Original Article

Clinical Characteristics of Irritant-Induced Occupational Asthma

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What is already known about this topic? A proportion of occupational asthma is induced by irritant agents, but the clinical picture of this asthma type is poorly known.

What does this article add to our knowledge? Patients with irritant-induced asthma (IIA) use asthma medications extensively and have frequent asthma exacerbations 6 months after occupational asthma diagnosis. Their short-term asthma outcomes appear poorer than that of sensitizer-induced occupational asthma.

How does this study impact current management guidelines? The patients with IIA should be carefully monitored after the occupational asthma diagnosis, and the poor asthma outcomes highlight the need for preventive actions.

BACKGROUND: Work is a substantial contributing factor of adult-onset asthma. A subtype of occupational asthma (OA) is caused by irritant agents, but knowledge of the clinical outcomes of irritant-induced asthma (IIA) is incomplete.
OBJECTIVES: To evaluate whether the clinical picture of IIA differs from that of sensitizer-induced OA.
METHODS: This retrospective study analyzed acute and subacute IIA patients diagnosed in an occupational medicine clinic during 2004 to 2018. Sixty-nine patients fulfilled the inclusion criteria, and their characteristics were analyzed at the time of the diagnosis and 6 months later. The results were compared with those of 2 subgroups of sensitizer-induced OA: 69 high-molecular-weight (HMW) and 89 low-molecular-weight (LMW) agent-induced OA patients.
RESULTS: Six months after the diagnosis, 30% of the patients with IIA needed daily short-acting β-agonists (SABA), 68% were treated with Global Initiative for Asthma, 2020 report (GINA) step 4-5 medication, and 24% of the patients had asthma exacerbation after the first appointment. IIA depicted inferiority to LMW-induced OA in daily need for SABA (odds ratio [OR]: 3.80, 95% confidence interval [CI]: 1.38-10.46), treatment with GINA step 4-5 medication (OR: 2.22, 95% CI: 1.08-4.57), and exacerbation (OR: 3.85, 95% CI: 1.35-11.04). IIA showed poorer results than HMW-induced OA in the latter 2 of these features (OR: 2.49, 95% CI: 1.07-5.79 and OR: 6.29, 95% CI: 1.53-25.83, respectively).
CONCLUSIONS: Six months after the OA diagnosis, a significant proportion of the patients with IIA remain symptomatic and the majority of these patients use asthma medications extensively suggesting uncontrolled asthma. The short-term outcomes of IIA appear poorer than that of sensitizer-induced OA. **(J Allergy Clin Immunol Pract 2022;■:■-■)**

Key words: *Asthma control; IIA; Irritant-induced asthma; Irritants; Occupational asthma; Prognosis*

Occupational asthma (OA) is either new-onset asthma or the activation of previously quiescent asthma, caused by the occupational environment.[1,2] High-molecular-weight (HMW) and low-molecular-weight agents (LMW) can elicit sensitizer-induced OA via immunologic mechanisms, whereas irritant agents can provoke irritant-induced asthma (IIA) via non-immunologic mechanisms. The recent American Thoracic Society/European Respiratory Society (ATS/ERS) statement claims that occupational exposures contribute to 16% of adult-onset asthma cases.[3] Whereas the clinical characteristics of sensitizer-induced OA are well known, IIA has been less intensively reported.[4-6] However, according to the most recent surveillance data, IIA represents 4% to 15% of work-related asthma, a figure that is most likely an underestimate.[7-9]

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Abbreviations used

ACT- Asthma Control Test
ATS- American Thoracic Society
BMI- body mass index
CI- Confidence interval
EAACI- European Academy of Allergy and Clinical Immunology
ERS- European Respiratory Society
FeNO- Fractional exhaled nitric oxide
FEV1 and FEV1%- Forced expiratory volume and predicted forced expiratory volume in first second
FIOH- Finnish Institute of Occupational Health
FVC and FVC%- Forced vital capacity and predicted forced vital capacity
GINA- Global Initiative for Asthma, 2020 report
HMW- High-molecular-weight
ICS- Inhaled corticosteroids
IIA- Irritant-induced asthma
LMW- Low-molecular-weight
NSBH- Nonspecific bronchial hyperreactivity
OA- Occupational asthma
OR- Odds ratios
SABA- Short-acting β-agonists
S-IgE- Serum total IgE
WTC- World Trade Center

Studies of irritant workplace exposures,[10-12] the World Trade Center (WTC) catastrophe,[13,14] and several epidemiological studies[15-17] have demonstrated that IIA is more diverse than reactive airways dysfunction syndrome, which was first described by Brooks et al.[18] The **European Academy of Allergy and Clinical Immunology** (EAACI) position paper by Vandenplas et al[6] proposed that IIA can be classified into "definite" (ie, acute), "probable" (ie, subacute), and "possible" (ie, low-dose) IIA, according to the level of evidence of the causal relationship between workplace exposures and the development of asthma. The authors showed that the level of certainty of the individual cases having occupational origins was sufficient in the first 2 of these. Although numerous irritant agents have been recognized as causal agents of IIA,[12,19] only 1 study has examined its long-term outcomes.[20]

We recently published the results of a series of 69 patients with occupational IIA, including an extensive analysis of their exposure.[12] The first aim of the present study was to evaluate whether the clinical characteristics of these 69 patients with IIA differed from those of individuals with sensitizer-induced OA. Second, we evaluated the asthma control, asthma medication, and lung function parameters of these 69 cases with IIA in detail, concentrating on acute and subacute IIA and the differences among the separate causative agent groups.

METHODS

Study design

This retrospective study evaluated patients who were diagnosed with IIA at the Finnish Institute of Occupational Health (FIOH) between the years 2004 and 2018. FIOH is a tertiary outpatient clinic that confirms most OA diagnoses in Finland (population of 5.5 million).

