AMERICAN HEALTH CONSULTANTS® A Medical Economics Company

INTERNAL MEDICINE ALERT®

A twice-monthly update of developments in internal and family medicine

American Health Consultants Home Page—http://www.ahcpub.com

CME for Physicians—http://www.cmeweb.com

Tamoxifen Cuts the Risk of Breast Cancer in Half

ABSTRACT & COMMENTARY

Synopsis: *Despite the risk of thromboembolism, the use of tamoxifen reduces a woman's risk of developing breast cancer by about 50%.*

Source: Fisher B, et al. *J Natl Cancer Inst* 1998;90:1371-1388.

One of the interesting secondary outcomes of the careful clinical studies conducted by the National Surgical Adjuvant Breast and Bowel Project (NSABP) and other multicenter groups through the years has been the observation that women with breast cancer who took adjuvant therapy with tamoxifen not only had a significantly lower rate of disease recurrence but, in addition, had a significantly lower risk of developing cancer in the contralateral breast.[1-4] Because women who have had breast cancer are at high risk of developing a second breast cancer, this secondary benefit from tamoxifen adjuvant therapy led to the notion that perhaps tamoxifen would be capable of influencing the risk of developing breast cancer in other high-risk groups. Tamoxifen has also been shown to have beneficial effects on the risk of cardiovascular disease, the development of osteoporosis, and possibly even the occurrence of dementia and Alzheimer's disease. Balanced against these substantial potential benefits was a small risk of developing estrogen-related complications, such as thromboembolic disease and endometrial cancer, because of the weakly estrogenic effects of tamoxifen.

In light of these considerations, NSABP implemented a randomized clinical trial (NSABP-P1) to examine whether tamoxifen could significantly lower the risk of developing breast cancer in a group of women considered to be at increased risk. Eligibility criteria included the following: age 60 years or older; age 35-59 years with a calculated five-year risk of 1.66% (note that the Breast Cancer Risk Assessment Tool used to calculate the risk [based upon the model of Gail et al[5]] is now available as an interactive computer program through the National Cancer Institute's Cancer Information Service at 1-800-4-CANCER or online at http://cancertrials.nci.nih.gov) or a history of lobular carcinoma in situ; a life expectancy of at least 10 years; a negative breast examination and mammogram within the past six

INSIDE

New heart failure clinical trial **page 171**

Narcotics and rheumatic diseases: A good mix? **page 172**

Outbreak of multidrug-resistant pneumococcal pneumonia: A stitch in time **page 173**

Pharmacology update: Leflunomide (Arava) **page 174**

months; and no history of thromboembolic disease or deep venous thrombosis. Women with an intact uterus had an endometrial tissue sampling before starting treatment. Primary outcome measures were the rate of development of breast cancer. Secondary outcome measures were the incidence of myocardial infarctions and the incidence of osteoporotic bone fractures.

From April 1992 through May 1997, 13,388 women (of 98,018 undergoing risk assessment) were randomly assigned to receive either tamoxifen 20 mg/d or oral, daily placebo for five years. The trial was a double-blind, placebo-controlled design; 6707 received placebo and 6681 received tamoxifen. Twenty-one percent of women stopped their assigned therapy prematurely—19.7% in the placebo group and 23.7% in the tamoxifen group. Complete follow-up was available on 92.4% of the participants.

In total, 368 invasive and noninvasive breast cancers developed among the 13,175 patients with follow-up, 244 on placebo, 123 on tamoxifen. Of these, 175 cases of those on placebo were invasive and 89 cases on tamoxifen were invasive ($P < 0.00001$ in favor of tamoxifen). The cumulative incidence through 69 months was 43.4 per 1000 women in the placebo group and 22 per 1000 women in the tamoxifen group. Thus, tamoxifen significantly reduced the risk of both invasive and noninvasive breast cancer. Significantly reduced risk was seen in women of all ages: younger than 49, 44% risk reduction (RR); 50-59, 51% RR, and older than 60, 55% RR. Risk was reduced in women with a history of lobular carcinoma in situ (56%) or atypical hyperplasia (86%). Significantly reduced risks were observed in all risk categories.

