Real-life Cretan asthma registry focused on severe asthma: On behalf of 'The Cretan registry of the use of Biologics in Severe Asthma'

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Abstract. Asthma diagnosis and management remains a challenging task for the medical community. The aim of the present study was to present the functional and inflammatory profiles of patients with difficult-to-treat asthma in a real-life clinical setting referred to the specialized asthma clinic at the University Hospital of Heraklion. The registry included a cohort of 267 patients who were referred to the severe asthma clinic. Patients were assessed with emphasis on the history of allergies, nasal polyposis or other comorbidities. Blood testing for eosinophils counts and total and specific IgE, and pulmonary function tests were performed at baseline. The median age of patients with asthma was 55 years old, 68.5% were women and 58.3% were never smokers. The vast majority presented with late onset asthma (75.7%), whereas eight (3%) patients were on oral corticosteroids. The median number of exacerbations during the last 12 months was 1 (0-3). Furthermore, 50.7% of patients had a positive serum allergy test, the median eosinophil count was 300 (188-508.5) cells/μl of blood and median total IgE level was 117.5 (29.4-360.5) IU/ml. Patients were retrospectively grouped in the following categories: Group 1, mild-moderate asthma; group 2, patients prescribed a step 4 or 5 asthma therapy according to Global Initiative for Asthma; and group 3, patients on biologic agents. Group 1 had significantly higher FEV1% than groups 2 and 3 (93.4 vs. 79.9 and 79.4%, respectively; P<0.001). Finally, the median Asthma Control Questionnaire 7 (ACQ7) score was 1.14, with patients from groups 2 and 3 presenting higher ACQ7 scores compared with group 1 patients as expected (1.1 and 2.1 vs. 0.7, respectively; P<0.001). To the best of our knowledge, this was the first real-life asthma study in Crete that demonstrated that severe asthmatics predominantly have late-onset asthma with airflow obstruction and uncontrolled symptoms.

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Introduction

Asthma is a heterogeneous disease, usually characterized by chronic airway inflammation. Severe asthma is defined as asthma that remains uncontrolled despite adherence with maximal optimized therapy (with high dose ICS-LABA) or that that requires high dose ICS-LABA to prevent it from becoming uncontrolled (1). Asthma is a common, chronic respiratory disease affecting 1-18% of the population worldwide. However, severe asthma remains underdiagnosed and poorly managed despite the emergence of new effective biological treatments (2).

Clinical recommendations regarding the treatment of severe asthma, established by ERS (European Respiratory Society)/ATS (American Thoracic Society) aimed to reduce the exacerbation frequency and to improve the quality of life of these patients. Specific attention has been made in individualized and phenotypic-driven management (3). It is argued that national and local asthma programs are more

effective than conventional treatment guidelines in improving asthma care and reducing costs (4).

Omalizumab, the first novel biologic approved for severe asthma changed the landscape in the management of the disease. Omalizumab is a recombinant monoclonal anti-IgE antibody that binds to free IgE and down-regulates high-affinity IgE receptors on mast cells as well as basophils, eosinophils and dendritic cells. It was the first and for a long time the only biological drug available in clinical practice for the add-on therapy of uncontrolled asthma. Its long-term effectiveness has been widely demonstrated by various studies (5,6). The second biologic therapy approved was Mepolizumab a humanized monoclonal antibody against interleukin-5. IL-5 involves in the maturation, recruitment and activation of eosinophils thus anti-IL-5 treatment such as mepolizumab proved to be an effective add-on treatment for severe eosinophilic asthma (7-9). Although mepolizumab binds circulating IL-5, benralizumab is another approved biologic agent for severe eosinophilic asthma and binds to IL-5 receptor α subunit, leading to apoptosis of eosinophils (1).

The prevalence of severe asthma varies widely among the different countries (ranging from 3.6% in the Netherlands to 8.1% in Denmark) (10,11). The International Severe Asthma Registry (ISAR) is the first global adult severe asthma registry which aims to improve our understanding of severe asthma through the implementation of existing and the generation of new knowledge in this field (12). In Greece the self-reported prevalence of physician diagnosed asthma was 9% in a nation-wide survey (13) which was in accordance with other recent surveys of self-reported prevalence of asthma (9.1%) (14). The aim of the present study was to provide real life data of referrals of patients with mainly (but not exclusively) uncontrolled or difficult to treat asthma in the community to an asthma expert centre. An additional aim was the establishment of a severe asthma registry in Crete since 2008 with characterization of patients at their baseline assessment.

Materials and methods

Patients. Patients with asthma uncontrolled or difficult to treat in the community, were mainly referred to the Heraklion University Hospital's asthma expert center between 2008 and 2019. The study was conducted in a retrospective manner.

All patients were evaluated systematically during a 1-day visit and according to the medical decisions made they were distributed into the following 3 groups: Group 1, patients with mild-moderate asthma; group 2, patients who were prescribed a step 4 or 5 asthma therapy according to Global Initiative for Asthma (GINA) (1), such as medium/high dose inhaled corticosteroids with or without LABA, oral corticosteroid, tiotropium or had a change in a step 4 or 5 treatment during the first visit and group 3, patients under treatment with a biologic agent such as omalizumab or mepolizumab.

