



by ELIZABETH KUMRU

Gold Standard Care for what price?

Study compares top treatments for rheumatoid arthritis

The best treatment for the best price.

All patients want that, but when rheumatologists have a choice between two effective “gold standard” treatments, one costing 15 times more than the other, the options blur.

UNMC’s James O’Dell, M.D., and rheumatologists from around the world want to know which medication can provide the best care at the most economical price.

Dr. O’Dell, professor of internal medicine and chief of the rheumatology and immunology section, began pondering this question eight years ago.

It’s a question the pharmaceutical companies didn’t necessarily want answered.

But the answer could save millions of dollars every year for patients and the government.

Dr. O’Dell initially turned to the manufacturers for answers, but pharmaceutical companies have little incentive to compare one treatment to a less expensive therapy. Additionally, the Food and Drug Administration has never required these comparisons.

Frustrated, he designed a first-of-its-kind comprehensive \$13 million study that will enroll 600 patients from 35 clinics and medical centers in the United States and Canada. The study, funded by Veterans Affairs (VA) and the Canadian Institute of Health Research, began in July and is expected to take nearly three years to complete.

Most rheumatoid arthritis studies have an 80 percent concentration of women, but because many patients will be enrolled through the VA, the study will have equal numbers of men and women.

The study, which took four years to develop, is called RACAT (pronounced rocket), an acronym for “Rheumatoid Arthritis: Comparison of Active Therapies.”

The random, double-blind study compares two therapies:

- + **A combination of methotrexate, hydroxychloroquine and sulfasalazine, which costs patients approximately \$1,000 a year, to**
- + **A combination of methotrexate and etanercept which costs patients approximately \$15,000 a year.**

THE DRUGS

Methotrexate, an immune suppression drug, has gained popularity among doctors as an initial disease modifying anti-rheumatic drug (DMARD) because of its effectiveness and relatively infrequent side effects.

Hydroxychloroquine, an anti-malarial drug, is considered a DMARD because it can decrease the pain and swelling of arthritis as well as possibly prevent joint damage and reduce the risk of long-term disability.

Sulfasalazine, an oral medication traditionally used to treat inflammatory bowel diseases, is used to treat rheumatoid arthritis in combination with anti-inflammatory medications.

Etanercept is a biologic medication that binds a protein in the circulation and in the joints that causes inflammation before it can act on its natural receptor to “switch on” inflammation. This effectively blocks the tumor necrosis factor inflammation messenger from calling out to the cells of inflammation.

Patients in the study will take one combination of drugs for 24 weeks. If, after that time, there is no improvement, they will be switched to the other combination for 24 weeks.

Taking the study a step further, Dr. O’Dell also will determine what role genetics play in the different treatments, or who responds better to which drug combination.

“We’ll look for genetic factors and biomarkers that predict disease progression and success or toxicity of the different strategies,” Dr. O’Dell said.

“Early treatment is the key to successfully managing this disease,” he said. “Our hope is that one day doctors will be able to prescribe the most effective treatment for their patients based on genetics. That will eliminate a lot of experimenting.”

More than 660 million people in the world, including 2 million in the United States, suffer from rheumatoid arthritis. The autoimmune disease causes chronic inflammation of the joints and other areas of the body, and affects people of all ages. Researchers have not been able to determine a cause or a cure for the disease, but treatments are available, with a goal of remission or near remission.

Methotrexate alone is an excellent, economical first-line therapy for a significant percentage of rheumatoid arthritis patients, Dr. O’Dell said. However, combination therapy is recommended for those patients who continue to have disease flares, which can result in permanent joint destruction.

In a 1996 study, Dr. O’Dell proved that triple therapy, a combination of three drugs – methotrexate, sulfasalazine and hydroxychloroquine – was 50 percent more effective in treating rheumatoid arthritis than methotrexate alone or the combination of sulfasalazine and hydroxychloroquine.

That study was conducted through the Rheumatoid Arthritis Investigational Network (RAIN), a group of rheumatologists and nurse-study coordinators in several states across the country. Dr. O’Dell founded RAIN in 1989; its home base is at UNMC.

