

*Rheumors,  
Volume 10, Number 1:  
Spring 2000*

## **The Dawn of a New Era For the Therapy of Rheumatoid Arthritis**

*By Evan L. Siegel, MD, FACR*

This is an exciting time for patients with Rheumatoid Arthritis and the physicians who treat them. After a decade marked by a dearth of any truly new therapies for this potentially disabling disease, a variety of new and exciting therapies have arrived. These new treatments represent both an evolution and a revolution in the way we think about the therapy of RA. The new and upcoming arsenal of medications has begun to address the dually vexing deficiencies of current therapies--a less than adequate degree of efficacy and a greater than acceptable degree of toxicity.

In general, Rheumatologists separate the therapies of Rheumatoid Arthritis into two categories. The first is anti-inflammatory therapy, meant to decrease inflammation and pain. This category includes medicines like aspirin and Ibuprofen. The second category is a group of medicines called Disease Modifying agents, or Remission Inducing agents, meant to slow the progression of the disease. These include drugs such as Methotrexate, Hydroxychloroquine, and gold. Major innovations have drastically improved our options in both of these categories.

In a prior issue of *Rheumors* the new drugs in the anti-inflammatory group, known as "Cox 2 Inhibitors" were discussed. Briefly, these are a new generation of non-steroidal anti-inflammatory drugs (NSAIDs) that are special because of significantly lower toxicity than the older drugs. NSAIDs have long been known to function through the inhibition of an enzyme called Cyclooxygenase (COX). This inhibition prevents the production of chemicals called prostaglandins, some of which are very important in promoting inflammation and causing pain. However, other prostaglandins also produced by COX are essential in the maintenance of normal bodily functions. They protect the stomach lining, allow cells called platelets to prevent excessive bleeding, and maintain adequate blood flow to the kidneys, among others. Older NSAIDs block the production of both types of prostaglandins. This allowed for effective blockade of pain and inflammation, but also promoted the serious side effects such as stomach ulcers, bruising and bleeding, and kidney failure.

Relatively recent research revealed that Cyclooxygenase actually exists in two forms, COX-1 and COX-2. COX-1 is responsible for producing the "housekeeping" prostaglandins, which are responsible for normal bodily functions. COX-2 is responsible for producing the prostaglandins associated with inflammation and pain. The new generation of NSAIDs selectively inhibits COX-2 and its products, leaving COX-1 available to continue to produce the helpful prostaglandins. Drugs already on the market in this category include *Celebrex* and *Vioxx*, with a few others already in the pipeline. It is important to realize that these drugs are not necessarily more effective in reducing pain or inflammation than older drugs, but do appear to be safer particularly with respect to

the risk of gastrointestinal ulceration. This improvement in the safety profile has allowed many individuals who were never able to tolerate NSAIDs in the past, to now reap the benefits of these helpful drugs.

The innovations that have taken place in the group of Disease Modifying Anti-Rheumatic Drugs (DMARDs) are perhaps even more astounding. New medications have found a way to interfere with the progression of Rheumatoid Arthritis at the most basic cellular levels. Once again, intensive research aimed at understanding the underlying mechanisms of Rheumatoid Arthritis has yielded tremendous benefit to those suffering from the disease.

It has become clear that in Rheumatoid Arthritis, white blood cells must communicate with each other for inflammation and joint destruction to continue. Two substances called cytokines have been shown to be the most important messengers in this communication. These are called TNF $\alpha$  and IL-1. These cytokines are released by one cell and received by another, stimulating the second cell to become an active participant in the inflammatory process. This knowledge has led to the development of an entirely new group of medications known as biologic agents, some of which have recently been approved by the FDA. The agents now on the market intercept the TNF $\alpha$  signal before it can ever reach the second cell, thereby slowing the entire disease process. Recent studies have confirmed that this downward regulation helps to prevent further joint destruction.

The two such drugs now available are *Enbrel* and *Remicade*. While the end result, inhibition of the effect of TNF $\alpha$  is the same, the mechanism and type of administration of these two drugs is very different. Enbrel is injected under the skin like insulin twice a week by the patient at home. Once absorbed, Enbrel acts like a sponge to soak up TNF $\alpha$  before it can be received by other cells. Remicade is given via intravenous infusion usually in a doctor's office. Remicade is a genetically engineered antibody that intercepts TNF $\alpha$  like a missile, again before it can have any effect on a target cell. Promising studies are now ongoing to evaluate medications that will inhibit the other cellular messenger, IL-1. The effect of modulation of other cytokines on the progression of RA is also under investigation.

