THE
Arthritis Research
NEWSLETTER

January 2003

Notes From the Director - 2002 Research Highlights

Happy New Year! And thanks to all of you who help so much by completing the research questionnaires. 2002 was a busy and successful year at the National Data Bank (NDB). The following are highlights from the research produced from your data:

RA Treatment does more than relieve symptoms

The major publication of 2002 regarded the treatment of rheumatoid arthritis. The research came from the NDB and Dr. H. Choi at Harvard University. It was reported in the Lancet Medical Journal that methotrexate increased life expectancy among persons with RA who used that treatment. This important study – the very first to show that RA treatment can do more than just relieve symptoms – received national press coverage and international recognition.

The 2002 American College of Rheumatology (ACR) Scientific Meeting the Largest Ever

The NDB presented 16 research topics at the 2002 National American College of Rheumatology meeting that was reported as the highest attended scientific meeting in ACR history. In 2001, the NDB was recognized as presenting more research results than any other U.S. university or research group, and in 2002 we were recognized again with second highest number of presentations. Many of the 2001 and 2002 presentations have been accepted for publication in medical journals.

Research is presented in many ways at national research meetings and typically those topics selected for lecture presentations, or discussion, are considered more important than poster presentations. At the 2002 ACR meeting the NDB presented 12 posters, 2 discussions, and 3 lecture presentations. The primary areas of research presented included Safety, Economics, RA Treatment, Clinical Aspects and Health Services.

Direct Medical Costs of RA, and the Cost of Disability get Attention

The 2002 ACR annual meeting was the first time the NDB published research specifically aimed at understanding and measuring the costs associated with rheumatoid arthritis treatment, disease severity and work disability, and overall lifetime direct medical costs. All of these topics are getting attention from national press. Some questions that have not always been easy to answer include how disability is defined and measured, and how do changes in disease activity impact the economics of arthritis patients and the burden expected on social programs.

Toward a Definition and Method of Assessment of Treatment Failure and Treatment Effectiveness: the Case of Leflunomide Versus Methotrexate

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Abstract

Aims. Time to treatment discontinuation is an accepted method of assessing treatment effectiveness in the community, but is susceptible to channeling bias, secular and cohort effects. In addition, discontinuation does not consider the addition of new DMARDs to insufficient therapies. In this report we expand the definition of treatment failure to include discontinuation or addition of a second DMARD to 1) examine leflunomide versus methotrexate effectiveness in clinical practice, 2) obtain an estimate of overall clinical effectiveness, and 3) to identify factors associated with treatment successes and failure. In addition, we test the feasibility of performing a clinical trial using a longitudinal data bank.

Methods. Using the National Data Bank for Rheumatic Diseases (NDB) longitudinal data bank, 1,431 patients who had not received either leflunomide or methotrexate (MTX) were followed from 1998 through 2001. Patients were assessed at 6 month intervals for periods up to 36 months by mailed questionnaires concerning DMARD therapy and demographic and RA severity factors. Life table methods and Cox regression were used to assess treatment failure, defined as time to discontinuation or to the addition of a second DMARD.

Results. For 756 patients on leflunomide, the failure rate was 55.5 per 100-patient years (PY), and the median time to failure was 15 (95% C.I. 13, 17) months. For 675 patients on MTX the failure rate was 57.3 per 100 PY, and the median failure time was 14 (12, 18) months. These differences were not significant. Overall, the rate of discontinuation was 78.8% of the failure rate. Discontinuation was predicted by adverse effects HR (1.76 (95% C.I. 1.51, 2.04)) and by clinical status prior to start on DMARD. These results were not affected by specific DMARD treatment. Greater than 77% of treatment failures related to additional therapy resulted in starting anti-TNF treatment.

