

The Emerging Role of Anti-TNF Therapy in the Treatment of Rheumatoid Arthritis

An interview with Peter E. Lipsky, MD, Professor in Arthritis Research, Professor of Internal Medicine and Microbiology, Director, Rheumatic Diseases Division, University of Texas Southwestern Medical Center, and Director, Harold C. Simmons Arthritis Research Center, Dallas, Texas.



Peter E. Lipsky, MD

Introduction

Dr. Peter Lipsky is a leading expert in the field of arthritis research. A member of the faculty at the international roundtable in Lausanne, Switzerland, February 19 and 20, 1999, he was comoderator of the roundtable discussion titled "New Therapies in Clinical Practice: Issues of Cost and Access."

Dr. Lipsky's work has been published in numerous leading peer-reviewed journals, including Journal of the American Medical Association, Arthritis and Rheumatism, Journal of Immunology, Journal of Clinical

Investigation, Annals of Internal Medicine, and the Journal of Rheumatology. He is a member of the National Institute of Arthritis and Musculoskeletal Skin Diseases Board of Scientific Counselors and the American College of Rheumatology Board of Directors. He serves on the editorial boards of the Journal of Immunology (editor-in-chief 1992 to 1997), Arthritis and Rheumatism, the Journal of Rheumatology, the Journal of Clinical Immunology, and Clinical Immunology and Immunopathology.

After earning his undergraduate degree from Cornell University, Dr. Lipsky received further training at New York University School of Medicine and Strong Memorial Hospital in Rochester, New York. Since 1975, he has been associated with the University of Texas Health Science Center in Dallas, Texas. He is currently Professor in Arthritis Research; Professor of Internal Medicine and Microbiology; and Director, Rheumatic Diseases Division, University of Texas Southwestern Medical Center; as well the director of the Harold C. Simmons Arthritis Research Center in Dallas.

AJMC: Methotrexate is currently the dominant drug for rheumatoid arthritis therapy. What qualities must a new agent have to challenge that dominance?

Dr. Lipsky: Clearly, a new agent either has to demonstrate more effec-

tiveness than methotrexate or provide relief for more patients than methotrexate currently provides.

AJMC: What kinds of issues would you like to see addressed in future clinical trials of anti-tumor necrosis factor (TNF) agents?

Dr. Lipsky: A number of issues have not yet been explored in detail. First, most of the current trials have been carried out in patients who have longstanding disease and who have failed most of the current disease-modifying anti-rheumatic drugs. I think it is very important to know whether the TNF-blocking agents would be effective in early disease, because patients with early disease have many fewer abnormalities in their joints and may be prevented from developing them with effective therapy.

The second issue relates to whether these agents can actually prevent damage to bone and joints. So far, we have no data with regard to radiographic evaluation of patients. We know these agents are effective as potent relievers of symptoms. It is very important to know whether they also can alter the course of the disease as measured by the impact on bone erosions.

We also need to learn the best way to administer these agents. There are questions about optimal dosing and frequency of administration. With regard to the infliximab, we don't yet know what the minimal effective dose is. With regard to etanercept, we don't know what the maximal effective dose is. We also don't know whether concomitant therapy will make these agents more effective or will make them effective at lower doses.

The final issue, which will be addressed in all the trials, is the potential for long-term toxicity. We don't have sufficient experience to know whether any side effects will occur as a result of long-term administration of these agents.

AJMC: Infliximab was approved by the Food and Drug Administration in August 1998 for treatment of Crohn's disease. What is its status with regard to approval for rheumatoid arthritis?

Dr. Lipsky: The phase III trial [ATTRACT (Anti-TNF Trial in Rheumatoid Arthritis with Concomitant Therapy)] has been completed—

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that's a 6-month trial of 428 patients who received concomitant methotrexate. In that trial, the efficacy and safety data were very impressive. To my knowledge, that information was presented to the FDA, which is currently going through the data and deciding whether infliximab should be licensed for use in rheumatoid arthritis.

AJMC: How is the mechanism of action of anti-TNF agents in rheumatoid arthritis different from that of traditional disease-modifying anti-rheumatic drugs?

