Symposium Proceedings

Changing Goals for Rheumatoid Arthritis Treatment:
Evidence and Insight
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Part 1
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Consensus Recommendations for the Assessment and Treatment of Rheumatoid Arthritis

The treatment of rheumatoid arthritis (RA) has changed dramatically during the last decade. The increasing use of methotrexate (MTX)[1-3], combination therapies[4-6], and anti-tumor necrosis factor (TNF) agents[7-12] has made obsolete the treatment algorithms that have been in effect since the end of World War II, more than 50 years ago. With new agents have come higher costs[13-17]. Insurers and other payers have been uncertain how to approach RA treatment, but often have fallen back on the older algorithms such as the RA treatment pyramid[18-21], and many clinicians still rely on these algorithms.

In the late autumn of 1999 we brought together a panel of rheumatology experts that included those with substantial experience and publications in clinical trials of RA treatments, assessment tool development, longitudinal assessment and outcome, and clinical practice. The group was charged with describing and evaluating the treatments, outcomes, assessments, and practices of the last half century. In addition, based on this evidence, they were asked to develop a consensus report for treatment of RA at the start of the 21st century. The committee was divided into subgroups, each of which worked on and produced research manuscripts concerning different aspects of the RA treatment question. These manuscripts are published separately as a part of this consensus symposium. In February 2000, the group met in Chicago for two days of discussion. The document below reflects the general consensus among these RA experts. Although this project was supported by Centocor, the company did not attend nor participate in the committee's deliberation. This work is entirely our own.

ASSESSMENT

The consequences of rheumatoid arthritis. RA is a chronic inflammatory disease that primarily effects large and small joints, but can also cause profound systemic alterations. The average duration of life following the onset of RA is about 27 years[22]. RA rarely remits[23], and then only briefly, and untreated maintains its severity over the lifetime of the patient[24]. Almost all patients suffer daily pain[24-26], and almost all patients have functional loss[24,27-37]. Although the severity of pain and functional loss spans a wide spectrum, from catastrophic and incapacitating illness to minor pain and limitation, almost all patients have some degree of limitation and discomfort from their illness. In addition, generally irreversible outcomes such as work disability[30,38-46], joint destruction and consequent surgery[47], and premature mortality are associated with the disease. Fully a quarter of RA patients may be expected to have a major joint replacement during their lifetime[47]. Among those who are working at the onset of RA, between 35 and 50% will be work disabled after 10 years, and 50 to 75% will be disabled after 20 years[38,39,44]. Mortality is doubled among patients with RA[22], and radiographic damage progresses inexorably[48-52].

A misunderstanding of RA has come about from colloquial clinical language. In the clinical evaluation of RA, physicians may write "doing well," but most often such statements reflect a comparative assessment with RA patients whose activity is much more severe, or a sense that the patient is, in fact, coping well with the illness. "Limited disease," another term that is used in describing a patient, similarly does not mean being pain-free or having normal function.

In understanding RA and its treatment and outcome, certain key terms must be defined.

Disease activity. Disease activity refers to the systemic and local inflammatory manifestations of RA. The key clinical abnormality is synovitis. But synovitis as observed does not capture all the content of disease activity. Therefore a series of surrogate markers are used to identify disease activity. In practice, these surrogates include counts of swollen joints, counts of tender joints, patient assessment of pain and global severity, assessment of functional disability, and assessments of acute phase reactants such as erythrocyte sedimentation rate (ESR) and C-reactive protein. The surrogates form the American College of Rheumatology (ACR) Core Set of assessment measures as well as measures suggested by European and international groups[53-57]. Although they are useful in clinical care as well as randomized clinic trials (RCT)[58],

not all the measures are ordinarily collected in clinical practice[59]. Detailed assessment methods for RA activity are described in a separate manuscript of this conference[37] and may be found elsewhere[56,60-68]. Certain other aspects of RA illness may also be representative of disease activity, such as vasculitis, but are usually not part of the routine evaluation of the illness.

Disease activity occurs over a spectrum of severity. As described elsewhere in these proceedings, disease activity can be quantified by the Disease Activity Score (DAS) of van der Heijde[67,68] or through the use of percentile values[29,37]. Using the latter method, the status of RA patients can be determined in comparison with others with RA.

