

Safety Tops Mothers' HPV Vaccine Concerns

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Safety, not sexuality, was a key factor in the reluctance of mothers to have their teenage daughters vaccinated against human papillomavirus, according to results from a study published in the *Journal of Adolescent Health*.

The Centers for Disease Control and Prevention's Advisory Committee on Immunization Practices currently recom-

mends a three-dose vaccine against the human papillomavirus (HPV) for all girls aged 11-12 years and young women aged 13-26 years. HPV has been identified as a leading cause of cervical cancer.

Previous studies have shown that parents were in favor of vaccination for adolescents but hesitant to vaccinate younger girls. In most cases, though, this resistance was not brought on by concerns that the vaccination might make teenage girls more likely to engage in risky sexual activities.

To examine the factors that influence parents' acceptance of the HPV vaccine, Susan L. Rosenthal, Ph.D., of the University of Texas Medical Branch in Galveston, Tex., and her colleagues interviewed mothers with daughters aged 11-17 years who were visitors to a university-based primary care clinic.

The study included complete results from 153 mothers of various ethnicities (average age 41 years) who completed a questionnaire. The questionnaire included

ratings of seven health beliefs including perceptions of HPV disease severity and barriers to vaccination, such as cost. The questionnaire also addressed aspects of the parent/child relationship, including how closely the girls' activities were monitored by parents and whether the parents had discussed topics such as birth control, dating, and making decisions about sex (*J. Adolesc. Health* 2008;43:239-45).

Overall, 18% (27) of the mothers had been offered the HPV vaccination for their

IMPORTANT SAFETY INFORMATION

Risk of Serious Infections

Infections, including serious infections leading to hospitalization or death, have been observed in patients treated with ENBREL. Infections have included bacterial sepsis and tuberculosis. Patients should be educated about the symptoms of infection and closely monitored for signs and symptoms of infection during and after treatment with ENBREL. Patients who develop an infection should be evaluated for appropriate antimicrobial treatment and, in patients who develop a serious infection, ENBREL should be discontinued.

Tuberculosis (frequently disseminated or extrapulmonary at clinical presentation) has been observed in patients receiving TNF-blocking agents, including ENBREL. Tuberculosis may be due to reactivation of latent tuberculosis infection or to new infection. Data from clinical trials and preclinical studies suggest that the risk of reactivation of latent tuberculosis infection is lower with ENBREL than with TNF-blocking monoclonal antibodies. Nonetheless, postmarketing cases of tuberculosis reactivation have been reported for TNF blockers, including ENBREL. Patients should be evaluated for tuberculosis risk factors and be tested for latent tuberculosis infection prior to initiating ENBREL and during treatment. Treatment of latent tuberculosis infection should be initiated prior to therapy with ENBREL. Treatment of latent tuberculosis in patients with a reactive tuberculin test reduces the risk of tuberculosis reactivation in patients receiving TNF blockers. Some patients who tested negative for latent tuberculosis prior to receiving ENBREL have developed active tuberculosis. Physicians should monitor patients receiving ENBREL for signs and symptoms of active tuberculosis, including patients who tested negative for latent tuberculosis infection.

Many of these serious infections occurred in patients predisposed to infection because of concomitant immunosuppressive therapy and/or their underlying disease. Do not start ENBREL in the presence of sepsis, active infections (including chronic or localized), or allergy to ENBREL or its components. Use caution in patients predisposed to infection, such as those with advanced or poorly controlled diabetes.

Neurologic Events

TNF inhibitors, including ENBREL, have been associated with rare cases of new onset or exacerbation of CNS demyelinating disorders (some presenting with mental status changes and some associated with permanent disability). Transverse myelitis, optic neuritis, multiple sclerosis, and cases of new onset or exacerbation of seizure disorders have been observed in association with ENBREL therapy. The causal relationship to ENBREL therapy remains unclear. Exercise caution when considering ENBREL for patients with these disorders.

