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Taxanes hypersensitivity is not a risk factor for severe reactions to SARS-CoV-2 vaccines

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Key words

COVID-19; vaccines; taxanes; drug hypersensitivity; polyethylene glycols.

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Impact statement

History of taxanes hypersensitivity is not a risk factor for anaphylaxis to SARS-CoV-2 vaccines but may contribute to a higher frequency of non-specific symptoms with a possible common non-IgE mechanism.

Summary

Background. *Hypersensitivity reactions (HSR) to taxanes have been related to a complement activation by their excipients, polyoxyethylated castor oil and Polysorbate 80, structurally related to those of SARS-CoV-2 vaccines. The aim of this study was to verify the presence of a higher risk of HSR to SARS-CoV-2 vaccines in patients with history of HSR to taxanes.* ***Methods.*** *Patients with history of HSR to taxanes were evaluated before the vaccination in our center and underwent skin tests for PEG and Polysorbate 80 (P&P). Some patients completed the vaccination course in other centers without prior P&P skin tests because they had not manifested taxanes hypersensitivity before vaccination, or because those tests were not available.* ***Results.*** *50 patients were evaluated. 100% of patients with history of hypersensitivity to taxanes completed the vaccine course with no cases of anaphylaxis. 33 underwent skin tests for P&P before the vaccination and no correlation was found between the positivity of P&P and taxanes skin tests ($p = 0.538$). 7 patients developed mild symptoms during skin tests and vaccination, similar but weaker than those suffered at the time of the taxane infusion, independently from the results of skin tests.* ***Conclusions.*** *In our cohort patients with history of reaction to taxanes were not at higher risk to develop anaphylaxis to SARS-CoV-2 vaccines. However, a common non-IgE mediated mechanism behind those HSRs cannot be completely excluded. This can only account for mild and harmless symptoms in case of SARS-CoV-2 vaccines. However, prudence is still recommended in these patients.*

Introduction

Taxanes are a family of chemotherapeutical agents that comprises paclitaxel, docetaxel and cabazitaxel. Those compounds are the second cause of hypersensitivity reactions (HSRs) amongst antineoplastic drugs involving up to 30% of patients treated**.** Actually, the HSRs incidence is less than 5% with premedication with steroids and antihistamine currently used (1). Paclitaxel, docetaxel and cabazitaxel share a common chemical structure and they are solubilized using structurally correlated compounds (2). Paclitaxel contains polyoxyethylated castor oil (Cremophor EL®), and docetaxel and cabazitaxel contains polysorbate 80. A new paclitaxel formulation (paclitaxel albumin-bound nanoparticles) does not contain polyoxyethylated castor oil. Despite the use of a premedication during taxanes regimens and new formulations, HRSs to taxanes are common in clinical practice (1). Most of HSRs to taxanes are immediate and the most common symptoms are localized or generalized flushing and chest, back or abdominal pain (2). Immediate HSRs to taxanes are primarily attributed to their excipients

mentioned above. Those compounds would be capable of complement activation with release of inflammatory mediators (3, 4). An IgE mediated hypothetical mechanism seems involved in less than 20% of patients (2). Since the introduction of first vaccines for severe acute respiratory syndrome Coronavirus 2 (SARS-CoV-2) in December 2020 a special focus has been given on HSRs to those products (5). The incidence of COVID-19 vaccine anaphylaxis was estimated at 7.91 cases per million doses. It has been postulated that surfactants of those vaccines, polyethylene glycol (PEG) for mRNA vaccines (Pfizer-BioNTech Comirnaty and Moderna Spikevax) and polysorbate 80 for non-mRNA vaccines (AstraZeneca Vaxzevria and Johnson & Johnson Janssen), would be the main cause of those HSRs. Once again, the main mechanism of hypersensitivity would be non-IgE mediated, like complement activation, while an IgE-mediated mechanism would be of minor importance, but still described in literature (7). Since polyoxyethylated castor oil, polysorbate and PEG are structurally correlated, it was postulated that patients with history of HSR to taxanes would have been at higher risk for HSRs to SARS-CoV-2 vaccines (8).

The aim of this study was to verify the presence of a higher risk of anaphylaxis to SARS-CoV-2 vaccines in patients with history of HSR to taxanes, and thus a possible cross-reactivity between those products.

