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Is CCL18 a potential biomarker of type-2 asthma endotypes?

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ABSTRACT

Objective: This exploratory cross-sectional study aimed to evaluate the associations between the chemokine ligand 18 (CCL18) blood level and phenotypic characteristics of asthma.

Methods: We evaluated in a sample of 173 asthmatic adult patients from the Cohort of Bronchial obstruction and Asthma (63.4% women; median age 50 ± interquartile range 27.5 years; median level of CCL18 was 44.1 ± interquartile range 27.5 ng/mL) the association between CCL18 blood level and allergic features of asthma using a multivariate analysis.

Results: We found an association between the log-transformed value of blood CCL18 and age (+0.7% [0.1; 1.3] per 1-year increase, $p = 0.033$), gender (−25.1% [−42; −3.2] in women, $p = 0.029$), and nasal polyposis (+38.1% [11.6; 70.9], $p = 0.004$). No association was observed between CCL18 level and the other main phenotypic characteristics of asthma.

Conclusions: Our exploratory study suggests that CCL18 is not an effective biomarker of allergic asthma endotype but may rather be a biomarker of tissue eosinophilia as supported by its association with nasal polyposis.

Abbreviations: CCL18: Chemokine (C-C motif) ligand 18; COBRA: Cohort of Bronchial obstruction and Asthma; IgE: Immunoglobulins E

KEYWORDS

Asthma; allergic; phenotype; endotype; biomarker; chemokine; CCL18

Asthma is a heterogeneous disease involving multiple pathophysiological mechanisms called endotypes. A personalized approach to treatment of asthma aims to target specific immune pathways using biologic therapies. Selecting the right biologic therapy requires to determine which endotype is involved in an individual patient, in particular type 2 (T2)-endotypes, for which biologic therapies are available. T2-endotypes broadly consist of the allergic and eosinophilic endotypes, which are targeted by anti-IgE and anti-IL5/IL5R antibodies, respectively, and more recently anti-IL4R

antibody. Currently, endotypes are characterized on the basis of clinical and biological features, called phenotypes. Basically, the allergic phenotype is defined by sensitization to aeroallergens and the presence of allergic rhinitis while the eosinophilic phenotype is designated by a blood eosinophils level above 300/mm³ and co-existence of nasal polyposis (1). Using these phenotypic criteria to choose a biologic therapy leads to 25%–39% of response failure (2,3). Therefore, identifying effective biomarkers of endotypes remains of major interest in asthma.

Table 1. Patient characteristics according to CCL18 level.

Variable	N	Whole population	CCL18 level		<i>p</i>
			≤ median	> median	
CCL18 (ng/mL), median ± IQR	173	44.1 ± 27.5	33.2 ± 13.1	60.8 ± 21.6	–
Demographic data					
Age (years), median ± IQR	171	50 ± 27.5	44 ± 28	56 ± 21.8	<0.001
Male gender, n (%)	172	63 (36.6)	28 (32.6)	35 (40.7)	0.34
BMI (kg/m ²), median ± IQR	172	24.4 ± 4.7	24.1 ± 5	25 ± 4.3	0.31
Smoking status, n (%)	171				0.50
Current smoker		1 (0.6)	0 (0)	1 (1.2)	
Former smoker		0 (0)	0 (0)	0 (0)	
Never smoker		170 (99.4)	86 (100)	84 (98.8)	
Comorbidities					
Ischemic heart disease, n (%)	172	5 (2.9)	1 (1.2)	4 (4.7)	0.37
Allergic conjunctivitis, n (%)	171	72 (42.1)	38 (44.2)	34 (40)	0.64
Atopic dermatitis, n (%)	171	37 (21.6)	19 (22.1)	18 (21.2)	>0.99
Allergic rhinitis, n (%)	170	120 (70.6)	67 (78.8)	53 (62.4)	0.028
Nasal polyposis, n (%)	170	38 (22.4)	11 (12.8)	27 (32.1)	0.003
Asthma characteristics					
Asthma control, n (%)	167				0.34
Optimal		70 (41.9)	40 (47.6)	30 (36.1)	
Suboptimal		51 (30.5)	23 (27.4)	28 (33.7)	
Unacceptable		46 (27.5)	21 (25)	25 (30.1)	
At least one exacerbation in the last year, n (%)	173	77 (44.5)	36 (41.4)	41 (47.7)	0.45
Inhaled corticosteroids, n (%)	173	153 (88.4)	73 (83.9)	80 (93)	0.09
Long-term oral corticosteroids, n (%)	173	28 (16.2)	10 (11.5)	18 (20.9)	0.10
Anti-IgE therapy, n (%)	173	31 (17.9)	11 (12.6)	20 (23.3)	0.08
Pulmonary function test					
FEV1/FVC ratio (%), median ± IQR	166	85.6 ± 18.7	87.7 ± 16.9	81.7 ± 21.9	0.06
FEV1/FVC ratio < 70%, n (%)	166	28 (16.9)	9 (10.6)	19 (23.5)	0.037
FEV1 observed/predicted (%), mean ± SD	166	81.7 ± 22	84.2 ± 21.6	79.1 ± 22.3	0.14
FVC observed/predicted (%), mean ± SD	166	96.7 ± 17.7	97.1 ± 19.1	96.3 ± 16.2	0.76
Biology					
Positive skin tests, n (%)	116	82 (70.7)	45 (79)	37 (62.7)	0.07
Total IgE blood test (UI/mL), median ± IQR	156	170 ± 443.8	135 ± 252.5	211 ± 560	0.020
Blood eosinophil (cells/mm ³), median ± IQR	150	215 ± 282.5	205 ± 269.3	235 ± 277.5	0.18
Blood eosinophil > 300 cells/mm ³ , n (%)	150	53 (35.3)	22 (30.6)	31 (39.7)	0.31

