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# Effectiveness and safety of dupilumab for the treatment of severe asthma in a real-life French multi-centre adult cohort

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## Abstract

**Background:** Dupilumab is a monoclonal anti-IL-4R $\alpha$  antibody developed for the treatment of severe asthma (SA). An early access programme for dupilumab was opened in France in SA patients experiencing unacceptable steroids side-effects and/or life-threatening exacerbations.

**Objective:** To assess changes in asthma control between baseline and 12 months of treatment.

**Methods:** Multi-centre (n = 13) retrospective real-life cohort study. This study is registered on ClinicalTrials.gov (NCT04022447).

**Results:** Overall, 64 patients with SA (median age 51, interquartile range [44-61]; 53% females) received dupilumab as add-on therapy to maximal standard of care; and 76% were on oral daily steroids at baseline. After 12 months, median asthma control test score improved from 14 [7-16] to 22 [17-24] ( $P < .001$ ); median forced expiratory volume in 1 seconds increased from 58% [47-75] to 68% [58-88] ( $P = .001$ ); and daily prednisone dose was reduced from 20 [10-30] to 5 [0-7] mg/d ( $P < .001$ ). Annual exacerbations decreased from 4 [2-7] to 1 [0-2] ( $P < .001$ ). Hypereosinophilia  $\geq 1500/\text{mm}^3$  was observed at least once during follow-up in 16 patients (25%), persisting after 6 months in 8 (14%) of them. Increase in blood eosinophil count did not modify the clinical response during the study period. Injection-site reaction was the most common side effect (14%). Three deaths were observed, none related to treatment by investigators.

**Conclusion & clinical relevance:** In this first real-life cohort study of predominantly steroid-dependent SA, dupilumab significantly improved asthma control and lung function and reduced oral steroids use and exacerbations rate. Despite limitations due to the retrospective study, these results are consistent with controlled trials efficacy data. Further studies are required to assess the clinical significance and long-term prognosis of sustained dupilumab-induced hypereosinophilia.

#### KEYWORDS

asthma, hypereosinophilia, oral steroid, side-effect, T2 inflammation

## 1 | INTRODUCTION

Severe asthma (SA) is defined as an uncontrolled disease despite adherence to high-dose inhaled corticosteroids (ICS) and long-acting beta-agonists (LABA).<sup>1</sup> It is a heterogeneous disease, affecting 3.7%-10% of asthma patients.<sup>2,3</sup> SA represents the very heart of the asthma problem, with tremendous health costs, high morbidity and significant mortality.<sup>2,4</sup>

The face of SA treatment has changed over the past decade as several treatments have recently achieved development and regulatory approvals, targeting eosinophilic asthma, a major phenotype of SA, characterized by high expression of type 2 (T2) cytokines. Among them, dupilumab is a fully human monoclonal antibody targeting the alpha subunit of the interleukin 4 (IL-4) receptor, blocking both IL-4 and IL-13 pathways.<sup>5</sup> Dupilumab was first developed for atopic dermatitis, then as add-on therapy for uncontrolled asthma.<sup>6</sup> Since the publication of the first clinical study of dupilumab in asthma, in 2013, the drug has been shown to significantly reduce the rate of exacerbations and oral CS (OCS) use while improving lung function and asthma control in phase 2b and 3 studies.<sup>5,7-9</sup>

Dupilumab was approved for SA treatment in Europe in March 2019. From September 2017 to January 2018, the French Health

Authority allowed dupilumab to be prescribed via an early access programme. A programme for nominative Authorization for Temporary Use (nATU) opened on physician request for SA patients who had reached a therapeutic dead end, demonstrated uncontrolled disease and/or unacceptable steroids side-effects, regardless of patients' T2 airway inflammation status.

Providing real-world evidence data is important to complement those obtained from randomized controlled trials (RCTs), reflecting routine clinical practice. In this nationwide real-life cohort study, we aimed to describe the population of SA patients who received dupilumab through this nATU programme and assess changes in asthma control 12 months after treatment initiation.

## 2 | MATERIAL AND METHODS

### 2.1 | Study design

We performed a nationwide non-interventional retrospective real-life cohort study in 13 French pulmonary medicine departments. All physicians who requested at least one nATU between September 2017 and January 2018 were contacted and asked to participate. Data were collected from September 2018 to May 2019 via an electronic form.

## 2.2 | Patients

To enter a patient in the nATU programme, physicians had to certify to the French Health Authority that the patient had uncontrolled SA with no available treatment option left, including no possibility to participate in a clinical trial, and that poor asthma control and/or severe steroid side-effects required urgent scaling-up treatment. Authorization was given by both the French Health Authority and the drug manufacturer Sanofi. Patients were not required to have eosinophilia or high level of fractional exhaled nitric oxide (FeNO) because the phase III RCT results were not published at that time.<sup>8,9</sup> However, patients were excluded from the nATU upon drug manufacturer request if they had presented hypereosinophilia  $>1500/\text{mm}^3$  in the previous year because symptomatic hypereosinophilia had been described with dupilumab use in this particular population.<sup>7</sup>

Investigators were free to decide on the frequency of visits, blood tests and lung function assessments and define the tools of control evaluation, in accordance with their usual practice.

