Other Conditions May Mimic Diaper Dermatitis

BY ROBERT FINN

SAN FRANCISCO — Don't ignore a seemingly simple case of diaper dermatitis, because this near-ubiquitous condition can mask something much more serious.

In fact, there are at least four "zebras" whose hoof beats may be sounding in diaper dermatitis, Dr. Sheila Fallon Friedlander said at a meeting sponsored by Skin Disease Education Foundation.

Because there is a higher incidence of infections in the elderly population in general, caution should be used in treating the elderly.

Pediatric Use

Pediatric Use ENBREL® is indicated for treatment of polyarticular-course juvenile idiopathic arthritis in patients ages 2 and older. For issues relevant to pediatric patients, in addition to other sections of the label, see also WARNINGS; PRECAUTIONS: Immunizations; and ADVERS ERACTIONS: Adverse Reactions in Patients with JIA. ENBREL® has not been studied in children < 2 years of age. The safety and efficacy of ENBREL® in pediatric patients with plaque psoriasis have not been studied.

ADVERSE REACTIONS Adverse Reactions in Adult Patients with RA, Psoriatic Arthritis, Ankylosing Spondylitis, or Plaque Psoriasis ENBREL® has been studied in 1442 patients with RA, followed for up to 80 months, in 169 patients with sporiatic arthritis for up to 24 months, in 222 patients with ankylosing spondylitis for up to 10 months, sund 1261 patients with plaque psoriasis for up to 15 months. In controlled trials, the proportion of ENBREL®-treated patients who discontinued treatment due to adverse events was approximately 4% in the indications studied. The vast majority of these patients were treated with 25 mg SC twice weekly. In plaque psoriasis studies, ENBREL® doses studied were 25 mg SC once a week, 25 mg SC twice a week, and 50 mg SC twice a week.

Injection Site Reactions

Injection Site Reactions In controlled trials in rheumatologic indications, approximately 37% of patients treated with ENBREL® developed injection site reactions. In controlled trials in patients with plaque psoriasis, 14% of patients treated with ENBREL® developed injection site reactions que as mild to moderate (erythema and/or itching, pain, or swelling) and generally did not necessitate drug discontinuation. Injection site reactions generally occurred in the first month and subsequently decreased in frequency. The mean duration of injection site reactions was 3 to 5 days. Seven percent of patients experienced redness at a previous injection site then subsequent injections were given. In post-marketing experience, injection site bleeding and bruising have also been observed in conjunction with ENBREL® therapy.

Infections In controlled trials, there were no differences in rates of infection among RA, psoriatic arthritis, ankylosing spondylitis, and plaque psoriasis patients treated with ENBREL[®] and those treated with placebo (or MTX for RA and psoriatic arthritis patients). The most common type of infection was upper respiratory infection, which occurred at a rate of approximately 20% among both ENBREL[®] and placebo-treated patients in RA, psoriatic arthritis, and AS trials, and at a rate of approximately 12% among both ENBREL[®], and placebo-treated patients in plaque psoriasis trials in the first 3 months of treatment. treated patients in plaque psoriasis trials in the first 3 months of treatment. In placebo-controlled trials in RA, psoriatic arthritis, ankylosing spondylitis, and plaque psoriasis no increase in the incidence of serious infections was observed (approximately 1% in both placebo- and ENBREL®-treated groups). In all clinical trials in RA, serious infections experienced by patients have included: pyelonephritis, bronchitis, septic arthritis, abdominal abscess, cellulitis, osteomyelitis, wound infection, pneumonia, foot abscess, leg ulcer, diarrhea, sinusitis, and sepsis. The rate of serious infections has not increased in open-label extension trials and is similar to that observed in ENBREL®- and placebo-treated patients from controlled trials. Serious infections, including usepsis and death, have also been reported during post-marketing use of ENBREL®. Some have occurred within a few weeks after initiating treatment with ENBREL®. Many of the antertex had underduing conditions (e.g., diabetes ENDRLE". Some have occurred within a tew weeks after initiating freatment with ENDREL®. Many of the patients had underlying conditions (e.g., diabetes, congestive heart failure, history of active or chronic infections) in addition to their rheumatoid arthritis (see **WARNINGS**). Data from a sepsis clinical trial not specifically in patients with R4 suggest that ENDREL® treatment may increase mortality in patients with established sepsis.⁹

