Clinical Communications

Phenotyping occupational asthma caused by platinum salts compared with other low−molecular weight agents

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Clinical Implications

Platinum-induced occupational asthma shares phenotypic characteristics with high−molecular weight protein agents (ie, concomitant rhinitis and marked postexposure increase in FeNO), which supports the involvement of IgE-mediated mechanisms different from those underlying asthma caused by other low−molecular weight agents.

Agents causing sensitizer-induced occupational asthma (OA) are conventionally categorized into high−molecular weight (HMW) and low−molecular weight (LMW) agents.[1] High−molecular weight agents are glycoproteins from vegetal, animal, and microbiological origin that induce asthma through IgE-mediated mechanisms. Low−molecular weight agents include reactive chemicals (eg, isocyanates, persulfate salts), transition metals, drugs, and wood dust that act as haptens binding to carrier proteins to initiate a specific immunologic response through mechanisms that remain largely uncertain.

Studies have highlighted clinical phenotypic differences between these two broad categories of sensitizers.[2-4] Occupational asthma caused by HMW agents is more frequently associated with atopy, work-related rhinitis, early asthmatic reactions, and a greater postexposure increase in FeNO, although pathophysiologic mechanisms driving these phenotypic characteristics have not been fully elucidated.

Occupational asthma caused by LMW platinum salts (Pt) is generally acknowledged to be related to an IgE-mediated mechanism based on skin prick test (SPT) responses to Pt that correlate strongly with specific inhalation challenges (SIC).[5,6]

This study aimed to characterize the phenotypic profile of subjects with Pt-induced OA by comparing them with cases of OA caused by other LMW and HMW agents.

We conducted this retrospective, observational study among subjects with OA documented by a positive SIC who were reported by tertiary centers participating in the European Network for the Phenotyping of Occupational Asthma study during 2006 to 2018.[3] We identified 14 subjects with OA induced by Pt who had available measurements of FeNO before and 24 hours after the SIC (Online Repository Text 1). These subjects were compared to 216 subjects with OA induced by other LMW agents and 255 subjects with OA caused by HMW agents who completed FeNO measurements (see Supplemental Study Design and Population in this article's Online Repository at www.jaci-inpractice.org). The study was approved by the local institutional review board of each participating center.

The data collection process as well as the methodology and interpretation of procedures were previously described elsewhere.[3] The methodology of SIC and SPT with Pt is further detailed in the Supplemental Procedures (in this article's Online Repository at www.jaci-inpractice.org).[5,7]

Continuous variables are presented as medians (interquartile ranges), and categorical variables as numbers and percentages. We compared groups of subjects using χ^2 or Fisher exact test for categorical variables and Wilcoxon rank-sum test for numerical variables. Statistical analysis was performed using R software (version 4.2.2, www.r-project.org, Vienna, Austria). P less than .05 was considered significant.

Subjects with Pt-induced OA were younger, had a shorter duration of exposure to the offending agent before the onset of asthma (ie, the latency period), had higher FVC and FEV_1 values, and used inhaled corticosteroids and short-acting β_2-agonists less often than did subjects with OA caused by both the other LMW agents (Table I) and the HMW agents (Table II). The median FEV_1/FVC ratio tended to be higher in subjects with Pt-induced OA, but the difference failed to reach statistical significance. Subjects with OA caused by Pt reported a shorter duration of work-related asthma symptoms during exposure at work compared with those with OA caused by HMW agents. Compared with OA caused by other LMW agents, subjects with Pt-induced OA more frequently experienced work-related rhinitis and contact dermatitis (Table I).

Peripheral blood eosinophil counts, total serum IgE levels, and baseline FeNO values did not significantly differ between subjects with OA caused by Pt and those with OA resulting from other LMW agents (Table I) and HMW agents (Table II). In contrast, subjects with Pt-induced OA had a significantly greater increase in postchallenge FeNO compared with other LMW agents (Table I), whereas the median postchallenge increase in FeNO did not differ significantly between OA caused by Pt and HMW agents (Table II). When the comparison was restricted to subjects who were not treated with inhaled corticosteroids at the time of the SIC, the median (interquartile range) postchallenge increase in FeNO remained significantly greater in subjects with Pt-induced OA (34 parts per billion [ppb] [13-55 ppb]) than in 106 corticosteroid-free subjects with OA resulting from other LMW agents (2 ppb [−1 to 10 ppb]; $P < .001$). Similar results were obtained pertaining to the postchallenge changes in FeNO when Pt-induced OA was compared separately with OA resulting from the most common LMW agents, isocyanates or persulfate salts (see Table E1 in this article's Online Repository at www.jaci-inpractice.org).