## 2.3 | Medication and dosing

All patients received subcutaneous dupilumab every 2 weeks in hospital outpatient clinics. A loading dose of 600 mg was given, according to the only protocol available at this time, and the following doses were 300 mg each.<sup>7</sup>

## 2.4 | End points and assessments

The objectives of the study were to describe the population included in the nATU programme and to evaluate effectiveness as a change in asthma control after 12 months, assessed by the Asthma Control Test (ACT), exacerbations and hospitalization rates, OCS courses, forced expiratory volume in 1 seconds (FEV1), and FEV1/forced vital capacity (FVC) ratio. Clinical response was defined as an ACT score  $\geq 20$ .<sup>10</sup> Safety end-points included the number of adverse events reported by each investigator. Physicians used the Global Evaluation of Treatment Effectiveness (GETE) scale to subjectively assess clinical response.<sup>11</sup> As a 5-point scale, the score classifies response according to the physician-assessed treatment efficacy as 1, excellent; 2, good; 3, moderate; 4, poor; or 5, symptoms worsening. A responder was defined as a patient with an excellent/good symptom score (1 or 2) with dupilumab treatment.

## 2.5 | Statistical analysis

Efficacy was assessed for all patients who completed a visit at 3, 6 and/or 12 months of follow-up. To highlight the missing data due to an inconsistent regular assessment, the number of patients concerned was given for each description or result. All results are expressed as median [interquartile range] for continuous variables, and number (%) for categorical

variables. The Wilcoxon signed-rank test was used to assess differences between baseline and each follow-up visit (3, 6 and 12 months) for outcomes. Statistical significance was considered at  $P < .05$ .

Subgroup analyses were also conducted on baseline omalizumab or mepolizumab use, at least one eosinophil count  $\geq 1500/\text{mm}^3$  during follow-up or not, baseline eosinophil count  $<$  or  $\geq 150/\text{mm}^3$ , baseline eosinophil count  $<$  or  $\geq 300/\text{mm}^3$ , baseline total IgE level  $>150$  kU/L, atopy and nasal polyps. Each subgroup was evaluated in terms of ACT and GETE score, on treatment FEV1 (mL), FEV1 (%) predicted, use of OCS and OCS dose at 12 months. Groups were compared by Wilcoxon rank-sum test for continuous variables and chi-square test or Fisher's exact test for categorical variables. To account for multiple comparison testing, the Bonferroni correction was used to correct the statistical significance threshold for each subgroup analysis (statistical significance threshold  $P = .008$  after correction).

Data analysis was performed by a dedicated statistician using SAS v9.4 (SAS Inst. Inc), and figures were obtained using R v3.5.1.

## 2.6 | Ethics

The protocol conforms the standards of the Declaration of Helsinki and was approved by the institutional review board of the *Société de Pneumologie de Langue Française* (CEPRO 2018-13). All patients were informed of the collection of their data. This study is registered on ClinicalTrials.gov (NCT04022447).

## 2.7 | Role of the funding source

No funding was provided for this study. Sanofi was not involved in study design, data collection, statistical analysis, the writing of the manuscript or decision to publish.

## 3 | RESULTS

### 3.1 | Patient characteristics

Between September 2017 and January 2018, 86 nATU requests were registered from 13 hospitals (11 university centres, 2 general hospitals); 17 patients did not eventually receive the treatment, and 69 were screened for the study (Figure 1). Among them, 64 patients received at least one treatment dose and completed at least one follow-up visit (Table 1), and 51 patients completed the 12 month follow-up (reported in Table S1).

Half of the patients (30/62) were current or former smokers with a history of more than 10 pack-years. The median age at diagnosis was 21 [10-40] years, and 20/61 (33%) patients were obese ( $\text{BMI} > 30 \text{ kg/m}^2$ ). During the 12 months before the first injection of dupilumab, the median exacerbation rate was 4 [3-9] exacerbations, and 28/58 (48%) patients had been hospitalized at least once for asthma. Five of 28 (18%) patients had been admitted to an intensive

care unit. Most patients had previously received GINA step 5 therapies [omalizumab, 52/62 (84%); mepolizumab, 10/62 (17%); bronchial thermoplasty, 4/60 (7%); immunosuppressive drugs, 7/60 (12%)]. Omalizumab and mepolizumab were stopped because of treatment failure in 86% and 80% of cases. One quarter of the patients (15/61) were previously included in phase II-III RCTs.

Lung function showed airway obstruction, with a median on treatment FEV1/FVC ratio of 58% [51-72] and FEV1% of 59% [46-78] and features of lung over-inflation assessed by elevated residual volume. For 34/64 (53%) patients, the blood eosinophil count was  $\geq 150/\text{mm}^3$  at baseline, and for 20/64 (31%), it was  $\geq 300/\text{mm}^3$ . FeNO measurement was not available in most centres. Many patients (47/62 [76%]) were on daily OCS at baseline, with a median dose of 20 [10.0-30.0] mg/d. Comorbidities were frequent: 61% atopy (38/62), 30% nasal polyps (18/60) and 53% gastro-oesophageal reflux disease (GERD; 30/57). Some comorbidities that may have been related to OCS included diabetes (10/56 [18%]), osteoporosis (21/56 [38%]) or hypertension (16/56 [29%]).

