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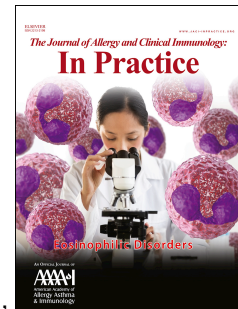
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Tolerance of the mRNA COVID-19 vaccines in patients with reported Taxane reactions

Leila A. Alenazy, MD, MMSc^{a,b*}, Kelsey Hinthner, MD^{a*}, Faisal ALMuhizi, MD^{a,c}, Michael Fein, MD^{a,d}, Christos Tsoukas MD^{a,d}, Moshe Ben-Shoshan, MD, MSc^{d,e}, Ana M. Copaescu, MD^{a,d,f}, Ghislaine Annie C Isabwe, MD^{a,d}

^aDivision of Allergy and Clinical Immunology, Department of Medicine, McGill University Health Centre (MUHC), McGill University, Montreal, Quebec, Canada

^bDivision of Allergy and Immunology, Department of Medicine, King Saud University Medical City, King Saud University, Riyadh, Saudi Arabia

^cDivision of Allergy and Immunology, Department of Internal Medicine, Security Forces Hospital Program, Riyadh, Saudi Arabia

^dThe Research Institute of the McGill University Health Centre, McGill University, Montreal, Quebec, Canada

^eDivision of Pediatric Allergy and Clinical Immunology, Department of Medicine, McGill University Health Centre, Montreal, Quebec, Canada

^fCentre for Antibiotic Allergy and Research, Department of Infectious Diseases, Austin Health, Heidelberg, Victoria, Australia

* These authors contributed equally to this work as first authors.

Corresponding author:

Ghislaine Annie C Isabwe.

Montreal General Hospital

1650 Cedar Avenue

Montreal, Quebec, Canada

Telephone number: +1(514) 934 -1934 ext. 42277

Email: ghislaine.isabwe@mcgill.ca

Conflict of interest

The authors do not have any conflicts of interest to declare.

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Clinical Implications

Patients that presented mild to moderate hypersensitivity reactions to taxanes, chemotherapeutic agents that contain the small molecular weight polyethylene glycol Cremophor EL, can safely receive the COVID-19 mRNA vaccines.

Taxanes are among the most common chemotherapeutic agents causing hypersensitivity reactions (HSRs).¹ Taxane immediate HSRs that occur with the first or second infusion are thought to be non-IgE-mediated and possibly related to the infusion solvents by complement activation, although recent studies revealed that many cases of taxane HSRs are IgE mediated based on positive skin test results and the proposed mechanism of cross-reactivity with tree pollen allergens.¹ Patients with history of taxane HSRs were initially considered at high risk of reacting to the mRNA COVID-19 vaccines. The US Center for Disease and Prevention initially recommended that patients with a history of anaphylaxis to the COVID-19 vaccine components should not receive the mRNA COVID-19 vaccines.² Paclitaxel, a commonly used taxane, contains Cremophor EL, a small molecular weight polyethylene glycol (PEG) present in the two mRNA COVID-19 vaccines: BNT162b2 Pfizer-BioNTech and mRNA-1273 Moderna. Paclitaxel contains 527mg/mL of PEG-35, whereas the two mRNA COVID-19 vaccines contain PEG 2,000 at concentration of 0.05mg/0.3 ml/dose.³ The role of PEG in mRNA COVID-19 vaccine anaphylaxis remains unknown. Docetaxel, another taxane, contains polysorbate 80, an excipient used in AstraZeneca and Janssen COVID-19 vaccines. These excipients were thought to be the primary cause of immediate hypersensitivity reactions to COVID-19 vaccines.⁴ To this end, we evaluated the safety of the COVID-19 vaccines in individuals with a prior history of taxane HSRs.

The patients were enrolled in a safety sub-study of a large prospective COVID-19 Vaccine study (ARCOV). The protocol was approved by McGill University Health Centre Research Institute institutional review board (ARCOV/2021-7510) and written informed consent was obtained from all the patients.

Following clinical detailed history of prior taxane reactions, patient underwent skin prick testing (SPT) using high and low molecular weight PEG and polysorbate 80, administered according to a previously published protocol as shown in Table EI.^{5,6} Patients were then challenged with PEG 3,350 (Lax-A-Day®), or had direct challenge with either the Pfizer-BioNTech, Moderna, or AstraZeneca COVID-19 vaccines. Patients were contacted one week after vaccination to assess for delayed reactions.

