

Avoiding Dyschromia Is Goal in Treating Dark Skin

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MIAMI BEACH — Prevention is the best therapy for patients of color regarding dermatologic procedures with a potential to cause postinflammatory hyperpigmentation changes, according to a presentation at the annual Masters of Pediatrics conference sponsored by the University of Miami.

“There are unique diseases and treat-

ments to consider in children with skin of color. Understanding these differences is essential when treating our patients,” said Dr. Heather Woolery-Lloyd, director of ethnic skin care, department of dermatology and cutaneous surgery, University of Miami.

Acne and atopic dermatitis put some patients with skin of color at an increased risk for hyperpigmentation. These changes can be very cosmetically disconcerting. For example, patients are most concerned

with pigmentation and not the acne itself when they have acne hyperpigmented macules, Dr. Woolery-Lloyd said.

Retinoids are recommended for patients younger than 16 years of age because they can improve both acne and pigmentation, Dr. Woolery-Lloyd said. Other therapeutic options include azelaic acid 15% gel or 20% cream. In addition, she recommended a moisturizer containing sunscreen and soy. The soy is beneficial because it inhibits melanogen-

esis, although it works slowly, she said.

For patients 16 years and older with acne and dyschromia, Dr. Woolery-Lloyd recommends hydroquinone applied only as needed to affected areas. Hydroquinone comes in different formulations, including 2% available over the counter, 4% available by prescription, and 6%-8% strengths prepared by a compounding pharmacy. Avoid continuous, long-term use, she advised.

Treatment of acne with hydroquinone can also cause dyschromia in patients of color. Advise patients not to rub hydroquinone in with their fingertips, Dr. Woolery-Lloyd said, to avoid a hypopigmented area around the acne lesion known as a

injection site when 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. 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 sepsis 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 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 RA suggest that ENBREL treatment may increase mortality in patients with established sepsis. 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. 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. **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 0.09 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. 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 (see **WARNINGS: Malignancies**). Sixty-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. 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-melanoma 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 2 squamous cell 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 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**). **Immunogenicity:** Patients with RA, psoriatic arthritis, ankylosing spondylitis, or plaque psoriasis were tested at multiple timepoints for antibodies to ENBREL. Antibodies to 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 JRA patients were similar to those seen in adult RA patients treated with ENBREL. The long-term immunogenicity of ENBREL is unknown. The data reflect the percentage of patients whose test results were considered 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 antibody positivity in an assay may be influenced by several factors including sample handling, 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. **Autoantibodies:** 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 $\geq 1:40$) was higher in patients treated with ENBREL (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 *Crithidia luciliae* 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 pattern of increased autoantibody development was seen in ENBREL patients compared to MTX patients. The impact of long-term treatment with ENBREL on the development of autoimmune diseases is unknown. Rare adverse event reports have described patients with rheumatoid factor positive and/or erosive RA who have developed additional autoantibodies in conjunction with rash and other features suggesting a lupus-like syndrome. **Other Adverse Reactions:** The following table 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.

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

Event	Placebo Controlled (N = 152)		Active Controlled (Study III) (N = 415)	
	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
Peripherical 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 JRA:** 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 JRA 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 JRA 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 JRA patients were generally mild and consistent with those commonly seen in outpatient pediatric populations. Two JRA 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 JRA 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 JRA, 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, pruritus, subcutaneous nodules, urticaria. **Rx only.** This brief summary is based on ENBREL prescribing information: 12/01/06.

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The “hydroquinone halo” around the treated area is due to over application.

“hydroquinone halo.” She suggested instead using a cotton-tipped applicator to spot treat facial lesions. Apply the agent to dark spots first and then apply a retinoid to the entire face.

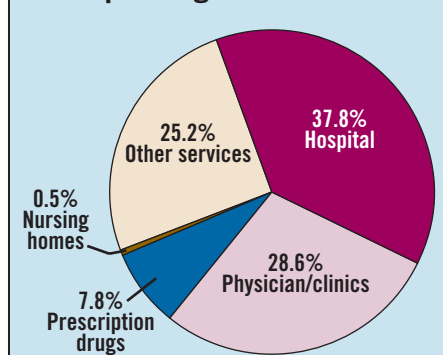
Postinflammatory hyperpigmentation can also be a challenge to treat in patients of color with atopic dermatitis, Dr. Woolery-Lloyd said. She suggested aggressive treatment to prevent permanent pigment changes. “Emphasize this to parents to improve compliance.” Prevention is particularly important because bleaching agents can irritate patients with atopic dermatitis.

Another tip is to educate patients about the expected duration of pigment changes. Remember that postinflammatory hyperpigmentation can take an average of 4 months to clear, Dr. Woolery-Lloyd said.

She had no relevant conflicts of interest to disclose.

DATA WATCH

Personal Health Care Spending for Children



Note: Numbers do not add up to 100 because of rounding.
 Source: 2004 data, Health Affairs 2007