We executed a systematic search of the FIOH patient register to identify patients with IIA. A multidisciplinary panel consisting of pulmonologists, occupational health physicians, and occupational toxicologist had set the initial diagnosis. After the preliminary search results, our group confirmed these diagnoses; an occupational toxicologist (KS) and an occupational physician (KK) screened the exposure details, and 2 lung physicians (JL, IL) evaluated the patients' clinical features.

The diagnostic criteria for IIA were: (1) exposure to a high concentration of an airborne irritant, (2) occurrence of asthma symptoms in a close temporal relationship to the exposure, (3) asthma verification by reversible obstruction or nonspecific bronchial hyperresponsiveness (NSBH), (4) persistence of symptoms for 3 months or more, (5) no evidence of active asthma in adulthood before the exposure, and (6) no other pulmonary disorder that explained the symptoms.

Our reference group to IIA was sensitizer-induced OA patients whose asthma was verified by a specific inhalation challenge at FIOH during 2006 to 2018. These patients had either HMW- or LMW-induced OA, which are 2 distinctive subgroups of sensitizer-induced OA.[2,5] All patients in HMW-induced OA group had flour-induced OA.

Source of data and definitions

FIOH patient records included all available data on the patients' encounters with health care professionals due to work-related respiratory symptoms preceding OA diagnosis, appointments to FIOH when OA was diagnosed, and a control appointment to FIOH 6 to 8 months after the diagnosis.

Asthma outcomes were the main variables in this study. The information on symptoms was collected from the patient records; for IIA the symptoms were recorded after the exposure event, and for the subgroups of sensitizer-induced OA they were registered when patients were exposed to the offending agent at work. Short-acting β-agonist (SABA) usage was divided into daily or less frequent need. An Asthma Control Test (ACT) assessed patients' symptom control. According to the GINA guideline, scores of 20 to 25 represented well-controlled asthma, 16 to 19 not well-controlled asthma, and 5 to 15 very poorly controlled asthma.[21] At least 3 days' intake of oral corticosteroids equivalent to prednisolone 30 mg or more due to breathing difficulties meant exacerbation. If information was missing in the medical records, this was interpreted as no exacerbation. Asthma medication was graded into treatment steps according to the GINA 2020 guideline.[21] Asthma treatment steps 4 and 5 were assessed to approximate severe asthma.

The patients with IIA were divided into acute and subacute types. The former type had only 1 high-level exposure event within 24 hours, whereas the latter type had repeated exposure events to high levels of airborne irritants during a period of more than 24 hours.[12] To be able to compare the state of asthma outcomes in varying exposures, we classified the irritant exposures on the basis of their chemical characteristics and hazard classifications[22] into (1) acids, (2) bases, (3) acids or bases or their mixtures, (4) oxidizing agents, and (5) other. This classification followed our recently reported classification[12] with some modifications to acquire a larger number of cases in each class. We defined atopy as having 1 or more positive reaction (wheal diameter of $\geq$3 mm) in the skin prick test panel for standardized environmental allergens (ALK-Abello, Horsholm, Denmark). Patients with a negative control wheal diameter of $\geq$2 mm were excluded from the analysis. The initiation time of inhaled corticosteroid (ICS) treatment was the first day when ICS was prescribed after the exposure. We recorded the patients' work status at each appointment and divided it into 5 categories: (1) unchanged job, (2) continuing to work but workplace or work tasks had changed, (3) unemployed, (4) sick leave, and (5) other (including re-education, retirement, or part-time job).

TABLE I. Causal agents of irritant- and sensitizer-induced asthma

		Sensitizer			n = 158
Irritant	n = 69	High-molecular-weight agent*	69	Low-molecular-weight agent	89
Mixtures	18	Rye	36	Isocyanates	38
Acid aerosols or fumes	13	Wheat	13	Acrylates	12
Base aerosols or fumes	9	Barley	11	Anhydrides	8
Mixture of acid and base aerosols or fumes	3	Oat	3	Metal working fluids	6
Acidic or alkaline dust	8	Buckwheat	3	Aldehydes	5
Inorganic gases	6	Soy	3	Colophony	5
Endotoxins	4			Epoxy	4
Oxidizing agents	2			Metals	2
Other chemicals	6			Other	9

*Flour-induced asthma represents high-molecular-weight agent induced-asthma in this study.

TABLE II. Demographic characteristics of the study population

		Sensitizer-induced asthma (n = 158)			
Characteristics	Irritant-induced asthma (n = 69)*	HMW-†induced asthma (n = 69)*	IIA vs HMW *P* value	LMW-induced asthma (n = 89)*	IIA vs LMW *P* value
Age (y)					
Median	47	40	**<.001**	44	.197
IQR	(40-54)	(31.5-49)		(35-54)	
Male	58 (84)	34 (49)	**<.001**	59 (66)	**.017**
Body mass index (kg/m^2)					
Median	28.1	26.8	**.041**	27.1	**.049**
IQR	(25.8-31.7)	(23.6-30.2)		(24.0-30.0)	
Smoking history					
Smoker	27 (39)	30 (43)	.730	56 (63)	**.004**
Nonsmoker	42 (61)	39 (57)		33 (37)	
Atopy‡ (n = 205)	24 (39)	45 (65)	**<.001**	41 (49)	.239
B-Eos (μg/L) (n = 218)					
Median	142	210	**.017**	160	.756
IQR	(85-255)	(100-360)		(90-245)	
S-IgE (kU/L) (n = 191)					
Median	49	179	**<.001**	56	.133
IQR	(19-128)	(89-525)		(32-268)	

B-Eos, Blood eosinophilia; *HMW*, high-molecular-weight agent; *IIA*, irritant-induced asthma; *LMW*, low-molecular-weight agent; *S-IgE*, serum total concentration of IgE. Bold indicates statistical significance ($P < .05$).

*Unless otherwise specified, the number of the patients was 227, 69 of whom had IIA. A total of 69 patients suffered from HMW-induced asthma and 89 from LMW-induced asthma. Numerical values expressed as median and interquartile ranges (IQR), and categorical values as n (% of patients involved).

†Flour-induced asthma represents HMW-induced asthma in this study.

‡One or more positive skin prick test reaction to common environmental allergens.