A more conventional DMARD has also recently become available. *Arava* works by interfering with the metabolism of certain white blood cells important to the immune reactions central to Rheumatoid Arthritis. Like Methotrexate and the agents mentioned above, Arava has been shown to decrease the signs and symptoms of RA. Another recently approved innovative therapy involves running the blood of patients with severe RA over a column of resins and returning it to their bodies. While this has been shown to be effective in some patients, the exact mechanism is unknown. Many other therapies exploiting the blossoming knowledge of the mechanism of RA are currently in the works.

In summary, there has been an explosion of new, effective therapies for Rheumatoid Arthritis, a disease for which the therapeutic options have been very limited for decades. More importantly, for the first time, therapeutic agents are being directed specifically at

the underlying molecular basis of the disease. This provides new and exciting hope for the millions who have been suffering from this oft-times debilitating disease.

## **POINTS ON JOINTS**

*By David Borenstein, MD, FACP, FACR*

### **FAILED BACK SYNDROME (FBS)**

Failed back syndrome describes a heterogeneous group of disorders associated with persistent back and leg pain after an intervention, usually spine surgery. Approximately 15 percent of all patients who undergo an initial surgical procedure will develop a failed back syndrome. The 2 major categories of individuals with FBS are those with an uncorrected anatomical abnormality that requires additional surgical intervention, and those with complications from surgical procedures. Of those individuals with FBS, 60 percent have complications from surgery, while 40 percent have an uncorrected lesion.

#### **Clinical Evaluation**

Three historical points are important in clarifying the source of a patient's complaints. The first is the number of previous lumbar spine operations the patient has undergone. Every operation, after the first, regardless of diagnosis, has a decreasing likelihood of improvement. Statistically, the second operation has a 50 percent chance of success. Beyond 2 operations, patients are more likely to be made worse than better. The second point is the determination of the pain-free interval following back surgery. An absence of any relief of pain suggests that the anatomic lesion was missed at the time of surgery. A pain-free interval of 1 to 6 months suggests the development of an infection or post surgical scar, epidural fibrosis or arachnoiditis. An interval 6 months or longer suggests a recurrent disc herniation at the same or different level. The location and distribution of pain are helpful historical factors. Pain in the low back is related to instability of the spine, infection or scarring. Leg pain is related to narrowing of the spinal canal for nerves (spinal stenosis) or a herniated intervertebral disc. The physical examination is important in identifying the status of old and new neurologic abnormalities. The presence of pain radiating to the foot with raising the leg suggests compression of a spinal nerve.

#### **Radiographic evaluation**

Radiographic evaluation of FBS patients is aided by the availability of the presurgical x-rays, MRs, CT scans, and myelograms for comparison of the pre- and postsurgical situations. The plain x-rays are useful to determine the extent and level of previous surgery (laminectomies). Standing lateral flexion-extension films of the lumbar spine determine the presence of instability. MR scan with contrast material is the most helpful test in differentiating a recurrent disc herniation with postsurgical scar. CT scan with myelography is the procedure necessary to determine the presence of arachnoiditis, an inflammatory process that envelopes the spinal nerves inside the spinal canal. Three-dimensional CT scans are utilized to visualize the integrity of the facet joints of the lumbar spine when investigating spinal stability.

#### **Management**

The best possible solution for preventing recurrent symptoms is to avoid inappropriate initial surgical intervention. Conservative management, including exercises, oral medications, and

