

Azithromycin Fizzled in CF Without *P. aeruginosa*

BY MARY ANN MOON

FROM JAMA

A 6-month course of azithromycin did not improve lung function in children and adolescents who had mild cystic fibrosis without *Pseudomonas aeruginosa* infection, according to a report.

The antibiotic failed to achieve the primary end point of improvement in forced expiratory volume in 1 second

(FEV₁) in a randomized controlled trial of 263 CF patients with mild disease, and it also did not decrease the need for intravenous or inhaled antibiotics or for hospitalization.

However, azithromycin achieved the exploratory end points of reducing pulmonary exacerbations, preventing initiation of other oral antibiotics, and increasing thin patients' weight and body mass index.

"Further studies of azithromycin are warranted to further investigate its potential use in this population," said Dr. Lisa Saiman of the pediatrics department at Columbia University, New York, and her associates (JAMA 2010;303:1707-15).

Azithromycin has both antimicrobial and anti-inflammatory activity, although its exact mechanism of action in CF is not yet known. It is recommended as chronic therapy for CF patients infected

with *P. aeruginosa*, but its use in children who do not have *P. aeruginosa* has not been well studied.

Dr. Saiman and her colleagues assessed the drug in relatively healthy CF patients aged 6-18 years who had an FEV₁ of at least 50% predicted and had negative cultures for *P. aeruginosa*. The study subjects were treated between 2007 and 2009 at 40 centers accredited for CF care throughout the United States and Canada.

The patients were randomly assigned to receive 2-3 daily azithromycin tablets (131 patients) or a matching placebo (132 patients) for 168 days, and were closely followed for 196 days. Adherence in the treatment and placebo groups was 90% and 91%, respectively, and only eight participants (five on active treatment and three

Tetanus Toxoid, Reduced Diphtheria Toxoid and Acellular Pertussis Vaccine Adsorbed



Brief Summary: Please see package insert for full prescribing information.

INDICATIONS AND USAGE Adacel vaccine is indicated for active booster immunization for the prevention of tetanus, diphtheria and pertussis as a single dose in persons 11 through 64 years of age. The use of Adacel vaccine as a primary series, or to complete the primary series, has not been studied. Vaccination with Adacel vaccine may not protect all of vaccinated individuals.

CONTRAINDICATIONS A severe allergic reaction (e.g., anaphylaxis) after a previous dose of Adacel vaccine or any other tetanus toxoid, diphtheria toxoid or pertussis containing vaccine or any other component of this vaccine is a contraindication to vaccination with Adacel vaccine. Because of uncertainty as to which component of the vaccine may be responsible, none of the components should be administered. Alternatively, such individuals may be referred to an allergist for evaluation if further immunizations are to be considered. (1,2) Encephalopathy within 7 days of a previous dose of a pertussis containing vaccine not attributable to another identifiable cause is a contraindication to vaccination with Adacel vaccine. (1-3)

WARNINGS Persons who experienced Arthus-type hypersensitivity reactions (e.g., severe local reactions associated with systemic symptoms) (4) following a prior dose of tetanus toxoid usually have high serum tetanus antitoxin levels and should not be given emergency doses of tetanus toxoid containing vaccines more frequently than every 10 years, even if the wound is neither deep nor minor. (1,2,5,6) If Guillain-Barré syndrome occurred within 6 weeks of receipt of prior vaccine containing tetanus toxoid, the decision to give Adacel vaccine or any vaccine containing tetanus toxoid should be based on careful consideration of the potential benefits and possible risks. (1-3) In the following situations, Adacel vaccine should generally be deferred:

- Moderate or severe acute illness with or without fever, until the acute illness resolves. (1,2)
- In adolescents, progressive neurologic disorder, including progressive encephalopathy, or uncontrolled epilepsy, until the condition has stabilized. (2)
- In adults, unstable neurologic condition (e.g., cerebrovascular events and acute encephalopathic conditions), until the condition has resolved or is stabilized. (1)

PRECAUTIONS General Before administration of Adacel vaccine, the patient's current health status and medical history should be reviewed in order to determine whether any contraindications exist and to assess the benefits and risks of vaccination. (See **CONTRAINDICATIONS** and **WARNINGS**.) Epinephrine Hydrochloride Solution (1:1,000) and other appropriate agents and equipment should be available for immediate use in case of anaphylactic or acute hypersensitivity reaction occurs. If Adacel vaccine is administered to immunocompromised persons, including persons receiving immunosuppressive therapy, the expected immune response may not be obtained.

