

POLICY & PRACTICE

Majority of TBIs Are Pediatric

Children and teens ages 5-18 years account for more than half of the 207,830 traumatic brain injuries related to sports or recreation that are treated in U.S. emergency departments each year, according to the Centers for Disease Control and Prevention. This population is at increased risk for concussion during sports and recreational activities, as well as long-term sequelae, delayed recovery, and cumulative consequences of multiple traumatic brain injuries, CDC researchers wrote in the July 27 issue of the *Morbidity and Mortality Weekly Report*. The activities associated with the greatest number of visits to the ED for traumatic brain injuries in this population included bicycling, football, playground activities, basketball, and soccer. The results are based on data from the National Electronic Injury Surveillance System—All Injury Program from 2001-2005. More information on traumatic brain injury, including physician tool kits, is available online at www.cdc.gov/ncipc/tbi/tbi.htm.

New Stem Cell Legislation Introduced

Members of Congress recently introduced legislation aimed at increasing research into stem cells without the creation or destruction of human embryos for research purposes. The bill, the "Patients First Act of 2007" (H.R. 2807) was introduced by Rep. J. Randy Forbes (R-Va.) and Rep. Daniel Lipinski (D-Ill.). The legislation directs the Department of Health and Human Services to support basic and applied stem cell research that does not involve the creation of a human embryo for research purposes or the destruction or discarding of a living human embryo. It also calls on the HHS secretary to submit a report to Congress detailing the funding of stem cell research. The bill was referred to the House Committee on Energy and Commerce.

APhA Urges Delay in Rx Rule

The American Pharmacists Association and three lawmakers have urged CMS to delay implementation of a new federal mandate requiring the use of tamper-resistant prescription pads for all Medicaid prescriptions beginning Oct. 1. Although many states have similar requirements, it will take much longer than 3 months to roll out such a program across the country, said APhA executive vice president and CEO John Gans in a statement. The three lawmakers—Rep. Charlie Wilson (D-Ohio), Rep. Marion Berry (D-Ark.), and Rep. Mike Ross (D-Ark.)—say that most physicians do not currently use this type of pads, nor are supplies readily available. "The tamperproof pad law was designed to prevent Medicaid fraud," the legislators said in a statement. "However, the timeline for implementation could result in patients being turned away from their pharmacies as of Oct. 1, 2007, if doctors fail to write prescriptions on 'tamper-resistant' paper." The congressmen have introduced a bill that would require only prescriptions for Class II narcotics to be written on the tamperproof prescription pads.

E-Prescribing Called 'Win-Win'

Electronic prescribing could prevent nearly 2 million medication errors and

save the federal government \$26 billion over the next decade—even after providing funds for equipment, training, and support—if physicians were required to use the technology for their Medicare patients, according to a study released by the Pharmaceutical Care Management Association. The study found that when physicians use e-prescribing to learn their patients' medication history and prescription choices, both patient safety and savings improve dramatically. However, fewer than 1 in 10 physicians actually use e-prescribing, according to PCMA. The

group, which represents pharmacy benefit managers, is pushing the Centers for Medicare and Medicaid Services to require e-prescribing for all Medicare Part D prescriptions by 2010.

Most Substance Abusers Work

A new survey by the Substance Abuse and Mental Health Services Administration shows that most of the nation's 16.4 million illicit drug users and 15 million heavy alcohol users are employed full time. The report, available at SAMHSA's Web site, is compiled from the 2002, 2003, and 2004 National Surveys on Drug Use and Health. The data are somewhat

misleading because full-time workers account for two-thirds of the survey population, according to SAMHSA. Illicit drug use was highest, at 19%, among the cohort aged 18-25 years, compared with 10% for those aged 26-34 years, 7% for those aged 35-49 years, and 3% for those aged 50-64 years. The highest rates of current use were among food service workers (17%) and construction workers (15%). Alcohol use was highest among construction, mining, excavation, and drilling workers (18%), and installation, maintenance, and repair workers (15%).