To the best of our knowledge, this study is the first to attempt to delineate the phenotypic characteristics of Pt-induced OA compared with other LMW agents causing OA. Despite the limited number of subjects, Pt-induced OA was strongly associated with work-related rhinitis and a marked postexposure increase in FeNO, characteristics previously related to HMW agents causing OA through an IgE-mediated mechanism. We made a similar observation in subjects with OA caused by

TABLE I. Clinical characteristics and airway inflammatory biomarkers of subjects with OA caused by platinum salts compared with other low−molecular weight agents

Characteristic	OA caused by platinum salts (n = 14)	OA caused by other low−molecular weight agents (n = 216)	*P*
Age, y	28 (23-40)	42 (34-51)	**.003**
Sex, male	9 (64.3)	93 (43.1)	.121
Body mass index, kg/m^2	27.0 (25.1-30.9)	26.4 (24.0-30.6)	.539
Smoking			.228
Current smoker	5 (35.7)	39 (18.9)	
Ex-smoker	2 (14.3)	64 (31.1)	
Never-smoker	7 (50.0)	103 (50.0)	
Atopy*	8 (57.1)	92 (44.4)	.355
Work-related rhinitis	12 (85.7)	115 (53.2)	**.018**
Work-related urticaria	3 (21.4)	16 (17.4)	.098
Work-related contact dermatitis	6 (42.9)	39 (18.1)	**.036**
Duration of exposure before asthma onset, mo	21 (12-48)	62 (12-156)	**.025**
Duration of symptomatic exposure, mo	12 (6-28)	24 (12-48)	.124
Interval since last work exposure, mo	4.5 (0.1-15.8)	1.6 (0.1-9.0)	.746
Inhaled corticosteroid use	1 (7.7)	110 (50.9)	**.002**
Inhaled short-acting β_2-agonist use	2 (15.4)	106 (49.1)	**.018**
Baseline spirometry:			
FVC (% predicted)	110 (101-115)	101 (91-111)	**.012**
FEV_1 (% predicted)	105 (96-110)	92 (82-102)	**.007**
FEV_1/FVC (%)	81 (74-83)	77 (71-82)	.276
Baseline nonspecific bronchial hyperresponsiveness			.819
Absent	6 (42.9)	78 (38.4)	
Mild	5 (35.7)	87 (42.9)	
Moderate to severe	3 (21.4)	38 (18.7)	
Pattern of bronchial response to specific inhalation challenge			.412
Isolated early reaction	8 (57.1)	70 (32.6)	
Isolated late reaction	3 (21.4)	66 (30.1)	
Dual reaction	2 (14.3)	51 (23.7)	
Blood eosinophils, cells/μL	(n = 14)	(n = 128)	
	215 (167-260)	200 (100-322)	.880
Total IgE, kU/L	(n = 13)	(n = 60)	
	117 (74-271)	72 (22-204)	.212
Baseline FeNO, ppb	30 (13-64)	19 (11-31)	.194
Postchallenge FeNO, ppb	77 (44-142)	23 (14-40)	**.002**
Postchallenge change in FeNO, ppb	34 (12-59)	2 (−1 to 9)	**<.001**

OA, occupational asthma; *ppb*, parts per billion.
Data are presented as n (%available data) of subjects or medians (interquartile ranges). Values in boldface are statistically significant.
*Atopy defined by the presence of a positive skin prick test to at least one common allergen.

acrylate compounds, although specific IgE antibodies directed against acrylates have not been investigated.[8] Altogether, these findings further highlight the heterogeneity of inflammatory and immune mechanisms involved in the initiation of OA caused by LMW agents.

Occupational asthma caused by Pt has presumably been related to an IgE-mediated mechanism because SPT responses to this metal are highly sensitive and specific for a diagnosis of Pt-induced OA ascertained by SIC.[5] Nevertheless, correlations between specific IgE antibodies directed against Pt salts conjugates and SPT results have been inconsistent.[6] The marked FeNO responses to an inhalation challenge with Pt compared with other LMW agents suggest a greater involvement of T_H2-type mechanisms in Pt-induced OA, but this would require confirmation through direct assessment of T_H2 cytokines in sputum samples.

Subjects with Pt-induced OA used significantly fewer asthma treatments and showed a trend toward a higher FEV_1/FVC ratio and a shorter duration of symptomatic exposure, presumably reflecting the identification of Pt-induced OA at an early stage through specific surveillance programs based on periodic SPT with Pt (see Supplemental Study design and population).

