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Early View

Research Letter

What drives rescue bronchodilators overuse in asthmatics? Demographic features, low FEV_1 and high sputum eosinophil counts

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What drives rescue bronchodilators overuse in asthmatics? Demographic features, low FEV_1 and high sputum eosinophil counts.

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Take home message

In a large cohort of 2167 patients seen in a secondary/tertiary hospital, we found that overuse of rescue bronchodilators was associated with young age, smoking habit, overweight, impaired spirometry and uncontrolled airway eosinophilic inflammation.

To the editor

Excessive use of short acting β2 agonists has been associated with increased asthma mortality[1] and recent large epidemiological studies conducted worldwide have clearly shown that exacerbation rate in asthmatics was correlated with the consumption of β2 agonist canisters.[2,3] These studies rely on the prescription records from electronic medical file and/or dispensation of the drug at the pharmacy level. However, there are much less studies based on the patient interview as well as on factors driving overuse of bronchodilators in a real-world setting.

To the best of our knowledge, there has been no study to explore the relationship between the patient reported overuse and the measurement of lung function and airway inflammation. Here we have conducted a large retrospective study leveraging our asthma clinic database to investigate the factors associated with high consumption of rescue bronchodilators as reported by the patient.

A cross-sectional retrospective study was conducted on asthmatics recruited from the asthma clinic of CHU Liege between 2011 and 2023. We selected 2167 asthmatics who had already been prescribed any asthma treatment except biologics. Among them, 589 were only treated with SABA or a combination of SABA/SAMA as needed while the majority of patients were receiving maintenance treatment including ICS/LABA (±LAMA) and/or montelukast and/or OCS. Patients underwent blood sampling, sputum induction and fraction of exhaled nitric oxide (FeNO) was measured by NIOX as previously reported.[4] They filled in an ACQ questionnaire and they were classified in three categories according to the item 6 which was : « on average, during the past week, how many puffs of short acting bronchodilators have you used each day ».[5] Category 1 was the non-users,

category 2 was the moderate user (1 to 4 puffs/d), category 3 was the overusers (5 to > 16 puffs/d). Using more than 4 puffs/d is going beyond the dose of salbutamol yielding optimal bronchodilation (that is inhaled 400 μg)[6].

The database used for this study was approved by the Ethics Committee of CHU Liege B70720096732 (2009/161) and all patients signed an informed consent.

Data from continuous variables were expressed as mean±SD or median (IQR) according to the distribution of the variable. As for continuous variables, demographic, spirometric and inflammatory features were compared between the three categories by using ANOVA or Kruskal-Wallis according to the distribution of the variables. In case of significance, pairwise comparisons were made by an unpaired t-test or a Mann-Whitney test. Data from categorical variables were expressed as proportion and the difference between the groups were analysed by performing a Chi-Square Test. Multiple logistic regression was performed to determine the variables which where independently associated with usage of rescue bronchodilators. P values < 0.05 were considered as statistically significant.

Thirteen percent of the patients (n=278) were classified as overusers, 42% were moderate users (n=900) and 45% (n= 989) were non-users of rescue bronchodilators. The use of rescue bronchodilators increased with the burden of maintenance treatment. Proportion of overusers were 8% (45/589), 7% (5/71), 7% (4/59), 10% (80/778) and 21% (118/570) in patients treated by SABA/SAMA only, montelukast only, ICS only, ICS-LABA and ICS-LABA + others respectively. The proportion of overusers in patients receiving OCS was 28% (19/69) and 22% (7/31) in a group of patients receiving other treatments (LAMA only, LABA only, LABA-LAMA and theophylline). Demographic, lung function and inflammatory parameters according to the use of rescue bronchodilators are given in Fig. 1A.

The proportion of current smokers gradually increased from 15% in the category of non-users to 29% in that of overusers ($p<0.001$). BMI was slightly higher in overusers than in non-users ($p<0.05$). Exacerbations rates in the 12 months prior to the visit were higher in overusers as compared to non-users and moderate users ($p<0.0001$ for both) and higher in moderate users as compared to non-users ($p<0.0001$).

FEV_1 % predicted, FEV_1/FVC % as well as PC20M gradually decreased from non-users to overusers ($p<0.0001$ for all). Moreover, the magnitude of the bronchodilation to salbutamol expressed as percent predicted increased from non-users to overusers ($p<0.01$).

Overusers had the greatest sputum eosinophil counts ($p<0.0001$ versus non-users, $p<0.01$ versus moderate users) while sputum neutrophil counts did not differ between the three groups. The proportions of patients with sputum eosinophil count ≥ 3% were 35% (251/712) in non-users, 39% (264/679) in moderate users and 51% (107/211) in overusers. There was no difference regarding FeNO levels between the three groups. With respect to systemic inflammatory parameters, overusers had significantly higher levels of total serum IgE, blood eosinophils and neutrophils as compared to non-users and moderate users (Fig. 1A). The proportion of patients with blood eosinophil counts ≥ 300/μl was 25% (236/937) in non-users, 26% (220/860) in moderate users and 36% (97/268) in overusers. After multiple logistic regression (Fig. 1B), young age, high BMI, current smoking, high exacerbations rate, low FEV1% predicted , low FEV1/FVC %, high blood neutrophil counts and high sputum eosinophil counts increased the risk of being overusers compared (n=156) to being non-overusers (n = 1146, merging moderate users and non-users).