Disease severity. Disease severity (severe disease) is identified by (1) persistent high levels of disease activity; (2) substantial structural damage, functional loss, work disability, radiographic abnormality, and joint replacement; and (3) a rapidly accelerating illness that is expected to produce future substantial structural damage and other adverse outcomes.

The relationship between disease activity and the outcomes of RA. Disease activity is responsible for current symptoms. Disease activity acting over time leads to structural damage, functional loss, work disability, radiographic abnormality, joint replacement, premature mortality, and increased costs[63,69-78]. The more severe the level of disease activity, the greater the risk of the longterm adverse outcomes and the shorter the duration to the outcomes[22,38,44,47,52,79].

Certain outcomes, such as work disability, can come about very quickly in the face of severe RA. Therefore very active disease can be considered as almost a medical emergency. But mild disease is not benign either, and leads to important damage and limitations even though it takes longer to get to those endpoints. It is a fundamental mistake to confuse tolerability and milder activity with good longterm outcome, for milder activity will also lead to functional loss and important life limitations.

TREATMENT

The goals of treatment. Given the role of disease activity in producing current symptoms and future damage and other adverse outcomes, the fundamental goal of treatment is to eliminate synovitis and disease activity; and where that is not possible the goal is to control synovitis and disease activity to the fullest extent possible.

Although these goals may seem commonplace, they represent a fundamental change in the approach to RA. ACR improvement criteria, which stress 20 or 50% improvement, may be required for RCT[53,55], but are not acceptable outcomes of RA treatment. The goal, from both the patient's perspective and the physician's, is to eliminate disease activity. Treatment failure, therefore, follows a simple definition: Treatment failure exists when disease activity is not controlled.

Beginning in the last decade of the 20th century a profound change came about in how experts viewed RA treatment. At the same time it slowly became apparent that the outcomes of RA were changing for the better[80-88]. A number of factors brought about these changes. MTX achieving full acceptance in the 1990s was perhaps most responsible[89-93]. But other factors were also important, including earlier initiation of disease modifying antirheumatic therapy (DMARD)[94-100] and combination therapy[4,5,94,101-106]. As the century ended anti-TNF therapy was introduced[107-109], and data from RCT indicated benefit beyond what might be expected from MTX treatment alone. In the wings stand other soon to be introduced "biotech" compounds.

With this change in therapy came a more general realization that it was possible to alter the outcome of RA for the better by appropriate use of treatment. But for almost the entirety of the 20th century prior to MTX, the outcome of RA was poor, and it was even difficult to detect treatment effect. Much of the century was concerned with identification and prevention of adverse effects of treatments, for if you could not really make patients better, at least, as the thought went, you would not make them worse. Many patients spoke of gold therapy as "the last resort," and in a sense it was. High rates of adverse reactions and discontinuations plagued gold therapy and other therapies such as sulfasalazine, penicillamine, azathioprine, and cyclosporin. A skillful and lucky physician might pilot the patient through these hazards, but it was never easy. But this outlook of limited benefit and adverse reactions has changed, and with it the principles of treatment have also changed.

Two other changes have occurred that have been important. First, measurement of RA disease activity and outcome has improved substantially, and it is now within the ability of practicing physicians to assess accurately the status, activity, and outcome of his or her patients[59,110]. The second important change is that brought about by cost constraints[111,112]. Because anti-TNF agents are expensive, controls have been placed on their use (by managed care in the US) even though they appear to be among the most effective treatments available. A second cost control involves the limited access to rheumatology experts that sometimes occurs, although rheumatologists are the persons most knowledgeable in the evaluation and prescription of RA therapy.

The pyramidal approach to RA treatment. The pyramidal approach to RA treatment recommended a "basic program" of nonsteroidal antiinflammatory drugs (NSAID), rest, heat, education, and physical therapy to which might be added, if necessary, DMARD therapy. Elsewhere in this symposium, Moreland, Russell, and Paulus review the various non-DMARD therapies that have been used in RA over the last half century. Examined over the course of decades, there is no scientific evidence to indicate that these recommendation therapies were in any way effective in substantially reducing symptoms or altering the course of RA. To the contrary, the recommendations have resulted in the delay in the use of DMARD, and to that extent have been harmful to patients

with RA. The basic program for RA treatment should be DMARD and/or biologic therapy.

