

DR. LESTER JUAY (Orcid ID : 0000-0003-3084-8814)

Article type : Letter to the Editor

Title Page

Article Type: Letter to the Editor

Proposed Title: Three cases of vesiculobullous non-IgE-mediated cutaneous reactions to tozinameran (Pfizer-BioNTech COVID-19 vaccine)

Authors and Contact Information:

1. (Corresponding Author)

Lester Juay, MRCP (UK), MMed Int Med (Singapore)

National University Hospital, Singapore

Address: 5 Lower Kent Ridge Road, Singapore 119074

Email: lester_juay@nuhs.edu.sg

ORCID ID: 0000-0003-3084-8814

2. Nisha Suyien Chandran, MRCP UK, MMed (Singapore)

National University Hospital, Singapore

Address: 5 Lower Kent Ridge Road, Singapore 119074

Email: nisha_suyien_chandran@nuhs.edu.sg

ORCID ID: 0000-0001-8225-0035

This article has been accepted for publication and undergone full peer review but has not been through the copyediting, typesetting, pagination and proofreading process, which may lead to differences between this version and the [Version of Record](#). Please cite this article as [doi: 10.1111/JDV.17581](https://doi.org/10.1111/JDV.17581)

This article is protected by copyright. All rights reserved

Acknowledgement: The patients in this manuscript have given written informed consent to publication of their case details.

Funding: This article has no funding source.

Conflict of Interest Declaration: The authors have no conflicts of interest to declare.

Consent for Publication: This manuscript has not been published and is not under consideration for publication elsewhere.

Word Count: 594 words

References: 9

Tables: 0

Figures: 4 (of which 2 are insets)

Keywords: Cutaneous reaction, cutaneous adverse drug reaction, tozinameran, COVID-19, RNA vaccine

Manuscript Text

Dear Editor,

There is a global uptake of vaccination against coronavirus disease 2019 (COVID-19). The Phase III trial of tozinameran, a ribonucleic acid (RNA) vaccine, demonstrated a risk of anaphylaxis at 11.1 cases per million doses¹. Little is known regarding various non-IgE-mediated cutaneous reactions arising from the use of these vaccines. We report three cases of non-IgE-mediated cutaneous reactions following tozinameran administration, in a tertiary hospital in Singapore.

A 51-year-old gentleman developed deep-seated vesicles over his palms 1 day after administration of the second dose of tozinameran. Examination revealed scattered deep vesicles over bilateral palms, with focal desquamation (Figs. 1(a) & 1(b)). He was diagnosed with acute dyshidrotic eczema and treated with topical betamethasone dipropionate ointment.

A 70-year-old lady was admitted to the hospital for an acute flare of bullous pemphigoid 2 weeks following administration of the first dose of tozinameran. She had a known history of biopsy-proven bullous pemphigoid which was controlled on tapering, low-dose prednisolone. Other drug and infective histories were unremarkable. Inpatient admission was required. Treatment consisted of prednisolone dose escalation to 0.5mg/kg/day, and application of clobetasol 0.05% cream.

A 38-year-old gentleman presented for fever and pruritic rashes, 5 days after administration of the second dose of tozinameran. Localising infective symptoms were absent. Drug history was otherwise unremarkable. Erythematous scaly plaques, studded with non-follicular pustules and desquamative scales over his trunk and limbs (Figs. 2(a) & 2(b)) was associated with marked neutrophilia. Fungal scrape was negative. Histology was supportive of the diagnosis of acute generalised exanthematous pustulosis (AGEP). Clinical resolution was achieved with topical mometasone cream.

These cases of non-allergic cutaneous reactions consisting of vesicobullous eruptions demonstrate varying degrees of severity. A case series of 12 patients with delayed large local

reactions to mRNA-1273 vaccine described an isolated patient developing papules over the palms 4 days after receiving the vaccine². Eczema flares following vaccination for mumps, measles, and rubella have been reported³. The pathomechanism of MMR-vaccine aggravating eczema was postulated to be that of increased interleukin-4 levels following infection by the live attenuated virions. Vaccinations may instigate a vigorous host immune response, thereby dysregulating the delicate Th1 and Th2 lymphocytic balance in these atopic individuals. The mechanism for RNA vaccine inducing vesicular eczema remains unknown.

