THE
Arthritis Research
NEWSLETTER
SUMMER 2000

On The Way – A New Biologic Agent, Kineret

FDA Weighs IL-1ra Application

The Food and Drug Administration (FDA) is expected to make a decision later this year on the newest biologic agent, IL-1ra. This product from the well-known biologic company, AMGEN, reduces inflammation in Rheumatoid Arthritis and similar illnesses.

In the body, cells communicate with each other by chemicals that are called cytokines. One of the most important of these cytokines is a molecule called IL-1. The term IL-1 refers to a communicating substance between white blood cells that is called 'interleukin-1.' No one calls it that, though. Instead it is referred to as IL-1. There are many interleukins, and each one has its own number (e.g., IL-12).

IL-1 has a number of functions, but one of the most important is to aid in the production of inflammation. In arthritis, inflammation means joint swelling, pain, and joint damage. IL-1 works by attaching itself to certain body cells in places called receptors. Only cells that have receptors for IL-1 can be activated by IL-1 to cause inflammation. One of the ways the body controls inflammation caused by IL-1 is through another molecule called IL-1 receptor antagonist or IL-1ra. The IL-1ra molecule binds to the IL-1 receptor, thus blocking it. Then IL-1 can't bind to the receptor. When this happens inflammation is reduced.

AMGEN is now producing IL-1ra (or IL-1 receptor antagonist). They call it Kineret."

Data about Kineret were presented at the 1999 American College of Rheumatology (ACR) meeting. In a controlled rheumatoid arthritis trial of 419 patients, Kineret combined with methotrexate showed that 42 percent of the Kineret/methotrexate patients achieved useful clinical benefit compared to 23 percent of patients receiving methotrexate alone. Kineret is given by a daily injection, much as insulin is given.

But one of the most important findings from the Kineret research is that Kineret appeared to substantially retard X-ray damage. What that means is that structural damage or damage to the bones and joints was reduced in persons receiving this treatment. Kineret has not yet been approved by the FDA, but if and when it is approved it may turn out to be another important drug in the treatment of RA.

WIN $1000

Return your research questionnaire within two weeks of receiving it and be eligible for one of three $1,000 awards. The research data bank can best contribute to research when the mailed questions are completed and returned as soon as possible. All persons who complete the questionnaire within a two-week period will be eligible for the award – given as a token of our gratitude in help with arthritis research. See back page for past winners.

Time is running out!

Getting Drugs Approved: The U.S. Food and Drug Administration

When congress established the FDA, it charged it with establishing that drugs are safe and effective. When a pharmaceutical company thinks it has a new drug that may be useful for treating an illness, the company first goes to the FDA. Together they design the studies that will establish safety and effectiveness. When the studies are completed, the company submits the data to the FDA for review and decision.

In making its decision, the FDA also seeks the opinion of its advisory committees. These are committees of doctors, other experts, and the public – even persons with arthritis are included.

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They are not usually part of the government and they are not employed by the drug companies. This way they are able to give an honest and fair opinion. The committee weighs the data, and then makes recommendations to the FDA. The FDA doesn't have to accept the recommendations of the committee, but they usually do. Recently Dr. Wolfe, National Data Bank director, appeared before the FDA as an expert witness regarding x-ray damage in RA. If you are interested in how the FDA works, you can get additional information on their web site (www.fda.gov).

Research Results from the National Data Bank

This year the National Data Bank (NDB) submitted many research results to the American College of Rheumatology annual meeting that will be held in Philadelphia in November. NDB research results were highly rated by the ACR review committee and will form important presentation at the annual meeting. Our research, of course, comes from the information that you provided. Here are some of the results

Infection is an important issue in arthritis, so we want to present some of the results in detail below. But other important studies that we will be presenting concern stomach ulcers and the new anti-inflammatory drugs, what makes people respond to one treatment and not the other, and a fascinating issue – whether arthritis is better according to season. More about these studies next time. But first we want to tell you about infection and arthritis.

Infection

One of the concerns that we have all had is about the safety of drugs, and particularly whether they weaken the immune system and allow infections – sometimes serious infection – to occur. This is a difficult issue because people with RA already have less responsive immune systems and are more likely to get infections. Also, if you have RA and you receive treatments, the persons receiving the most immune altering treatments are usually those who have the most active RA, and are those who are at the greatest risk for infection.

Another problem concerning serious infections is that they do not occur very frequently and when we see an infection it might not be due to RA or to treatment, but just to chance alone. So how do we figure this all out?