Conclusion. In an observational clinical trial using a contemporary longitudinal data bank, with time to treatment failure as the outcome, leflunomide and MTX had equal effectiveness as measured by time to treatment failure. Treatment failure rates were substantially greater than noted historically. Given the availability of many efficacious additional treatments, this increase in failure rate appears to reflect a greater propensity to discontinue and/or add therapy.

Demographic and severity variables. Table 1 describes the demographic, treatment, and clinical severity variables for the study participants. Although patients did not differ in age, sex or other demographic characteristics, patients beginning leflunomide had slightly more severe RA compared to those in MTX.

Variable	MTX (N=675) Mean (SD) or %	Leflunomide (N=756) Mean (SD) or %	t (chi-2)	P-value
Age (years)	59.87 (14.14)	58.96 (12.31)	1.203	0.196
Sex (% male)	20.59	21.43	(0.1500)	0.698
'White' (%)	90.22	91.53	(0.7434)	0.389
High school graduates (%)	87.70	89.95	(1.817)	0.178
College graduates (%)	24.33	26.23	(0.6745)	0.411
Total family income ($)	41,896 (27,714)	43,730 (28,284)	-1.236	0.217
Comorbidity (0-11)	2.20 (1.84)	2.16 (1.72)	0.1678	0.867
Disease duration (years)	12.21 (10.82)	13.28 (10.38)	-1.908	0.057
Prior Prednisone (%)	54.22	66.78	(32.06)	0.000
Number of previous DMARDs (%)			(29.89)	0.000
0	27.11	23.81		
1	49.48	43.92		
2	18.37	21.03		
3	4.89	7.94		
4	0.15	2.78		
5	0.00	0.53		
HAQ disability (0-3)	1.22 (0.71)	1.30 (0.68)	-2.328	0.020
Pain (0-10)	4.53 (2.79)	4.61 (2.66)	- 0523	0.601
Global severity (0-1)	3.99 (2.61)	3.90 (2.35)	0.681	0.496
Fatigue (0-10)	4.79 (3.03)	5.18 (2.80)	-2.544	0.011
Sleep disturbance (0-10)	4.06 (3.20)	4.06 (3.13)	0.004	0.997
Satisfaction with health (-2 to 2)	0.09 (1.27)	0.12 (1.19)	+0.569	0.570

The rate of treatment failure among RA patients receiving leflunomide or methotrexate. The survival curves and median time to treatment failure was similar for patients beginning on MTX and for those starting leflunomide (log rank test, Chi-sq=0.30, p=0.584). As shown in Table 2 and Figure 1a, the median time to treatment failure was 14 (95% CI 12, 18) months for MTX and 15 (95% CI 13, 17) months for leflunomide. The treatment failure rate was 57.3 and 55.5 per 100 patient-years for MTX and leflunomide, respectively. The survival curves were not significantly different after adjusting for the following major covariates of Table 1: age, sex, disease duration, total income, prednisone use, previous DMARDS, and pre-treatment values of HAQ and fatigue (log rank test, Chi-sq = 0, p = 1.000).

HERAPY (ROUP	PATIENTS	TIME AT RISK (PATIENT-YEARS)	FAILURE RATE PER 100 PATIENT-YEARS	25% [95% CI] (MONTHS)	50% [95% CI] (MONTHS)	75% [95% CI] (MONTHS)
Treatment failure: discontinuation or addition of DMARD						
TX	675	499.7	57.3	6 [4, 6]	14 [12,18]	-
eflunomide	756	749.3	55.5	6 [4, 6]	15 [13,17]	-
Sub-analyses						
Treatment discontinuation: discontinuation of DMARDs among all patients						
TX	675	559.8	33.2	9 [6, 12]	-	-
eflunomide	756	909.8	42.4	6 [5, 6]	22 [17, 28]	-
Treatment discontinuation sub-analysis: discontinuations of DMARD only						
TX	165	89.4	265	2 [1, 2]	4 [3, 6]	7 [6, 11]
eflunomide	317	592.8	173	2 [2, 3]	5 [4, 6]	10 [9, 11]
Treatment addition sub-analysis: addition of DMARD(s) only						
TX	114	62	184	2 [1, 2]	5 [3, 6]	10 [7, 12]
eflunomide	94	82	115	4 [2, 5]	10 [6, 12]	16 [13, 19]