Tamoxifen-treated patients did not have a reduced risk of myocardial infarction, but this may be related to the length of follow-up. Bone fractures were significantly reduced in the tamoxifen arm. Endometrial cancer occurred with increased incidence on the tamoxifen arm: 36 cases (13/1000 women) vs. 16 cases (5.4/1000 women) on the placebo arm. All the cancers on the tamoxifen arm were FIGO stage I. More women who received tamoxifen developed deep vein thrombosis (35 vs 22) and pulmonary embolus (18 vs 6). The incidence of strokes and cataracts was not significantly different on the two arms.

COMMENT BY DAN LONGO, MD, FACP

Well, it's hard to imagine news much better than this. The use of tamoxifen reduces a woman's risk of developing breast cancer by about 50%. A bonus from the treatment is a reduction in osteoporosis and the morbidity associated with fractures. At this particular time of follow-up, tamoxifen has not yet shown a beneficial effect on deaths from heart disease, but only a small fraction of patients have died so far. This study did not assess cognitive endpoints, but it is also possible that tamoxifen-treated patients will have less age-related cognitive impairment.

With these documented and not-yet-documented gains come some downside risks. The risks of thromboembolic disease and endometrial cancer are somewhat increased by taking tamoxifen. However, the balance of risk and benefit is overwhelmingly in favor of benefit. The subset of patients with genetic mutations that increase their risk has not yet been examined; however, blood samples are available to determine BRCA1 and BRCA2 phenotypes and such correlations will be made in future analyses. In addition, given the broad efficacy of tamoxifen in diverse risk groups, the question must be asked about how high the risk must be before the risk-benefit ratio is favorable. Modifications of the existing algorithms are currently being made to help with these decisions.

Furthermore, we may not yet have gotten all the benefit that is possible to obtain from tamoxifen use. The question remains open whether longer duration of tamoxifen treatment would exert greater benefits. In addition, it is not yet clear whether the newer selective estrogen receptor modulators (SERMs), such as raloxifene, will have different or greater effects than tamoxifen. Ongoing studies, including NSABP-P2, are addressing this question. The success of this study makes interpretation of other ongoing studies somewhat complicated. In my opinion, it is no longer

Internal Medicine Alert, ISSN 0195-315X, is published twice monthly by American Health Consultants, 3525 Piedmont Rd., NE, Bldg. 6, Suite 400, Atlanta, GA 30305.

GROUP PUBLISHER: Donald R. Johnston.

ASSISTANT MANAGING EDITOR: Robin Mason.

MARKETING MANAGER: Debra Zelnio.

GST Registration Number: R128870672.

Second class postage paid at Atlanta, GA.

POSTMASTER: Send address changes to ***Internal Medicine Alert***, P.O. Box 740059, Atlanta, GA 30374.

Back issues: $15. Missing issues with be fulfilled by Customer Service free of charge when contacted within one month of the missing issue's date.

Subscriber Information

Customer Service: 1-800-688-2421.

Customer Service E-Mail Address: custserv@ahcpub.com

Editorial E-Mail Address: robin.mason@medec.com

World-Wide Web: http://www.ahcpub.com

Subscription Prices

United States

$189 per year (Student/Resident rate: $95).

Multiple Copies

1-9 additional copies: $95 each; 10 or more copies: $57 each.

Outside the United States

$219 per year plus GST (Student/Resident rate: $110 plus GST).

Accreditation

American Health Consultants is accredited by the Accreditation Council for Continuing Medical Education (ACCME) to sponsor CME for physicians. American Health Consultants designates this CME activity for 40 credit hours of Category 1 of the Physician's Recognition Award of the AMA. This CME activity was planned and produced in accordance with the ACCME Essentials. This program has been reviewed and is acceptable for up to 40 Prescribed hours by the American Academy of Family Physicians. Term of approval is for one year from beginning of distribution date of January 1, 1998 with option to request yearly renewal. The program is also approved by the American Osteopathic Association for 40 Category 2B credit hours. **For CME credit, add $75.**

Questions & Comments

Please call **Robin Mason,** Assistant Managing Editor, at (404) 262-5517 between 8:30 a.m. and 4:30 p.m. ET, Monday-Friday.