From January 1st to October 31st 2021, 26 patients with a history of reactions to cremophor-bound paclitaxel (n=23), docetaxel (n=2), or both cremophor-bound paclitaxel and docetaxel (n=1) were assessed (Table I). All were female and mostly Caucasian (n=22, 84.6%). Cutaneous symptoms (flushing 65%, urticaria 7.6%, pruritis 3.8%) were the most common initial symptoms followed by respiratory (dyspnea 42.3%), back pain (38.5%), and chest heaviness (15.4%). Vital sign changes such as hypertension and throat tightness were 3.8% in respectively. Initial reactions presented with 4 phenotypes: type I non-IgE mediated (50%), cytokine-release reactions (23%), mixed immediate reactions (23%), and delayed-type IV reactions (3.8%). The severity of the initial HSRs ranged between mild (n=7, 27%), moderate (n=18, 69%), and severe (n=1, 3.5%), according to the Brown's grading criteria.⁷ Except for one patient, all HSRs were immediate, occurring within 60 minutes of infusion. None had prior anaphylactic reaction to taxanes and no one required epinephrine. Following the HSRs, most patients subsequently tolerated paclitaxel and/or docetaxel with premedication (antihistamine H1 and H2 receptor antagonists, and/or corticosteroids, n=25) and slower infusions (n=22, 84.6%). One patient underwent desensitization to paclitaxel (3.85%), two were switched to an alternative drug (7.7%) and one patient discontinued paclitaxel (n=1, 3.85%). On enrollment, SPT to PEG and PEG-derivatives, performed in 19 patients (73%) were negative. Three out of 26 patients (11.5%)

underwent PEG 3,350 (Lax-A-Day®) graded challenge with negative results. After testing, all the patients successfully received the COVID-19 vaccine, without evidence of immediate or delayed HSR; (Table II). No patients were treated with premedication prior to receiving the COVID-19 vaccine. They all safely received the one of the mRNA COVID-19 vaccinee (Table EII).

All but one of our patients that tolerated the mRNA vaccines had a prior mild to moderate taxane HSRs. This individual had a severe HSRs (pneumonitis) following Paclitaxel and tolerated the Moderna vaccine well. In a recent similar study, the majority of patients that presented severe HSRs to paclitaxel and/or docetaxel tolerated the COVID-19 mRNA vaccine, except two patients with a docetaxel HSR who had mild symptoms to the mRNA COVID-19 vaccine treated with antihistamines alone.⁸

One patient that reacted to PEG-doxorubicin and paclitaxel, had a negative SPT, a negative oral challenge to PEG 3350 (Lax-A-Day®) and tolerated Pfizer-BioNTech vaccine. This finding is comparable to a recent case series of patients with previous immediate HSRs to pegaspargase, containing PEG 5,000 that tolerated the mRNA COVID-19 vaccines.⁹

We performed standardized and comprehensive skin testing with castor oil and low as well as higher concentrations of PEG, although the predictive values could not be determined as all patients tolerated COVID-19 vaccine. However, the concentrations utilized did not appear to be irritating in our study cohort.

To our knowledge, our study is the largest safety evaluation of COVID-19 vaccines in patients with prior reactions to chemotherapies containing PEG-derivatives. The main limitations of our study stem from being a single institution study with a small sample size. It is important to note

that not all patients had SPT to all the PEG-derivatives including PEG 20,000, Cremophor EL, and polysorbate 80, because at study initiation our SPT and challenge protocol for testing for potential COVID-19 vaccine HSRs were still being established. All patients had negative SPT to higher and lower molecular weight PEG-derivatives, suggesting that they would be less likely to react to the PEG derivatives used in our study. In addition, patients who did not undergo skin testing tolerated the COVID-19 vaccine, therefore, skin testing is not needed to evaluate the safety of COVID-19 vaccines after taxane HSRs. All these patients also tolerated the COVID-19 vaccine. Thus, all the patients with previous HSRs to paclitaxel (containing the excipient Cremophor EL) or docetaxel (containing the excipient polysorbate 80) safely tolerated the COVID-19 vaccine.

All the patients in this study were able to receive the COVID-19 vaccine without immediate or delayed reactions. We were able to show that patients with a history of a taxane HSR who tolerated subsequent infusions with premedication, can receive the COVID-19 vaccines safely without SPT or premedication.

In conclusion, patients with HSRs to paclitaxel and/or docetaxel regardless of severity do not have an increased risk of developing HSRs to the Pfizer and Moderna mRNA vaccines. Patients with a history of a taxane HSR can receive the COVID-19 vaccines safely without prior SPT and premedication.