This study suggests that the phenotypic characteristics (ie, concomitant work-related rhinitis and a greater postexposure increase in FeNO) usually linked to HMW agents are actually related to an underlying IgE-mediated mechanism rather than

TABLE II. Characteristics of subjects with OA induced by platinum salts compared with high–molecular weight agents

Characteristic	OA caused by platinum salts (n = 14)	OA caused by high–molecular weight agents (n = 225)	*P*
Age, y	28 (23-40)	38 (31-48)	**.012**
Sex, male	9 (64.3)	167 (65.5)	.999
Smoking			.522
Current smoker	5 (35.7)	52 (20.9)	
Ex-smoker	2 (14.3)	55 (22.1)	
Never-smoker	7 (50.0)	142 (57.0)	
Atopy*	8 (57.1)	154 (60.9)	.781
Work-related rhinitis	12 (85.7)	216 (84.7)	.999
Work-related urticaria	3 (21.4)	44 (17.2)	.717
Work-related contact dermatitis	6 (42.9)	51 (20.0)	.084
Exposure before asthma onset, mo	21 (12-48)	72 (41-149)	**<.001**
Duration of symptomatic exposure, mo	12 (6-28)	24 (12-72)	**.044**
Interval since last work exposure, mo	4.5 (0.1-15.8)	1.00 (0.1-8.0)	.654
Inhaled corticosteroid use	1 (7.7)	131 (51.4)	**.002**
Inhaled short-acting β_2-agonist use	2 (15.4)	144 (56.5)	**.004**
Baseline spirometry			
FVC (% predicted	110 (101-115)	99 (91-107)	**<.001**
FEV_1 (% predicted)	105 (96-110)	90 (79-100)	**<.001**
FEV_1/FVC (%)	81 (74-83)	76 (70-81)	.077
Baseline nonspecific bronchial hyperresponsiveness			.348
Absent	6 (42.9)	60 (24.2)	
Mild	5 (35.7)	115 (46.4)	
Moderate to severe	3 (21.4)	72 (29.0)	
Pattern of bronchial response to specific inhalation challenge			.541
Isolated early reaction	8 (57.1)	150 (58.8)	
Isolated late reaction	3 (21.4)	30 (11.8)	
Dual reaction	2 (14.3)	61 (23.9)	
Blood eosinophils, cells/μL	215 (167-260)	270 (134-401)	.372
	(n = 14)	(n = 183)	
Total IgE, kU/L	117 (74-271)	162 (67-400)	.484
	(n = 13)	(n = 62)	
Baseline FeNO, ppb	30 (13-64)	25 (13-41)	.738
Postchallenge FeNO, ppb	77 (44-142)	44 (24-84)	.121
Postchallenge change in FeNO, ppb	34 (12-59)	14 (3-39)	.086

OA, occupational asthma; *ppb*, parts per billion.
Data are presented as n (%available data) of subjects or medians (interquartile ranges). Values in boldface are statistically significant.
*Atopy defined by the presence of a positive skin prick test to at least one common allergen.

the proteinaceous nature or molecular weight category of the causal agent.

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ONLINE REPOSITORY

SUPPLEMENTAL STUDY DESIGN AND POPULATION

This retrospective study was conducted among the European Network for the Phenotyping of Occupational Asthma (E-PHOCAS) cohort. The E-PHOCAS cohort recruited data from 1,298 subjects with a diagnosis of occupational asthma (OA), ascertained by a positive specific inhalation challenge (SIC) between January 2006 and December 2018. The list of investigators participating in the E-PHOCAS study is available from the authors.

Fourteen subjects with OA caused by platinum salts (Pt) and available assessments of FeNO at baseline and 24 hours after the SIC were identified in the E-PHOCAS database. Thirteen subjects were catalyst production plant or metal refinery workers who had been referred for medical evaluation through workplace surveillance programs based on skin prick testing (SPT) with Pt conducted in Germany. The remaining subject was a chemical laboratory technician. At the time of the SIC with Pt, seven subjects were removed from exposure and five had reduced exposure to Pt. At that time, SPT with Pt was positive in 11 of the 14 subjects with Pt-induced OA.

A total of 245 subjects with OA caused by low−molecular weight (LMW) agents other than Pt agents had available measurements of FeNO at baseline and 24 hours after challenge exposure. Of the 245 subjects with OA caused by various LMW agents, we excluded those with acrylate-induced OA that share similarities to high−molecular weight (HMW) agents (n = 16) and those with positive specific IgE antibodies, including acid anhydrides (n = 5) and isocyanates (n = 8). This resulted in the identification of 216 control subjects with OA induced by other LMW agents. These LMW agents included persulfate salts (n = 51), isocyanates (n = 37), various cleaning products and disinfectants (n = 29), quaternary ammonium compounds (n = 19), various metals (n = 14), welding fumes (n = 14), metal working fluids (n = 13), wood dust (n = 11), epoxy resins (n = 8), amines (n = 6), drugs (n = 4), colophony (n = 3), and various other agents (n = 7).

Subjects with Pt-induced OA were also compared with 255 subjects with OA caused by HMW agents identified in the E-PHOCAS cohort. These subjects were selected based on available pre- and post-SIC FeNO data. The HMW agents included flour (n = 168), latex (n = 16), enzymes (n = 15), fish and seafood (n = 9), insects and derived products (n = 13), spices (n = 3), mold (n = 3), various plant-derived products (n = 17), and various animals and derived products (n = 11).