Statement of Financial Disclosure

American Health Consultants does not receive material commercial support for any of its continuing medical education publications. In order to reveal any potential bias in this publication, and in accordance with Accreditation Council for Continuing Medical Education guidelines, a statement of financial disclosure of editorial board members is published with the annual index.

appropriate to include a placebo arm in breast cancer prevention studies. The new SERMs need to be demonstrated to be superior to tamoxifen rather than placebo. Primary care physicians should develop a level of comfort using the risk assessment tool and applying it to individual patients. If an individual is found to be at increased risk of breast cancer, the first choice would be to enter the patient on a prospective randomized trial. If that is not possible, women should be informed of the risks and benefits of tamoxifen use and be permitted to obtain the benefits proven in this landmark study. (*Dr. Longo is Scientific Director, National Institute on Aging, Baltimore, MD.*) ❖

References

1. Scottish Clinical Trials Office, Edinburgh. *Lancet* 1987;2:171-175.
2. Fisher B, et al. *N Engl J Med* 1989;320:479-484.
3. CRC Adjuvant Breast Trial Working Party. *Br J Cancer* 1988;57:604-607.
4. Rutqvist LE, et al. *J Natl Cancer Inst* 1991;83: 1299-1306.
5. Gail MH, et al. *J Natl Cancer Inst* 1989;81:1879-1886.

New Heart Failure Clinical Trial

ABSTRACT & COMMENTARY

Synopsis: *The results of CIBIS-II were reported at the Second Annual Scientific Meeting of the Heart Failure Society of America that should influence physician practice in the care of patients with left ventricular dysfunction and heart failure.*

Source: The Second Annual Scientific Meeting of the Heart Failure Society of America, Boca Raton, FL. September 13-16, 1998.

This important trial evaluated the effects of bisoprolol, a selective beta 1 beta-blocker, in patients with heart failure. The trial was stopped prematurely at the second interim analysis because of positive results in the beta blocker arm. Approximately 2600 patients from throughout Europe with Class III or IV congestive heart failure were slowly up-titrated with bisoprolol or placebo over a period of several months. All were on an angiotensin converting enzyme (ACE) inhibitor and diuretics. Entry criteria included an ejection fraction (EF) of less than 35%; 16% of the patients were Class IV. Eighty percent were male, and more than 50% had coronary artery disease. The primary end point was all-cause mortality; a variety of traditional secondary end points were assessed. At the time the trial was stopped, all-cause mortality had decreased in the beta blocker group by 32% (P = 0.0005); death rates were 17.3% placebo vs. 11.8% bisoprolol, with a rate of 12% per year in the placebo arm and 8.2% in the beta blocker cohort. Average follow-up at trial cessation was 1.4 years. There was a 45% decrease in sudden death and a slight favorable trend in deaths from heart failure or unknown causes. There were no significant differences in outcome in subjects with an ischemic etiology (50% reduction in deaths) or different functional class. Total and heart failure hospitalizations were decreased in the beta blocker group. Virtually all secondary end points were positively affected, including in-hospital deaths. Withdrawal rates were 15% for both placebo and bisoprolol. In summary, CIBIS-2 resulted in a 32% reduction in all-cause mortality, 45% reduction in sudden death, 30% reduction in hospitalization for CHF, and 15% reduction in all-cause hospitalization. No significant adverse reactions occurred. The authors conclude that only 25 patients would need to be treated with bisoprolol to save one life.

COMMENT BY JONATHAN ABRAMS, MD

This important study confirms recent meta-analysis (*Circulation*, 1998;98:1184) demonstrating an advantage in death or heart failure hospitalization as well as EF in more than 3000 patients receiving a beta blocker who have congestive heart failure. While the mortality rates in CIBIS II suggest that these patients may have been less sick than traditional Class III-IV classification, the data are concordant with the recent carvedilol studies as well as outcomes in a number of small beta blocker trials. Thus, it would appear that all patients who have congestive heart failure with substantial depression of EF should be given a beta blocker unless there are contra-indications. Certainly, this is an attractive policy for stable Class II-III subjects. The question as to whether selective, non-selective, or vasodilator-beta blockers are superior is unresolved and awaits the results of ongoing trials (BEST, COMET, COPERNICUS). Recently, the MERIT-HT study was stopped because of a major benefit of long-acting metoprolol in 4000 cases of II-IV subjects with an EF less than 40%. The data are not available yet, but this study, along with CIBIS II and the carvedilol trials, underscores that beta blockers clearly increase survival in heart failure with impaired LV systolic function. (*Dr. Abrams is Professor of Medicine, Division of Cardiology, University of New Mexico, Albuquerque.*) ❖

Narcotics and Rheumatic Diseases: A Good Mix?

