

POLICY & PRACTICE

Arthritis Top 10

The development of experimental biological agents to treat rheumatoid arthritis is 1 of the top 10 arthritis advances of last year, according to a list compiled by the Arthritis Foundation. The group also noted successes in the new scientific discoveries about a gene linked to the increased risk of RA, lupus, and other autoimmune conditions; the use of predictive markers to improve RA diagnosis and outcomes; and research that shows the effectiveness of a combination of diet and exercise on improving function and reducing knee pain in

overweight patients with knee osteoarthritis. Also among the top 10: research that suggests doxycycline could slow osteoarthritis progression and a potential new therapy to slow bone loss; Medicare's pilot project to provide some coverage of self-injected medications to 50,000 beneficiaries with rheumatoid and psoriatic arthritis; the first arthritis-specific federal legislation in more than 30 years—the Arthritis Prevention, Control, and Cure Act of 2004; the Joint Commission on Accreditation of Healthcare Organizations' wrong-site surgery protocol; and experts'

introduction of 51 quality measures for people with osteoarthritis, rheumatoid arthritis, or anyone using analgesics.

Guidance on Inpatient Status

To help physicians do a better job of admitting patients to the hospital, the Centers for Medicare and Medicaid Services should simplify its use of the terms "observation" and "inpatient admission," a federal advisory panel has recommended. The Practicing Physicians Advisory Council drew up the resolution after CMS officials indicated that there was some "confusion" between hospitals and admitting physicians on patient status.

Specifically, there are times when a hospital admits a patient to inpatient status when the physician intended the patient to be admitted for observation. The panel recommended that CMS provide this guidance on the "MedLearn Matters" Web site, which posts articles to Medicare providers that help them understand new or changed Medicare policy.

Payments for the Elderly

U.S. seniors spent an average of \$11,089 out of pocket on health care goods and services in 1999, but nearly half that amount was reimbursed by Medicare, and another 15% was paid for by Medicaid, according to a CMS report. The amount spent by seniors was quadruple the average of \$2,793 for people under age 65. "What this report shows is the importance of our efforts to bring down the high cost of health care for America's seniors," CMS Administrator Mark B. McClellan, M.D., said in a statement. Although people aged 65 and over made up only 13% of the population in 1999, they accounted for 36% of personal health care spending, according to the report. Conversely, children made up 29% of the population but accounted only for 12% of personal health care spending.

Impact of Drug Advertisements

It's a good source for informing and educating patients about prescription drugs, but direct-to-consumer advertising also has its disadvantages, the Food and Drug Administration concluded from the results of three surveys. Two of the surveys focused on patients, but a third questioned 250 primary care physicians and 250 specialists on direct-to-consumer advertising's role in influencing practice patterns and patient interactions. Among physicians, 41% said direct-to-consumer advertising exposure had its benefits, increasing patient awareness about conditions and treatments. But another 41% thought exposure to an advertisement resulted in patient confusion about the effectiveness of the drug. Primary care physicians (38%) were more likely than were specialists (27%) to rate direct-to-consumer advertising as having a somewhat or very negative effect on their patients and practice.

Patients See Few Improvements

Many Americans haven't seen an improvement in health care quality since the release of the Institute of Medicine's report on medical errors 5 years ago. A telephone survey of 2,012 adults found that 40% thought the quality of health care has gotten worse over this time period, compared with the 17% who thought it had improved. Overall, 38% thought that quality of care stayed the same. Forty-eight percent said they were concerned about the safety of the medical care they received, and 55% said they were dissatisfied with the quality of care—up from 44% in a similar survey conducted 4 years ago. Patients with chronic conditions were more likely than were other consumers to express concerns about their quality of care, and to report experiences with medical errors. Survey sponsors included the Kaiser Family Foundation, the Agency for Healthcare Research and Quality, and the Harvard School of Public Health.