First, we can compare persons who have RA with those who have other illnesses such as osteoarthritis (OA) or fibromyalgia. If infection occurs more frequently in RA than the other groups we can know that it is either RA or its treatment that causes the infection.

We found that the risk of infection was increased in Rheumatoid Arthritis.

Here is what we will be reporting at the fall ACR meeting. During 1998 and 1999 we received replies from 9,756 persons with RA and 2,729 with OA. Those who replied were being treated by 631 US rheumatologists from all over the US. We found that the risk of infection was increased in RA. Compared to those with OA, the risks were increased as follows: 2.4 times for lung infections, 2.6 times for blood infection, 5.7 times for skin infections, 1.9 times for joint infections, and 1.2 times for kidney infections. Before this research became available rheumatologists thought that infection might be increased but they had no idea of the magnitude of the increase. By having so many of you answer these questions we were able to accurately describe what happens in RA and OA.

But what causes infection?

To be sure we were examining serious infections, we turned to data about hospitalizations that were related to infection. The major risk factors were functional disability and prednisone use. We found several consistent results regardless of whether we were reviewing lung, skin or blood infections. Functional difficulty, which is a measure of severity of illness, and prednisone use were related to infection, but treatment with drugs such as methotrexate or the newer biologic agents were not associated with increased risk of infection. Interestingly, we were able to extend these results to shingles (Herpes Zoster), too.

We can be sure about methotrexate and the risk of infection because methotrexate has been used for many years, but the data on Remicade and Enbrel are less certain because not as many people are taking these drugs. Which leads us into the issue of infection and the newer drugs such as Enbrel, Remicade, and Kineret. After we receive the results from the questionnaire that is being mailed with this newsletter we may be able to provide definitive, accurate information about the safety of these new treatments.

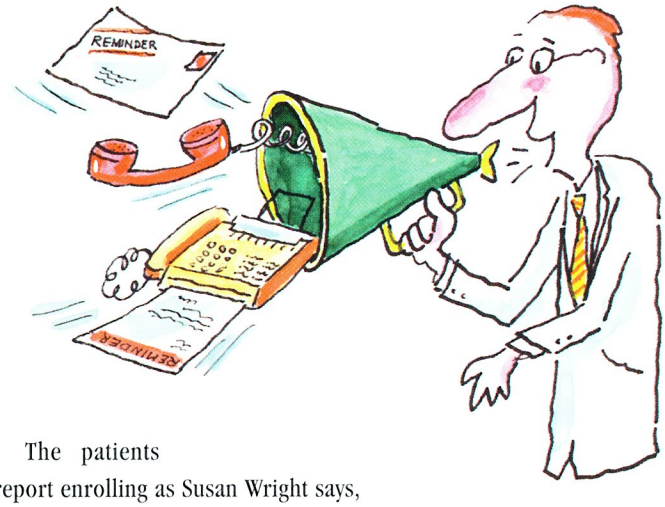
What is a long-term arthritis study? Longer than you think!

We are often asked, "How long does this study last?" or "How long does this go on?" To answer this question, we asked some of our real "heroes."

> In 1983 she was diagnosed with cancer and given methotrexate. "After one month, joints moved that hadn't moved for years."

In 1980 when there was no Arthritis Research Center or National Data Bank, a study was begun to judge the effects of auranofin, an oral gold compound. Almost 400 patients with rheumatoid arthritis were enrolled and asked to complete a questionnaire each 6 months. 86 of these patients are not only still completing questionnaires, but remarkably, have completed every questionnaire. An additional group are still in the study but have missed an occasional reporting period. Since this study started, thousands of other patients have joined the research efforts by agreeing to complete questionnaires. Over 1,000 of these patients have been completing questionnaires for 10 years or more. These efforts result in volumes of new information each time that a group of questionnaires is analyzed.

An informal poll of these 86 outstanding people reveals a synopsis of the progress of arthritis research in the past 20 years. The patients now range in age from 40's to 90's and were diagnosed with rheumatoid arthritis at least 20 years ago.



The patients report enrolling as Susan Wright says, "back when Dr Wolfe still had reddish hair." The usual treatments at that time were aspirin, which frequently caused ringing in the ears, and hot wax baths, which were "messy" and didn't always work very well. Those who had been diagnosed previously, some as early as the 1940's, uniformly report their choices of treatment were very limited. Ruth Hyde reports being in a trial of gold injections in the 1940's. Blanche Craft reports using aspirin because gold was to be used "only as a last resort" and recalls attending a seminar in the 1970s when a participant asked Dr Wolfe about a new medicine, Ascriptin, and he replied he'd seen good results. Drugs such as Motrin and Naprosyn were subjects of drug trials in the 1970's and 80's.