### 3.2 | Efficacy

The main changes in asthma control settings are presented in Tables 2 and Figure 2. At 12 months, median ACT score had increased from 14 [7-16] to 22 [17-24] ( $P < .001$ ). Improvement was rapid at 3 months and progressed constantly for the next 9 months: ACT

score was  $\geq 20$  for 16/33 (48%) patients at 3 months, 24/44 (55%) at 6 months and 26/39 (67%) at 12 months. After 1 year, 25/32 (78%) patients showed an increase of at least 5 points in ACT score. After 12 months, exacerbation rate was reduced by 75% as compared with baseline (from 4 [2-7] to 1 [0-2];  $P < .001$ ). For 40/51 (78%) patients, the exacerbation rate was reduced  $\geq 50\%$ . At 12 months, median OCS dose (equivalent prednisolone) was reduced from 20 [10-30] to 5 [0-7] mg/day ( $P < .001$ ) and 12/51 (24%) patients were weaned from OCS. For 28/36 (78%) patients, the OCS dose was reduced by 50% or more. Median ICS dose was also significantly reduced.

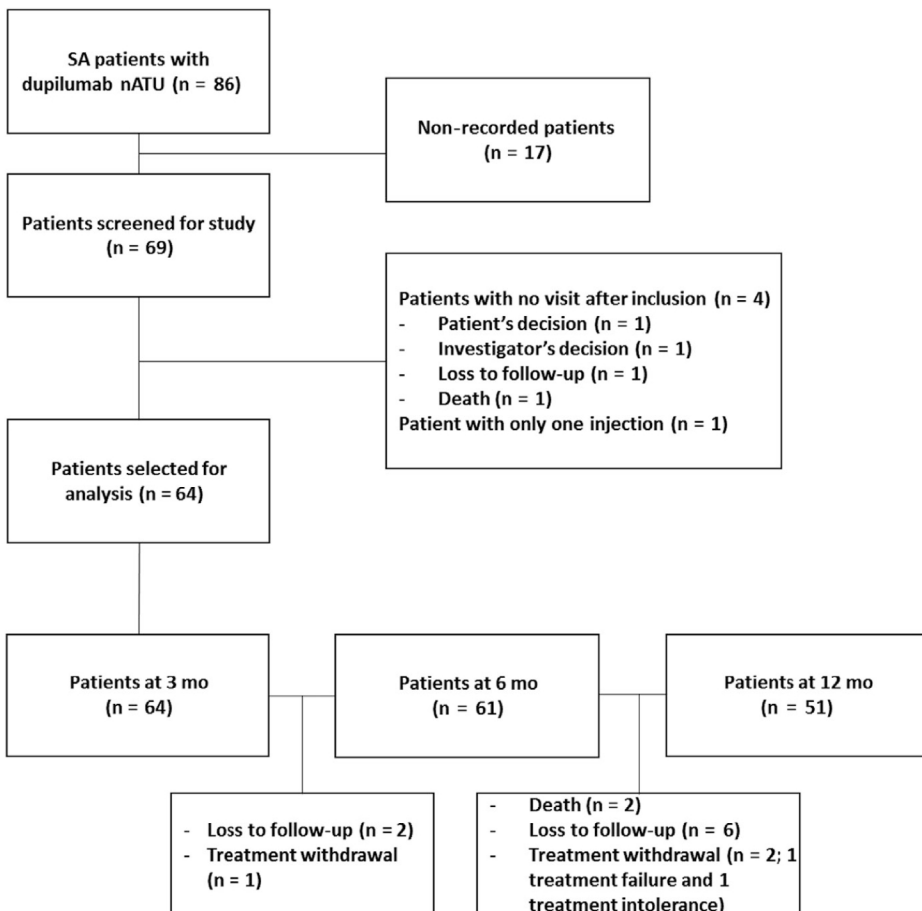
Median FEV1 (%) predicted increased from 58% [47-76] to 68% [58-88] ( $P < .001$ ) at 12 months, with a median gain of 200 mL (Table 2).

For a subjective evaluation, the GETE score evolved in parallel: physicians gave a rank of 1 or 2 (excellent or good response) for 68% of patients after 3 months of treatment, 78% at month 6 and 78% also after completing the 12-month visit (Figure 2).

### 3.3 | Exploratory outcomes

#### 3.3.1 | Responders and non-responders

Forty patients (78%) were considered responders (GETE score 1 or 2) at 12 months. Their clinical baseline characteristics did not differ from non-responders (GETE score 3-5) (data not shown).



**FIGURE 1** Flow chart of patients with severe asthma in the nominative Authorization for Temporary Use (nATU) programme