—Mary Ellen Schneider



62.5 mg and 125 mg film-coated tablets

Use of TRACLEER® requires attention to two significant concerns: 1) potential for serious liver injury, and 2) potential damage to a fetus.

WARNING: Potential liver injury. TRACLEER causes at least 3-fold upper limit of normal ULIN elevation of liver aminotransferases (ALT and AST) in about 11% of patients, accompanied by elevated bilirubin in a small number of cases. Because these changes are a marker for potential serious liver injury, they should be monitored prior to initiation of treatment and monthly thereafter. Potential liver injury and DOSAGE AND ADMINISTRATION. To date, in a setting of close monitoring, elevations have been reversible, within a few days to 3 weeks, either spontaneously or after discontinuation or continuation of treatment. Elevations in aminotransferases require close monitoring. DOSAGE AND ADMINISTRATION. TRACLEER should generally be avoided in patients with elevated aminotransferases (>3 x ULN) at baseline because monitoring liver injury may be more difficult. If liver aminotransferase elevations are accompanied by clinical symptoms of liver injury (such as nausea, vomiting, fever, abdominal pain, jaundice, or fatigue), TRACLEER should be stopped. There is no experience with the re-introduction of TRACLEER in these circumstances.

CONTRAINDICATIONS: Pregnancy. TRACLEER (bosentan) is very likely to produce major birth defects if used by pregnant women, as this effect has been conclusively shown in rodent studies. (See CONTRAINDICATIONS.) Therefore, pregnancy must be excluded before the start of treatment with TRACLEER and prevented thereafter by the use of a reliable method of contraception. Hormonal contraceptives, including oral, injectable and implantable contraceptives should not be used as the sole means of contraception because these may not be effective in patients receiving TRACLEER. (See Precautions: Drug Interactions.) Monthly pregnancy tests should be obtained.

Because of potential liver injury and in an effort to make the change of fetal exposure to TRACLEER (bosentan) as small as possible, TRACLEER may be prescribed only through the TRACLEER Access Program by calling 1 866 228 3266. Adverse events can be reported directly to the FDA at 1 800 555 0161.

INDICATIONS AND USAGE: TRACLEER is indicated for the treatment of pulmonary arterial hypertension in patients with WHO Class II or III symptoms, to improve exercise ability and decrease the rate of clinical worsening.

CONTRAINDICATIONS: TRACLEER is contraindicated in pregnancy, with concomitant use of cyclosporine A, with concomitant use of glyburide, and in patients who are hypersensitive to bosentan or any component of the medication.

Pregnancy Category X: TRACLEER is expected to cause fetal harm if administered to pregnant women. The similarity of malformations induced by bosentan and those observed in endothelial knockout mice and in animals treated with other endothelin receptor antagonist indicates that teratogenicity is a class effect of these drugs. There are no data on the use of TRACLEER in pregnant women. TRACLEER should be started only in patients known not to be pregnant. For female patients of childbearing potential, a prescription should be issued for the progestin-only oral contraceptive pills. The patient assures the prescriber that she is not sexually active or provides negative results from a urine or serum pregnancy test performed during the first 5 days of a normal menstrual period and at least 11 days after the last unprotected act of sexual intercourse. Follow-up urine or serum pregnancy tests should be obtained monthly thereafter. If elevated aminotransferase TRACLEER. The patient must be advised that if there is any delay in onset of menses or any other reason to suspect pregnancy, she must notify the physician immediately for pregnancy testing. If the pregnancy test is positive, the physician and patient must discuss the risk to the fetus.