Materials and methods

This was an observational clinical study approved by the Ethics Committee of Area Vasta Emilia Centro, Regione Emilia Romagna (CE-AVEC) (identification code 422/2021/Oss/AOUBo) and performed according to the Declaration of Helsinki guidelines. All patients signed an informed consent before enrolling into the study. We enrolled patients evaluated in our center for previous or subsequent immediate systemic HSR to taxanes who underwent a vaccination course for SARS-CoV-2 (2 doses) during 2021. Patients were subdivided into 3 groups:

1. Patients with history of HSR to taxanes who underwent an allergy evaluation before the vaccination for SARS-CoV-2 in our center. We included either patients who had underwent skin tests for taxanes in our center and patients with a clinical diagnosis of HSR to taxanes made in another center. All patients underwent skin test for PEG and polysorbate (P&P) before the vaccination.
2. Patients with history of HSR to taxanes and vaccinated for SARS-CoV-2 in another center. These patients completed the vaccination course in another center with a previous allergy evaluation but without skin test for P&P because unavailable.
3. Patients already vaccinated for SARS-CoV-2 who presented later a HSR to taxanes. All those patients underwent skin test for taxanes.

Skin test for taxanes were performed with paclitaxel and docetaxel, according to known non-irritant concentrations (NIC) (9). Prick tests were then carried out with a solution of taxanes at a concentration of 6 mg/mL for paclitaxel and 1 mg/mL for docetaxel. In the case of a negative result in the prick test, an intradermal test with 0.03 mL of paclitaxel with a concentration of 0.06 mg/mL and 0.03 mL of docetaxel with a concentration of 0.01 mg/mL was performed. Skin test for PEG and polysorbate (P&P) were performed with a methylprednisolone preparation containing PEG (Depomedrol®) (skin prick tests (SPT) at 40 mg/ml, intradermal tests (ID) at 0.4 and 4.0 mg/ml), a triamcinolone preparation (Triacort®) containing polysorbate 80 (SPT at 40 mg/ml, ID at 0.4 and 4.0 mg/ml), a pneumococcal polysaccharide conjugate vaccine (Prevenar®) containing polysorbate 80 (SPT undiluted and ID at a dilution of 1:100), and PEG 4000 (Movicol®) (SPT diluted 1:100, 1:10 and undiluted). Skin tests were performed according to ENDA/EAACI Drug Allergy Interest Group position paper, ENDA position paper on Allergies and COVID-19 vaccines (10, 12) and guidelines of Italian Allergy Societies. All skin tests included

Table I *- Patient's clinical features.*

	Total		Group 1		Group 2		Group 3	
Sex (female)	49	98%	32	97.0%	17	100%	7	100%
Paclitaxel HRS	46	92%	33	100%	13	76.5%	7	100%
Docetaxel HRS	4	8%	0	0	4	23.5%	0	
Reaction to the first dose	39	78%	26	78.8%	13	76.5%	6	85.7%
Reaction to the second dose	11	22%	7	21.2%	4	23.5%	1	14.3%
Brown 1	18	36%	16	48.5%	2	11.8%	0	
Brown 2	26	52%	15	45.5%	11	64.7%	4	57.1%
Brown 3	6	12%	2	6.0%	4	23.5%	3	42.9%

were performed by our team. Skin tests positivity was defined as a wheal measuring at least 3 mm larger than that elicited by the negative control. Severity of HSR to taxanes was recorded according to Brown's grading system for generalized hypersensitivity reactions (11). Symptoms presented during skin tests for P&P and vaccinations for SARS-CoV-2 were recorded.
Continuous variables are expressed as a mean and standard deviation (SD), or as a median and interquartile range (IQR), as appropriate. Categorical variables are expressed as frequencies and percentages. Statistical analysis (χ^2) was performed with the software JASP (Version 0.16.3), University of Amsterdam (The Netherlands).

Results

A total of 50 patients were enrolled, 49 females and 1 male, with a median age of 61.5 years (IQR 45-78).

