Lung nucleosomes containing histone 3.1: a new biomarker for monitoring asthma response to mepolizumab?

Granger V.[1,2], Chollet-Martin S.[1,2], de Chaisemartin L.[1,2], Camille Taillé C [3,4]

[1] Service d'Immunologie "Autoimmunité, Hypersensibilités et Biothérapies", Hôpital Bichat, APHP, [2]Université Paris-Saclay, Inserm, « Inflammation, microbiome immunosurveillance », 91190 Orsay, France,[3]Pneumology Department, Reference Center for Rare Pulmonary Diseases, Bichat Hospital, APHP, Paris, France, [4]Institut National de la Santé et de la Recherche Médicale, Unit 1152, University of Paris Cité, Paris, France.

BACKGROUND

A growing number of studies highlight the relevance of **cell free nucleosomes** as biomarkers of **acute and chronic inflammatory diseases** such as sepsis, acute respiratory distress syndrome or cancer. Here, we evaluated the **association of cell-free H3.1 nucleosomes**, a new surrogate marker for extracellular chromatin, in **severe asthma patients treated by anti-IL-5 therapies**

METHODS

Nucleosomes containing histone 3.1 (**Nu.H3.1**), or citrullinated histone H3R8 (**Nu.Cit-H3R8**) were measured in **bronchoalveolar lavage fluid** (BAL) supernatants from **27 severe asthma patients** of the REMOMEPO study, **before mepolizumab introduction** (J0: N=23), **at 6 months** (M6: N=23) and at **12 months** (M12: N=17), using novel sandwich ELISA immunoassays (Belgian Volition, Isnes, Namur, Belgium). Longitudinal analyses investigated the associations between their variations at M6 and M12 and concomitant asthma characteristics (clinical response assessed according to the GETE score, asthma control, pulmonary function).

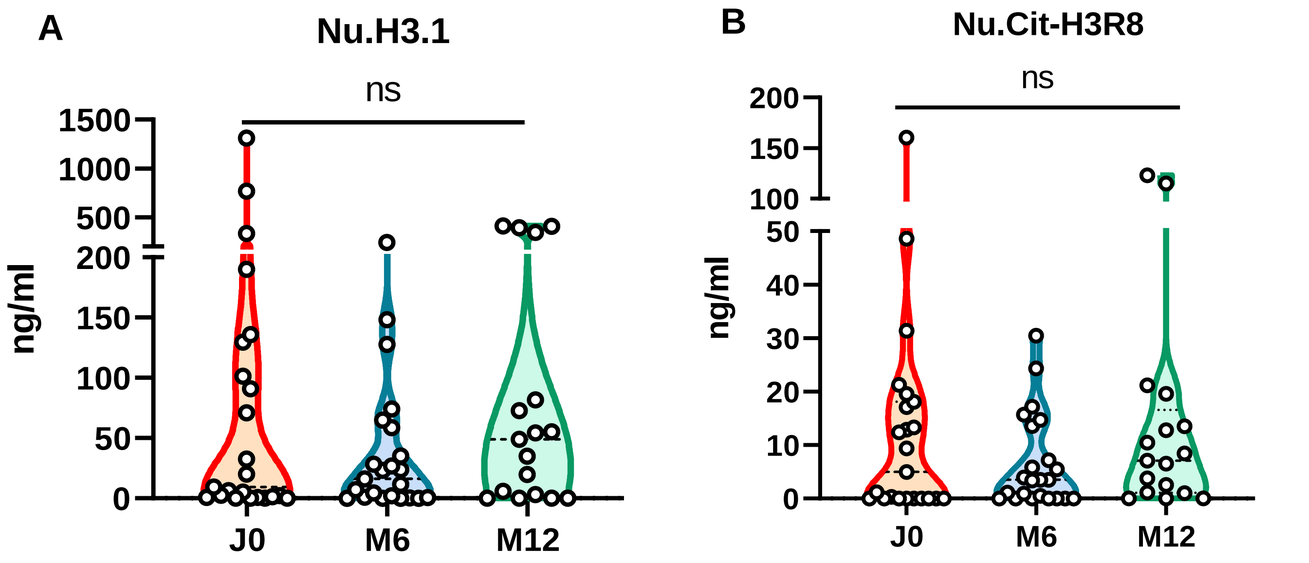
Baseline demographic, clinical and laboratory features of the Cohort

Participants, n	27
Age (Mean ± SD)	50.8±11.9
Sex (Women %)	60.0
Body mass index, Kg.m^{-2} (Mean ± SD)	27.1±5.7
Smoking habits (%)	
Non-smoker	48.0
Ex-smoker	52.0
Age of asthma onset (Mean ± SD)	29.7±17.0
Exacerbations (past 6 months), median [Q1-Q3]	2.0 [1.5-3.5]
Asthma control (ACT) median [Q1-Q3]	15 [12-18]
Uncontrolled (ACT<20) %	88.0
Controlled (ACT≥20) %	12.0
Clinical response at M12	
Optimal (GETE 1) %	62.5
Sub-optimal (GETE 2) %	37.5
OCS %	48.0
FEV$_1$ % pred (Mean ± SD)	74.1±21.8
FEV1/FVC (Mean ± SD)	65.2±12.7
Atopy %	28.0
Total IgE IU.ml^{-1} median [Q1-Q3]	188 [135-389]
Blood Eosinophils Count cells.mm^{-3} median [Q1-Q3]	410 [200-520]
Serum EDN ng.ml^{-1} median [Q1-Q3]	67 [48-219]
BAL Eosinophils Count cells 10^3 ml^{-1} median [Q1-Q3]	31.7 [10.7-225.0]