We used a standard flow-volume spirometer (Spirostar USB Medikro, Kuopio, Finland) to measure lung function in accordance with the guidelines[23] and used the predicted values of Viljanen.[24] Histamine and methacholine challenge tests assessed NSBH, and the results were graded as hyperreactivity or no hyperreactivity.[25,26]

The fractional exhaled nitric oxide (FeNO) test was measured using an online chemiluminescence analyzer (NIOX; Aerocrine AB, Solna, Sweden) in compliance with ATS/ERS recommendations.[27] Serum total IgE (S-IgE) was measured using the Phadia UniCAP System (Phadia, Uppsala, Sweden). S-IgE and blood eosinophilia were collected at the first FIOH appointment.

Statistical analysis

We used IBM SPSS version 27.0.1.0 for the data analyses. We presented categorical variables as the number and percentage of patients, and quantitative data as the median and interquartile range. We used Fisher's exact test with categorical variables and the Mann-Whitney *U* test with quantitative data to analyze the differences between IIA and HMW- or LMW-induced OA, and between different IIA subgroups.

Regression analyses were performed on variables that described asthma control or lung function parameters. The models were adjusted for age, body mass index (BMI), sex, presence of atopy, and smoking history. Age and smoking history showed a strong intercorrelation, and therefore, the latter was divided into 2 categories: smokers and nonsmokers. The cutoff value was set to 10 pack-years or more. Binary logistic regression was used with a daily need for SABA, ACT score of $\leq$19, treatment with GINA step 4 or 5 medication, and exacerbation after previous FIOH appointment. *P* values of $<.05$ and a 95% confidence interval (CI) with a lower limit of >1 were regarded as significant.

TABLE III. Clinical characteristics and work status of patients with IIA compared with those with HMW-* and LMW-induced asthma, 2 subgroups of sensitizer-induced OA, at the time of occupational asthma diagnosis

		Sensitizer-induced asthma (n = 158)			
Characteristics	**Irritant-induced asthma (n = 69)†**	**HMW-*induced asthma (n = 69)†**	**IIA vs HMW *P* value**	**LMW-induced asthma (n = 89)†**	**IIA vs LMW *P* value**
Respiratory symptoms‡					
Coughing	61 (88)	54 (78)	.170	67 (75)	**.042**
Wheezing	35 (51)	41 (59)	.392	57 (64)	.105
Dyspnea	65 (94)	59 (86)	.157	79 (89)	.271
Sputum	34 (49)	29 (42)	.494	32 (36)	.105
Other symptoms‡					
Rhinitis	47 (68)	58 (84)	**.045**	50 (56)	.141
Conjunctivitis	28 (41)	28 (41)	1.000	17 (19)	**.004**
Dermatitis	13 (19)	26 (38)	**.023**	19 (21)	.842
Duration of symptoms (mo)§					
Median	16	24	**.017**	29	**<.001**
IQR	(9.5-37.5)	(13-65)		(16-51)	
Short-acting β-agonist daily (n = 219)	24 (39)	8 (12)	**<.001**	7 (8)	**<.001**
Exacerbation during last year	22 (32)	3 (4)	**<.001**	5 (6)	**<.001**
Exacerbation without exposure to the causal agent	13 (19)	3 (4)	**.015**	4 (4)	**.008**
ICS daily dose (μg)					
Median	800	800	.057	800	**.044**
IQR	(400-1200)	(400-800)		(0-800)	
GINA treatment step‖					
1-3	33 (48)	48 (70)	**.015**	58 (65)	**.035**
4-5	36 (52)	21 (30)		31 (35)	
FVC% (n = 225)					
Median	93.5	96	.342	92	.741
IQR	(84.5-100)	(86-103.5)		(86-100.5)	
FEV1% (n = 225)					
Median	85.5	87	.529	89	.338
IQR	(77.5-95)	(79-94.5)		(80.5-95.5)	
FEV1% < 80% (n = 225)	22 (32)	18 (26)	.456	20 (23)	.205
FEV1/FVC (n = 225)					
Median	0.76	0.78	.238	0.78	.190
IQR	(0.72-0.795)	(0.725-0.81)		(0.725-0.81)	
FEV1/FVC < 0.70 (n = 225)	12 (18)	10 (14)	.649	12 (14)	.510
Nonspecific bronchial hyperreactivity (n = 190)	32 (59)	37 (62)	.849	41 (54)	.593
FeNO (ppb) (n = 198)					
Median	13	23	**<.001**	16.5	**.018**
IQR	(7-21.5)	(15-33)		(10-33)	
Work status			.053		**.017**
Same work	32 (46)	24 (35)		23 (26)	
Adjusted work	11 (16)	15 (22)		22 (25)	
Unemployed	7 (10)	2 (3)		7 (8)	
Sick leave	13 (19)	25 (36)		33 (37)	
Other	6 (9)	3 (4)		4 (4)	

FeNO, Fractional exhaled nitric oxide; *FEV1 and FEV1%*, forced expiratory volume and predicted forced expiratory volume in first second; *FVC and FVC%*, forced vital capacity and predicted forced vital capacity; *HMW*, high-molecular-weight agent; *ICS*, inhaled corticosteroids, *IIA*, irritant-induced asthma; *LMW*, low-molecular-weight agent; *OA*, occupational asthma; *ppb*, parts per billion.

Bold indicates statistical significance ($P < .05$).

*Flour-induced asthma represents HMW-induced asthma in this study.

†Unless otherwise specified, the number of patients was 227, 69 of whom had IIA. A total of 69 patients suffered from HMW-induced asthma and 89 from LMW-induced asthma. Numerical values expressed as median and interquartile ranges (IQR), and categorical values as n (% of patients involved).

‡The IIA patients' symptoms after the exposure event and in sensitizer-induced asthma cases when exposed to the offending agent at work.

§Duration of symptoms (months) before occupational asthma diagnosis.

‖Global Initiative for Asthma (GINA) treatment step classification follows 2020 report.