ABSTRACT & COMMENTARY

Synopsis: *A retrospective review of narcotic use in patients treated in a rheumatology clinic found substantial efficacy, no trend toward higher doses or increased frequency of use over time, and a reassuringly small number of patients with addictive behavior.*

Source: Ytterberg SR, et al. *Arthritis Rheum* 1998;41: 1603-1612.

When narcotic drugs are being considered for use in patients who have neither self-limited nor terminal illnesses, patients and their physicians have concerns about adverse effects including: addiction, constipation, the increased risk of falls, and other accidental injuries due to drowsiness. Physicians must also worry about illegal diversion of narcotic drugs and may fear loss of license or other sanctions if their prescribing is found only to be supporting addicts' "habits." Ytterberg and colleagues retrospectively reviewed narcotic drug use in 266 patients seen in a rheumatology clinic in a university medical school affiliated Veterans Affair Medical Center. The patients had an mean age of about 61 years and nearly all were men. A variety of musculoskeletal problems were represented, chiefly rheumatoid arthritis, spondyloarthropathies, and a variety of connective tissue diseases. Only 1-3% of patients surveyed had osteoarthritis. Forty five percent of all patients seen in rheumatology clinic during the 3 years had received at least one prescription for narcotics, 53% of those used the drugs on a short-term basis (less than three months), and 47% received them on a long term basis (≥ 3 months). Two hundred sixty-six patients who received prescriptions for narcotics were surveyed by telephone and were asked about pain relief, side effects, and substance abuse ("street" drugs and alcohol). Most patients received prescriptions for either codeine or oxycodone. Pharmacy records were reviewed and medical records were reviewed for patients who had an escalation in dose of more than the equivalent of 60 mg of codeine per day to identify the reason for the increased dose. Using a 0-10 scale for pain before and after analgesic use, patients reported a mean of about 8 before and 3.6 after a dose of analgesic. Side effects were reported by almost 40% of patients with nausea and constipation being the most frequent complaints, followed by sleepiness and other non-specific sleep, mood, and equilibrium disorders. Of all those receiving narcotics, 32 had escalations in dosage. Of these, 12 patients had temporary escalations related to surgical procedures, trauma, or worsening of their diseases, while one patient's dose increase was unexplained. Twenty patients had dosage escalations that continued. Of these, 14 increases were ascribed to disease progression or intercurrent illnesses such as herpes zoster, two required joint arthroplasty, one had trauma, and three were unexplained. Of the four patients with unexplained dosage escalations, all had behaviors noted that were consistent with abusive use including drug seeking behavior, reported intoxication by family members, and asking multiple physicians for an increased dose or an earlier than expected request for new prescription. These patterns of abusive behavior were not strongly correlated with prior history of drug or alcohol abuse. Ytterberg et al conclude that risks of abuse and addiction are exaggerated and that narcotic analgesics are underutilized in patients with chronic rheumatic diseases.

COMMENT BY JERRY M. GREENE, MD, FACR

The findings of this retrospective study are reassuring, especially the small number of patients (4 of 266) whose increased demands for narcotic analgesics were indicative of drug addiction and abuse. On the other hand, each of the four patients identified as exhibiting drug-abuse behavior had a legitimate painful illness for which a narcotic analgesic was prescribed. One fears that prescribing narcotics on a chronic basis for a single patient who then demonstrates drug seeking or other addiction behavior could be a license-losing, potentially career-ending mishap. However, certain situations make use of narcotic analgesics an attractive alternative for patients with arthritis. For example, in my opinion, the risk of bleeding with the combination of NSAIDs and warfarin anticoagulation outweighs the small risk of addiction. The pain of many rheumatic diseases may be well controlled with a tailored anti-inflammatory and disease-modifying regimen, including, perhaps, low dose prednisone. But when anti-inflammatory treatment is ineffective or inappropriate and narcotic drug therapy is contemplated, the results of Ytterberg and colleagues can be shared with patients as part of the process of informed consent. The reportedly low risk of addiction in this patient population may allay patients' fears, allowing cautious use and providing needed pain relief.