**TABLE 1** Demographic and clinical baseline characteristics of the patients with severe asthma in the nominative Authorization for Temporary Use (nATU) programme who received at least one injection of dupilumab and completed one follow-up visit in the first 12 mo of treatment (n = 64)

|                          |  | N  | Median [IQR] or n (%) |
|--------------------------|--|----|-----------------------|
| Demographics             | Age (y), median [IQR]  | 64 | 51 [44-61]            |
|                          | Sex: female, n (%)   | 64 | 34 (53.1)             |
|                          | Age at diagnosis (y), median [IQR]   | 58 | 21 [10-40]            |
|                          | BMI (Kg/m <sup>2</sup> ), median [IQR]                                     | 61 | 27 [23-31]            |
|                          | Obesity, n (%)   | 61 | 20 (32.8)             |
|                          | Current smokers, n (%)   | 62 | 1 (1.6)               |
|                          | Former smokers, n (%)  | 62 | 30 (48.4)             |
| Comorbidities            | Atopy, n (%)   | 62 | 38 (61.3)             |
|                          | Atopic dermatitis, n (%)   | 37 | 6 (16.2)              |
|                          | Food allergy, n (%)  | 38 | 5 (13.2)              |
|                          | Nasal polyps, n (%)  | 60 | 18 (30.0)             |
|                          | AERD, n (%)  | 34 | 16 (47.1)             |
|                          | GERD, n (%)  | 57 | 30 (52.6)             |
|                          | Hypertension, n (%)  | 56 | 16 (28.6)             |
|                          | OSA, n (%)   | 56 | 21 (37.5)             |
|                          | Diabetes, n (%)  | 56 | 10 (17.9)             |
|                          | Osteoporosis, n (%)  | 56 | 21 (37.5)             |
|                          | Depression, n (%)  | 55 | 10/57 (17.5)          |
| Ongoing treatments       | Dose of ICS (µg/d), median [IQR]   | 60 | 800 [800-1600]        |
|                          | LABA, n (%)  | 62 | 61 (95.2)             |
|                          | Azithromycin, n (%)  | 62 | 11 (17.7)             |
|                          | LAMA, n (%)  | 61 | 36 (59.0)             |
|                          | LTRA, n (%)  | 62 | 28 (43.7)             |
|                          | Daily OCS, yes, n (%)  | 62 | 47 (75.8)             |
|                          | Dose of prednisone (mg/d), median [IQR]                                    | 47 | 20 [10-30]            |
| Previous treatments      | Omalizumab, n (%)  | 62 | 52 (83.9)             |
|                          | Mepolizumab, n (%)   | 62 | 10 (16.7)             |
|                          | Bronchial thermoplasty, n (%)  | 60 | 4 (6.7)               |
|                          | Immunosuppressive drugs, n (%)   | 60 | 7 (11.7)              |
|                          | Research protocol, n (%)   | 61 | 15 (24.6)             |
| Asthma control           | Exacerbations during the 12 previous months, median [IQR] (3 missing data) | 57 | 4 [3-9]               |
|                          | Hospitalization in the past 12 mo: yes, n (%)                              | 58 | 28 (48.3)             |
|                          | ICU stay: yes, n (%)   | 28 | 5 (17.9)              |
|                          | Hospitalizations, med [IQR]  | 26 | 2 [1-3]               |
|                          | Non-scheduled visits in the past 12 mo: yes, n (%)                         | 60 | 40 (66.7)             |
|                          | Non-scheduled visits, median [IQR]   | 38 | 3 [2-6]               |
|                          | ACT score, median [IQR]  | 44 | 12 [7-16]             |
| Pulmonary function tests | FEV1/FVC (%), median [IQR]   | 50 | 58 [51-72]            |
|                          | FEV1 (% predicted)   | 56 | 59 [46-78]            |
|                          | FEV1 (mL), median [IQR]  | 54 | 1785 [1160-2250]      |
|                          | TLC (% predicted)  | 21 | 115 [103-128]         |
|                          | RV (% predicted)   | 21 | 158 [143-207]         |

(Continues)

**TABLE 1** (Continued)

|            |   | <b>N</b> | <b>Median [IQR] or n (%)</b> |
|------------|---|----------|------------------------------|
| Blood test | Total IgE level (kU/L), median [IQR]  | 40       | 214 [61-437]                 |
|            | Max blood eosinophil count in previous year (/mm <sup>3</sup> ), median [IQR] | 52       | 365 [215-870]                |
|            | Blood eosinophil count at baseline (/mm <sup>3</sup> ), median [IQR]          | 54       | 240 [100-470]                |
|            | Blood eosinophil count at baseline $\geq 150/\text{mm}^3$ , n (%)             | 64       | 34 (53.1)                    |
|            | Blood eosinophil count at baseline $\geq 300/\text{mm}^3$ , n (%)             | 64       | 20 (31.3)                    |

Abbreviations: ACT, Asthma Control Test; AERD, aspirin-exacerbated respiratory disease; ATL, leukotriene receptor antagonist; BMI, body mass index; FEV1, pre-bronchodilator forced expiratory volume in 1 s, measured on treatment; FVC, forced vital capacity; GERD, gastro-oesophageal reflux disease; ICS, inhaled corticosteroids; ICU, intensive care unit; IQR, interquartile range; LABA, long-acting beta-agonist; LAMA, long-acting muscarinic agonist; OSA, obstructive sleep apnoea; pre-BD FEV1 (%), pre-bronchodilator forced expiratory volume in 1 s predicted, measured on treatment; RV, residual volume; TLC, total lung capacity.

### 3.3.2 | Previous treatment with a biologic

Asthma Control Test score at 12 months did not differ by previous omalizumab treatment or not (21 [17-23] vs 24 [24-24],  $P = .127$ ) or previous mepolizumab treatment or not (21 [14-24] vs 22 [19-24],  $P = .259$ ). Similarly, GETE score, FEV1, OCS use and dose did not differ between subgroups (Table S2A,B).