This study shows that overusers of rescue bronchodilators represent 13% of the patients seen in an asthma clinic of a secondary/tertiary care centre, in which most of the patients were receiving maintenance treatment with ICS/LABA.

The relationship between rescue bronchodilators overuse and the rate of exacerbations is striking. Adding overuse of rescue bronchodilators in a risk prediction model of exacerbations in the future might be interesting to enhance the value of a model limited to biomarkers.[7,8] While the link between overuse of rescue bronchodilators and current smoking, overweight and exacerbation rate aligns with previous studies[2,3,9,10], it is the first study to show a relationship between overuse of rescue bronchodilators and the magnitude of sputum eosinophil counts in a real life setting. Our finding supports the concept that uncontrolled airway eosinophilia may trigger symptoms pushing patients to use reliever medications. Overuse of rescue medication should prompt the clinician to investigate the airway eosinophil content. Our study lends support to the MART strategy as well as to adding anti-IL-5 treatment in severe eosinophilic patients who continue to overuse bronchodilators. In two recent studies, sputum eosinophils have been found to correlate with the intensity of cough.[11,12] Interestingly, in contrast to sputum eosinophils, FeNO levels did not show the same relationship with rescue bronchodilators overuse. The impact of current smoking, known to dramatically reduce FeNO [13,14] may certainly blunt the relationship. Along with sputum eosinophil counts, blood eosinophil and neutrophil counts and total IgE were also increased in overusers. However, these systemic biomarkers were not anymore considered as independent risk factors after the multiple logistic regression, thereby indicating that sputum eosinophils remain the main determinant of reliever overuse among inflammatory parameters. Even when selecting

patients without smoking history, FeNO was not associated with overuse of bronchodilators after multiple logistic regression (n=606, data not shown).

Another finding that emerged from the current study is the importance of airflow limitation in triggering the use of rescue bronchodilators. In a large cohort of asthmatics receiving ICS/LABA we have recently found that impaired FEV_1 was related to dyspnea and chest tightness.[11] It is understandable that patients seek to improve airway calibre by using bronchodilator when feeling out of breath, even more so that the magnitude of bronchodilation to salbutamol appears to be greater in our cohort of overusers. In addition, the fact that young age makes asthmatics feel more intensively chest tightness[11] would explain why young age favours excessive reliever usage in the current study.

Limitation of our study to one week of observation precludes any conclusion on the long term use of β2 agonists so that we cannot exclude that patients classified as overusers the week they were investigated could have been in an exacerbations state[15] and have become non-users or moderate users a few weeks or months later. Conversely, some of our non or moderate users may have experienced later period with higher use of rescue bronchodilators. Another limitation concerns the potential non adherence to maintenance treatment as it is often the case in real-life, even in severe asthmatics[16] and good adherence to ICS-LABA was found to reduce SABA overdispensing.[16]

We conclude that approximately 15% of asthmatics referred to a secondary/tertiary centre overuse rescue bronchodilators, a clinical situation which is associated, not only with young age, smoking and overweight, but also with impaired spirometry and increased airway eosinophilic inflammation.

DECLARATIONS

Ethics approval and consent to participate

The study was approved by the CHU Liège ethics committee. Signed informed consent was obtained from patients upon their entry into the asthma clinic at CHU Liège. They agreed to the use of their clinical data and the health outcomes they reported in the routine setting for research purposes.

Competing interests

Outside of this submitted work, RL received unrestricted research grants from GSK, AstraZeneca, Sanofi and Chiesi, lecture or adboard fees from GSK, AZ, Novartis and Sonafi and participation on a data safety monitoring board from AstraZeneca. Outside of this submitted work, FS received grants or contracts from GSK, AstraZeneca, Chiesi and Novartis, consulting fees from GSK, AstraZeneca, Chiesi and Novartis, and lectures for GSK, AstraZeneca, Chiesi and Novartis. The rest of the authors declare that they have no relevant conflicts of interest.

Authors' contributions

FL, FS and RL contributed to the conception of the study. FG, VP, MS, FS and RL contributed to data acquisition. FL and RL performed statistical analysis. FL, GP, FS, and RL drafted and critically revised the work. All authors gave final approval of the manuscript.

