

Roundtable I: Practice Patterns for Treating Rheumatoid Arthritis

Discussion Facilitators: Carol M. Ziminski, MD; and James R. O'Dell, MD

Discussion Facilitators

Carol M. Ziminski, MD, FACP
Associate Professor of Medicine
Deputy Director
Johns Hopkins Rheumatology Division
at Good Samaritan Hospital
Baltimore, Maryland

James R. O'Dell, MD
Professor and Chair of Rheumatology
Program Director
Department of Internal Medicine
University of Nebraska Medical Center
Omaha, Nebraska

Discussion Participants

Sameer Abu-Samrah, MD
Alan G. Bayham, RPh
Robert N. Cluck, MD
Mike Gilliam, PharmD
D. Mark Mahler, MD, MBA
John Seidenfeld, MD, MSHA
Leonard Tamsky, MD
Randy F. Vogenberg, RPh, PhD

Whenever a new drug comes to market—particularly if it's within a novel class—practical questions surface as to how that drug can best be implemented in clinical practice and for which patients it will prove most efficacious. In addition, questions about side effects, how the new drug fits in with more established medications, and what the long-term consequences are likely to be must also be taken into consideration.

Guidelines from the American College of Rheumatology

Dr. O'Dell: The most recent rheumatoid arthritis (RA) guidelines are about 3 years old. I don't think there

are any data on whether or not anyone adhered to them. I think we use the osteoarthritis (OA) guidelines a lot more.

The current RA guidelines were almost outdated by the time they were finished. They say nothing about combination therapy, for example. Studies show that 25% of RA patients are now treated with combination disease-modifying antirheumatic drugs (DMARDs).¹ At the time the guidelines were being put together, the studies to support combination therapy were in the process of being published, so it did not seem appropriate to include them.^{2,3}

Dr. Cluck: I'm sure you understand the extreme urgency for having guide-

lines that we can all work by. In the healthcare and managed care environment we're in, we are trying to get network compliance and to ensure the right patients get the right therapy. It's therefore imperative that we have appropriate guidelines.

An outdated guideline is probably better than none at all, because at least you can make revisions. Right now, we don't know exactly what to do with the new medications as they arrive because there's no consensus.

Dr. O'Dell: If you try to develop guidelines based on data—which is what we like to be able to do—you'll find there really aren't any good data to help us address all the questions. For instance, there are no comparative studies with any of the new biologic agents versus more established agents. The only studies we have right now compare etanercept or infliximab with placebo.^{4,5}

What we really need are studies that address the question in a methotrexate-failure patient. For example, should you add etanercept to that patient's program? Or should you add sulfasalazine and hydroxychloroquine to the methotrexate? There are good data to show that combination DMARDs work. But how does that compare with etanercept? Nobody knows.

The treatment paradigm now in this country is methotrexate and only after leflunomide has failed. Are you going to add leflunomide to a patient who's doing suboptimally on methotrexate? Many clinicians are doing that, but most of the data show the combination can produce liver enzyme elevations and other problems.⁶

Dr. Ziminski: Some guidelines are better than no guidelines, but if you're held to out-of-date guidelines, then you may be forced into practice patterns that are not good. Physicians who are in practice have

a sense of the order in which they would treat patients, but they may not necessarily follow rigid guidelines. Nobody is using the expensive drugs first, but treatment approaches are certainly more aggressive than they were years before.

Dr. Mahler: I'd go a step further and say that from the health plan side, I'm not as inclined to push the generation of guidelines beyond the available database. Until such time as evidence-based guidelines come out, we need to focus our energies on case management and make sure people get the appropriate level of subspecialty care.

Predictors for Response

Mr. Bayham: With the absence of any clear-cut clinical guidelines to use with these newer agents, what about the evidence for predictors for response? Do we have any clear predictors?