Only four patients had unexplained escalation in narcotic use and all four demonstrated addictive behaviors such as seeking early prescriptions or increased dosage, or soliciting multiple physicians for narcotics. ❖

Outbreak of Multidrug-Resistant Pneumococcal Pneumonia: A Stitch in Time

ABSTRACT & COMMENTARY

Synopsis: *In 84 nursing home residents, only three of whom had received pneumococcal vaccination, a multidrug-resisant Streptococcus pneumoniae serotype 23F was isolated from either the blood or sputum of 4% with pneumonia and from the nasal pharyngeal specimens of 23% of those without pneumonia.*

Source: Nuorti J, et al. *JAMA* 1998;338:1861-1868.

In 84 residents of a nursing home, only three of whom had received pneumococcal vaccination, a multidrug-resistant *S. pneumoniae* serotype 23F was isolated from either the blood or sputum of 4% with pneumonia and from the nasal pharyngeal specimens of 23% of those without pneumonia. Following the use of pneumococcal vaccination and prophylactic antibiotics, there were no additional cases of pneumonia and rates of colonization declined significantly.

Pneumonia in the elderly remains a significant and persistent public health problem. Rates of pneumonia increase significantly after age 65 (10-20 fold) and the mortality rate increases up to five times. Morbidity and prolonged recovery are the rule. Pneumococcal pneumonia is the most common bacterial pneumonia resulting in hospitalization. Mortality for bacteremic pneumonia remains at 25%. Drug-resistant pneumococcal disease is increasingly common throughout the United States with rates of both intermediate and highly resistant strains approaching 40-50% in some geographic regions.[1-3] These organisms are frequently resistant not only to penicillin but to macrolides, cephalosporins, and trimethoprim-sulfamethoxazole combinations. Pneumoccal vaccination has been recognized as effective and cost effective in preventing pneumonia and mortality in the elderly, but rates of vaccination remain below one-third for eligible elderly patients. Recently, the Centers for Disease Control (CDC) reported on an outbreak of multidrug-resistant *S. pneumoniae* serotype 23F in a nursing home population in rural Oklahoma. In a group of 84 patients, only three had been vaccinated against pneumococcus. An epidemiologic investigation of both invasive infection and pneumococcal carriage was undertaken. A retrospective cohort study compared attack rates among colonized and non-colonized residents who had pneumonia and remained asymptomatic. The median age of the patient population was 85 and 92% were over age 65. Illness developed in 13%, all of whom had lobar consolidation on chest x-ray. Bacteremia resulted in death four three of four patients and only 4% had pneumococcal vaccination while 71% had received influenza vaccinations. The outbreak strain identified as *S. pneumoniae* serotype 23F was isolated in 23% of the residents (17 of 74) and two of 69 employees. Following the interventions, which included pneumococcal polysaccharide vaccination and penicillin 500 mg, three times per day; Ofloxacin 400 mg, twice per day for one week, the recovery of serotype 23F declined to only three residents and none of the employees. In the cohort study, colonization and attack rates were significantly higher among those taking antibiotics at the time of illness. Antecedent respiratory tract infection in the two weeks prior to illness was not associated with colonization. Invasive infection was more likely to develop in patients who had been hospitalized the previous year (relative risk of 3.3), who had pneumonia during the previous year (relative risk of 5.6), and who needed assistance with taking medications (relative risk of 3.7).

COMMENT BY ALAN M. FEIN, MD

Pneumonia in the elderly remains a devastating problem despite the use of antibiotics. Interestingly, neither influenza vaccination nor pneumococcal vaccine which are both independently, effective in preventing pneumonia and co-morbid illness, are fully employed. Recent data from the CDC indicates that less than half of those eligible for influenza vaccination and less than one-third of those eligible for pneumococcal vaccination are receiving this intervention. These numbers may be higher in certain ethnic group, those with less access to medical care, or those with lower socioeconomic status. At the same time, these effective preventive strategies are not being employed and the use of antibiotics is increasing. This results in a rising prevalence of multidrug-resistant pneumococci which are often multidrug-resistant. In this study, all isolates had intermediate resistance to penicillin and cefotaxime, were resistant to trimethoprim-sulfamethoxazole and erythromycin, but were sensitive to vancomycin. The intervention that abruptly halted the epidemic included vaccination of patients and staff and the use of prophylactic antibiotics. This simple program proved highly effective in eliminating the carriage of the organism and the development of invasive disease. Drug-resistant pneumococcal infection is associated with extremes of age and the excessive use of antibiotics in patients who are often treated sporadically

and empirically for respiratory infection. As in other studies, colonization by penicillin resistant *S. pneumoniae* was associated with multiple factors which, in addition to the use of antibiotics, may serve as surrogates for antibiotic use (i.e., hospitalization and having had pneumonia within the last year). This highly resistant strain (23F) was transmitted from person to person and, as suggested by its culture, from both patients and staff. Previous work has underscored the importance of pneumococcal vaccination in preventing the development of drug-resistant invasive infections. Most drug-resistant serotypes are included within the 23 valent vaccine and, as pointed out in this study, is a highly effective intervention. Even with reduced antibody response, it is highly cost effective.