### 3.3.3 | Blood eosinophilia and clinical response

Asthma Control Test score at 12 months did not differ with blood eosinophil count  $< \text{or} \geq 150/\text{mm}^3$  at baseline (21 [17-24] vs 22 [19-23],  $P = .500$ ), nor did GETE score, FEV1, or OCS use and dose. Similarly, clinical response was comparable with baseline blood eosinophil count  $< \text{or} \geq 300/\text{mm}^3$  (Table S3).

### 3.3.4 | Atopy and clinical response

Patients with a baseline total IgE level  $\geq \text{or} < 150$  kU/L had a similar ACT score, GETE and lung function at 12 months, and the proportion of patients on OCS was similar in the 2 groups. Similar data were observed in patients with or without atopy, except for a lower ACT score (20 vs 24,  $P = .041$ ) in those with atopy (Table S4 and S5).

### 3.3.5 | Nasal polyps and clinical response

Patients with nasal polyps had better lung function at 12 months (2400.0 [1750.0-3090.0] vs 1810.0 [1130.0-2500.0],  $P = .0321$ ) but similar clinical response, evaluated by ACT score or OCS use, than patients without polyps (Table S6).

## 3.4 | Blood eosinophil count

Median eosinophil exhibited a trend towards increase in the overall sample that did not reach statistical significance between baseline

and 12 months (250 [100-470] vs 341 [125-761],  $P = .167$ ), but 50% of patients showed increased eosinophil count, by  $\geq 20\%$ , during follow-up. Overall, 16 (25%) patients had at least 1 eosinophil count  $\geq 1500/\text{mm}^3$  during follow-up, with a maximal value 5300/ $\text{mm}^3$  observed (Figure 3). Four (6%) of these patients had at least one eosinophil count  $\geq 3000/\text{mm}^3$ . Half of the events occurred during the first 6 months, then returned to eosinophil levels comparable to baseline measures (Figure 3). Eight (14%) patients retained an eosinophil count  $\geq 1500/\text{mm}^3$  after 6 months. The details of the eosinophil counts measured during follow-up for patients with at least 1 eosinophil count  $\geq 1500/\text{mm}^3$  are reported in Supplementary material (Table S7). No cardiac, neurological or specific lung disease was reported during or after those measurements. None of these patients met the diagnostic criteria for allergic bronchopulmonary aspergillosis or vasculitis. Thus, hypereosinophilia cases were considered asymptomatic. An increase in blood eosinophil count  $\geq 1500 \text{ mm}^3$  during dupilumab treatment was not associated with poorer response to treatment at 12 months: the ACT score was 21 [17-24] versus 22 [19-24] for patients with and without blood eosinophil count  $\geq 1500/\text{mm}^3$  during treatment ( $P = .294$ ). GETE scores were not significantly different, nor was FEV1 (68 [58-92] vs 66 [36-76],  $P = .095$ ) or OCS use and dose (7 [5-35] vs 5 [5-9]  $P = .186$ ). The two groups did not differ in baseline eosinophil count (220/ $\text{mm}^3$  [100-400] vs 350/ $\text{mm}^3$  [80-630],  $P = .291$ ). No dupilumab discontinuation was necessary for any patient showing hypereosinophilia during treatment.

## 3.5 | Safety

Overall, 13 patients discontinued dupilumab during the study (treatment failure,  $n = 1$ ; lost to follow-up,  $n = 8$ ; patient preference,  $n = 1$ ; intolerance,  $n = 1$ ; death,  $n = 2$ ) (Figure 1). An early death had also been recorded for one patient after 2 injections, without any follow-up visit. The most common adverse events (AEs) were injection-site reactions (14% patients), asthenia (6%), infection (3%) and headache (5%). One AE (spontaneous bruising during menstruation) led to treatment discontinuation (Table 3).

**TABLE 2** Summary of main asthma control outcomes for patients with severe asthma during treatment in the nATU programme at each follow-up visit