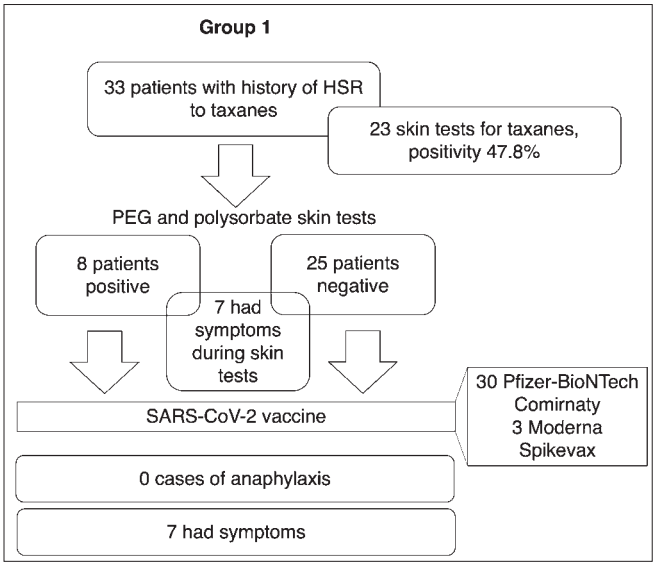
Taxanes HSR

46 patients suffered from an immediate HSR to paclitaxel (polyoxyethylated castor oil) and 4 to docetaxel (polysorbate 80). 39 HSR occurred during the first infusion of taxane. 11 patients reacted to a taxane infusion at the II dose, 9 to Paclitaxel and 2 to Docetaxel. Amongst them only one resulted positive to skin tests for Taxanes, and 2 resulted positive to P&P skin tests. 18 patients had a HRS graded 1 (17 paclitaxel, 1 docetaxel), 26 patients graded 2 (24 paclitaxel, 2 docetaxel) and 6 patients graded 3 (5 paclitaxel, 1 docetaxel) according to Brown's classification (**table I**).
A total of 40 patients had performed skin tests for taxanes and 15 had a positive result (37.5%). No correlation was found between severity of HSR and skin tests positivity (χ^2 = 2.842, p = 0.242).

Patients who underwent an allergy evaluation before the vaccination for SARS-CoV-2 (Group 1)

Figure 1 graphically represents the diagnostic process of patients included in group 1. 33 patients with history of HSR to taxanes were sent for an allergy evaluation before the vaccination course.

Figure 1 *- Diagnostic process of patients included in group 1: patients with history of HSR to taxanes who underwent an allergy evaluation before the vaccination for SARS-CoV-2 in our center.*



Specific vaccine products used are indicate; HRS: hypersensitivity reaction; PEG: polyethylene glycol.

Table II *- Details of skin test positivity of patients resulted positive to PEG 3350 for Depomedrol and polysorbate 80 for both Triacort and Prevenar skin tests. If the test resulted positive, the dilution is specified.*

	Depomedrol® (PEG3350)		Triacort® (polysorbate 80)		Prevenar® (polysorbate 80)		PEG 4000	Correlations	
Patient	SPT	ID	SPT	ID	SPT	ID (dilution)	SPT (dilution)	Symptoms	Taxanes ST
1	-	-	-	0.04	-	-	-	Pos.	Pos.
2	-	-	-	0.4	-	1:100	-	-	-
3	-	-	-	0.4	-	1:100	-	-	Pos.
4	-	-	-	-	-	1:100	-	-	-
5	-	0.4	-	0.4	-	-	-	-	-
6	-	-	-	-	-	1:100	1:10	-	-
7	-	-	-	-	-	1:100	-	Pos.	-
8	-	-	-	-	-	1:100	-	-	Pos.

SPT: skin prick test; ID: intradermal test (mg/ml). On the right is defined if these patients suffered from symptoms during skin tests and after the vaccination, and/or if resulted positive to skin tests (ST) to taxanes. Pos. means positive/present. - means negative results.