Information for Vaccine Recipients and/or Parent or Guardian Before administration of Adacel vaccine, health-care providers should inform the vaccine recipient and/or parent or guardian of the benefits and risks. The health-care provider should inform the vaccine recipient and/or parent or guardian about the potential for adverse reactions that have been temporally associated with Adacel vaccine or other vaccines containing similar components. The health-care provider should provide the Vaccine Information Statements (VIS) that are required by the National Childhood Vaccine Injury Act of 1986 to be given with each immunization. The vaccine recipient and/or parent or guardian should be instructed to report any serious adverse reactions to their health-care provider. Females of child-bearing potential should be informed that Sanofi Pasteur Inc. maintains a pregnancy surveillance system to collect data on pregnancy outcomes and newborn health status outcomes following vaccination with Adacel vaccine during pregnancy. If they are pregnant or become aware they were pregnant at the time of Adacel vaccine immunization, they are encouraged to contact directly or have their health-care professional contact Sanofi Pasteur Inc. at 1-800-822-2463 (1-800-VACCINE). Reporting adverse events after vaccination to VAERS (Vaccine Adverse Event Reporting System) by recipients and/or parents or guardian should be encouraged. The toll-free number for VAERS forms and information is 1-800-822-7967. Reporting forms may also be obtained at the VAERS website at www.vaers.hhs.gov.

Drug Interactions Immunosuppressive therapies, including irradiation, antimetabolites, alkylating agents, cytotoxic drugs and corticosteroids (used in greater than physiologic doses), may reduce the immune response to vaccines. (See **PRECAUTIONS, General**.) For information regarding simultaneous administration with other vaccines refer to the **ADVERSE REACTIONS** and **DOSE AND ADMINISTRATION** sections.

Carcinogenesis, Mutagenesis, Impairment of Fertility No studies have been performed with Adacel vaccine to evaluate carcinogenicity, mutagenicity potential, or impairment of fertility.

Pregnancy Category C Animal reproduction studies have not been conducted with Adacel vaccine. It is also not known whether Adacel vaccine can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. Adacel vaccine should be given to a pregnant woman only if clearly needed. Animal fertility studies have not been conducted with Adacel vaccine. The effect of Adacel vaccine on embryo-fetal and pre-weaning development was evaluated in two developmental toxicity studies using pregnant rabbits. Animals were administered Adacel vaccine twice prior to gestation, during the period of organogenesis (gestation day 6) and later during pregnancy on gestation day 29, 0.5 mL/rabbit/occasion (a 17-fold increase compared to the human dose of Adacel vaccine on a body weight basis), by intramuscular injection. No adverse effects on pregnancy, parturition, lactation, embryo-fetal or pre-weaning development were observed. There were no vaccine related fetal malformations or other evidence of teratogenicity noted in this study. (7)

Nursing Mothers It is not known whether Adacel vaccine is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when Adacel vaccine is given to a nursing woman.

Pediatric Use Adacel vaccine is not indicated for individuals less than 11 years of age. (See **INDICATIONS AND USAGE**.) For immunization of persons 6 weeks through 6 years of age against diphtheria, tetanus and pertussis refer to manufacturers' package inserts for DTaP vaccines.

Geriatric Use Adacel vaccine is not indicated for individuals 65 years of age and older. No data are available regarding the safety and effectiveness of Adacel vaccine in individuals 65 years of age and older as clinical studies of Adacel vaccine did not include participants in the geriatric population.

