Severe asthma care trajectories: the French RAMSES cohort

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Abstract

Background The French RAMSES study is an observational prospective multicentre real-life cohort including severe asthmatic subjects. The objective of the study was to compare the characteristics of patients, in terms of phenotype and asthma care trajectories, between those managed by tertiary referral centres (TRCs) or secondary care centres (SCCs).

Methods Patients were prospectively recruited and enrolled for a 5-year follow-up. Patients' characteristics were analysed at inclusion and compared between TRCs and SCCs.

Results 52 centres (24 TRCs and 28 SCCs) included 2046 patients: 1502 (73.4%) were included by a TRC and 544 (26.6%) by a SCC. Patients were mainly women (62%), 53±15 years old, 67% with Asthma Control Test <20; at inclusion, 14% received oral corticosteroids (OCS) and 66% biologics. Compared with the SCC group, the TRC group had more frequent comorbidities and lower blood eosinophil counts (262 *versus* 340 mm^{-3}; p=0.0036). OCS and biologics use did not differ between groups, but patients in the TRC group benefited more frequently from an educational programme (26% *versus* 18%; p=0.0008) and received more frequently two or more sequential lines of biologics (33% *versus* 24%; p=0.0105). In-depth investigations were more frequently performed in the TRC group (allergy tests: 74% *versus* 62%; p<0.0001; exhaled nitric oxide fraction: 56% *versus* 21%; p<0.0001; induced sputum: 6% *versus* 3%; p=0.0390).

Conclusions Phenotypes and care trajectories differed in the RAMSES cohort between SCCs and TRCs, probably related to different levels of asthma severity and differences in medical resources and practices among centres. This highlights the need for standardisation of severe asthma care.

Introduction

Asthma is a heterogeneous disease characterised by chronic inflammation with airway remodelling and high morbidity. The severe forms of asthma affect 5–10% of an estimated 262 million asthma sufferers worldwide [1]. Severe asthma is defined by the requirement for treatment with high-dose inhaled corticosteroids and a co-controller or systemic corticosteroids for ⩾50% of the previous year [2]. The burden of severe asthma appears both clinical and economic.

Severe asthma is a highly heterogeneous disease in terms of phenotypes and endotypes. During the past decade, significant progress has been made in the understanding of its underlying mechanisms. Many of these advances have been achieved through patient phenotyping allowing the development of novel treatments such as biological therapies. Severe asthma registries appear crucial to the global effort to decipher severe asthma mechanisms, identify biomarkers, analyse the real-life effectiveness of therapeutic strategies and participate in the overall improvement of severe asthma management [3, 4]. Recent international severe asthma registries highlighted important differences in treatment strategies across Europe and worldwide [5, 6]. One of the main challenges to face in the next years will be to improve and standardise the delivery of severe asthma care regarding the implementation of treatment strategies and optimisation of comorbidities management in secondary and tertiary care centres.

The RAMSES cohort (Research on Severe Asthma; ClinicalTrials.gov: NCT04077528) is an ongoing study aiming to analyse the use, benefits and risks of Step 5 Global Initiative for Asthma (GINA) treatment strategies in French adults suffering from severe asthma in France. In France, the healthcare system is made up of a fully integrated network of public hospitals, private hospitals and private practice, including secondary and tertiary care centres, among which patients are free to decide where they wish to receive medical care, without financial consideration, since they all belong to the same social security system. The centres participating in the RAMSES study include secondary care centres (SCCs) and tertiary referral centres (TRCs). We hypothesised that although complementary in a shared effort on severe asthma management, SCCs and TRCs may differ in terms of severe asthma population and management, which might be related to geographical location or potential human and material resources. The primary aim of this study was to describe the baseline characteristics of severe asthma patients (including phenotype) and to compare asthma care trajectories between SCCs and TRCs.

Material and methods

Study design

The RAMSES study is a French nationwide observational prospective multicentre cohort that included incident and prevalent severe asthma patients from September 2019 to September 2022. Patient care and choices of treatment were not influenced by participation in RAMSES, reflecting real-life practices. Study participation was open to all pneumologists taking care of severe asthma patients in France. Solicitations were made through the Allergy and Asthma Working Group of the French Society of Pneumology, the national clinical investigation network of severe asthma (CRISALIS) and their contacts. Centres were defined as either SCCs (non-academic general hospitals, or private clinics or practices) or TRCs (university hospitals).