Dr. O'Dell: We have very good predictors of who's going to do poorly. You could draw up some guidelines that include rheumatoid factor positivity, elevated sedimentation rates, functional measurements, and genetic typing for a certain at-risk allele status, which we don't do as routinely as clinical tests—but we're not very far from doing so. If we could get predictive values in a differential fashion, that would be very useful.

So we can tell who's going to do poorly. What we need is information on how we can make decisions based upon that to make the patient better. Using shared-epitope status to predict response to methotrexate is promising. That is, if a patient's shared-epitope status is positive, then the chances of doing well on methotrexate therapy are small. If the patient is shared-epitope negative, he or she will do great on methotrexate alone.^{6,7} We could treat people who are shared-epitope negative with methotrexate alone,

for example, and if they're shared-epitope positive, maybe they need combination therapy right off the bat.

In the Finnish trial using the combination of methotrexate, sulfasalazine, and hydroxychloroquine, the combination was dramatically effective in that group of patients, particularly if they were shared-epitope positive.³

So far there's no information that predicts those people who are going to do well on anti-tumor necrosis factor (TNF) therapy (that is, TNF blockade, whether or not you are talking about the antibody or the soluble receptor).

Dr. Abu-Samrah: There have been studies to show that after a period of being on anti-TNF, the patient may rebound, or the disease process will return to baseline.⁴ Is there any interest in studies to show that if we resume the first- or second-line treatment early after anti-TNF treatment, these patients will do better? We can't keep them on anti-TNF for the rest of their lives—just given the cost component alone. We know that it's not disease modifying based on all the data that are available so far.

Dr. Ziminski: Etanercept is so new that we do not have long-term data. We do know that if the agent is stopped—either methotrexate or etanercept—the disease process can re-emerge.⁵

Dr. O'Dell: There are no data available yet to say that biological agents modify X rays. However, they clearly *do* modify the disease. Everything we've seen that modifies the disease to the degree that these drugs do has ultimately been shown to modify erosions.

Induction Versus Maintenance Therapy

Dr. O'Dell: The whole idea of induction therapy versus maintenance

therapy is something we've never had the luxury of looking at in RA. We've never been successful in withdrawing any medication from a rheumatoid patient and having that patient continue to do well long term.

Treating RA patients aggressively and then backing off is a great concept. The COBRA [*Combinatietherapie Bij Reumatoide Artritis*] trial was the first confirmation we had that you could actually do that.⁸ Whether or not we'll be able to do that with the anti-TNF approaches is unclear.

The Primary Care Physician and the Specialist

Dr. Vogenberg: What has been the experience of everyone here of having patients go between primary care physicians (PCPs) and specialists? Does it seem to be working? And what might be a good model for how a rheumatologist can work with a PCP to better manage or detect whether the patient's doing better or worse for optimal management and use of these new biologicals, which are very expensive?

Dr. O'Dell: Most plans that I am aware of are trying to limit the use of etanercept. Since etanercept is so far the only anti-TNF that has been approved for RA, it is mostly rheumatologists who are prescribing it and doing the patient follow up. Those rheumatologists are hopefully going to get better at choosing the patients and are not going to have some of the problems we've seen with patients treated with etanercept who developed infections and died. I would not necessarily want to develop a plan in which PCPs were heavily involved with using anti-TNF therapies because I believe rheumatologists should do that.

If you treat patients with RA early, regardless of which medicine you select, they're going to do much better. Maybe many of them aren't going

to need the other therapies later on. That's where the PCPs can be most effective—either in getting patients diagnosed correctly or getting them referred to a rheumatologist earlier. Patients are so much more responsive in the early stages of this disease and are more responsive to cheaper drugs—and any disability that might be experienced can be arrested before it starts.

Dr. Abu-Samrah: So when you refer for early detection and early treatment, you don't necessarily mean that we begin with biological agents as first-line treatments?

Dr. O'Dell: Right now there's no evidence to support early use of biological agents as initial therapy in RA. A study would have to show an incredibly big benefit to those patients to make it reasonable to use one of the biological agents as initial therapy because there are still potential risks that aren't completely defined yet. If you treat RA patients early, those patients are generally going to have an opportunity to do very well on lots of other therapies.