Dr. Lipsky: Traditional disease-modifying anti-rheumatic drugs usually have had a broad spectrum of actions on a number of cellular processes. Frequently, as is the case with methotrexate, we know that these agents have anti-inflammatory and immunosuppressive activities, but we don't know precisely how they actually work—what specific step in the pathway of inflammation they block. As a result, it has been difficult to optimize their use. Questions, such

as what the appropriate cotherapies would be and whether biochemical or pharmacologic endpoints have been achieved, have been hard to answer. This is because these drugs really were employed as a result of empiric observations and not from mechanism-based studies.

The TNF-blocking agents are the first group of highly specific agents that target one specific step in the pathway of inflammation—namely, the step that is mediated by TNF. Therefore, these are our first highly targeted therapies. We deduced their activities from laboratory experiments, and they have now been proven to be effective in clinical trials.

I anticipate we will have more of these highly specific, highly targeted therapies in the future, but these drugs represent the first step in that direction.

AJMC: Under what circumstances might use of anti-TNF agents be cost effective?

Dr. Lipsky: The question has to do with how one evaluates the cost of rheumatoid arthritis. If one looks at the broad picture and recognizes that this is a chronic disease in which loss of work and disability are predicted outcomes and that therapies like the TNF-blocking agents may be able to prevent or delay those outcomes, while improving the quality of life, they become very cost-effective agents.

I think that understanding the potential cost effectiveness of TNF-blocking agents requires altering one's mindset in terms of expectations about rheumatoid arthritis therapy. In the past, we considered all therapies to be modestly effective, but the outcome inevitable. Now we can think of these new agents as extremely effective in blocking signs and symptoms in some patients. We might know in the near future whether they also block the progression to disability.

We can anticipate that patients treated with these agents will be able to maintain their activities of daily living and maintain their occupations. That has an enormous impact on the indirect cost of a chronic disease like rheumatoid arthritis. It is important to think about agents like these not only in terms of the direct costs of the drug, but also in terms of the direct and indirect costs of rheumatoid arthritis to the patient, the patient's family, and the society.

AJMC: Can anti-TNF agents be used alone, or must they be combined with methotrexate to suppress their immunogenicity?

Dr. Lipsky: That's a question that we need to examine in great detail. We have seen that these agents are effective when used alone, but the trials have been relatively short term. We also have seen that they can be used safely with methotrexate. At least with regard to infliximab, concomitant administration with methotrexate appears to decrease the likelihood of developing resistance to these therapies.

However, to date, the use of TNF-blocking agents alone has not been directly compared with their use in combination with methotrexate. That's an important issue to assess quickly. We need to find out whether we can utilize these drugs over a prolonged period with or without methotrexate and what would be the best way to preserve the effectiveness of these highly potent agents.

AJMC: Is there any evidence that anti-TNF agents can induce remission in rheumatoid arthritis patients?

Dr. Lipsky: The studies are really too short term to evaluate that issue completely. A number of patients certainly have profound responses to this therapeutic approach. Whether that is actually remission—meaning not only

that the disease is quiescent, but also that the therapy can be stopped and the disease does not recur—is not currently known. What we do know is that these agents are very powerful means to suppress disease activity. Whether long-term administration—1 or perhaps 2 years—might actually induce remissions is another thing that needs to be studied in detail.

AJMC: What is the role of anti-TNF agents in combination therapy?

Dr. Lipsky: We know that these drugs can be administered safely with methotrexate and the impact is dramatic and prolonged. We don't know whether they can be administered safely with other disease-modifying antirheumatic drugs. That is something we need to determine in future studies.

AJMC: Is there any evidence that aggressive treatment of early

rheumatoid arthritis produces a better long-term outcome than treating patients with established disease?

Dr. Lipsky: That is our anticipation, but again, it needs to be tested, especially with these new powerful agents.

AJMC: What kind of research would be helpful regarding individual characteristics of rheumatoid arthritis patients?

Dr. Lipsky: At the moment, we know that the majority of patients respond to TNF-blocking agents, but not all of them do. We do not know yet the characteristics of an individual patient that determine whether he or she will respond to these agents. I think a critical issue is to examine both responders and nonresponders in molecular detail to try to understand which patients will respond and which ones won't.