Dupilumab effectiveness in Biologic-Naïve and switched severe asthma in real life

To the Editor, this retrospective observational study reports our 18-month real-life experience with dupilumab in 115 patients with severe asthma (including 68 patients who switched from another biologic: 17 from anti-IgE, 32 from anti-IL-5 and 19 from anti-IL-5R and 47 biologic-naïve patients) recruited at the University Hospital of Liege, Belgium between 2020 and 2025. The time between the switch from the prior biologic to dupilumab was 44 (35-52) days and the reasons of the change were: persistent exacerbations (n=10); uncontrolled nasal polyposis (n=15); concomitant severe atopic dermatitis (n=3); lack of asthma control (n=5); or a mix of those associated with fall of lung function and/or inability to stop maintenance oral corticosteroids (mOCS, n=35).

Out of the 115 patients, 64 had an 18-month visit. Only 13 stopped the dupilumab after 6 months due to insufficient response mainly in terms of exacerbations persistence or absence of asthma polyposis/asthma control.

Recent randomized clinical trials (RCTs) showed that dupilumab improved asthma control, reduced the exacerbation rate and fractional exhaled nitric oxide (FeNO), and improved lung function and forced oscillation technique (FOT) parameters in patients with moderate-to-severe asthma [1,2].

In this study, we analyzed, as primary outcome, the impact of dupilumab on exacerbation rate. The secondary outcomes included the impact on mOCS, daily dose of inhaled corticosteroids (ICS), asthma control and quality of life (assessed by ACT, ACQ and AQLQ), lung function assessed by spirometry and FOT, systemic inflammation and airway inflammation evaluated with FeNO and induced sputum cell counts.

The demography characteristics of the patients are presented in the supplementary material table 1 and the results were addressed for the whole cohort (supplementary material table 2), for the cohort of patients who switched and for the biologic-naïve cohort (supplementary material table 3 and 4)

The evolution of exacerbation rate since baseline was studied using a negative binomial regression model with repeated measurements. The exacerbation rate significantly decreased from baseline (OR=8.86, CI: 5.3-14.7, $p<0.0001$ for 6 months vs baseline and OR=7.37, CI: 4.4-12.4, $p<0.0001$ for 18 months vs baseline). After 6 months, the average reduction was 88.8 ± 31.8% and was 91.0 ± 20.2% after 18 months in the whole population. The exacerbation rate was significantly reduced over time in the group of patients who switched and in the biologic-naïve group. The reduction was significantly higher in the group of biologic-naïve patients compared to patients who switched

(adjusted OR=8.76, CI: 5.3-14.6, p<0.0001 for 6 months vs baseline and adjusted OR=7.45, CI: 4.2-13.1, p<0.0001 for 18 months vs baseline; group: adjusted OR=3.03, CI: 2.0-4.6, p<0.0001 between both groups, Figure 1A). The result was similar when the model was adjusted for age, smoking status (pack-years), presence of nasal polyposis, OCS and blood eosinophils.

The linear mixed model was not able to assess the impact on OCS dose reduction due to a limited amount of data. The reduction of ICS dose equivalent was not significant. ACT, ACQ and AQLQ scores significantly improved from baseline (p<0.0001). All the lung function parameters evaluated positively over time. The pre-bronchodilation (BD) and post-BD FEV_1 varied over time (p=0.0007 or 0.0005 in L, p<0.0001 in percentages), especially during the first 6 months after baseline with, on average, a lung function improvement (increase of 0.12±0.36 L or 4.51±11.57% in pre-BD and increase of 0.12±0.34 L or 4.31±10.90 % in post-BD). When we looked closely, 58 patients (50.4%) and 27 patients (42.2%) had an increase of pre-BD FEV_1 of at least 100 ml after 6 months and 18 months respectively. No significant evolution from baseline was detected for oscillometry. FeNO decreased significantly from baseline (p<0.0001, decrease from 33ppb at baseline to 19.5ppb after 6 months or 16ppb after 18 months). A significant change from baseline was detected for total serum IgE (p<0.0001) and blood eosinophil counts (BEC, p<0.0001).

By adjusting by covariates, most of continuous measures did not significantly differ between the switched and the biologic-naïve patients. Nevertheless, the ACQ score improved more significantly in the biologic-naïve group (interaction p=0.035, Figure 1B), the BEC significantly increased from baseline in the switch group but not in the biologic naïve group (interaction p < 0.0001, Figure 1C) and there was a significant decrease of plasma fibrinogen between baseline and the 18-month visit only for the switch group (interaction p=0.0012, Figure 1D). A trend (interaction p=0.051) for a higher decrease in sputum eosinophil percentage (SEP) was also observed in the biologic-naïve group after the first 6 months of dupilumab (Figure 1E).

The rebound in BEC within the biologic-switched cohort was mainly observed in the group of patients treated with anti-IL5/IL-5R treatment (Figure 2 and supplementary material Table 5), and a rise in BEC after stopping anti IL-5 therapy was already showed in the literature [3]. In contrast, the SEP trajectory tended to diverge in the biologic-naïve group. Indeed, a trend for a decrease was observed in the biologic naive group that could be explained by a reduction in eotaxin production mediated by IL-4 and IL-13 [4].

The clinical significance of this increase in BEC was analyzed in the 11 patients who presented a BEC ≥ 1000 cells/ µl at 6 months and who had a follow-up at 18 months vs 52 patients who presented a value < 1000 cells/ µl at 6 months and who had a 18-month visit. None had deleterious effects of this hypereosinophilia. This confirmed what was recently reported [4,5] and showed that dupilumab, in contrast to anti IL-5 and anti-IL-5R therapy, does not control systemic eosinophilic inflammation but probably inhibits eosinophil recruitment and activation, thereby resulting in a clinical improvement. Univariate logistic regression was considered to model the association between an improvement in post-BD FEV_1 expressed as predicted % (delta between 6 and 18 months ≥ 0% vs <0%) and a set of covariates. We found that the presence of nasal polyposis (OR:3; CI: 1.1-8.6, p=0.04) and a previous treatment with mepolizumab (OR:3; CI: 1.048-9.276) were linked to a stable/improved lung function. We evaluated if a persistent high BEC at 6 months ≥ 1000 cells/ µl (OR=8.1; CI: 1.8-56.5, p=0.012) and a high SEP at 6 months (OR=1.1; CI: 1.022-1;221, p=0.026 for n=37 data) impacted lung function and found that they were associated with a stable/improved lung function, suggesting the absence of eosinophil activation under dupilumab treatment. The multivariate logistic regression analysis combining mepolizumab and BEC at 6 months ≥ 1000 cells/ µl showed that the impact of mepolizumab disappeared when associated with high BEC. The model did not find significant association between BEC or SEP at 6 months after dupilumab and an improvement of ACT or ACQ at 18 months.