TABLE IV. Clinical characteristics and work status of the patients with IIA compared with those with HMW-* and LMW-induced asthma, 2 subgroups of sensitizer-induced OA, at the control appointment at FIOH 6 to 8 months after the occupational asthma diagnosis

		Sensitizer-induced asthma (n = 154)			
Characteristics	**Irritant-induced asthma (n = 66)†**	**HMW-*induced asthma (n = 65)†**	**IIA vs HMW *P* value**	**LMW-induced asthma (n = 89)†**	**IIA vs LMW *P* value**
Short-acting β-agonist daily (n = 204)	17 (30)	7 (8)	**.024**	7 (8)	**.001**
ACT (n = 122)‡					
Median	17	21.5	**<.001**	22	**<.001**
IQR	(12.5-20)	(19-23)		(17-24.5)	
Exacerbation after previous appointment§	16 (24)	5 (8)	**.016**	6 (7)	**.002**
ICS daily dose (μg)					
Median	800	800	.070	800	.676
IQR	(640-1200)	(450-880)		(400-1000)	
GINA treatment step‖					
1-3	21 (32)	39 (60)	**.002**	45 (51)	**.022**
4-5	45 (68)	26 (40)		44 (49)	
FVC% (n = 209)					
Median	92	93	**.035**	91	.336
IQR	(81.5-100.5)	(86-105)		(85-99)	
FEV1% (n = 212)					
Median	86	87	.102	87	.198
IQR	(75.5-93.5)	(80-98)		(79.5-95)	
FEV1% < 80% (n = 212)	21 (33)	14 (23)	.232	22 (25)	.361
FEV1/FVC (n = 209)					
Median	0.76	0.79	**.049**	0.77	**.031**
IQR	(0.725-0.785)	(0.73-0.81)		(0.74-0.81)	
FEV1/FVC < 0.70 (n = 209)	12 (19)	7 (11)	.320	12 (14)	.501
Nonspecific bronchial hyperreactivity (n = 132)	23 (54)	22 (52)	1.000	21 (45)	.527
FeNO (ppb) (n = 182)					
Median	13	17	**.022**	14.5	.778
IQR	(7-20)	(10-27)		(9.5-25.5)	
Work status (n = 222)			**.007**		**<.001**
Same work	16 (24)	3 (4)		2 (2)	
Adjusted work	15 (23)	23 (34)		28 (32)	
Unemployed	4 (6)	5 (7)		9 (10)	
Sick leave	18 (27)	14 (21)		22 (25)	
Other	13 (20)	22 (33)		28 (31)	

ACT, Asthma Control Test results graded from 5 to 25; *FeNO*, fractional exhaled nitric oxide; *FEV1 and FEV1%*, forced expiratory volume and predicted forced expiratory volume in first second; *FIOH*, Finnish Institute of Occupational Health; *FVC and FVC%*, forced vital capacity and predicted forced vital capacity; *HMW*, high-molecular-weight agent; *ICS*, Inhaled corticosteroids; *IIA*, irritant-induced asthma; *LMW*, low-molecular-weight agent; *OA*, occupational asthma; *ppb*, parts per billion.
Bold indicates statistical significance ($P < .05$).
*Flour-induced asthma represents HMW-induced asthma in this study.
†Unless otherwise specified, the number of patients was 220, 66 of whom had IIA. A total of 65 patients suffered from HMW-induced asthma and 89 from LMW-induced asthma. Numerical values expressed as median and interquartile ranges (IQR), categorical values as n (% of patients involved).
‡Thirty-six IIA, 38 HMW-induced OA, and 47 LMW-induced OA patients completed the ACT questionnaire.
§None of the subjects who had exacerbation were exposed to the causal agent at work.
‖Global Initiative for Asthma (GINA) treatment step classification follows 2020 report.

Ethics

This study was approved by the ethics committee of Helsinki University Central Hospital (approval number HUS/611/2020). According to the local legislation and ethical committees, no patient approval was needed for this retrospective study, as no patient intervention was performed at FIOH.

RESULTS

We analyzed 227 patients with OA. Sixty-nine had IIA, of whom 30 had acute and 39 subacute IIA. A total of 158 patients fulfilled the sensitizer-induced OA criteria: 69 of these had HMW-induced OA and 89 LMW-induced OA (Table I).

Comparison of IIA and subgroups of sensitizer-induced OA

The patients with IIA were more frequently men and had a higher BMI than patients with HMW- or LMW-induced OA (Table II). They were also older, had less atopy, and had lower blood eosinophil counts and S-IgE values than those with HMW-induced asthma. A similar trend was observed in comparison with LMW-induced asthma, but the differences were statistically insignificant. The patients in the LMW-induced OA group were more frequently smokers than the patients with IIA.

Table III depicts the clinical characteristics and work status at the time of OA diagnosis. During disease initiation, a cough was

TABLE V. Odds ratios (OR) for poor asthma outcome among the patients with IIA compared with those with HMW-* and LMW-induced asthma, 2 subgroups of sensitizer-induced OA, 6 to 8 months after the occupational asthma diagnosis

Characteristics	OR (95% CI)†	*P* value
Short-acting β-agonists daily		
IIA: HMW-induced asthma	2.09 (0.72-6.05)	.174
IIA: LMW-induced asthma	3.80 (1.38-10.46)	**.010**
Asthma Control Test score of ≤19		
IIA: HMW-induced asthma	3.12 (0.93-10.69)	.066
IIA: LMW-induced asthma	3.55 (1.22-10.34)	**.020**
Exacerbation after previous appointment		
IIA: HMW-induced asthma	6.29 (1.53-25.83)	**.011**
IIA: LMW-induced asthma	3.85 (1.35-11.04)	**.012**
GINA step 4 or 5 medication		
IIA: HMW-induced asthma	2.49 (1.07-5.79)	**.034**
IIA: LMW-induced asthma	2.22 (1.08-4.57)	**.031**

