Editorial

Rheumatoid Arthritis: Time for Trials of Therapeutic Targets

What is the therapeutic target for rheumatoid therapy? What, exactly, should the rheumatologist be aiming to achieve with antirheumatic therapy for the patient with rheumatoid arthritis from week to week, from visit to visit? And what is the evidence that achieving a short term target gives the patient worthwhile longterm benefit?

Consider a common clinical scenario: a woman aged 50 with an 8 year history of RA. In the early years, she had a great deal of pain, stiffness, and functional limitation, but improved greatly on treatment with methotrexate (MTX) 17.5 mg weekly. She now has little pain and stiffness, almost normal function, and has resumed fulltime work as a teacher. Examination shows early but definite subluxation of metacarpophalangeal and metatarsophalangeal joints and soft tissue swelling without tenderness in the wrists and several small joints of the hands and feet. Her hemoglobin is 110 g/l, the C-reactive protein (CRP) elevated at 30 mg/l (normal < 10 mg/l), and the erythrocyte sedimentation rate (ESR) is 40 mm/h. By our standard guides, her disease state is "active," but she feels "very well," too well, she argues, to increase her weekly dose of MTX given her fears about "drugs and their side effects." In the face of such "consumer satisfaction," how many rheumatologists would argue strongly to increase antirheumatic therapy? What would they give her by way of evidence for the benefit? If the patient did agree to increased therapy, what increase would be appropriate? Should treatment be increased until soft tissue swelling has been eliminated, or the ESR or CRP made normal, or something else? And what is the evidence that this course will yield more benefit than toxicity? Is this patient better served in the long term by accepting her own assessment and allowing activity, and presumably damage, quietly to proceed?

The need for satisfactory answers to these questions becomes more pressing as RA therapy evolves, as our colleagues in basic science deliver more effective and focused therapies to restrain "disease activity." The big change in RA therapy began with MTX, not least because clinicians recognized a dose-response effect: if the patient was not doing so well, the weekly dose could be increased. It had become possible for the clinician to effect a change, to fashion a response. New agents, such as leflunomide[1,2] and the "biologicals," anti-tumor necrosis factor therapies[3–5], and interleukin 1 receptor antagonist[6], and combination therapies extend this flexibility. But to use this newfound capacity to best effect, we need a clear idea of what can and should be achieved, a clear target.

Contrast the situation in other areas of internal medicine. The physician managing hypertension or diabetes, for example, does not initiate therapy with an unfocused expectation that it will prove helpful. Specific targets have been defined by their effect on longer term outcomes. The evidence that underpins these recommendations has required large, longterm studies, aided in their design by the established epidemiological links between a process, its surrogate, and an outcome.

In the process we term hypertension, the surrogate is the sphygmomanometer reading, the outcome a cardiovascular or cerebrovascular event. The Hypertension Optimal Treatment Study found that when > 18,000 patients from 26 countries were randomized to different target blood pressure levels, the lowest incidence of major cardiovascular events occurred at a mean achieved diastolic blood pressure of 82.6 mm Hg[7]. On the basis of such studies, the 1999 WHO-ISH Guidelines for the Management of Hypertension[8] recommend that the target blood pressure is < 130/85 for individuals younger than 65 years, or those with renal insufficiency or diabetes, and < 140/90 for people older than 65 years. In diabetes (the process), surrogates include the blood sugar level and glycated hemoglobin; the longterm outcomes are micro- and macro-vascular disease. The UK Prospective Diabetes Study (UKPDS) showed that "intensive" management of type 2 diabetes, which aimed at (although it did not always achieve) a fasting plasma glucose < 6 mmol/l, substantially reduced the risk of microvascular, if not macrovascular outcomes compared with conventional management using diet alone[9]. Targets for treatment of type 2 diabetes have been established: fasting blood sugar ≤ 6 mmol/l, random blood sugar 4–7 mmol/l, HbA_{1c} ≤ 7%.

