

POLICY & PRACTICE

NIAMS Rewards Collaboration

The National Institute of Arthritis and Musculoskeletal and Skin Disease has completed its first year of making grants to foster collaboration across disciplines. In 2008, the Building Interdisciplinary Research Teams (BIRT) Awards program made 1-year grants to support researchers who are already receiving NIAMS grants but who wish to work with scientists outside their normal circle. Grants were given to researchers who combined developmental biology with systems biology, soft tissue biology with imaging technologies, tissue engineering with immunology, and tissue engineering with developmental biology. In one project, researchers at the University of Pittsburgh are using elevated magnet field strengths to make magnetic resonance images of cartilage closer in resolution to optical coherence tomography images.

FDA Cracks Down on False Claims

The Food and Drug Administration and the owners of Wilderness Family Naturals have signed a consent decree that prohibits the company from making unapproved claims that its products prevent or cure diseases. Directly or through the Web sites it controlled, the company has claimed product benefits related to arthritis; chronic fatigue syndrome; HIV infection and AIDS; heart disease; hyperthyroidism; diabetes; and cancer. None of the company's products—ranging from coconut oil to spices and vitamin supplements—had been approved by the FDA for disease treatment.

COX-2s May Have Cut Bleeding

The increased use of cyclooxygenase-2 inhibitors (COX-2) instead of older NSAIDs may have contributed to a decline in hospitalizations for upper gastrointestinal bleeding, according to the Agency for Healthcare Research and Quality. From 1998 to 2006, the number of hospitalizations for upper GI bleeding per 100,000 people decreased 14%. Other medical advances—such as the 1994 recommendation by the National Institutes of Health to aggressively treat of *Helicobacter pylori* and more widespread use of proton pump inhibitors to control gastroesophageal reflux disease—also may have helped, said the AHRQ. However, hospitalizations for lower GI bleeding increased 8% from 1998 to 2006. The findings

are based on data from the Healthcare Cost and Utilization Project 1998 and the 2006 Nationwide Inpatient Sample, a database of hospital inpatient stays.

The Ideal FDA Commissioner?

The next commissioner of the FDA should be a proven manager who can rise above politics, according to a coalition of a patient advocacy groups. The group of more than 30 organizations wrote a letter to Health and Human Services secretary-designate Tom Daschle calling for the Obama administration to fill the FDA post quickly. Candidates for the job shouldn't be excluded because of ties to the pharmaceutical or device industries, the coalition advised.

CMS Looks at Incentive Sharing

Under current federal rules governing patient referrals, physicians can't share incentive payments for quality improvement. But that might change, a Centers for Medicare and Medicaid Services official told the Practicing Physicians Advisory Council (PPAC) last month. The CMS proposed an exception under rules governing physician payment for 2009, but opposition—mainly from medical device manufacturers—killed it, said Lisa Ohrin, acting director of the Division of Technical Payment Policy at the Center for Medicare Management. She said, however, that allowing incentive payments is a priority for the CMS, so the agency will again propose allowing physicians to share the payments.

RAC Program Heavily Criticized

Medicare's effort to recover overpayments made to physicians and hospitals and to make good on underpayments—dubbed the Recovery Audit Contractor program—was lambasted by members of the PPAC. The program is on hold while the Government Accountability Office studies whether the CMS has properly implemented it. During a demonstration, RAC auditors found \$1 billion in improper payments among \$317 billion worth of claims, a CMS official reported to PPAC. As of July 2008, about 7% of those were overturned on appeal. Once the program is restarted—expected by February—there will be limits on the number of years of claims an auditor can examine and how many records can be requested.

—Mary Ellen Schneider

Table 10:
Percent of RA Patients Reporting Adverse Events in Controlled Clinical Trials*

Event	Placebo Controlled		Active Controlled (Study III)	
	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. 33: 03/2008

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