

Clinical Opportunities of Anti-TNF Therapies in Rheumatoid Arthritis: An International Roundtable

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This Special Report supplement to *The American Journal of Managed Care* presents highlights of an international roundtable on anti-tumor necrosis factor (TNF) therapies for rheumatoid arthritis (RA) held in Lausanne, Switzerland, on February 19 and 20, 1999. During this meeting, participants from the United States and Europe discussed the emerging role of anti-TNF therapies, as well as issues related to methotrexate (MTX), the dominant drug in RA therapy; the present and future state of combination therapy; and the pharmacoeconomics of the new therapies.

Rheumatoid arthritis is a chronic autoimmune disorder that exacts a high toll in morbidity and mortality. It is characterized by hypertrophy and inflammation of the lining (synovium) of the joint, leading to joint destruction and instability and chronic pain. This disease affects about 2.5 million people in the United States (approximately 1% of the population) and is about 3 times more common in women than in men.¹ The most common age of onset is in the middle years of life, but it can also develop in children and the elderly. RA frequently results in work disability, functional disability, and joint replacement surgery. About 75% of affected

patients develop functional disability, and those with severe RA may die prematurely as a result of the disease.²

It is known that the proinflammatory cytokine TNF- α plays a critical pathogenic role in RA.³ The new anti-TNF agents are capable of binding to and neutralizing TNF, and their use has been associated with substantial improvement in disease. Etanercept was approved by the FDA in September 1998 for treatment of RA in patients who have failed to respond to other disease-modifying antirheumatic drugs.⁴ Infliximab was approved by the FDA in August 1998 for treatment of Crohn's disease; like RA, Crohn's disease is a chronic inflammatory disorder characterized by overproduction of TNF. This drug is now under FDA consideration for treatment of RA.⁵ Both of these agents have a rapid onset of action, and they have demonstrated efficacy in short-term trials. However, long-term data on effectiveness and safety are not yet available. Questions about dosing of anti-TNF agents, their use in combination therapy, and defining the appropriate target populations also remain to be answered.

Methotrexate has been used to treat RA patients for 20 years and has been studied more thoroughly in

clinical trials than any other agent for RA. To date, no drug has been shown to be more effective. For patients who have an inadequate response to single-drug therapy, combination therapy is widely used and has been shown to be effective. Determining the role that new anti-TNF therapies will have in treatment of RA is currently being studied.

Anti-TNF agents represent the first step in rational drug design for the treatment of rheumatoid arthritis. Their mechanism of action is well understood, having evolved logically from laboratory-based investigations of the pathogenesis of inflammation in the rheumatoid joint. In contrast, the mechanism of action of traditional agents such as MTX remains obscure. While other immune mechanisms and inflammatory molecules such as interleukin-1 may also contribute to the pathogenesis of RA, inflammatory processes that directly result from TNF can be expected to be inhibited by anti-TNF therapies. The challenge for rheumatologists is to define the most appropriate target population for treatment with TNF-blocking agents. For example, is anti-TNF therapy effective in the treatment of early RA? Is there an advantage to the use of anti-TNF therapy in combination with traditional disease-modifying antirheumatic drugs (DMARDs)? Can TNF blocking agents be used as a substitute for pulsed corticosteroids for the management of acute flare-ups of disease? Are anti-TNF therapies safe during pregnancy?

The fact that the new anti-TNF therapies are more expensive than existing therapies for RA may affect access in a managed care environment. However, RA is an expensive disease. Patients with RA not only utilize substantial medical resources, they also incur indirect costs in disability and lost wages

that are generally much greater than the direct costs. Because the cost of this disease is high, preventing its progression is likely to be cost saving. At the roundtable it was suggested that rheumatologists can advocate for those patients who they think are appropriate candidates for anti-TNF therapy by educating managed care and government decision makers about RA and its often complex treatment options and by developing evidence-based standards for the application of anti-TNF therapy.

Through the exchange of opinions and knowledge, participants in this international roundtable identified key issues and questions that will need to be answered as we move for-

ACRONYM LIST

The following acronyms appear within the pages of this Special Report supplement:

ACR	American College of Rheumatology
ATTRACT	Anti-TNF Trial in Rheumatoid Arthritis with Concomitant Therapy
COX	Cyclooxygenase
DMARDs	Disease-modifying antirheumatic drugs
FDA	Food and Drug Administration
GI	Gastrointestinal
MTX	Methotrexate
NSAIDs	Nonsteroidal anti-inflammatory drugs
OA	Osteoarthritis
QALY	Quality-adjusted life year
Q-TWIST	Quality-adjusted time without symptoms and toxicity
RA	Rheumatoid arthritis
SPERA	Standard Protocol to Evaluate Rheumatoid Arthritis
TNF	Tumor necrosis factor

ward into a new era in the treatment of rheumatoid arthritis.

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