THE
Arthritis Research
WINTER 1999
NEWSLETTER

The New Drugs Arrive–how good are they?

Celebrex – Fewer Stomach Problems

Antiinflammatory drugs can be very helpful. They reduce pain and swelling, aches and pains, cramps and fever. The list of this type of drug includes aspirin, Naprosyn, Aleve, Motrin, Ibuprofen, Daypro, Relafen and many more. The official name for these drugs is *non-steroidal antiinflammatory drugs* or *NSAIDs*, for short. They are called 'non-steroidal' because they don't contain steroids – that is they don't contain cortisone or prednisone. As good as they are, NSAIDs can cause problems. They can cause important stomach distress, including ulcers, stomach pain, and stomach bleeding, and many people simply can't take these drugs because of such side effects.

Why does this happen?

NSAIDs work by interfering with an enzyme called COX that helps produce inflammation. In recent years it was discovered that cyclooxygenase or 'COX' exists in two distinct forms – COX-1 and COX-2. Both forms reduce inflammation, but COX-1 inhibition causes stomach problems by interfering with natural protective effects in the stomach. COX-1 inhibition also can lead to kidney problems and bleeding problems. COX-2 inhibition leads to none of these problems, yet it still relieves inflammation. All of the NSAIDs currently available are COX-1 drugs, but in February the first COX-2 drug will be released. This drug, developed by Searle laboratories, is called Celebrex™ (celecoxib). By the time you read this Celebrex may already be available in the pharmacies. Later this year another COX-2 inhibitor called Vioxx, and made by Merck, Inc. should gain Food and Drug Administration (FDA) approval.

How good is Celebrex?

If you have had ulcers or stomach problems in the past that made it difficult for you to use NSAIDs or if you are older and therefore at higher risk for stomach problems, then Celebrex may be just the medication for you if you need an antiinflammatory drug. Others who may benefit from using a COX-2 drug rather than a usual NSAID are those with kidney problems or those taking blood thinners. Still, remember this: Celebrex is no stronger than any of the older COX-1 NSAIDs and it costs more than over the counter medications like Aleve or ibuprofen. But if you are looking for a safer medication this may be it. Celebrex is approved for osteoarthritis (OA) and rheumatoid arthritis (RA). It is also likely to be effective for other pain conditions.

DMARDS

These are drugs that reduce or halt the damage caused by rheumatoid arthritis. Unlike NSAIDs that reduce arthritis symptoms almost as soon as you take them, DMARDS usually take a number of months to work. When they start to work they reduce or stop the underlying activity of the arthritis. This reduces pain and swelling, improves function, and reduces or stops damage to joints and cartilage. When DMARDS work, they are much more powerful than NSAIDs. A good analogy to use in comparing NSAIDs and DMARDs is that DMARDs are like sun screens that prevent sunburn but NSAIDs are like sunburn lotions you apply after you have the sunburn. The last months of 1998 saw the release of two new DMARDS that should be of great help to people with RA. The first is called ARAVA™ (leflunomide) and the second is Enbrel™ (entanercept).

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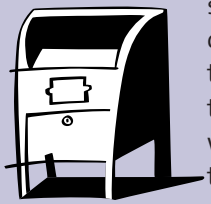
Win $1000

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 weeks period will be eligible for the award – given as a token of our gratitude in help with arthritis research.

Time is running out!



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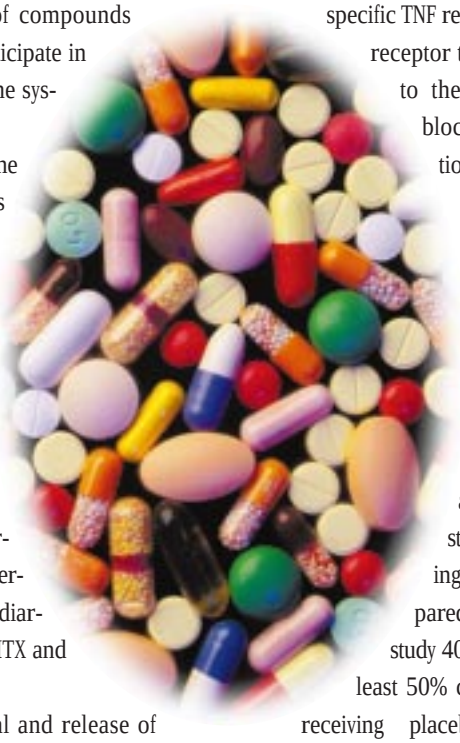
ARAVA

Overall, studies done before the general release of ARAVA have shown it to be equal to methotrexate (MTX) and sulfasalazine (SSZ). As an effective DMARD, it improves pain swelling and function, and reduces x-ray damage. Unlike other DMARDs, ARAVA begins to work about one month after it is first started, and reaches its maximum benefit after about three months. ARAVA appears to work by inhibiting the formation of compounds called pyrimidines that participate in the regulation of the immune system.

ARAVA is easy to take and most people taking it had few side effects.