27 patients with severe asthma were recruited from the REMOMEPO study
28% were atopic and 88% had a poor control of the disease before mepolizumab administration. The mean age was 50.8 years and 60% were women.

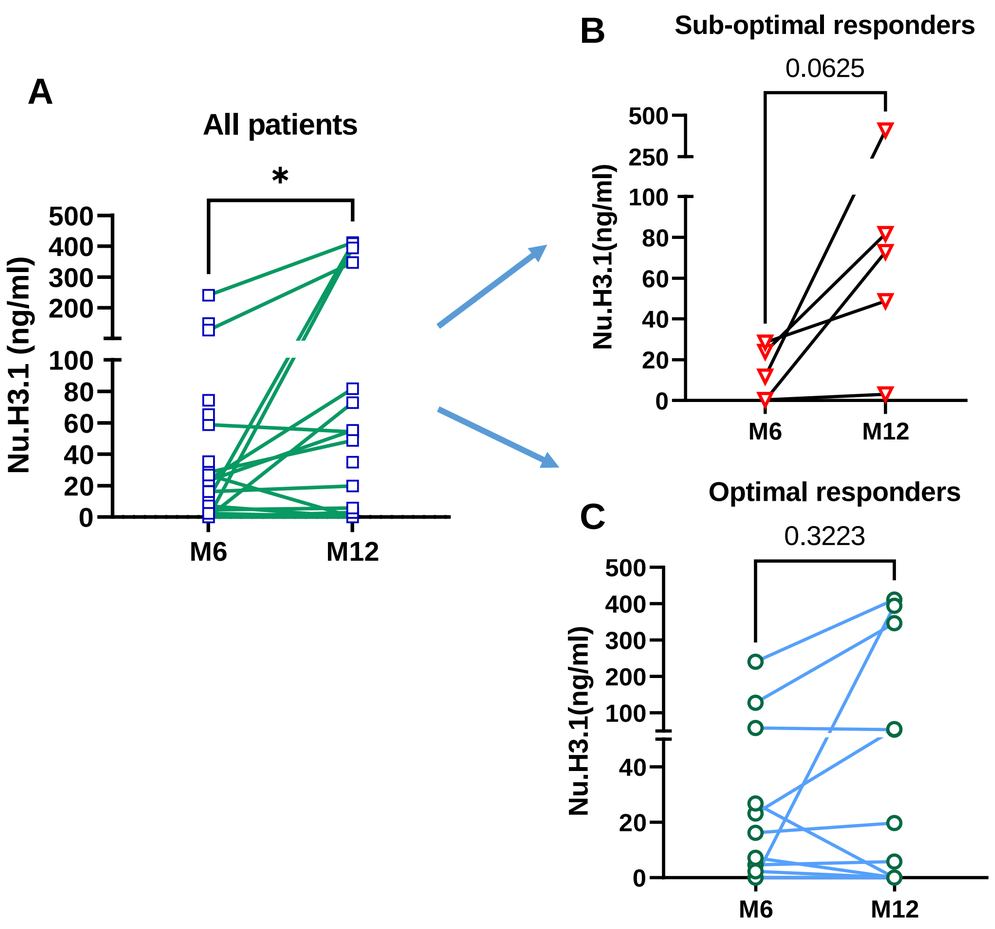
FEV1, forced expiratory volume; FVC, forced vital capacity ; ACT, Asthma control test; GETE, global evaluation of treatment effectiveness; EDN, Eosinophil-Derived Neurotoxin; BAL, bronchoalveolar lavage fluid; OCS, oral corticosteroids

Nucleosomes level remained stable in BAL during the first year of mepolizumab administration