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TABLE I. Characteristics of patients with cremophor-bound paclitaxel or docetaxel reactions referred for allergy evaluation prior to receiving the COVID-19 vaccine (N=26)

Characteristics	Patients, n (%)
Age mean (years)	61
Sex	
Female	26 (100)
Ethnicity	
Caucasian	22 (84.6)
Asian	2 (7.7)
Middle Eastern	2 (7.7)
Atopic history	
Chronic spontaneous urticaria	1 (3.8)
Allergic rhinitis	4 (15.4)
Food allergy	2 (7.7)
Cancer type	
Breast	3 (11.5)
Gynecological	21 (80.7)
Gastroenterology	2 (7.7)
Taxanes type	
Cremophor-bound Paclitaxel	23 (88.5)
Docetaxel	2 (7.7)
Cremophor-bound Paclitaxel and Docetaxel	1 (3.84)
Time since index reaction	
Less than 1 year	9 (34.6)
1-5 years	15 (58)
>5 years ^a	2 (7.7)
Infusion number	
First	16 (61.5)
Second	10 (38.5)
Onset of HSRs ^b	
< 5 minutes	3 (11.5)
< 1 hour	22 (84.62)
> 24 hours ^c	1 (3.85)
Reactions phenotypes	
Type I non-IgE mediated	13 (50)
Cytokine-release reaction (CRR)	6 (23)
Mixed reactions	6 (23)
Delayed Type IV reaction	1 (3.85)
Severity of HSRs	
Mild	7 (27)
Moderate	18 (69)

Severe ^d	1 (3.5)
Management of Reactions	
Antihistamines	23 (88.5)
Steroids	23 (88.5)
Other ^d	2 (7.7)
Future tolerance of subsequent dose	
Premedication ^e and slow infusion rate ^f	22 (84.6)
Desensitization	1 (3.85)
Alternative chemotherapy ^g	2 (7.7)
Discontinued ^c	1 (3.85)

^a one patient unknown

^b according to Browns' criteria⁷

^c pneumonitis

^d Acetaminophen and steroids (n=1) or no treatment (n=1)

^e pretreatment with dexamethasone 20mg po 60 minutes prior taxane infusion (n=1),

pretreatment with dexamethasone 20mg po at 20:00 and 02:00, dexamethasone 10mg IV 60 minutes prior taxane transfusion (n=1)

pretreatment with dexamethasone 10mg IV 60 minutes prior, famotidine 20mg IV and diphenhydramine 50mg IV 30 minutes prior to taxane infusion (n=3)

pretreatment with dexamethasone 20mg po at 20:00 and 02:00, dexamethasone 10mg IV 60 minutes prior, famotidine 20mg IV and diphenhydramine 50mg IV 30 minutes prior to taxane infusion (n=12)

pretreatment with cetirizine 20mg and montelukast 10mg for 3 days, dexamethasone 20mg po at 20:00 and 02:00, dexamethasone 10mg IV 60 minutes prior, famotidine 20mg IV and diphenhydramine 50mg IV 30 minutes prior to taxane infusion (n=5)

^f Increase the rate every 15 minutes until at full rate (n=2), reduce the rate by 50% for the first 15 minutes, if no reaction, rate was increased to full rate (n=9), rate reduced by 30% for the entire infusion (n=7), rate reduced by 50% for the entire infusion (n=4)

^g Adriamycin (non-PEGylated Doxorubicin) or Abraxane (nab-paclitaxel: Nanoparticle albumin-bound paclitaxel) a Cremophor EL-free.

TABLE II. Interventions made for COVID-19 vaccine testing and challenge in patients with cremophor-bound Paclitaxel or Docetaxel HSRs (N=26)

Interventions	Patients, n (%)
Skin prick testing (SPT)	19 (73)
PEG and PEG-derivatives ^a	19 (100)
Polysorbates 80	13 (68.4)
Triamcinolone 40 mg/ml	6 (31.6)
Result of SPT	
Negative	19 (100)
Lax-A-Day (PEG 3350) challenge	3 (11.5)
Negative	3 (100)
COVID-19 vaccines	
Pfizer-BioNTech	21(80.8)
Moderna	4 (15.4)
AstraZeneca	1 (3.85)
Location received COVID-19 vaccine	
Community Vaccination Centre	25 (96.2)
Allergy clinic ^b	1 (3.85)
Outcomes for COVID-19 vaccines	
No Immediate or Delayed HSRs	26 (100)

^a PEG 35 (Cremophor EL), PEG 3000 (Macrogol 50%), PEG 3350 (Lax-A-Day), PEG 20,000 (Macrogol)

^b Patient's preference to receive Pfizer-BioNTech instead of Moderna which offered in the community at that time

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