.

PHASES OF DISEASE

The duration of rheumatoid disease can be viewed in 3 major phases. The first is the initial assessment, then the management of patients with stable disease, and ideally remission (although unfortunately and more commonly there is resistance).

A great deal has been written about the initial phase of RA and it is not our purpose to review that evidence here. It is important that primary care physicians are aware of the efficacy of treatment of early RA and that the flow of patients from primary care to secondary care is well organized. For most people this involves setting up specialist early arthritis clinics, the advantages of which are well documented. These clinics allow patients to be assessed in a standardized fashion, answering questions that include whether or not inflammatory disease is present, whether it is persistent, and how severe it will be. Once it is established that a patient has inflammatory persistent disease, a DMARD is deemed as appropriate therapy.

After patients have been established on DMARD therapy (either alone or in combination) and do not experience toxicity, the question is what is the possibility of increasing therapy without unacceptable toxicity. This is one of the biggest remaining questions in rheumatology and there are no easy answers. For some therapies, the question is purely financial: how much can one justify spending to get a small improvement in outcome? For others it is toxicity: is it worth risking unknown toxicity for an unknown benefit? Research is attempting to address these questions.

Ideally, patients should reach an endpoint where their disease is in complete or near complete remission. This is the ideal and the management of these patients becomes simply an issue of if, or when, to stop the therapy. However, there are still many patients who, despite increasing therapy, do not have an acceptable reduction of disease activity. These are the patients who either develop toxicity with treatments or are non-responsive to DMARD and who would benefit from resistant clinics. This logic has recently been reviewed[6]. An algorithm for management (Figure 1) suggests one approach that we have been using at Leeds. This algorithm, linked in with our Early Arthritis program (LEAP YEAR program), has a standardized approach of monotherapy followed by rapid introduction of combination therapy.

FUTURE ISSUES

As demonstrated above, the management of RA is becoming increasingly evidence based, and any new therapy has to provide advantages over existing treatments.

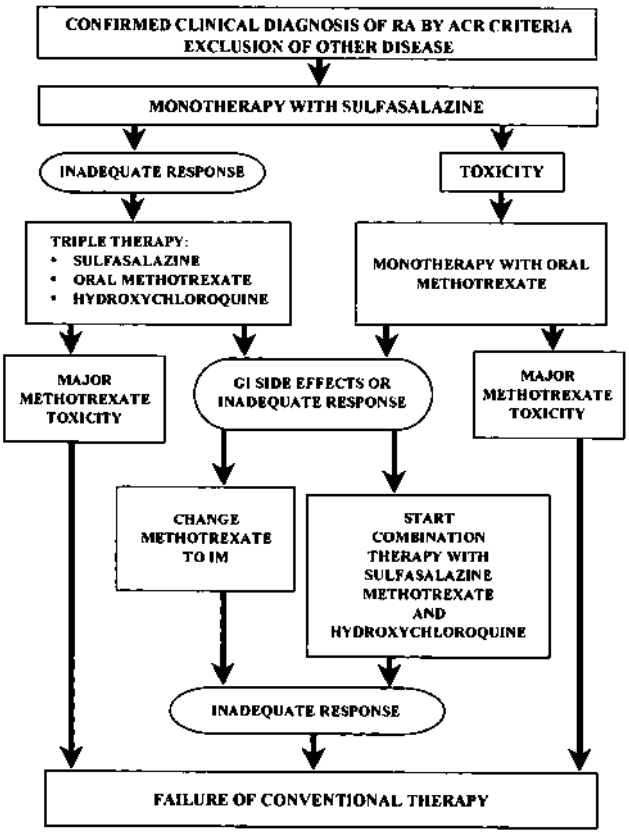

Figure 1. Algorithm for optimizing therapy and determining the failure of conventional therapy[10]. (Reprinted with permission. Bingham S, Emery P. Rheumatology 2000;39:2-5, and Oxford University Press.)

What are the issues for the future? The review of studies comparing initial therapies has shown that rapid suppression of inflammation is beneficial. However, it has not been equivocally demonstrated that initially introducing complex therapy benefits the average patient. Further studies will be required in this area. The use of triple therapy is of great interest and is probably the most effective use of conventional therapy[7]. Clinical studies have clearly shown the important interactions between DMARD[8,9]. The question of whether or not all patients should be exposed to aggressive treatment remains unanswered and further studies are needed. A cost benefit analysis of the use of steroids will need to be reexamined in the future as well as better monitoring of the side effects of steroids.

STRUCTURAL MODIFICATION

It is clear that adequate suppression of synovitis does have a major impact on structural damage and it is likely that structural damage will be reduced in the future to a virtually undetectable level. Sensitive imaging techniques such as MRI will be able to distinguish between active therapies, but only if there is detectable progression of the disease. In the future, clinical studies may focus more on subjective variables, as the objective ones may be adequately controlled. In using complex therapy, particularly biologics, the question of whether there should be attempts at resetting the disease permanently arises. Additional studies will be required to address this possibility.

I hope that this supplement will provide further insight into the evolving concepts in the treatment of RA. Hilary Capell provides a longterm perspective of adverse effects and potential toxicities accompanying the chronic use of DMARD, an important consideration in light of the potential of decades of multiple drug treatment. The trend to use DMARD earlier in the disease, and the fact that a high percentage of patients with RA are women in their child bearing years, brings specific issues of drug management discussed by Barry Bresnihan. James O'Dell addresses the challenging issue of which DMARD options to consider given a suboptimal response to MTX. Maxime Dougados comments on the diagnosis and treatment of ankylosing spondylitis, a rheumatic disease with a prevalence similar to RA. An overview of the rationale and clinical results of biologic agents, the latest addition to the RA treatment armamentarium, is provided by Joachim Kalden.

We are in one of the most exciting eras of research of this disease. Although our understanding is still evolving, major developments in disease management have been made towards finding the optimal treatment with the ultimate aim of improving outcomes for all patients with RA.

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