Many of the participants have been in drug trials with varying degrees of success; and most report trying a variety of drugs in a search to find something helpful. For a majority, that search reached a milestone when they discovered methotrexate.

Methotrexate had been used as a chemo-therapeutic agent for cancer, and as Doris Sundberg says, "we were really scared of it."

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Long-term participants key to successful research

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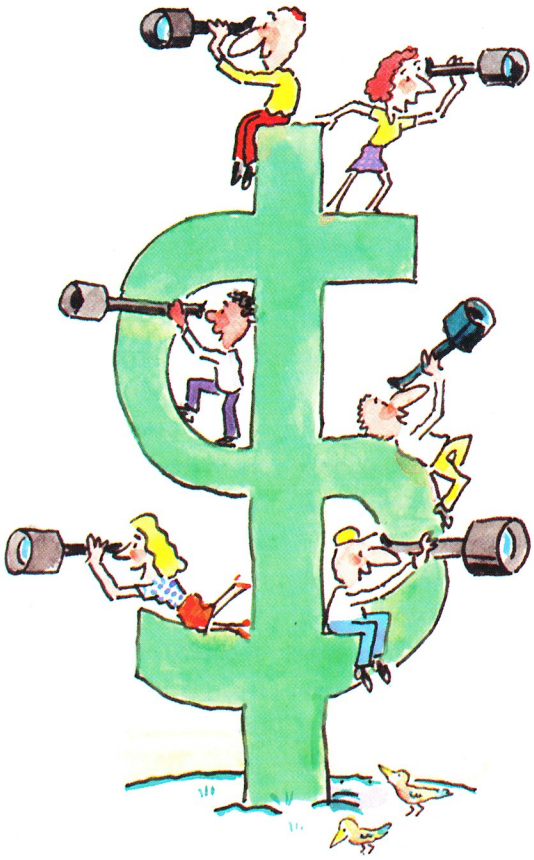
Dwight Pierce reports his surgeon had said, "it's used for cancer, but give it a try." Ruth Ann Stites had no problem with that part. In 1983 she was diagnosed with cancer and given methotrexate. She was told it might affect her arthritis and she says, "after one month, joints moved that hadn't moved for years."

Most of these participants are successful enough with their current treatments that they have not tried any of the new group of drugs now on the market, but appreciate knowing they are available should their treatments become inadequate. They do, however, tend to agree on the benefits of education and exercise, with it's associated muscle strengthening and weight control. Phyllis Wise reports that when she was diagnosed 20 years ago, she went to the library and found one book containing a single one-page reference to rheumatoid arthritis. Since then educational materials have proliferated.

But have the questionnaires done any good? In the years since the beginning of the research projects, Dr Wolfe and colleagues have used information from them to write hundreds of articles and reports read by physicians around the world. They were among the first to advise doctors that arthritis medications could lead to stomach irritations. In the middle 1980's, they published articles on the effectiveness of gold, predicting disability, and the usefulnessof the HAQ (a part of the questionnaire) in a clinical setting.

Beginning in 1988, they published articles on the effectiveness of methotrexate, and its usefulness regardless of disease severity. In the 1990's, they wrote articles on smoking and arthritis, the benefits of early intervention with disease modifying drugs, and the use of methotrexate to decrease the chances of getting leukemia or lymphoma. Just last week these data were reviewed at the FDA meeting in the assessment of new arthritis treatments.



These 86 long-term participants feel good about their contribution and plan to continue. Several participants echoed the comment made by Nancy Johnson, whose mother was very crippled with the disease. "If it helps me, wonderful; but if it helps my child, or my grandchild, or any stranger, it's worth it"

Others contributing to this article include Madge Biggs, Nelda Coleman, Jerry Cowell, Freeda Gable, Valerhy Harmon, Luetta Havlik, Cecelia Huddleston, Don Jones, Rose Jost, Pauline Michael, Elaine Nix, Arlon Postlewaite, Margaret Smith, Rex Sumpter, Wilma Schuster, Frances Siemens, Karen Street, Loretta Ward, Milford Weaver, Betty Lucas and three others who prefer to remain anonymous. Bravo!

THREE $1,000 AWARDS TO ARTHRITIS RESEARCH PARTICIPANTS

WHO WON?

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