POLICY & PRACTICE

VA Accepts POWs' Osteoporosis

Officials at the Department of Veterans Affairs are proposing to extend benefits to former prisoners of war who suffer from disabling osteoporosis. In a proposed rule, the VA seeks to establish a presumption of service connection for osteoporosis that's at least 10% disabling in veterans held at least 30 days as POWs. Several studies have shown that POWs suffered serious bone loss following captivity because of dietary deficiencies during their imprisonment.

New Site for Arthritis Patients

The Arthritis Foundation has launched a new online resource to inspire people with arthritis to engage in physical activity. The "Let's Move Together" Web site (www.letsmovetogether.org) includes exercise tips, suggestions on how to incorporate movement into daily activities, and a physical activity tracker. The site explains the health benefits of activities such as stationary cycling, walking, gardening, and water aerobics. It also includes blogs and message boards for personal stories from arthritis patients. "Physical activity, such as walking, is crucial to managing joint pain, improving mobility, and reducing fatigue often associated with arthritis," Dr. Patience White, chief public health officer for the Arthritis Foundation, said in a statement. The site includes information on local Arthritis Walk events around the country.

OA Initiative Biospecimens Available

Researchers can now obtain serum, plasma, DNA, and other biospecimens collected as part of the Osteoarthritis Initiative. The Osteoarthritis Initiative is a research partnership between the National Institutes of Health and private industry that aims to improve the diagnosis and monitoring of osteoarthritis. The study, which began enrolling participants in 2004, includes men and women age 45 and older who are at risk for developing osteroarthritis and those who early disease. Biospecimens are available for the entire cohort (4,796 participants) for the baseline, 12-month, and 24-month follow-up visits. A committee appointed by NIH will review researcher requests for biospecimens based on significance, approach, innovation, investigator qualifications, plans for data sharing, and research environment. The committee will also take into account the potential for the proposed research to advance the understanding or treatment of osteoarthritis.

FDA Posts Guidance on Handouts

The FDA has issued updated guidance for manufacturers that distribute journal articles or other scientific publications concerning off-label uses for their FDA-approved drugs, devices, or biologics. On its Web site, the agency suggests that distributed journal articles be only from organizations using editorial boards with "demonstrated expertise in the subject of the article," independence to review articles, and fully disclosed conflicts of interest. Authors and editors should also disclose conflicts. Acceptable articles can't be from special supplements funded even partially by a manufacturer. In its presentation to practitioners, an article shouldn't be highlighted, otherwise marked up, or attached to promotional materials.

PhRMA Revises Ad Guidelines

The Pharmaceutical Research and Manufacturers of America recently advised drug makers to state when actors portray medical professionals in direct-to-consumer drug advertisements and to acknowledge any compensation given to real medical professionals in ads. In addition, the new, nonbinding guidelines support the inclusion of "black box" warnings in the ads, and reinforce that companies shouldn't promote off-label uses. Rep. John Dingell (D-Mich.), who has led investigations into direct-to-consumer ads, commended PhRMA for the new guidelines but noted that the organization hasn't endorsed a 2-year prohibition on such ads for newly approved drugs, as recommended by the Institute of Medicine.

New EHR Certification Options

The Certification Commission for Healthcare Information Technology plans to endorse ambulatory electronic health record (EHR) products that offer advanced capabilities in four new areas: clinical research, dermatology, advanced interoperability, and advanced quality. The CCHIT currently offers voluntary certification in both the ambulatory and inpatient settings to vendors of EHRs that support basic clinical tasks, are able to send and receive information, and provide security for medical information. The new options for product certification would be added in 2010. The CCHIT is recognized by the federal government as the official reviewer of products in health information technology. CCHIT chair Dr. Mark Leavitt said in a statement that in the next few years, the commission may develop optional add-on certifications.

