

Assessment of Antihistamines and Corticosteroids as Premedication in Rapid Drug Desensitization to Paclitaxel: Outcomes in 155 Procedures



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What is already known about this topic? Rapid drug desensitization is a helpful therapeutic tool that enables paclitaxel to be safely administered to paclitaxel-hypersensitive patients.

What does this article add to our knowledge? It is unclear whether systematic premedication with antihistamines and corticosteroids makes rapid drug desensitization to paclitaxel safer.

How does this study impact current management guidelines? Premedication regimens for rapid drug desensitization may be increasingly tailored to prevent adverse effects from unnecessary systematic administration of drugs.

BACKGROUND: In early clinical trials, infusion reactions during the administration of taxanes were managed using systematic premedication with antihistamines and corticosteroids before standard infusions. Consequently, these premedications are also administered before rapid drug desensitization (RDD) with taxanes. However, their role in RDD has not been studied.

OBJECTIVE: To assess the need for premedication with antihistamines and corticosteroids to prevent hypersensitivity reactions in RDD to paclitaxel.

METHODS: Over a 4-year period, we selected patients with confirmed hypersensitivity to paclitaxel (positive skin testing and/or drug provocation testing results) who had received paclitaxel through RDD. These patients were assigned to 2 prospective noninception cohorts: one cohort premedicated with antihistamine and corticosteroids and another cohort that was not.

RESULTS: We assessed 66 paclitaxel-reactive patients, of whom 22 met the inclusion criteria. A total of 155 RDDs to paclitaxel were performed. There were no significant differences in tolerance to RDD between the cohorts.

CONCLUSIONS: Administering systematic premedication with corticosteroids and antihistamines had no significant effect on

the effectiveness or safety of RDD in patients with confirmed hypersensitivity to paclitaxel in the study population. Moreover, these premedications can mask early signs of hypersensitivity and delay treatment. We believe that systematic premedication with these drugs for patients undergoing RDD should be carefully and individually assessed if their only purpose is to prevent breakthrough reactions during RDD. © 2017 American Academy of Allergy, Asthma & Immunology (J Allergy Clin Immunol Pract 2018;6:1356-62)

Key words: Drug allergy; Paclitaxel; Hypersensitivity; Desensitization; Chemotherapy; Premedication

Taxanes are antineoplastic drugs that are widely used to treat solid tumors.¹⁻³ However, their administration is often associated with unwanted infusion reactions, which sometimes require withdrawal of taxane therapy and substitution with alternative treatments.^{1,3}

A high incidence of immediate infusion reactions was recorded in early clinical trials with the taxane known as Taxol (paclitaxel).⁴⁻⁶ The frequency of these infusion reactions was reduced by premedication with antihistamines and corticosteroids. Therefore, the summary of product characteristics prepared for Taxol recommended premedication with 20 mg dexamethasone, 50 mg ranitidine, and 5 mg diphenhydramine.³

Even with premedication, up to 10% of patients experience an infusion reaction to taxanes.^{7,8} Consequently, rapid drug desensitization (RDD) may be necessary to ensure safe delivery of first-choice therapy. RDD is a therapeutic technique that induces a temporary state of tolerance to the drug responsible for a proven drug hypersensitivity reaction (DHR).^{9,10} Paclitaxel RDD protocols use the same premedication (including corticosteroids and antihistamines) as used in standard regimens.^{1,8-11} However, previous studies¹¹⁻¹⁴ report good results with RDD protocols that do not involve premedications for the prevention of DHRs to drugs other than taxanes.

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Abbreviations used

DHR- Drug hypersensitivity reaction

DPT- Drug provocation testing

IDT- Intradermal test

RCUH- Ramon y Cajal University Hospital

RDD- Rapid drug desensitization

SPT- Skin prick test

ST- Skin testing

Drug interactions and adverse effects have been observed with the administration of corticosteroids (eg, hyperglycemia and immunosuppression) and antihistamines (eg, drowsiness and electrocardiogram alterations).¹⁵⁻¹⁸ Therefore, the unnecessary use of these medications should be avoided whenever possible. In fact, some groups have studied whether premedication with corticosteroids before standard sessions of paclitaxel may be withdrawn in nonreactive patients after several uneventful regular infusions, with promising results.² In addition, *in vitro* studies suggest that dexamethasone can interfere with the cytotoxic action of paclitaxel and its effect on cell apoptosis.^{19,20}

To our knowledge, it remains unclear whether paclitaxel-reactive patients who undergo paclitaxel RDD—designed to induce tolerance to drugs causing DHRs—really need additional premedication with the corticosteroids and antihistamines administered in standard regimens.

The primary outcome of this study was to assess the need for premedication with antihistamines and corticosteroids used as premedication to prevent DHRs in RDD to paclitaxel.