N—number of patients with no-missing data; IQR—interquartile range; SD—standard deviation; BMI—body mass index; FEV1—forced expiratory volume in 1 s; FVC—forced vital capacity.

Characteristics of patients with values lower or higher than the median of CCL18 were compared using Student's *t* tests or Wilcoxon tests if non-normal distribution for quantitative variables, and using exact Fisher tests for qualitative variables.

The chemokine ligand 18 (CCL18) is a potential biomarker of allergic asthma. Indeed, it is elevated in bronchoalveolar lavage and serum from untreated allergic asthmatic patients (4) and in many allergic conditions, such as atopic dermatitis, allergic rhinitis and vernal conjunctivitis (5,6). Moreover, CCL18 has a pro-T2 activity including the ability to recruit Th2 cells and basophils, to activate basophils and to induce macrophages alternative maturation (5). However, there is a lack of data on the relationship between CCL18 levels and asthma endotypes.

Biomarkers help for providing an understanding of the molecular pathways and the discovery of new targets for novel therapies. For clinical practice, biomarkers can be used for several purposes, in particular disease diagnosis and staging, assessment of disease progression and treatment response. Useful biomarkers must be strongly associated, and, beyond, accurately predict clinical disease outcomes leading to obtain high predictive values.

In order to evaluate CCL18 as a potential biomarker of asthma endotypes, this exploratory study

aimed to evaluate, as a first step, the associations between CCL18 levels and phenotypic characteristics of asthma.

This cross-sectional study included a sample of patients from the Cohort of Bronchial obstruction and Asthma (COBRA), which included asthma patients aged between 18 and 85 years from January 2007 to December 2015 in 12 French academic institutions (7). All severities and levels of asthma control were included. The COBRA cohort was approved by the CPP Ile-de-France I ethics committee (number 09–11962) and all subjects gave their written informed consent.

The following data were collected: demographic and clinical characteristics including asthma control (GINA 2006 classification [optimal, suboptimal, unacceptable], at least one exacerbation in the last year), skin prick-tests with 11 aero-allergens, total immunoglobulins E (IgE) and blood eosinophil levels, and spirometry. Serum level of CCL18 was measured from the COBRA biological collection by Specific Enzyme Linked Immunosorbent assay according to

Table 2. Association between CCL18 levels and patient characteristics.