—Mary Ellen Schneider

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Other Adverse Reactions
Table 10 summarizes events reported in at least 3% of all patients with higher incidence in patients treated with ENBREL compared to controls in placebo-controlled RA trials (including the combination methotrexate trial) and relevant events from Study III. In placebo-controlled plaque psoriasis trials, the percentages of patients reporting injection site reactions were lower in the placebo dose group (6.4%) than in the ENBREL dose groups (15.5%) in Studies I and II. Otherwise, the percentages of patients reporting adverse events in the 50 mg twice a week dose group were similar to those observed in the 25 mg twice a week dose group or placebo group. In psoriasis Study I, there were no serious adverse events of worsening psoriasis following withdrawal of study drug. However, adverse events of worsening psoriasis including three serious adverse events were observed during the course of the clinical trials. Urticaria and non-infectious hepatitis were observed in a small number of patients and angioedema was observed in one patient in clinical studies. Urticaria and angioedema have also been reported in spontaneous post-marketing reports. Adverse events in psoriatic arthritis, ankylosing spondylitis, and plaque psoriasis trials were similar to those reported in RA clinical trials.

Table 10:

Percent of RA Patients Reporting Adverse Events in Controlled Clinical Trials*

	Placebo Controlled		Active Controlled (Study III)	
	Percent of patients		Percent of patients	
Event	Placebo† (N = 152)	ENBREL (N = 349)	MTX (N = 217)	ENBREL (N = 415)
Injection site reaction	10	37	7	34
Infection (total)**	32	35	72	64
Non-upper respiratory infection (non-URI)**	32	38	60	51
Upper respiratory infection (URI)**	16	29	39	31
Headache	13	17	27	24
Nausea	10	9	29	15
Rhinitis	8	12	14	16
Dizziness	5	7	11	8
Pharyngitis	5	7	9	6
Cough	3	6	6	5
Asthenia	3	5	12	11
Abdominal pain	3	5	10	10
Rash	3	5	23	14
Peripheral edema	3	2	4	8
Respiratory disorder	1	5	NA	NA
Dyspepsia	1	4	10	11
Sinusitis	2	3	3	5
Vomiting	-	3	8	5
Mouth ulcer	1	2	14	6
Alopecia	1	1	12	6
Pneumonitis ("MTX lung")	-	-	2	0

* Includes data from the 6-month study in which patients received concurrent MTX therapy.
† The duration of exposure for patients receiving placebo was less than the ENBREL-treated patients.
** Infection (total) includes data from all three placebo-controlled trials. Non-URI and URI include data only from the two placebo-controlled trials where infections were collected separately from adverse events (placebo N = 110, ENBREL N = 213).

In controlled trials of RA and psoriatic arthritis, rates of serious adverse events were seen at a frequency of approximately 5% among ENBREL- and control-treated patients. In controlled trials of plaque psoriasis, rates of serious adverse events were seen at a frequency of < 1.5% among ENBREL- and placebo-treated patients in the first 3 months of treatment. Among patients with RA in placebo-controlled, active-controlled, and open-label trials of ENBREL, malignancies (see **WARNINGS: Malignancies, ADVERSE REACTIONS: Malignancies**) and infections (see **ADVERSE REACTIONS: Infections**) were the most common serious adverse events observed. Other infrequent serious adverse events observed in RA, psoriatic arthritis, ankylosing spondylitis, or plaque psoriasis clinical trials are listed by body system below:

Cardiovascular: heart failure, myocardial infarction, myocardial ischemia, hypertension, hypotension, deep vein thrombosis, thrombophlebitis
Digestive: cholecystitis, pancreatitis, gastrointestinal hemorrhage, appendicitis
Hematologic/Lymphatic: lymphadenopathy
Musculoskeletal: bursitis, polymyositis
Nervous: cerebral ischemia, depression, multiple sclerosis (see **WARNINGS: Neurologic Events**)
Respiratory: dyspnea, pulmonary embolism, sarcoidosis
Skin: worsening psoriasis
Urogenital: membranous glomerulonephropathy, kidney calculus

In a randomized controlled trial in which 51 patients with RA received ENBREL 50 mg twice weekly and 25 patients received ENBREL 25 mg twice weekly, the following serious adverse events were observed in the 50 mg twice weekly arm: gastrointestinal bleeding, normal pressure hydrocephalus, seizure, and stroke. No serious adverse events were observed in the 25 mg arm.