Superresponse at 6 months and remission at 18 months were defined as 0 exacerbation, no OCS, ACT ≥20 or ACQ ≤ 1.5 and FEV_1 ≥80%, we observed that 31% of patients (n=36/115) were super-responders after 6 months with 23% of biologic-naïve patients (=11/47) and 37% of switchers (25/68). After 18 months of treatment with dupilumab, 41% patients achieved remission (=26/64) including 26% of biologic-naïve patients (=7/23) and 46% of patients who switched (=19/41).

In conclusion, this study confirms the long-term efficacy of dupilumab in both naïve and biologic-switched patients [6]. Although the sample size was limited, this real-world analysis provides valuable insights into the multifaceted effects of dupilumab in biologic-naïve and switched severe asthma patients, a facet less explored in previous RCTs.

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Data sharing: The datasets used during the current study are available from the corresponding author on reasonable request.

Acknowledgements: CM and **MS** participated in the study design, performed the research and data analysis and wrote the manuscript; **AO**, **NM, RB, FR, SG, SG, MSN, AR, VP, FG**, **SZ and CS** participated in the sputum induction and processing and patient data collection. **ME** performed and reviewed the statistical analyses. **CD**, **FS** and **RL** designed the study and interpreted the data. All authors participated in the manuscript reviewing and gave final approval of the manuscript and ensured that questions related to the accuracy or integrity of any part of the work were appropriately investigated and resolved. The authors thank the pneumology department staff of the CHU of Liege, Belgium and the EOS program number O-0001422RG3330.

Conflict of interests: CM, MS, AO, NB, RB, FR, SG, SG, MSN, AR, VP, FG, SZ, CS, ME and CD have no conflicts to declare. **RL** and **FS** had educational and research grants from GSK, AstraZeneca, Sanofi, Novartis and Chiesi. Also, **RL** and **FS** received consulting fees from GSK and AstraZeneca (national and international advisory boards). **RL** and **FS** received lecture fees from GSK, AstraZeneca, Novartis and Chiesi.

Figure Legend

Figure 1A Evolution of annualized asthma exacerbation rate, globally and in both groups (mean and SE)

Figure 1B Evolution of ACQ scores (mean and SE), by group and globally

Figure 1C Evolution of BEC (mean and SE), by group and globally

Figure 1D Evolution of blood fibrinogen (mean and SE), by group and globally

Figure 1E Evolution of SEP (mean and SE), by group and globally

Figure 2 Evolution of BEC (mean ± SE) with respect to the previous biotherapy

Figure 1

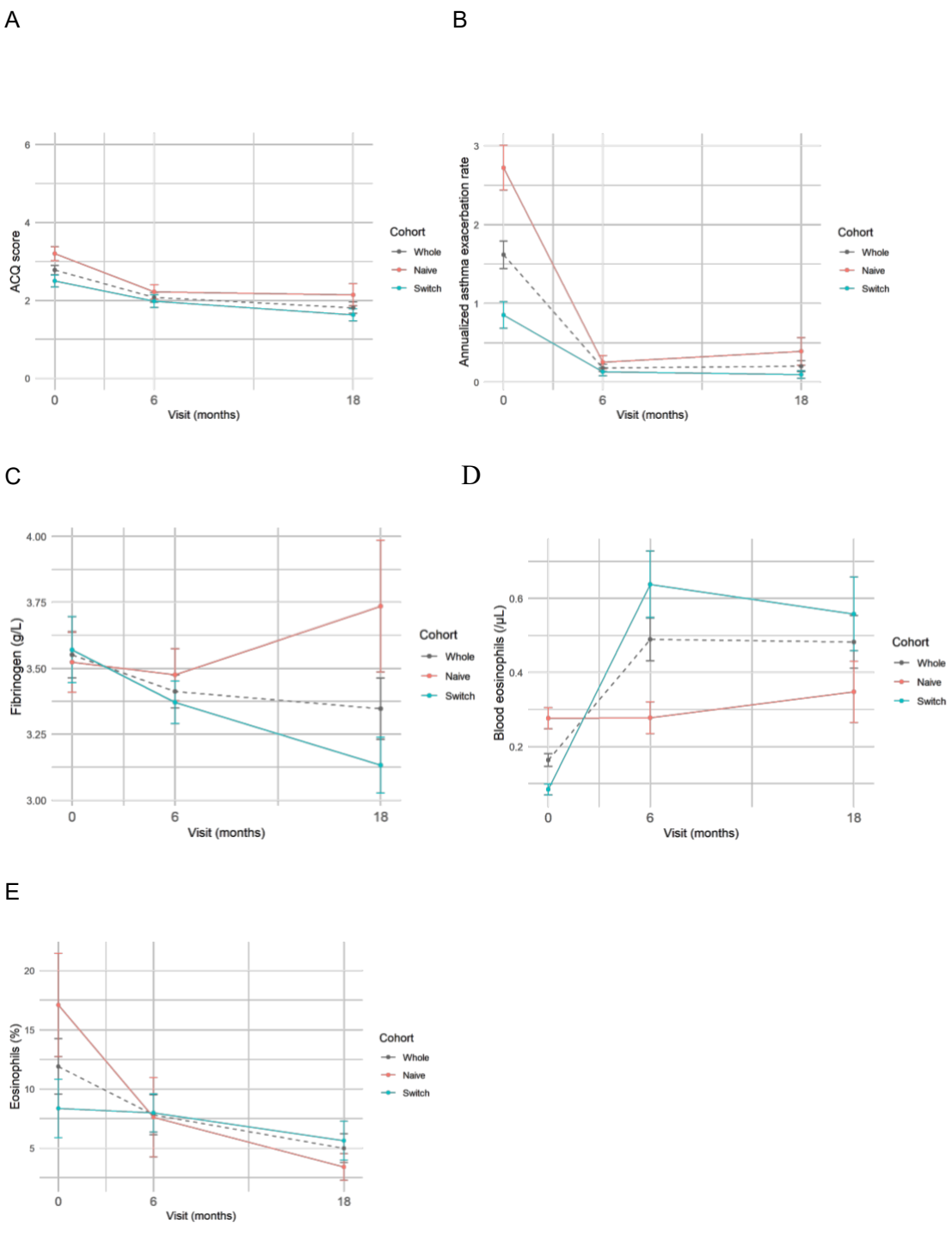
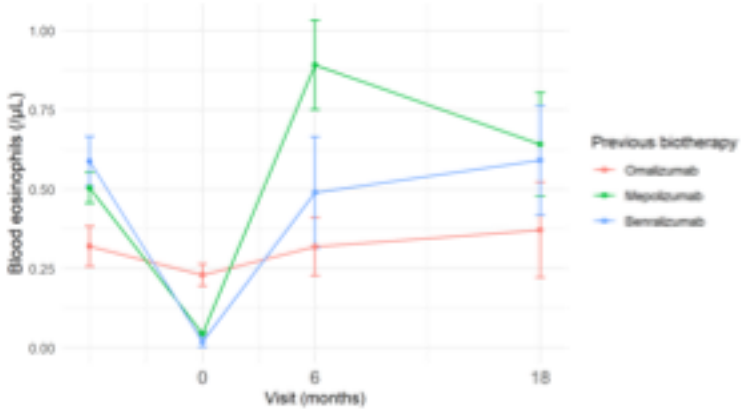