In patients who received both ENBREL[®] and anakinra for up to 24 weeks, the incidence of serious infections was 7%. The most common infections consisted of bacterial pneumonia (4 cases) and cellulitis (4 cases). One patient with pulmonary fibrosis and pneumonia died due to respiratory failure.

winn puminonary incress and pretmonia died due to respiratory failure. In post-marketing experience in rheumatologic indications, infections have been observed with various pathogens including viral, bacterial, fungal, and protozoal organisms. Infections have been noted in all organ systems and have been reported in patients receiving ENBREL® alone or in combination with immunosuppressive agents.

In clinical trials in plaque psoriasis, serious infections experienced by ENBREL®-treated patients have included: cellulitis, gastroenteritis, pneumonia, abscess, and osteomyelitis.

In global clinical studies of 20,070 patients (28,308 patient-years of therapy), tuberculosis was observed in approximately 0.01% of patients. In 15,438 patients (23,524 patient-years of therapy) from clinical studies in the US and Canada, tuberculosis was observed in approximately 0.007% of patients. These studies include reports of pulmonary and extra-pulmonary tuberculosis (see **WARNINGS**).

Malignancies

Malignancies Patients have been observed in clinical trials with ENBREL® for over five years. Among 4462 rheumatoid arthritis patients treated with ENBREL® in clinical trials for a mean of 27 months (approximately 10000 patient-years of therapy), 9 lymphomas were observed for a rate of 0.99 cases per 100 patient-years. This is 3-fold higher than the rate of lymphomas expected in the general population based on the Surveillance, Epidemiology, and End Results Database.¹⁰ An increased rate of lymphoma up to several fold has been reported in the rheumatoid arthritis patient population, and may be further increased in patients with more severe disease activity^{11,10} (see WARNINGS: Malignancies). Sity-seven malignancies, other than lymphoma, were observed. Of these, the most common malignancies were colon, breast, lung, and prostate, which were similar in type and number to what would be expected in the general population.¹⁰ Analysis of the cancer rates at 6 month intervals suggest constant rates over five years of observation. In the placebo-controlled portions of the psoriasis studies, 8 of 933 patients who received ENBREL® at any dose were diagnosed with a malignancy compared to 1 of 414 patients who received placebo. Among the 1261 patients with psoriasis who received ENBREL® at any dose in the controlled and uncontrolled portions of the psoriasis studies (1062 patient-years), a total of 22 patients were diagnosed with 23 malignancies: 9 patients with non-cutaneous solid tumors, 12 patients with 13 non-melanom skin cancers (8 basal, 5 squamous), and 1 patient with non-Hodgkin's lymphoma. Among the placebo-treated patients (90 patient-years of observation 1 patient was diagnosed with 22 squamous), cancers. The size of the placebo group and limited duration of the controlled portions of studies precludes the ability to draw firm conclusions. Among 89 patients with Weener's oranulomatosis receiving FNRREI®

Among 89 patients with Wegener's granulomatosis receiving ENBREL® in a randomized, placebo-controlled trial, 5 experienced a variety of non-cutaneous solid malignancies compared with none receiving placebo (see WARNINGS: Malignancies)

Immunoaenicity

Patients with RA, psoriatic arthritis, ankylosing spondylitis, or plaque psoriasis were tested at multiple timepoints for antibodies to ENBREL[®]. Antibodies to

That's why diaper dermatitis should be treated. Failure to respond to treatment may be your first hint that something unusual is happening.