The use of NSAID and/or analgesics. Not all patients benefit from or require NSAID and/or analgesic therapy, and there is no evidence that these treatments alter the course of RA[113,114]. In addition, NSAID may cause adverse effects[113,115]. Therefore the use of these agents should be considered optional. Many patients may achieve important reduction in symptoms from NSAID and/or analgesics. Therefore their use should be determined on a case by case basis. In many instances occasional use of NSAID will suffice. Whether regular, full dose NSAID use is helpful, compared to intermittent, reduced doses should be determined by trial in the individual patient.

Analgesics do not help in the control of RA disease activity, but can be helpful adjuncts for pain control. Both opiod and non-opiod analgesics can be useful. As with NSAID, analgesics should not be used as substitute for DMARD/biologic therapy when control of disease activity is required.

The Selection and Use of DMARD and/or Biologic (D/B) Agents

Who should be treated with D/B therapy? DMARD and/or biologics improve the signs, symptoms, and outcomes of RA. With rare exceptions, all RA patients should receive DMARD therapy. Since the goal of therapy is to control disease activity, this control should be sought through D/B therapy regardless of age except when concomitant or comorbid illness limits therapy. D/B therapy is tolerated equally in all age groups[116,117].

When to treat with D/B therapy. Treatment with D/B therapy should be begun as soon as possible after RA is diagnosed. Early treatment with D/B therapy is beneficial since effective therapy will retard outcomes such as work disability and may prevent or delay functional loss[82,96,98,99,103,118-125]. Additionally, some data suggest that early treatment may alter the disease course by acting within "a window of opportunity." This latter point has not been extensively studied, but the benefits of treatment compared to delayed treatment are quite clear.

DMARD treatment is helpful in disease of long duration, too. The duration of disease should not be an indication for not using D/B therapy. The indication for treatment is the presence of disease activity, not the duration of disease.

The choice of a specific DMARD. Not all DMARD are equivalent or useful[1,126]. Auranofin rarely works and cyclophosphamide is too toxic[127-129]. These DMARD should almost never be used in RA treatment. Longitudinal observational studies (LOS) and rheumatologist-preference studies indicate that MTX is the most effective RA treatment by far[126]. There is little LOS data on leflunomide, etanercept, or infliximab, but RCT indicate that leflunomide and MTX are equivalent in efficacy[130] and that etanercept and infliximab (often in combination with MTX) are superior to MTX alone[108,109,131-133].

The most effective DMARD should be used first in the treatment of RA. For most patients this means MTX or leflunomide. There is little reason to recommend less effective DMARD as the drug of first choice except in some patients with very limited disease activity.

In the choice of RA therapy, however, the patient's preference is most important. Patients should be educated about the benefits and risks of treatment, but also about the risk of no treatment[36,134], something not usually considered by patients. Patients may wish to alter these treatment recommendations based on reasons of cost, convenience, or risk aversion, and these wishes should be respected. Additionally, psychological and social factors must be considered in D/B prescription.

Because many patients will respond adequately to MTX or leflunomide therapy, we do not recommend the use of etanercept or infliximab as first therapies, since only limited data exist on their effectiveness in these situations. However, recent reports regarding etanercept in recent onset RA suggest that anti-TNF agents may play a future role as first line treatments of RA. In the case of patients with very active disease, the use of anti-TNF agents together with MTX or leflunomide may be indicated together as first line treatment. There is no simple rule as to the order of treatments, and the use of D/B drugs in combination is clinically appropriate in the case of severe disease or where disease activity is not adequately controlled.

DMARD dosage. A full trial of a DMARD requires adequate dosage. Unless limited by toxicity, MTX dosage should be increased to 20 mg per week or greater unless an adequate response is achieved at a lower dosage. Full doses of sulfasalazine are 3 g per day. Anti-TNF agents are prescribed on fixed schedules. There are no data yet available to recommend "maximum" doses, although it is possible such information will appear in the future.