Hematologic Events

Rare cases of pancytopenia, including aplastic anemia, some fatal, have been reported. The causal relationship to ENBREL therapy is unclear. Exercise caution in patients who have a previous history of significant hematologic abnormalities. Advise patients to seek immediate medical attention if they develop signs or symptoms of blood dyscrasias or infection. Consider discontinuing ENBREL if significant hematologic abnormalities are confirmed.

Malignancies

In clinical trials of all TNF inhibitors, more cases of lymphoma were seen compared to control patients. The risk of lymphoma may be up to several-fold higher in RA and psoriasis patients; the role of TNF inhibitors in the development of malignancies is unknown. In clinical trials, the incidence of malignancies other than lymphoma has not increased with exposure to ENBREL and is similar to what would be expected in the general population.

Hepatitis B Reactivation

TNF inhibitors, including ENBREL, have been associated with reactivation of hepatitis B virus (HBV) in chronic carriers of this virus. The majority of these reports occurred in patients on concomitant immunosuppressive agents, which may also contribute to HBV reactivation. Prescribers should exercise caution in prescribing TNF blockers for patients identified as carriers of HBV.

Adverse Events

The most commonly reported adverse events in RA clinical trials were injection site reaction, infection, and headache. In clinical trials of all other adult indications, adverse events were similar to those reported in RA clinical trials.

*Please see brief summary
of Prescribing Information
on adjacent pages.*



daughters but had not chosen it, and did not plan to vaccinate their daughters within the next year, while 34% (52) had not been offered the vaccination and did not plan to vaccinate their daughters within the next year. Another 22% (34) had not been offered the vaccine but were aware of it and planned to vaccinate their daughters within the next year, and 26% (40) of the mothers reported that their daughters had started or completed the vaccination series.

None of the mothers whose daughters had been vaccinated said they viewed the vaccine as unsafe, but objections to the vaccine were focused mostly on the lack of safety data because of the newness of

the vaccine. Mothers who were offered the vaccine but did not plan to vaccinate their daughters within the year often cited a lack of information about the vaccine, and some cited a lack of urgency based on their perceptions of their daughters' likely exposure to HPV.

Significant predictors of HPV vaccination after a multivariate analysis were mothers who had less than a high school education, had a history of sexually transmitted infections, had monitored their daughters' activities with peers, and had thought their daughters would not mind getting the shots.

There was no significant association be-

tween HPV vaccine acceptance and the ages and ethnicities of the mothers and daughters, the daughters' dating status, mothers' history of HPV, mother/daughter discussion of sex topics, or the general family environment.

"Although the study was not designed to examine the process of and impact of physician counseling, it appeared that those who had been counseled had more positive attitudes toward the vaccine and understood better the reasons for vaccinating their daughters prior to initiation of sexual activity," the researchers noted.

The study was limited by the relatively small sample and by the university setting,

which might have provided more education to parents and daughters than would other settings. But the results suggest that even those parents and daughters who were counseled about the HPV vaccine wanted more information, and further studies are needed to determine the most effective ways to provide more education, the researchers wrote.

Many mothers who were not planning to vaccinate their daughters within the next year planned to vaccinate them eventually, they added.

The study was funded by grants from Merck & Co. and the National Institutes of Health. ■

Enbrel® (etanercept) Brief Summary

SEE PACKAGE INSERT FOR FULL PRESCRIBING INFORMATION

INDICATIONS AND USAGE

ENBREL® is indicated for reducing signs and symptoms, inducing major clinical response, inhibiting the progression of structural damage, and improving physical function in patients with moderately to severely active rheumatoid arthritis. ENBREL® can be initiated in combination with methotrexate (MTX) or used alone.

ENBREL® is indicated for reducing signs and symptoms of moderately to severely active polyarticular juvenile idiopathic arthritis in patients ages 2 and older.

ENBREL® is indicated for reducing signs and symptoms, inhibiting the progression of structural damage of active arthritis, and improving physical function in patients with psoriatic arthritis. ENBREL® can be used in combination with methotrexate in patients who do not respond adequately to methotrexate alone.