DMARD	Treatment failure by DMARD addition (%)	Treatment failure by discontinuation (%)	All treatment failures (N)
MTX	40.9	59.1	100% (279)
Leflunomide	32.9	77.1	100% (411)

Tables 2 and 3 and Figures 1c and 1d provide additional insight into the discontinuation/addition process. As shown in Table 3, for patients who were treatment failures, more patients failed MTX than leflunomide by adding additional DMARD(s) (40.9% vs. 32.9%), but more discontinued leflunomide than MTX (77.1% vs. 59.1%). Additions were not only more frequent among MTX patients, but they also occurred much earlier (Figure 1c) (log rank test, Chi-sq=13.83, p=0.000). Conversely, treatment differences related to discontinuation (Figure 1d) were not statistically significant (log rank test, Chi-sq=3.25, p=0.072).

Why is the discontinuation/addition pattern for treatment failure different among leflunomide and MTX treated patients? As noted above, patients on leflunomide were more likely to be treatment failures because of discontinuation, and MTX patients because of the use of additional DMARD therapy. Table 4 shows that the major additions in therapy were with anti-TNF agents, and that MTX patients were more likely to add infliximab, but leflunomide patients were slightly more likely to add etanercept. Multinomial logistic regression using infliximab, etanercept and other treatments as dependent variables and age, sex, disease duration, education, income and ethnic origin as explanatory variables suggested a possible role of total family income per US$10,000 (Odds Ratio (OR) 1.11 (95% C.I. 0.989, 1.249)). In univariate analysis the income OR was 1.12 (95% C.I. 1.005, 1.246).

DMARD therapy	MTX (N=114) %	Leflunomide (N=94) %
Etanercept	21.1	44.7
Infliximab	56.1	38.3
Hydroxychloroquine	9.6	7.4
Sulfasalazine	8.8	6.4
Minocycline	2.6	4.3
Azathioprine	1.8	3.2
MTX	-	0.0
Leflunomide	0.9	-

Predicting treatment failure. To study treatment failure, we used demographic variables, treatment and severity variables obtained just prior to treatment start, and AE data occurring prior to treatment failure. In univariate analyses, AE was the strongest predictor of treatment failure (Table 5). Health satisfaction was the highest ranked clinical variable as a predictor of drug status, followed by global severity, fatigue and pain.

In a multivariate model of treatment failure (Table 6), only AE, comorbidity, pain, satisfaction with health and global severity were significant at a level of 0.1 or less. Addition of treatment group had no appreciable effect on regression hazard ratios. In addition, treatment effect was not significant when added to the model in Table 6 (H.R. 0.96 (95% C.I. 0.820, 1.119).

Variable	Hazard Ratio	S.E.	Z	p-value	95% C.I.	95% C.I.
Treatment Side effects (yes/no)	1.76	0.13	7.37	0.000	1.51	2.04
Global severity (0-10)	1.10	0.02	5.93	0.000	1.06	1.13
Health satisfaction (-2 to 2)	1.20	0.04	5.65	0.000	1.12	1.27
Pain (0-10)	1.08	0.02	5.60	0.000	1.05	1.11
Fatigue (0-10)	1.06	0.01	4.58	0.000	1.04	1.09
Health satisfaction (no/yes)	1.43	0.11	4.52	0.000	1.23	1.66
Health Assessment Questionnaire (HAQ) (0-3)	1.26	0.07	4.20	0.000	1.13	1.41
Sleep disturbance (0-10)	1.05	0.01	4.05	0.000	1.03	1.07
Number of comorbid conditions	1.08	0.02	3.99	0.000	1.04	1.13
High School graduate (yes/no)	0.87	0.10	-1.29	0.197	0.68	1.08
Age (years)	1.00	0.00	-1.19	0.233	0.99	1.00
Prior prednisone (yes/no)	1.10	0.09	1.17	0.243	0.94	1.28
Total income (US$)	1.00	0.00	-0.84	0.398	1.00	1.00
Male gender (yes/no)	0.85	0.09	-0.54	0.589	0.79	1.14
Disease duration (years)	1.00	0.00	-0.29	0.770	0.99	1.01
Number of prior DMARDs	1.00	0.04	-0.05	0.961	0.92	1.08