There are parallels for RA. The process is rheumatoid synovitis, "disease activity," by which we mean that composite of synovial inflammation and proliferation that causes enduring harm. One important outcome is bone and cartilage damage, a rheumatological equivalent of stroke and myocardial infarction. But we lack a clear surrogate for rheumatoid synovitis, an equivalent to blood pressure or

blood sugar. We are therefore a step further away from knowing the level of surrogate control that would significantly limit longterm damage. If rheumatology is to follow these models, it confronts a double challenge: first to identify an adequate surrogate for "disease activity state" and then determine its target level.

The notion raises some issues. The potential for confusion from reliance on surrogate markers as endpoints has been discussed, particularly in the cardiovascular literature[10,11]. Criticism is leveled at acceptance, particularly by regulatory authorities, of the following sequence: identifying risk factors for a certain morbidity and mortality, demonstrating that an intervention favorably affects those risk factors, and then assuming that the intervention therefore reduces morbidity and/or mortality. Of the several errors in this line of argument, one lies in assuming that it does not matter how the surrogate target is achieved. In hypertension, for example, the Antihypertensive and Lipid-Lowering treatment to prevent Heart Attack Trial (ALLHAT) and metaanalyses of other trials now show that blood pressure reduction is important in reducing coronary heart disease events, but so is the way in which blood pressure is lowered: some drugs produce better longterm outcomes than others[12,13]. In the model we are advocating, the surrogate we seek is asked to reflect the disease process; its influence on one longterm outcome, bone and cartilage damage, is the point under evaluation, so that there is no question of substituting the surrogate for the main outcome of interest. But to start evaluating the usefulness of synovitis surrogates in guiding rheumatoid therapy it would be easier to assume that it does not matter how the surrogate target is achieved. If the surrogate target is shown to be of value, the next step is to determine whether its mode of achievement is important. That is what has happened in cardiovascular research: stepwise acquisition of evidence, justifying larger and more focused trials (ALLHAT includes > 42,000 patients, with a mean planned followup of 6 years), has produced increasingly refined evidence based recommendations[14].

Given the powerful antirheumatic therapies now available, is the search for a treatment goal still worth the effort? Some may consider the treatment aim in RA to be straightforward: to achieve and maintain a state of disease remission. But it is by no means clear that current therapies secure "remission" for patients over the long haul; and more important, our notions of "remission" remain to be proven.

If by "remission" we mean the American College of Rheumatology Remission Criteria provisionally defined in 1981[15], at least 5 of 6 criteria must be satisfied: morning stiffness lasting < 15 minutes; no fatigue; no joint pain; no joint tenderness or pain on motion; no soft tissue swelling in joints or tendons; an ESR < 30 mm/h in women and < 20 mm/h in men. This may be achievable in early disease, where most if not all symptoms and signs are due to disease activity, but even in this group clinical experience suggests that, for one reason or another, such remission is rarely sustained[16,17]. Most patients with RA under our care have established disease and for them "remission" by these criteria is often impossible, because the requirements mix up potentially reversible "activity" measures, such as ESR and soft tissue swelling, with features that could equally reflect irreversible change, such as pain, joint tenderness, and pain on motion. For those with anatomical damage, achieving a state of "remission" by these criteria is generally unachievable, yet, if synovitis remains "active," its control remains just as important as for those with early disease. What is the appropriate target of therapy for this large group of patients?

Some may see the ACR response criteria[18] — ACR 20, 50, or 70 — as appropriate goals. But that would be to mistake the purpose of these measures of drug efficacy. An ACR response means that there has been a percentage improvement, a relative change, in the number of swollen and tender joints and in at least 3 of 5 of the patient global, the physician global, function, pain, and an acute phase reactant. An ACR response in 80% of patients taking drug A but only 20% taking drug B indicates something about the effectiveness of the two drugs and of one drug relative to another, but it says little about the adequacy of disease control in the individual patient. If in response to antirheumatic therapy a patient with 28 swollen and tender joints showed an ACR 50 response, treatment could be said to be highly effective, but with 14 joints still active, the disease is hardly well controlled and there could be little assurance that longterm damage was being adequately curtailed. So relative response criteria will not serve the purpose of an individual patient treatment goal. Rather, we need to define an absolute treatment target, and then test the effectiveness of meeting this target.