Population and data collection

Adult severe asthmatic subjects defined as per the 2014 European Respiratory Society/American Thoracic Society guideline definition [2] or receiving Step 5 GINA treatment, including long-term oral corticosteroids (OCS), biologics or bronchial thermoplasty, were prospectively recruited and enrolled for 5 years. Baseline and subsequent data collection were scheduled during routine clinical assessments as part of their usual follow-up, usually one visit every 6 months.

Variables

Among all baseline variables collected, we described and compared characteristics and care trajectories of severe asthma patients on key prespecified variables: age at inclusion, gender, body mass index, smoking history, reported comorbidities, asthma characteristics, asthma control score, exacerbations in the past year, lung function (past 12 months), current treatments, treatment adherence as reported by the patient and the investigator, questionnaires assessing asthma-related quality of life and burden (Asthma Quality of Life Questionnaire (AQLQ), Hospital Anxiety and Depression Scale (HADS) and EuroQol EQ-5D-3L), history of asthma-related investigations (blood eosinophils in the past 2 years, antineutrophil cytoplasmic antibody

(ANCA), quantitative serum immunoglobulin tests, total IgE, allergy tests, *i.e.* skin prick test and/or specific IgE, exhaled nitric oxide fraction (F_{ENO}), sputum analyses, bronchoscopy and 6-min walk test), and multidisciplinary management (patient education programme and pulmonary rehabilitation) ever performed. Ex-smokers were defined as patients who stopped smoking before the inclusion visit. In case of several measurements available for the same variable in the past 2 years, the highest value was considered for this study. Regarding biological treatment, patients were considered either naive, in a first line of a biologic, or, when the previous line of biologic had to be stopped (*e.g.* due to side-effects or inefficacy), in a second, third or fourth sequential line of biological treatment.

Statistical analyses

Continuous variables were described by mean with standard deviation or median (interquartile range (IQR)) and categorical variables by frequency (percentage). To compare baseline characteristics or patient care trajectories between types of centres, Pearson's Chi-squared test or Fisher's exact test (for categorical variables) and the t-test or Wilcoxon test (for continuous variables) were performed as appropriate. Correction for multiple comparisons was carried out using the Benjamini–Hochberg method. p-values<0.05 were considered statistically significant (two-tailed test). A mapping comparison was conducted to compare the distance between the patient's home and centre according to the type of centre. Statistical analyses were performed using R version 4.1.0 (www.rstudio.com).

Ethics and regulatory

The study protocol was approved by an independent ethics committee (Comité De Protection Des Personnes Sud-Est IV, ID-RCB: 2018-A03282-53). Before enrolment, all patients were informed and orally consented to participate in the study.

Results

RAMSES cohort

From September 2019 to September 2022, a total of 2046 patients were included in the RAMSES cohort in 52 centres. Patients' characteristics are detailed in table 1. Briefly, patients were mainly women (62%), with a mean±SD age of 53±15 years. Reported comorbidities were frequent, including chronic rhinosinusitis (58.7%), nasal polyps (42.2%), gastro-oesophageal reflux disease (GORD) (32.8%), obesity (28.1%), allergic rhinitis (17.4%) and a history of anxiety and/or depression (15.6%). Cardiovascular diseases affected 21.3% of the patients and 10.4% suffered from osteoporosis.

At inclusion, 63.9% of the subjects had uncontrolled asthma (Asthma Control Test (ACT) <20); 62.3% had at least one exacerbation in the past year, with a mean annual exacerbation rate of 4.0±4.1. Type 2 (T2) biomarkers were high in more than half of patients: 49.5% had blood eosinophil counts $\geqslant300\,mm^{-3}$, 69.5% had F_{ENO} levels $\geqslant20$ ppb and sensitisation to at least one aeroallergen was identified in 53.4%.

Treatment adherence was considered optimal by investigators in 64% of the patients, the technical use of an inhaler device was correct for 79% of the subjects. Step 5 GINA treatments included long-term OCS ($\geqslant6$ months in the past year; 14.2%) and biologics (66%), with 12.7% receiving both OCS and biologics at inclusion (table 2).