METHODS

Patient population and study design

We assessed all paclitaxel-reactive patients referred to the Ramon y Cajal University Hospital (RCUH) Desensitization Program between January 2011 and January 2015. Patients underwent the same diagnostic protocol to confirm or exclude hypersensitivity to paclitaxel.

To ensure the highest quality of the data obtained, only those patients who received paclitaxel by means of RDD after a confirmed diagnosis of hypersensitivity to paclitaxel (positive skin test results and/or positive drug provocation test results) were selected. These selected patients were assigned to 2 prospective noninception cohorts.

Cohort A included all patients selected from January 2011 to December 2012. The patients had received premedication with corticosteroids (dexamethasone 20 mg) and antihistamines (dexchlorpheniramine 5 mg) before the administration of paclitaxel through RDD.

Cohort B included all patients selected from January 2013 to December 2014. None of these patients had received premedication with corticosteroids or antihistamines before the administration of paclitaxel by means of RDD.

Informed consent statement

The RCUH Ethics Committee approved the study protocol and validated the informed consent documents, which were signed by the patient, allergist, and referring physician.

Diagnostic protocol: Clinical history/initial reaction

Signs and symptoms from initial reactions and characteristics of patients were collected as in previous studies by our group.^{11-14,21-23}

The severity of the initial reaction was classified into 3 groups according to Brown²⁴: Grade 1 or mild reactions (skin and subcutaneous tissue only), defined as generalized erythema, urticaria, periorbital edema, or angioedema; grade 2 or moderate reactions (features suggesting respiratory, cardiovascular, or gastrointestinal involvement), defined as dyspnea, stridor, wheeze, nausea, vomiting, dizziness (presyncope), diaphoresis, chest/throat tightness, or abdominal pain; grade 3 or severe reactions (hypoxia, hypotension, or neurologic compromise), defined as cyanosis or peripheral oxygen saturation of 92% or less at any stage, hypotension (systolic blood pressure <90 mm Hg in adults), confusion, collapse, loss of consciousness, or incontinence.

Diagnostic protocol: Risk assessment

As in previous studies by our group,^{11-14,21-23} patients were classified as high-risk or medium/low-risk.

We considered high-risk patients to be those who met any of the following criteria: previous life-threatening reaction (such as a history of intubation and cardiovascular collapse), comorbidities where exposure might provoke situations beyond medical control (such as unavoidable use of beta-blockers, mastocytosis, uncontrolled asthma or lung disease with EFV₁ <1 L), and pregnancy.

Diagnostic protocol: Skin testing

Trained personnel in adequate settings performed skin testing (ST) and assessed the results in all referred patients according to previous articles.^{11-14,21-23} Skin prick test (SPT) concentrations for paclitaxel were 1 and 6 mg/mL, and the intradermal test (IDT) concentration was 1 mg/mL.^{11-14,21-23} Positive results with IDT concentrations of 6 mg/mL were not considered as positives because recent findings suggest that this concentration may be irritant.²²

For SPT, a drop of the drug at the maximal concentration was applied to the volar surface of the forearm using an SPT lancet. If the result was negative, IDT was performed (0.03 mL of the drug was injected intradermally into the volar surface of the forearm). A positive reaction was defined as a wheal with a diameter at least 3 mm larger than that produced by a negative control (saline solution). Histamine (10 mg/mL for SPT and 0.01 mg/mL for IDT) was used as a positive control.

Diagnostic protocol: Drug provocation test

Patients were assessed for drug provocation testing (DPT), which involves the controlled administration of a drug to study DHRs and is considered to be the criterion standard for establishing or excluding a diagnosis of hypersensitivity.^{22-23,25} The final multidisciplinary decision on DPT was based on a safety-first policy and on a thorough assessment of the benefits for the patient. The patient was empowered to make the final decision by considering 2 fundamental cornerstones: (1) data on the indication and need for treatment of the referring oncologist, and (2) data on the risk assessment of the allergist. As in previous articles by our group,^{11-14,21-23} high-risk patients were encouraged to avoid DPT. A recent study found that positive ST with nonirritant concentrations is a good predictor of a diagnosis of hypersensitivity to paclitaxel²²; therefore, patients with such profile were discouraged to undergo DPT. However, we have found negative DPT results in paclitaxel-reactive patients with positive IDT result with the irritant 6 mg/mL concentrations²²; thus, patients with this profile were not necessarily discouraged to undergo DPT provided their risk assessment was favorable.