In summary, pneumococcal disease remains a persistent risk to the elderly living at home and even more so in chronic care facilities. The importance of pneumococcal vaccination must be stressed given the high fatality once bacteremia or meningitis supervenes. Pneumonia in the elderly is both common and late to be recognized. The use of pneumococcal vaccination needs to be more effectively brought into the mainstream of preventive care. ❖

Pharmacology Update

Leflunomide (Arava)

By William T. Elliott, MD
and James Chan, PharmD, PhD

The fda recently approved a new disease modifying agent for the treatment of rheumatoid arthritis (RA), the first new drug to be approved for this indication in more than a decade. Leflunomide (Arava-Hoechst Marion Roussel) was given a priority review by the FDA and was approved with the indication of retarding the structural damage of the disease, the first medication of it's kind to receive this indication.

Leflunomide seems to work by causing cell arrest of lymphocytes involved in the autoimmune process. The drug is a de novo uridine synthesis inhibitor. It acts by inhibiting dihydroorotate dehydrogenase and tyrosine kinases with the former action predominating.[1,6] This action is postulated to arrest stimulated cells at the G1 phase, thereby not allowing the production of ribonuc leotides needed to proceed to the S phase.[1] Leflunomide is metabolized to an active metabolite (A77 1726) which has a long elimination half-life of approximately 16 days.

The drug is marketed by Hoechst Marion Roussel and is manufactured in France by Usiphar.

Indications

For the treatment of active rheumatoid arthritis to reduce signs and symptoms and to retard structural damage as evidenced by X-ray erosions and joint space narrowing.[2]

Dosing Information

Leflunomide is supplied as 10 mg, 20 mg, and 100 mg tablets. Due to the long elimination half-life, a loading dose is needed to achieve steady-state concentration more quickly. A loading dose of one 100 mg tablet daily for three days is recommended. A daily dose of 20 mg is recommended as a maintenance dose. If there are problems with tolerance, the dose may be reduced to 10 mg[2]. NSAIDs and low-dose corticosteroids may be used concomitantly with leflunomide.[2]

Should leflunomide need to be discontinued for pregnancy or other reasons, the elimination half-life can be reduced from over 1 week to about 1 day by administering cholestyramine 8 g three times daily for 11 days.[2]

Potential Advantages

Leflunomide provides an alternative to disease-modifying antirheumatic drugs (DMARDs) such as methotrexate or sulfasalazine particularly when the latter agents are not tolerated. Leflunomide does not seem to be associated with (albeit rare) severe and occasionally life-threatening toxicities that are seen with methotrexate such as pulmonary toxicity and myelosuppression. In the European comparative trial two cases of agranulocytosis were reported with sulfasalazine (n = 132) and none in the leflunomide group.[9] Coadministration of folate is not necessary.

Potential Disadvantages

Due to its potential teratogenic effect, leflunomide is contraindicated in women who are or may become pregnant. In addition, men wishing to father a child should consider discontinuing leflunomide.[2] Elevation of liver enzymes (ALT and AST) occurs in 5-10% of patients in clinical trials. Elevations were generally mild (2 x ULN). ALT should be performed at baseline and monitored monthly for several months. If the levels are stable, further levels should be determined by the individual clinical situation.[2] Leflunomide is not recommended in patients with hepatic insufficiency and should be used with caution in patients with renal insufficiency.