Asthma burden appeared to be important: the patients exhibited a marked alteration in quality of life (AQLQ 4.7±1.3 and EQ-5D-3L 0.73±0.28). The HADS questionnaire revealed symptom scores suggesting anxiety and depression in 39.4% and 21.7% of the patients, respectively (table 1).

Severe asthma in SCCs and TRCs

Among the 2046 patients included, 1502 (73.4%) were included by 24 TRCs and 544 (26.6%) by 28 SCCs (tables 1 and 2, and figure 1).

Severe asthma phenotypes in the SCC and TRC groups

We first compared patients' phenotypes between the SCC and TRC groups. Patients did not differ in terms of age, gender or smoking history, but did differ in terms in comorbidities: compared with the SCC group, the TRC group was characterised by more frequent GORD (35.2% *versus* 22.4%; p<0.0001), chronic rhinosinusitis (60.7% *versus* 53.5%; p=0.0133) and osteoporosis (12.3% *versus* 5.3%; p<0.0001). Asthma control was similar in both groups in terms of ACT scores. However, the proportion of patients requiring an emergency room visit or hospitalisation for severe exacerbation in the past year was higher in the SCC group (24.6% *versus* 17.7%; p=0.0022 and 23.2% *versus* 16.0%; p=0.0011 respectively).

TABLE 1 Baseline patient characteristics				
	Total	TRC	SCC	p-value
Patients	2046	1502	544	
Age, years	53.3±15.2	53.5±15.3	52.7±15.0	0.3134
Female	1271 (62.1)	931 (62)	340 (62.5)	0.8761
BMI, kg·m^{-2} (n=1983)	27.5±5.8	27.4±5.9	27.8±5.6	0.1342
<18.5 kg·m^{-2}	47 (2.4)	39 (2.7)	8 (1.6)	
18.5–24.9 kg·m^{-2}	704 (35.5)	538 (36.6)	166 (32.3)	0.1903
25–29.9 kg·m^{-2}	674 (34.0)	482 (32.8)	192 (37.4)	
≥30 kg·m^{-2}	558 (28.1)	410 (27.9)	148 (28.8)	
Smoking history (n=1966)				
Current smoker	113 (5.7)	72 (5.0)	41 (7.9)	
Never-smoker	1121 (57.0)	843 (58.2)	278 (53.7)	0.0621
Ex-smoker	732 (37.2)	533 (36.8)	199 (38.4)	
Comorbidities				
Chronic rhinosinusitis	1202 (58.7)	911 (60.7)	291 (53.5)	0.0133
Nasal polyps	863 (42.2)	662 (44.1)	201 (36.9)	0.3914
GORD	651 (31.8)	529 (35.2)	122 (22.4)	<0.0001
Allergic rhinitis	356 (17.4)	257 (17.1)	99 (18.2)	0.6459
Obstructive sleep apnoea	298 (14.6)	219 (14.6)	79 (14.5)	0.9776