Variable	Univariate analysis		Multivariate analysis (<i>n</i> = 133)	
	% change [95%CI]	<i>p</i>	% change [95%CI]	<i>p</i>
Demographic data				
Age, per 1-year increase	1.2 [0.7; 1.6]	<0.001	0.7 [0.1; 1.3]	0.033
Gender (reference = male)	−14.7 [−27.3; 0.1]	0.05	−25.1 [−42; −3.2]	0.029
BMI per 1 kg/m ² increase	2.0 [−0.5; 4.7]	0.12	0 [−3.2; 3.2]	0.98
Comorbidities				
Ischemic heart disease	82 [15.3; 187.2]	0.011	51.8 [−5.7; 144.6]	0.09
Allergic conjunctivitis	−9.9 [−23.1; 5.6]	0.20	−6.5 [−22; 12.1]	0.47
Atopic dermatitis	−12.9 [−27.9; 5.3]	0.16	−7.1 [−25.9; 16.5]	0.53
Allergic rhinitis	−11 [−25.1; 5.7]	0.19	−9.6 [−26.3; 10.9]	0.34
Nasal polyposis	49.9 [25.3; 79.4]	<0.001	38.1 [11.6; 70.9]	0.004
Asthma characteristics				
Asthma control (reference = optimal)	—	—	—	—
Suboptimal	4.6 [−13.6; 26.6]	0.64	−1.4 [−20.5; 22.5]	0.90
Unacceptable	10.8 [−9; 34.9]	0.31	−1.5 [−21; 22.7]	0.89
At least one exacerbation in the last year	5.7 [−9.6; 23.6]	0.49	—	—
Inhaled corticosteroids	27.1 [−0.1; 61.7]	0.05	17.3 [−11.3; 55.2]	0.27
Long-term oral corticosteroids	16.2 [−5.8; 43.4]	0.16	3.5 [−19.2; 32.8]	0.78
Anti-IgE therapy	10.6 [−9.7; 35.4]	0.33	12.4 [−11.6; 42.9]	0.34
Spirometry testing				
FEV1/FVC ratio, per 1 % increase	−0.6 [−1.2; −0.1]	0.029	−0.1 [−0.7; 0.6]	0.80
FEV1/FVC ratio < 70%	24 [0.4; 53.2]	0.047	—	—
FEV1 observed/predicted, per 1 % increase	−0.3 [−0.7; 0]	0.06	—	—
FVC observed/predicted, per 1 % increase	−0.2 [−0.6; 0.3]	0.44	—	—
Outcomes of asthma phenotype				
Positive skin tests	0.2 [−19.2; 24.4]	0.98	—	—
Total IgE blood test, per 100 UI/mL increase	0.8 [−0.7; 2.4]	0.30	0.3 [−1.3; 1.9]	0.75
Blood eosinophil, per 100 cell/mm ³ increase	0.6 [−0.6; 1.8]	0.34	—	—
Blood eosinophil/ > 300 cells/mm ³	16.5 [−2.5; 39.1]	0.09	3.2 [−15; 25.3]	0.75

the manufacturer's instructions. Coating (MAB394 monoclonal antibody) and biotinylated (BAF394 polyclonal antibody) antibodies were provided by R&D system. Recombinant human CCL18 (394-PA; R&D system) was used as standard diluted from 2000 pg/ml to 31.25 pg/ml.

In order to evaluate the association between CCL18 levels and patients' characteristics, we log-transformed CCL18 values to obtain normalized distribution. Then, we studied associations using (i) univariate linear regressions, and (ii) a multivariate linear regression model. This model included outcomes of the disease—excluding collinear variables (e.g. allergic rhinitis with positive prick tests)—and was adjusted for potential confounding factors defined *a priori* (sex, age, height, body mass index, coronary heart disease, conjunctivitis, atopic dermatitis, oral and inhaled corticosteroids and anti-IgE therapy). Since CCL18 values were log-transformed, the regression coefficients were expressed as the percent of change in CCL18 levels [95% confidence interval] per unit of change in the explanatory variable. To this end, they were back-transformed (multiplying by 100 and subtracting 100%). In addition, we performed a sensitivity analysis in patients with an unacceptable asthma control (only the univariate analysis was performed due to low number of patients). Statistical analyzes were performed using R software, version 3.6.2 (R Core Team

(2019). R: A language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria). The threshold for statistical significance was set at *p* < 0.05.