|                            | Asthma Control Test score | Number of exacerbations | FEV1 (mL)        | FEV1 (%)        | OCS dose <sup>a</sup> | ICS dose <sup>a</sup> |
|----------------------------|---------------------------|-------------------------|------------------|-----------------|-----------------------|-----------------------|
| Analysis at 3 mo (N = 64)  |                           |                         |                  |                 |                       |                       |
| N                          | 30                        | /                       | 32               | 34              | 49                    | 60                    |
| Baseline                   | 11 [7-15]                 |                         | 1690 [1030-2115] | 53 [42-71]      | 20 [10-30]            | 800 [800-1600]        |
| 3 mo                       | 19 [13-22]                |                         | 1864 [1205-2490] | 67 [45-81]      | 10 [7-15]             | 800 [400-800]         |
| Difference                 | 7 [1-11]                  |                         | 230 [10-610]     | 8 [1-18]        | -5 [-18 to 0]         | 0 [-360 to 0]         |
| P-value                    | <i>P</i> < .001           |                         | <i>P</i> < .001  | <i>P</i> < .001 | <i>P</i> < .001       | <i>P</i> < .001       |
| Analysis at 6 mo (N = 61)  |                           |                         |                  |                 |                       |                       |
| N                          | 39                        | /                       | 43               | 45              | 45                    | 57                    |
| Baseline                   | 11 [6-16]                 |                         | 1550 [1010-2250] | 55 [45-76]      | 20 [10-30]            | 800 [800-1600]        |
| 6 mo                       | 20 [12-22]                |                         | 2060 [1290-2490] | 66 [53-92]      | 7 [0-15]              | 800 [600-800]         |
| Difference                 | 6 [2-9]                   |                         | 180 [-30 to 530] | 9 [2-17]        | -10 [-20 to -5]       | 0 [-320 to 0]         |
| P-value                    | <i>P</i> < .001           |                         | <i>P</i> < .001  | <i>P</i> < .001 | <i>P</i> < .001       | <i>P</i> < .001       |
| Analysis at 12 mo (N = 51) |                           |                         |                  |                 |                       |                       |
| N                          | 32                        | 41                      | 39               | 42              | 37                    | 47                    |
| Baseline                   | 14 [7-16]                 | 4 [2-7]                 | 1780 [1190-2170] | 58 [47-76]      | 20 [10-30]            | 800 [800-1600]        |
| 12 mo                      | 22 [17-24]                | 1 [0-2]                 | 1940 [1250-2670] | 68 [58-88]      | 5 [0-7]               | 800 [400-800]         |
| Difference                 | 9 [5-12]                  | -3 [-5 to -2]           | 200 [-30 to 620] | 10 [1-19]       | -13 [-20 to -5]       | 0 [-800 to 0]         |
| P-value                    | <i>P</i> < .001           | <i>P</i> < .001         | <i>P</i> < .001  | <i>P</i> < .001 | <i>P</i> < .001       | <i>P</i> < .001       |

Note: *P*-value of the Wilcoxon signed-rank test.

Abbreviations: FEV<sub>1</sub>, forced expiratory volume in 1 sec, measured on treatment; ICS, inhaled corticosteroids (expressed in beclomethasone equivalent dose); IQR, interquartile range; OCS, oral corticosteroids.

<sup>a</sup>In the comparisons, patients not receiving an OCS or ICS were considered to have a dose of OCS or ICS of 0.

**TABLE 3** Adverse events reported by investigators for patients with severe asthma in the nATU programme who received at least one injection of dupilumab and completed one follow-up visit in the first 12 months of treatment (n = 64)

| Adverse events            | N of patients (%) |
|---------------------------|-------------------|
| Injection-site reaction   | 9 (14.1)          |
| Asthenia                  | 4 (6.3)           |
| Conjunctivitis            | 3 (4.7)           |
| Infection                 | 2 (3.1)           |
| Headache                  | 3 (4.7)           |
| Tinnitus                  | 1 (1.6)           |
| Spontaneous skin bruising | 1 (1.6)           |
| Nausea                    | 1 (1.6)           |
| Pruritus                  | 1 (1.6)           |
| Diabetes                  | 1 (1.6)           |
| Acute coronary syndrome   | 1 (1.6)           |
| Anaphylaxia               | 0 (0)             |

Three patients died, after 2, 20 and 23 injections, respectively. The first one died during sleep, but no post-mortem examination was performed. Causes of death were severe asthma exacerbation and congestive pulmonary oedema for the 2 others. Each case is

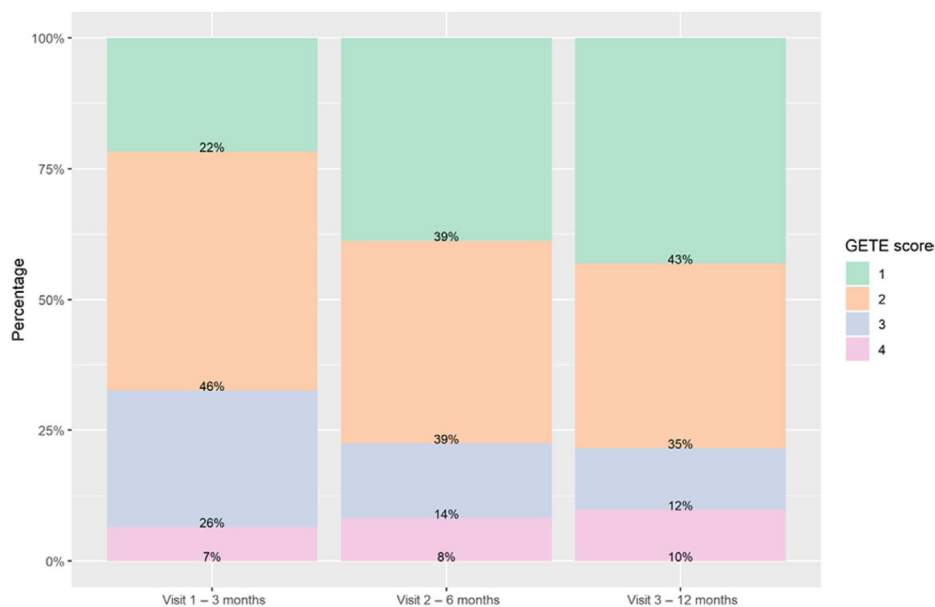
detailed in Supplemental data (Table S8). All 3 had been on daily OCS for years with daily doses as high as 30 mg/d (n = 2) and 40 mg/d (n = 1), with numerous comorbidities. No increase in blood eosinophils count was observed in patients 2 and 3.