CI, Confidence interval; *GINA step*, Global Initiative for Asthma treatment step classification follows 2020 report; *HMW*, high-molecular-weight agent; *IIA*, irritant-induced asthma; *LMW*, low-molecular-weight agent; *OA*, occupational asthma.
Bold indicates statistical significance ($P < .05$).
*Flour-induced asthma represents HMW-induced asthma in this study.
†Variables adjusted for age, sex, body mass index, atopy, and smoking history of 10 pack-years or more.

a predominant sign of IIA and was more frequent than in LMW-induced asthma ($P = .042$). Conjunctivitis was also more frequent in IIA than in LMW-induced asthma ($P = .004$), whereas rhinitis and dermatitis were more often reported in patients with HMW-induced OA. Both patients with HMW- and LMW-induced OA had been symptomatic for longer than the patients with IIA before OA diagnosis (.017 and <.001, respectively). The patients with IIA used more asthma medications than the other groups. Neither lung function parameters nor NSBH differed between the groups, but the FeNO level was lower in the IIA group than in the other groups.

Table IV shows the clinical characteristics and work status at the control appointment 6 to 8 months after OA diagnosis, when asthma treatment was stabilized. The need for daily SABA was more frequent ($P = .024$, $P = .001$, respectively), and the ACT results were lower ($P < .001$, $P < .001$, respectively) among patients with IIA than among those with HMW- or LMW-induced OA, but only half of the patients had filled the questionnaire. They also had more exacerbations ($P = .016$, $P = .002$, respectively). The majority of the patients with IIA (68%) used GINA treatment step 4 or 5 asthma medication, and they had a higher treatment step ($P = .002$, $P = .022$, respectively) than the other groups. Patients with HMW-induced OA showed higher predicted forced vital capacity (FVC%) and FeNO than those with IIA. The forced expiratory volume in first second (FEV1)/forced vital capacity (FVC) ratio was lower in IIA compared with other groups, but no statistically significant difference was detected in NSBH. Less than half of the patients with IIA were actively in working life at the time of the control, but they had retained the same work task more often than those with HMW- and LMW-induced asthma.

Risk of poor asthma outcomes

Table V demonstrates how patients with IIA retained inferior asthma outcomes in daily need of SABA, ACT score of ≤19, exacerbation after previous appointment, and GINA step 4 or 5 medication in comparison with LMW-induced OA after the adjustments. Furthermore, the latter 2 of these features remained statistically significant when they were compared with HMW-induced OA. However, the difference in FVC% or FEV1/FVC at the control appointment lost statistical significance after the adjustments.

Subtypes, causative agents, and ICS initiation

We compared the characteristics of acute and subacute IIA (Tables E1 and E2, available in this article's Online Repository at www.jaci-inpractice.org), and these subtypes appeared similar to each other. Regression analyses revealed that the only significantly different feature of asthma outcome was that the patients with acute IIA reported more exacerbations during the control appointment than those with subacute IIA (odds ratio: 11.68, 95% CI: 2.62-52.08; $P = .001$).

We also analyzed whether asthma outcomes or lung function parameters differed among the patients who were exposed to different types of irritant agents according to their chemical properties (Tables E3-E6, available in this article's Online Repository at www.jaci-inpractice.org). Oxidizing agents revealed lower lung function parameters, but these differences were insignificant when adjusted for smoking history. Generally, the asthma control and lung function parameters of the groups appeared analogous at the control appointment.

ICS initiation time showed no effect on asthma outcomes or lung function parameters (Table E7, available in this article's Online Repository at www.jaci-inpractice.org).

DISCUSSION

This study followed the clinical characteristics of patients with OA at the FIOH appointment where OA diagnosis was confirmed and at the control appointment 6 months later. The need for daily SABA and GINA treatment step 4 or 5 asthma medication was more frequent among IIA cases, and the patients with IIA had more exacerbations, indicating poorer asthma outcomes. The results from the 2 appointments were comparable, but the results from the control appointment emphasized these differences because in many cases regular asthma medication was introduced or adjusted in the first appointment. The comparison between acute and subacute IIA revealed no major differences, although the patients with acute IIA reported more exacerbations than those with subacute IIA.

Only a few previous studies have addressed the prognosis of IIA using limited data on the features of asthma outcomes. Many of these have reported that up to 90% of patients with IIA had remained symptomatic in the follow-up,[11,20,28,29] which reflects the poor asthma control of patients with IIA seen in this study. Malo et al[20] showed that patients with IIA had high symptom scores at long-term follow-up. Tarlo et al[30] noticed that patients with asthma aggravated by irritant exposures and no prior asthma diagnosis had the worst prognosis at follow-up. Our results are in line with these observations and denote that the asthma outcomes of acute and subacute IIA were inferior to those of sensitizer-induced OA. Interestingly, the lung function parameters of these OA categories were comparable.

The reason for poorer asthma outcomes in IIA remains unresolved. One possible explanation might be the expected differences between the pathological mechanism of the asthma types. Previous studies have demonstrated that IIA is associated with neutrophilic inflammation[31,32] and thicker basement membrane.[31-33]

Furthermore, neutrophilic work-related asthma has shown poorer asthma control,[34] and, generally, noneosinophilic asthma has had an unsatisfactory response to anti-inflammatory therapy.[35-37] Neutrophilic inflammation and chronic remodeling may explain a part of the deficient asthma control seen in IIA.

A substantial portion of assumed severe asthma is difficult-to-treat asthma.[38] In general, comorbidities affect asthma control, and clinicians should consider differential diagnostics with inadequate response to regular asthma medications.[39] The WTC rescue/recovery workers had a high number of comorbidities, and almost 70% of the workers with asthma had poor or very poor asthma control.[14,40] Poorly or very poorly controlled asthma had a strong association with comorbid mental health conditions. It is unlikely that these people represent all patients with IIA, but Malo et al[20] found that one-third of their acute patients with IIA had psychiatric comorbidities in their long-term follow-up study. Finally, occupational irritants have also been associated with laryngeal dysfunction,[41-43] which, in turn, is linked to reduced asthma control.[44,45] Lack of sputum samples, bronchial biopsies, mental health questionnaires, or laryngeal evaluations limit generalizing these interpretations to include the results presented in this retrospective study.