A
B
C
D
E
ACQ score
Annualized asthma exacerbation rate
Fibrinogen (g/L)
Blood eosinophils (/μL)
Eosinophils (%)
Visit (months)
Cohort
Whole
Naive
Switch

Figure 2


1.00
0.75
0.50
0.25
0.00
Blood eosinophils (/µL)
0
6
18
Visit (months)
Previous biotherapy
Omalizumab
Mepolizumab
Benralizumab

Supplementary material

Table 1 Baseline characteristics of patients from the whole cohort (N=115) and comparison between two groups

Variable	N	Whole cohort n (%) Mean ± SD Med (Q1; Q3)	N	Biologic-Naïve patients n (%) Mean ± SD Med (Q1; Q3)	N	Switched Patients n (%) Mean ± SD Med (Q1; Q3)	p-value
Sex, M	115	54 (47.0)	47	26 (55.3)	68	28 (41.2)	0.14
Age (years)	115	54.3 ± 15.1	47	57.5 ± 15.6	68	52.1 ± 14.4	0.059
BMI (kg/m²)	115	25.9 ± 5.1	47	26.5 ± 5.1	68	25.5 ± 5.0	0.33
Smoking status	115		47		68		0.0061*
NS		57 (49.6)		15 (31.9)		42 (61.8)	
ES		45 (39.1)		24 (51.1)		21 (30.9)	
CS		13 (11.3)		8 (17.0)		5 (7.4)	
(Ex-) and Non smoker	115	58 (50.4)	47	32 (68.1)	68	26 (38.2)	0.0016*
Current smoker	115	13 (11.3)	47	8 (17.0)	68	5 (7.4)	0.11
Pack-years	114	1 (0; 20)	46	13.3 (0.0; 33.0)	68	0.0 (0.0; 12.5)	0.0013*
Atopy	115	66 (57.4)	47	26 (55.3)	68	40 (58.8)	0.71
Nasal polyposis	115	51 (44.3)	47	12 (25.5)	68	39 (57.4)	0.0007*
Exacerbation rate	115	1 (0; 2)	47	2 (2; 3)	68	0 (0; 1)	<.0001*
ACT score	111	13.59 ± 5.84	45	12.33 ± 5.40	66	14.45 ± 6.01	0.060
ACQ score	113	2.78 ± 1.30	45	3.20 ± 1.22	68	2.50 ± 1.29	0.0043*
AQLQ score	112	4.06 ± 1.43	45	3.73 ± 1.29	67	4.28 ± 1.48	0.043*
ICS(beclomethasone equivalent)	115	1500 (1000; 2000)	47	1000 (1000; 2000)	68	1600 (1000; 2000)	0.35
OCS (yes/no – dose in mg)	115	9 (7.8)	47	7 (14.9)	68	2 (2.9)	0.019*
OCS dose (mg)	9	6.00 (4.00; 8.00)	7	6.00 (4.00; 10.00)	2	4.00 (4.00; 4.00)	0.12
Pre-BD FEV_1 (L)	115	1.97 ± 0.78	47	1.71 ± 0.62	68	2.16 ± 0.82	0.0020*
Pre-BD FEV_1 (predicted%)	115	64.46 ± 19.04	47	57.83 ± 19.05	68	69.04 ± 17.76	0.0016*
Post-BD FEV_1 (L)	115	2.14 ± 0.83	47	1.88 ± 0.70	68	2.33 ± 0.87	0.0041*
Post-BD FEV_1 (predicted%)	115	69.83 ± 19.63	47	63.17 ± 19.69	68	74.44 ± 18.35	0.0021*
Pre-BD FVC (L)	115	2.96 ± 0.90	47	2.67 ± 0.75	68	3.16 ± 0.95	0.0038*
Pre-BD FVC (predicted%)	115	76.76 ± 15.73	47	70.68 ± 15.91	68	80.96 ± 14.26	0.0004*
Post-BD FVC (L)	115	3.11 ± 0.91	47	2.86 ± 0.78	68	3.28 ± 0.95	0.015*
Post-BD FVC (predicted%)	114	80.81 ± 14.85	46	75.74 ± 15.09	68	84.24 ± 13.76	0.0024*
Pre-BD FEV_1/FVC (%)	115	65.93 ± 12.55	47	63.57 ± 12.75	68	67.56 ± 12.23	0.094
Post-BD FEV_1/FVC (%)	115	68.05 ± 13.50	47	64.96 ± 13.55	68	70.19 ± 13.15	0.041*
FeNO (ppb)	115	33.0 (20.0; 68.0)	47	29.0 (19.0; 54.0)	68	41.50 (21.00; 71.00)	0.20
Blood neutrophils (/µL)	114	4.07 (3.25; 5.76)	47	4.81 (3.53; 6.10)	67	3.75 (2.98; 5.21)	0.016*
Blood eosinophils (/µL)	114	0.11 (0.02; 0.22)	47	0.20 (0.15; 0.42)	67	0.04 (0.00; 0.12)	<.0001*
Total serum IgE (kU/L)	71	181.0 (47.7; 536.0)	34	222.0 (42.0; 866.0)	37	150.00 (51.60; 287.00)	0.43
CRP (mg/l)	106	1.70 (1.00; 4.80)	42	2.40 (1.30; 5.90)	64	1.60 (1.00; 4.30)	0.23
Plasma fibrinogen (g/l)	88	3.55 ± 0.82	35	3.52 ± 0.68	53	3.57 ± 0.91	0.79
Sputum weight (g)	74	2.35 (1.50; 3.46)	29	2.12 (1.10; 2.70)	45	2.46 (1.61; 3.46)	0.34
Squamous cells (%)	73	13.00 (5.00; 25.00)	29	8.00 (5.00; 22.00)	44	14.50 (5.50; 27.50)	0.33
Sputum viability (%)	73	80.00 (68.00; 88.00)	29	80.00 (72.00; 88.00)	44	77.50 (62.50; 88.00)	0.31
Sputum cell number (10^6 cell/g)	73	1.80 (0.84; 4.27)	29	2.26 (1.10; 6.05)	44	1.58 (0.75; 3.87)	0.14
Sputum macrophages (%)	69	18.50 (13.25; 28.00)	28	16.25 (9.25; 25.88)	41	19.25 (15.00; 30.50)	0.10
Sputum neutrophils (%)	69	66.25 (46.00; 80.00)	28	64.25 (47.00; 80.10)	41	67.00 (42.00; 79.50)	0.73
Sputum eosinophils (%)	69	3.00 (0.50; 14.25)	28	5.63 (1.63; 24.63)	41	1.00 (0.00; 7.50)	0.015*
Sputum lymphocytes (%)	69	1.00 (0.25; 2.00)	28	0.75 (0.00; 1.63)	41	1.25 (0.50; 2.00)	0.16
Sputum epithelial cells (%)	69	1.00 (0.20; 3.80)	28	1.25 (0.00; 5.13)	41	1.00 (0.25; 3.00)	0.84
R5	95	5.00 ± 1.90	39	4.80 ± 1.84	56	5.13 ± 1.95	0.41
R19	95	3.62 ± 1.16	39	3.48 ± 1.25	56	3.71 ± 1.10	0.36
R5-19	95	1.38 ± 1.10	39	1.32 ± 0.98	56	1.42 ± 1.18	0.65
AX	95	17.85 (5.97; 33.60)	39	18.19 (7.28; 34.49)	56	17.30 (5.63; 32.13)	0.43
Fres	95	21.63 ± 6.84	39	21.95 ± 5.93	56	21.41 ± 7.45	0.70
X5	95	-1.97 (-3.35; -1.10)	39	-1.96 (-4.13; -1.43)	56	-2.01 (-2.94; -1.08)	0.39