Zinc deficiency is the first of these zebras. The baby will present with dermatitis in an acral distribution: hands, feet, face, and genitals. The parent will often mention that the baby has diarrhea and is not growing as well as she should. If you suspect a zinc deficiency, look

the TNF receptor portion or other protein components of the ENBREL® drug product were detected at least once in sera of approximately 6% of adult patients with RA, psoriatic arthritis, ankylosing spondylitis, or plaque psoriasis. These antibodies were all non-neutralizing. No apparent correlation of antibody development to clinical response or adverse events was observed. Results from JIA patients were similar to those seen in adult RA patients treated with ENBREL®. The long-term immunogenicity of ENBREL® is unknown. The date sefficient to account of antiboth whose het count were applied

The data reflect the percentage of patients whose test results were considered positive for antibodies to ${\sf ENBREL}^{\circ}$ in an ELISA assay, and are highly

positive for antibodies to ENBREL[®] in an ELISA assay, and are highly dependent on the sensitivity and specificity of the assay. Additionally, the observed incidence of any antibody positivity in an assay is highly dependent on several factors including assay sensitivity and specificity, assay methodology, sample handling, timing of sample collection, concomitant medications, and underlying disease. For these reasons, comparison of the incidence of antibodies to ENBREL[®] with the incidence of antibodies to other products may be misleading.

Patients with RA had serum samples tested for autoantibodies at multiple timepoints. In RA Studies I and II, the percentage of patients evaluated for antinuclear antibodies (ANA) who developed new positive ANA (titer ± 1:40) was higher in patients treated with ENBREL® (11%) than in placebo-treated

was higher in patients treated with FNBFLE[®] (11%) than in placebo-treated patients (5%). The percentage of patients who developed new positive anti-double-stranded DNA antibodies was also higher by radioimmunoassay (15% of patients treated with ENBREL® compared to 4% of placebo-treated patients) and by Crititidia lucilica assay (3% of patients treated with ENBREL® compared to none of placebo-treated patients). The proportion of patients treated with ENBREL® who developed anticardiolipin antibodies was similarly increased compared to placebo-treated patients. In Study III, no patient increased autoantibody development was seen in ENBREL® patients.

auximmune diseases is unknown. Rare adverse event reports have described patients with rheumatoid factor positive and/or ensive RA who have developed additional autoantibodies in conjunction with rash and other features suggesting a lupus-like syndrome.

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 summarized relations remoting interface site reactions were lower in the

The impact of long-term treatment with ENBREL® on the autoimmune diseases is unknown. Rare adverse event repor

Autoantibodies

to MTX patients.

Event

Headache

Nausea

Rhinitis

Rash

Diaestive:

Other Adverse Reactions

at alkaline phosphatase while you're waiting for zinc levels to come back from the lab. A low alkaline phosphatase level should make you suspicious of zinc, said Dr. Friedlander of the University of California, San Diego.

Langerhans cell histiocytosis (LCH) is the next zebra. Thought by many to be a clonal proliferative disorder, LCH has a wide variability in presentation and prognosis.

Hematologic/Lymphatic:	lymphadenopathy
Musculoskeletal:	bursitis, polymyositis
Nervous:	cerebral ischemia, depression,
	multiple sclerosis (see WARNINGS:
	Neurologic Events)
Respiratory:	dyspnea, pulmonary embolism, sarcoidosi
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

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. Eptly-three of 69 (69%) oblighten with IIA experienced an infection while

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 nfection 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), advorniand patient (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

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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. Addit

lditional 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 info v. 35: 12/2008 Manufactured by:

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5,395,760; 5,605,690; 5,945,397; 6,201,105; 6,572,852; Re. 36,755 AMGEN[®] Wyeth[®]

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Dr. Friedlander described one case in which the baby had rashes in his intertriginous areas. Her first thought was Candida and, indeed, antifungals seemed to help a little bit. Adding topical steroids helped a little bit more, but the rashes never fully cleared. On top of that, the mother was noticing some small pink papules elsewhere on the baby's body.