Anxiety and/or depression history	319 (15.6)	240 (16.0)	79 (14.5)	0.5447
Osteoporosis	213 (10.4)	184 (12.3)	29 (5.3)	<0.0001
Cardiovascular disease	435 (21.3)	323 (21.5)	112 (20.6)	0.7225
Diabetes mellitus	182 (8.9)	130 (8.7)	52 (9.6)	0.6256
Treatment adherence				
Drug intake as prescribed (n=1105)	707 (64.0)	468 (67.7)	239 (57.7)	0.0035
Correct technical use of inhaler device	1614 (78.9)	1184 (78.8)	430 (79)	0.9362
ACT score (n=1966)	15.9±5.9	15.9±5.9	15.7±5.8	0.5977
<15	839 (42.7)	613 (42.3)	226 (43.8)	
15–19	468 (23.8)	339 (23.4)	129 (25.0)	0.5431
≥20	659 (33.5)	498 (34.3)	161 (31.2)	
Exacerbations				
In the past year	1275 (62.3)	959 (63.8)	316 (58.1)	0.0457
Per patient, n (if at least one per patient)	4.0±4.1	4.0±4.2	4.1±3.7	0.2238
Emergency room visit in the past year	400 (19.6)	266 (17.7)	134 (24.6)	0.0022
Hospitalisation in the past year	367 (17.9)	241 (16.0)	126 (23.2)	0.0011
Intensive care unit, ever	442 (21.6)	312 (20.8)	130 (23.9)	0.2476
Intubation, ever	155 (7.6)	121 (8.1)	34 (6.2)	0.3134
Asthma phenotype				
Blood eosinophils, mm^{-3} (n=1568)	290 (100–600)	261.5 (100.0–570.0)	340.0 (132.0–692.5)	0.0036
<150 mm^{-3}	501 (32.0)	393 (33.2)	108 (28.0)	
150–299 mm^{-3}	291 (18.6)	234 (19.8)	57 (14.8)	0.0068
≥300 mm^{-3}	776 (49.5)	555 (47.0)	221 (57.3)	
F_{ENO}, ppb (n=752)	32.0 (17.0–64.1)	31.0 (17.0–64.0)	37.0 (18.1–83.0)	0.4164
≥20 ppb	523 (69.5)	474 (69.3)	49 (72.1)	0.7090
Aeroallergen sensitisation (n=1454)	793 (54.5)	582 (52.2)	211 (62.4)	0.0036
Lung function				
FEV$_1$, % pred (n=1712)	77.1±21.7	77.8±21.8	75.1±21.6	0.0634
FEV$_1$/FVC, % (n=1678)	67.2±17.7	66.9±19.3	68.3±11.9	0.0296
Fixed airflow limitation (FEV$_1$/FVC <70%) (n=1678)	936 (55.8)	719 (57.6)	217 (50.6)	0.0345
RV/TLC (n=644)	77.0±41.3	63.2±36.6	96.5±39.7	<0.0001
Asthma burden				
AQLQ score (n=1950)	4.7±1.3	4.8±1.3	4.4±1.3	<0.0001
EQ-5D-3L score (n=1904)	0.73±0.27	0.74±0.27	0.70±0.29	0.0120
HADS Anxiety score >7 at inclusion (n=1885)	742 (39.4)	545 (39.2)	197 (39.9)	0.8398
HADS Depression score >7 at inclusion (n=1911)	414 (21.7)	296 (21.0)	118 (23.5)	0.3998