## 4 | DISCUSSION

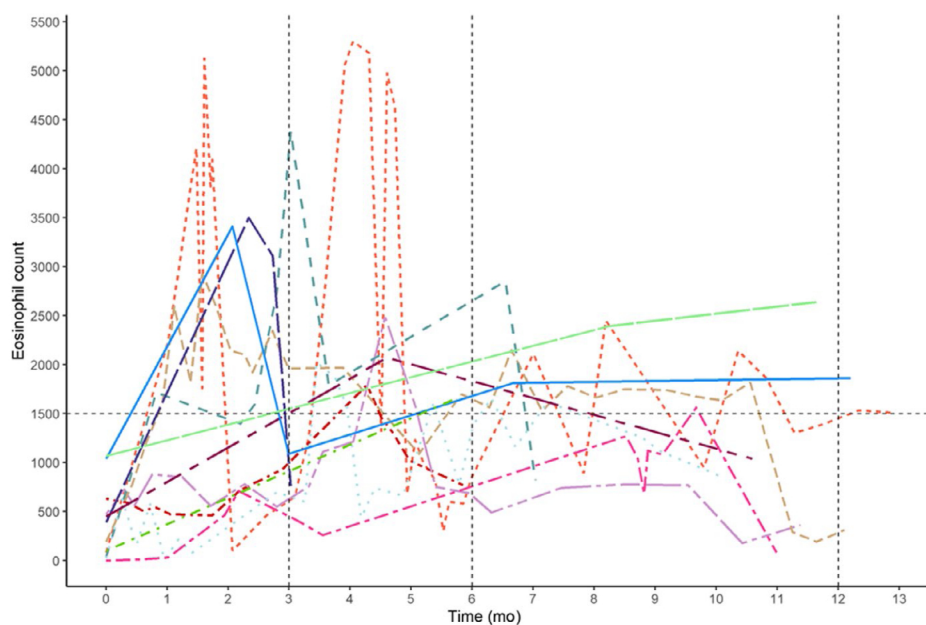
To the best of our knowledge, our study is the first to evaluate add-on dupilumab therapy in real-life SA patients. Despite the retrospective and uncontrolled design of the study, significant improvement in asthma control and lung function, the reduction in oral steroids consumption agrees with results observed in phase III RCTs.<sup>7-9</sup>

The purpose of real-life studies is to confirm, complement and extend the findings of RCTs to better understand how efficacy data translate to the point of care in daily clinical practice. Only 9.8% of patients followed in an expert centre in the United Kingdom were eligible for an RCT.<sup>12</sup> In France, 23% of patients are excluded from such studies because of their smoking status and 50% because they received chronic OCS therapy.<sup>13</sup> Thus, open-label efficacy studies address the critical question of whether a drug works under conditions of greater heterogeneity in patients, providers and settings. Our study population illustrates this point. Nearly half of the patients were former smokers with >10 pack-years, all theoretically excluded





**FIGURE 2** Distribution of Global Evaluation of Treatment Effectiveness (GETE) score (defined by the physician) after 3, 6 and 12 mo. Analysis included all 51 patients who completed the survey at 12 mo, so no patient had an evaluation of 5 (impaired asthma). Score 1: excellent response; 2: good response; 3: medium response; 4: no response; 5: impaired



**FIGURE 3** Evolution of eosinophil count over the 12 months of dupilumab treatment in the 16 patients with at least 1 eosinophil count  $\geq 1500/\text{mm}^3$ . Each line represents a patient with eosinophil counts at each follow-up visit

from RCTs.<sup>7-9</sup> Our patients probably represent the most extreme spectrum of SA because of the recruitment process: many had failed to respond to available GINA step 5 therapeutics because 84% had previously received omalizumab, 17% mepolizumab (by participation in clinical trials or an early access programme because mepolizumab was marketed in France only at the beginning of 2018) and 12% immunosuppressive drugs. Daily doses of OCS at inclusion were much higher than in the VENTURE study (mean dose  $23.5 \pm 15$  mg/d in our study vs  $11.75 \pm 3.54$  mg/d after adjustment).<sup>8</sup> As compared with data from dupilumab RCTs, our patients had more frequent exacerbations (median of 4 in the previous year vs mean 2.01-2.37), ages were wider ranged, and there were more men than usually observed (almost half our population as compared with 40%). Such differences, with more severe disease and less selected populations, have also been observed to the same extent in real-life studies of omalizumab and mepolizumab.<sup>14,15</sup>

Besides patient heterogeneity, our findings are consistent with RCT efficacy and safety data. We observed an early gain in asthma control: ACT score rapidly increased by 3 months, continued to improve and eventually gained a median of 8.5 [5-12] points after 12-month therapy. The OCS-sparing effect was important to assess, because OCS side-effects were frequently argued for nATU requirement. The reduction of the OCS dose (20 to 5 mg/d) was slightly lower than what was observed in the OCS-sparing VENTURE study.<sup>8</sup> Indeed, the proportion of patients with decreased dose by  $\geq 50\%$  was 78% at 12 months as compared with 80% at 6 months in the VENTURE study, and the proportion of patients weaned from OCS was 24% in our population as compared with 48% in the VENTURE study.<sup>8</sup> These differences could be due to lack of a definite OCS-sparing protocol proposed to investigators in our study, which may have slowed the dose decrease. Notably, some investigators reported being cautious during OCS dose reduction in patients

with increasing eosinophil count. The exacerbation rate greatly decreased from a median of 4 [3-7] to 1 [0-2] in our study versus a mean of  $2.09 \pm 2.15$  to  $0.27-0.52$  (95% confidence interval 0.45-0.61) in the QUEST study.<sup>9</sup> We also observed a statistical and clinically significant increase in FEV1 (median gain of 200 mL at 12 months), as previously reported.<sup>9</sup>

