

Assessing New Therapies for RA: Defining New Expectations for Treatment New Therapies in Clinical Practice: Issues of Cost and Access

Highlighted in this summary are comments focused on the cost of anti-tumor necrosis factor (TNF) agents and gaining access to them in a managed care environment. Other issues under discussion included selection of appropriate patients to receive these new agents, when to prescribe these agents and who should prescribe them, and the importance of collecting long-term data about how well patients are doing under different therapies.

Participants outlined 3 important points. First, decision makers in managed care and government need to be educated not only about treatment options (eg, early aggressive therapy), but also about rheumatoid arthritis (RA) itself. Second, although anti-TNF agents have demonstrated efficacy, long-term data on the safety and effectiveness of these agents are not yet available. Finally, even without long-term data, these agents can and should be used in selected patients; however, they should be prescribed only by experts in rheumatology.

Need for Education

Participants extensively discussed how use of the new anti-TNF agents can be justified to decision makers in managed care and government. There are roles for both rheumatologists and patients in influencing decisions about availability of new therapies. It was noted that the opinions of administrators or health maintenance organizations in the United States often

are influenced by campaigns around either patient satisfaction or litigation.

Lobbying efforts by individual patient groups were mentioned. Patients older than age 65 years who have to pay out of pocket for anti-TNF therapy were suggested as one potential group. It was mentioned that statements from patients tend to have more political clout than statements only from experts, who sometimes are perceived as a self-interested lobby.

Several participants commented that an important part of any campaign to gain acceptance for these new agents is education about RA itself. One participant made the point that some people mistakenly believe that RA is the same disease as osteoarthritis, which "everybody" has. Decision makers need to understand that RA is a costly, complicated disease that exacts a high toll in morbidity and mortality. It affects about 2.5 million people in the United States (~1% of the population) and is about 3 times more common in women than men; RA frequently leads to work disability, functional disability, joint replacement surgery, and premature death.¹

Education is important because, compared with other high-cost diseases such as kidney failure, RA has relatively low visibility. It was noted that Medicare will pay for dialysis. Furthermore, there is an attempt under way to get Medicare to pay for outpatient care for multiple sclerosis. Like RA, multiple sclerosis can

be costly to treat (eg, cost of beta-interferon). So cost, in and of itself, does not seem to be the only issue.

How Anti-TNF Agents Work

It is now known that the proinflammatory cytokine TNF- α plays a critical pathogenic role in at least a large subset of patients with RA.² Anti-TNF agents work by blocking, or neutralizing, the activity of TNF. One participant noted that these are the first agents introduced for treatment of RA for which the mechanism of action is actually known. They are the first agents to be targeted specifically against one inflammatory molecule.

Efficacy Versus Effectiveness

Efficacy means, in a clinical trial longer than 6 months or a year, that an agent has demonstrated benefit over placebo. Participants agreed that the efficacy of anti-TNF agents has been demonstrated. *Effectiveness* means that over 5 or 10 years, the drug really controls the disease. Evidence of effectiveness of the anti-TNF agents will not be available for several years.

Rheumatologists have several expectations for anti-TNF therapy. One is that this therapy will reduce or remove objective evidence of inflammation. Another is that it will not only maintain function, but also prevent damage. In addition, it is hoped that this therapy will be effective against all those aspects of disease that are dependent on the proinflammatory effects of TNF.

One participant noted another expectation associated with anti-TNF therapy: that the therapy will enhance patients' feeling of well-being (an effect not always seen with traditional therapies). This effect has been observed in clinical trials. The patient's sense of well-being may improve adherence, which in turn may increase effectiveness.

Need for Long-Term Data

Trial Design. Over the next few years, rheumatologists would like to see data on the use of anti-TNF agents in (1) early RA patients, (2) different kinds of induction therapies, and (3) consecutive maintenance therapies. Dose-response trials to control synovitis and to try to achieve remission would provide valuable information. Effectiveness trials with predetermined endpoints (eg, hospitalization, joint replacement surgery, tapering of steroid doses) were also mentioned as important.