ENBREL® is indicated for reducing signs and symptoms in patients with active ankylosing spondylitis.

ENBREL® is indicated for the treatment of adult patients (18 years or older) with chronic moderate to severe plaque psoriasis who are candidates for systemic therapy or phototherapy.

WARNING

RISK OF INFECTIONS

Infections, including serious infections leading to hospitalization or death, have been observed in patients treated with ENBREL® (see **WARNINGS** and **ADVERSE REACTIONS**). Infections have included bacterial sepsis and tuberculosis. Patients should be educated about the symptoms of infection and closely monitored for signs and symptoms of infection during and after treatment with ENBREL®. Patients who develop an infection should be evaluated for appropriate antimicrobial treatment and, in patients who develop a serious infection, ENBREL® should be discontinued.

Tuberculosis (frequently disseminated or extrapulmonary at clinical presentation) has been observed in patients receiving TNF-blocking agents, including ENBREL®. Tuberculosis may be due to reactivation of latent tuberculosis infection or to new infection. Data from clinical trials and preclinical studies suggest that the risk of reactivation of latent tuberculosis infection is lower with ENBREL® than with TNF-blocking monoclonal antibodies. Nonetheless, postmarketing cases of tuberculosis reactivation have been reported for TNF blockers, including ENBREL®. Patients should be evaluated for tuberculosis risk factors and be tested for latent tuberculosis infection prior to initiating ENBREL® and during treatment. Treatment of latent tuberculosis infection should be initiated prior to therapy with ENBREL®. Treatment of latent tuberculosis in patients with a reactive tuberculin test reduces the risk of tuberculosis reactivation in patients receiving TNF blockers. Some patients who tested negative for latent tuberculosis prior to receiving ENBREL® have developed active tuberculosis. Physicians should monitor patients receiving ENBREL® for signs and symptoms of active tuberculosis, including patients who tested negative for latent tuberculosis infection.

CONTRAINDICATIONS

ENBREL® should not be administered to patients with sepsis or with known hypersensitivity to ENBREL® or any of its components.

WARNINGS

Infections

In post-marketing reports, serious infections and sepsis, include fatalities, have been reported with the use of ENBREL®. Many of the serious infections have occurred in patients on concomitant immunosuppressive therapy that, in addition to their underlying disease, could predispose them to infections. Patients who develop a new infection while undergoing treatment with ENBREL® should be monitored closely. Administration of ENBREL® should be discontinued if a patient develops a serious infection or sepsis. Treatment with ENBREL® should not be initiated in patients with active infections, including chronic or localized infections. Physicians should exercise caution when considering the use of ENBREL® in patients with a history of recurring infections or with underlying conditions which may predispose patients to infections, such as advanced or poorly controlled diabetes (see **PRECAUTIONS** and **ADVERSE REACTIONS: Infections**).

Cases of tuberculosis have been observed in patients receiving TNF-blocking agents, including ENBREL®. Tuberculosis may be caused by reactivation of latent tuberculosis infection or new infection. Data from clinical trials and preclinical studies suggest that the risk of reactivation of latent tuberculosis infection is lower with ENBREL® than with TNF-blocking monoclonal antibodies. Nonetheless, postmarketing cases of tuberculosis reactivation have been reported for TNF blockers, including ENBREL®. Patients should be evaluated for tuberculosis risk factors and be tested for latent tuberculosis infection. Treatment of latent tuberculosis infections should be initiated prior to therapy with ENBREL®. Patients receiving ENBREL® should be monitored closely for signs and symptoms of active tuberculosis. The possibility of tuberculosis should be considered, especially in patients who have traveled to countries with a high prevalence of tuberculosis or had close contact with a person with active tuberculosis. All patients treated with ENBREL® should have a thorough history taken prior to initiating therapy.