Randomized controlled trials have focused on the value of baseline eosinophil count to predict clinical response and showed that counts  $\geq 150$  or  $\geq 300/\text{mm}^3$  were associated with better outcomes, leading to the European Medicines Agency and US Food and Drug Administration decisions to limit dupilumab to T2 asthma. nATU was granted before the publication of phase III studies, which allowed for prescribing dupilumab regardless of baseline eosinophil count or T2 status, because patients were included in the VENTURE and QUEST studies with no minimum requirement regarding T2 status.<sup>8,9</sup> Blood eosinophil count in our population (median  $240/\text{mm}^3$  [100-470]) was close to that in the VENTURE population (median  $260/\text{mm}^3$  [140-480]). In fact, half of our patients had an eosinophil count  $\geq 150/\text{mm}^3$  at inclusion, although most received daily OCS, therefore meeting current criteria for T2 asthma, as defined by the GINA consortium.

In our population, baseline blood eosinophil and total IgE level count did not affect changes in ACT score, OCS-sparing effect or FEV1. Similarly, the proportion of patients with GETE score 1 or 2 did not differ by blood eosinophil count: 17 (70.8%) with  $<150/\text{mm}^3$  and 23 (85.2%) with  $\geq 150/\text{mm}^3$  ( $P = .2$ ) and 26 (74.3%) with  $<300/\text{mm}^3$  and 14 (87.5%) with  $\geq 300/\text{mm}^3$  ( $P = .44$ ) were considered excellent or good responders. The VENTURE study evidenced treatment efficacy, regardless of baseline eosinophil counts.<sup>8</sup> However, more robust results were observed in patients with high T2 status, defined by FeNO level or blood eosinophil count in the QUEST study and in the pivotal study.<sup>5,9</sup> This discrepancy may be due to the poor value of blood eosinophil count to detect T2 status well in patients receiving chronic OCS.

Dupilumab was overall well tolerated. Three (4.7%) cases of conjunctivitis were reported, never identified in asthma trials. However, all these patients also had atopic dermatitis, a situation associated with dupilumab-induced ocular side-effects.<sup>16</sup> None of the encountered deaths was considered related to treatment by investigators or to an increase in eosinophil count. Comorbidities were numerous in each case. Their causal link was specifically raised in 2 cases. For the patient who died during sleep after 2 injections, no post-mortem examination was performed to determine the exact cause of death.

Hypereosinophilia was at the centre of physicians' concerns. We evidenced a high rate of hypereosinophilia: 25% and 6.3% of patients presented blood eosinophil count  $\geq 1500/\text{mm}^3$  and  $3000/\text{mm}^3$ , respectively, at least once during follow-up. A blood eosinophil count  $>3000/\text{mm}^3$  was reported in 13% of OCS-dependent patients included in the VENTURE study but only 1.2% in the QUEST study.<sup>8,9</sup> However, in our study, blood tests were not performed at the same frequency in all centres, and patients with an increase in blood eosinophil count at the first assessment had a higher number of subsequent blood analyses, so this prevalence should be taken with caution. Hypereosinophilia did not affect the clinical or

functional response, was always asymptomatic and did not lead to treatment discontinuation.

Little is known about the physiological features explaining hypereosinophilia induced by dupilumab. For the T2 airway inflammation pathway, when blocking IL-4 and IL-13, dupilumab may set free the IL-5 pathway, thus leading to eosinophil egress from bone marrow while at the same time blocking eosinophil activation and recruitment to tissue by modulating eotaxin 3 levels and adhesion molecule expression.<sup>17</sup> However, this increase is not transient because 8 patients still had hypereosinophilia  $\geq 1500/\text{mm}^3$  after 6 months. Therefore, we chose to recommend regular blood smear analysis and yearly cardiac function monitoring for patients with counts remaining  $\geq 1500/\text{mm}^3$ . Further studies are required to understand the significance of elevated eosinophil count induced by dupilumab.

Our study has some limitations related to its small number of patients and uncontrolled retrospective design. Corollary missing data were due to different care settings and variable monitoring practices among investigatory sites. This situation could have reduced the statistical power to explore predictive factors associated with good response. Nevertheless, the observed heterogeneity did not impair the significant evidence that dupilumab improved numerous asthma outcomes in this setting.

Therefore, these data from a real-life cohort study provide early evidence that add-on dupilumab therapy significantly improves asthma outcomes in patients with SA cared for in a real-life environment. Larger cohorts are needed to improve and extend these data. More specifically, systematic monitoring of blood eosinophil count under treatment is needed to assess the significance and prognosis of the increase in blood eosinophil count, especially when sustained, in a substantial subset of patients.

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