ARAVA is easy to take: one pill a day. Most persons receiving ARAVA had few side effects in the studies done before it was approved by FDA. The common side effect (about 3%) was abnormal liver tests (or in medical talk, elevation of liver function tests (LFT)). The most common side effect to ARAVA was diarrhea. Overall, it occurred in about 17% of persons who received ARAVA. By comparison, diarrhea occurred in about 15% of those on MTX and 12% of those receiving placebo.



Studies that come before the approval and release of drugs establish that they are safe and effective over a short period of use. But such studies leave unanswered questions. For example, can ARAVA be combined with other DMARDS to increase its overall effectiveness? Will long term side effects occur that were not evident in the pre-release studies? Will the effect of the drug increase or lessen over time? Will the effectiveness or the side effect rate of ARAVA be altered in older or younger people or in those taking other arthritis drugs. Questions like these can be answered by the National Data Bank surveys that you participate in. In fact, the NDB is about the only way we will really understand the place of drugs like ARAVA since most non-data bank studies will not have enough people taking ARAVA to answers questions accurately.

Make way for Enbrel

Enbrel is a DMARD like none before. It is a protein made from tumor necrosis factor (TNF) receptor and human immunoglobulin. Wow! Let's explain this a bit. An immunoglobulin is a protein that participates in immune antibody response. Tumor necrosis factor (TNF) is a cytokine made by the body. A cytokine is something made in cells that allows different cells to communicate with each other. There are many types of cytokines. TNF is involved in normal inflammatory and immune functions within the body, and plays an important part in the inflammation of rheumatoid arthritis. In fact, elevated levels of TNF are found in the joints fluid of persons with RA. For inflammation to develop TNF must bind to certain places on cells called receptors. In fact, TNF binds to a specific TNF receptor. Enbrel works by binding to the TNF receptor thereby preventing real TNF from binding to the TNF receptor. If the receptor site is blocked then TNF cannot produce inflammation. Less inflammation, far less arthritis!

Does it work?

In studies performed before the FDA approval, persons who received Enbrel had less swelling and pain, better function and improvement in their sedimentation rates (ESR) and C-reactive protein (CRP) tests. The ESR and CRP are measures of the amount of inflammation in the body. In one study, after six months 59% of persons receiving Enbrel improved by 20% or more compared to 11% not receiving Enbrel. In the same study 40% of those receiving Enbrel improved by at least 50% compared to 5% receiving placebo, and 15% improved by 70%. Will it work better in real life compared to studies? Maybe, see the discussion below.

Use, side effects

Enbrel is given by injection twice a week. It is not necessary to have a physician or nurse give the injection because Enbrel is designed for you to give your own injection. Enbrel begins working one to two weeks after starting treatment, and the maximum response is seen within two months. In the pre-release studies the only side effect that was more common in persons receiving Enbrel compared to those receiving placebo was mild redness, itching or pain at the injection site.

Questions?

Contact our Research Director, Nancy Flowers by email at research@arthritis-research.org or try our web site. You can find us at www.arthritis-research.org. Postal inquiries should go to National Data Bank For Rheumatic Disease
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A National Research Data Bank Begins

There are two kinds of studies. The randomized controlled trial (RCT) is the major method by which scientists answer questions regarding treatment effectiveness. In the RCT, persons who agree to participate in the trial are assigned by random chance to receive one treatment or the other. When neither the investigator (usually a doctor) nor the persons receiving the treatment know which treatment they are receiving, the trial is called a double-blind RCT. Most scientific trials are double blinded. The RCT is a powerful tool for answering some treatment questions. All of the arthritis drugs that have reached the market have done so via the RCT. That includes Celebrex, ARAVA and Enbrel discussed in this newsletter.

Dr. Frederick Wolfe began collecting data on arthritis in 1974.

But there are a number of problems with the use of RCTs. The first problem is that RCTs don't last long enough. The reason for this is that it is usually not possible to keep people receiving experimental treatments for a long time, particularly when the treatments may not be working well. Because of the problem of short term trials, many good results seen in RCTs have turned out to be quite poor in the long run. In addition, RCTs exclude people with mild arthritis or too severe arthritis, those who are too young and too old, those with other complicating medical conditions or on certain non-arthritis medications.

The other source is the longitudinal data bank. Data bank studies can answer questions about treatment effectiveness and long term side effects that cannot be answered with RCTs. And they can answer other questions. In longitudinal data bank studies, persons with arthritis are studied over and over again, often by questionnaire, for many years or even decades. Data bank studies can answer questions about quality of life, ability to function and work, stress, best tests, predicting outcomes and more. Which brings us to the National Data Bank.

The National Data Bank

The roots of the NDB begin in 1974 when Dr. Frederick Wolfe began collecting computerized data on patients with arthritis. Dr. Wolfe was the first person to collect arthritis information in the clinic with the use of a computer. Personal computers had not yet been invented. Dr. Wolfe developed and wrote the first computer programs specifically designed for arthritis. By the end of the decade Wolfe had joined with the American Rheumatism Association Medical Information System (ARAMIS) as part of a nation-wide effort to collect arthritis data. By the mid 1980s 4 centers were involved actively in this program: Stanford University, The University of Saskatchewan in Canada, Vanderbilt University and the Arthritis Center in Wichita. The Wichita group led by Wolfe and Dr. Theodore Pincus at Vanderbilt were unique in that they collected data in the clinic as well as using mailed questionnaires.

