Clinical Dermatology and Investigations

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Hypothesis

COVID-19 Arm: Delayed Post-vaccination Cutaneous Hypersensitivity

This article was published in the following Scient Open Access Journal:
Clinical Dermatology and Investigations
Received August 21, 2021; **Accepted** August 30, 2021; **Published** September 02, 2021

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Summary

The etiology of COVID-19 delayed post-vaccination cutaneous hypersensitivity (COVID Arm) remains unknown. We propose that the observed pathology results from locally activated mast cells triggered by the Spike protein in COVID-19 vaccines (predominately by mRNA-1273). Candidate treatments are proposed based on observed efficacy in COVID-19 patient responses that align with the proposed hypothesis of locally activated mast cells.

Messenger RNA (mRNA) and adenoviral vectored COVID-19 vaccines encoding the SARS-CoV-2 Spike protein employ gene therapy technology to express a viral protein in the cells of vaccine recipients. In theory and practice, this strategy elicits cellular and humoral immune responses akin to natural viral infection without co-expression of evolved viral functions that facilitate escape from immune surveillance. However, when an expressed viral protein has intrinsic immunomodulatory activities, then it becomes more than just an antigen.

Delayed post-vaccination cutaneous hypersensitivity, "COVID Arm", "COVID vaccine arm" [1], or delayed sensitivity reactions (DSR) appears 5 to 9 days after vaccination in 2.1% (312 of 15,210) of vaccine participants receiving the mRNA-1273 SARS-CoV-2 vaccine [2,3]. These reactions are characterized by delayed onset of erythema, induration, and tenderness that resolve over the following 4 to 5 days [2]. Most patients develop the hypersensitivity following the second vaccine dose [4]. These reactions are not limited to the injection site [5]. Cutaneous reactions including urticaria (hives) are also observed at low levels associated with the CoronaVac vaccine [6], BNT162b2 (Pfizer-BioNTech) [1,7], and AZD1222 (AstraZeneca) [7]. The majority of cases are reported following vaccination with mRNA-1273 SARS-CoV-2 vaccine [5,8-10]. Delayed hypersensitivity reactions have been misdiagnosed as cellulitis (a common bacterial skin infection) [11]. Rare immunogenic dermal filler reactions after vaccination have also been reported [12]. In common, these COVID-19 vaccines express a version of the SARS-CoV-2 Spike protein in host cells with differences in dosage and expression levels.

Hypothesis

We posit that expression of functional SARS-CoV-2 Spike protein may activate mast cells in susceptible vaccinees. We propose a pathogenesis model which may account for this form of vaccine reactogenicity (inflammatory response to vaccination). Multiple COVID-19 vaccines include or encode a full-length SARS-CoV-2 Spike protein as a key antigen. By inference of parallel functionality of SARS-CoV-1 Spike protein, the vaccine-associated SARS-CoV-2 Spike protein likely interacts with the Tumor Necrosis Factor alpha (TNF-α)-converting enzyme (TACE), thereby inducing TNF-α production akin to that observed for the wild type SARS-CoV-1 Spike protein [13]. The SARS-CoV-1 Spike protein activates the nuclear factor kappa B (NF-dB) pathway by inducing I-κBα degradation [14]. Supporting this parallel functionality of SARS-CoV-2 and SARS-CoV-1 Spike proteins, elevated TNF-α levels are observed in COVID-19 patients [15]. TNF-α stimulates COX-2 expression [16] resulting in elevated levels of prostaglandin E_2 (PGE_2) and additional inflammatory molecules [17]. Excessive levels of PGE_2 were observed in the urine of COVID-19 patients [17]. Elevated PGE_2 levels are likely to locally activate mast cell degranulation cascades [18]. Enrichment of mast cells is not observed histologically [3]; but mast cell enrichment is not required for this model. The localized Spike expression level varies by vaccine (highest for mRNA-1273) and may exceed a minimum activation threshold for individuals who develop COVID arm. This pathogenesis model proposes that the observed delayed cutaneous hypersensitivity results from a self-reinforcing dysfunctional feedback loop of histamine and other

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inflammatory molecules released from these locally activated mast cells.

Proposed evaluation and treatment options for this hypothesis

Based on this model, it is proposed that celecoxib [17,19] (a COX-2 inhibitor), famotidine [20] (targeting mast cells histamine receptor H2 [HRH2] receptor), cetirizine (targeting mast cells histamine H1 [HRH1] receptor) [21], dexchlorpheniramine (HRH1) [21], montelukast (leukotriene receptor antagonist) [22], and aspirin (mast cell stabilizer and COX-2 inhibitor) [23, 24] treatments may exhibit efficacy for treating COVID-19 vaccine recipients experiencing "COVID Arm". Antihistamines (including cetirizine and famotidine) [8] have been used to treat a small number of COVID-19 vaccinees with delayed post-vaccination cutaneous hypersensitivity [3,8]. Premedication with H1 and H2 antihistamines followed by montelukast after vaccination has been used in conjunction with Pfizer-BioNTech BNT162b2 vaccine for two health care workers with cutaneous and systemic mastocytosis [25]. By targeting mast cells and COX-2-related pathways, post-vaccination treatment with these agents may provide relief to individuals experiencing the signs and symptoms of delayed cutaneous hypersensitivity reactions.

Acknowledgments

The author acknowledges the Department of Defense (DoD), Defense Threat Reduction Agency (DTRA), and the Joint Science and Technology Office (JSTO) of the Chemical and Biological Defense Program (CBDP) for their support under the Discovery of Medical countermeasures Against Novel Entities (DOMANE) initiative.

DISTRIBUTION STATEMENT A. Approved for public release. Distribution is unlimited.

Funding

This material is based upon work supported under Air Force Contract No. FA8702-15-D-0001. Any opinions, findings, conclusions or recommendations expressed in this material are those of the author(s) and do not necessarily reflect the views of the U.S. Air Force.

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