Data were compared with Student t-test or Kruskal-Wallis' test according to the distribution. * = significant difference between patients who switched from another biotherapy or not, $p<0.05$. FEV_1: forced expiration volume in 1s; BD: bronchodilation; coefficient; FVC: forced vital capacity; CRP: C reactive protein; OCS: oral corticosteroids ICS: inhaled corticosteroids; FeNO: fraction of exhaled nitric oxide. R5: resistance at 5 Hz; R20: resistance at 20 Hz; AX: area of reactance; Fres: resonant frequency; X5: reactance at 5 Hz.

Table 2. Evolution of the clinical and inflammatory characteristics of the patients 6 and 18 months after dupilumab (n=115)

Parameter	Visit	N	Value at each visit Mean ± SD Med (Q1; Q3)	Change (visit-baseline) Mean ± SD CI 95%	GLMM Coeff vs baseline	SE	p-value
Pre-BD FEV_1 (L)							0.0007
	Baseline	115	1.97 ± 0.78		0		
	6 months	115	2.10 ± 0.79	0.12 ± 0.36 0.06-0.19	0.12	0.033	*
	18 months	64	2.17 ± 0.88	0.11 ± 0.41 0.00-0.21	0.10	0.042	
Pre-BD FEV_1 (%)							<0.0001
	Baseline	115	64.46 ± 19.04		0		
	6 months	115	68.97 ± 19.02	4.51 ± 11.57 2.38-6.65	4.51	1.07	*
	18 months	64	70.05 ± 21.36	4.50 ± 13.08 1.23-7.77	4.44	1.35	*
Post-BD FEV_1 (L)							0.0005
	Baseline	115	2.14 ± 0.83		0		
	6 months	115	2.26 ± 0.83	0.12 ± 0.34 0.05-0.18	0.12	0.030	*
	18 months	63	2.28 ± 0.93	0.03 ± 0.34 -0.06-0.11	0.03	0.038	
Post-BD FEV_1 (%)							<0.0001
	Baseline	115	69.83 ± 19.63		0		
	6 months	115	74.15 ± 19.57	4.31 ± 10.90 2.30-6.33	4.31	0.97	*
	18 months	63	73.30 ± 21.49	1.86 ± 11.09 -0.94-4.65	2.16	1.23	
Pre-BD FVC (L)							0.0008
	Baseline	115	2.96 ± 0.90		0.00		
	6 months	115	3.09 ± 0.89	0.13 ± 0.39 0.06-0.20	0.13	0.035	*
	18 months	64	3.18 ± 0.97	0.09 ± 0.43 -0.01-0.20	0.11	0.045	
Pre-BD FVC (%)							<0.0001
	Baseline	115	76.76 ± 15.73		0.00		
	6 months	115	80.65 ± 15.20	3.90 ± 9.79 2.09-5.70	3.90	0.92	*
	18 months	64	82.00 ± 15.70	3.50 ± 10.88 0.78-6.22	4.04	1.15	*
Post-BD FVC (L)							0.0032
	Baseline	115	3.11 ± 0.91		0.00		
	6 months	115	3.22 ± 0.87	0.11 ± 0.36 0.05-0.18	0.11	0.033	*
	18 months	63	3.29 ± 0.96	0.06 ± 0.40 -0.04-0.16	0.08	0.042	
Post-BD FVC (%)							0.0001
	Baseline	114	80.81 ± 14.85		0.00		
	6 months	115	84.27 ± 14.91	3.59 ± 9.24 1.87-5.30	3.56	0.86	*
	18 months	63	84.59 ± 14.82	2.87 ± 10.22 0.30-5.45	3.24	1.08	*
Pre-BD FEV_1/FVC (%)							0.051
	Baseline	115	65.93 ± 12.55		0.00		
	6 months	115	67.20 ± 12.63	1.27 ± 5.84 0.19-2.35	1.27	0.54	
	18 months	64	66.98 ± 13.62	1.58 ± 6.73 -0.10-3.26	1.10	0.68	
Post-BD FEV_1/FVC (%)							0.0040
	Baseline	115	68.05 ± 13.50		0.00		
	6 months	115	69.35 ± 13.26	1.30 ± 5.32 0.31-2.28	1.30	0.50	*
	18 months	63	67.92 ± 14.40	-0.59 ± 6.22 -2.15-0.98	-0.63	0.64	
FeNO (ppb)**							<0.0001
	Baseline	115	33.0 (20.0 ; 68.0)	Reduction (%)	0.00		
	6 months	114	19.5 (13.0 ; 32.0)	29.6 ± 54.5 19.5-39.7	-0.59	0.068	*
	18 months	64	16.0 (12.0 ; 32.0)	41.0 ± 44.9 29.8-52.3	-0.73	0.084	*
ACT score (5-25)							<0.0001
	Baseline	111	13.59 ± 5.84		0		
	6 months	113	16.91 ± 5.60		3.36	0.45	*
	18 months	63	18.25 ± 5.37		3.78	0.56	*
ACQ score (0-6)							<0.0001
	Baseline	113	2.78 ± 1.30		0		
	6 months	114	2.07 ± 1.32		-0.71	0.097	*
	18 months	64	1.81 ± 1.15		-0.80	0.12	*
AQLQ score (1-7)							<0.0001
	Baseline	112	4.06 ± 1.43		0		
	6 months	114	4.71 ± 1.39		0.67	0.098	*
	18 months	64	4.95 ± 1.43		0.73	0.12	*
Blood neutrophils (/µL)**							0.86
	Baseline	114	4.07 (3.25 ; 5.76)		0.000		
	6 months	114	4.09 (3.10 ; 5.63)		0.008	0.036	
	18 months	64	4.08 (3.28 ; 5.69)		0.024	0.045	
Blood eosinophils (/µL)**							<0.0001
	Baseline	114	0.11 (0.02 ; 0.22)		0.00		
	6 months	114	0.22 (0.09 ; 0.71)		0.98	0.17	*
	18 months	64	0.30 (0.10 ; 0.78)		1.11	0.20	*