WARNINGS: Potential Liver Injury. Elevations in ALT and AST by more than 3x ULN were observed in 11% of bosentan-treated patients (N = 698) compared to 2% of placebo-treated patients (N = 203). The combination of hepatocellular injury (increases in aminotransferases of >3 x ULN) and increase in total bilirubin (>3 x ULN) is a marker for potential serious liver injury. Elevations of AST and/or ALT associated with dose-dependent, acute, both early and late in treatment, usually progress slowly, are typically asymptomatic, and to date have been reversible after treatment interruption or cessation. These aminotransferase elevations may reverse spontaneously while continuing treatment with TRACLEER. Liver aminotransferase levels must be measured prior to initiation of treatment and monthly thereafter. If elevated aminotransferase levels are seen, changes in monitoring and treatment must be initiated. If liver aminotransferase elevations are accompanied by clinical symptoms of liver injury (such as nausea, vomiting, fever, abdominal pain, jaundice, or unusual lethargy or fatigue) or increases in bilirubin levels, TRACLEER should be stopped. There is no experience with the re-introduction of TRACLEER in these circumstances. Pre-existing Liver Impairment: TRACLEER should generally be avoided in patients with moderate or severe liver impairment. In addition, TRACLEER should generally be avoided in patients with elevated aminotransferases.

PRECAUTIONS: Hematologic Changes: Treatment with TRACLEER caused dose-related decreases in hemoglobin and hematocrit. The overall mean decrease in hemoglobin concentration in bosentan-treated patients was 0.9 g/dl (change to end of treatment). Most of this decrease was observed in patients with normal hemoglobin levels at baseline. In patients with normal hemoglobin levels stabilized by 4-12 weeks of bosentan treatment. In placebo-controlled studies of 11 g of bosentan, marked decreases in hemoglobin (>15% decrease from baseline resulting in values of all g/dl) were observed in 8% of bosentan-treated patients and in 2% of placebo-treated patients. In 8% of cases, the decrease occurred during the first 8 weeks of bosentan treatment. During the course of the bosentan concentration remained within normal limits in 86% of bosentan-treated patients compared to 76% of placebo patients. The explanation for the change in hemoglobin is not known, but it does not appear to be hemorrhagic or hemolytic. It is recommended that hemoglobin concentrations be checked after 1 and 2 months, and every 3 months thereafter. If a marked decrease in hemoglobin concentration occurs, further evaluation should be undertaken to determine the cause and need for specific treatment. Fluid retention in a placebo-controlled trial of patients with severe chronic heart failure, there was an increased incidence of hospitalization for CHF associated with weight gain and increased leg edema during the first 4-8 weeks of treatment with TRACLEER. In addition, there have been numerous post-marketing reports of fluid retention in patients with pulmonary hypertension, occurring within weeks after starting TRACLEER. Patients requiring intervention with a diuretic, fluid management, or hospitalization for decompensating heart failure.

Information for Patients: Patients are advised to consult the TRACLEER Medication Guide on the safe use of TRACLEER. The physician should discuss with the patient the importance of monthly monitoring of serum aminotransferases and urine or serum pregnancy tests. Patients should be instructed to stop taking TRACLEER if they experience any symptoms of liver injury, including nausea, vomiting, fever, abdominal pain, jaundice, or unusual lethargy or fatigue, and to contact their physician immediately. The physician should discuss with the patient the importance of using an effective birth control method and the importance of using a reliable method of contraception and measures to prevent pregnancy with their female partners. Input from a gynecologist or similar expert on adequate contraception should be sought as needed.