epidural injections are effective in the vast majority of individuals with back or leg pain. Less than 5 percent of individuals with spinal disorders require surgical intervention. Therapy for the FBS patient must be directed to the specific cause of their recurrent or persistent symptoms. Individuals with a recurrent or retained intervertebral disc fragment with incapacitating leg pain require a repeat lumbar spine surgery to remove the offending disc fragment. More than 90 percent should benefit from the procedure. FBS patients with spinal instability are treated initially with exercises and external supports in the forms of stabilization braces. Anesthetic injections identify structures that cause persistent pain. Spinal fusion operations with or without metal stabilization devices are utilized in FBS patients with intolerable back or leg pain secondary to instability. The potentially most difficult group of individuals with FBS is patients who are not surgical candidates. These individuals had multiple surgical procedures with persistent pain. Patients with arachnoiditis or epidural fibrosis constricting a spinal nerve are also not benefited by surgical intervention. These individuals benefit from chronic pain therapy. Therapy of chronic pain is a multifaceted program involving components of physical conditioning, oral drug therapy, injections, and/or spinal cord implantable stimulators. No evidence exists demonstrating the benefit of manipulation in the therapy of FBS patients. Active physical therapies that increase the capacity of individuals to complete tasks of daily living are helpful. Oral therapy includes a wide variety of medications that are useful as analgesics or anti-inflammatory drugs. The new COX-2 inhibitors have not been tested in individuals with FBS syndrome. However, the COX-2 inhibitors have analgesic and anti-inflammatory properties with less risk of toxicity. These drugs will prove to be beneficial with less risk for FBS patients. Narcotic analgesics are required to control the pain severity associated with FBS. Long-acting narcotics, used in the setting of improvement of function, are very helpful in controlling pain for a 24-hour period, while limiting drug-related toxicities. Medications that work in the central nervous system to increase the tone in the body's pain inhibitory pathway are useful adjuncts to analgesic medication. Examples of these medications are tricyclic antidepressants (amitriptyline, doxepin) and gabapentin. Patients with intractable pain are candidates for spinal cord stimulators. These stimulators are placed directly on the affected nerves. The stimulators produce small electrical currents that produce a tingling sensation that replaces the pain in the nerve. However, these stimulators require an additional surgery for implantation that may result in additional scarring.

Although FBS syndrome is a difficult clinical problem, appropriate diagnostic and therapeutic interventions are available to improve the medical condition of individuals with chronic pain.

## **Answers To Your Questions**

By Norman S. Koval, MD, FACP, FACR

### **Q. What is vertebroplasty?**

A. Vertebroplasty is a technique whereby methyl methacrylate (bone cement) is inserted into a vertebral body that has collapsed (fractured). The procedure is used in any pathologic condition that increases the fragility of the vertebral body. It is performed under radiographic imaging to make sure that the needle attached to the syringe holding the methyl methacrylate is in proper position.

The procedure has two objectives:

1. Reduction of pain (analgesia)
2. Solidification (increasing the strength of the vertebral body)

The three major pathologic indications for vertebroplasty are osteoporotic vertebral crush fractures, malignant tumors of the spine yielding pain, and vertebral hemangiomas.

Osteoporosis predisposes the vertebral bodies to spontaneous fractures, often induced by simple, minor trauma. The pain induced by the compression fracture can be alleviated with vertebroplasty.

Many malignant spinal tumors, such as those caused by metastases, lymphomas, or myelomas may have accompanying back pain which may be alleviated with the technique of vertebroplasty.

Vertebral hemangiomas are common and benign lesions of the spinal column. These are congenital abnormalities where blood vessels traverse the vertebral body decreasing its inherent strength. They are usually asymptomatic, but on occasion may cause significant pain with vertebral collapse.

Physicians at Arthritis & Rheumatism Associates, P.C., have seen numerous patients who have successfully undergone this procedure under the direction of an invasive radiologist. The procedure is performed at various institutions in the Washington, DC area. This is not an experimental technique, but a well-recognized procedure for alleviating pain that has already been in use in excess of 15 years.

## Answers To Your Questions

By Robert L. Rosenberg, MD, FACR

### **Q. What are SERMS and how can they be used for osteoporosis?**

- A. Selective Estrogen Receptor Modulators (SERMS) are non hormone chemicals that cause estrogen (female hormone) like effects in some tissues and block estrogen effects in other tissues. Tamoxifen (*Nolvadex*) has been available for a number of years and is used to prevent and treat breast cancer. Tamoxifen has also been shown to modestly increase bone density.

Raloxifene (*Evista*) a new SERM has been available for almost two years and has a unique therapeutic profile. Raloxifene acts like estrogen in bone to increase bone density and reduce the risk of fracture. It has been shown to reduce spine fractures by over 50% over a three-year period. Raloxifene also reduces hip and wrist fracture risk, but not as dramatically. Like estrogen, it also reduces cholesterol and has a positive effect on other cardiac disease risk factors. Raloxifene's ultimate effect on altering the risk of heart disease is currently being studied.

Unlike estrogen, Raloxifene has been demonstrated to have no stimulatory effects on the breast or the uterus. Four-year studies have demonstrated that raloxifene dramatically reduces new cases of breast cancer in older postmenopausal women. Those women on raloxifene had 76% fewer cases of invasive breast cancer and 90% fewer cases of estrogen receptor positive breast cancer than the group receiving a placebo (inactive drug). It's role in breast cancer prevention for high risk and younger patients is currently being studied. Raloxifene does not cause uterine bleeding and does not increase the risk of uterine cancer.