Parameter			Value at each visit	Change (visit-baseline)	GLMM		
	Visit	N	Mean ± SD Med (Q1; Q3)	Mean ± SD CI 95%	Coeff vs baseline	SE	p-value
Total serum IgE (kU/L)**							<0.0001
	Baseline	71	181.0 (47.7 ; 536.0)		0.00		
	6 months	107	101.0 (35.5 ; 252.0)		-0.64	0.080	*
	18 months	59	49.0 (18.0 ; 136.0)		-1.48	0.096	*
CRP (mg/L)**							0.82
	Baseline	106	1.70 (1.00 ; 4.80)		0.000		
	6 months	113	2.20 (1.00 ; 6.60)		0.051	0.12	
	18 months	64	2.50 (1.40 ; 4.70)		0.082	0.14	
Plasma fibrinogen (g/L)							0.35
	Baseline	88	3.55 ± 0.82		0.00		
	6 months	107	3.41 ± 0.64		-0.10	0.084	
	18 months	62	3.35 ± 0.92		-0.13	0.099	
Sputum weight (g)**							0.11
	Baseline	74	2.35 (1.50 ; 3.46)		0.00		
	6 months	60	2.19 (1.04 ; 4.25)		-0.17	0.12	
	18 months	31	2.06 (1.20 ; 3.62)		-0.30	0.15	
Squamous cells (%)**							0.34
	Baseline	73	13.00 (5.00 ; 25.00)		0.00		
	6 months	58	15.00 (6.00 ; 35.00)		0.24	0.24	
	18 months	31	10.00 (4.00 ; 26.00)		-0.20	0.30	
Sputum viability (%)**							0.17
	Baseline	73	80.0 (68.0 ; 88.0)		0.00		
	6 months	58	83.5 (70.0 ; 91.0)		0.16	0.13	
	18 months	31	86.0 (76.0 ; 92.0)		0.28	0.16	
Sputum cell number (10^6 cell/g)**							0.018
	Baseline	73	1.80 (0.84 ; 4.27)		0.00		
	6 months	58	1.35 (0.49 ; 2.56)		-0.43	0.21	
	18 months	31	1.97 (0.76 ; 8.16)		0.29	0.26	
Sputum macrophages (%)							0.89
	Baseline	69	21.71 ± 14.62		0.00		
	6 months	56	22.56 ± 16.17		0.93	2.32	
	18 months	28	23.04 ± 13.51		1.17	2.98	
Sputum neutrophils (%)							0.35
	Baseline	69	61.77 ± 23.76		0.00		
	6 months	56	64.81 ± 20.03		3.67	3.16	
	18 months	28	67.41 ± 18.28		4.96	4.08	
Sputum eosinophils (%)**							0.73
	Baseline	69	3.00 (0.50 ; 14.25)		0.00		
	6 months	56	2.78 (0.38 ; 12.13)		-0.23	0.41	
	18 months	28	2.70 (0.25 ; 6.88)		-0.39	0.53	
Sputum lymphocytes (%)**							0.13
	Baseline	69	1.00 (0.25 ; 2.00)		0.00		
	6 months	56	1.00 (0.25 ; 2.63)		0.11	0.21	
	18 months	28	0.50 (0.00 ; 1.88)		-0.46	0.27	
Sputum epithelial cells (%)**							0.68
	Baseline	69	1.00 (0.20 ; 3.80)		0.00		
	6 months	56	0.75 (0.00 ; 3.75)		-0.16	0.30	
	18 months	28	2.13 (0.25 ; 5.30)		0.18	0.38	
R5							0.085
	Baseline	95	5.00 ± 1.90		0.00		
	6 months	102	4.70 ± 2.08		-0.31	0.15	
	18 months	57	4.56 ± 1.79		-0.33	0.19	
R19							0.096
	Baseline	95	3.62 ± 1.16		0.00		
	6 months	102	3.45 ± 1.17		-0.17	0.090	
	18 months	57	3.34 ± 0.94		-0.20	0.11	
R5-19							0.28
	Baseline	95	1.38 ± 1.10		0.00		
	6 months	102	1.25 ± 1.18		-0.14	0.092	
	18 months	57	1.22 ± 1.05		-0.14	0.12	
AX**							0.15
	Baseline	95	17.85 (5.97 ; 33.60)		0.00		
	6 months	102	11.71 (4.53 ; 27.65)		-0.17	0.096	
	18 months	57	12.66 (4.03 ; 26.75)		-0.19	0.12	
Fres							0.041
	Baseline	95	21.63 ± 6.84		0.00		
	6 months	102	20.36 ± 6.56		-1.41	0.65	