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Upon questioning, the mother noted that the baby wasn't growing very well and also was experiencing some vomiting and diarrhea. When Dr. Friedlander did a physical exam, she noticed that the baby's liver was enlarged. (Other babies with LCH have enlarged spleens.) And those pink papules? Those were purpuric papules of petechiae.

"When you see that, you need to see Red Alert," Dr. Friedlander said. "You have scaly papules; hemorrhagic, purpuric, petechial lesions; and paronychial involvement." LCH sometimes looks like seborrheic dermatitis, but the physician's job is to recognize it and refer the child to a pediatric oncologist.

The third zebra goes by the unwieldy name "recurrent toxin-mediated perineal erythema." Dr. Friedlander described one little girl with a recurrent red, scaly eruption in her groin area that never responded to the typical diaper dermatitis treatments. The mother mentioned that the eruption often was accompanied by fever and a red tongue.

"Well, certainly when we see a red tongue, we think of a toxin-mediated disorder," Dr. Friedlander said. "If the patient is febrile and looks sick, you need to get blood culture; you need to get a [sedimentation] rate. And, certainly, get cultures of the pharynx, the perianal area, and lesional skin."

Of all the zebras, Kawasaki disease is the one you least want to miss. "If you recognize it early, you can save a life," Dr. Friedlander said. The first hint often is a red perianal rash. Start worrying if you learn that the child has had a high fever for 4 or 5 days, has a strawberry tongue, and is unusually crabby.

The child with Kawasaki disease will often have conjunctivitis but of a specific type. The eye will not be purulent, and there won't be an exudate. And if you look closely, you may see that the conjunctivitis is sparing the limbus-the area where the cornea meets the sclera. The child may have cervical lymphadenopathy, and the rash can be variable. "It's pretty much a polymorphous eruption, but [it doesn't] blister," Dr. Friedlander said.

Two lab values can be especially noteworthy in Kawasaki disease. The C-reactive protein level will be 3 mg/dL or higher, and the sedimentation rate will be 40 mm/hr or more. You also should order labs to rule out pyuria, meningitis, hepatitis, hypoalbuminemia, and thrombocytosis.

Dr. Friedlander disclosed serving as a consultant and a researcher for Barrier Therapeutics Inc., which makes a prescription ointment for diaper rash.

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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 land II. Otherwise, the percentages of patients reporting adverse events in the 50 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 poriatic arthritis, ankylosing spondylits, 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 Act ntrolled (Study III) Controlled Percent of patients Percent of patients Placebo[†] (N = 152) **ENBREL®** MTX ENBREL[®] (N = 415) (N = 349)(N = 217) Injection site reaction Infection (total)** 10 32 37 35 34 64 7 72 Non-upper respiratory infection (non-URI)** Upper respiratory infection (URI)** 32 60 51 38 29 17 9 16 13 10 8 39 27 29 14 11 9 6 12 10 23 4 31 24 15 16 5 11 10 14 8 NA 11 5 12 7 7 Dizziness Pharyngitis Cough Asthenia Abdominal pain

Peripheral edema Respiratory disorder 4 NA 10 3 Dyspepsia Sinusitis Sinusius Vomiting Mouth ulcer Alopecia 12 ("MTX lung") 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 includes data from all three 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 In controlled trials of HA and psonatic 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 aperiasic gliorial trials are lifeted by body certem balow: averse events buserved in FA, psoriaut attimus, ankytosing sj or plaque psoriasis clinical trials are listed by body system below Cardiovascular: heart failure, myocardial infarction, myocardial ischemia, hypertension, hypotension, deep vein thrombosis thrombophlebitis

cholecystitis, pancreatitis, gastrointestinal hemorrhage, appendicitis