Drug Interactions: Bosentan is metabolized by CYP2C3 and CYP2A6. Inhibition of these isoenzymes may increase the plasma concentration of bosentan. Bosentan is an inhibitor of CYP2A6 and CYP2C3. Consequently, plasma concentrations of drugs metabolized by these two isoenzymes will be decreased when TRACLEER is co-administered. Contraceptives: Specific interaction studies have not been performed to evaluate the effect of co-administration of bosentan and hormonal contraceptives, including oral, injectable or implantable contraceptives. Since many of these drugs are metabolized by CYP2A6, there is a possibility of failure of contraception when TRACLEER is co-administered. Women should not rely on hormonal contraception alone when taking TRACLEER. Cyclosporine A: During the first day of concomitant administration, trough concentrations of bosentan were 2-fold. No dose adjustment of bosentan is necessary. Plasma concentrations were 3- to 4-fold higher than in the absence of cyclosporine A. (See CONTRAINDICATIONS.) Tacrolimus: Co-administration of tacrolimus and bosentan has not been studied in man. Co-administration of tacrolimus and bosentan resulted in markedly increased plasma concentrations of tacrolimus. Bosentan may be expected to affect the pharmacokinetics of tacrolimus and bosentan are used together. Glyburide: An increased risk of elevated liver aminotransferases was observed in patients receiving concomitant therapy with glyburide (See CONTRAINDICATIONS). Alternative hypoglycemic agents should be considered. Bosentan also has potential to interact with oral hypoglycemic agents that are primarily metabolized by CYP2C3 or CYP2A6. The possibility of worsened glucose control in patients using these agents should be considered. Ketconazole: Co-administration of bosentan 125 mg bid and ketconazole, a potent CYP2A6 inhibitor, increased the plasma concentrations of bosentan. Bosentan is a substrate of CYP2A6. Consequently, plasma concentrations increased effects of bosentan should be considered. Simvastatin and Other Statins: Co-administration of bosentan decreased the plasma concentrations of simvastatin in CYP2A6 substrate, and its active β -hydroxy acid metabolite, by approximately 50%. The plasma concentrations of bosentan were not affected. Bosentan may be expected to affect the plasma concentrations of other statins that have significant metabolites by CYP2A6, eg, lovastatin and atorvastatin. The possibility of reduced statin efficacy should be considered. Patients using CYP2A6 metabolized statins should have cholesterol levels monitored after TRACLEER therapy. Warfarin: Co-administration of bosentan 500 mg bid for 5 days decreased the plasma concentrations of both S-warfarin (a CYP2C3 substrate) and R-warfarin (a CYP2A6 substrate) by 25 and 38%, respectively. Clinical experience with concomitant administration of bosentan and warfarin in patients with pulmonary hypertension has shown no clinically significant changes in INR or warfarin dose (baseline vs. end of the clinical studies), and the need to change the warfarin dose during the trials due to INR or drug to adverse events were similar among bosentan- and placebo-treated patients. Digoxin, Nitroglycerin and Losartan: Bosentan has not been studied for any pharmacokinetic interactions with digoxin and nitroglycerin, and losartan has no effect on plasma levels of bosentan.

Carcinogenesis, Mutagenesis, Impairment of Fertility: Two years of dietary administration of bosentan to mice produced an increased incidence of adenocarcinomas of the forestomach. The maximum tolerated dose (MTD) of 125 mg b.i.d., on a mg/m² basis. In the same study, doses greater than about 32 times the MTD were associated with an increased incidence of colon adenomas in both males and females. In rats, dietary administration of bosentan for 2 years was associated with an increased incidence of brain astrocytomas in males at doses about 16 times the MTD. Impairment of Fertility: Many endothelin receptor antagonists have profound effects on the histology and function of the testes in animals. These drugs have been shown to induce atrophy of the seminiferous tubules of the testes and to reduce sperm counts and male fertility in rats when administered for longer than 10 weeks. Where studied, testicular tubule atrophy and decreases in male fertility followed by endothelin receptor antagonists appear reversible. In fertility studies in which male and female rats were treated with bosentan at oral doses up to 50 times the MTD on a mg/m² basis, no effect on male or female fertility was observed. An increased incidence of testicular tubule atrophy was observed in rats given bosentan orally at doses as low as about 4 times the MTD for two years but not at doses as high as about 50 times the MTD for 6 months. An increased incidence of testicular tubule atrophy was observed in rats when administered orally at doses about 75 times the MTD or in dogs treated up to 12 months at doses up to about 50 times the MTD. There are no data on the effects of bosentan or other endothelin receptor antagonists on testicular function in man.

