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

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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 coronavirus 2019 (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—immunoglobulin E (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 coronavirus 2019 (COVID-19) vaccines. The U.S. Centers for Disease Control 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 2 mRNA COVID-19 vaccines: BNT162b2 Pfizer-BioNTech and mRNA-1273 Moderna. Paclitaxel contains 527 mg/mL of PEG-35, whereas the 2 mRNA COVID-19 vaccines contain PEG 2000 at concentration of 0.05 mg/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 substudy 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 E1 (available in this article's Online Repository at www.jaci-inpractice.org).[5,6] Patients were then challenged with PEG 3350 (Lax-A-Day), or had direct challenge with either the Pfizer-BioNTech, the Moderna, or the AstraZeneca COVID-19 vaccines. Patients were contacted 1 week after vaccination to assess for delayed reactions.

From January 1 to October 31, 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 White (n = 22; 84.6%). Cutaneous symptoms (flushing 65%; urticaria 7.6%; pruritus 3.8%) were the most common initial symptoms followed by respiratory (dyspnea 42.3%), back pain (38.5%), and chest heaviness (15.4%). We found that less common symptoms were throat tightness (3.8%) and hypertension (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 Brown's grading criteria.[7] Except for 1 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%), 2 were switched to an alternative drug (7.7%), and 1 patient discontinued paclitaxel (n = 1; 3.85%). On enrollment, SPT to PEG and PEG derivatives, performed in 19 patients (73%), were negative. Three of 26 patients (11.5%) underwent PEG 3350 (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 1 of the mRNA COVID-19 vaccines (Table E2; available in this article's Online Repository at www.jaci-inpractice.org).

All but 1 of our patients that tolerated the mRNA vaccines had a prior mild-to-moderate taxane HSR. 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 2 patients with a docetaxel HSR who had mild symptoms to the mRNA COVID-19 vaccine treated with antihistamines alone.[8]

One patient who 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 with a recent case series of patients with previous immediate HSRs to pegaspargase, containing PEG 5000 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 because 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

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, y, mean	61
Sex	
Female	26 (100)
Ethnicity	
White	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	
<1 y	9 (34.6)
1−5 years	15 (58)
>5 y*	2 (7.7)
Infusion number	
First	16 (61.5)
Second	10 (38.5)
Onset of HSRs†	
<5 min	3 (11.5)
<1 h	22 (84.62)
>24 h‡	1 (3.85)
Reactions phenotypes	
Type I non−IgE-mediated	13 (50)
Cytokine-release reaction	6 (23)
Mixed reactions	6 (23)
Delayed type IV reaction	1 (3.85)
Severity of HSRs	
Mild	7 (27)
Moderate	18 (69)
Severed	1 (3.5)
Management of reactions	
Antihistamines	23 (88.5)
Steroids	23 (88.5)
Other§	2 (7.7)
Future tolerance of subsequent dose	
Premedication‖ and slow infusion rate¶	22 (84.6)
Desensitization	1 (3.85)
Alternative chemotherapy#	2 (7.7)
Discontinued‡	1 (3.85)

IV, Intravenously; *PO,* by mouth.
*One patient unknown.
†According to Browns' criteria.[7]
‡Pneumonitis.
§Acetaminophen and steroids (n = 1) or no treatment (n = 1).
‖Pretreatment with dexamethasone 20 mg PO 60 min prior to taxane infusion (n = 1), pretreatment with dexamethasone 20 mg PO at 10 PM and 2 AM, dexamethasone 10 mg intravenously (IV) 60 min prior to taxane transfusion (n = 1), pretreatment with dexamethasone 10 mg IV 60 min prior, famotidine 20 mg IV and diphenhydramine 50 mg IV 30 min prior to taxane infusion (n = 3), pretreatment with dexamethasone 20 mg PO at 10 PM and 2 AM, dexamethasone 10 mg IV 60 minutes prior, famotidine 20 mg IV, and diphenhydramine 50 mg IV 30 min prior to taxane infusion (n = 12), pretreatment with cetirizine 20 mg and montelukast 10 mg for 3 d, dexamethasone 20 mg PO at 10 PM and 2 AM, dexamethasone 10 mg IV 60 min prior, famotidine 20 mg IV and diphenhydramine 50 mg IV 30 min prior to taxane infusion (n = 5).
¶Increase the rate every 15 min until at full rate (n = 2), reduce the rate by 50% for the first 15 mins, 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).
#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 (%)
SPT	19 (73)
PEG and PEG derivatives*	19 (100)
Polysorbate 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†	1 (3.85)
Outcomes for COVID-19 vaccines	
No immediate or delayed HSRs	26 (100)

*PEG 35 (cremophor EL), PEG 3000 (macrogol 50%), PEG 3350 (Lax-A-Day), PEG 20000 (macrogol).
†Patient's preference to receive Pfizer-BioNTech instead of Moderna, which was offered in the community at that time.

