Use of the LC16m8 Smallpox Vaccine in Immunocompromised Individuals Is Still Too Risky

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We read with some concern the report by Yokote et al. (1), in which the authors recommend that LC16m8, a replicating smallpox vaccine licensed in Japan, be considered for use in persons who are immunocompromised. The authors presented new data from mouse models comparing the virulence of LC16m8 to that of other replication-competent smallpox vaccines; however, they fail to disclose that the current package insert for the licensed product lists as contraindicated those persons that (i) have an illness causing severe abnormality in immune function or are undergoing immune-suppressive treatments and (ii) have generalized skin disease which may lead to complications associated with vaccination (2).

Replicating smallpox vaccines, including DryVax, ACAM2000, and LC16m8, are comprised of a live vaccinia virus that is administered to the skin via a process called scarification. Following administration, vaccinia replication produces a localized infection or “take” that is associated with induction of immunity to smallpox. Historically, replicating smallpox vaccines have been associated with side effects ranging from frequent events such as autoinoculation to rare but life-threatening events such as eczema vaccinatum and encephalitis. LC16m8, a small-plaque and smallpox-forming variant virus derived from the Lister strain, has been shown in multiple nonclinical studies, including the work described here, to be less virulent than its parental strain. How- ever, as described by Yamaguchi et al. (3), analysis of 8,544 vaccinations in children with LC16m8 resulted in one case of eczema vaccinatum, nine cases of autoinoculation, and eight cases of vaccinia virus infection. While these symptoms of the infections were described as mild, the replication of LC16m8 may clearly present a hazard to those individuals who may have difficulty mounting an effective immune response to viral infections, which is consistent with the contraindications noted on the product label.

In the absence of specific clinical evaluation of LC16m8 in immunocompromised (e.g., HIV-positive) individuals and/or those suffering from active skin barrier disorders that are linked to immune function (e.g., eczema), it would appear to be premature to consider the use of LC16m8 in populations that are at elevated risk of serious and potentially life-threatening side effects associated with uncontrolled or widespread disseminated vaccinia virus infections. While much is made of a 2013 World Health Organization advisory group’s recommendations regarding LC16m8, it should be noted that group did not recommend the use of LC16m8 in individuals with compromised immune systems. Indeed, that advisory group specifically indicated that modified vaccinia Ankara—Bavarian Nordic (Imvanex), a nonreplicating smallpox vaccine comprised of modified vaccinia virus Ankara (MVA), should be considered for use, where approved, in individuals for whom replicating smallpox vaccines are contraindicated due to immunodeficiencies, immunosuppressive therapies, or atopic dermatitis (4). Furthermore, Yokote et al. generally implied the poor immunogenicity of replication-deficient vaccinia virus vaccines. This suggestion is also contrasted by recent data in a murine model of human smallpox showing the possibility of protective efficacy even with very low doses of MVA vaccine (5).

Importantly, in the absence of specific action by regulatory agencies charged with ensuring the safety and efficacy of approved medical products, it seems unwise to promote the use of LC16m8 in immunocompromised individuals on the basis of limited nonclinical studies.

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