D/B treatment failure. As indicated above, treatment failure means the inability to control or eliminate disease activity after an adequate trial of the D/B. In general, an adequate trial is 5 months for injectable gold, 6 months for penicillamine, 4 months for hydroxychloroquine, and 3 months for all other DMARD and biologics. In some instances a full response may take longer than the times listed above and it may be appropriate to wait longer if in the view of the clinician an adequate response may be achieved by additional treatment time.

If a patient fails MTX and leflunomide, it is unlikely that he will have an adequate response to DMARD such as hydroxychloroquine, sulfasalazine, injectable gold, or azathioprine. In such situations treatment with combination therapy such as with the 3 drug combination of MTX, sulfasalazine, and hydroxychloroquine, or with etanercept or infliximab may be indicated without successive trials of gold, sulfasalazine, penicillamine, or azathioprine. This is particularly true when disease activity is high. When a patient is ill and disease activity is uncontrolled, that patient deserves the best available treatment, not the worst.

Corticosteroids. The role of corticosteroids in the treatment of RA remains controversial[135-138], primarily because of concerns regarding the possibility of unacceptable levels of toxicity and longterm limited benefit. Although there seems to be strong evidence that steroids can improve some outcomes[139], rheumatologists remain divided over their use. When used, steroids should accompany D/B therapy and not be a substitute for such therapy. The use of NSAID and prednisone alone is not ordinarily appropriate treatment for RA.

Treatment algorithms. The committee's recommendations reflect general standards for the treatment of RA. But each patient's care must be individualized. For some patients the recommendations here will be too aggressive and for others they will be too limited.

The evaluation of RA status and activity. To understand whether therapy is needed or works, disease activity must be documented. While it is appropriate to do this for patient care reasons alone, 3rd party payers increasingly require documentation to support use of modern therapies. Disease activity can be documented using the items of the ACR core set[55], including patient visual analog pain and global severity scales, ESR or CRP, a count of swollen and tender joints, and a functional scale such as the Health Assessment Questionnaire (HAQ) or the modified (M) HAQ. But performing and recording detailed tender and swollen joint counts at each clinic visit can be burdensome to the point of interfering with patient care, and may not be required for good patient care. Therefore while the most comprehensive evaluation can be performed using all of the ACR core set items, a reduced set of measures can perform almost as well[37,59].

The pain, global severity, and HAQ/MHAQ assessments can be obtained directly from the patient by self-report questionnaire[37,59]. When used with acute phase reactants, these measures can provide necessary documentation. Detailed swollen and tender joints add still more information, but can be replaced with either shortened swollen joint counts or shortened tender joint counts, or possibly both, as described elsewhere in the symposium[37]. Other documentation, such as grip strength or morning stiffness, can also be helpful. Regardless of the documentation employed, it is important that they be recorded serially and not on a hit or miss basis[37,59].

RECOMMENDATIONS

In the consensus recommendations below we suggest a general set of guidelines by which RA can be treated more effectively. But guidelines are just guidelines. They are not absolute recommendations or inflexible rules, nor are they meant to be. There will be times when the correct decision will not be the one we have recommended here. Individual patient differences, patient preferences, and the presence of psychosocial factors and comorbid conditions will often dictate the correct management course. The knowledgeable physician, who always knows more about his or her patient than a committee of experts, may appropriately treat more or less aggressively than we have recommended. We hope that these guidelines will be used by physicians and insurance companies to appreciate the new paradigms in RA treatment, and to extend this change in approach to RA patients everywhere.