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 20000, 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 E1. Protocol for preparing polyethylene glycol derivatives solutions for SPT

Compound	Product no.	Concentration	Preparation method
Polysorbate 80*	P1754*	20% wt./vol	Dilute 2 mL of polysorbate 80 in 8 mL sterile water. Vortex the suspension to ensure correct mixing.
PEG 35 (cremophor EL)	238470*	100% wt./vol (527 mg/mL)	Prepare PEG 35 at a concentration of 527 mg/mL diluted in 50% ethanol. Vortex until a clear solution was obtained.
PEG 3000†	819015*	50% wt./vol	Dilute 5 g of PEG 3000 in 5 mL sterile water in a 15-mL tube. After tightening the lid and sealing with parafilm, place the tube on rotator at 37°C for 2 h or longer until dissolved completely. Centrifuge the tubes (500 × g, 5 min, 20°C), adjust the volume to 10 mL with sterile water. Vortex to ensure correct mixing.
PEG 3350	Lax-A-Day	50% wt./vol	Dilute 17 g of PEG 3,350 in 34 mL sterile water. Vortex the solution until a clear solution is obtained.
PEG 20000†	813300*	0.01%−10% wt./vol	Dilute 4 g of PEG 20000 in 14 mL sterile water in 50 mL tube. After tightening the lid and sealing with parafilm, place the tube on a tube rotator at 37°C for 2 h or longer until dissolved completely. Centrifuge the tubes (500 × g, 5 min, 20°C), then adjust the volume to 20 mL with sterile water. Vortex the suspension to ensure correct mixing. Serial dilutions were made in 4 separate tubes: - 10% PEG 20000: add 8 mL of 20% PEG 20000 with 8 mL sterile water. - 1% PEG 20000: add 2 mL of 10% PEG 20000 with 18 mL sterile water. - 0.1% PEG 20000: Add 2 mL of 1% PEG 20000 with 18 mL sterile water. - 0.01% PEG 20000: add 2 mL of 0.1% PEG 20000 with 18 mL sterile water. Vortex each dilution to ensure correct mixing before preparing the next dilution step.

*Millipore Sigma.

†For PEG 300, PEG 3000, polysorbate 80, and PEG 20000, the dilutions were adopted from previously published protocol from Garvey et al.[5] The solutions were transferred to a sterile vial and kept in the fridge at 4°C temperature for multiple uses over 6 mos. Because the procedure is presumed nonsterile, the solutions should be used only for SPTs. Normal saline (negative) and histamine (positive) SPT were used as controls.

TABLE E2. The outcomes of the patients with a history of HSRs to cremophor-bound paclitaxel or docetaxel, who were desensitized to cremophor-bound paclitaxel, received an alternative chemotherapy or discontinued paclitaxel. They all tolerated the mRNA COVID-19 vaccines.

		Taxanes reactions			COVID-19 vaccine			
ID	Age/sex	Drug	Onset severity	Outcome	PEG SPT	PEG challenge*	Vaccine type	Tolerated vaccine
1	68/F	Paclitaxel	<1 h Moderate	Tolerated nab-Paxlitaxel (Cremophor EL free)†	Negative	Negative	Pfizer	Yes
2	59/F	Docetaxel	<1 h Moderate	Tolerated non-PEGylated Doxorubicin	Negative	Not performed	Moderna	Yes
3	60/F	Paclitaxel	<1 h Moderate	Desensitized to Paclitaxel	Negative	Not performed	Pfizer	Yes
4	45/F	Paclitaxel	>24 h Severe‡	Discontinued all chemotherapy	Negative	Not performed	Moderna	Yes

*PEG 3350 (Lax-A-Day) graded challenge.
†These patients did not tolerate paclitaxel with premedications and a slower infusion rate.
‡Pneumonitis.