The group established a serum, plasma, urine and blood bank for investigational purposes. Dr. O’Dell’s original observations of genetic predictors were the first of their kind and have altered the way patients are treated. The current study brings together an impressive coalition of public and private health centers across two



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University of California-San Francisco

countries. In addition to the 10 sites in the RAIN network, Dr. O'Dell recruited 15 Veterans Affairs Medical Centers and 10 Canadian Rheumatology Research Consortium (CRRC) sites.

One of those sites, the San Francisco VA Medical Center, is slated to enroll 20 patients, said David Daikh, M.D., Ph.D.,

chief of rheumatology at the VA center, and associate professor of medicine at the University of California-San Francisco.

“This is an exciting, groundbreaking study that will answer important questions about the effective and economical treatments for patients with rheumatoid arthritis. As we gain more understanding

about the disease and more therapies are developed, we can begin to turn our attention to the next big frontier of targeting therapeutics. That's where the genetic data will be helpful,” he said.

The VA and CRRC now spend more than \$50 million every year on these expensive therapies and are very interested in the results of this study, Dr. O'Dell said.

“I think clinicians around the world will use this information to make better judgments for their patients who have rheumatoid arthritis,” he said. 📺

Rheumatoid arthritis registry fills important niche by CHUCK BROWN

A registry created by Nebraska researchers and containing information about military veterans with rheumatoid arthritis may offer important insights into male rheumatoid arthritis sufferers.

“The veterans registry allows researchers to examine specific medical and biological information about hundreds of male rheumatoid arthritis sufferers to see what genetic and environmental factors may have played a role in the patients' disease,” said Ted Mikuls, M.D., an associate professor of rheumatology at UNMC who oversees the registry.

Rheumatoid arthritis often affects women between 20 and 50 years of age. Men are usually affected later in life.

“While fewer males may suffer from rheumatoid arthritis, they still compose a significant portion of the population with the disease,” said Dr. Mikuls, who also serves as a rheumatologist with the VA Nebraska-Western Iowa Health Care System. “Because the veteran population is so overwhelmingly male, we are in a special position to gather information about men suffering from the disease.”

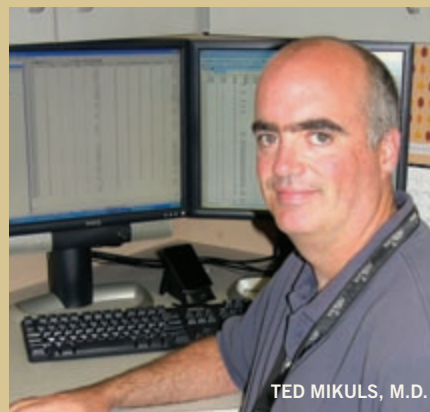
Males account for more than 90 percent of the roughly 900 veterans with information in the Veterans Affairs Rheumatoid Arthritis registry (VARA) – making it perhaps the nation's top source of information about male rheumatoid arthritis sufferers, Dr. Mikuls said.

Dr. Mikuls and Amy Canella, M.D., an assistant professor of rheumatology at UNMC who also works at the Omaha VA, started VARA in 2002.

VA medical centers in Omaha, Denver, Dallas, Washington, D.C., and Salt Lake City contribute information to the database. More centers are expected to join the registry.

Leading rheumatoid arthritis scientists from around the nation, including Peter Gregersen, M.D., of The Feinstein Institute for Medical Research in Manhasset, N.Y., and James O'Dell, M.D., chief of UNMC's rheumatology and immunology section, have expressed interest in the data collected in VARA.

“You don't usually find such a well-defined cohort,” said Dr. Gregersen, who has led the world's largest effort to identify the genes involved in rheumatoid arthritis.



Dr. Gregersen has mined hundreds of millions of genotypes from VARA that he plans to use in his research.

Being able to look at such a specified group of rheumatoid arthritis sufferers may offer insight into how genetic and environmental factors play into the cause of rheumatoid arthritis, he said.

VARA is a truly unique and powerful resource thanks to the combination of a well defined clinical cohort with radiographic data, serological studies, DNA information and banked biological material, Dr. O'Dell said.

“VARA is certain to teach us much about rheumatoid arthritis for years to come,” he said.