That doesn't mean, however, that there won't be certain patients who aren't going to do well on initial therapy—regular DMARD therapy. With some of these patients, you may have to progress to biological agents more quickly than we might have considered doing in the past. Most clinicians are not even yet advocating a combination of DMARDs for treating patients initially, although there's emerging data to indicate that may be a better way to go. Most researchers—even those who have done several combination studies—are still advocating rapid step-up therapy.

Dr. Ziminski: Often the PCP may think a certain process is going on and just wants confirmation of the diagnosis and the regimen for the patient. We often work in combination and

consultation with primary providers. Rheumatologists support, clarify, guide, and then deal with the potential disease-modifying agents as well as side effects. I think working together can be very effective.

Underutilization of Physical and Occupational Therapy

Dr. Gilliam: I am struck by the underutilization of physical therapy (PT) and occupational therapy (OT). We're talking about early or more aggressive intervention with pharmacologic agents, but I'm wondering if those agents, combined with PT and OT, might help the outcome as well.

Dr. Ziminski: Certainly PT and OT can have a significant benefit for patients in terms of pain relief, improving activities of daily living, and functional status over the long term.^{9,10}

However, OT and PT aren't free, either. Patients and physicians are often concerned about getting that part of the loop involved. But rheumatologists are much more likely to refer to therapists early on than PCPs are. And a targeted, joint-protective regimen can be very beneficial to these patients. Getting the patient to participate and understand the importance of this and then continuing the activities at home is a lifelong process.

Dr. Gilliam: Why has there been resistance to involve OT and PT? Has it been because of the payer situation?

Dr. O'Dell: There are lots of reasons. One is that even though we have a strong belief in the usefulness of PT and OT—and clearly, once people have progressed to a certain stage it's very valuable—it's been very difficult to show the benefit on a cost-benefit analysis.

I would play the Devil's advocate. If we can treat patients in the first 3 to 6 months of the appearance of disease

symptomology, maybe we could decrease the ideal amount of OT and PT to one half, or one third, or even one tenth of the current amount, because we treated them early.

To clarify, when we talk about early therapy, we're not necessarily talking about expensive treatments. We can treat people very effectively up front with inexpensive drugs like methotrexate—particularly if we use the liquid form—which costs pennies a day. We can use bridge therapy with prednisone, which is very cheap initially. And if DMARDs are successful, then we're successful in getting people off steroids.

Identifying Appropriate Patients for Biologic Agents

Dr. Abu-Samrah: The literature has helped us identify guidelines as to who are the appropriate patients to start with the biological agents. So far, I have not really had enough data to help me say that this patient, who we've started on the biological agents, is not responding and it's time to stop the agent. Is there anything available?

Dr. O'Dell: That's a very important question. We hear that if patients are going to do well, they're going to do well in the first 3 months, and if you look at the data from the anti-TNF strategies it's very clear.^{4,5} But in a real-world situation, how does a rheumatologist really know if the patient is doing better?

One of the problems in evaluating response to anti-TNF therapy is that people feel great because they don't have TNF in their blood anymore; it's being blocked. But does that always mean that the disease is subsiding as well? In many cases the answer is yes and in some cases the answer is no. But how do we tell which one is which?

Most rheumatologists don't do complete joint counts or draw sedimentation rates on a routine basis

because that's just not their practice or because the health plan they're participating in wouldn't pay for it. Clearly, if some of those criteria were in place to help document improvement with these agents, I think that would be appropriate.

Quality Outcomes for Tracking

Dr. Seidenfeld: Variability is a big problem. If we did a survey for joint replacements, we might find that in 5 or 6 different areas of the United States, there are widely varying rates. So from my point of view as a medical director, what are the metrics we should be looking at? What kind of things should we be profiling? Obviously, joint replacement is one of them.