In addition to direct effects, work-related asthma contributes to health care utilization, unemployment, quality of life, and psychiatric comorbidities.[34,46,47] The EAACI position paper suggested that patients with IIA could continue in their work tasks if their asthma was not severe.[6] Working status was a secondary focus in this study, but the results still raised questions. Less than half of the patients were actively in working life 6 to 8 months after OA diagnosis, and only a few of them did the same work task. For sensitizer-induced OA this was expected, as avoidance of exposure is usually recommended.[2] However, the small number of patients with IIA who remained in their original jobs (24%) was surprising, although some previous studies reported similar figures.[28-30,48]

Returning to the IIA subtypes, Brooks et al[49] concluded that atopic status contributed to not-so-sudden (ie, subacute) IIA, with 88% of these patients being atopic compared with 52% of sudden-onset (ie, acute) patients. In this study, atopic status was an insignificant prognostic marker, as 44% of acute and 35% of patients with subacute IIA had a positive skin prick test (Table E1, available in this article's Online Repository at www.jaci-inpractice.org). We are not aware of other studies that have compared these 2 subtypes. Our results illustrate a notable similarity between the asthma outcomes of acute and subacute IIA. The only statistically significant differences were initial rhinitis and the number of exacerbations at the control appointment. The former was more frequent in subacute IIA and the latter in acute IIA.

It has been speculated that the chemical properties of the irritant agent and the timing of inhaled cortisone initiation affect the prognosis of IIA.[50] In these data, the chemical classes were indistinguishable in respect of initial symptoms after exposure or asthma outcomes and lung function parameters at the control appointment. Oxidizing agents showed lower FVC and FEV1, but smoking history affected the individual values. Generally, the level of exposure might have varied among patients and a larger sample size may have produced more distinguishable differences. The timing of ICS initiation was also irrelevant to prognosis, although a retrospective study design is not ideal for analyzing the effect of medication.

Strengths and limitations

To our knowledge, this is the largest study that compared clinical differences between irritant-induced and sensitizer-induced OA. We were able to analyze each patient in detail and obtain a more comprehensive view of their asthma outcomes than previous studies, and we also had reliable information on their exposure.

This study identified 30 patients with acute and 39 patients with subacute IIA in an occupational medicine clinic, but it is likely that numerous cases remained undiagnosed. We cannot rule out selection bias in our patient selection. The patients in this study might represent more severe examples of IIA, but this also applies to sensitizer-induced asthma cases, and we consider the groups comparable in this respect.

We are not aware of any previous studies that have compared the asthma outcomes of acute and subacute IIA or the effect of the causative irritant agent. This can be regarded as a strength of this study, although the number of patients in each category was limited.

As the diagnosis of IIA depends on clinical history,[2,6] reporting bias may be possible. Therefore, a multidisciplinary panel set the initial OA diagnosis, and we reassessed whether each patient met our criteria for IIA.

Because of its retrospective nature, this study registered the symptoms from patient records. A standardized questionnaire would have enhanced reliability. Furthermore, IIA and sensitizer-induced asthma differed in their demographic characteristics, which was noticed with patients with HMW-induced OA in particular. The FEV1/FVC ratio was analyzed as an absolute value that disregarded decline with aging. However, statistical adjustment counterbalanced these imperfections.

CONCLUSIONS

This study analyzed patients with acute and subacute IIA at the time of OA diagnosis and 6 to 8 months later. It illustrated that 68% of the patients with IIA used GINA step 4 or 5 asthma medication, 30% needed SABA daily, and that 24% of them had had asthma exacerbation 6 to 8 months after OA diagnosis. The patients with IIA had more exacerbations and used more medications than the patients with sensitizer-induced OA, indicating poorer asthma outcomes.

Our results show that the patients with IIA should be carefully monitored and treated after the OA diagnosis. They also highlight the value of primary prevention, regardless of the reason behind the inferior asthma outcomes. Confronting the root causes of exposure and transmitting knowledge to workplaces is essential.

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ONLINE REPOSITORY

COMPARISON OF CAUSATIVE AGENTS OF IRRITANT-INDUCED ASTHMA

Methods

We grouped the irritant exposures according to their hazard classification[E1] and physical form as described earlier.[E2] Because of the small number of cases in each category, we formed 4 new chemical classes: acids (n = 19), bases (n = 16), oxidizing agents (n = 6), and combined corrosive agents (n = 29). The last group comprised acids, bases, and other chemicals with the hazard classification of Skin Corr 1A or Skin Corr 1B. We compared each of the groups with all the other cases combined.

TABLE E1. Demographic and clinical characteristics and work status of acute and subacute irritant-induced asthma at the time of occupational asthma diagnosis