It is not recommended in patients with severe immunodefficiency, bone marrow dysplasia, or severe uncontrolled infections; use of live virus vaccines should be avoided during or for a period of time after stopping leflunomide.[2]

Common side effects include diarrhea (17-27%) and rash (10-12%).[2] These side effects appear to be more common than with methotrexate.[2]

Rifampin increases the peak levels of leflunomide by about 40% and caution should be exercised during con-

comitant therapy.[2] The FDA has requested that Hoechst conduct a drug-interaction study involving cytochrome P450 3A4 inhibitors such as erythromycin or ketoconazole.[3]

Comments

The approval of leflunomide was based on three controlled trials (2 European and 1 U S/Canada) involving 1839 patients and treatment durations of up to 52 weeks. Efficacy was assessed by improvement of signs and symptoms and by radiographic assessment of structural damage. Relief of signs and symptoms was determined by using American College of Rheumatology (ACR) 20 Responder Index. A responder is a patient who had 20% improvement in both tender and swollen joint counts and in three of the following five criteria: physician global assessment, patient global assessment, function/disability measure, visual analog pain scale, and erythrocyte sedimentation rate or C-reactive protein. Progression of structural damage was assessed radiographically using the Sharp Score, a composite score of erosions and joint space narrowing in hands/wrists and forefeet.[2]

One trial compared leflunomide with placebo and methotrexate, another compared leflunomide with placebo and sulfasalzine, and the third compared methotrexate with leflunomide. Leflunomide was dosed at 20 mg daily following an initial loading dose of 100 mg/day for three days, methotrexate was dosed at 7.5 mg/week increasing to 15 mg/week, and sulfasalazine was dosed at 2 g/day. Results indicate that the efficiacy of leflunomide is similar to methotrexate and sulfasalazine and superior to placebo. One study, however, indicated that methotrexate showed a higher response rate than leflunomide (69% vs. 56%), although there was no significant difference in Sharp Scores.[2] Treatment effect is generally evident by one month and stablized by 3-6 months.[2] Additional details of one of the phase III trials, in abstract form, suggested that leflunomide-treated patients may achieve sustained response earlier and of longer duration, with greater improvement in quality of life scores compared to methotrexate.[7,8]

Clinical Implications

Rheumatoid arthritis affects about 1% of the general population. Initial pharmacotherapy of rheumatoid arthritis is generally nonsteroidal anti-inflammatory drugs (NSAIDs). Patients in whom disease remains active after adequate treatment with NSAIDs are candidates for DMARD therapy such as methotrexate, sulfasalazine, and hydroxchloroquine.[4] Methotrexate is often selected as the initial DMARD as it is effective and generally well tolerated. Over 50% of patients taking methotrexate conti nue for three years or longer,[4,5] however GI symptoms, stomatitis, alopecia, and rare, but potentially serious, myelosuppression or pulmonary toxicity have been reported. Leflunomide provides an alterative to methotrexate and other DMARDs. Pulmonary toxicity has not been reported with leflunomide, although GI symptoms such as diarrhea seem to be more frequent. The efficiacy of leflunomide in patients not responding to methotrexate or other DMARDs remains to be determined. Rheumatology consultation should be considered before initiating DMARD therapy.

Leflunomide is expensive, the average wholesale cost is $8 per day or about $3000 per year. This is more than twice the cost for methotrexate (15 mg/week, not including the cost of folate) and more than 10 times the cost for sulfasalazine (2 g/d). ❖

References

1. Fox RI. *J Rheumatol Suppl* 1998;53:20-26.
2. Arava Product Information. Hoechst Marion Roussel, Inc. September 1998.
3. FDC Report, The Pink Sheet. September 14, 1998.
4. American College of Rheumatology. *Arthritis Rheum* 1996;713-722.
5. Kremer JM. *Rheumatic Diseases Clinics of North America* 1998;24:651-657.
6. Cherwinski HM, et al. *J Pharmacol Exp Ther* 1995;275:1043-1049.
7. Furst D, et al. *Arthritis Rheum* 1998;41:9(suppl) abstract 734.
8. Tugwell P, et al. *Arthritis Rheum* 1998;41:9(suppl) abstract 732.
9. Smolen JS, et al. *Arthritis Rheum* 1998;41:9(suppl) abstract 594.

CME Questions

28. Of 266 patients treated in a rheumatology clinic who received prescriptions for narcotic analgesics, how many were found to have behavior that was consistent with addiction?

a. None
b. Four
c. Eight
d. 32
e. 61

29. Which of the following statements is true regarding women at increased risk of breast cancer?

a. Tamoxifen use daily for 10 years significantly reduces the risk of breast cancer.
b. Tamoxifen use daily for two years significantly reduces the risk of breast cancer.
c. Tamoxifen use daily for five years significantly reduces the risk of breast cancer.
d. The beneficial effects of tamoxifen on breast cancer risk are outweighed by toxicities associated with tamoxifen use.
e. Tamoxifen and raloxifene are equally effective in the prevention of breast cancer.