In a 24-week study of concurrent ENBREL® and anakinra therapy, the rate of serious infections in the combination arm (7%) was higher than with ENBREL® alone (0%). The combination of ENBREL® and anakinra did not result in higher ACR response rates compared to ENBREL® alone (see **CLINICAL STUDIES: Clinical Response and ADVERSE REACTIONS: Infections**). Concurrent therapy with ENBREL® and anakinra is not recommended.

Neurologic Events

Treatment with ENBREL® and other agents that inhibit TNF have been associated with rare cases of new onset or exacerbation of central nervous system demyelinating disorders, some presenting with mental status changes and some associated with permanent disability. Cases of transverse myelitis, optic neuritis, multiple sclerosis, and new onset or exacerbation of seizure disorders have been observed in association with ENBREL® therapy. The causal relationship to ENBREL® therapy remains unclear. While no clinical trials have been performed evaluating ENBREL® therapy in patients with multiple sclerosis, other TNF antagonists administered to patients with multiple sclerosis have been associated with increases in disease activity.^{7,8} Prescribers should exercise caution in considering the use of ENBREL® in patients with preexisting or recent-onset central nervous system demyelinating disorders (see **ADVERSE REACTIONS**).

Hematologic Events

Rare reports of pancytopenia including aplastic anemia, some with a fatal outcome, have been reported in patients treated with ENBREL®. The causal relationship to ENBREL® therapy remains unclear. Although no high risk group has been identified, caution should be exercised in patients being treated with ENBREL® who have a previous history of significant hematologic abnormalities. All patients should be advised to seek immediate medical attention if they develop signs and symptoms suggestive of blood dyscrasias or infection (e.g., persistent fever, bruising, bleeding, pallor) while on ENBREL®. Discontinuation of ENBREL® therapy should be considered in patients with confirmed significant hematologic abnormalities.

Two percent of patients treated concurrently with ENBREL® and anakinra developed neutropenia (ANC < 1 x 10⁹/L). While neutropenic, one patient developed cellulitis which recovered with antibiotic therapy.

Malignancies

In the controlled portions of clinical trials of all the TNF-blocking agents, more cases of lymphoma have been observed among patients receiving the TNF blocker compared to control patients. During the controlled portions of ENBREL® trials, 3 lymphomas were observed among 4509 ENBREL®-treated patients versus 0 among 2040 control patients (duration of controlled treatment ranged from 3 to 24 months). In the controlled and open-label portions of clinical trials of ENBREL®, 9 lymphomas were observed in 5723 patients over approximately 11201 patient years of therapy. This is 3-fold higher than that expected in the general population. While patients with rheumatoid arthritis or psoriasis, particularly those with highly active disease, may be at a higher risk (up to several fold) for the development of lymphoma, the potential role of TNF-blocking therapy in the development of malignancies is not known (see **ADVERSE REACTIONS: Malignancies**).^{11,12}

In a randomized, placebo-controlled study of 180 patients with Wegener's granulomatosis where ENBREL® was added to standard treatment (including cyclophosphamide, methotrexate, and corticosteroids), patients receiving ENBREL® experienced more non-cutaneous solid malignancies than patients receiving placebo (see **ADVERSE REACTIONS: Malignancies**). The addition of ENBREL® to standard treatment was not associated with improved clinical outcomes when compared with standard therapy alone. The use of ENBREL® in patients with Wegener's granulomatosis receiving immunosuppressive agents is not recommended. The use of ENBREL® in patients receiving concurrent cyclophosphamide therapy is not recommended.