Doctors all over the United States will be involved in the Data Bank.

Drs. Wolfe and Pincus saw important defects in the data collection process. There were too few doctors and too few patients involved. With too few doctors the research results would not be truly national, and they might reflect the practice style of a few people.

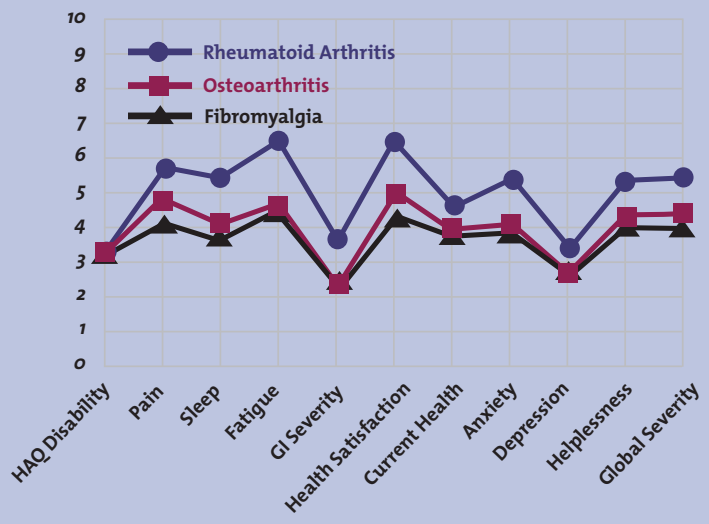
In 1998, Dr. Wolfe founded the National Data Bank. He wrote to rheumatologists all over the United States asking them to ask their patients to participate. By the summer of 1998 over 12,000 persons had completed enrollment forms. Beginning in the fall, the NDB began enrolling arthritis practices in the data bank. In this method, the NDB and the clinic doctors wrote to all persons seen in their clinics and asked them if they would participate in the research data bank. By the Spring of this year we hope to have over 10,000 persons with rheumatoid arthritis and 10,000 with osteoarthritis in the data bank. We will also be following people with fibromyalgia.

A full list of all participating rheumatologists is available on the NDB web site.

The Wichita-based staff of the National Data Bank is dedicated to collecting arthritis information.

What is a data bank?

It is a computerized record of tests, treatments, results and individual facts about each person with arthritis. From these data it is possible to see the forces that produce the outcomes of arthritis: outcomes that include pain, joint damage and the ability to work and function. With such a data bank we can identify those factors that lead to better outcomes.



Severity scores for NDB participants for scales that measure problems with function, pain, fatigue, stomach problems, satisfaction with health, anxiety, depression, helplessness and overall severity. Zero is best and 10 is worst. Those with fibromyalgia report more severe symptoms.

For a data bank to work the data must be absolutely confidential. We make sure that only the research staff can see your identifying data. They look at the questionnaire to see if it is complete and to make sure that your name and address are correct for mailing. Once your information is in our research data bank your name is removed for research purposes. That is, any researcher using the data bank for medical research cannot identify you. Your name and medical information will not be available to any one else. We do not give away names or sell them, or make them available to anyone else. We have been collecting arthritis data for more than 25 years, and during that time no outside person has ever had access to anyone's name. No one ever will.

Using and sharing the data.

The purpose of the data bank is to do research about arthritis that will improve the lives of persons with arthritis. To do this we share the data with other researchers outside of the NDB staff. As we indicated above, all identifiers are removed when we do this. Just as an example, we shared data with researchers in England to explore the possible relationship between arthritis and cancer, and we shared NDB data among researchers in the US, United Kingdom, Switzerland and the Netherlands in an effort to develop better methods to measure function. The three major experts in x-rays in RA in the US and Europe have all cooperated in x-ray studies with us using data bank data, and major experts in OA x-rays have also used our data. The best way to improve research is to share data. That is one of the major goals of the National Data Bank.

Questions about the data bank? Call us, send email or see our web site.

You can always call us for questions about the NBD research (1-800-323-5871). Our email address is research@arthritis-research.org. A really good way to find out information about the NDB is to look at our web site. You can find us at www.arthritis-research.org . The web site has information that may be of interest to you. There are the frequently asked questions (FAQs) with the answers, and list of the research publications from our data bank research. Some of the forms that we use in research questionnaires will be posted there for doctors to use and for you to see. There will even be actual research papers and results of presentations of data bank research that were made at national and international meetings. Try it out, and let us know if you want anything else placed on the web site.

Current activities: Important results from current data bank research

At the annual meeting of the American College of rheumatology, Dr. Wolfe presented results from the analysis of 25 years of data bank research in two separate plenary presentations. In the first, data bank research showed that methotrexate (MTX) was associated with increased life expectancy. The second study showed that MTX did not cause lymphoma (a form of cancer). These two studies were important because the showed that MTX was safe and that the worries regarding possible long term side effects were unfounded. In fact, people receiving MTX did better than those who did not receive it. The full text of these reports is available on the NDB web site, www.arthritis-research.org .