Characteristics	Acute IIA (n = 30)*	Subacute IIA (n = 39)*	*P* value
Age (y)			.208
Median	45	50	
IQR	(39-52)	(41-55)	
Male	25 (83)	33 (85)	1.000
BMI (kg/m^2)			.780
Median	28.7	27.8	
IQR	(26.0-31.6)	(25.5-31.7)	
Smoking history			.137
Smoker	15 (50)	12 (31)	
Nonsmoker	15 (50)	27 (69)	
Atopy (n = 62†)	11 (44)	13 (35)	.597
B-Eos (μg/L) (n = 64)			.582
Median	144	140	
IQR	(85-220)	(90-280)	
S-IgE (kU/L) (n = 63)			.460
Median	73	41	
IQR	(19-188)	(19-118)	
Respiratory symptoms‡			
Coughing	26 (87)	35 (90)	.720
Wheezing	12 (40)	23 (59)	.148
Dyspnea	28 (93)	37 (95)	1.000
Sputum	15 (50)	19 (49)	1.000
Other symptoms			
Rhinitis	16 (53)	31 (79)	**.036**
Conjunctivitis	14 (47)	14 (36)	.460
Dermatitis	5 (17)	8 (21)	.764
Short-acting β-agonist daily (n = 61)	10 (40)	14 (39)	1.000
ACT (n = 39)§			.965
Median	16	15	
IQR	(11-19)	(12-20)	
Exacerbation during last year	11 (37)	11 (28)	.603
Exacerbation without exposure to the causal agent	10 (33)	3 (8)	**.011**
ICS daily dose (μg)			.054
Median	1000	800	
IQR	(800-1600)	(100-900)	
GINA treatment step‖			.052
1-3	10 (33)	23 (59)	
4-5	20 (67)	16 (41)	
FVC% (n = 68)			.564
Median	91	96	
IQR	(86-98)	(80.5-101)	
FEV1% (n = 68)			.687
Median	86	85	
IQR	(79-91)	(76-99)	
FEV1% < 80% (n = 68)	8 (28)	14 (36)	.602
FEV1/FVC (n = 68)			.980
Median	0.76	0.76	
IQR	(0.71-0.79)	(0.72-0.80)	
FEV1/FVC < 0.70 (n = 68)	5 (17)	7 (18)	1.000
Nonspecific bronchial hyperreactivity (n = 54)	13 (54)	19 (63)	.582
FeNO (ppb) (n = 68)			.104
Median	11.5	14.5	
IQR	(7.0-17.0)	(9.0-25.0)	
Work status			.067

(continued)

TABLE E1. *(Continued)*

Characteristics	Acute IIA (n = 30)*	Subacute IIA (n = 39)*	*P* value
Same work	11 (37)	21 (54)	
Adjusted work	8 (27)	3 (8)	
Unemployed	2 (7)	5 (13)	
Sick leave	8 (27)	5 (13)	
Other	1 (3)	5 (13)	

ACT, Asthma control test; *B-Eos*, blood eosinophilia; *FeNO*, fractional exhaled nitric oxide; *FEV1 and FEV1%*, forced expiratory volume and predicted forced expiratory volume in first second; *FVC and FVC%*, forced vital capacity and predicted forced vital capacity; *ICS*, Inhaled corticosteroids; *ppb*, parts per billion; *S-IgE*, serum total concentration of IgE.

Bold indicates statistical significance ($P < .05$).

*Unless otherwise specified, the number of the patients was 69, 30 of whom had acute IIA and 39 subacute IIA. Numerical values expressed as median and interquartile ranges (IQR), and categorical values as n (% of patients involved).

†One or more positive skin prick test reactions to common environmental allergens.

‡The patients' symptoms after exposure event.

§Fourteen acute and 25 subacute IIA patients completed the ACT questionnaire.

‖Global Initiative for Asthma (GINA) treatment step classification follows 2020 report.

TABLE E2. Clinical characteristics and work status of the patients with acute and subacute irritant-induced asthma 6 to 8 months after occupational asthma diagnosis

Variable	Acute (n = 28)*	Subacute (n = 38)*	*P* value
Short-acting β-agonist daily (n = 57)	9 (38)	8 (24)	.381
ACT (n = 36)†			.124
Median	15	18	
IQR	(12-17)	(14-20)	
Exacerbation after previous appointment‡	13 (46)	3 (8)	**<.001**
ICS daily dose (μg)			.151
Median	880	800	
IQR	(800-1800)	(400-1000)	
GINA treatment step§			.790
1-3	8 (29)	13 (34)	
4-5	20 (71)	25 (66)	
FVC% (n = 63)			.058
Median	84	96	
IQR	(80-94.5)	(82-102.5)	
FEV1% (n = 63)			.160
Median	83	86.5	
IQR	(71.5-87.5)	(77-96.5)	
FEV1% < 80% (n = 63)	11 (41)	10 (28)	.296
FEV1/FVC (n = 63)			.743
Median	0.76	0.76	
IQR	(0.72-0.79)	(0.725-0.78)	
FEV1/FVC < 0.70 (n = 63)	6 (22)	6 (17)	.747
Nonspecific bronchial hyperreactivity (n = 43)	5 (36)	18 (62)	.191
FeNO, ppb (n = 58)			.192
Median	11	15	
IQR	(6.5-16)	(7-20)	
Work status			.306
Same work	6 (21)	10 (26)	
Adjusted work	9 (32)	6 (16)	
Unemployed	1 (4)	3 (8)	
Sick leave	9 (32)	9 (24)	
Other	3 (11)	10 (26)	

ACT, Asthma Control Test; *FeNO*, fractional exhaled nitric oxide, *FEV1 and FEV1%*, forced expiratory volume and predicted forced expiratory volume in first second; *FVC and FVC%*, forced vital capacity and predicted forced vital capacity; *ICS*, inhaled corticosteroids; *ppb*, parts per billion.
Bold indicates statistical significance ($P < .05$).
*Unless otherwise specified, the number of the patients was 66, 28 of whom had acute IIA and 38 subacute IIA. Numerical values expressed as median and interquartile ranges (IQR), categorical values as n (% of patients involved).
†Eleven acute and 25 subacute IIA patients completed the ACT questionnaire.
‡None of the subjects who had exacerbation were exposed to the causal agent at work.
§Global Initiative for Asthma (GINA) treatment step classification follows 2020 report.

TABLE E3. Clinical characteristics of the patients with irritant-induced asthma 6 to 8 months after occupational asthma diagnosis, classification according to agents' chemical properties: acids vs others

Characteristics	Acids (n = 19)*	Other agents (n = 47)*	*P* value
Short-acting β-agonists daily (n = 57)	6 (35)	11 (28)	.547
Exacerbation after previous appointment	5 (26)	11 (23)	1.000
GINA treatment step†			1.000
1-3	6 (32)	15 (32)	
4-5	13 (68)	32 (68)	
FVC%			.867
Median	93	88	
IQR	(81-102)	(82-97)	
FEV1%			.508
Median	86.5	84	
IQR	(77-99)	(75-91)	
FEV1/FVC ratio			.122
Median	0.78	0.75	
IQR	(0.73-0.79)	(0.72-0.78)	

FEV1 and FEV1%, Forced expiratory volume and predicted forced expiratory volume in first second; *FVC and FVC%*, forced vital capacity and predicted forced vital capacity.
*Unless otherwise specified, the number of the patients was 66, 19 of whom were exposed to acidic agents and 47 to other agents. Numerical values expressed as median and interquartile ranges (IQR), categorical values as n (% of patients involved).
†Global Initiative for Asthma (GINA) treatment step classification follows 2020 report.