DPT was performed during the next scheduled treatment and following the same detailed recommendations described in recent articles by our group.^{11-14,21-23} For DPT, we carefully administered the desired dose of the culprit drug according to the manufacturer's

TABLE I. RCUH RDD protocol for a total dose of 200 mg of paclitaxel (diluted in 250 mL of 0.9% saline solution) originally meant to be infused in 1 h at a 250 mL/h rate

Total dose	200 mg	Solution concentration	Total dose in each solution (mg)	Drug
Solution A	250 mL	0.016 mg/mL	4.0	Paclitaxel
Solution B	250 mL	0.160 mg/mL	40.0	Paclitaxel
Solution C	250 mL	0.8 mg/mL	200.0	Paclitaxel

Step	Solution	Rate (mL/h)	Administered volume (mL)	Time (min)	Administered dose (mg)	Cumulative dose infused (mg)
1	A	88	22	15	0.0	0.0
2	A	100	25	15	0.4	0.4
3	A	200	50	15	0.8	1.2
4	A	400	100	15	1.6	2.8
5	B	88	22	15	0.0	2.8
6	B	100	25	15	4.0	6.8
7	B	200	50	15	8.0	14.8
8	B	400	100	15	16.0	30.8
9	C	88	22	15		
10	C	125	31.25	15	169.2	200.0
10'	C	250	218.75	52.5		

Not all the volume in solutions A, B, or C is infused. We start the protocol with solution A containing a 1/50 dilution, then solution B with a 1/5 dilution, and we end with a final solution C containing a full concentration of the culprit drug. Total dose to be infused during solution C is calculated by subtracting the cumulative dose administered in steps 1-8 from the total desired dose.

Whenever needed because of a positive skin test result or high-risk patients, additional solutions with lower concentrations than solution A may be added before solution A to ensure a more cautious starting dose, and whenever possible as determined on the basis of an end-point titration.

Each solution uses an individual infusion line previously primed with 22 mL of the dilutor substance. Steps 1, 5, and 9 are considered "line flushing steps" (in which 22 mL of the dilutor substance is administered).

Step 10 may be adapted to the desired final infusion rate according to the standard regimes indicated by the referred oncologist (additional steps may be added to reach higher infusion rates while maintaining a dose increasing by 2- to 2.5-fold with each step).

instructions in a supervised environment. Infusion rates were the same as for standard regimens. No additional premedication was used for the procedure (except for standard premedications according to the manufacturer's/institutional protocols).²² DPT with paclitaxel is a risky technique that needs to be performed by expert personnel in adequate settings (medical intensive care unit).^{22,25} DPT result was considered positive in those patients who showed an objective DHR.^{11-14,21-23,25} Patients with a positive DPT received the full dose of their treatment despite the result of their DPT by means of a restart protocol, as in previous studies.²²

Diagnostic protocol: Final diagnosis

- Positive diagnosis of hypersensitivity: An unequivocal clinical history was not considered sufficient, patients needed to also show positive ST and/or positive DPT result.
- Negative diagnosis of hypersensitivity: Negative DPT result.
- Patients who could not meet criteria for a positive or negative diagnosis were considered inconclusive.

Rapid drug desensitization

RDD candidates included those patients with an indication for treatment with paclitaxel (confirmed by the referring oncologist) and with either a positive diagnostic protocol for paclitaxel hypersensitivity (positive ST and/or positive DPT result) or an inconclusive diagnostic protocol for hypersensitivity (eg, a high-risk assessment preventing the patient from DPT).

The final multidisciplinary decision on RDD was based on a safety-first policy and on a thorough assessment of the benefits for the patient. The patient was empowered to make the final decision by considering 2 fundamental cornerstones: (1) data on the indication and need for treatment of the referring oncologist, and (2) data on the risk assessment of the allergist.

Patients with a negative diagnostic protocol (negative DPT result) were not candidates for RDD and continued with their regular chemotherapy sessions (hypersensitivity was ruled out). Patients who did not give their consent for RDD or who did not need treatment with paclitaxel were not candidates for RDD. Patients with late reactions occurring beyond 48 hours after infusion, severe immunocytotoxic reactions, vasculitis, bullous skin diseases (eg, Stevens-Johnson syndrome/toxic epidermal necrolysis, or drug reaction with eosinophilia and systemic symptoms/drug-induced hypersensitivity syndrome) were excluded from RDD.

RDD was performed following our previously validated protocol,¹¹ which is designed to last approximately 4 hours and enables single-morning desensitizations. Table I presents a practical example of an RDD protocol designed for 1 of the study patients.

Breakthrough reactions were recorded and classified into 3 groups according to a previous classification by Brown.²⁴

Selected patients

Patients were selected for the study cohorts after following the diagnostic protocol (see above). Only patients with a confirmed diagnosis of hypersensitivity to paclitaxel (positive ST and/or positive DPT result) who had undergone RDD were included.

Patients with a negative ST result who avoided DPT were excluded from this study, even if they had undergone RDD (in such patients DPT was not performed, and, therefore, hypersensitivity could not be confirmed). Moreover, we excluded patients who had to take antihistamines or corticosteroids for any reason.

