Vaccine 32 (2014) 4758–4765

Contents lists available at ScienceDirect

Vaccine

journal homepage: www.elsevier.com/locate/vaccine

Ischemic cardiac events and other adverse events following ACAM2000® smallpox vaccine in the Vaccine Adverse Event Reporting System☆

Michael M. McNeil[a,*], Maria Cano[a], Elaine R. Miller[a], Brett W. Petersen[b], Renata J.M. Engler[c], Marthe G. Bryant-Genevier[d]

[a] Immunization Safety Office, Division of Healthcare Quality Promotion, National Center for Emerging and Zoonotic Infectious Diseases, Centers for Disease Control and Prevention, United States
[b] Poxvirus and Rabies Branch, Division of High-Consequence Pathogens and Pathology, National Center for Emerging and Zoonotic Infectious Diseases, Centers for Disease Control and Prevention, United States
[c] Vaccine Healthcare Centers Network, Military Vaccine Agency, US Army Public Health Command, Walter Reed National Military Medical Center, 8901 Wisconsin Avenue, Bethesda, MD 20889-5600, United States
[d] Office of Biostatistics and Epidemiology, Center for Biologics Evaluation and Research, Food and Drug Administration, United States

ARTICLE INFO

Article history:
Received 3 April 2014
Received in revised form 22 May 2014
Accepted 6 June 2014
Available online 18 June 2014

Keywords:
ACAM2000®
Ischemic cardiac events
Myocarditis
Pericarditis
Myo/pericarditis

ABSTRACT

Background: The Vaccine Adverse Event Reporting System (VAERS) is a passive reporting system, used for monitoring the safety of all US licensed vaccines. In March 2008, ACAM2000® replaced Dryvax® as the only licensed smallpox vaccine and is administered to all persons entering military service and certain civilian researchers. In 2011, routine data mining of VAERS identified a vaccine safety concern resulting in acute ischemic cardiac events (ICE) following ACAM2000®.
Methods: During March 1, 2008 through June 30, 2013, we reviewed all serious reports received following ACAM2000® and classified them by diagnostic category. We identified possible ICE cases by searching the Medical Dictionary for Regulatory Affairs (MedDRA®) terms for "myocardial ischaemia," "acute myocardial infarction," "myocardial infarction," and "ischaemia," and applied standardized surveillance case definitions.
Results: VAERS received 1149 reports following ACAM2000® administration; 169 (14.7%) were serious (resulting in permanent disability, hospitalization or prolongation of hospitalization, life-threatening illness or death), including one death. The two most frequent diagnostic categories for serious reports were cardiovascular and other infectious conditions. The MedDRA® search found 31 reports of possible ICE after receipt of ACAM2000® vaccine. Of a total 30 possible ICE cases with demographic information, all but one was male; the age range was 20–45 years (median 32) and median interval to onset of symptoms was 12 days. On clinical review there were 16 cases of myocarditis/pericarditis and 15 ICE cases.
Conclusions: Our review of the data mining signal did not substantiate the concerns about ICE after ACAM2000®. Our study also suggests that with current pre-vaccination screening, cardiac morbidity in generally healthy vaccinated populations remains uncommon.

Published by Elsevier Ltd.

☆ The views, findings and conclusions in this report are those of the authors and do not reflect the official policy or position of the Centers for Disease Control and Prevention, the Departments of the Army/Navy/Air Force, Department of Defense, nor the US Government. Use of trade names and commercial sources is for identification only and does not imply endorsement by the Centers for Disease Control and Prevention, the US Department of Health and Human Services, the Departments of the Army/Navy/Air Force, the Department of Defense, or the US Government. Mention of a product or company name does not constitute endorsement by the CDC. None of the authors have conflicts of interest to declare. Because VAERS is a routine surveillance program that does not meet the definition of research, it is not subject to institutional review board review and informed consent requirements.

* Corresponding author at: MS D-26, Centers for Disease Control and Prevention, 1600 Clifton Road NE, Atlanta, GA 30333, United States. Tel.: +1 404 639 0542; fax: +1 404 639 8834.
E-mail address: mmm2@cdc.gov (M.M. McNeil).

http://dx.doi.org/10.1016/j.vaccine.2014.06.034
0264-410X/Published by Elsevier Ltd.

1. Introduction

In June 2001, the Advisory Committee on Immunization Practices (ACIP) made recommendations for using smallpox vaccine to protect persons working with orthopox viruses and to prepare for a possible terrorist attack [1]. In December 2002, the US Department of Defense (DOD) began vaccination as part of a national program of preparedness against biological attack [2]. On January 24, 2003, the US Department of Health and Human Services (DHHS) authorized voluntary smallpox vaccination of civilians, including healthcare workers and members of smallpox teams identified by state or local health departments, who might be called on to monitor or treat persons exposed to smallpox [3]. These programs used the first generation calf lymph vaccinia vaccine (Dryvax®, Wyeth) and focused exclusively on healthy adults.