The important point is that any of the indicators of "remission" — ACR criteria, the Disease Activity Score[19], a swollen joint count, levels of acute phase reactants — used singly or in combination as a guide to "disease activity" are implied surrogates for the underlying synovial process. When we speak of a patient as being "in remission" by one or other set of criteria, we are using secondary indicators, surrogates, to infer that disease has become inactive, that synovitis induced damage progression has stopped. Whether the achievement and maintenance of any of these states, using available therapies, really will guarantee less anatomical damage over the long term must be established.

There is hardly an alternative then but to begin the slow, sequential task of selecting and testing single or combination surrogates, assessing the feasibility of changing them with our therapies, evaluating the usefulness of target levels against longer term outcomes, learning whether a target achieved by one therapeutic strategy is as good as that achieved by another.

For this task we need a new type of clinical trial — a trial

that tests targets or objectives rather than drugs. The question posed by a standard randomized controlled trial is whether a new therapy is as good as or better than placebo or another antirheumatic drug. The new model would ask whether attainment of one treatment target is better than another in limiting the development of damage. In other words, how close does the treatment target come to being a reliable and valid surrogate of disease activity.

The design is straightforward. Within the setting of a randomized controlled design, the effect of achieving target levels of various short term targets, surrogates for disease activity, would be evaluated against a longterm outcome. Different longterm outcomes could be selected, e.g., clinical damage, as assessed by the Joint Alignment and Motion Scale[20], or function, as assessed by the Health Assessment Questionnaire (HAQ score). We prefer anatomic damage as the longterm consequence of interest because it is important and because it can be quantified over one or 2 years by radiographic scores[21] or more sensitively by magnetic resonance imaging (MRI)[22]. More problematic is the choice of short term target (STT). The STT must relate to rheumatoid synovial "activity" and it must be clinically feasible. Alternatives range from acute phase reactants to the prometalloproteinases, or interleukins, clinical measures such as the swollen or tender joint counts, or the Disease Activity Score (DAS). With little compelling evidence that any one of these is clearly the best surrogate for "disease activity," the choice is arbitrary. So is the target level. Given their known relationship to radiological damage, a CRP held within the normal range[23], a DAS < 2.4[23], or a low swollen joint count[24] may all be reasonable STT. Patients entering the trial would be randomized to one of several arms, for example, to one of the STT cited — a normal CRP or DAS < 2.4 — or to a control "usual care" arm. Randomization of the STT is an essential design feature of this study, to ensure study validity, such as is required for testing any therapeutic intervention. Patients would be assessed monthly, and if their allocated STT were out of range, treatment would be increased according to an agreed algorithm, given that this was considered safe. The drugs, doses, and combinations would not themselves be the focus of interest; the aim would be to use treatment aggressively enough to bring and maintain the allocated STT within range, in much the same way that increased and combination drug therapy is used to control hypertension. Depending on factors such as drug toxicity, compliance, and responsiveness to therapy, the STT would show a spectrum of responses, being brought within the target range for all, part, or none of the study period. Analysis would determine the degree to which attainment of a STT resulted in reduced joint damage over the period of the study.

The model has potential problems. The STT chosen may not be a valid surrogate of "disease activity," but only by starting with STT that have some face validity and testing them prospectively can we decide which should be set aside, and which are promising and need further testing. Some targets, such as the CRP, may be influenced by processes other than synovitis, but awareness of this problem is its best solution. The surrogate for "disease activity" may differ in early and in late disease, but only by including patients across the spectrum of disease duration and activity will these discrepancies become evident. Patients and doctors may be resistant to "treating a test" or a target, rather than the patient, but both can be brought to understand the importance of the information to be derived from the study. The aggressiveness of the treatment algorithm may cause unacceptable toxicity, but this is unlikely if drugs, doses, and combinations are not beyond clinical experience and are carefully monitored according to standards of good clinical practice. There may be insufficient radiological progression over the trial period to provide a result, hence the importance of validating scoring systems for more sensitive techniques, like MRI, and taking care to determine the sample size realistically. The final result may be confounded by the effects of specific drugs, as in the field of hypertension, but only by showing first that control of a surrogate is useful in preventing damage progression can we proceed to determine whether the mode of influencing the target is more important than its achievement.