TABLE E4. Clinical characteristics of the patients with irritant-induced asthma 6 to 8 months after occupational asthma diagnosis, classification according to agents' chemical properties: bases vs others

Characteristics	Bases (n = 16)*	Other agents (n = 50)*	*P* value
Short-acting β-agonists daily (n = 57)	6 (40)	11 (26)	.341
Exacerbation after previous appointment	5 (31)	11 (22)	.509
GINA treatment step†			1.000
1-3	5 (31)	16 (32)	
4-5	11 (68)	34 (68)	
FVC%			.586
Median	94	88	
IQR	(82-99.5)	(81-100.5)	
FEV1%			.301
Median	88.5	84	
IQR	(77-95.5)	(74.5-91.5)	
FEV1/FVC ratio			.516
Median	0.77	0.76	
IQR	(0.72-0.79)	(0.725-0.785)	

FEV1 and FEV1%, Forced expiratory volume and predicted forced expiratory volume in first second; *FVC and FVC%*, forced vital capacity and predicted forced vital capacity.
*Unless otherwise specified, the number of the patients was 66, 16 of whom were exposed to alkali agents and 50 to other agents. Numerical values expressed as median and interquartile ranges (IQR), and categorical values as n (% of patients involved).
†Global Initiative for Asthma (GINA) treatment step classification follows 2020 report.

TABLE E5. Clinical characteristics of the patients with irritant-induced asthma 6 to 8 months after occupational asthma diagnosis, classification according to agents' chemical properties: oxidizing agents vs others

Characteristics	Oxidizing agents (n = 6)*	Other agents (n = 60)*	*P* value
Short-acting β-agonists daily (n = 57)	2 (33)	15 (29)	1.000
Exacerbation after previous appointment	2 (33)	14 (23)	.627
GINA treatment step†			1.000
1-3	2 (33)	19 (32)	
4-5	4 (67)	41 (68)	
FVC%			.069
Median	81	93	
IQR	(70-84)	(82-102)	
FEV1%			**.049**
Median	70	86	
IQR	(68-80)	(77-94)	
FEV1/FVC ratio			.706
Median	0.775	0.76	
IQR	(0.68-0.79)	(0.73-0.78)	

FEV1 and FEV1%, Forced expiratory volume and predicted forced expiratory volume in first second; *FVC and FVC%*, forced vital capacity and predicted forced vital capacity. Bold indicates statistical significance ($P < .05$).

*Unless otherwise specified, the number of the patients was 66, 6 of whom were exposed to oxidizing agents and 60 to other agents. Numerical values expressed as median and interquartile ranges (IQR), categorical values as n (% of patients involved).

†Global Initiative for Asthma (GINA) treatment step classification follows 2020 report.

TABLE E6. Clinical characteristics of the patients with irritant-induced asthma 6 to 8 months after occupational asthma diagnosis, classification according to agents' chemical properties: combined corrosive agents vs others

Characteristics	Corrosive agents (n = 29)*	Other agents (n = 37)*	*P* value
Short-acting β-agonists daily (n = 57)	10 (38)	7 (23)	.249
Exacerbation after previous appointment	8 (28)	8 (22)	.773
GINA treatment step†			.292
1-3	7 (24)	14 (38)	
4-5	22 (76)	23 (62)	
FVC%			.317
Median	94	86	
IQR	(82-102)	(80.5-97.5)	
FEV1%			.089
Median	87	81	
IQR	(78-99)	(74.5-89)	
FEV1/FVC ratio			**.008**
Median	0.78	0.74	
IQR	(0.745-0.805)	(0.71-0.77)	

FEV1 and FEV1%, Forced expiratory volume and predicted forced expiratory volume in first second; *FVC and FVC%*, forced vital capacity and predicted forced vital capacity. Bold indicates statistical significance ($P < .05$).

*Unless otherwise specified, the number of the patients was 66, 29 of whom were exposed to combined corrosive agents (hazard classification of Skin Corr 1A or Skin Corr 1B) and 37 to other agents. Numerical values expressed as median and interquartile ranges (IQR), and categorical values as n (% of patients involved).

†Global Initiative for Asthma (GINA) treatment step classification follows 2020 report.

TABLE E7. Clinical characteristics of patients with irritant-induced asthma 6 to 8 months after the occupational asthma diagnosis, classification according to initiation time of inhaled corticosteroids within 1 week or more of exposure event

Characteristics	ICS ≤ 1 wk (n = 18)*	ICS > 1 wk (n = 48)*	*P* value
Short-acting β-agonists daily (n = 57)	3 (19)	14 (34)	.342
Exacerbation after previous appointment	6 (33)	10 (21)	.340
GINA treatment step†			.555
1-3	7 (39)	14 (29)	
4-5	11 (61)	34 (71)	
FVC%			.365
Median	85.5	95	
IQR	(82-93)	(81-102)	
FEV1%			.330
Median	81	86	
IQR	(74-87)	(77-94)	
FEV1/FVC ratio			.669
Median	0.755	0.77	
IQR	(0.71-0.78)	(0.73-0.79)	

ICS, Inhaled corticosteroids; *FEV1 and FEV1%,* forced expiratory volume and predicted forced expiratory volume in first second; *FVC and FVC%,* forced vital capacity and predicted forced vital capacity.

*Unless otherwise specified, the number of the patients was 66, 18 of whom initiated inhaled corticosteroids within 1 week of exposure event and 48 initiated after 1 week. Numerical values expressed as median and interquartile range (IQR), and categorical values as n (% of patients involved).

†Global Initiative for Asthma (GINA) treatment step classification follows 2020 report.

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