Parameter			Value at each visit	Change (visit-baseline)	GLMM		
	Visit	N	Mean ± SD Med (Q1; Q3)	Mean ± SD CI 95%	Coeff vs baseline	SE	p-value
X5**	18 months	57	19.81 ± 6.63		-1.70	0.80	0.43
	Baseline	95	-1.97 (-3.35 ; -1.10)		0.00		
	6 months	102	-1.68 (-3.20 ; -1.01)		0.07	0.063	
	18 months	57	-1.69 (-2.85 ; -0.95)		0.08	0.079	

* Significant change from baseline based on Scheffé pairwise comparison

** GLMM based on log-transformed variables

FEV_1: forced expiration volume in 1s; BD: bronchodilation; coefficient; FVC: forced vital capacity; CRP: C reactive protein; OCS: oral corticosteroids ICS: inhaled corticosteroids; FeNO: fraction of exhaled nitric oxide. R5: resistance at 5 Hz; R20: resistance at 20 Hz; AX: area of reactance; Fres: resonant frequency; X5: reactance at 5 Hz.

Table 3. Evolution of the clinical and inflammatory characteristics of patients with switch (n=68) and for biologic-naïve patients (n=47) 6 and 18 months after dupilumab.

Parameter	Visit	Switched patients(N=68) N	Mean ± SD Med (Q1; Q3)	Biologic-Naïve patients (N=47) N	Mean ± SD Med (Q1; Q3)
Pre-BD FEV_1 (L)					
	Baseline	68	2.16 ± 0.82	47	1.71 ± 0.62
	6 months	68	2.26 ± 0.81	47	1.87 ± 0.70
	18 months	41	2.31 ± 0.87	23	1.92 ± 0.85
Pre-BD FEV_1 (%)					
	Baseline	68	69.04 ± 17.76	47	57.83 ± 19.05
	6 months	68	72.94 ± 17.96	47	63.23 ± 19.25
	18 months	41	73.71 ± 20.56	23	63.52 ± 21.63
Post-BD FEV_1 (L)					
	Baseline	68	2.33 ± 0.87	47	1.88 ± 0.70
	6 months	68	2.43 ± 0.86	47	2.02 ± 0.72
	18 months	41	2.47 ± 0.93	22	1.91 ± 0.83
Post-BD FEV_1 (%)					
	Baseline	68	74.44 ± 18.35	47	63.17 ± 19.69
	6 months	68	78.46 ± 18.96	47	67.91 ± 18.92
	18 months	41	78.46 ± 20.34	22	63.68 ± 20.65
Pre-BD FVC (L)					
	Baseline	68	3.16 ± 0.95	47	2.67 ± 0.75
	6 months	68	3.24 ± 0.91	47	2.86 ± 0.81
	18 months	41	3.30 ± 0.99	23	2.97 ± 0.93
Pre-BD FVC (%)					
	Baseline	68	80.96 ± 14.26	47	70.68 ± 15.91
	6 months	68	83.84 ± 14.35	47	76.04 ± 15.36
	18 months	41	83.98 ± 15.38	23	78.48 ± 15.99
Post-BD FVC (L)					
	Baseline	68	3.28 ± 0.95*	47	2.86 ± 0.78
	6 months	68	3.36 ± 0.91*	47	3.02 ± 0.79
	18 months	41	3.44 ± 0.98	22	3.02 ± 0.89
Post-BD FVC (%)					
	Baseline	68	84.24 ± 13.76	46	75.74 ± 15.09
	6 months	68	87.10 ± 15.08	47	80.17 ± 13.82
	18 months	41	87.37 ± 14.43	22	79.41 ± 14.44
Pre-BD FEV_1/FVC (%)					
	Baseline	68	67.56 ± 12.23	47	63.57 ± 12.75
	6 months	68	68.94 ± 12.61	47	64.68 ± 12.35
	18 months	41	69.59 ± 13.48	23	62.35 ± 12.86
Post-BD FEV_1/FVC (%)					
	Baseline	68	70.19 ± 13.15	47	64.96 ± 13.55
	6 months	68	71.60 ± 13.01	47	66.09 ± 13.06
	18 months	41	71.37 ± 14.06	22	61.50 ± 13.00
FeNO (ppb)					
	Baseline	68	41.5 (21.0 ; 71.0)	47	29.0 (19.0 ; 54.0)
	6 months	68	20.5 (15.0 ; 38.0)	46	17.5 (12.0 ; 25.0)
	18 months	41	18.0 (12.0 ; 35.0)	23	15.0 (12.0 ; 27.0)
ACT score (5-25)					
	Baseline	66	14.45 ± 6.01	45	12.33 ± 5.40
	6 months	67	17.18 ± 5.47	46	16.52 ± 5.83
	18 months	40	19.30 ± 4.75	23	16.43 ± 5.99
ACQ score (0-6)					
	Baseline	68	2.50 ± 1.29	45	3.20 ± 1.22
	6 months	68	1.98 ± 1.35	46	2.22 ± 1.26
	18 months	41	1.62 ± 0.99	23	2.14 ± 1.35
AQLQ score (1-7)					
	Baseline	67	4.28 ± 1.48	45	3.73 ± 1.29
	6 months	68	4.75 ± 1.49	46	4.66 ± 1.25
	18 months	41	5.15 ± 1.38	23	4.60 ± 1.49
Blood neutrophils (/µL)					
	Baseline	67	3.75 (2.98 ; 5.21)	47	4.81 (3.53 ; 6.10)
	6 months	67	3.88 (2.94 ; 5.05)	47	5.14 (3.78 ; 6.13)
	18 months	41	3.59 (3.00 ; 4.73)	23	4.54 (4.02 ; 6.51)
Blood eosinophils (/µL)					
	Baseline	67	0.04 (0.00 ; 0.12)	47	0.20 (0.15 ; 0.42)
	6 months	67	0.37 (0.09 ; 1.01)	47	0.16 (0.08 ; 0.37)
	18 months	41	0.31 (0.14 ; 0.83)	23	0.20 (0.08 ; 0.41)