Dr. Mahler: From the case-management perspective, clinical indicators and outcomes need to be identified along with regular monitoring, so we can track these for case management purposes. We want to get people into appropriate levels of care based on the result of indicators such as sedimentation rate and the Health Assessment Questionnaire.

Dr. Ziminski: As Dr. O'Dell said, most physicians in their real-life office setting are not going to document joint counts every time. Adding 5 to 10 minutes to each patient's evaluation for perhaps 20 patients over the course of a day might be asking too much of already very busy physicians. Laboratory parameters, markers of inflammation like the sedimentation rate or the C-reactive protein (CRP), can also serve as useful guidelines. These measurements don't usually change quickly, so they're not something that needs to be followed every week.

Dr. O'Dell: Those are the data you are going to need to make decisions about a particular patient. If a patient doesn't meet our requirements for contin-

ued anti-TNF therapy after 3 or 4 months of treatment, there must be data to show they don't meet the requirements. Maybe collecting the data will necessitate the rheumatologist billing at a different level for that kind of visit. That would be a lot cheaper than buying the drug for another month or two.

Dr. Gilliam: Regarding the question about who collects the data, maybe we should identify what some of those indicators should be, because for example, at the health plan level we might dedicate a nurse to collect the data.

Dr. O'Dell: Right now I would use the ACR (American College of Rheumatology) 20 core set criteria.¹¹ It is not a tremendous burden for a trained observer to use those in an examination time frame or in a clinic. If the observers know what they're doing and have the appropriate forms, it takes about 5 or 10 minutes. Then of course, the sedimentation rate has to be ordered and the patient has to fill out the Health Assessment Questionnaire.

Dr. Ziminski: If a decision to continue anti-TNF therapy is going to be made at around the third month, I'm not sure at that time that a baseline and a single data point would be enough. With an individual—as opposed to a statistical patient population—you may want a 6-week mark, or at 1, 2, and 3 months.

Dr. Cluck: Dr. O'Dell, since we don't have objective data, what would you consider to be the prerequisites that would have to be fulfilled before you would utilize the biological agents? What do you think would be necessary as elements?

Dr. O'Dell: A very firm diagnosis of RA! That seems obvious, but I don't know that it's necessarily obvious in some situations. And the way we

define therapy in the United States is in response to methotrexate. So you'd want the patients to have failed methotrexate as a minimum. One way to fail methotrexate is by not tolerating it.

Failing methotrexate may or may not be an issue depending upon whether or not methotrexate can protect against antibody development with some of the anti-TNF compounds. If I were writing criteria for that, I would say something like "adequate doses of methotrexate up to 20 mg subcutaneously." There's a group of patients who will respond to parenteral methotrexate but won't respond well to oral methotrexate. Most rheumatologists will tell you that if you push oral methotrexate up to a certain dose (between 17.5 mg and 25 mg a week), you can then switch to parenteral therapy. And the parenteral therapy can be subcutaneous injections, which work just as well as intramuscular injections and patients can give it to themselves. So I would require that they fail that as a minimum. The more difficult question is whether or not you also require that they fail combinations that have been shown to be more effective than methotrexate.

Dr. Abu-Samrah: When you mentioned failing methotrexate on the level of not tolerating, do you mean not tolerating the oral methotrexate?

Dr. O'Dell: It depends on the side effect. Most of the side effects from oral will also be seen with subcutaneous. Our ability to get around oral side effects by using subcutaneous injections is not always successful. I would want the patient, the PCP, and the rheumatologist to know that they could use folic acid to nullify some of those nuisance toxicities. Most rheumatologists know to do this because most of our data say folic acid does not interfere with efficacy, although some new data suggest that it might.

Newer NSAIDs

Dr. Vogenberg: Dr. Ziminski, I'd like to get a sense of where you see newer nonsteroidal anti-inflammatory drugs (NSAIDs), such as the COX-2 (cyclooxygenase-2) inhibitors, fitting within other therapeutic approaches.