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A)

	Total population (n=2167)	Non users (n=G8G)	Moderate users (n=G00)	Overusers (n=278)	ANOVA/Kruskal-Wallis test
Age (years)	51 (36-62)	53 (37-63)	48 (35-60)***	48,5 (40-60)	0,0037
Female gender N (%)	1274 (59)	576 (58)	536 (60)	166 (60)	/
BMI, kg/m²	26.7 ± 5.190	26.4 ± 5.007	26.8 ± 5.360	27.4 ± 5.261*	0,0403
Atopy, N (%)	1045 (52)	465 (50)	429 (52)	151 (57)	/
Smoking status, N (%)					
- Non smokers	1176 (54)	562 (57)	492 (55)	122 (44)	/
- Current smokers	422 (20)	149 (15)	190 (21)***	82 (29)****††	
- Ex smokers	570 (26)	278 (28)	218 (24)	74 (27)	
Season, N (%)					
- Summer	20 (441)	22 (215)	18 (160)	24 (66)	/
- Autumn	29 (633)	27.5 (272)	32 (287)	27 (74)	
- Winter	25 (532)	23 (230)	26 (232)	25 (70)	
- Spring	26 (561)	27.5 (272)	24 (221)	24 (68)	
Exacerbations in previous 12 months (n/patient/year)	0 (0-1)	0 (0-1)	0 (0-1)****	1 (0-2.75)****††††	<0,0001
FEV_1, % predicted	83 ± 21	87 ± 19	83 ± 21****	68 ± 22****††††	<0,0001
FEV_1/FVC, %	74 ± 11	76 ± 10	74 ± 12**	68 ± 13****††††	<0,0001
BDR, % predicted	4.1 ± 10	3.3 ± 10	4.8 ± 10**	5.4 ± 9*	0,0019
PC20M, mg/mL *(n=1125)*	3.4 (0.6-22)	4.7 (1-22)	2.5 (0.5-22)***	1.7 (0.2-7.7)**	<0,0001
FeNO, ppb *(n=2073)*	22 (13-40)	22 (13-37)	21 (12-41)	24 (11-52)	0,6702
Sputum eosinophils, % *(n=1C02)*	1.4 (0.2-7.2)	1.2 (0.2-5.6)	1.6 (0.2-7.6)	3 (0.4-20)****††	<0,0001
Sputum neutrophils, % *(n=1C02)*	61 (37-80)	63 (41-79)	59 (34-80)	58 (35-80)	0,1681
Blood eosinophils, cells/µL *(n=20C7)*	172 (100-316)	160 (92-300)	178 (101-300)	221 (107-386)***†	0,0009
Blood neutrophils, cells/µL *(n=20C7)*	3996 (3160-5312)	3954 (3108-5016)	3942 (3146-5315)	4662 (3600-6109)**††	0,0024
Total serum IgE, kU/L *(n=2018)*	101 (33-292)	96 (31-281)	96 (32-272)	136 (6-472)**††	0,0024

B)

Variables	Overusers *versus* Non-overusers		
	Odds ratio	*S5% CI*	*P-value*
Intercept	0,8083	0,1381 to 4,635	0,8120
Age	0,9750	0,9618 to 0,9883	0,0003(***)
Gender (male)	0,9132	0,6329 to 1,313	0,6252
BMI	1,056	1,020 to 1,094	0,0023(**)
Smoking habits			
- Current smokers	2,013	1,284 to 3,148	0,0022(**)
- Ex-smokers	1,531	0,9658 to 2,423	0,0689
Season			
- Autumn	0,6682	0,4077 to 1,094	0,1084
- Winter	0,7833	0,4694 to 1,302	0,3468
- Spring	0,8911	0,5389 to 1,472	0,6520
Exacerbations in previous 12 months (n/patient/year)	1,313	1,195 to 1,446	<0,0001(****)
FEV_1, % predicted	0,9818	0,9694 to 0,9943	0,0045(**)
FEV_1/FVC,%	0,9773	0,9554 to 0,9992	0,0444(*)
BDR, % predicted	1,003	0,9826 to 1,028	0,7763
FeNO, ppb	1,003	0,9977 to 1,007	0,2756
Sputum eosinophils, %	1,020	1,007 to 1,033	0,0028(**)
Sputum neutrophils, %	1,003	0,9945 to 1,012	0,4777
Blood eosinophils, cells/µL	0,5636	0,2909 to 1,005	0,0670
Blood neutrophils, cells/µL	1,064	1,022 to 1,118	0,0068(**)
Total serum IgE, kU/L	1,000	1,000 to 1,000	0,1048

A) Patient characteristics in the whole asthma cohort according to the use of rescue bronchodilators. Results are expressed as mean +/- SD or median (IQR): * p < 0.5 ; ** p < 0.01 ;*** p < 0.001 ; **** p < 0.0001 compared with non-users group and † p < 0.5 ; †† p < 0.01 ; ††† p< 0.001 ; †††† p < 0.0001 compared with moderate users group after unpaired t-test or Mann- Whitney according to the distribution.
BMI : body mass index; FEV1 : forced expiratory volume in 1 second; FVC : forced vital capacity; BDR : bronchodilation response
Seasons : Winter is December – January – February ; Spring is March – April – May; Summer is June – July – August ; Autumn is September – October – November.

B) Factors predicting overuse of rescue medication after multivariable logistic regression in the whole cohort