—Mary Ellen Schneider



BRIEF SUMMARY OF FULL PRESCRIBING INFORMATION

INDICATIONS AND USAGE

Rebif® (interferon-beta-1a) is indicated for the treatment of patients with relapsing forms of multiple sclerosis to decrease the frequency of clinical exacerbations and delay the accumulation of physical disability. The efficacy of Rebif® in chronic progressive multiple sclerosis has not been established.

Clinical Studies

Two multicenter studies evaluated the safety and efficacy of Rebif® in patients with relapsing-remitting multiple sclerosis. Study 1 demonstrated that Rebif® significantly reduced the number of relapses per patient compared to placebo at 2 years. Study 2 was a comparative trial comparing Rebif® 44 mcg sc tiw and Avonex® 30 mcg im qw. The results of this trial demonstrated that patients treated with Rebif® 44 mcg sc tiw were more likely to remain relapse-free at 24 and 48 weeks than were patients treated with Avonex® 30 mcg im qw. Adverse reactions over 48 weeks were generally similar between the two treatment groups. Exceptions included injection site disorders (83% of patients on Rebif® vs. 28% of patients on Avonex®), hepatic function disorders (18% on Rebif® vs. 10% on Avonex®), and leukopenia (6% on Rebif® vs. <1% on Avonex®), which were observed with greater frequency in the Rebif® group compared to the Avonex® group.

CONTRAINDICATIONS

Rebif® (interferon beta-1a) is contraindicated in patients with a history of hypersensitivity to natural or recombinant interferon, human albumin, mannitol USP, sodium acetate, or Water for Injection USP.

WARNINGS

Rebif® (interferon beta-1a) should be used with caution in patients with depression, a condition that is common in people with multiple sclerosis. Depression, suicidal ideation, and suicide attempts have been reported to occur with increased frequency in patients receiving interferon compounds, including Rebif®. Patients should be advised to report immediately any symptoms of depression and/or suicidal ideation to the prescribing physician. If a patient develops depression, cessation of treatment with Rebif® should be considered.

Severe liver injury, including some cases of hepatic failure requiring liver transplantation has been reported rarely in patients taking Rebif®. Symptoms of liver dysfunction began from one to six months following the initiation of Rebif®. If jaundice or other symptoms of liver dysfunction appear, treatment with Rebif® should be discontinued immediately due to the potential for rapid progression to liver failure. Asymptomatic elevation of hepatic transaminases (particularly SGPT) is common with interferon therapy (see ADVERSE REACTIONS). Rebif® should be initiated with caution in patients with active liver disease, alcohol abuse, increased serum SGPT (>2.5 times ULN), or a history of significant liver disease. Also, the potential risk of Rebif® used in combination with known hepatotoxic products should be considered prior to Rebif® administration, or when adding new agents to the regimen of patients already on Rebif®. Reduction of Rebif® dose should be considered if SGPT rises above 5 times the upper limit of normal. The dose may be gradually re-escalated when enzyme levels have normalized.

Anaphylaxis and other allergic reactions (some severe) have been reported as a rare complication of Rebif®. Other allergic reactions have included skin rash and urticaria, and have ranged from mild to severe without a clear relationship to dose or duration of exposure. Several allergic reactions, some severe, have occurred after prolonged use.

PRECAUTIONS

General: Caution should be exercised when administering Rebif® to patients with pre-existing seizure disorders. Seizures have been associated with the use of beta interferons. A relationship between occurrence of seizures and the use of Rebif® has not been established. Leukopenia and new or worsening thyroid abnormalities have developed in some patients treated with Rebif®. Regular monitoring for these conditions is recommended.

Information for Patients: All patients should be instructed to read the Rebif® Medication Guide supplied to them. Patients should be cautioned not to change the dosage or the schedule of administration without medical consultation. Patients should be informed of the most common and the most severe adverse reactions associated with the use of Rebif®. Patients should be advised of the symptoms associated with these conditions, and to report them to their physician.