Dr. Ziminski: The newest COX-2 inhibitors, celecoxib and rofecoxib, are useful in that they have the potential for decreasing the risk of gastrointestinal side effects, but this is not absolute. They're not clearly more effective than the older NSAIDs.¹² And I don't think the COX-2s are going to be the answer to everything, nor will they prevent our need for agents that have the potential for shutting off disease.

Dr. O'Dell: If the physician is relying too much on nonsteroidals to treat RA, then there's something wrong. The NSAIDs are not a significant treatment for RA and that goes back to getting patients to see rheumatologists early. You sometimes have a PCP treating RA with what I call a "musical nonsteroidal approach," which means they skip from one to the next and back again. Nowadays they're likely to include celecoxib in that musical approach, which if they use it at full dose, 200 mg twice a day, costs about \$140 a month. That is a lot more expensive than treating them with methotrexate and low-dose prednisone.

Patient Management with Biological Agents

Dr. Cluck: If you had a patient on etanercept, what should be the minimum visitation frequency for regular maintenance?

Dr. O'Dell: I would have them come in for monthly visits when initiating therapy. The money you save by discovering a problem or preventing a

catastrophe early would be well spent. As for maintenance, nobody has experience with very many people on these drugs after a year. I would advocate monitoring fairly frequently, maybe monthly in the first 6 months initially, then perhaps every 2 to 3 months after a period of time.

Dr. Gilliam: If you have a patient that has gone through the methotrexate or combination therapy and there is clearly a treatment failure, what's going to determine whether you look at leflunomide, etanercept, infliximab, or a combination?

Dr. O'Dell: We've done a lot of studies with the combination of sulfasalazine and hydroxychloroquine.^{2,3} It works for a good number of patients and it's well tolerated. In our clinic, if a patient isn't doing well on methotrexate sulfasalazine/hydroxychloroquine is added to methotrexate and if *that* doesn't work, then we generally move on to etanercept. Our tendency right now is to continue the methotrexate when we start etanercept.

Some people I know have added etanercept to that full combination. Where we fit leflunomide into our algorithm for treating RA is more problematic because most of our patients are already on methotrexate, and they're usually partial responders. Then we may add the leflunomide to methotrexate

We use leflunomide frequently for patients who don't like methotrexate, which is a fair number. They're doing okay, but they just don't like being sick (flulike symptoms for a couple of days a week). They take it anyway and they're glad to take it because it helps their RA so much. Drugs that block TNF make you feel great, but we're still trying to decide exactly what the effect is on joints and erosions.

We're very interested in exploring leflunomide in combination with standard DMARDs such as sulfasalazine and hydroxychloroquine,

and we're trying to do studies in that area right now.

The other issue is alcohol consumption and there aren't prohibitions to taking leflunomide with alcohol. Some people believe you can drink 2 high balls a night and can still take leflunomide. I'm somewhat incredulous that a lot of people don't seem to be all that worried about liver enzyme elevations on that drug.

Dr. Tamsky: In Phoenix, I'm not sure I've heard many rheumatologists talking about combination therapy. Most are saying that their next response after methotrexate failure is to use biologics. Is that reasonable? What's going to happen when I ask, "Have you tried combination drugs first?"

Dr. O'Dell: Rheumatologists in the Phoenix area have participated very heavily in many of the drug trials, so they have had a fair amount of experience. Rheumatologists are like anybody else—they're impressed with what they've seen work. Sometimes combination therapy is a difficult sell. Based on the data, however, your question would be very reasonable.

Dr. Tamsky: That's my problem. Why should I choose the much more expensive drug first, which is still new, and still may have side effects that have not yet been discovered, instead of a less expensive product that looks likely to be as effective?

Dr. Abu-Samrah: I'm probably in the same position, because I'm the one who deals with the medical prior authorization on these new agents. We often get pushed by specialists and patients to approve something. This treatment is not life saving. The disease itself is not a life-and-death disease—at least in the short term. So I might approve it for 1 month or at least the first 3 months. Then I will push for objective proof that this medication has made a significant differ-

ence in the disease inflammatory process, if not radiographically, before I continue to approve it.