Data are presented as n, mean±SD, n (%) or median (interquartile range), unless otherwise stated. Unless specified, values are available for all 2046 patients. TRC: tertiary referral centre; SCC: secondary care centre; BMI: body mass index; GORD: gastro-oesophageal reflux disease; ACT: Asthma Control Test; F_{ENO}: exhaled nitric oxide fraction; FEV$_1$: forced expiratory volume in 1 s; FVC: forced vital capacity; RV: residual volume; TLC: total lung capacity; AQLQ: Asthma Quality of Life Questionnaire; EQ-5D-3L: EuroQol EQ-5D-3L; HADS: Hospital Anxiety and Depression Scale. p-values are from Pearson's Chi-squared test or Fisher's exact test (for categorical variables) and the t-test or Wilcoxon test (for continuous variables), as appropriate. Correction for multiple comparisons was carried out using the Benjamini–Hochberg method.

TABLE 2 Patient care trajectories

	Total	TRC	SCC	p-value
Patients	2046	1502	544	
Time between inclusion and event, years				
First visit in the centre (n=1977)	3.3 (0.7–7.6)	3.1 (0.5–7.1)	4.0 (1.1–8.9)	<0.0001
Onset of symptoms (n=1342)	23.0±17.0	23.5±17.1	21.3±16.4	0.0954
Asthma diagnosis (n=1867)	22.5±17.1	22.6±17.2	22.0±16.9	0.5977
Severe asthma diagnosis (n=1878)	9.3±10.8	10.2±11.4	6.9±8.6	<0.0001
Investigations performed				
Spirometry	1995 (97.5)	1468 (97.7)	527 (96.9)	0.4164
Blood eosinophils	1806 (88.3)	1328 (88.4)	478 (87.9)	0.7910
ANCA	1145 (56.0)	896 (59.7)	249 (45.8)	<0.0001
Quantitative serum immunoglobulin tests	1561 (76.3)	1208 (80.4)	353 (64.9)	<0.0001
Allergy tests (skin prick tests, specific IgE)	1454 (71.1)	1116 (74.3)	338 (62.1)	<0.0001
F_{ENO}	952 (46.5)	840 (55.9)	112 (20.6)	<0.0001
6-min walk test	145 (7.1)	110 (7.3)	35 (6.4)	0.5977
Bronchoscopy	395 (19.3)	299 (19.9)	96 (17.6)	0.4101
Induced sputum	109 (5.3)	91 (6.1)	18 (3.3)	0.0390
Treatment at inclusion				
Inhaled corticosteroid	1859 (90.9)	1398 (93.1)	461 (84.7)	<0.0001
Long-acting β_2-agonist	1865 (91.2)	1400 (93.2)	465 (85.5)	<0.0001
Long-acting muscarinic antagonist	1109 (54.2)	834 (55.5)	275 (50.6)	0.1041
Montelukast	699 (34.2)	475 (31.6)	224 (41.2)	0.0003
Long-term azithromycin	194 (9.5)	163 (10.9)	31 (5.7)	0.0020
Long-term oral corticosteroid	290 (14.2)	219 (14.6)	71 (13.1)	0.5079
Biologic	1356 (66.3)	1010 (67.2)	346 (63.6)	0.2407
First line	944 (69.6)	681 (67.4)	263 (76.0)	0.0105
Second line or higher[#]	412 (30.4)	329 (32.6)	83 (24.0)	
Interventional clinical trial	178 (8.7)	146 (9.7)	32 (5.9)	0.0214
Bronchial thermoplasty	32 (1.6)	30 (2.0)	2 (0.4)	0.0272
Multidisciplinary management				
Patient education (n=1971)	475 (24.1)	379 (26.3)	96 (18.1)	0.0008
Pulmonary rehabilitation (n=1980)	412 (20.8)	348 (24.0)	64 (12.1)	<0.0001

Data are presented as n, mean (interquartile range), mean±SD or n (%), unless otherwise stated. Unless specified, values are available for all 2046 patients. TRC: tertiary referral centre; SCC: secondary care centre; ANCA: antineutrophil cytoplasmic antibody; F_{ENO}: exhaled nitric oxide fraction. #: second, third or fourth sequential line of biological treatment. p-values are from Pearson's Chi-squared test or Fisher's exact test (for categorical variables) and the t-test or Wilcoxon test (for continuous variables), as appropriate. Correction for multiple comparisons was carried out using the Benjamini–Hochberg method.

The stratification of severe asthma patients depending on blood eosinophil counts per class (<150, 150–299 and ⩾300 mm^{-3}) identified different distributions between the TRC and SCC groups (p=0.0068) with more TRC patients exhibiting low blood eosinophil counts. The median blood eosinophil count was lower in the TRC group compared with the SCC group (261.5 versus 340 mm^{-3}; p=0.0036).

A more pronounced alteration of quality of life was observed in the SCC group compared with the TRC group (AQLQ 4.8±1.3 versus 4.4±1.3; p<0.0001 and EQ-5D-3L 0.74±0.27 versus 0.70±0.29; p=0.0120).

Asthma care trajectories in the SCC and TRC groups

We next analysed asthma care trajectories in the SCC and TRC groups. The time between inclusion and first symptoms, and between inclusion and asthma diagnosis, did not differ between groups. The patients in the TRC group had an older diagnosis of severe asthma (median (IQR) 6 (3–13) versus 4 (1–9) years; p<0.0001) and a shorter follow-up in the recruiting centre (3.1 (0.5–7.1) versus 4.0 (1.1–8.9) years; p<0.0001). The median distance between the patient's home and inclusion care centre was 25 (7–67) km for the TRC group and 7 (3–17) km for the SCC group (p<0.0001) (figure 1).