Drug-induced bullous pemphigoid remains incompletely understood⁴. The pathomechanistic concept of molecular mimicry with the RNA vaccine is postulated, with SARS-CoV-2 spike proteins produced leading to activation of CD4+ T-cells and initiation or rekindling of the autoimmune cascade. Bullous pemphigoid following vaccinations usually has a short latency of days⁵.

More than 90% of cases of AGEP are drug-induced.⁶ A case series of childhood AGEP reported 2 cases of vaccine-related AGEP⁷, while a pregnant lady of 10-week gestation developed AGEP 1 day after influenza vaccination⁸. Tozinameran consists of lipid and mRNA nanoparticles. AGEP may be induced via the RNA molecule, lipid vehicle or the eventual proteins arising from the translation of RNA. The propensity for components of the RNA vaccine to induce non-allergic cutaneous reactions remains insufficiently characterised. Preliminary case series have documented delayed large local reactions, termed "COVID arm"², and various other reactions in a registry-based report of 414 cases⁹. These delayed cutaneous manifestations may be related to the host immune response instead of true vaccine allergies.

We opine that most delayed, mild non-IgE-mediated cutaneous reactions do not contraindicate further doses of the same vaccine, as these reactions are often transient and self-limiting, where the benefits of a completed vaccination schedule outweigh the potential morbidity following such reactions. Knowledge of both allergic and non-allergic cutaneous reactions to various COVID-19 vaccines is useful in the current mass vaccination exercises worldwide.

References

1. Shimabukuro T, Nair N. Allergic Reactions Including Anaphylaxis After Receipt of the First Dose of Pfizer-BioNTech COVID-19 Vaccine. *JAMA*. 2021;325(8):780-781.
2. Blumenthal KG, Freeman EE, Saff RR, et al. Delayed Large Local Reactions to mRNA-1273 Vaccine against SARS-CoV-2. *N Engl J Med*. 2021;384(13):1273-1277.
3. Olesen AB, Juul S, Thestrup-Pedersen K. Atopic dermatitis is increased following vaccination for measles, mumps and rubella or measles infection. *Acta Derm Venereol*. 2003;83(6):445-450.
4. Verheyden MJ, Bilgic A, Murrell DF. A Systematic Review of Drug-Induced Pemphigoid. *Acta Derm Venereol*. 2020;100(15):adv00224.
5. Rosenblatt AE, Stein SL. Cutaneous reactions to vaccinations. *Clin Dermatol*. 2015;33(3):327-332.
6. Szatkowski J, Schwartz RA. Acute generalized exanthematous pustulosis (AGEP): A review and update. *J Am Acad Dermatol*. 2015;73(5):843-848.
7. Zhang JL, Chen X, Li J, Xie HF. Clinical analysis of childhood acute generalized exanthematous pustulosis. *Zhongguo Dang Dai Er Ke Za Zhi*. 2008 Aug;10(4):497-9.
8. Matsuo S, Nishizawa A, Oshio-Yoshii A, Satoh T. Influenza vaccine-induced acute generalized exanthematous pustulosis during pregnancy. *J Dermatol*. 2017;44(5):598-599.
9. McMahon DE, Amerson E, Rosenbach M, et al. Cutaneous Reactions Reported after Moderna and Pfizer COVID-19 Vaccination: A Registry-Based Study of 414 Cases [published online ahead of print, 2021 Apr 7]. *J Am Acad Dermatol*. 2021;S0190-9622(21)00658-7.

Figure Legends

Fig. 1(a): Erythematous vesicles on bilateral palms.

Fig. 1(b): Deep-seated tense vesicles on the palmar aspect.

Fig. 2(a): Extensive erythematous plaques with crops of non-follicular pustules over the trunk and limbs of this patient with AGEP.

Fig. 2(b): Non-follicular pustules on an erythematous plaque.



jd_v_17581_f1.png



jd_v_17581_f2.png