The model also has exciting potentials and advantages. The notion of disease activity surrogates, testable in the form of a short term target, will generate a practical link between basic and clinical research in RA, allowing the opportunity to develop potential surrogates that can be tested clinically in a trial of this type. The design also provides a model to test complex therapeutic strategies, such as initial target control with one agent and its maintenance with an alternative, less costly drug combination. The delineation of responders and nonresponders and their characteristics will also become easier when a goal is clearly defined. The funding of the new antirheumatic drugs is resisted by government and insurers when these are expensive by comparison with MTX. It should become easier to define the role of new agents and to argue for their subsidy if, having proved their worth against placebos and competitors by the usual ACR or European League Against Rheumatism response criteria, they then prove capable of attaining a damage-limiting target, unachievable by other and cheaper therapies.

Finally, both the clinician and the patient need help to better use the powerful new antirheumatics. It is now as unacceptable that clinicians undertreat active disease and expose the patient to its damaging consequences as it has ever been to overtreat and expose them to toxicity. Simply using clinical judgment to determine the level of patients' disease activity state, particularly in established disease, is an unreliable exercise, and it is especially in this group, the great majority of people currently suffering from RA, that a

good surrogate of disease activity is most required. The clinician needs a guide by which to adjust therapy from visit to visit to give the best chance of preserved structure and function over the decades of this persistent disease. Patients want to know that their agreement to more aggressive therapy is justified by the evidence backing the longterm consequences of alternative decisions. Time then to expand our clinical research, to start trials of a new kind, prospectively designed randomized controlled trials that test targets against outcomes.

JOHN EDMONDS, MB, BS, MA, FRACP,
Professor of Rheumatology,
University of New South Wales,
Director of Rheumatology,
St. George Hospital, Sydney;
MARISSA LASSERE, MB, BS (Hons), Grad Dip Epi, PhD, FRACP, FAFPHM,
Senior Lecturer in Medicine,
University of New South Wales 2217,
Senior Lecturer in Public Health and Community Medicine,
Sydney University,
Staff Specialist in Rheumatology,
St. George Hospital, Sydney, Australia.

Address reprint requests to Prof. Edmonds, Department of Rheumatology, Gray Street, Kogarah, NSW 2217, Australia.

