Pros and Cons of Pediatric Wart Therapy Weighed

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STANFORD, CALIF. — Two approved therapies for pediatric warts and several off-label options each carry advantages and disadvantages that can help inform treatment selection.

Watchful waiting may be the best option because most pediatric warts are self-limiting, but when you or the parents decide it is time for treatment, consider the child's age, personality, and the number and location of the lesions, Dr. Lillian F. Soohoo said at a pediatric update sponsored by Stanford (Calif.) University.

Up to two-thirds of pediatric warts resolve within 2 years without treatment. "I usually wait until a child is 9 years old before I begin talking about painful therapy" to remove warts, said Dr. Soohoo of the university.

She never restrains children for such therapy.

She described the pros and cons of the two approved treatments—salicylic acid or cryotherapy—and discussed several off-label therapies being used to treat pediatric warts:

► **Salicylic acid.** Many over-the-counter preparations are available in the form of topical solutions, gels, pads, patches, or plasters containing 17%-40% salicylic acid, depending on the product.

Dr. Soohoo generally doesn't use the 40% preparations in younger children but may use them in teenagers, who have thicker skin.

The advantages of salicylic acid start with cure rates of 70%-80%. These preparations are readily available, inexpensive, and may be combined with other therapies, Dr. Soohoo said.

Salicylic acid requires daily applications for weeks or months to be effective, however, so diligence on the part of the patient or parents is a must, she said.

Many parents resist this over-the-counter therapy and demand a prescription-strength treatment.

Salicylic acid also can cause irritation of the skin, eye, and mucous membranes, she said.

► **Cryotherapy.** The most effective version of cryotherapy for pediatric warts is liquid nitrogen, which provides cure rates of 50%-80%. Less effective versions include Verruca-Freeze (chlorodifluoromethane and propane), Histofreezer (dimethyl ether and propane), or Wartner (dimethyl ether and propane), which produce less than half the chill of liquid nitrogen, she said.

Leading the disadvantages of cryotherapy is the pain it causes, which usually is too traumatic for patients under 9 years of age.

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Treatment Choice Decided by Age, Type of Wart

Dr. Soohoo's preferred wart treatments depend on the patient's age and type of warts, as shown in the following:

► **Common and plantar warts.** For children under age 9 years, salicylic acid is first-line therapy, "but usually by the time parents see me, they've tried this," she said. Cantharidin plus Aldara are her next choice, with squaric acid a "distant third" choice.

For older children, salicylic acid plus liquid nitrogen would be her first choice for therapy, "but often they're too busy to come back" for repeat treatments, in which case she opts for topical 5-fluorouracil instead. *Candida* antigen injections are a distant third choice for these warts.

► **Flat warts.** Dr. Soohoo would pick tretinoin cream first, with light cryotherapy as her second choice. Sometimes Aldara can be used on these warts, "but with caution," she said.

► **Periungual warts.** Cryotherapy plus salicylic acid comprise first-line treatment for periungual warts in Dr. Soohoo's office. Second in line is topical 5-fluorouracil. Her third option is cantharidin applied in the office plus Aldara applied at home. Rarely, she resorts to *Candida* antigen injections or squaric acid for these warts.

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
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 during the first 3 months of treatment. All injection site reactions were described 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 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.[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.

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
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.[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[11,12] (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.[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-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 JIA 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 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.

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 ≥ 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
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. 33: 03/2008

Manufactured by:
Immunex Corporation
Thousand Oaks, CA 91320-1799
U.S. License Number 1132
Marketed by Amgen and Wyeth Pharmaceuticals

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Immunex U.S. Patent Numbers:
5,395,760; 5,605,690; 5,945,397; 6,201,105; 6,572,852; Re. 36,755

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Cryotherapy usually requires repeat treatments, and can cause scarring or doughnut-wart (also called ring wart) recurrences.

Dr. Soohoo's cryotherapy technique starts by asking the child to hold an ice pack to the wart to pretreat the area, then applying liquid nitrogen to the wart and a 2-mm surrounding area for 3-6 seconds until the tissue is white.

Allow the area to thaw completely and repeat.

Schedule the patient for a follow-up visit in 2-4 weeks and discuss blister care with the parents.

▶ **Cantharidin.** A topical preparation made of purified secretions from the blister beetle (*Cantharis vesicatoria*), cantharidin can be applied in the office and will cause blistering and desquamation of the wart at home.

Cantharidin is easy to administer in the office, has a low risk for scarring, and both the application and the blistering are painless if applied appropriately.

Cantharidin is highly toxic if ingested and so is not approved for wart treatment, but the Food and Drug Administration in 1998 said it will not take regulatory action if its use is limited to topical use in the professional office setting, according to Dr. Soohoo.

Cantharidin is easy to administer in the office, has a low risk for scarring, and both the application and the blistering are painless if applied appropriately.

The blistering occurs within 24-48 hours and takes 4-7 days to heal.

There have been some reports of lymphangitis or lymphedema associated with cantharidin use.

The wooden end of a cotton-tipped applicator can be used to apply a small drop to each lesion.

Allow it to dry completely, then cover with tape, and advise parents to wash off the treated area 4-6 hours later, or sooner if burning or pain develops, Dr. Soohoo advised.

Discuss blister care with parents. If needed, repeat treatment in 2 weeks.

▶ **Immunotherapy.** Although not approved for common pediatric warts, topical 5% imiquimod cream (Aldara) often is used and is approved for treatment of genital warts in patients aged 12 years and older.

Aldara cream is painless, well tolerated by all ages, and may induce immunity to warts.

On the downside, it requires 4 months or more of nightly applications and is expensive, although many insurers now cover it for the treatment of warts, she said. To avoid irritation, do not use it to treat warts on the face, neck, or occluded areas like the diaper area or genitals, she advised.

It causes erythema in 30% of cases and, in rare cases, has been associated with flulike symptoms, fever, or photosensitivity.

Dr. Soohoo reserves another off-label topical immunotherapy, squaric acid dibutyl ester, for recalcitrant warts. The treatment seems to be painless and induces immunity to human papillomavirus. It can cause an allergic contact dermatitis, however, and should not be used for facial warts because of irritation.

Start use of squaric acid dibutyl ester by applying a 2% solution to a small, quarter-size area of normal skin on the forearm and wait 2 weeks to check for sensitization, she recommended.

If none occurs, parents could apply a 0.2% solution to warts 3-7 times per week.

An intralesional immunotherapy, *Candida* antigen injection, is more painful.

The injections are thought to be less painful than cryotherapy but still too painful for young children, she said.

Some teenagers may tolerate it. It seems to be effective and induces immunity but is expensive and can cause itching as well as pain at the treatment site.

▶ **Other off-label therapies.** Among other off-label therapies, topical 5-fluorouracil can be applied to warts daily for 6 weeks.

"I use it a fair amount in older kids and teens, especially if they're too busy to come back for visits," Dr. Soohoo said. It is an FDA Pregnancy Category X and is available in compounded formulations by mail order from pharmacies.

Topical retinoic acid has been applied to flat warts on the face for up to 8 weeks of daily treatment but can cause local skin irritation, she said.

A study of pulsed dye laser therapy in 56 children found no support for its use as first-line therapy for pediatric warts (J. Am. Acad. Dermatol. 2007;56:205-10).

Duct tape does not work as monotherapy but may boost the efficacy of other topical therapies when used in combination, she concluded.

Dr. Soohoo reported no conflicts of interest. ■