Hepatitis B Virus Reactivation

Use of TNF blockers, including ENBREL®, has been associated with reactivation of hepatitis B virus (HBV) in patients who are chronic carriers of this virus. In some instances, HBV reactivation occurring in conjunction with TNF blocker therapy has been fatal. The majority of these reports have occurred in patients concomitantly receiving other medications that suppress the immune system, which may also contribute to HBV reactivation. Patients at risk for HBV infection should be evaluated for prior evidence of HBV infection before initiating TNF blocker therapy. Prescribers should exercise caution in prescribing TNF blockers for patients identified as carriers of HBV. Adequate data are not available on the safety or efficacy of treating patients who are carriers of HBV with anti-viral therapy in conjunction with TNF blocker therapy to prevent HBV reactivation. Patients who are carriers of HBV and require treatment with ENBREL® should be closely monitored for clinical and laboratory signs of active HBV infection throughout therapy and for several months following termination of therapy. In patients who develop HBV reactivation, consideration should be given to stopping ENBREL® and initiating anti-viral therapy with appropriate supportive treatment. The safety of resuming ENBREL® therapy after HBV reactivation is controlled is not known. Therefore, prescribers should weigh the risks and benefits when considering resumption of therapy in this situation.

PRECAUTIONS

General

Allergic reactions associated with administration of ENBREL® during clinical trials have been reported in < 2% of patients. If an anaphylactic reaction or other serious allergic reaction occurs, administration of ENBREL® should be discontinued immediately and appropriate therapy initiated.

Caution: The needle cap on the prefilled syringe and on the SureClick™ autoinjector contains dry natural rubber (a derivative of latex) which may cause allergic reactions in individuals sensitive to latex.

Information for Patients

Patients or their caregivers should be provided the ENBREL® "Medication Guide" and provided an opportunity to read it and ask questions prior to initiation of therapy. The health care provider should ask the patient questions to determine any risk factors for treatment. Patients developing signs and symptoms of infection should seek medical evaluation immediately.

Latex Sensitivity Allergies

ENBREL® is provided as a single-use prefilled syringe, a single-use prefilled SureClick™ autoinjector, or a multiple-use vial. The patient or caregiver should be informed that the needle cap on the prefilled syringe and on the SureClick™ autoinjector contains dry natural rubber (a derivative of latex), which should not be handled by persons sensitive to latex.

Administration of ENBREL®

If a patient or caregiver is to administer ENBREL®, the patient or caregiver should be instructed in injection techniques and how to measure and administer the correct dose (see the ENBREL® (etanercept) "Medication Guide"). The first injection should be performed under the supervision of a qualified health care professional. The patient's or caregiver's ability to inject subcutaneously should be assessed. Patients and caregivers should be instructed in the technique as well as proper syringe and needle disposal, and be cautioned against reuse of needles and syringes. A puncture-resistant container for disposal of needles, syringes, and autoinjectors should be used. If the product is intended for multiple use, additional syringes, needles, and alcohol swabs will be required.

Patients with Heart Failure

Two large clinical trials evaluating the use of ENBREL® in the treatment of heart failure were terminated early due to lack of efficacy. Results of one study suggested higher mortality in patients treated with ENBREL® 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 **ADVERSE REACTIONS: Patients with Heart Failure**). There have been post-marketing reports of worsening of congestive heart failure (CHF), with and without identifiable precipitating factors, in patients taking ENBREL®. There have also been rare reports of new onset CHF, including CHF in patients

without known preexisting cardiovascular disease. Some of these patients have been under 50 years of age. Physicians should exercise caution when using ENBREL® in patients who also have heart failure, and monitor patients carefully.

Immunosuppression

Anti-TNF therapies, including ENBREL®, affect host defenses against infections and malignancies since TNF mediates inflammation and modulates cellular immune responses. In a study of 49 patients with RA treated with ENBREL®, there was no evidence of depression of delayed-type hypersensitivity, depression of immunoglobulin levels, or change in enumeration of effector cell populations. The impact of treatment with ENBREL® on the development and course of malignancies, as well as active and/or chronic infections, is not fully understood (see **WARNINGS: Malignancies, ADVERSE REACTIONS: Infections, and Malignancies**). The safety and efficacy of ENBREL® in patients with immunosuppression or chronic infections have not been evaluated.