Pregnancy, Teratogenic Effects, Category X: SPECIAL POPULATIONS: Nursing Mothers: It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, breastfeeding while taking TRACLEER is not recommended. Pediatric Use: Safety and efficacy in pediatric patients have not been established. Use in Elderly Patients: Subject to a clinical experience with TRACLEER in cases aged 65 and older, bosentan should be used with caution in elderly patients. Subject to a clinical experience with TRACLEER in elderly and younger patients.

ADVERSE REACTIONS: Safety data on bosentan were obtained from 12 clinical studies (8 placebo-controlled and 4 open-label) in 777 patients with pulmonary arterial hypertension, and other diseases. Treatment discontinuations due to adverse events other than those related to pulmonary hypertension during the clinical trials in patients with pulmonary arterial hypertension were more frequent on bosentan (5%; 8/165 patients) than on placebo (3%; 2/82 patients). In this database the only cause of discontinuations > 1%, and occurring more often on bosentan than on placebo was liver function. In placebo-controlled studies of bosentan in pulmonary arterial hypertension and for other diseases (primarily heart failure), a total of 677 patients were treated with bosentan at daily doses ranging from 100 mg to 2000 mg and 288 patients were treated with placebo. The duration of treatment ranged from 4 weeks to 16 months. For the adverse drug reactions that occurred in > 2% of bosentan-treated patients and were not observed in placebo-treated patients, the differences between bosentan and placebo (z: % difference) were headache (16% vs. 13%), flushing (7% vs. 2%), abnormal hepatic function (6% vs. 2%), leg edema (5% vs. 1%), and anemia (5% vs. 1%). Additional adverse reactions that occurred in > 3% of bosentan-treated patients but were not observed in placebo-treated patients were: nasopharyngitis (11% vs. 6%), hypotension (10% vs. 6%), palpitations (6% vs. 1%), dyspepsia (4% vs. 0%), edema (4% vs. 3%), fatigue (4% vs. 1%), and pruritus (4% vs. 0%).

Long-Term Treatment: The long-term follow-up of the patients who were treated with TRACLEER in the two pivotal studies and their open-label extensions (N=225) shows that 83% and 84% of patients were still alive at 1 and 2 years, respectively, with no start of treatment with TRACLEER. These estimates may be influenced by the presence of iproprosteno treatment which was administered to 43/225 patients. Without a control group, these data must be interpreted cautiously and cannot be interpreted as an improvement in survival.

Special Considerations: Patients with Congestive Heart Failure: CAPRA based on the results of a pair of studies with 1613 subjects, bosentan is not effective in the treatment of CHF with left ventricular dysfunction.

OVERDOSE: Bosentan has been given as a single dose of up to 2400 mg in normal volunteers, or up to 2000 mg/day for 2 months in patients, without any major clinical consequences. The most common side effect was headache mild to moderate severity. There is no specific experience of overdose with bosentan beyond the doses described above. Massive overdose may result in pronounced hypotension requiring active cardiovascular support.

DOSE AND ADMINISTRATION: TRACLEER treatment should be initiated at a dose of 62.5 mg b.i.d. for 4 weeks and then adjusted to the maintenance dose of 125 mg b.i.d. Doses above 125 mg b.i.d. did not appear to confer additional benefit sufficient to offset the increased risk of liver injury. Tablets should be administered morning and evening with or without food.

Dosage Adjustment and Monitoring in Patients Developing Aminotransferase Abnormalities

ALT/AST levels	Treatment and monitoring recommendations
> 3 and ≤ 5x ULN	Confirm by another aminotransferase test if confirmed, reduce the daily dose or interrupt treatment, and monitor aminotransferase levels at least every 2 weeks. If the aminotransferase levels return to pre-treatment values, continue or re-introduce the treatment at appropriate dose.
> 5 and ≤ 8x ULN	Confirm by another aminotransferase test if confirmed, stop treatment and monitor aminotransferase levels at least every 2 weeks. Once the aminotransferase levels return to pre-treatment values, consider re-introduction of the treatment (see below).
> 8 x ULN	Treatment should be stopped and re-introduction of TRACLEER should not be considered. There is no experience with the re-introduction of TRACLEER in these circumstances.