As part of these military and civilian smallpox vaccination programs, DOD and the Centers for Disease Control and Prevention (CDC) conducted enhanced vaccine safety monitoring for possible adverse events (AEs) [4]. Enhanced VAERS monitoring involves performing clinical review of medical records or available documentation (e.g., diagnostic tests) for selected medical adverse events that are reported to VAERS). These programs reported a previously underappreciated relationship between smallpox vaccine and acute cardiac AEs [5–10]. Although reports of myo/pericarditis (MPC) predominated, possible ischemic cardiac events (ICE) were also identified [11–14]. The civilian program was severely curtailed after 10 months with contributing factors for the relatively low turnout of volunteers for immunization including a concern about possible rare vaccine adverse events combined with the failure to find Iraqi bioweapons which seemed to diminish the threat; however, a very limited civilian program vaccinating mainly high risk laboratory/research personnel is ongoing with smallpox vaccine supplied by CDC. In contrast, the military program has continued to the present [15]. On August 31, 2007, the new second generation, clonal, Vero cell cultured vaccinia vaccine ACAM2000® (Sanofi Pasteur Biologics Co.) was approved by the FDA for use in the US [16]. On February 29, 2008, a notice was published informing providers that ACAM2000® vaccine was replacing the calf lymph vaccinia vaccine (Dryvax®) and that all lots of Dryvax® expired on that date [17].

The DOD smallpox vaccination program utilizes a pre-vaccination screening algorithm based on CDC Advisory Committee on Immunization Practices (ACIP) recommendations to identify and defer the administration of smallpox vaccine to persons with known underlying heart disease, with or without symptoms, or who have three or more known major cardiac risk factors (i.e., hypertension, diabetes, hypercholesterolemia, heart disease at age 50 years in a first-degree relative, and smoking) [18]. The ACIP did not recommend special medical follow-up for persons with cardiovascular risk factors who have been vaccinated but advised that persons with risk factors or known atherosclerotic coronary artery disease should be routinely cared for by their physicians.

Under a post marketing commitment (PMC), the DOD, FDA, CDC and the vaccine manufacturer are gathering additional safety information on AEs following administration of ACAM2000® utilizing the Vaccine Adverse Event Reporting System (VAERS) [19]. On March 25, 2011, the Medical Dictionary for Regulatory Activities (MedDRA®) coding term "acute myocardial infarction" and ACAM2000® exceeded a predetermined data mining threshold in the VAERS database, which warranted further investigation (see Section 2.3). To better understand the possible association of ICE and ACAM2000®, we conducted an in-depth clinical review of VAERS data to confirm reports of ICE following ACAM2000® and included all data through June 30, 2013.

2. Methods

2.1. VAERS database

VAERS, co-administered by CDC and the Food and Drug Administration (FDA), is a national passive surveillance system that accepts reports from healthcare and vaccine providers, manufacturers, and vaccine recipients or their caregivers [20]. Information on age, sex, medical history, vaccines and AEs are collected on the VAERS form, and signs and symptoms of AEs are coded by trained personnel using the MedDRA® terms [21]. Reports are coded as serious, as defined by the Code of Federal Regulations, if at least one of the following was reported: death, life-threatening illness, hospitalization or prolonged hospitalization, or permanent disability [22]. As part of the routine surveillance activities, medical records are requested only for serious reports submitted by vaccinees or healthcare providers.

2.2. Review of ACAM2000® VAERS reports

We identified and reviewed US VAERS reports received by June 30, 2013 for persons vaccinated with ACAM2000® smallpox vaccine from March 1, 2008 through June 30, 2013 (including those with missing vaccination dates). Two medical officers conducted independent clinical review of all VAERS reports, and the primary AEs reported were categorized into one of the following diagnostic categories [23]; allergic (including anaphylaxis), cardiovascular (including cerebrovascular accident), ENT (ears-nose-throat), gastrointestinal, local reaction, musculoskeletal, neurologic (including GBS, narcolepsy and seizures), pregnancy-specific events, psychiatric, respiratory (including influenza-like illness, pneumonia, and non-infectious upper/lower respiratory conditions), other infectious, other non-infectious (e.g., diabetes, thrombocytopenia, dermatologic conditions), and death. Known serious smallpox vaccine AEs (eczema vaccinatum, generalized vaccinia, progressive vaccinia), and inadvertent inoculation of vaccinia virus (e.g., autoinoculation, contact transmission) were classified under "other infectious" category [4]. Reports without any AE per se that were submitted to VAERS as a result of administering the vaccine at an inappropriate site, schedule or dosage or to a person of inappropriate age or with contraindication to smallpox vaccine (excluding pregnancy) were classified as a vaccination error. A review of medical records, if available, of VAERS reports was conducted to verify the diagnosis. If no medical record was available, the CDC medical officer determined a possible diagnosis to classify reports by diagnostic category. Reports suggestive of anaphylaxis were verified using the Brighton Criteria [24] or if medical records included physician diagnosis of anaphylaxis. Cause of death was verified by autopsy report or death certificate.

2.3. FDA data mining

Empirical Bayesian data mining techniques are routinely used with the VAERS database to assess disproportionate reporting of AEs for all US licensed vaccines, including smallpox vaccine [25,26]. To identify vaccine-event pairs for further evaluation, we applied the criteria suggested by Szarfman et al. [26].

2.4. Identification of possible ICE cases

To better understand the possible association between ACAM2000® and ICE, we identified possible ICE cases since 2008, by searching the VAERS database using the MedDRA® terms for "myocardial ischaemia," "acute myocardial infarction," "myocardial infarction," and "ischaemia" for reports of persons vaccinated with ACAM2000® smallpox vaccine from March 1, 2008 through