ADVERSE REACTIONS The safety of Adacel vaccine was evaluated in 4 clinical studies. A total of 5,841 individuals 11-64 years of age inclusive (3,393 adolescents 11-17 years of age and 2,448 adults 18-64 years) received a single dose of Adacel vaccine. The principal safety study was a randomized, observer-blind, active controlled trial that enrolled participants 11-17 years of age (Adacel vaccine N = 1,184; Td vaccine N = 792) and 18-64 years of age (Adacel vaccine N = 1,752; Td vaccine N = 573). Study participants had not received tetanus or diphtheria containing vaccines within the previous 5 years. Solicited local and systemic reactions and unsolicited adverse events were monitored daily for 14 days post-vaccination using a diary card. From days 14-28 post-vaccination, information on adverse events necessitating a medical contact, such as a telephone call, visit to an emergency room, physician's office or hospitalization, was obtained via telephone interview or at an interim clinic visit. From days 28 to 6 months post-vaccination, participants were monitored for unexpected visits to a physician's office or to an emergency room, onset of serious illness and hospitalizations. Information regarding adverse events that occurred in the 6 month post-vaccination time period was obtained from the participant via telephone. Approximately 96% of participants completed the 6-month follow-up evaluation. In the concomitant vaccination study with Adacel and Hepatitis B vaccines, local and systemic adverse events were monitored daily for 14 days post-vaccination using a diary card. Local adverse events were only monitored at site/arm of vaccine administration. Unsolicited reactions (including immediate reactions, serious adverse events and events that elicited seeking medical attention) were collected at a clinic visit or via telephone interview for the duration of the trial, i.e., up to six months post-vaccination. In the concomitant vaccination study with Adacel vaccine and trivalent inactivated influenza vaccine, local and systemic adverse events were monitored for 14 days post-vaccination using a diary card. All unsolicited reactions occurring through day 14 were collected. From day 14 to the end of the trial, i.e., up to 84 days, only events that elicited seeking medical attention were collected. In all the studies, participants were monitored for serious adverse events throughout the duration of the study. Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a vaccine cannot be directly compared to rates in the clinical trials of another vaccine and may not reflect the rates observed in practice. The adverse reaction information from clinical trials does, however, provide a basis for identifying the adverse events that appear to be related to vaccine use and for approximating rates of those events.

Serious Adverse Events in All Safety Studies Throughout the 6-month follow-up period in the principal safety study, serious adverse events were reported in 1.5% of Adacel vaccine recipients and 1.4% in Td vaccine recipients. Two serious adverse events in adults were neurologic events that occurred within 28 days of Adacel vaccine administration; one severe migraine with unilateral facial paralysis and one diagnosis of nerve compression in neck and left arm. Similar or lower rates of serious adverse events were reported in the other trials and there were no additional neurologic events reported.

Solicited Adverse Events in the Principal Safety Study Most solicited adverse events (erythema, swelling, pain and fever) that occurred during Days 0-14 following one dose of Adacel vaccine or Td vaccine were reported at a similar frequency. Few participants

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(<1%) sought medical attention for these reactions. Pain at the injection site was the most common adverse reaction occurring in 63 to 78% of all vaccinees. In addition, overall rates of pain were higher in adolescent recipients of Adacel vaccine compared to Td vaccine recipients. Rates of moderate and severe pain in adolescents did not significantly differ between the Adacel vaccine and Td vaccine groups. Among adults the rates of pain, after receipt of Adacel vaccine or Td vaccine, did not significantly differ. Fever of 38°C and higher was uncommon, although in the adolescent age group, it occurred significantly more frequently in Adacel vaccine recipients than Td vaccine recipients. (7) Among other solicited adverse events headache was the most frequent systemic reaction and was usually of mild to moderate intensity. In general, the rates of the events following Adacel vaccine were comparable with those observed with Td vaccine. Local and systemic reactions occurred at similar rates in Adacel vaccine and Td vaccine recipients in the 3 day post-vaccination period. Most local reactions occurred within the first 3 days after vaccination (with a mean duration of less than 3 days). The rates of unsolicited adverse events reported from days 14-28 post-vaccination were comparable between the two groups, as were the rates of unsolicited adverse events from day 28 through 6 months. There were no spontaneous reports of whole-arm swelling of the injected limb in this study, nor in the other three studies which contributed to the safety database for Adacel vaccine.

Adverse Events in the Concomitant Vaccine Studies

Local and Systemic Reactions when Given with Hepatitis B Vaccine The rates reported for fever and injection site pain (at the Adacel vaccine administration site) were similar when Adacel and Hep B vaccines were given concurrently or separately. However, the rates of injection site erythema (23.4% for concomitant vaccination and 21.4% for separate administration) and swelling (23.9% for concomitant vaccination and 17.9% for separate administration) at the Adacel vaccine administration site were increased when co-administered. Swollen and/or sore joints were reported by 22.5% for concomitant vaccination and 17.9% for separate administration. The rates of generalized body aches in the individuals who reported swollen and/or sore joints were 86.7% for concomitant vaccination and 72.2% for separate administration. Most joint complaints were mild in intensity with a mean duration of 1.8 days. The incidence of other solicited and unsolicited adverse events were not different between the 2 study groups. (7)