Parameter	Visit	Switched patients(N=68) N	Switched patients(N=68) Mean ± SD Med (Q1; Q3)	Biologic-Naïve patients (N=47) N	Biologic-Naïve patients (N=47) Mean ± SD Med (Q1; Q3)
Total serum IgE (kU/L)					
	Baseline	37	150.0 (51.6 ; 287.0)	34	222.0 (42.0 ; 866.0)
	6 months	63	89.3 (39.0 ; 242.0)	44	121.0 (33.1 ; 321.0)
	18 months	38	44.0 (18.0 ; 129.0)	21	63.0 (27.0 ; 234.0)
CRP (mg/L)					
	Baseline	64	1.60 (1.00 ; 4.30)	42	2.40 (1.30 ; 5.90)
	6 months	67	1.60 (1.00 ; 4.50)	46	5.00 (1.40 ; 8.10)
	18 months	41	2.30 (1.10 ; 3.80)	23	3.40 (1.60 ; 8.50)
Plasma fibrinogen (g/L)					
	Baseline	53	3.57 ± 0.91	35	3.52 ± 0.68
	6 months	65	3.37 ± 0.65	42	3.48 ± 0.64
	18 months	40	3.13 ± 0.67	22	3.74 ± 1.17
Sputum weight (g)					
	Baseline	45	2.46 (1.61 ; 3.46)	29	2.12 (1.10 ; 2.70)
	6 months	35	2.50 (0.90 ; 4.80)	25	1.80 (1.17 ; 3.83)
	18 months	22	2.63 (1.74 ; 3.94)	9	1.36 (0.74 ; 1.48)
Squamous cells (%)					
	Baseline	44	14.50 (5.50 ; 27.50)	29	8.00 (5.00 ; 22.00)
	6 months	34	12.00 (6.00 ; 33.00)	24	22.50 (6.50 ; 46.50)
	18 months	22	9.50 (4.00 ; 26.00)	9	10.00 (3.00 ; 19.00)
Sputum viability (%)					
	Baseline	44	77.5 (62.5 ; 88.0)	29	80.0 (72.0 ; 88.0)
	6 months	34	80.0 (65.0 ; 88.0)	24	88.0 (75.5 ; 92.5)
	18 months	22	86.5 (77.0 ; 92.0)	9	76.0 (75.0 ; 91.0)
Sputum cell number (10^6 cell/g)					
	Baseline	44	1.58 (0.75 ; 3.87)	29	2.26 (1.10 ; 6.05)
	6 months	34	1.43 (0.62 ; 3.66)	24	1.28 (0.48 ; 2.37)
	18 months	22	1.93 (0.62 ; 3.50)	9	3.34 (1.97 ; 9.15)
Sputum macrophages (%)					
	Baseline	41	24.74 ± 16.44	28	17.28 ± 10.20
	6 months	32	23.00 ± 16.32	24	21.97 ± 16.30
	18 months	20	24.96 ± 14.21	8	18.25 ± 10.93
Sputum neutrophils (%)					
	Baseline	41	62.09 ± 23.36	28	61.31 ± 24.76
	6 months	32	64.20 ± 19.64	24	65.62 ± 20.94
	18 months	20	63.84 ± 19.41	8	76.31 ± 11.78
Sputum eosinophils (%)					
	Baseline	41	1.00 (0.00 ; 7.50)	28	5.63 (1.63 ; 24.63)
	6 months	32	3.58 (0.25 ; 16.75)	24	2.13 (0.63 ; 4.50)
	18 months	20	2.70 (0.25 ; 9.00)	8	2.75 (0.88 ; 5.25)
Sputum lymphocytes (%)					
	Baseline	41	1.25 (0.50 ; 2.00)	28	0.75 (0.00 ; 1.63)
	6 months	32	1.00 (0.25 ; 3.00)	24	1.00 (0.25 ; 2.38)
	18 months	20	0.88 (0.00 ; 2.10)	8	0.50 (0.00 ; 0.63)
Sputum epithelial cells (%)					
	Baseline	41	1.00 (0.25 ; 3.00)	28	1.25 (0.00 ; 5.13)
	6 months	32	0.75 (0.13 ; 3.00)	24	0.50 (0.00 ; 5.13)
	18 months	20	2.90 (0.63 ; 5.80)	8	0.00 (0.00 ; 1.50)
R5					
	Baseline	56	5.13 ± 1.95	39	4.80 ± 1.84
	6 months	61	4.87 ± 2.14	41	4.45 ± 1.99
	18 months	35	4.84 ± 1.65	22	4.13 ± 1.94
R19					
	Baseline	56	3.71 ± 1.10	39	3.48 ± 1.25
	6 months	61	3.60 ± 1.15	41	3.23 ± 1.18
	18 months	35	3.55 ± 0.85	22	3.00 ± 1.00
R5-19					
	Baseline	56	1.42 ± 1.18	39	1.32 ± 0.98
	6 months	61	1.26 ± 1.24	41	1.22 ± 1.10
	18 months	35	1.29 ± 1.02	22	1.12 ± 1.12
AX					
	Baseline	56	17.30 (5.63 ; 32.13)	39	18.19 (7.28 ; 34.49)
	6 months	61	10.85 (4.23 ; 24.31)	41	16.99 (5.54 ; 35.85)
	18 months	35	15.37 (5.85 ; 26.75)	22	10.14 (2.71 ; 27.03)
Fres					
	Baseline	56	21.41 ± 7.45	39	21.95 ± 5.93
	6 months	61	19.91 ± 6.15	41	21.03 ± 7.15

Parameter	Visit	Switched patients(N=68) N	Mean ± SD Med (Q1; Q3)	Biologic-Naïve patients (N=47) N	Mean ± SD Med (Q1; Q3)
	18 months	35	20.24 ± 6.63	22	19.13 ± 6.73
X5					
	Baseline	56	-2.01 (-2.94 ; -1.08)	39	-1.96 (-4.13 ; -1.43)
	6 months	61	-1.63 (-2.65 ; -1.01)	41	-1.85 (-3.45 ; -1.17)
	18 months	35	-1.77 (-2.76 ; -0.98)	22	-1.53 (-2.88 ; -0.85)

FEV_1: forced expiration volume in 1s; BD: bronchodilation; coefficient; FVC: forced vital capacity; CRP: C reactive protein; OCS: oral corticosteroids ICS: inhaled corticosteroids; FeNO: fraction of exhaled nitric oxide. R5: resistance at 5 Hz; R20: resistance at 20 Hz; AX: area of reactance; Fres: resonant frequency; X5: reactance at 5 Hz.