If TRACLEER is re-introduced it should be at the starting dose; aminotransferase levels should be checked within 3 days and thereafter according to the recommendations above. If liver aminotransferase elevations are accompanied by clinical symptoms of liver injury (such as nausea, vomiting, fever, abdominal pain, jaundice, or unusual lethargy or fatigue) or increases in bilirubin (> 3 x ULN), treatment should be stopped. There is no experience with the re-introduction of TRACLEER in these circumstances. Use in Women of Child-bearing Potential: TRACLEER treatment should only be initiated in women of child-bearing potential following a negative pregnancy test and only in those who practice adequate contraception that should be exercised in dose selection for elderly patients given the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy in this age group. Dosage Adjustment in Hepatically Impaired Patients: The influence of liver impairment on the pharmacokinetics of TRACLEER has not been evaluated. There is no specific experience of overdose with bosentan beyond the doses described above. Patients with moderate or severe liver impairment would be expected to increase exposure to bosentan. There are no specific data on dose-giving in hepatically impaired patients; caution should be exercised in patients with mildly impaired liver function. TRACLEER should generally be avoided in patients with moderate or severe liver impairment. In addition, TRACLEER should generally be avoided in pediatric patients who have not been established. Dosage Adjustment in Patients with Low Body Weight: In patients with a body weight below 40 kg but who are over 12 years of age the recommended initial and maintenance dose is 62.5 mg b.i.d. (below 40 kg), limited to approximately 25% of body weight. No evidence of a dose-effect relationship in patients with a low body weight below 40 kg has been observed. Nevertheless, to avoid the potential for clinical deterioration, gradual dose reduction (62.5 mg bid for 3 to 4 days) should be considered.

HOW SUPPLIED: 62.5 mg film-coated, round, bicovex, orange-white tablets, embossed with identification marking "62.5". 125 mg film-coated, round, bicovex, orange-white tablets, embossed with identification marking "125". NDC 62512-102-06. Bottle containing 60 tablets. Rx only.

Storage and Stability: 25°C (77°F). Excursions are permitted between 15°C and 30°C (59°F and 86°F). (See USP Controlled Room Temperature).

References: See pages 1, 2, 3, and 11. 1. Zornerman HJ. Hypertension. The adverse effects of drugs and other chemicals on the liver. Second ed. Philadelphia: Lippincott, 1995. **References for previous page:** 1. Braunwald E, Fauci AS, Kasper DL, Hauser SL, Longo D, Jameson JL, eds. *Harrison's Principles of Internal Medicine*. Vol. 2. 15th ed. New York: McGraw-Hill; 2001. 2. Minao O, Dweck RL, Arrigola AC. Manifestations of scleroderma pulmonary disease. *Clin Chest Med* 1998; 37(3): 731-731. 3. Frerking A, Ganev SP, Rubin LA. Primary pulmonary hypertension. *Lancet* 1998; 352(9179): 725-4. 4. Rich S, et al. Primary pulmonary hypertension: executive summary. *World Symposium—Primary Pulmonary Hypertension*. 1998. Evan, France; September 8-10, 1998. 5. Braunwald E, Zipes DP, Libby P, eds. *Heart Disease*. 2 vols. 6th ed. Philadelphia, Pa: WB Saunders Co; 2001:1621-1918. 6. Rubin LA, Badesch DB, Barré RJ, et al. Bosentan therapy for pulmonary arterial hypertension. *N Engl J Med* 2002; 346: 988-903. 7. Tracleer (bosentan) full prescribing information. *Action Pharmaceuticals Inc., Inc.*. 2003. 8. Data on file, Actelion Pharmaceuticals.

Manufactured by: Patheon Inc. Mississauga, Ontario, CANADA

Marketed by: Actelion Pharmaceuticals Inc. South San Francisco, CA