23 patients had been tested for taxanes in our center and 11 (47.8%) resulted positive to skin tests.
All 33 patients performed skin tests for P&P. 8 patients (24.2%) had positive skin tests, all for polysorbate 80 of whom 2 patients resulted positive also for PEG (**table II**).
Among the 23 patients tested either for taxanes and P&P, 3 patients resulted positive to both (**table II**). They were all women, aged between 62 and 65 years. All 3 reacted to Paclitaxel at the first infusion, with a reaction severity graded 1 in 2 cases and 2 in 1 case. No correlation was found between positivity to taxane and P&P skin tests (χ^2 = 0.379, P-value 0.538) (**table III**).
All 33 patients received 2 doses of a mRNA vaccine (30 Pfizer-BioNTech Comirnaty and 3 Moderna Spikevax) with no case of anaphylaxis. All these patients received a premedication with antihistamine (cetirizine 10 mg, 1 h before the vaccination) for safety, as established by local guidelines at the time of the study. In patients resulted positive to skin tests for P&P the vaccine Pfizer-BioNTech Comirnaty was also administered with fractioned doses for desensitization purpose as suggested in DAIG-ENDA position paper (0.05, 0.1, 0.15 milliliters) (12).
7 patients presented similar symptoms during skin tests for P&P and vaccination. 2/7 had positive skin test for P&P (**table III**), 2/7 patients had positive skin tests for taxanes, of whom 1 had positive skin tests for both. Symptoms were immediate and similar between patient with positive and negative skin tests. Amongst the 5 patients who resulted negative to skin tests, symptoms were flushing (3/5), back, thorax or abdominal pain (4/5), paresthesia (1/4). Amongst the 2 patients who resulted positive to skin tests, symptoms were flushing (1/2), back, thorax or abdominal pain (2/2), and no one presented paresthesia. Those symptoms were referred as similar but milder compared to those presented with the taxane infusion and were self-limited. No patient presented dyspnea or hypotension and vital signs were normal. Symptoms were self-limited. All these patients had history of HSR to paclitaxel.

Patients with history of HRS to taxanes and vaccinated for SARS-CoV-2 in another center (Group 2)

10 patients had been tested for taxane hypersensitivity in our center but underwent the vaccination course in another center with previous allergy evaluation but without skin tests for P&P because unavailable. Only 1 patient had resulted positive to skin tests to taxanes, for paclitaxel. Those patients received: Pfizer-BioNTech Comirnaty in 7 patients, AstraZeneca Vaxzevria in 2 patients and Johnson & Johnson Janssen in 1 patient, no patients received Moderna Spikevax. No patients suffered from an HSR during the vaccination course.

Patients already vaccinated for SARS-CoV-2 who presented later a HSR to taxanes (Group 3)

7 patients completed a 2 doses vaccination course for SARS-CoV-2 during 2021, all with Pfizer-BioNTech Comirnaty with complete tolerance. Those patients later started a chemotherapy with paclitaxel and developed an immediate HSR. In particular, six out of seven patients reacted to the first dose of Paclitaxel, 1 at a second dose of Paclitaxel. Those patients underwent skin tests for taxanes, and 2 patients resulted positive.
Figure 2 graphically represents the diagnostic process of patients included in group 2 and 3.

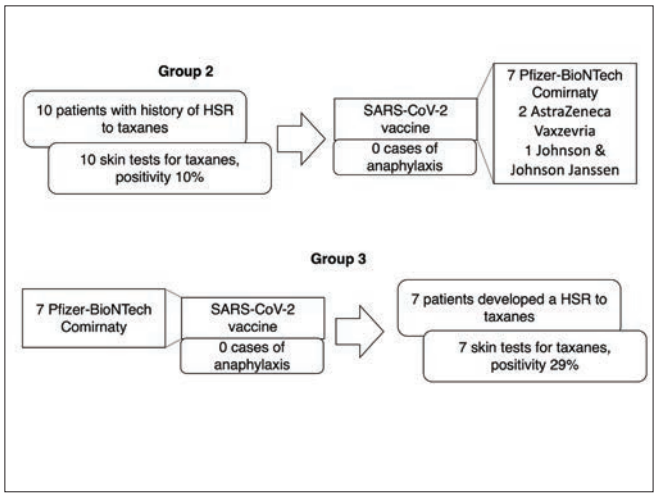
Discussion

In total 43 patients with history of HSR to taxanes (Group 1 and 2) completed a vaccination course for SARS-CoV-2 with no cases of anaphylaxis. This is consistent with a case series published by Banerji *et al.* (13). In our cohort, a higher percentage of patients resulted positive to skin tests for P&P (24.2% *vs* 4.7%). This may be due to the different sample size. Another difference is that the majority of them resulted positive to polysorbate 80 rather than PEG. It is of interest that amongst patients in group 2, 3 patients were vaccinated with a vaccine containing polysorbate 80 with tolerance. Patients with positive skin tests for PEG and/or polysorbate tolerated the vaccination with antihistamine premedication and fractioned doses with desensitization purpose, and it is not possible to establish the tolerance without these measures. Furthermore, patients vaccinated without prior skin tests for P&P (10 patients) tolerated the vaccine without premedication nor fractioned doses. Therefore, the efficacy of those measures in preventing anaphylactic reactions is impossible to establish in the present study.