The patients in the TRC group more frequently underwent investigations for severe asthma differential diagnosis or phenotyping, including allergy tests (74.3% versus 62.1%; p<0.0001), F_{ENO} measurements (55.9% versus 20.6%; p<0.0001), induced sputum analysis (6.1% versus 3.3%; p=0.0390) or ANCA
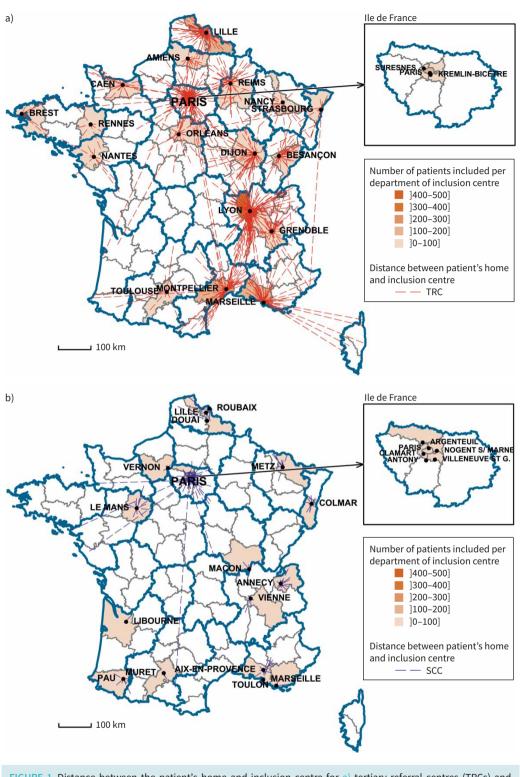
FIGURE 1 Distance between the patient's home and inclusion centre for a) tertiary referral centres (TRCs) and b) secondary care centres (SCCs) in metropolitan France.

(59.7% *versus* 45.8% p<0.0001) (table 2). No differences were observed for blood analyses for eosinophils (88.4% *versus* 87.9% p=0.7910) or bronchoscopy (19.9% *versus* 17.6%; p=0.4101).

The analysis of therapeutic management identified different treatment strategies between both groups: at inclusion, patients in the TRC group were more likely to receive long-term azithromycin treatment (10.9%

versus 5.7%; p=0.0020) and more frequently benefited from a multidisciplinary care approach, including patient education (26.3% *versus* 18.1%; p=0.0008) and pulmonary rehabilitation (24.0% *versus* 12.1%; p<0.0001). Patients in the SCC group were more frequently treated with montelukast (31.6% *versus* 41.2%; p=0.0003). Although the number of patients with past or current treatment with biologics did not differ between groups, patients in the TRC group received more frequently several sequential lines of biologics compared with the SCC group (32.6% *versus* 24.0%; p=0.0105). Patients in the TRC group were also more frequently included in a therapeutic clinical trial (9.7% *versus* 5.9%; p=0.0214).

Discussion

In this study, we present the first description of the RAMSES cohort and point out important differences in terms of severe asthma phenotype and asthma care trajectories between SCCs and TRCs.

RAMSES is currently one of the largest nationwide registries of severe asthmatic subjects in Europe [7–11]. The main demographic and phenotypic features of the RAMSES cohort appear similar to the other national and international registries: female predominance, 50–60 years old, asthma onset in the second decade, T2-high phenotype in half of patients, and most frequent comorbidities including GORD, ear/nose/throat (ENT) diseases and obesity [5, 7–13]. The rate of ex- and current smokers in RAMSES was slightly higher than in the COBRA (38%) and U-BIOPRED (26%) cohorts [9, 13]. Asthma was frequently uncontrolled (66.5% with ACT <20; 42.7% with ACT <15), with a mean of 4 exacerbations in the past year. The objectives of the RAMSES study, focusing on efficacy and security of biologics, and thus favouring the inclusion of patients initiating such treatments, may represent a selection bias for uncontrolled subjects with a recent history of exacerbation, as in the recently published UK Severe Asthma Registry [11]. However, similar rates of uncontrolled asthma were reported in the French academic COBRA (60%) and non-academic FASE-CPHG (70%) cohorts [9, 10], and across European registries included in SHARP (54–100%) [5]. Maintenance OCS use (14.2%) was much lower than in previous severe asthma registries: 34–50% in studies including patients before 2017 [6, 9, 13]. This could be due either to differences between countries in prescription habits over time, in the availability of biologics or maybe in self-limitation in OCS use in the context of the coronavirus disease 2019 (COVID-19) pandemic [14, 15]. Despite a decrease in maintenance OCS use, this 14.2% rate remains important, with several potential side-effects as observed in our population which exhibited frequent long-term corticosteroid-induced or -worsened diseases, including osteoporosis and diabetes, that are known to be associated with the level of the daily dose used [16]. These results highlight the still unmet needs for severe asthma management improvement.