The data from this study suggest the methods we used here may be helpful to judge actual effectiveness in clinical practice. Because we analyzed patients from many rheumatologists, the results are a reasonable reflection of contemporary practice, and using standardized questionnaires, the same level of information is obtained from each patient. We believe that the use of treatment failure rather than treatment discontinuation is an important advance in assessing treatment value. Besides being helpful in comparing drugs that may have different pathways for failure, the method also provides an insight into overall treatment effectiveness.

In summary, we have performed a clinical trial using a contemporary longitudinal data bank. Using time to treatment failure as the outcome, the results were similar for leflunomide and MTX. The effect of adverse events was equal on both treatment arms, and AEs were the most important predictor of outcome. But non-predicted failure was the most important effect. Treatment failure rather than treatment discontinuation more accurately describes treatment effect. Finally, it is possible to conduct a clinical trial in the setting of an observational study, as we have shown here.

Conclusions

Supported by a grant from Aventis Pharmaceuticals

KM survival estimates of treatment failure and DMARD discontinuation

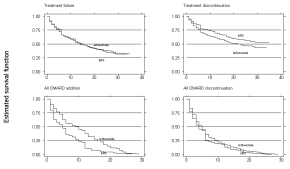


Figure 1a (Left upper) Kaplan-Meier survival estimates for 675 and 756 patients treated with MTX and leflunomide, respectively. Failure is treatment discontinuation or use of additional DMARD therapy.

Figure 1b (Right upper) Kaplan-Meier survival estimates for 675 and 756 patients treated with MTX and leflunomide, respectively. Failure is treatment discontinuation.

Figure 1c (Left lower) Kaplan-Meier survival estimates for 114 and 94 patients treated with MTX and leflunomide, respectively. Only patients adding additional therapy are analyzed. Failure is the use of additional DMARD therapy.

Figure 1d (Left right) Kaplan-Meier survival estimates for 165 and 317 patients treated with MTX and leflunomide, respectively. Only patients discontinuing therapy are analyzed. Failure is treatment discontinuation

The Relationship Between Methotrexate and Arava Generate Larger Questions

Liver function is monitored for patients taking either Methotrexate or Arava. The NBD presented data from a long-term study (data provided by you) of 14,997 patients who have used these medications. The data indicated a low rate of serious liver problems. The lecture presentation generated a lot of interest at the 2002 ACR meeting and was one of the highest attended events. Discussions from this presentation and other related topics lead to questions about the effect of newer medications and how they gain acceptance over time, and how medication failure is defined. Both of these areas are currently being researched.

Dr. Wolfe and NDB staff talk to Rheumatologists at the 2002 ACR Meeting in New Orleans.

... as debates over Medicare and social security disability payments continue, collecting accurate work history and disability data are becoming critical ...

CHORD Health Outcomes in Rheumatic Diseases Fellowship Program

In 2002 the NDB along with Vanderbilt University lead a fellowship training program in rheumatology aimed at providing broad experience in arthritis research for new rheumatologists.