Technical Aspects

Dr. Mahler: Should methotrexate not be used for patients who drink alcohol regularly but have normal liver enzymes?

Dr. O'Dell: The answer is not known. All of the studies that have been done to show us how safe methotrexate is and how we can follow methotrexate to make it safe have been done in people who are allegedly not drinking. So we have essentially no data on people who are actually consuming alcohol.

So could you safely consume alcohol and take methotrexate, as long as your liver enzyme tests were okay? We don't know, so I advocate against it. If I have a patient who drinks, I tell them to limit it to one drink a month. Other physicians tell them they can't have anything to drink. And other physicians just ignore it.

Dr. Ziminski: We see much less hepatotoxicity than we feared when we started using methotrexate on a regular basis. Also, those who are diabetic and already have fatty livers may have more tendency to have hepatic dysfunction; they are the populations that have more trouble tolerating methotrexate.

The American College of Rheumatology's guidelines have changed so that liver biopsies after 1.5 years at certain cumulative doses are not required any more.

Dr. Mahler: For patients who are on methotrexate, are there any other medications commonly used by these patients that can have liver toxicity that we should be aware of for the possibility of drug-to-drug interactions? What other types of contraindications should we be aware of?

Dr. O'Dell: The most obvious is leflunomide, and I don't think we know what the liver enzyme elevations that we see with leflunomide really mean. I don't think that combination is contraindicated, but we need to carefully monitor liver enzymes and adjust the doses of those 2 drugs when used together so we don't have liver dysfunction.

There are liver toxicities with azathioprine that are well known and we certainly use methotrexate and azathioprine together in the treatment of RA. There's some liver toxicity associated with sulfasalazine and again, that combination is used commonly, yet we don't see very many problems with that.

Dr. Ziminski: Also, these days there are many other agents—alternative remedies such as echinacea, St. John's Wort, ginkgo root, ginseng—patients use. Nobody really knows what's in them; these alternative agents and over-the-counter medications might put patients at as much risk for toxicity as the drugs we prescribe. Unless they're specifically asked, patients may not say they are taking these things.

Dr. Mahler: With the newer agents, what specific kinds of infections should be looked for? In particular, are there prophylactic or preventive strategies we should be considering in case management, such as the use of the pneumococcal vaccine? Should people be on any kind of prophylactic antibiotics?

Dr. O'Dell: We don't know what to do exactly. Tumor necrosis factor isn't the reason there is RA, but it's one of the mediators. To think that we're not going to have infections, particularly if we don't use the drug very carefully, is extremely naive. Tuberculosis is another infection that people have particular concern about.

Some of the patients who have had trouble are those who probably shouldn't have been started on the drug in the first place: patients with draining ulcers from RA, with vasculitis, etc. So it's very important we select the patients who are going to be put on these drugs appropriately.

Joint infections have seemed to be a problem in some patients on etanercept. If they're using etanercept and they suddenly develop a joint that's painful or swollen out of proportion with the rest of their joints, you should stop the etanercept and get the joint aspirated to make sure it's not septic.

Efficacy Versus Convenience

Dr. Abu-Samrah: In the era of cost containment, patient preference and convenience is very much put aside. The focus is on what is efficacious rather than what is convenient. How do we, in the managed care industry or the healthcare industry at large, make this message clear to patients?

Dr. Ziminski: That's part of our job of educating patients so they understand all the implications and the advantages and disadvantages of each agent. Even with simpler medicines, all we can really do is recommend. We can't force patients to take things.

The bottom of the pyramid, whether it's flipped sideways, up, or down, is getting the patient involved and informed as to what's going on. Patients are also aware of costs. So they recognize that medications need to be not only in their health interest, but also in their pocketbook interest.