Female patients should be cautioned about the abortifacient potential of Rebif®.

Patients should be instructed in the use of aseptic technique when administering Rebif®. Appropriate instruction for self-injection or injection by another person should be provided, including careful review of the Rebif® Medication Guide. If a patient is to self-administer Rebif®, the physical and cognitive ability of that patient to self-administer and properly dispose of syringes should be assessed. The initial injection should be performed under the supervision of an appropriately qualified health care professional. Patients should be advised of the importance of rotating sites of injection with each dose, to minimize the likelihood of severe injection site reactions or necrosis.

Laboratory Tests: In addition to those laboratory tests normally required for monitoring patients with multiple sclerosis, blood cell counts and liver function tests are recommended at regular intervals (1, 3, and 6 months) following introduction of Rebif® therapy and then periodically thereafter in the absence of clinical symptoms. Thyroid function tests are recommended every 6 months in patients with a history of thyroid dysfunction or as clinically indicated. Patients with myelosuppression may require more intensive monitoring of complete blood cell counts, with differential and platelet counts.

Immunization: Patients taking Rebif® may receive concomitant influenza vaccination and achieve similar positive antibody response to the vaccination as patients not receiving Rebif®. The exact relationship of antibody titers to vaccine efficacy is unknown in patients taking Rebif®.

Drug Interactions: Drug interaction studies have not been conducted with Rebif®. Due to its potential to cause neutropenia and lymphopenia, proper monitoring of patients is required if Rebif® is given in combination with myelosuppressive agents. Also, the potential for hepatic injury should be considered when Rebif® is used in combination with other products associated with hepatic injury, or when new agents are added to the regimen of patients already on Rebif® (see WARNINGS).

Carcinogenesis, Mutagenesis, Impairment of Fertility: No carcinogenicity data for Rebif® are available in animals or humans. Rebif® was not mutagenic when tested in the Ames bacterial test and in an *in vitro* cytogenetic assay in human lymphocytes in the presence and absence of metabolic activation. No studies have been conducted to evaluate the effects of Rebif® on fertility in humans. In studies in normally cycling female cynomolgus monkeys given daily sc injections of Rebif® for six months at doses of up to 9 times the recommended weekly human dose (based on body surface area), no effects were observed on either menstrual cycling or serum estradiol levels. The validity of extrapolating doses used in animal studies to human doses is not established. In male monkeys, the same doses of Rebif® had no demonstrable adverse effects on sperm count, motility, morphology, or function.

Pregnancy Category C: Rebif® treatment has been associated with significant increases in embryolethal or abortifacient effects in cynomolgus monkeys administered doses approximately 2 times the cumulative weekly human dose (based on either body weight or surface area) either during the period of organogenesis (gestation day 21-89) or later in pregnancy. There were no fetal malformations or other evidence of teratogenesis noted in these studies. These effects are consistent with the abortifacient effects of other type I interferons. There are no adequate and well-controlled studies of Rebif® in pregnant women. However, in Studies 1 and 2, there were 2 spontaneous abortions observed and 5 fetuses carried to term among 7 women in the Rebif® groups. If a woman becomes pregnant or plans to become pregnant while taking Rebif®, she should be informed about the potential hazards to the fetus and discontinuation of Rebif® should be considered. A pregnancy registry has been established to monitor pregnancy outcomes of women exposed to Rebif® while pregnant. Register patients online at www.RebifPregnancyRegistry.com or call MS LifeLines™ at 1-877-447-3243.

Nursing Mothers: It is not known whether Rebif® is excreted in human milk.

Pediatric Use: The safety and effectiveness of Rebif® in pediatric patients have not been studied.

Geriatric Use: Clinical studies of Rebif® did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently than younger subjects.