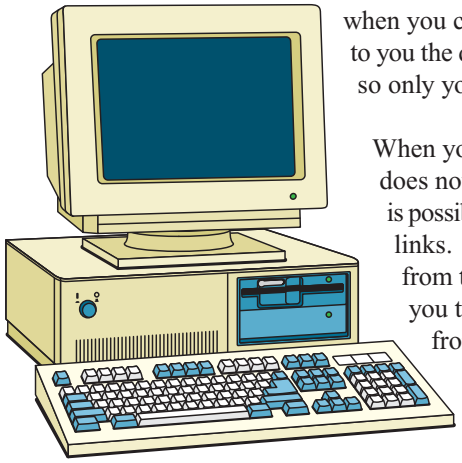
Until now there have been no training programs in the US for rheumatologists-in-training that are designed to study the outcomes of rheumatoid arthritis, osteoarthritis and fibromyalgia as they are influenced by treatment. The CHORD program addresses these issues by providing specific training in research method and data collection. A fellow is a physician who is undergoing special training in rheumatology research.

Under the direction of Dr. Fred Wolfe (NDB) and Dr. Ted Pincus (Vanderbilt University), 15 CHORD fellows were selected. The fellows have designed research studies that range from determining rates of cancer, to developing databases of RA patients in Argentina and Portugal. In order to integrate the foreign data into the NDB, the NDB is translating our usual questionnaire into Spanish and Portuguese. The completion date for these questionnaires is early 2003. These are exciting projects as they will move NDB and rheumatology research into the global arena.

Other CHORD projects include:
1). Steroids: good or bad?
2). The effect of fatigue on working persons with arthritis.
3). Determine the rate and predictors of infection in RA;
4). What happens to the dose of Remicade? Does it go up or remain stable?
5). Stress and arthritis.
6). How safe is methotrexate? How often should laboratory tests be done?
7). How common are ulcers? How can they be prevented?
8). Do non-steroidal anti-inflammatory medications (NSAIDs) interfere with the protective effect of aspirin in the prevention of heart attacks?
9). Do fat lowering drugs called “statins” help with the inflammation of arthritis?
And many more …

Web Quest: Preparing for 2003

January 2003 brings us to our third on-line research questionnaire. We call them WebQuests. The first two WebQuests were very successful with over 1000 questionnaires completed each time. Thanks to everyone who participated and gave us feedback to make the on-line questionnaire more efficient and user-friendly.



The last time our goal was to make the WebQuest faster, more convenient and easier to use. Your feedback indicated that we made some progress, but there were still some bugs. We have corrected the bugs and redesigned parts of the questionnaire to be even easier to use.

For those of you who have *never* filled out the questionnaire on-line, the following summarizes the steps necessary. You may need to upgrade your web browser (Internet Explorer or Netscape) before you start the WebQuest. If you completed the WebQuest last time, updating your browser is *not required*.

I. Requirements to run the WebQuest: make sure you have the latest browser upgrade

The WebQuest uses the very latest in browser technology to enhance web pages and decrease the time it takes to complete the questionnaire. In order for the WebQuest to operate efficiently you need to have Internet Explorer version 5.5 (or higher) or Netscape 6.0 (or higher). If you don't know what version you have, click on 'help' when you are in your browser, then go to 'about.' It will display the version you are using. If you are a Mac user the WebQuest will work with Netscape for Mac version 6.1 and higher. However, we recommend using the Netscape 7.0.

To get the newest version updates for Internet Explorer or Netscape go to our website at and click on WebQuest. Then follow the instructions.

II. How to complete the WebQuest: using your Private Link

The NDB will email you a private link. A private link is a special code that only you will have. It's called a link because when you click on it in your email message it will take to you the questionnaire. Only you will receive this link, so only you will have access to your data.

When you receive the email click on the link. If it does not bring up the first page of the WebQuest, it is possible that your email program does not recognize links. In that case you will need to copy the link from the email to the browser. Paste it in the place you type in the URLs or addresses you use to go from site to site.

If you have never copied a link before it may be a bit tricky. Instructions can be found on our website at under WebQuest.