By Louis Kuritzky, MD

Dietary Sodium Reduction

Dietary sodium restriction is sometimes helpful in management of hypertension, both as a mechanism to lower blood pressure as a sole intervention, and as a method to enhance responsiveness to some antihypertensive medications. On the other hand, adverse impact on glucose metabolism, probably as a consequence of RAA activation attendant to sodium restriction, is concerning. The literature has been inconclusive, in normotensive and hypertensive patients, about whether sodium restriction worsens insulin resistance. The current study investigated the effect of varying levels of sodium restriction on blood pressure and insulin resistance in hypertensive patients (n = 12).

Subjects were admitted to a research ward and after seven days on a normal diet (200 mmoL sodium), insulin resistance was measured by the euglycemic hyperinsulinemic glucose clamp method. Subsequently, patients were subjected to sodium restriction of either moderate (= 100 mmol/d) or strict (= 30 mmol/d) degree.

The change from normal diet to moderate sodium restriction produced only a slight increase in renin levels, but no changes in insulin, glucose, norepinephrine, or aldosterone. Strict sodium restriction, on the other hand, resulted in a 41% increase in fasting insulin, and significant reduction of insulin sensitivity. Moderate sodium restriction is associated with minimal perturbation of glucose homeostasis and neurohumors; strict sodium restriction may result in consequential compensations in norepinephrine and insulin sensitivity. ❖

Gomi T, et al. Am J Hypertens 1998; 11(9):1048-1055.

Intensive Blood-Glucose Control with Metformin

The united kingdom prospective Diabetes Study (UKPDS) has reported recently in their prospective trial (n = 4075) that intensive blood glucose control with sulphonylureas or insulin reduces risk of microvascular complications. A subgroup of this population (n = 753) was followed for over 10 years comparing diet control with metformin; additionally, the metformin recipients were also compared with patients receiving sulfonylureas or insulin for tight control. A final subgroup analysis allowed patients who had not achieved optimum glucose control on maximum sulfonylurea dose to either add metformin, or continue on their same regimen.

The metformin treatment group enjoyed a number of benefits when compared with conventional (standard dose sulfonylurea or insulin) therapy: 36% lower all-cause mortality, 42% lower diabetes related mortality, and 32% lower incidence of any diabetes-related endpoint. Patients who had metformin added to their regimen of sulfonylurea due to inadequate glucose control did not demonstrate improvements in mortal endpoints, but did trend toward better hemoglobin A-1-C levels, and did not gain as much weight. These data support consideration of metformin as first-line therapy in Type 2 diabetes. ❖

UK Prospective Diabetes Study Group Lancet 1998;352:854-365.

Low-Dose Hydrocortisone for Treatment of Chronic Fatigue Syndrome

The definition of chronic fatigue syndrome (CFS) includes new onset of severe, unexplained fatigue for at least six months, plus at least four of the following symptoms: memory/concentration deficits, sore throat, tender lymph nodes, muscle pain, multijoint pain, new headaches, unrefreshing sleep, and prolonged postexertional malaise. There has been some literature documentation of reduced cosyntropin responsiveness in CFS patients (30% less cortisol response over 24 hours). Since this aberration suggests a role of insufficient cortisol in CFS patients, McKenzie and associates undertook a randomized trial of low-dose hydrocortisone for CFS (n = 70).

Patients received 20-30 mg hydrocortisone each morning, and 5 mg each evening for 12 weeks. Patients recorded symptoms and well-being on several different scales. The trial was blinded and placebo controlled.

Cortisone therapy was associated with modest symptomatic improvement in some, but not all measurement tools. One-third of cortisone recipients had measurable adrenal suppression secondary to treatment. McKenzie et al conclude that though cortisone treatment did produce some favorable changes, the consequences and frequency of adrenal suppression are to great to consider this therapy appropriate for clinical use. ❖

McKenzie R, et al JAMA 1998;280:1061-1066.

In Future Issues:

Should Patients with Atrial Flutter be Anticoagulated?