Adverse Reactions in Patients with JIA
In general, the adverse events in pediatric patients were similar in frequency and type as those seen in adult patients (see **WARNINGS** and other sections under **ADVERSE REACTIONS**). Differences from adults and other special considerations are discussed in the following paragraphs.
Severe adverse reactions reported in 69 JIA patients ages 4 to 17 years included varicella (see also **PRECAUTIONS: Immunizations**), gastroenteritis, depression/personality disorder, cutaneous ulcer, esophagitis/gastritis, group A streptococcal septic shock, Type 1 diabetes mellitus, and soft tissue and post-operative wound infection.
Forty-three of 69 (62%) children with JIA experienced an infection while receiving ENBREL during three months of study (part 1 open-label), and the frequency and severity of infections was similar in 58 patients completing 12 months of open-label extension therapy. The types of infections reported in JIA patients were generally mild and consistent with those commonly seen in outpatient pediatric populations. Two JIA patients developed varicella infection and signs and symptoms of aseptic meningitis which resolved without sequelae.
The following adverse events were reported more commonly in 69 JIA patients receiving 3 months of ENBREL compared to the 349 adult RA patients in placebo-controlled trials. These included headache (19% of patients, 1.7 events per patient-year), nausea (9%, 1.0 events per patient-year), abdominal pain (19%, 0.74 events per patient-year), and vomiting (13%, 0.74 events per patient-year).
In open-label clinical studies of children with JIA, adverse events reported in those aged 2 to 4 years were similar to adverse events reported in older children.
In post-marketing experience, the following additional serious adverse events have been reported in pediatric patients: abscess with bacteremia, optic neuritis, pancytopenia, seizures, tuberculous arthritis, urinary tract infection (see **WARNINGS**), coagulopathy, cutaneous vasculitis, and transaminase elevations. The frequency of these events and their causal relationship to ENBREL therapy are unknown.

Patients with Heart Failure
Two randomized placebo-controlled studies have been performed in patients with CHF. In one study, patients received either ENBREL 25 mg twice weekly, 25 mg three times weekly, or placebo. In a second study, patients received either ENBREL 25 mg once weekly, 25 mg twice weekly, or placebo. Results of the first study suggested higher mortality in patients treated with ENBREL at either schedule compared to placebo. Results of the second study did not corroborate these observations. Analyses did not identify specific factors associated with increased risk of adverse outcomes in heart failure patients treated with ENBREL (see **PRECAUTIONS: Patients with Heart Failure**).

Adverse Reaction Information from Spontaneous Reports
Adverse events have been reported during post-approval use of ENBREL. Because these events are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to ENBREL exposure.
Additional adverse events are listed by body system below:

Body as a whole: angioedema, fatigue, fever, flu syndrome, generalized pain, weight gain
Cardiovascular: chest pain, vasodilation (flushing), new-onset congestive heart failure (see **PRECAUTIONS: Patients with Heart Failure**)
Digestive: altered sense of taste, anorexia, diarrhea, dry mouth, intestinal perforation
Hematologic/Lymphatic: adenopathy, anemia, aplastic anemia, leukopenia, neutropenia, pancytopenia, thrombocytopenia (see **WARNINGS**)
Hepatobiliary: autoimmune hepatitis
Musculoskeletal: joint pain, lupus-like syndrome with manifestations including rash consistent with subacute or discoid lupus
Nervous: paresthesias, stroke, seizures, and central nervous system events suggestive of multiple sclerosis or isolated demyelinating conditions such as transverse myelitis or optic neuritis (see **WARNINGS**)
Ocular: dry eyes, ocular inflammation
Respiratory: dyspnea, interstitial lung disease, pulmonary disease, worsening of prior lung disorder
Skin: cutaneous vasculitis, erythema multiforme, Stevens-Johnson syndrome, toxic epidermal necrolysis, pruritus, subcutaneous nodules, urticaria

Rx Only. This brief summary is based on ENBREL prescribing information v. 35: 12/2008

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