Rheumatoid arthritis

Will our current success in treating rheumatoid arthritis hinder new drug development? That is the question!!

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This remains a problem—suggestions from colleagues welcome!

Who would have thought 10 years or even 5 years ago that our current success in treating rheumatoid arthritis (RA) could have an adverse effect on future drug development? Even a decade ago this question would have been considered moot owing to the limited number of effective treatments available then for RA. Since that time therapeutic advances have made a substantial impact on the ability to control this disease.

PROGRESS OVER THE PAST 20 YEARS

To understand the problems that we now face in drug development in RA it is important to look back and see how far we have progressed over the past 20 years. In 1985 many rheumatologists considered RA to be a slowly progressing disease, one in which radiographic damage required years to become evident. The approach to treatment was the "pyramid" concept: a sedate escalation from aspirin and non-steroidal anti-inflammatory drugs (NSAIDs), then to corticosteroids, and finally, the eventual introduction of slow acting antirheumatic drugs, which included antimalarial agents, gold salts, and D-penicillamine.

The year 1985 was a watershed year for therapeutics in RA: the first placebo controlled trials were published, which validated the effectiveness of low dose weekly methotrexate (MTX) in RA.[1–3] Twenty years later MTX has become the "standard of care", both as a monotherapy for RA and as the "anchor" drug in combination treatments. What has changed most over the past two decades is an appreciation of the need for early and aggressive intervention with disease modifying treatments. Seminal studies, primarily from Europe, show that disease modifying treatments, regardless of the type, lead to a better outcome than NSAIDs or low dose prednisone alone in improving clinical disease activity.[4–6] Studies have established that control of synovitis with drug treatment, particularly combination treatments, not only improves the symptoms and signs of clinical disease but also has an impressive impact on slowing the rate of radiographic progression.[7 8]

Over the past decade we have also seen the remarkable effects of anti-tumour necrosis factor (TNF) treatment on the disease course. Few of the rheumatologists who were involved in the early development programmes of anti-TNFα treatments would have accurately predicted the substantial effect of this treatment on disease activity, quality of life, and function and diminished radiographic progression.

CURRENT TREATMENT STATUS

What we can say in 2005 is that many of our patients with RA are doing pretty well. In fact, in randomised studies evaluating response rates (the ACR20 or EULAR Disease Activity Score (DAS)) 60–70% of patients treated with anti-TNF treatment plus MTX[9 10] or with tight control of disease by using synthetic disease modifying antirheumatic drugs (DMARDs)[8] achieve this level of response. Impressive improvement in function and radiographic stabilisation has also been noted.

> "In 2000 patients with RA are doing better than in 1985"

Pincus and colleagues recently reported that in their practice patients are doing proportionately better today than the patients he treated 20 years ago.[11] In 1985 the median swollen joint count in those patients was 12, with a median Health Assessment Questionnaire (HAQ) score of 1.0, whereas in 2000 the swollen joint count was 5, with an HAQ score of 0.4. In 1985 MTX was taken by only 10% of his patients compared with 76% of his patients in 2000.[11]

WHAT THEN IS THE PROBLEM?

So, what is the problem? The problem is that not all patients are helped by our current treatments either because of drug intolerance and toxicity or lack of response. Additionally, complete remission, defined as no painful and no swollen joints, is rarely seen and the ability to stop background disease modifying treatment without eliciting a flare is an exceptional event.

Given the high cost of the biological agents some of our patients may also have difficulty obtaining these effective treatments. As the popularity of biological response modifiers increases there is concern that the insurance carriers or healthcare authorities may institute policies to restrict their use further, which will limit access to this class of drugs.

In the United States an attempt to restrict access could be reflected first in higher drug co-payments—that is, the amount the patients must themselves pay to receive treatment. For a patient who is now responsible for 10% of the annual cost of the drug which increases to 20% for anti-TNF treatment, the annual cost would increase from $1500 to over $3000, which in many cases would make this treatment unaffordable.

In Europe, healthcare authorities may restrict access by limiting further the number of patients who can receive such treatment.

Are patients satisfied with where they are now? If you ask patients what they want from treatment the responses are wide ranging: improved disease activity and function, less pain, a cure, less drug toxicity, and stable and affordable drug pricing. Is this much different from what we, as rheumatologists, would like to achieve? I think not!

EVALUATION OF NEW TREATMENTS

So how do we evaluate new treatments in the light of our current successes in RA treatment? Firstly, the science of performing clinical trials in RA has been refined and standardised. There are now validated end points for defining response rates, such as the ACR20 score and the EULAR DAS, validated measures of functional and quality of life instruments, and a consensus for scoring radiographic damage, which are accepted by investigators and the regulatory authorities for drug review and approval. These advances in the science of clinical trials in RA have increased our ability to evaluate new treatments for RA. In addition, unlike 20 years ago, when most studies of disease modifying treatments were performed in academic centres, clinical studies are now

performed throughout the world in both academic and community based practices. This leads to more generalisable studies from a wider based study population and has allowed easier and more efficient subject recruitment.

