



BRIEF COMMUNICATION

Allergy to IXIARO and BIKEN Japanese Encephalitis Vaccines

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We describe an allergic reaction to both mouse brain-derived BIKEN and Vero cell-derived IXIARO Japanese encephalitis (JE) vaccines in a single traveler. In the absence of the stabilizers and murine proteins in the BIKEN vaccine, a common factor in both vaccines is likely to be responsible, possibly JE virus antigen itself.

Japanese encephalitis (JE) is a mosquito-borne flavivirus and the leading cause of vaccine-preventable encephalitis in Asia.¹ Less than 1% of humans infected with JE virus develop clinical disease, yet up to 30,000 symptomatic cases of JE are still reported annually and this figure is probably an underestimate.² JE has a case-fatality rate of 20%–30%, and of those surviving, as many as 25%–50% may suffer from long-term neurologic or psychiatric sequelae.² There is no curative treatment for symptomatic JE and in endemic countries vaccination remains an important public health priority.

The risk for travelers from nonendemic countries is estimated to be in the region of one case per million travelers.¹ However, the risk for those staying in rural areas for long periods is estimated to be similar to that of the susceptible resident population and is considered an indication for vaccination.² Two JE vaccines have been available for use in the UK: an inactivated mouse brain-derived vaccine (JE-VAX/BIKEN [JE-MB]) and an inactivated Vero cell culture-derived vaccine (IXIARO [JE-VC]). An adverse safety profile and multiple reports of moderate to severe hypersensitivity-type reactions associated with vaccination led to the cessation of JE-MB production by one manufacturer in 2006 (Sanofi Pasteur MSD), although this continues in Korea (Green Cross).^{2,3}

JE-MB was prepared by intracerebral inoculation of neonatal mice with JE Nakayama-NIH strain.⁴ Adverse

events have been estimated to occur at a rate of 1–17 per 10,000 vaccines and included generalized urticaria, angioedema, and respiratory distress.⁵ These reactions have been attributed to the use of gelatin or thimerosal stabilizers or residual murine neural proteins, although none has been proven causative.^{1,5} The WHO placed a high priority on the development of new vaccines and in 2009 the JE-VC (IXIARO) vaccine completed Phase III trials. This vaccine is an inactivated, alum adjuvanted vaccine, manufactured in cultured Vero cells from the SA14-14-2 strain, and is formulated in serum-free medium without gelatin, thimerosal, or other stabilizers.⁶ Noninferiority to the JE-MB vaccine by immunogenicity and antibody titers was demonstrated with a favorable safety profile.⁷ Adverse events were generally mild, and this vaccine has replaced JE-MB vaccine in clinical use in adults and is close to doing so for children.⁷ We describe a case of allergic reaction to both the JE-MB (BIKEN) and the JE-VC (IXIARO) vaccines in one patient.

Case Report

MB was a 67-year-old retired therapist traveling to rural India for 5 months for voluntary work in a school. She had no significant past medical history and no known allergies. She had not previously been vaccinated against JE but was felt to be at significant risk. She received 3 × 1 mL subcutaneous doses of JE-MB (BIKEN) vaccine on days 0, 7, and 28, accompanied by 3 × 1 mL intradermal doses of human diploid cell rabies vaccine. Following the third dose, she developed an urticarial rash all over her body and experienced mild respiratory disturbance. She was treated with intramuscular antihistamine, the

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symptoms resolved, and she did not require admission to hospital.

Three years later MB was returning to rural India as a tourist. Serology revealed no IgG antibodies to JE and after discussion of the likely risks with a vaccine that was unlikely to constitute a similar risk she elected to be revaccinated with JE-VC (IXIARO) vaccine. She suffered no immediate reaction and was discharged home after 2 hours observation in our outpatient department. Three days later, she noted an itchy, papular rash at her hairline and on her inner wrists, which, the next day, spread to her scalp and upper body. This remained pruritic and appeared urticarial. She took 10 mg of cetirizine, 8 mg of chlorphenamine, and after 5 days from onset her symptoms had resolved. There was no associated respiratory distress. Three months later, serology revealed IgG to JE.

Discussion

Adverse events such as rash and urticaria are recognized complications of JE-MB vaccination, and have been noted to occur as many as 17 days following vaccination and in as many as 5% of vaccinees.⁴ Similarly, adverse reactions to JE-VC may occur up to 8 days following vaccination.⁸ In the safety studies for JE-VC, one case of generalized urticaria was noted 8 days following vaccination, and treated with cetirizine hydrochloride with symptom resolution after 3 days,⁹ a similar event to that occurring in our patient.

Adverse reactions following a prior dose of JE-MB manifesting as generalized urticaria and angioedema are considered contraindications to further vaccination.⁴ Those with previous urticarial reactions following hymenoptera envenomation, drugs, or other provocations were at greater risk of reaction to JE-MB.⁴ The JE-VC vaccine does not contain the stabilizers and excipients of the JE-MB vaccine and we considered it a safe option for boosting immunity in this patient. JE-VC contains protamine sulphate, associated with hypersensitivity reactions, but this is not seen in JE-MB.²

Compared to a vaccine excipient placebo, JE-VC was seen to have a comparable proportion and severity of adverse reactions, and compared to JE-MB, JE-VC recipients had significantly fewer local reactions.^{7–9} Furthermore, no hypersensitivity reactions featuring angioedema have been reported in JE-VC recipients. When compared to JE-MB, JE-VC had a reported hypersensitivity rate of 3.6/100,000 doses compared to 8.4.⁸ Indeed, the context of an improved safety profile and fatal JE cases in those not covered by current vaccination recommendations has prompted consideration of broader vaccine coverage.³ Few data exist on the use of JE-VC vaccine to boost immunity following a primary course of JE-MB. Both are derived from different viral strains, and in this case, follow-up serology indicated protective immunity after one dose of JE-VC. Previously, a primary series of JE-VC was recommended to all travelers regardless of prior

vaccination history, but a recent study has demonstrated the efficacy of a single dose of JE-VC in JE-MB-primed travelers.¹⁰ This would suggest that the viral strains Nakayama and SA14-14-2 are immunologically similar and elicit cross-reactive immune responses. This may underlie the allergic reaction in this case. The similar nature of the reactions to both JE-MB/rabies and later JE-VC lead us to hypothesize that the JE vaccine precipitated the allergic reaction in both vaccination schedules.

Decline in antibody levels occurs with both vaccines after 1 year and booster doses may be needed in travelers with continued risk.² In the case we have reported, we will repeat serology, and if the risk benefit analysis favors a further booster dose we may consider experimental boosting intradermally at one-fifth of the normal dose with anti-histamine cover. This approach has been successful with egg-allergic yellow fever vaccine recipients.¹¹

Conclusion

JE-VC vaccine is associated with a lower risk of adverse events than JE-MC vaccines. We describe a case in which a similar allergic response occurred to both JE-MB and JE-VC vaccines. In the absence of identifiable allergenic excipients, this may represent an allergy to the JE virus antigen. Cross-reactivity between the JE-MB and the JE-VC vaccines remains poorly understood. While JE-VC undergoes post-marketing surveillance, we recommend vigilance and reporting of adverse reactions to improve the characterization of the safety profile of this new vaccine.

Declaration of Interests

The authors state that they have no conflicts of interest.

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