Defining variables

The effectiveness of RDD was measured using the dichotomous variable "tolerance," for which "yes" meant that the patient was able to receive the complete dose of paclitaxel as prescribed by the

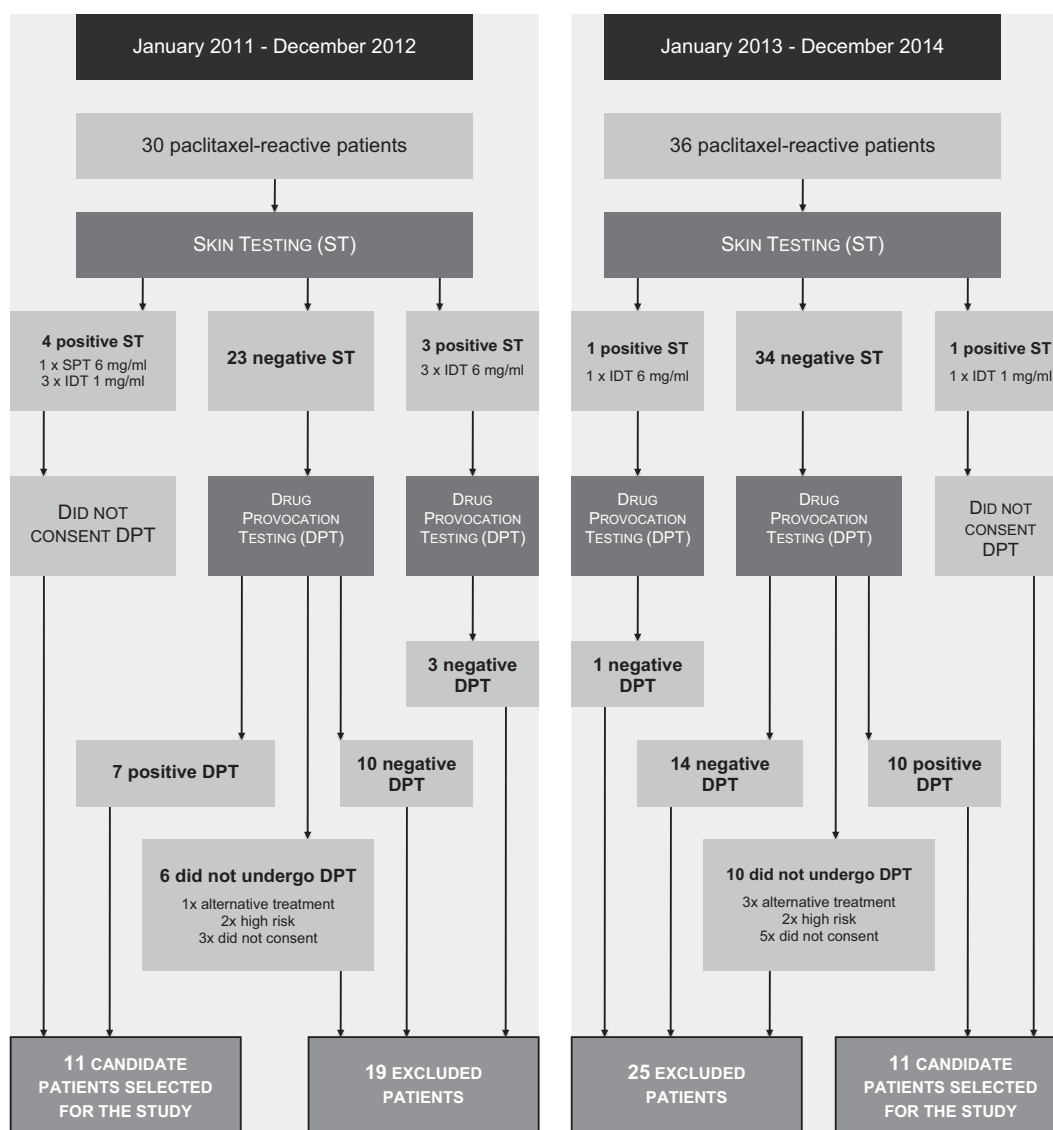


FIGURE 1. Patient flow chart.

referring physician and “no” meant that the patient was not able to receive it, regardless of the reason.

The safety of RDD was measured using the dichotomous variable “breakthrough reactions during the first desensitization,” for which “yes” meant that the patient presented a breakthrough reaction during the first RDD and “no” meant that the patients experienced no breakthrough reactions during the first RDD.

Breakthrough reactions and their severity (based on the Brown classification)^{11-14,21-24} were recorded during all RDDs.

Statistical analysis

Null hypothesis: If the effectiveness and safety of RDD are independent of premedication with antihistamines and corticosteroids, there will be no significant differences in the outcome variables between the cohorts.

Our experience showed that around 13 to 14 paclitaxel-reactive patients were referred to us every year.^{11,22} Given the expected small sample size and the need to compare dichotomous categorical

variables, we selected our statistical significance test accordingly: the null hypothesis was tested using Fisher exact test to compare variables between the groups. The analysis was performed using Stata 13 (StataCorp, College Station, Texas).