III. Reporting Errors

Occasionally people have run into errors after they successfully updated the Browser and linked to the WebQuest. We would like to know if you have any problems or errors. If you get an error we need as much detail as possible about the error to understand the problem and help fix it. The best data you can send us are the details of the last page you made it to. Better yet is to email the page too us. This way we can isolate the problem, correct it, and let you know when the problem is resolved.

For more details on updating your browser please visit our web site at www.arthritis-research.org under WebQuest

To send us the "problem" web page please review the instructions at www. arthritis-research.org under WebQuest.

Thanks again for your feedback and patience. We expect this version of the WebQuest to be very useful and easy, and we do not expect significant changes in the future. If you completed the WebQuest last time you will be automatically emailed a new invitation. If you are interested in trying the on-line questionnaire for the first time, or if your email address has changed, please e-mail us at webquest@arthritis-research.org or call us at 1-800-323-5871. We will send you everything you need to get started.

FOR MORE INFORMATION OR TO PARTICIPATE

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Glucosamine Intervention Trial for Osteoarthritis : The GAIT Study

For several years dietary supplements such as glucosamine hydrochloride and chondroitin sulfate have been recommended for the treatment of osteoarthritis. Osteoarthritis (OA) is a degenerative joint disease affecting approximately 20.7 million Americans. According to the National Institutes of Health (NIH), OA can be as debilitating as heart disease and accounts for nearly 7 million physician visits every year. Yearly medical expenses for musculoskeletal diseases, which include OA, cost Americans $65 billion.

Glucosamine and chondroitin are over-the-counter nutritional supplements, readily available to the public in supermarkets, department stores, and health food stores. Manufacturers claim that these substances may alleviate symptoms of arthritis and joint pain, yet, no clinical studies have been performed to prove or disprove these claims.

Both the Arthritis Foundation and the FDA have expressed concern regarding the lack of clinical research. Also, there is the additional problem (see the section titled “In Brief, What’s Coming”) regarding control over product purity. Anywhere from 33% to 50% of the Glucosamine / Chondroitin supplements available in the US do not contain the amount of ingredient listed on the bottle.

To help address this problem, and determine the effectiveness of Glucosamine / Chondroitin in a controlled, scientific environment, the NIH decided to initiate a clinical research study for the treatment of osteoarthritis of the knee. The NDB is one of the original 13 sites nationally that started this study in January 2001 which will continue until third quarter 2004.

If you would like to find out more about the GAIT study or where you can participate if you wish, please visit the GAIT study web site at www.nihgait.org and look under ‘Sites’.

Infliximab (Remicade) Safety Registry Participants – don’t forget to take your Infusion Information sheet with you to your next infusion appointment if you have not already filled it out and sent it back to us. Thanks, we appreciate your help !!

2002 American College of Rheumatology Lecture Presentation Abstracts:

1). Low Rates of Serious Liver Toxicity to Leflumomide (LEF) and Methotrxate (MTX): A Longitudinal Surveillance Study of 14,997 LEF and MTX Exposures in . (Treatment)

2). The Economic Consequences of Changes in Disease Activity, Functional Status, and Utility Measure in Patients with Rheumatoid Arthritis. (Economics)

3). Lifetime Direct Medical Costs of Rheumatoid Arthritis. (Economics)