Immunizations

Most psoriatic arthritis patients receiving ENBREL® were able to mount effective B-cell immune responses to pneumococcal polysaccharide vaccine, but titers in aggregate were moderately lower and fewer patients had two-fold rises in titers compared to patients not receiving ENBREL®. The clinical significance of this is unknown. Patients receiving ENBREL® may receive concurrent vaccinations, except for live vaccines. No data are available on the secondary transmission of infection by live vaccines in patients receiving ENBREL® (see **PRECAUTIONS: Immunosuppression**).

It is recommended that JIA patients, if possible, be brought up to date with all immunizations in agreement with current immunization guidelines prior to initiating ENBREL® therapy. Patients with a significant exposure to varicella virus should temporarily discontinue ENBREL® therapy and be considered for prophylactic treatment with Varicella Zoster Immune Globulin.

Autoimmunity

Treatment with ENBREL® may result in the formation of autoantibodies (see **ADVERSE REACTIONS: Autoantibodies**) and, rarely, in the development of a lupus-like syndrome or autoimmune hepatitis (see **ADVERSE REACTIONS: Adverse Reaction Information from Spontaneous Reports**), which may resolve following withdrawal of ENBREL®. If a patient develops symptoms and findings suggestive of a lupus-like syndrome or autoimmune hepatitis following treatment with ENBREL®, treatment should be discontinued and the patient should be carefully evaluated.

Drug Interactions

Specific drug interaction studies have not been conducted with ENBREL®. However, it was observed that the pharmacokinetics of ENBREL® was unaltered by concomitant methotrexate in rheumatoid arthritis patients.

In a study in which patients with active RA were treated for up to 24 weeks with concurrent ENBREL® and anakinra therapy, a 7% rate of serious infections was observed, which was higher than that observed with ENBREL® alone (0%) (see also **WARNINGS**). Two percent of patients treated concurrently with ENBREL® and anakinra developed neutropenia (ANC < 1 x 10⁹/L).

In a study of patients with Wegener's granulomatosis, the addition of ENBREL® to standard therapy (including cyclophosphamide) was associated with a higher incidence of non-cutaneous solid malignancies. The use of ENBREL® in patients receiving concurrent cyclophosphamide therapy is not recommended (see **WARNINGS: Malignancies and ADVERSE REACTIONS: Malignancies**).

Patients in a clinical study who were on established therapy with sulfasalazine, to which ENBREL® was added, were noted to develop a mild decrease in mean neutrophil counts in comparison to groups treated with either ENBREL® or sulfasalazine alone. The clinical significance of this observation is unknown.

Carcinogenesis, Mutagenesis, and Impairment of Fertility

Long-term animal studies have not been conducted to evaluate the carcinogenic potential of ENBREL® or its effect on fertility. Mutagenesis studies were conducted in vitro and in vivo, and no evidence of mutagenic activity was observed.

Pregnancy (Category B)

Developmental toxicity studies have been performed in rats and rabbits at doses ranging from 60- to 100-fold higher than the human dose and have revealed no evidence of harm to the fetus due to ENBREL®. There are, however, no studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

Pregnancy Registry: To monitor outcomes of pregnant women exposed to ENBREL®, a pregnancy registry has been established. Physicians are encouraged to register patients by calling 1-877-311-8972.

Nursing Mothers

It is not known whether ENBREL® is excreted in human milk or absorbed systemically after ingestion. Because many drugs and immunoglobulins are excreted in human milk, and because of the potential for serious adverse reactions in nursing infants from ENBREL®, a decision should be made whether to discontinue nursing or to discontinue the drug.

Geriatric Use

A total of 480 RA patients and 89 plaque psoriasis patients ages 65 years or older have been studied in clinical trials. No overall differences in safety or effectiveness were observed between these patients and younger patients. Because there is a higher incidence of infections in the elderly population in general, caution should be used in treating the elderly.

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 ADVERSE REACTIONS: 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 psoriatic arthritis for up to 24 months, in 222 patients with ankylosing spondylitis for up to 10 months, and 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