RESULTS

Patient characteristics and initial reaction

We assessed 30 paclitaxel-reactive patients between January 2011 and December 2012 and 36 paclitaxel-reactive patients between January 2013 and December 2014.

After completing the diagnostic protocol, 22 patients met the inclusion criteria (11 in each cohort). The patient flow chart is shown in Figure 1. Women accounted for 86% of the sample (19 of 22; cohort A, 10 of 11; cohort B, 9 of 11). Mean age was 63 years in cohort A and 57 years in cohort B.

Most patients presented with a severe initial reaction (grade 3): 64% (7 of 11) in cohort A and 54% (6 of 11) in cohort B. All patients were being treated for malignancy, mostly for breast

TABLE II. Characteristics of patients who met the inclusion criteria for the study**Patients included in cohort A**

(January 2011 - December 2012)*

No.	Age	Sex	Grading initial DHR (Brown)	Elapsed time (min)	Previous DHR before initial DHR	Previous uneventful exposures to paclitaxel	ST	Tolerance to target DPT dose RDD	RDD Breakthrough reactions severity (Brown)	Performed RDDs	Type of cancer	BRCA 1/2 mutation
1	43	F	3	<15	—	2	SPT 6 mg/mL NP	Yes	—	1	Breast	NP
2	65	F	1	<15	—	1	IDT 1 mg/mL NP	Yes	—	5	Cervical	NP
3	72	F	3	<15	—	1	— +	Yes	—	9	Breast	Negative
4	76	F	2	<15	—	0	— +	Yes	—	11	Breast	NP
5	70	M	3	<15	—	2	— +	Yes	—	3	Lung	Negative
6	80	F	1	<15	—	4	IDT 1 mg/mL NP	Yes	—	3	Ovarian	NP
7	72	F	2	<15	—	1	IDT 1 mg/mL NP	Yes	—	4	Endometrial	NP
8	51	F	3	<15	—	1	— +	Yes	—	4	Ovarian	NP
9	67	F	3	<15	—	0	— +	Yes	—	1	Endometrial	NP
10	58	F	3	<15	—	0	— +	Yes	—	40	Breast	NP
11	40	F	3	<15	—	1	— +	No	3	0	Breast	NP

Patients included in cohort B

(January 2013 - December 2014)†

No.	Age	Sex	Grading initial DHR (Brown)	Elapsed time (min)	Previous DHR before initial DHR	Previous uneventful exposures to paclitaxel	ST	Tolerance to target DPT dose RDD	RDD Breakthrough reactions severity (Brown)	Performed RDDs	Type of cancer	BRCA 1/2 mutation
12	65	F	2	<15	—	4	— +	Yes	—	8	Peritoneal	NP
13	22	F	2	<15	—	1	— +	Yes	—	1	Neuroendocrine	NP
14	44	F	3	<15	—	1	— +	Yes	1	23	Breast	NP
15	79	F	3	<15	—	1	IDT 1 mg/mL NP	Yes	—	6	Peritoneal	NP
16	75	F	2	30	—	7	— +	Yes	—	6	Peritoneal	NP
17	52	F	3	<15	—	1	— +	Yes	—	6	Breast	Negative
18	36	F	2	<15	—	2	— +	Yes	—	6	Breast	Negative
19	63	F	3	<15	—	0	— +	Yes	—	5	Ovarian	Negative
20	61	F	2	30	—	1	— +	Yes	—	4	Ovarian	NP
21	81	M	3	<15	—	0	— +	Yes	1	5	Colorectal	NP
22	51	M	3	<15	—	0	— +	Yes	—	4	Esophageal	NP

F, Female; M, male; NP, Not performed (patient did not consent after receiving a thorough explanation of the individual risks).

*Patients received premedication with corticosteroids (dexamethasone 20 mg) and antihistamines (dexchlorpheniramine 5 mg) before the administration of paclitaxel through RDD.

†None of these patients received premedication with corticosteroids or antihistamines before the administration of paclitaxel by means of RDD.

cancer (8 of 22 [36%]) and ovarian cancer (4 of 22 [18%]). The other types of cancer recorded were peritoneal cancer (3 of 22 [13.6%]), endometrial cancer (2 of 22 [9.1%]), cervical cancer (1 of 22 [4.5%]), colorectal cancer (1 of 22 [4.5%]), neuroendocrine tumor (1 of 22 [4.5%]), lung cancer (1 of 22 [4.5%]), and esophageal cancer (1 of 22 [4.5%]). Further patient characteristics are presented in Table II.

Desensitization outcomes

A total of 155 RDDs were performed in 22 patients with confirmed hypersensitivity to paclitaxel (positive ST or positive DPT result). Of the 22 patients, 21 (95%) successfully received their target dose of paclitaxel through the RCUH RDD 10-step protocol. One patient revoked her consent to finish the RDD procedure after a severe breakthrough reaction and rejected further attempts.