Table 4. Joint effect of time and groups on all continuous parameters adjusted by covariates (age, pack-years, presence of nasal polyposis, baseline OCS and baseline blood eosinophils)

Parameter	Group effect p-value	Time effect p-value	Interaction p-value
Pre-BD FEV_1 (L)	0.40	0.0004	0.54
Pre-BD FEV_1 (%)	0.42	<.0001	0.69
Post-BD FEV_1 (L)	0.33	0.0003	0.46
Post-BD FEV_1 (%)	0.33	<.0001	0.40
Pre-BD FVC (L)	0.27	0.0003	0.22
Pre-BD FVC (%)	0.17	<.0001	0.32
Post-BD FVC (L)	0.29	0.0018	0.29
Post-BD FVC (%)	0.17	<.0001	0.31
Pre-BD FEV_1/FVC (%)	0.73	0.047	0.96
Post-BD FEV_1/FVC (%)	0.91	0.0031	0.70
FeNO (ppb)**	0.91	<.0001	0.78
ACT score (5-25)	0.78	<.0001	0.092
ACQ score (0-6)	0.76	<.0001	0.035
AQLQ score (1-7)	1.00	<.0001	0.071
Blood neutrophils (/µL)**	0.10	0.83	0.56
Blood eosinophils (/µL)**	0.17	<.0001	<.0001
Total serum IgE (kU/L)**	0.95	<.0001	0.17
CRP (mg/L)**	0.026	0.49	0.14
Plasma fibrinogen (g/L)	0.45	0.80	0.0012
Sputum weight (g)**	0.083	0.031	0.12
Sputum squamous cells (%)**	0.96	0.38	0.35
Sputum viability (%)**	0.67	0.21	0.24
Sputum cell number (10^6 cell/g)**	0.75	0.011	0.33
Sputum macrophages (%)	0.28	0.82	0.45
Sputum neutrophils (%)	0.22	0.19	0.36
Sputum eosinophils (%)**	0.71	0.50	0.051
Sputum lymphocytes (%)**	0.41	0.14	0.65
Sputum epithelial cells (%)**	0.076	0.80	0.079
R5	0.080	0.048	0.69
R19	0.11	0.044	0.42
R5-19	0.13	0.24	0.98
AX**	0.45	0.11	0.51
Fres	0.59	0.043	0.70
X5**	0.37	0.33	0.54

** GLMM based on log-transformed variables

FEV_1: forced expiration volume in 1s; BD: bronchodilation; coefficient; FVC: forced vital capacity; CRP: C reactive protein; OCS: oral corticosteroids ICS: inhaled corticosteroids; FeNO: fraction of exhaled nitric oxide. R5: resistance at 5 Hz; R20: resistance at 20 Hz; AX: area of reactance; Fres: resonant frequency; X5: reactance at 5 Hz.

Table 5 Joint effect of time and previous biotherapy on blood eosinophils (/µL – log-transformed)

Effect	p-value	Simple effect (interaction of time and biotherapy)		
		Biotherapy	**p-value**	**Significant differences between visits**
Biotherapy	<0.0001			
Visit	0.0066			
Interaction	<0.0001			
		Omalizumab	0.79	/
		Mepolizumab	<0.0001	Baseline vs 3 other visits
		Benralizumab	<0.0001	Baseline vs 3 other visits ; before vs 6 months

Material and Methods

Patients and Study design

Inclusion criteria included a diagnosis of severe asthma defined according to European Respiratory Society (ERS)/ American Thoracic Society (ATS) criteria [1]. The presence of nasal polyps was diagnosed by an Ear-Nose-Throat specialist. For all patients, the treatment was stable at the time of sampling and the time between baseline and the next evaluation was close to 6 and 18 months, which corresponds to a reimbursement criterion. An exacerbation was defined as an increase in symptoms requiring a treatment with OCS for at least 3 days or an admission in an emergency room. The Ethics committee of CHU Liege approved this study (2005-181) and all subjects gave written informed consent for participation.

Respiratory function and FOT parameters measurement

Spirometry was performed before and after the inhalation of a bronchodilator agent according to the ATS/ERS standard criteria [2]. FeNO was measured using NiOX at a flow rate of 50 mL/s (Aerocrine, Solna, Sweden). The FOT measures were performed with a Resmond Pro Full medical device (Restech). The resistances were measured at 5 Hz and 20 Hz (R5 and R20), the reactance at 5 Hz (X5). The area of reactance (AX) was obtained as well as the resonant frequency (Fres).

Blood and sputum samples

The blood samples were processed and analyzed by the routine laboratory of the CHU of Liege for leukocyte counts, C- reactive protein (CRP) and fibrinogen levels. The sputum was induced and processed as previously described [3,4].

Statistical analysis

Categorical variables were presented as numbers and percentages for each category, and continuous variables were summarized as mean ± standard deviation (SD) or as median and quartiles (Q1; Q3) for skewed distributions. The evolution of the rate of exacerbations (count variable) was studied by a negative binomial regression model with repeated measurements (GEE model). The evolution of continuous parameters were analyzed by a general linear mixed model (GLMM) with time as categorical fixed effect including the random intercept for each subject. If required, a Pairwise Scheffé comparison was performed between visits and/or groups. In case of asymmetric distribution, a logarithm transformation was applied. Comparisons between cohorts of patients were performed using chi-square or Fisher exact test for categorical variables and Student t-test or Kruskal-Wallis for continuous variables. Results were considered to be significant at the 5% critical level ($p<0.05$). Data analyses were performed using SAS software (version 9.4). GraphPad Prism 7 (GraphPad Software San Diego, CA, USA) was used for the univariate logistic regressions and R software (version 4.4.1) for graphics. All analyses were done on the maximum available data.

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