One hundred seventy-three patients were included, mostly women (63.4%) with a median ± interquartile range age of 50 ± 27.5 years (Table 1). A majority of subjects (88.4%) received inhaled corticosteroids, 16.2% long-term oral corticosteroids, and 17.9% anti-IgE therapy. Asthma control was unacceptable and suboptimal in 27.5% and 30.5% of patients, respectively. A total of 70.7% patients had at least one positive skin prick-tests, and 35.3% showed blood eosinophilia >300 cells/mm³. The median level of CCL18 was 44.1 ± 27.5 ng/mL.

In univariate analysis, CCL18 level was associated with age (+1.2%, [0.7; 1.6] per 1-year increase, *p* < 0.001), ischemic heart disease (+82% [15.3; 187.2], *p* = 0.011), nasal polyposis (+49.9% [25.3; 79.4], *p* < 0.001), and FEV1/FVC ratio (−0.6% [−1.2; −0.1] per 1-percent increase, *p* = 0.029). In multivariate analysis, we observed an association with age (+0.7% [0.1; 1.3] per 1-year increase, *p* = 0.033), gender (−25.1% [−42; −3.2] in women, *p* = 0.029) and nasal polyposis (+38.1% [11.6; 70.9], *p* = 0.004) (Table 2). In patients with unacceptable asthma control, CCL18 level was associated with nasal polyposis (+60.2% [11; 131.3], *p* = 0.016) in univariate analysis (data not shown).

In this study that investigated CCL18 as a potential biomarker of allergic asthma endotypes, we only observed a significant but moderate association between CCL18 level and nasal polyposis in multivariate analysis, as previously reported (8) in particular in eosinophilic nasal polyposis (9). We did not find any significant association between CCL18 and asthma control, phenotypic features of allergic asthma and blood eosinophilia neither in the whole population, nor in poorly controlled patients who were likely to have active airway inflammation. Other studies with larger samples might be able to observe statistically significant associations with these asthma outcomes, but the strength of the association, which must be high for a biomarker to be potentially useful, is independent of the statistical power and unlikely to be much higher than in our study.

The main limits of the study were the presence of missing data, the lack of induced sputum preventing from eosinophilic airway inflammation evaluation, and the heterogeneity in severity and level of control of asthma.

Conclusion: Although additional studies on homogeneous populations in terms of severity and treatments could improve the relevance of our results, our exploratory study suggests that CCL18 is not an effective biomarker of allergic asthma endotype. However, the link between CCL18 and nasal polyposis, an eosinophilic airway disease associated with a better response to anti-IL5R therapy, suggests to study CCL18 as a biomarker of eosinophilic asthma endotype using eosinophils count in induced sputum. In addition, CCL18 should be evaluated as a biomarker of response to type 2-targeted therapies, in particular the anti-IL5 therapies.

Declaration of interest

There are no specific conflicts of interest for this study.

Helen Fouquet, Jonathan Giovannelli, Patricia de Nadaï and Joanne Balsamelli declare no conflict of interest.

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Authors' contribution

Helen Fouquet substantially contributed to conception and design of the study, acquisition of data, analysis and interpretation of data, participated in revising the manuscript for important intellectual content and gave final approval of the version to be submitted version.

Jonathan Giovannelli and Cécile Chenivresse substantially contributed to conception and design of the study, acquisition of data, analysis and interpretation of data, participated in drafting the manuscript and gave final approval of the version to be submitted version.

Patricia de Nadaï and Joanne Balsamelli substantially contributed to acquisition of data, analysis and interpretation of data, participated in revising the manuscript for important intellectual content and gave final approval of the version to be submitted version.

Patrick Berger, Arnaud Bourdin, Pascal Chanez, Stéphanie Fry, Thierry Perez, Antoine Magnan, Marina Pretolani, Camille Taillé, Anne Tscopoulos substantially contributed to acquisition of data, participated in revising the manuscript for important intellectual content and gave final approval of the version to be submitted version.

Data availability statement

Data supporting the findings of this study are available within the article. Raw data can be provided upon justified request to the corresponding author.

Ethics approval and consent to participate

The COBRA cohort was approved by the CPP Ile-de-France I ethics committee (number 09–11962) and all subjects gave their written informed consent.

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