No reactions were recorded in 98% of the RDDs. Immediate breakthrough reactions occurred in only 3 of 155 desensitizations: 1 of 81 in cohort A and 2 of 74 in cohort B. These 3 breakthrough reactions occurred in 3 of 22 patients: 1 of 11 in cohort A and 2 of 11 in cohort B. Two breakthrough reactions were mild (grade 1) and 1 (in cohort A) was severe (grade 3). No delayed reactions were recorded.

All breakthrough reactions occurred during the first RDD during the infusion of solution C (steps 9-10). All breakthrough reactions occurred in patients with grade 3 initial reactions; however, most patients with a grade 3 initial reaction did not experience a breakthrough reaction during RDD.

Statistical analysis

No differences in effectiveness or safety were found between the cohorts (Table III).

TABLE III. Statistical analysis comparing tolerance and breakthrough reactions between both cohorts

Comparison of variable "tolerance" between cohorts A and B			
Cohort	Tolerance		Total
	No	Yes	
A	1	10	11
B	0	11	11
Total	1	21	22

Comparison of variable "breakthrough reactions during the first desensitization" between cohorts A and B			
Cohort	Breakthrough reactions		Total
	No	Yes	
A	10	1	11
B	9	2	11
Total	19	3	22

Fisher exact test = 1.000.

1-sided Fisher exact test = 0.500.

DISCUSSION

A total of 155 RDDs were performed in 22 patients with confirmed hypersensitivity to paclitaxel (positive ST or positive DPT result) using the RCUH 10-step RDD protocol. All patients except 1 (who revoked her consent to finish the procedure) reached their target dose, thus proving the effectiveness of this short protocol in administering paclitaxel to paclitaxel-reactive patients (with either IgE-dependent or IgE-independent immediate DHRs) and confirming findings previously reported by our group.¹¹

No reactions were recorded in 98% of RDDs; however, 3 of 22 patients experienced a breakthrough reaction. All reactions occurred during the last step of the first RDD, and most reactions (67%) were mild.

In a previous study on RDD by our group,¹¹ where most RDDs were for paclitaxel (137 of 189), we recorded no reactions in 94% of RDDs and 61.5% of reactions were mild. A recent publication on DHRs to taxanes and RDD reported 29 immediate hypersensitivity reactions (21%) and 20 delayed reactions (14%) in 138 patients who underwent desensitization; most of these reactions (83%) were mild.⁷ We observed a slightly better safety profile (despite the lack of premedication with antihistamines and corticosteroids in cohort B) than previously reported by our and other groups.^{1,7-9,11,26}

The statistical analysis revealed no differences in effectiveness or safety between cohort A (premedication with antihistamines and corticosteroids) and cohort B (no premedication with antihistamines or corticosteroids). Only 1 patient could not receive the target paclitaxel dose after a severe breakthrough reaction (the only severe breakthrough reaction of all 155 RDDs); interestingly, this patient had received premedication with antihistamines and corticosteroids.

Our process for selecting patients was very strict. We based our approach on the framework we use in our daily clinical practice.²¹ Our approach involves "thinking globally and acting locally and focusing on continual improvement and process optimization strategies," such as investigating the optimal tailored premedications for RDD to different drugs. However, as a cornerstone of high-quality research on drug allergy, we take

into account that DPT (whenever possible, according to risk assessment) should be the diagnostic criterion standard before RDD.²¹ In a recent study,²² we found DPT to be of vital importance for avoiding RDDs in nonhypersensitive patients (hypersensitivity was ruled out in up to 40% of all taxane-reactive patients thanks to a diagnostic protocol including DPT, with 65% of the taxane DPT results being negative). Thus, selecting patients with a confirmed diagnosis of hypersensitivity to taxanes (after a diagnostic protocol including DPT) was key to avoiding the selection bias of including nonhypersensitive patients.

Recent studies^{7,27} have tried to determine which factors could act as predictors of DHRs during challenge or RDD. Hope et al²⁷ found 3 strong predictors for higher risks during challenges with acetylsalicylic acid, namely, baseline FEV₁ value of less than 80% predicted, previous visits to the emergency department for asthma, and nonuse of leukotriene-modifying drugs. On the basis of these findings, the authors recommend premedication with leukotriene-modifying drugs for acetylsalicylic acid challenges. However, direct comparisons with acetylsalicylic acid challenges or desensitizations need to be made with caution, as the mechanisms involved are likely to be different. Picard et al⁷ found several predictors for reactions (during desensitization or challenge) to taxanes, namely, atopy, older age, flushing, and cancer type (ovarian, fallopian tube, or peritoneal). Unfortunately, premedication was not studied as a possible risk factor. In our study, which was based on high-quality selection of patients with confirmed hypersensitivity to paclitaxel by means of ST and DPT, premedication with antihistamines and corticosteroids made no difference to the outcome (breakthrough reactions during RDD). Further studies are needed to find the optimal premedication regimens, if any, which should be used before RDD.