Table III *- On the left, results of skin tests of patients tested both for taxanes, PEG and polysorbate (P&P). On the right, results of skin tests for PEG and polysorbate, and patients who presented symptoms during skin tests.*

	Taxanes skin tests				**Symptoms**		
P&P skin tests	Negative	Positive	Total	P&P skin tests	Negative	Positive	Total
Negative	10	8	18	Negative	20	5	25
Positive	2	3	5	Positive	6	2	8
Total	12	11	23	Total	26	7	33

Figure 2 *- Diagnostic process of patients included in group 2 and 3. Group 2: patients with history of HRS to taxanes and vaccinated for SARS-CoV-2 in another center. Group 3: patients already vaccinated for SARS-CoV-2 who presented later a HSR to taxanes.*



Specific vaccine products used are indicated; HRS: hypersensitivity reaction.

No correlation was found between skin tests positivity for taxanes and P&P. Therefore, it seems even more doubtful a possible IgE mediated mechanisms of cross-reactivity between them.

Skin tests were performed according to the Italian Allergology Societies' guidelines at the time of the study, including Prevenar® and Triacort® (containing polysorbate 80). Our center's experience showed us heterogeneity of results perhaps due to individual factors. Future studies on the accuracy of these skin test would be useful and goes beyond the aims of the present study.

7 patients presented similar symptoms during skin tests for P&P and vaccination. Those symptoms were referred milder during vaccination than during skin tests, probably due to the antihistamine premedication, and similar but milder to those suffered during taxane infusion. It is of interests that only 2/7 patients had positive skin tests for P&P and 2/7 for taxanes.

One patient resulted positive both to Triacort® (polysorbate) and paclitaxel (polyoxyethylated castor oil) during skin tests. This patient is the only one in whom an IgE mechanism is conceivable. Anyway, also in this patient the vaccination course was positively completed with antihistamine premedication and fractioned doses with desensitization purpose.

Overall, it is possible to hypothesize that excipients of vaccine activated a non-IgE mediated mechanism, like complement activation, similar to taxanes excipients. SARS-CoV-2 vaccine contains very little quantities of excipients compared to taxanes and they have different administration routes, therefore milder symptoms would be expected.

Furthermore, in the absence of a proper control/placebo group, given the presence of non-specific symptoms, it is not completely possible to exclude that these patients were somehow psychologically influenced.

7 patients completely tolerated 2 doses of SARS-CoV-2 vaccine and later suffered from an HSR to taxanes. Despite in those patients P&P skin tests were not performed, it's even more difficult to establish a possible cross-reactivity between these compounds. A mechanism of sensitization seems unlikely.

Patients with history of HSR to taxanes do not seem to be at higher risk of anaphylactic reactions to SARS-CoV-2 vaccines. However, in our opinion an allergy evaluation prior to the vaccination remains cautious in these patients. PEG and polysorbate skin tests seem of limited value in the management process of these patients but could drive the choice of the most appropriate vaccine strategy.

Our data suggest a doubtful cross reactivity between excipients of taxanes and SARS-CoV-2 vaccines. Indeed, the high percentage of P&P skin test positivity and of patients with symptoms during skin tests and vaccination does not let to exclude it. Symptoms occurred even in patients with negative skin tests.

Limitations of this investigation are small sample size and study design (observational research without a control group).

Given those premises, some patients presented similar mild symptoms with skin tests and vaccine, like those suffered with taxanes. It is not possible to exclude that these symptoms were due to a non-IgE mediated mechanism similar to the one activated by taxane excipients. Antihistamine premedication may mitigate symptoms in these patients. In more general terms, antihistamine premedication and longer observation after the vaccination are still prudent in these patients.

Fundings

None.

Contributions

GaC, AR: conceptualization, data curation, writing – review & editing. AR: formal analysis. AR, BB, SL, DL, GiC: investigation. GaC, FP: methodology, project administration, supervision, validation. BB, SL, GiC: visualization. GaC, AR, DL: writing – original draft.

Conflict of interests

The authors declare that they have no conflict of interests.

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