Raloxifene is relatively free of side effects. Some patients, especially those recently menopausal, may experience hot flashes or leg cramps. The risk of blood clot formation is increased in a way similar to the increase seen with all estrogen like products.

Raloxifene has been approved for the prevention and treatment of osteoporosis. Many new drugs for osteoporosis are in the pipeline, and together with currently available medications, will allow us to tailor prevention and treatment strategies for patients at risk for osteoporotic fracture. Discuss your risk factors for osteoporosis with your doctor.

## **RHEUMINATIONS**

### **Clinical Trials 2000**

*By Herbert S.B. Baraf, MD, FACP, FACR*

Clinical research has been an essential part of this practice since we initiated our first drug trial in 1982. Clinical trials have afforded our physicians, and our patients, the opportunity to be at the forefront of innovation and advancement in rheumatologic therapy. We have participated in the development of major therapeutic breakthroughs and our doctors and patients who have participated in the drug study program, have shared a special pride in their involvement in this process.

The past year has seen the introduction of Enbrel, the first approved biologic response modifier for Rheumatoid Arthritis, and a number of our patients took part in its development. Nearly two hundred and fifty of our patients have participated in NSAID trials of the new selective COX-2 inhibitors (such as Celebrex and Vioxx) that promise to help control inflammation without causing stomach damage. Many other patients have assisted us in the evaluation of a diverse group of treatments for a variety of illnesses that promise to make the lives of all of us more comfortable and more productive.

As a result of all of this activity, our **Center for Rheumatology and Bone Research** grew by leaps and bounds in 1999. When our research program first started in 1982, in downtown Silver Spring, we used the staff lunchroom as its headquarters. This year we opened a new, modern facility contiguous with the medical practice, to accommodate a busy staff that has grown to ten in number. We have conducted close to 125 clinical trials over the years and have gained a national reputation in the pharmaceutical industry as a first rate site. Our office on K Street, N.W., in Washington, D.C., (now in its fourth year) has relied on the talent and experience of Drs. Borenstein and Lawson to grow into a productive clinical research unit.

In the past few years, we have worked with the leaders of the pharmaceutical industry. Merck, Pfizer, Searle, Johnson & Johnson, Roche, Amgen, Wyeth-Ayerst, Dupont and Proctor & Gamble, among others, have looked to us for assistance in evaluating new therapies. We encourage our patients, if interested, to participate in clinical trials. Sometimes it is simply for the experience and other times in hopes of finding a solution where conventional therapy has failed. Whatever the reason, if you participate, you can be assured that an experienced team of dedicated clinical research professionals will guide you through the process and assist in the evaluations.

For patients interested in participating in clinical research we have a number of actively enrolling and anticipated new protocols:

**RHEUMATOID ARTHRITIS (RA):** We are currently recruiting patients with RA for participation in a study evaluating two new selective COX-2 inhibitors. (Maryland & D.C.)

We are engaged in the evaluation of five new Disease Modifying Anti-Rheumatic Drugs (DMARDS) for patients at various stages of their RA. DMARDS in general are slow acting agents that retard the progression of this disease preventing joint destruction and deformity. (Maryland & D.C.)

**OSTEOARTHRITIS OF THE KNEES OR HIP:** We have a number of different programs that are actively enrolling. Evaluation of new selective COX-2 inhibitors is ongoing. This winter and spring we plan to begin a program to study the cartilage-stabilizing effect of a drug previously used for osteoporosis. It is hoped that this treatment will prevent osteoarthritis from progressing.

We have recently initiated a study comparing Tylenol to a Cox-2 inhibitor for osteoarthritic pain.

**LOW BACK PAIN:** Two programs in D.C. and one in Maryland are currently under way evaluating medication for pain control for chronic backache.

**FIBROMYALGIA:** We are conducting our first clinical trial evaluating a treatment for this condition. The program is being conducted in the D.C. office.

In all of these programs diagnostic testing, medication and physician visits are *free* of charge. We would be delighted to review the specifics of these programs with you. Please feel free to discuss these programs with your physician on your next visit to the office. If you know someone who is not a patient of our practice who might be interested in learning more, please refer him or her to our study staff at 301-942-6610 for additional details concerning both Maryland and D.C. programs.