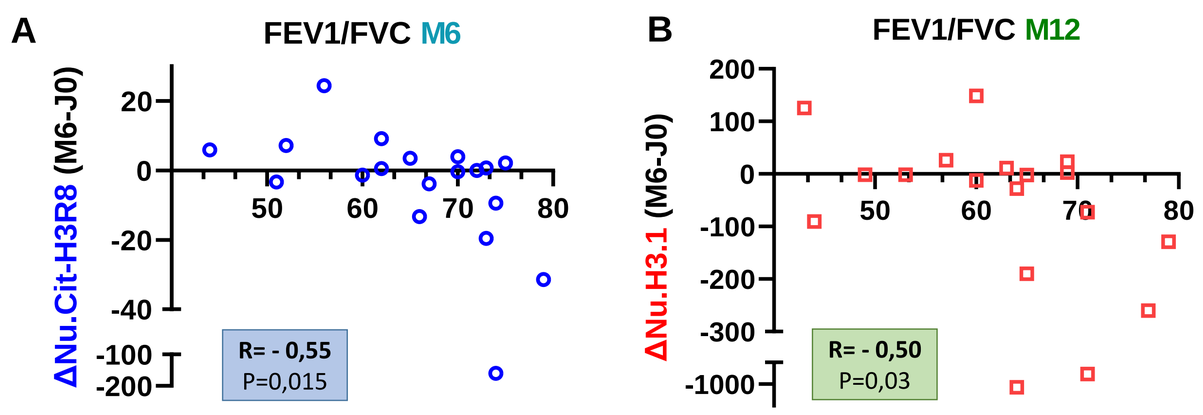
(A) BAL Nu.H3.1 levels did not significantly differ before/after mepolizumab introduction (J0: 9 [0.7-130] ng/ml ; M6: 16 [0.7-59] ng/ml ; M12: 49 [1.5-214], p = 0.15)
(B) Nu.Cit-H3R8 were present at low level in BAL and remained stable during the first year of mepolizumab administration (J0: 5 [0-18] ng/ml ; M6: 4 [0-14] ng/ml ; M12: 7 [1-17] ng/ml, p = 0.30).
Mixed-effects models were used for statistical analysis

Increase in BAL Nu.H3.1 level at M12 seems to be associated with sub-optimal clinical response to mepolizumab



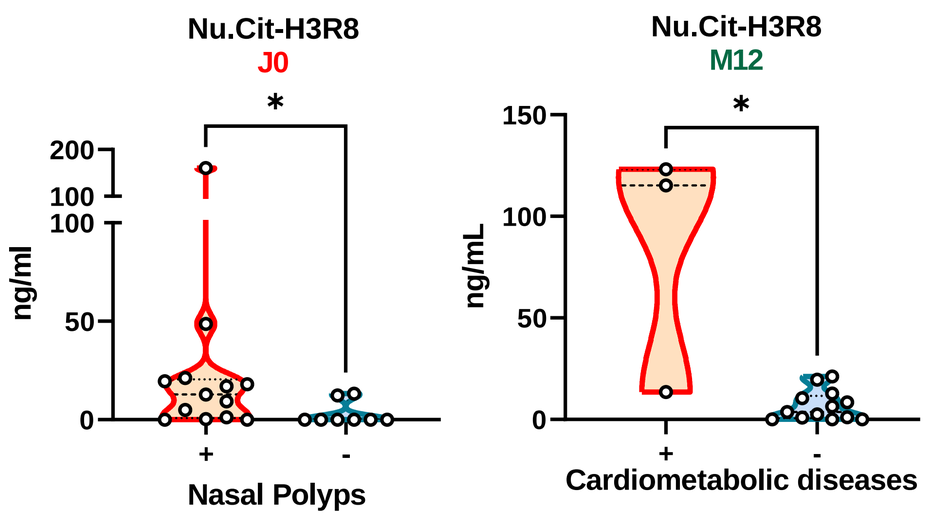
BAL Nu.H3.1 Kinetic was restricted to the M6-M12 period in all patients (A), sub-optimal responders (B) and optimal responders (C)
Non parametric paired analyses showed a significant increase in Nu.H3.1 level at M12 compared to M6 (A : p=0,03), in particular among patients with sub-optimal clinical response (B : p=0,06), whereas NuH3.1 did not significantly differ between M6 and M12 among optimal responders (C: p=0,3)

Reduction in nucleosomes levels at M6 was associated with higher FEV1/FVC at M6 and M12



(A) Absolute Nu.Cit-H3R variation in BAL (delta Nu.Cit-H3R8 = Nu.Cit-H3R8 at M6 – Nu.Cit-H3R8 at J0) was negatively correlated with FEV1/FVC at M6
(B) Absolute Nu.H3.1 variation in BAL (delta Nu.H3.1 = Nu.H3.1 at M6 – Nu.H3.1 at J0) was negatively correlated with FEV1/FVC at M12
R= spearman correlation coefficient

Presence of nasal polyps or cardiometabolic diseases are potential confounding factors for BAL nucleosomes monitoring



(A) Baseline Nu.Cit-H3R8 was significantly higher among patients with nasal polyps (With nasal polyps: 13 [1-20] ng/ml ; without nasal polyps: 0 [0-9] ng/ml, p = 0,01)
(B) At M12, Nu.Cit-H3R8 was significantly higher among patients with cardiometabolic diseases (With cardiometabolic diseases : 115 [14-123] ng/ml ; Without cardiometabolic diseases : 4 [0,5-12] ng/ml, p = 0,01)

Conclusion : The concentration of **lung Nu.H3.1 nucleosomes** seems linked to **clinical response** and **pulmonary function improvement** in patient treated with **mepolizumab**. Because of potential confounding factors, larger-scale studies are needed to confirm the interest of this potential new biomarker to monitor mepolizumab response during asthma.