Important differences in severe asthma management exist across Europe and worldwide [5, 6], including differences in national regulations and health system structures [17]. These differences might also be in part due to different human and material resources and biologic availability. As an example, a recent survey focusing on the use of biologics and performed in 28 European countries participating in SHARP identified disparities in the number of biologics available (two to five drugs), the requirement for patient financial contribution in nine of the 28 countries and limitations regarding prescribers, restricted to pulmonologists in four of the 28 countries [18]. Previous studies identified that severe asthma care organisation within dedicated severe asthma centres led to a significant improvement in asthma symptoms [19]. We identified, at a national scale, differences in severe asthma phenotypes between SCCs and TRCs. In France, patients are free to choose their care centre and a referral from a general practitioner, although usual, is not mandatory to access a SCC or TRC. In accordance with French regulations, the initial biologic prescription must be issued by a physician affiliated with a hospital (either secondary or tertiary), while subsequent renewals are permissible through pulmonologists, allergologists, paediatricians, dermatologists, ENT or internal medicine specialists. Non-compliance with this regulation may subject patients to the risk of non-reimbursement of drug costs by the national health insurance. In our study, TRCs appeared to manage more complex severe asthma patients, characterised by a long history of severe asthma, more frequent comorbidities, low blood eosinophil counts and multiple previous lines of biologics. As a result, those TRC-managed patients benefit from more frequent investigations for differential diagnoses or associated comorbidities. It must be pointed out that despite national [20] and international [2, 21] guidelines for severe asthma management, 29% of the subjects did not benefit from allergy testing and 12% were not assessed for blood eosinophils counts. Other phenotyping tools, depending on the local availability of material resources, were more scarcely used, including F_{ENO} measurement, which is not reimbursed by health insurance in France (46.5%), or induced sputum (5.3%), with important differences between the TRC and SCC groups, confirming the FASE-CPHG cohort description where 4.4% of the patients were assessed for F_{ENO} [10] and reflecting the national disparity of resources.

In addition to different phenotypes, we observed different care trajectories: TRC patients were more likely to receive less conventional treatment strategies, including azithromycin and bronchial thermoplasty, and to

participate in clinical trials. A recent meta-analysis including 25 studies *versus* placebo (about 2000 patients) suggested an effect of macrolides on reducing severe exacerbations and asthma symptoms [22]. However, those studies were performed on highly selected patients. Moreover, long-term macrolide treatment raises concerns about antimicrobial resistance, which is a major public health issue [21]. Such treatment strategy should be discussed on a case-to-case basis in multidisciplinary severe asthma-dedicated meetings, as recommended in France.

Less than 25% of the patients benefited from patient education. Patient education aims to encourage adherence, and provide skills in inhaler device use and self-management, to control symptoms and reduce the risk of exacerbations. It is recommended for all patients with asthma, with a special focus on difficult-to-treat asthma [23]. Among the 52 RAMSES investigation centres, only 21 (40%) were able to provide a patient education programme certified by national health authorities, representing half of TRCs (12 out of 24 (50%)) and one-third of SCCs (nine out of 28 (32%)) involved in the current study [24]. This appears largely undersized, especially in SCCs, given the estimated 4 million people affected by asthma in France, of which 4.5% have severe asthma [25].

Several limitations must be pointed out. First, as already mentioned, the objectives of the RAMSES cohort focusing on efficacy and security of biologics favouring the inclusion of patients initiating such treatments, by centres experienced in severe asthma management, may represent a selection bias for uncontrolled subjects. Second, the reasons why some investigations were not performed were not collected, whether they were deemed unnecessary, too complex to organise or not available locally. In addition, data regarding the history of care centres attended by patients before their inclusion in the cohort were not available. Whether the differences observed in our study can be extended to other European countries, although suggested, remains to be investigated [17]. Despite those limitations, our study reveals that TRCs and SCCs provide complimentary management of severe asthmatic subjects and suggests that a shared effort is necessary to improve severe asthma care.

Conclusion

In conclusion, this first analysis of the RAMSES cohort, one of the largest national registries of severe asthmatic subjects in Europe, identified different phenotypes and care trajectories depending on the type (secondary or tertiary) of the care centre. These results suggest different levels of asthma severity and differences in medical resources and practices among centres. They also highlight the need for standardisation of severe asthma care at a national level.

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