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One potential trial design involves aggressive induction therapy followed by maintenance therapy. Anti-TNF therapy could be included either early, late, or throughout the course of the trial to see whether remissions could be induced with that therapy. Such a trial would enable researchers to examine the possibility of synergy between multiple medications.

It was mentioned that trials should include patients other than those who have failed to respond to methotrexate (MTX) therapy for RA, because "MTX failures" are only a subset of RA patients. When patients who have failed to respond to MTX are enrolled in a study, it was suggested that trials be designed to compare anti-TNF therapy with other options that would actually be used

by a rheumatologist in that clinical situation. In other words, instead of comparing an anti-TNF agent with placebo in patients who failed to respond to MTX, researchers should compare the anti-TNF agent with MTX plus hydroxychloroquine, sulfasalazine, or both. Such a trial would be directed toward answering a clinical question that is important to rheumatologists: How do we utilize these drugs in true practice?

Safety

Long-term data on the safety of anti-TNF agents are vital. These agents block the effects of TNF, a component of the immune system, and there is theoretical concern that they could cause an increase in infections and/or malignancies. A very small fraction of patients receiving anti-TNF agents have had severe adverse events. Whether these agents are as safe as MTX will not be known for several years.

It was stated that rheumatologists should talk honestly with their patients about the lack of long-term safety data. Patients who fail to respond to combination therapy or MTX might be willing to accept the risks.

Patient Monitoring

One point made during the discussions was that clinical rheumatologists should collect standardized information on how well their patients are doing with various therapies. It was noted that better therapies have been developed for cancer, diabetes, and hypertension by means of clinical protocols and that rheumatologists should do the same.

Ongoing data collection is particularly important in the case of anti-TNF therapy, for which the long-term outcomes are not yet known. In the United States, Frederick Wolfe, MD, has established the National Databank for Rheumatic Disease, which enables monitoring by questionnaire. Pincus and colleagues developed a means of

monitoring patients called the Standard Protocol to Evaluate Rheumatoid Arthritis (SPERA).³ This proposed 4-page questionnaire would enable rheumatologists to annually review their patients and provide all the information necessary to generate adequate outcome studies.

Who Should Receive Anti-TNF Agents?

Patients with RA who do not respond adequately to MTX alone are one group who would be candidates for therapy with anti-TNF agents. Patients who have had a poor response to combination therapy with traditional disease-modifying antirheumatic drugs (DMARDs) are also potential candidates. Patients who require corticosteroids, at a dose that is clearly going to be detrimental to them over several years, may benefit from an anti-TNF agent if it allows successful tapering of the steroid. Some rheumatologists believe that anti-TNF therapy should be used for all patients who require tight control of their disease.

Patients who are too frail to try MTX because of poor renal or cardiac function might also be candidates for anti-TNF therapy, as would patients who should not take MTX for other reasons (eg, excessive alcohol use). One participant suggested that anti-TNF therapy may be useful in controlling disease in patients who are attempting to become pregnant. (Methotrexate, because of its teratogenic properties, must be discontinued for 3 months before a patient attempts to become pregnant, often leading to severe flare-up of the disease.) Anti-TNF agents have not exhibited teratogenic effects in the fetuses of pregnant animals, but their potential effects on human fetuses are unknown. Currently, Food and Drug Administration (FDA) labeling warns against the use of etanercept in established pregnancies.

Who Should Prescribe Anti-TNF Agents?

Participants cautioned against the unrestricted use of anti-TNF agents by physicians who are not experts in rheumatology (eg, internists, family practitioners). They made the point that payers would probably not be in favor of all those physicians having access to these expensive therapies. Limiting use to rheumatologists not only might have a favorable economic impact, but it also would result in better care because RA is often inaccurately diagnosed by nonrheumatologists. It was generally agreed that these new therapies have a demonstrated benefit and that they should be used appropriately by experts in the area.

Conclusion

Anti-TNF therapies are new additions to the armamentarium for treatment of RA. Because they are new, there are questions regarding

dosages, toxicities, long-term effects, and appropriate target populations. Roundtable participants agreed that their use should be restricted to experts in rheumatology who are trained in the use of these agents. These experts should develop evidence-based standards for the application of anti-TNF therapies.

... REFERENCES ...

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