SUPPLEMENTAL PROCEDURES

Skin prick testing with platinum salts was completed using sodium hexachloroplatinate (Na_2PtCl_6) in saline. Skin prick tests were performed in duplicate with 10-fold increasing concentrations from 10^{-6} up to 1 mg/mL. Reactions were read at 20 min. Sensitization was considered when the wheal diameter was 4 mm or greater.

Specific inhalation challenges with platinum salts were performed by inhaling nebulized sodium hexachloroplatinate (Na_2PtCl_6) diluted in phosphate-buffered saline solution administered by a dosimeter in 13-step quadrupling concentrations with cumulative doses ranging of 2.7 to 60 μg.

Data on inflammatory cells in induced sputum samples collected during the specific inhalation challenge procedure were not considered in this study to avoid a potential bias, because nine of 10 subjects with platinum salt−induced OA and available sputum data were recruited from a single center (Bochum, Germany).

TABLE E1. Characteristics of subjects with OA induced by platinum salts compared with isocyanates and persulfate salts

Characteristic	OA caused by platinum salts (n = 14)	OA caused by isocyanates (n = 37)	*P*	OA caused by persulfate salts (n = 51)	*P*
Age, y	28 (23-40)	42 (36-54)	**.004**	31 (29-44)	.180
Sex, male	9 (64.3)	28 (75.7)	.489	0	**<.001**
Smoking			.138		.399
Current smoker	5 (35.7)	7 (20.0)		9 (19.6)	
Ex-smoker	2 (14.3)	15 (42.9)		13 (28.3)	
Never-smoker	7 (50.0)	13 (37.1)		24 (52.2)	
Atopy*	8 (57.1)	12 (32.4)	.107	23 (46.0)	.461
Work-related rhinitis	12 (85.7)	11 (29.8)	**<.001**	39 (76.5)	.716
Work-related urticaria	3 (21.4)	1 (2.7)	**.058**	5 (10.0)	.357
Work-related contact dermatitis	6 (42.9)	2 (5.4)	**.003**	14 (28.0)	.336
Exposure before asthma onset, mo	21 (12-48)	36 (7-102)	.314	108 (24-186))	**.002**
Duration of symptomatic exposure, mo	12 (6-28)	24 (11-36)	.208	32 (12-48)	.064
Interval since last work exposure, mo	4.5 (0.1-15.8)	4.0 (0.2-9.0)	.941	1.0 (0.1-5.5)	.525
Inhaled corticosteroid use	1 (7.7)	26 (70.3)	**<.001**	19 (37.3)	.059
Inhaled short-acting β_2-agonist use	2 (15.4)	106 (49.1)	**.018**	27 (52.9)	.055
Baseline spirometry					
FVC (% predicted)	110 (101-115)	99 (86-103)	**.004**	103 (96-110)	**.044**
FEV_1 (% predicted)	105 (96-110)	87 (79-101)	**.004**	95 (88-104)	.059
FEV_1/FVC (%)	81 (74-83)	76 (71-79)	.160	81 (76-84)	.905
Baseline nonspecific bronchial hyperresponsiveness			1.000		.651
Absent	6 (42.9)	14 (41.2)		21 (42.9)	
Mild	5 (35.7)	13 (38.2)		22 (44.9)	
Moderate to severe	3 (21.4)	7 (20.6)		6 (12.2)	
Pattern of bronchial response to specific inhalation challenge			.084		.210
Isolated early reaction	8 (57.1)	7 (18.9)		15 (29.4)	
Isolated late reaction	3 (21.4)	15 (40.5)		21 (41.2)	
Dual reaction	2 (14.3)	11 (29.7)		5 (9.8)	
Blood eosinophils, cells/μL	215 (167-260)	190 (102-298)	1.000	176 (100-267)	.601
	(n = 14)	(n = 22)		(n = 28)	
Total IgE, kU/L	117 (74-271)	53 (14-196)	.144	32 (16-124)	.142
	(n = 13)	(n = 18)		(n = 12)	
Baseline FeNO, ppb	30 (13-64)	17 (12-23)	.123	17 (11-26)	.100
Postchallenge FeNO, ppb	77 (44-142)	23 (15-43)	**.016**	21 (14-34)	**.001**
Postchallenge change in FeNO, ppb	34 (12-59)	5 (1-18)	**.015**	1 (−2 to 6)	**<.001**

OA, occupational asthma; *ppb*, parts per billion.

Data are presented as n (%available data) of subjects or medians (interquartile ranges). Values in boldface are statistically significant.

*Atopy defined by the presence of a positive skin prick test to at least one common allergen.