Local and Systemic Reactions when Given with Trivalent Inactivated Influenza Vaccine The rates of fever and injection site erythema and swelling were similar for recipients of concurrent and separate administration of Adacel vaccine and Td vaccine. However, pain at the Adacel vaccine injection site occurred at statistically higher rates following concurrent administration (66.6% versus separate administration (60.8%)). The rates of sore and/or swollen joints were 13% for concurrent administration and 9% for separate administration. Most joint complaints were mild in intensity with a mean duration of 2.0 days. The incidence of other solicited and unsolicited adverse events were similar between the 2 study groups. (7)

Additional Studies An additional 1,806 adolescents received Adacel vaccine as part of the lot consistency study used to support Adacel vaccine licensure. This study was a randomized, double-blind, multi-center trial designed to assess lot consistency as measured by the safety and immunogenicity of 3 lots of Adacel vaccine when given as a booster dose to adolescents 11-17 years of age inclusive. Local and systemic adverse events were monitored for 14 days post-vaccination using a diary card. Unsolicited adverse events and serious adverse events were collected for 28 days post-vaccination. Pain was the most frequently reported local adverse event occurring in approximately 80% of all participants. Headache was the most frequently reported systemic event occurring in approximately 44% of all participants. Sore and/or swollen joints were reported by approximately 14% of participants. Most joint complaints were mild in intensity with a mean duration of 2.0 days. (7) An additional 962 adolescents and adults received Adacel vaccine in three supportive Canadian studies used as the basis for licensure in other countries. Within these clinical trials, the rates of local and systemic reactions following Adacel vaccine were similar to those reported in the four principal trials in the US with the exception of a higher rate (86%) of adults experiencing any local injection site pain. The rate of severe pain (0.8%), however, was comparable to the rates reported in four principal trials conducted in the US. (7) There was one spontaneous report of whole-arm swelling of the injected limb among the 277 Td vaccine recipients, and two spontaneous reports among the 962 Adacel vaccine recipients in the supportive Canadian studies.

Postmarketing Reports The following adverse events have been spontaneously reported during the post-marketing use of Adacel vaccine in the US and other countries. Because these events are reported voluntarily from a population of uncertain size, it is not possible to reliably estimate their frequency or establish a causal relationship to vaccine exposure. The following adverse events were included based on severity, frequency of reporting or the strength of causal association to Adacel vaccine. *General disorders and administration site conditions:* Large injection site reactions (>50 mm), extensive limb swelling from the injection site beyond one or both joints. *Injection site bruising, sterile abscess, Nervous system disorders:* Parosmia, hypoesthesia, Guillain-Barré syndrome, facial palsy, convulsion, syncope, myelitis. *Immune system disorders:* Anaphylactic reaction, hypersensitivity reaction (angioedema, edema, rash, hypotension) *Skin and subcutaneous tissue disorders:* Pruritus, urticaria. *Musculoskeletal and connective tissue disorders:* Myositis, muscle spasm. *Cardiac disorders:* Myocarditis.

Additional Adverse Events Additional adverse events, included in this section, have been reported in conjunction with receipt of vaccines containing diphtheria, tetanus toxoids and/or pertussis antigens. Arthus-type hypersensitivity reactions, characterized by severe local reactions (generally starting 2-8 hours after an injection), may follow receipt of tetanus toxoid. Such reactions may be associated with high levels of circulating antitoxin in persons who have had overly frequent injections of tetanus toxoid. (8) (See **WARNINGS**.) Persistent nodules at the site of injection have been reported following the use of adsorbed products. (4) Certain neurological conditions have been reported in temporal association with some tetanus toxoid containing vaccines or tetanus and diphtheria toxoid containing vaccines. A review by the Institute of Medicine (IOM) concluded that the evidence favors acceptance of a causal relation between tetanus toxoid and both brachial neuritis and Guillain-Barré syndrome. Other neurological conditions that have been reported include: demyelinating diseases of the central nervous system, peripheral mononeuropathies, and cranial mononeuropathies. The IOM has concluded that the evidence is inadequate to accept or reject a causal relation between these conditions and vaccines containing tetanus and/or diphtheria toxoids.