2002 American College of Rheumatology Poster Abstracts:

1). Work Disability in a National Sample of RA Patients (Economics)
2). Substantial, Clinically Important Decreases in Disease Severity and Work Disability are Associated with Increased Levels of Education in Patients with Rheumatic Diseases (Economics)
3). Tracking an Epidemic Illness with Self-Report Questionnaires: Ross River Virus Epidemic Polyarthritis (Health Services)
4). The Safety of Disease Modifying Anti Rheumatic Drugs and Biologic Therapy (DBT) in Rheumatoid Arthritis (Safety)
5). Satisfaction and Preference for NSAIDs and COX-2 Specific Inhibitors among Patients with Rheumatoid Arthritis (Safety)
6). The Measurement of Fatigue in Rheumatoid Arthritis (Clinical)
7). Toward an Epidemiology of NSAID and COX-2 Specific Inhibitor Efficacy Equivalence (Treatment)
8). The Characteristics and Patterns of Analgesic use in Rheumatoid Arthritis (Treatment)
9). Toward an Acceptable Definition of DMARD Failure and Abnormal Health Status in RA (Treatment)
10). The Epidemiology of GI Drugs Use Among Persons with RA, OA and Fibromyalgia (Treatment)
11). Measurement of Infliximab Effectiveness in Clinical Practice (Treatment)

2002 American College of Rheumatology Poster Discussion Presentation Abstracts:

1). Toward a Definition and Method of Assessment of Treatment Failure and Treatment Effectiveness: The Case of Leflunomide versus Methotrexate. (Safety)

2). Safety Data from a Registry of Patients Receiving Infliximab – Preliminary Report After 1 Year (Safety)

Three $1,000 Awards to Arthritis Research Participants:

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 questionnaires are completed and returned as soon as possible. Anyone who completes the questionnaire within two weeks of receiving it will be eligible for the award – given as a token of our gratitude in help with arthritis research. The winners from the last questionnaire were Sharon Hanson of Derby, KS; Julianne Behling of Tulsa, OK; Barbara Monroe of Lee's Summit, MO. Congratulations to all !

News from the NDB Staff:

Some Changes to Expect –

We are trying harder than ever to make the questionnaire simple and straightforward without losing any critical information we need to continue research. Below are a few changes you can expect to see in 2003:

1).The questionnaire has been simplified! You will notice that the joint surgery section and the disability payment section have been significantly reduced.

2).The multi-dimensional fatigue section and the sleep section have both been removed from the questionnaire. We can get much of this information from other questions so we tried to reduce redundancy as much as possible.

3). In the July 2002 Newsletter we told you about a project called QALY that is designed to collect "health state" information from people with and without arthritis. This project has been delayed (we didn't get to in 2002), but we still intend to send out CD-ROMs in 2003 to collect data. If you have a computer and a little time, we think you will find this project to be fun, and it will be very helpful in medical research.

The NDB staff donated more than $200 and 600 lbs of food to local food banks to help make Christmas 2002 a little brighter for our neighbors.

In Brief, What's Coming...

Many of you have asked for information about new medications or treatments, and what other things are happening in arthritis research. So, we have added this section to the newsletter hoping these items will be of interest to you.

✦ The "chronic shortage of manufacturing capacity" for Enbrel is coming to an end. Those of you who have had trouble getting this powerful biologic agent should find getting the medication to be easier from now on.

✦ Abbott Laboratories filed for FDA approval in April 2002 of a new biologic drug Humira. They are expecting approval during the first quarter 2003. Humira is expected to compete with Enbrel, Remicade and Kineret for treatment of Rheumatoid Arthritis. Look for the new drug in the Spring of 2003.

✦ The American College of Rheumatology News issued a "Treatment Alert" in the November/December 2002 issue. They report that Aristospan and Aristocort production has been temporarily suspended due to manufacturing problems at Fujisawa Healthcare, Inc. These are cortisone like products that are used for injections into joints. Plans are in place to relocate the manufacturing plant and resume production in late 2003.

✦ An independent test of Glucosamine and Chondroitin was conducted by ConsumerLab.com to see if the products contained the labeled amounts of the claimed ingredients. These supplements are typically used to slow the progression of osteoarthritis and reduce pain. ConsumerLab.com reported that 1/3 of the products did not pass the test, and about 50% of the Glucosamine / Chondroitin combination products failed due to low levels of Chondroitin. Currently supplements do not fall under the FDA jurisdiction and are not regulated to FDA standards.

If you have any questions or would like additional information please contact us at 800-323-5871 or email at