1. The fundamental goal of RA treatment is to eliminate synovitis and disease activity.
2. With few exceptions, all patients should be treated with a DMARD or a biologic agent. Exceptions are based on comorbid conditions, age, patient preference, or the presence of very limited disease activity.
3. When disease activity is present, the treatment recommendations apply regardless of duration of disease or patient's age.
4. The most effective DMARD should be used first.
5. In the US, the most commonly used DMARD is methotrexate. A treatment program that includes MTX or an equivalent drug is appropriate for 85% of RA patients at the initial clinical evaluations.
6. DMARD should be used at full doses unless full treatment effect is gained at lower dosage or limiting toxicity is reached. For MTX the full dose is at least 20 mg per week; for sulfasalazine it is 3 g per day.
7. Treatment should be begun promptly following rheumatology evaluation[112,140-142]. The initial evaluation of RA usually takes one to two rheumatology visits. It is sometimes desirable to await the results of laboratory tests and/or the response to therapy given at the first visit before starting definitive RA treatment. But this delay should be conditioned on specific needs, and first visit definitive treatment may be appropriate.
8. A patient fails a DMARD/biologic if the disease activity is not adequately controlled.
9. In general, an adequate DMARD trial is 5 months for injectable gold, 6 months for penicillamine, 4 months for hydroxychloroquine, and 3 months for all other DMARD and biologics. In some instances a full response may take longer than the times listed above and it may be appropriate to wait longer if in the view of the clinician an adequate response may be achieved by additional treatment duration.
10. When adequate control in not achieved, the DMARD should be changed or another DMARD or biologic agent added.
11. There is a hierarchy of DMARD/biologics. Patients who do not respond adequately to MTX or leflunomide will only occasionally respond to another DMARD. In such patients the switch to or addition of a biologic may be indicated without further DMARD trials. Alternatively, triple drug combination with MTX, sulfasalazine, and hydroxychloroquine may be indicated, as may the addition of cyclosporine.
12. Most patients will not respond completely to DMARD/biologic therapy. In such patients the most effective treatment should be used, and continuous switching from one DMARD to the next is not generally good policy or likely to be effective.
13. Biologics may be appropriate at any time during the treat-

ment process depending upon disease and response. Anticytokine therapy should not be reserved for advanced disease or DMARD resistant disease, and appropriately should be used to treat rapidly advancing, aggressive disease.
14. Prognostic factors should be considered in the prescription of DMARD, including radiographic progression.
15. Weak (auranofin) and toxic (cytoxan) DMARD are seldom used and not advised.
16. Corticosteroids remain controversial because of concerns about toxicity, but many rheumatologists believe that low dose (10 mg or less) is effective and safe.
17. The use of NSAID and/or simple analgesics is not required, but is an adjuvant that is suitable for some patients. It is not correct to condition DMARD use on a trial of NSAID.
18. All treatments must consider the medical, social, psychological, and economic status of the patient. Patient preferences are important.
19. Toxicity of drugs should be considered in their prescription.
20. Treatment initiation and assessment of treatment success require rheumatologic assessment of disease activity. That process should be modeled on the ACR core criteria and includes assessments of pain, global severity, function, acute phase reactants, and joint counts, at a minimum.

FREDERICK WOLFE, MD,
National Data Bank for Rheumatic Diseases—Arthritis Research Center Foundation, Inc. and University of Kansas School of Medicine, Wichita, Kansas;
JACK J. CUSH,
Arthritis Center, Presbyterian Hospital of Dallas, Dallas, Texas;
JAMES R. O'DELL, MD,
Professor of Medicine, University of Nebraska School of Medicine, Omaha, Nebraska;
ARTHUR KAVANAUGH, MD,
Associate Professor of Medicine, University of California at San Diego, San Diego, California;
JOEL M. KREMER,
Professor of Medicine, Albany Medical College, Albany, New York;
NANCY E. LANE, MD,
Associate Professor of Medicine and Rheumatology, University of California at San Francisco, San Francisco, California;
LARRY W. MORELAND, MD,
Professor of Medicine, Director, UAB Pittman General Clinical Research Center, The University of Alabama at Birmingham, Birmingham, Alabama 35294;
HAROLD E. PAULUS, MD,
Professor of Medicine, University of California Los Angeles, Los Angeles, California 90095;
THEODORE PINCUS, MD,
Professor of Medicine, Vanderbilt University, Nashville, Tennessee, USA;
ANTHONY S. RUSSELL, MD,
University of Alberta, Edmonton, Alberta, Canada;
KENNETH R. WILSKIE, MD,
Virgina Mason Clinic, Seattle, Washington, USA.

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