Reporting of Adverse Events The National Vaccine Injury Compensation Program, established by the National Childhood Vaccine Injury Act of 1986, requires physicians and other health-care providers who administer vaccines to maintain permanent vaccination records of the manufacturer and lot number of the vaccine administered in the vaccine recipient's permanent medical record along with the date of administration of the vaccine and the name, address and title of the person administering the vaccine. The Act further requires the health-care professional to report to the US Department of Health and Human Services the occurrence following immunization of any event set forth in the Vaccine Injury Table. These include anaphylaxis or anaphylactic shock within 7 days; brachial neuritis within 28 days; an acute complication or sequelae (including death) of an illness, disability, injury, or condition referred to above, or any events that would contraindicate further doses of vaccine, according to this Adacel vaccine package insert. (9-11) The US Department of Health and Human Services has established the Vaccine Adverse Event Reporting System (VAERS) to accept all reports of suspected adverse events after the administration of any vaccine. Reporting of all adverse events occurring after vaccine administration is encouraged from vaccine recipients, parents/guardians and the health-care provider. Adverse events following immunization should be reported to VAERS. Reporting forms and information about reporting requirements or completion of the form can be obtained from VAERS through a toll-free number 1-800-822-7967 or visit the VAERS website at www.vaers.hhs.gov. (9-11) Health-care providers should also report these events to Sanofi Pasteur Inc., Discovery Drive, Swiftwater, PA 18370 or call 1-800-822-2463 (1-800-VACCINE).

DOSE AND ADMINISTRATION Adacel vaccine should be administered as a single injection of one dose (0.5 mL) by the intramuscular route. Adacel vaccine should not be combined through reconstitution or mixed with any other vaccine. Just before use, shake the vial well until a uniform, white, cloudy suspension results. Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit. If these conditions exist, the vaccine should not be administered. When administering a dose from a rubber-stoppered vial, do not remove either the stopper or the metal seal holding it in place. The preferred site is into the deltoid muscle. The vaccine should not be injected into the gluteal area or areas where there is a major nerve trunk. Do NOT administer this product intravenously or subcutaneously. Five years should have elapsed since the recipient's last dose of tetanus toxoid, diphtheria toxoid and/or pertussis containing vaccine. There are no data to support repeat administration of Adacel vaccine. The use of Adacel vaccine as a primary series or to complete the primary series for tetanus, diphtheria, or pertussis has not been studied.

STORAGE Store at 2° to 8°C (35° to 46°F). DO NOT FREEZE. Product which has been exposed to freezing should not be used. Do not use after expiration date.

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VITALS

Major Finding: Mean FEV₁ was 2.13 at baseline and 2.22 at 6 months with the active drug, compared with 2.12 at baseline and 2.20 at 6 months with placebo.

Data Source: A 6-month placebo-controlled study of azithromycin in 263 relatively healthy children and adolescents with CF who had negative cultures for *P. aeruginosa*.

Disclosures: CF Foundation Therapeutics Inc. funded the study, and Pfizer Inc. supplied the azithromycin and the placebo. Dr. Saiman reported ties to Pfizer Inc., maker of azithromycin, and Ardis Pharmaceuticals LLC, Bayer, CF Foundation Therapeutics Inc., Chiesi Pharmaceuticals Inc., Gilead Sciences Inc., Johnson & Johnson, Mpx Pharmaceuticals Inc., Novartis, SmithKline Beecham Inc., and Transave Inc.

on placebo) withdrew from the study.

Azithromycin did not improve FEV₁, compared with placebo. Mean FEV₁ was 2.13 at baseline and 2.22 at 6 months with the active drug, compared with 2.12 at baseline and 2.20 at 6 months with placebo. Similarly, azithromycin failed to improve other indicators of pulmonary function, such as forced vital capacity and forced midexpiratory flow rate. There were no differences between the treatment and placebo groups in the number of hospitalizations or the need for IV or inhaled antibiotics.

However, azithromycin decreased the number of pulmonary exacerbations by nearly half and the need for new oral antibiotics by 27%, compared with placebo. It was also associated with a significant weight gain (0.58 kg) and a significant increase in body mass index (0.34 units). The drug was well tolerated, producing no increase in the rates of nausea, diarrhea, wheezing, and serious or nonserious adverse events, compared with placebo.

The only significant differences between the two groups in treatment-emergent pathogens were found with macrolide-resistant *Staphylococcus aureus* and *Haemophilus influenzae*. Azithromycin users had 27% and 7% more emergence of those organisms, respectively, than did placebo participants. ■

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