All the study patients had already experienced DHRs during paclitaxel infusions and received premedication before their infusions. Therefore, premedications had already failed to prevent DHRs (both initial reactions during the regular infusions and reactions during confirmatory DPTs). It seems reasonable to believe that these drugs would be of little additional help whenever administered before RDD, which, alone, is meant to prevent DHRs.

However, sometimes, daily clinical practice^{1,8-11} encourages the use of premedication with antihistamines and corticosteroids before RDD, even if we find no evidence for these recommendations based on systematic studies.

On the other hand, interesting data reported by our group cast doubt on the role of antihistamines and corticosteroids as useful premedication for RDD to various drugs^{11,13,14}; the excellent safety profile we observed obviated systematic addition of these premedications for RDD. Moreover, in a study by Breslow et al,²⁸ premedication with acetylsalicylic acid and montelukast proved superior to methylprednisolone and successfully prevented breakthrough reactions during RDDs to platinum-based chemotherapy in patients who presented skin reactions despite antihistamine therapy. In addition, Herrero et al²⁹ support avoiding this type of premedication not to mask early signs of anaphylaxis. This is consistent with our clinical experience, because we observed that premedication with these agents may hide early signs of hypersensitivity and delay treatment, thus explaining the onset of more severe breakthrough reactions during RDD in the group using these premedications.

Data on the toxicity of corticosteroids and antihistamines are especially relevant for patients who may need to undergo many RDDs. It is clear that avoiding the unnecessary use of antihistamines and corticosteroids will prevent patients from experiencing adverse effects to them¹⁵⁻¹⁸ or interference with the cytotoxic action of paclitaxel and its effect on cell apoptosis.^{19,20}

In the light of these data, we believe that administering systematic premedication with corticosteroids and antihistamines may not play a significant role in improving the effectiveness and safety of RDD in patients with confirmed hypersensitivity to paclitaxel. We believe that the systematic use of these premedications for RDD should be carefully and individually discussed if their only purpose is to prevent breakthrough reactions during RDD.

Our study is limited by its small sample size, which prevents us from generalizing our results. We believe that further studies in other, larger populations are necessary before clear recommendations can be established.