WHICH PATIENTS SHOULD BE STUDIED?

Perhaps the answer to the question of the future of RA treatment should begin with a consideration of the best patient population to study. The easiest population to study now is the group of patients for whom anti-TNF treatments have failed. These patients represent the greatest challenge for the rheumatologist. However, many sponsors are reluctant to include these patients in the early phases of testing, because there is a concern that this particular cohort represents an inherently ''refractory population''.

> ''Failure of anti-TNF treatment does not preclude response to other treatments''

However, there are no data to support such a bias. A patient for whom anti-TNF treatment fails may well respond to other treatments relying on a different mechanism of action. For example, there are reports of patients who when anti-TNF treatment has failed have favourable responses to abatacept (a costimulatory blockade molecule).[12] In addition, results from the rituximab study of a similar population will be available soon and hopefully will also demonstrate a positive outcome.

Perhaps yet another population is of even greater interest than the group for whom anti-TNF treatment has failed. These are the majority of patients who are currently receiving disease modifying treatment that may include anti-TNF treatment, but who still have some degree of active arthritis; in other words, the ''partial responders''. It is on this group that we may want to concentrate our greatest efforts because they represent the greatest unmet need.

How many patients in a rheumatology practice could qualify for enrolment in a new clinical trial using current study eligibility criteria (six or more painful and swollen joints and a raised erythrocyte sedimentation rate or C reactive protein)? Sokka and Pincus reported that fewer than 15% of patients in the Pincus practice would qualify for such a clinical trial, yet many of those patients could be characterised as ''partial responders'', never mind ''in remission''.[13]

A similar scenario exists at our centre where we have enrolled 900 patients in an RA registry called BRASS. Of those patients receiving MTX, which represents about 65% of our BRASS cohort, only 20% would currently qualify for a clinical study using the current disease activity measures, but very few are in remission. We need to redefine active disease for entry into our clinical studies so that we can study patients who are doing well but are far from being in remission.

TRIAL DESIGN

Another difficulty with designing trials now is the knowledge that radiographic damage can occur as early as 3–6 months after the onset of RA. Is it ethical to do placebo controlled monotherapy trials beyond 12–16 weeks in light of this knowledge? Another popular design is one in which chronic MTX is the background treatment and patients receive additionally either the study drug or placebo. In these studies the MTX dose is fixed and the study duration ranges from 24 to 104 weeks. Multiple studies show that the group receiving MTX plus placebo has greater radiographic progression over time.[9 10 14] In light of this finding is it appropriate or ethical to enrol patients in 1 and 2 year controlled trials in which the MTX dose is kept constant, because many of these patients will incur radiographic progression by the end of the trial.

> ''Radiographic damage can occur in the first few months, so is it ethical to have a placebo arm?''

One solution to this problem is the active comparator study with a non-inferiority outcome, in which patients are randomised to receive either an active comparator or the study drug with or without background MTX. Although this type of study would require a large number of patients because the sample size is calculated on the premise that the study drug is ''non-inferior'' to the active comparator, it would be easy to recruit for this study design—no placebo arm!!—and would alleviate the concern about radiographic progression, which is built into the methodology of current placebo controlled trials.

Another interesting design is the randomised withdrawal study, which was used quite successfully in the study of etanercept in juvenile RA.[15] In this design all patients receive the study drug in the open initial dosing phase and then the best responders are randomised to receive the study drug or placebo in the second phase of the study with the primary end point being time to flare.

What about combining a new biological agent with anti-TNF treatment? Our experience to date with combining targeted biological treatments has not been reassuring. Limited efficacy and increased infection have been reported in two recent trials: one, the addition of anakinra (interleukin 1 receptor antagonist) plus etanercept,[16] and the other, a recently completed trial of abatacept with background biological DMARDs.[17] In another case, outside the field of rheumatology, the disturbing events resulting from the addition of β-interferon plus natalizumab give us pause for thought about the wisdom of using combination biological agents to treat RA.[18 19]

SOME QUESTIONS REMAIN

So we are still left with the question of how to design clinical trials for those patients who have had a positive response with MTX plus a biological agent but still continue to have some degree of active rheumatoid disease. Do we add the study drug to MTX plus the biological agent with the goal to replace the initial biological agent? Do we design the study to look at triple drug treatment in RA with the end point being ACR70 or remission? If we are to make advances we need to develop new trial designs in light of both the current successes and the existing limitations in study paradigms to developing new treatments for RA. I welcome the thoughts of my colleagues around the world on how to deal with this problem.

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