

Gardasil Prevents HPV, Genital Warts in Males

BY MIRIAM E. TUCKER

ATLANTA — Merck & Co.'s human papillomavirus vaccine Gardasil was efficacious against persistent infections and genital warts caused by the vaccine strains, in a randomized, double-blind, placebo-controlled study of more than 4,000 adolescent and young adult males.

The study, funded by Merck, was planned as a 36-month follow-up but

was stopped early based on efficacy and safety data at a mean of 29 months, according to Dr. Richard M. Haupt, executive director of clinical research, Merck Research Laboratories, Whitehouse Station, N.J. The company submitted a biologics licensing application to the Food and Drug Administration in December 2008 for the use of Gardasil in males aged 9-26 years.

Of the four HPV strains in Gardasil,

HPV-16 and HPV-18 are responsible for the majority of HPV-related penile, anal, and oropharyngeal cancers and their associated precancers in males. The other two strains, HPV-6 and HPV-11, cause more than 90% of genital warts and recurrent respiratory papillomatosis.

"Gardasil is highly efficacious against HPV-6/11/16/18-related persistent infections and genital warts in men. This efficacy may also translate to reduced

transmission of vaccine type strains between sexual partners," Dr. Haupt said at a meeting of the Centers for Disease Control and Prevention's Advisory Committee on Immunization Practices.

The study included 3,463 heterosexual men aged 16-23 years and 602 men aged 16-26 years who have sex with men. Participants with more than five lifetime sexual partners were excluded. At baseline, just 17% of the total group was positive to at least one of the vaccine HPV strains by either serology or polymerase chain reaction testing, meaning that a large majority (83%) was susceptible.

The primary end point was vaccine efficacy against all external genital lesions.

In the per-protocol population, overall efficacy was 90%, driven primarily by the prevention of genital warts: 28 of 1,408 placebo subjects developed condyloma, compared with 3 of 1,397 who received

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 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 \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 *Criethidia lucilliae* 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*

Event	Placebo Controlled (N = 152)		Active Controlled (Study III) (N = 415)	
	Percent of patients	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 controlled 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 myelinitis 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. 36: 04/2009

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"We believe there is a real ... benefit to adding male vaccination to the already-recognized female vaccination."

DR. HAUPT

Gardasil, for an efficacy of 89%. Efficacy against PIN 1/2/3 was 100%, but the numbers were small (3 vs. 0 cases).

Efficacy against persistent infection—defined as two or more consecutive positive samples with the same HPV strain 6 months apart—was 86% (101 placebo subjects vs. 15 who got Gardasil). The vaccine was highly immunogenic, with seroconversion rates at 7 months ranging from 97% for anti-HPV-18 antibodies to 99% for anti-HPV-6. At 24 months, seroconversion rates remained high for all strains except for anti-HPV-18, which dropped to 62%. However, efficacy remained high against all strains, he noted.

Adverse event rates did not differ significantly between groups. Injection site reactions were the most common adverse event. No serious vaccine-related adverse events were reported, and only two Gardasil and three placebo participants discontinued the study because of vaccine-related adverse events.

Because efficacy studies that include genital sampling and questions about sexual behavior are not feasible in sexually naive young adolescent boys, the FDA allowed Merck to use immunogenicity "bridging" data to represent vaccine efficacy in 9- to 15-year-old boys in order to gain approval for use in that age group.

Immune responses to each of the four vaccine strains were actually more than twice as high among 1,073 boys aged 9-15 years as they were among 2,025 boys 16-26 years old, while there were no significant differences in adverse events between the younger and older cohorts.

"We believe there is a real public health benefit to adding male vaccination to the already-recognized female vaccination," Dr. Haupt concluded.