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REFERENCES

- Feldweg AM, Lee CW, Matulonis UA, Castells M. Rapid desensitization for hypersensitivity reactions to paclitaxel and docetaxel: a new standard protocol used in 77 successful treatments. *Gynecol Oncol* 2005;96:824-9.
- Berger MJ, Dunlea LJ, Rettig AE, Lustberg MB, Phillips GS, Shapiro CL. Feasibility of stopping paclitaxel premedication after two doses in patients not experiencing a previous infusion hypersensitivity reaction. *Support Care Cancer* 2012;20:1991-7.
- Taxol prescribing information. Available from: http://www.aemps.gob.es/cima/pdfs/es/ft/60210/60210_ft.pdf. Accessed August 10, 2017.
- Wiernik PH, Schwartz EL, Strauman JJ, Dutcher JP, Lipton RB, Paietta E. Phase I clinical and pharmacokinetic study of taxol. *Cancer Res* 1987;47:2486-93.
- Weiss RB, Donehower RC, Wiernik PH, Ohnuma T, Gralla RJ, Trump DL, et al. Hypersensitivity reactions from Taxol. *J Clin Oncol* 1990;8:1263-8.
- Rowinsky EK, Eisenhauer EA, Chaudhry V, Arbuck SG, Donehower RC. Clinical toxicities encountered with paclitaxel (Taxol). *Semin Oncol* 1993;20:1-15.
- Picard M, Pur L, Caiado J, Giavina-Bianchi P, Galvão VR, Berlin ST, et al. Risk stratification and skin testing to guide re-exposure in taxane-induced hypersensitivity reactions. *J Allergy Clin Immunol* 2016;137:1154-64.
- Castells MC, Tennant NM, Sloane DE, Hsu FI, Barrett NA, Hong DI, et al. Hypersensitivity reactions to chemotherapy: outcomes and safety of rapid desensitization in 413 cases. *J Allergy Clin Immunol* 2008;122:574-80.
- Liu A, Fanning L, Chong H, Fernandez J, Sloane D, Sancho-Serra M, et al. Desensitization regimens for drug allergy: state of the art in the 21st century. *Clin Exp Allergy* 2011;41:1679-89.
- Cernadas JR, Brockow K, Romano A, Aberer W, Torres MJ, Bircher A, et al. General considerations on rapid desensitization for drug hypersensitivity — a consensus statement. *Allergy* 2010;65:1357-66.
- Madrigal-Burgaleta R, Berges-Gimeno MP, Angel-Pereira D, Ferreira-Monteagudo R, Guillen-Ponce C, Pueyo C, et al. Hypersensitivity and desensitization to antineoplastic agents: outcomes of 189 procedures with a new short protocol and novel diagnostic tools assessment. *Allergy* 2013;68:853-61.
- Urena-Tavera A, Zamora-Verduga M, Madrigal-Burgaleta R, Angel-Pereira D, Berges-Gimeno MP, Alvarez-Cuesta E. Hypersensitivity reactions to racemic calcium folinate (leucovorin) during FOLFOX and FOLFIRI chemotherapy administrations. *J Allergy Clin Immunol* 2015;135:1066-7.
- Angel-Pereira D, Berges-Gimeno MP, Madrigal-Burgaleta R, Urena-Tavera MA, Zamora-Verduga M, Alvarez-Cuesta E. Successful rapid desensitization to methylprednisolone sodium hemisuccinate: a case report. *J Allergy Clin Immunol Pract* 2014;2:346-8.
- Madrigal-Burgaleta R, Berges-Gimeno MP, Angel-Pereira D, Guillen-Ponce C, Sanz ML, Alvarez-Cuesta E. Desensitizing oxaliplatin-induced fever: a case report. *J Investig Allergol Clin Immunol* 2013;23:435-6.
- Arnaldi G, Angeli A, Atkinson AB, Bertagna X, Cavagnini F, Chrousos GP, et al. Diagnosis and complications of Cushing's syndrome: a consensus statement. *J Clin Endocrinol Metab* 2003;88:5593-602.
- Strehl C, Bijlsma JW, de Wit M, Boers M, Caeyers N, Cutolo M, et al. Defining conditions where long-term glucocorticoid treatment has an acceptably low level of harm to facilitate implementation of existing recommendations: viewpoints from an EULAR task force. *Ann Rheum Dis* 2016;75:952-7.
- Dexamethasone prescribing information. Available from: http://www.aemps.gob.es/cima/pdfs/es/ft/32224/FT_32224.pdf. Accessed August 10, 2017.
- Dexchlorpheniramine prescribing information. Available from: http://www.aemps.gob.es/cima/pdfs/es/ft/40135/40135_ft.pdf. Accessed August 10, 2017.
- Morita M, Suyama H, Igishi T, Shigeoka Y, Kodani M, Hashimoto K, et al. Dexamethasone inhibits paclitaxel-induced cytotoxic activity through retinoblastoma protein dephosphorylation in non-small cell lung cancer cells. *Int J Oncol* 2007;30:187-92.
- Hou WJ, Guan JH, Dong Q, Han YH, Zhang R. Dexamethasone inhibits the effect of paclitaxel on human ovarian carcinoma xenografts in nude mice. *Eur Rev Med Pharmacol Sci* 2013;17:2902-8.
- Alvarez-Cuesta E, Madrigal-Burgaleta R, Berges-Gimeno MP, Angel-Pereira D. Rapid desensitization to chemotherapy and monoclonal antibodies is effective and safe. Reply. *Allergy* 2013;68:1483-4.
- Alvarez-Cuesta E, Madrigal-Burgaleta R, Angel-Pereira D, Urena-Tavera A, Zamora-Verduga M, Lopez-Gonzalez P, et al. Delving into cornerstones of hypersensitivity to antineoplastic and biological agents: value of diagnostic tools prior to desensitization. *Allergy* 2015;70:784-94.
- Solano-Solares E, Madrigal-Burgaleta R, Carpio-Escalona LV, Bernal-Rubio L, Berges-Gimeno MP, Alvarez-Cuesta E. Chemotherapy in mastocytosis: administration issues, hypersensitivity, and rapid drug administration. *J Investig Allergol Clin Immunol* 2017;27:315-7.
- Brown SG. Clinical features and severity grading of anaphylaxis. *J Allergy Clin Immunol* 2004;114:371-6.
- Aberer W, Bircher A, Romano A, Blanca M, Campi P, Fernandez J, et al. Drug provocation testing in the diagnosis of drug hypersensitivity reactions: general considerations. *Allergy* 2003;58:854-63.
- Picard M, Castells MC. Re-visiting hypersensitivity reactions to taxanes: a comprehensive review. *Clin Rev Allergy Immunol* 2015;49:177-91.
- Hope AP, Woessner KA, Simon RA, Stevenson DD. Rational approach to aspirin dosing during oral challenges and desensitization of patients with aspirin-exacerbated respiratory disease. *J Allergy Clin Immunol* 2009;123:406-10.
- Breslow RG, Caiado J, Castells MC. Acetylsalicylic acid and montelukast block mast cell mediator-related symptoms during rapid desensitization. *Ann Allergy Asthma Immunol* 2009;102:155-60.
- Herrero T, Tornero P, Infante S, Fuentes V, Sanchez MN, De Barrio M, et al. Diagnosis and management of hypersensitivity reactions caused by oxaliplatin. *J Investig Allergol Clin Immunol* 2006;16:327-30.

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