Comparing the Newer Agents

Dr. O'Dell: For some patients, being able to give themselves a subcutaneous shot twice a week is an advantage. For others, there may be an advantage to being able to get intra-

venous therapy. Clearly there are patients with deformities who would prefer an intravenous therapy or maybe the physician would prefer it to maintain a bit more control. One way to maintain more control is have the patient come in every 2 months to get an injection.

Intravenous therapy may also be an advantage with regard to Medicare. Depending on how it's looked at, infliximab therapy may be paid for when etanercept isn't, because it's an intravenous therapy.

Dr. Mahler: What about the differences in immunogenicity between the 2 agents?

Dr. O'Dell: I think that's a big difference. It appears that the most effective way to give infliximab in RA is in conjunction with methotrexate, whereas etanercept can probably be used effectively with or without methotrexate.¹³

Now that may not be a huge difference, and if you use methotrexate with infliximab it appears to be just fine in the studies that we have so far.¹³ In practice, most people who are on etanercept are going to be on methotrexate anyway. But it certainly looks like methotrexate is going to be used with infliximab and not necessarily with etanercept.

... REFERENCES ...

1. O'Dell J. Combination DMARD therapy for rheumatoid arthritis: Apparent universal acceptance [Abstract]. *Arthritis Rheum* 1997;40 (Suppl 9):S50.
2. O'Dell JR, Haire CE, Erikson N, et al. Treatment of rheumatoid arthritis with methotrexate alone, sulfasalazine and hydroxychloroquine, or a combination of all three medications. *N Engl J Med* 1996;334:1287-1291.
3. Mottonen T, Hannonen P, Leirisalo-Repo M, et al. Comparison of combination therapy with single-drug therapy in early rheumatoid arthritis: A randomized trial. *Lancet* 1999;353:1568-1573.
4. Elliott MJ, Maini RN, Feldmann M, et al. Randomised double-blind comparison of chimeric monoclonal antibody to tumour necrosis factor alpha (cA2) versus placebo in rheumatoid arthritis. *Lancet* 1994;344:1105-1110.
5. Moreland LW, Baumgartner SW, Schiff MH, et al. Treatment of rheumatoid arthritis with a recombinant human tumor necrosis factor receptor (p75)-Fc fusion protein. *New Engl J Med* 1997;337:141-147.
6. O'Dell JR, Nepom BS, Haire C, et al. HLA-DRB1 typing in rheumatoid arthritis: Predicting response to specific treatments. *Ann Rheum Dis* 1998;57:209-213.
7. Weinblatt ME, Kremer JM, Coblyn JS, et al. Leflunomide plus methotrexate in refractory RA: A pilot study [Abstract]. *Arthritis Rheum* 1997; 40(Suppl 9):S193.
8. Boers M, Verhoeven AC, Markusse HM, et al. Randomised comparison of combined step-down prednisolone, methotrexate and sulphasalazine with sulphasalazine alone in early rheumatoid arthritis. *Lancet* 1998; 351:220.
9. Semble EL, Loeser RF, Wise CM. Therapeutic exercise for rheumatoid arthritis and osteoarthritis. *Semin Arthritis Rheum* 1990;20:32-40.
10. Ytterberg SR, Mahowald ML, Krug HE. Exercise for arthritis. *Balliere's Clin Rheum* 1994;8:161-187.
11. Felson DT, Anderson JJ, Boers M, et al. American College of Rheumatology preliminary definition of improvement in rheumatoid arthritis. *Arthritis Rheum* 1995;38: 727-735.
12. Mandell BF. COX 2-selective NSAIDs: Biology, promises, and concerns. *Cleve Clin J Med* 1999;66:285-292.
13. Lipsky P, St. Clair W, Kavanaugh A, et al. Long-term control of signs and symptoms of rheumatoid arthritis with chimeric monoclonal anti-TNF α antibody (infliximab) in patients with active disease on methotrexate [Abstract]. *Arthritis Rheum* 1998;41(Suppl 9): S364.