Review of: "Successful Desensitization to mRNA COVID-19 Vaccine in a Case Series of Patients With a History of Anaphylaxis to the First Vaccine Dose"

Blanka Kaplan, Sherry Farzan, Gina Coscia[1]

1 Northwell Health

Potential competing interests: The author(s) declared that no potential competing interests exist.

The authors report the safety and efficacy of desensitization to the second dose of a SARS-COV-2 mRNA vaccine in 6 patients who were determined to have anaphylaxis after receiving the first dose. All of the patients were women, with the majority having a history of reactions to medications or vaccines. We commend the authors who ensured that a second mRNA vaccine dose was safely administered under close physician observation to these high-risk patients. However, we have a few concerns about the manuscript that we would like to discuss.

1. Patient selection:

A history of anaphylaxis to the first dose of a SARS-COV-2 mRNA vaccine is an inclusion criterion for these six patients who underwent desensitization. Review of presented data indicates that patient 2 doesn't fulfill criteria for anaphylaxis since urticaria was the only immediate presenting symptom. Her angioedema was delayed (24 hours after vaccination) suggesting a non-IgE medicated mechanism. But even a combination of urticaria and angioedema would fall under Grade 2 symptoms and would not fulfill anaphylaxis criteria according to author's cited source (Cardona et al. doi: 10.1016/j.waojou.2020.100472). Patient 4 had dizziness (among other symptoms) after the first and second Pfizer vaccines, and documented hypotension after the 2nd vaccine, but the authors called this reaction "vasovagal" and treated it with intravenous fluids rather than epinephrine. None of the patients had confirmatory tests for anaphylaxis, such as tryptase. Therefore, **we question if these patients truly had vaccine-induced anaphylaxis?**

2. Patient description:

Prednisone is listed as a premedication for patient 2, in Table 2, but it is our understanding that it is part of her daily maintenance for steroid- dependent spondyloarthritis. This **gives a false impression that prednisone was used for premedication.**

3. Skin testing to excipients:

Extensive excipient skin testing, including polyethylene glycol (PEG) preparations of different molecular weights and polysorbate 80, was performed in six patients that underwent desensitization. None of the patients had positive immediate skin testing, which is consistent with lack of IgE-mediated sensitivity to PEG and polysorbate 80. These findings are consistent with growing body of published data, reporting that excipient skin testing is not helpful for patients with symptoms suggestive of immediate hypersensitivity reactions to COVID-19 vaccines. Delayed skin test reactivity to

Cremophor EL (in 2 of 6 patients) and PEG (in 1 of 6 patients) does not support IgE-mediated hypersensitivity as a mechanism, has unclear clinical implications, and does not call for desensitization to a culprit vaccine.
The authors cite some of the published manuscripts reporting a limited role of excipient skin testing for evaluation of COVID-19 vaccine reactions (Greenhawt et al. doi: 10.1016/j.jaip.2021.06.025; Wolfson et al. doi: 10.1016/j.jaip.2021.06.010), but posit that the irritating effect of preparations such as Refresh Tears is responsible for poor specificity of excipient testing. We agree that PEG and polysorbate 80 have poor specificity for a diagnosis of hypersensitivity reactions to COVID-19 vaccines. In fact, we demonstrated that people who had allergic symptoms after the first mRNA vaccine and had a positive PEG (methylprednisolone acetate) skin test, subsequently tolerated challenge with oral PEG with only mild subjective symptoms and tolerated a subsequent dose of COVID-19 vaccine (Kaplan et al. DOI: 10.1016/j.anai.2021.10.019). A recent publication by Otani (doi: 10.1016/j.anai.2022.03.006) further underscores that people with a history of reactions to PEG and polysorbate, can safely tolerate COVID-19 vaccines. Therefore, the logical conclusion is that **severe allergic reactions to COVID-19 vaccines are not caused by hypersensitivity to PEG and polysorbate 80.**

4. Need for desensitization:

All six patients tolerated second mRNA vaccine via three (Pfizer-BioNTech® BNT162b2) or four-step (Moderna® mRNA-1273) administration. This raises two questions. Is 3 to 4-step administration considered a desensitization? Was desensitization necessary in these patients?

- Three to four step administration protocols can be used for a cautious graded challenge, therefore raising uncertainty if patients were truly “desensitized” or, rather just tolerated graded administration of the second vaccine dose.
- Furthermore, although premedication is generally administered during desensitizations, only half of the patients (3/6) were premedicated prior to the procedure. Three other patients were not premedicated, as it is typically done for the challenge procedure, suggesting that it was **a cautious challenge rather than desensitization.**
- As to the second question, at this time there are compelling published data indicating safety of one-dose administration in people with immediate reactions to the 1st dose of COVID vaccine. A meta-analysis of 1366 individuals with allergic reactions to the first dose of SARS-COV-2 vaccines found that only 6 patients (0.16%) developed severe immediate allergic reactions after the 2nd dose of the mRNA vaccine and **graded vaccine administration did not alter safety** (Chu et al. doi:10.1001/jamainternmed.2021.8515).

In summary, it is unclear if all six presented patients had anaphylaxis to the first dose of the mRNA vaccine. At this time there is ample published evidence that skin testing to PEG and polysorbate 80 is not helpful in predicting allergic reactions to COVID-19 vaccines and graded challenge/desensitization does not add safety to COVID-19 vaccination, making desensitization unnecessary. Given the fact that it is unclear whether these patients truly had anaphylaxis, and whether they truly underwent desensitizations, it may be warranted to change the title of the manuscript.