ADVERSE REACTIONS

The most frequently reported serious adverse reactions with Rebif® were psychiatric disorders including depression and suicidal ideation or attempt (see WARNINGS). The incidence of depression of any severity in the Rebif®-treated groups and placebo-treated group was approximately 25%. In post-marketing experience, Rebif® administration has been rarely associated with severe liver dysfunction, including hepatic failure requiring liver transplantation (see WARNINGS). The most commonly reported adverse reactions were injection site disorders, influenza-like symptoms (headache, fatigue, fever, rigors, chest pain, backpain, myalgia), abdominal pain, depression, elevation of liver enzymes and hematologic abnormalities. The most frequently reported adverse reactions resulting in clinical intervention (e.g., discontinuation of Rebif®, adjustment in dosage, or the need for concomitant medication to treat an adverse reaction symptom) were injection site disorders, influenza-like symptoms, depression and elevation of liver enzymes (See WARNINGS). Injection site necrosis was rare.

Table 1. Adverse Reactions and Laboratory Abnormalities in Study 1

BODY SYSTEM Preferred Term	Rebif® Placebo tiw (n=187)	Rebif® 22 mcg tiw (n=189)	44mcg tiw (n=184)
BODY AS A WHOLE			
Influenza-like symptoms	51%	56%	59%
Headache	63%	65%	70%
Fatigue	36%	33%	41%
Fever	16%	25%	28%
Rigors	5%	6%	13%
Chest Pain	5%	6%	8%
Malaise	1%	4%	5%
INJECTION SITE DISORDERS			
Injection Site Reaction	39%	89%	92%
Injection Site Necrosis	0%	1%	3%
CENTRAL & PERIPHERAL NERVOUS SYSTEM DISORDERS			
Hypertonia	5%	7%	6%
Coordination Abnormal	2%	5%	4%
Convulsions	2%	5%	4%
ENDOCRINE DISORDERS			
Thyroid Disorder	3%	4%	6%
GASTROINTESTINAL SYSTEM DISORDERS			
Abdominal Pain	17%	22%	20%
Dry Mouth	1%	1%	5%
LIVER AND BILIARY SYSTEM DISORDERS			
SGPT Increased	4%	20%	27%
SGOT Increased	4%	10%	17%
Hepatic Function Abnormal	2%	4%	9%
Bilirubinaemia	1%	3%	2%
MUSCULO-SKELETAL SYSTEM DISORDERS			
Myalgia	20%	25%	25%
Back Pain	20%	23%	25%
Skeletal Pain	10%	15%	10%
HEMATOLOGIC DISORDERS			
Leukopenia	14%	28%	36%
Lymphadenopathy	8%	11%	12%
Thrombocytopenia	2%	2%	8%
Anemia	3%	3%	5%
PSYCHIATRIC DISORDERS			
Somnolence	1%	4%	5%
SKIN DISORDERS			
Rash Erythematous	3%	7%	5%
Rash Maculo-Papular	2%	5%	4%
URINARY SYSTEM DISORDERS			
Micturition Frequency	4%	2%	7%
Urinary Incontinence	2%	4%	2%
VISION DISORDERS			
Vision Abnormal	7%	7%	13%
Xerophthalmia	0%	3%	1%

Rebif® is intended for use under the guidance and supervision of a physician. It is recommended that physicians or qualified medical personnel train patients in the proper technique for self-administering subcutaneous injections using the pre-filled syringe. Patients should be advised to rotate sites for sc injections. Concurrent use of analgesics and/or antipyretics may help ameliorate flu-like symptoms on treatment days. Rebif® should be inspected visually for particulate matter and discoloration prior to administration.

Rx only.

Manufacturer: EMD Serono, Inc., Rockland, MA 02370

Co-marketed by: EMD Serono, Inc., Rockland, MA 02370
Pfizer, Inc., New York, NY 10017

Rebif is a registered trademark of EMD Serono, Inc.
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