REFERENCES

1. Strand V, Cohen S, Schiff M, et al. Treatment of active rheumatoid arthritis with leflunomide compared with placebo and methotrexate. Arch Intern Med 1999;159:2542-50.
2. Smolen JS, Kalden JR, Scott DL, et al. Efficacy and safety of leflunomide compared with placebo and sulphasalazine in active rheumatoid arthritis: a double-blind, randomised, multicentre trial. Lancet 1999;353:259-66.
3. Bathon JM, Martin RW, Fleischmann RM, et al. A comparison of etanercept and methotrexate in patients with early rheumatoid arthritis. New Engl J Med 2000;343:1586-93.
4. Elliott MJ, Maini RN, Feldmann M, et al. Randomised double-blind comparison of chimeric monoclonal antibody to tumour necrosis factor (cA2) versus placebo in rheumatoid arthritis. Lancet 1994;344:1105-10.
5. Van de Putte LBA, Rau R, Breedveld FC, et al. One year efficacy results of the fully human anti-TNF antibody D2E7 in rheumatoid arthritis [abstract]. Arthritis Rheum 2000;43 Suppl:S269.
6. Bresnihan B, Alvaro-Garcia JM, Cobby M, et al. Treatment of rheumatoid arthritis with recombinant human interleukin-1 receptor antagonist. Arthritis Rheum 1998;41:2196-204.
7. Hansson L, Zanchetti A, Carruthers SG, et al. Effects of intensive blood-pressure lowering and low dose aspirin in patients with hypertension: principal results of the Hypertension Optimal Treatment (HOT) randomised trial. Lancet 1998;351:1755-62.
8. World Health Organization-International Society of Hypertension. Guidelines Subcommittee. 1999 WHO-ISH guidelines for the management of hypertension. J Hypertens 1999;17:151-83.
9. UK Prospective Diabetes Study (UKPDS) Group. Intensive blood glucose control with sulphonylureas or insulin compared with conventional treatment and risk complications in patients with type 2 diabetes (UKPDS 33). Lancet 1998;352:837-53.
10. Fleming TR, DeMets DL. Surrogate end points in clinical trials: are we being misled? Ann Intern Med 1996;125:605-13.
11. Psaty BM, Weiss NS, Furberg CD, et al. Surrogate end points, health outcomes, and the drug-approval process for the treatment of risk factors for cardiovascular disease. JAMA 1999;282:786-90.
12. The ALLHAT Officers and Coordinators for the ALLHAT Collaborative Research Group. Major cardiovascular events in hypertensive patients randomized to doxazosin vs chlorthalidone. The Antihypertensive and Lipid-Lowering treatment to prevent Heart Attack Trial (ALLHAT). JAMA 2000;283:1967-75.
13. Furberg CD, Psaty BM, Pahor M, Alderman MH. Clinical implications of recent findings from the antihypertensive and lipid lowering treatment to prevent heart attack trial (ALLHAT) and other studies of hypertension. Ann Intern Med 2001;135:1074-8.
14. Kaplan NM. Management of hypertension in patients with type 2 diabetes mellitus: guidelines based on current evidence. Ann Intern Med 2001;135:1079-83.
15. Pinals RS, Masi AT, Larsen RA, et al. Preliminary criteria for clinical remission in rheumatoid arthritis. Arthritis Rheum 1981;24:1308-15.
16. Wolfe F, Ross K, Hawley DJ, et al. The prognosis of RA and undifferentiated polyarthritis syndrome in the clinic: a study of 114 patients. J Rheumatol 1993;20:2005-9.
17. Suarez-Almazor M, Soskolne CL, Saunders LD, Russell AS. Outcome of RA. A 1985 inception cohort study. J Rheumatol 1994;21:1438-46.
18. Felson DT, Anderson JJ, Boers M, et al. The American College of Rheumatology preliminary core set of disease activity measures for rheumatoid arthritis clinical trials. Arthritis Rheum 1993;36:729-40.
19. van Gestel AM, Prevoo MLL, van't Hof MA, et al. Development and validation of the European League Against Rheumatism response criteria for rheumatoid arthritis. Arthritis Rheum 1996;39:34-40.
20. Spiegel TM, Spiegel JS, Paulus HE. The Joint Alignment and Motion Scale: A simple measure of joint deformity in patients with rheumatoid arthritis. J Rheumatol 1987;14:887-92.
21. Van der Heijde D, Lassere M, Edmonds J, et al. Minimal clinically important differences in plain films in RA: group discussions, conclusions and recommendations. J Rheumatol 2001;28:914-7.
22. McQueen FM, Stewart N, Crabbe J, et al. Magnetic resonance imaging of the wrist in early rheumatoid arthritis reveals a high prevalence of erosions at four months after symptom onset. Ann Rheum Dis 1998;57:350-6.
23. Van Leeuwen MA, van Rijswijk MH, Sluiter WJ, et al. Individual relationship between progression of radiological damage and the acute phase response in early RA. Towards development of a decision support system. J Rheumatol 1997;24:20-7.
24. Boers M, Kostense PJ, Verhoeven AC, et al. Inflammation and damage in an individual joints predict further damage in that joint in patients with early rheumatoid arthritis. Arthritis Rheum 2001;44:2242-46l.