Patients' demographics were documented, including age, gender and nationality as well as certain clinical parameters such as the body mass index, smoking status (non-smoker, ex-smoker, current smoker), history of comorbidities, allergies and asthma age of onset (late-onset if 18 years old or older), history of exacerbations in the last 12 months and use of

inhaled medication and oral steroids were recorded. Data on spirometry especially pre-bronchodilation forced expiratory volume in 1 sec (FEV_1), and blood testing for blood eosinophil count, total and specific serum IgE were provided where available.

The presence of self-reported comorbidities was included in the evaluation such as: eczema, allergic rhinitis, nasal polyps, chronic rhinosinusitis, atopic disease, hypertension, diabetes, hyperlipidemia, chronic heart or other cardiovascular disease, anxiety, depression, obstructive sleep apnea, gastroesophageal reflux disease, medication intake such as nonsteroidal anti-inflammatory drugs and angiotensin-converting enzyme inhibitors.

Data on the patients' medication regarding asthma and the Asthma Control Questionnaire 7 (ACQ7) were obtained. A lower score corresponds to better asthma control, using a minimal clinically important difference of 0.5, which indicates the minimal difference in mean scores that is regarded as important (15,16). Data presented for patients currently on biologics are from the baseline assessment prior to initiation of biologics including omalizumab, mepolizumab or combination.

Statistical analysis. Current analysis included data until December 2019. Distribution of continuous variables was assessed. Data were expressed as median (interquartile range), and for categorical variables as counts (percentage). Statistical analysis was performed using R studio [R version 3.6.2 (2019-12-12)]. Kruskal-Wallis test was used for comparison of non-parametric continuous variables and Chi-square or Fisher's exact for the comparison of categorical variables. $P<0.05$ was considered to indicate a statistically significant difference. As anticipated in a real life study, the data set contains a substantial number of missing data.

Results

Patients' baseline characteristics. Patients' baseline data are displayed in Table I. The total number of patients included in the study was 198. A total of 109 patients (55.1%) were characterized as difficult to treat asthma at the time of presentation, whereas 63 patients (31.8%) were categorized as having mild to moderate asthma and 26 (13.1%) out of the total were already on biologic agent, either omalizumab (46.2%) or mepolizumab (53.8%). The median age of asthma patients referred to our center was 55 years old and 183 (68.5%) of the subjects were females. Patients presenting with mild to moderate asthma were younger than those with severe asthma and those already on biologic agent at the time of presentation, in a statistically significant way (median age of 45 vs. 57 and 60.5, respectively P<0.001). Most of the patients included in the study were never smokers (154 patients, 58.3%) while the median BMI of the participants was 28.7.

Asthma parameters. The asthma related variables of the study population are shown in Table II. Most patients had late onset asthma (137 subjects, 75.7%). 8 patients (3%) were on oral corticosteroids. The vast majority of patients were classified in group 2. The median number of exacerbations during the last 12 months was 1 (0-3).

Table I. Baseline demographic characteristics of patients with asthma.

| Characteristics | Groups included in present study (n=198) | | | Total registry patients (n=267) | P-value |
	Group 1 (n=63)	Group 2 (n=109)	Group 3 (n=26)		
Age, years, median (interquartile range)	45 (32-59)	57 (47-68)	61 (44-67)	55 (43-65)	<0.001
Sex					0.307
Male, n (%)	21 (33.3)	26 (23.9)	9 (34.6)	84 (31.5)	
Female, n (%)	42 (66.7)	83 (76.1)	17 (65.4)	183 (68.5)	
Smoking status					0.081
Non-smoker, n (%)	32 (51.6)	63 (57.8)	15 (57.7)	154 (58.3)	
Ex-smoker, n (%)	11 (17.7)	27 (24.8)	9 (34.6)	59 (22.3)	
Current smoker, n (%)	19 (30.6)	19 (17.4)	2 (7.7)	51 (19.3)	
Pack-years[a], median (interquartile range)	0.0 (0.0-12.0)	0.0 (0.0-20.0)	2.5 (0.0-23.8)	0.0 (0.0-17.0)	0.498
BMI, median (interquartile range)	26.7 (22.4-30.7)	29.7 (24.8-33.2)	30.4 (25.9-35.0)	28.7 (24.6-33.1)	0.025

[a]Calculated by multiplying the number of packs of cigarettes smoked per day by the number of years the person smoked. Group 1, patients with mild-moderate asthma; group 2, patients with difficult-to-treat asthma on long-acting muscarinic antagonists and/or high dose inhaled corticosteroids; group 3, patients with severe asthma on biologic agent (omalizumab/mepolizumab). BMI, body mass index.

Table II. Asthma parameters.

| Characteristics | Groups included in present study (n=198) | | | Total registry patients (n=267) | P-value |
	Group 1 (n=63)	Group 2 (n=109)	Group 3 (n=26)		
Asthma onset					0.006
Early, n (%)	18 (40.9)	13 (16.3)	4 (17.4)	44 (24.3)	
Late, n (%)	26 (59.1)	67 (83.8)	19 (82.6)	137 (75.7)	
Maintenance OCS, n (%)	0 (0.0)	5 (4.6)	1 (3.8)	8 (3.0)	<0.001
Exacerbations in prior year, median (interquartile range)	0 (0-1)	1 (1-3)	1 (1-3)	1 (2)	0.001
Predicted % FEV1, median (interquartile range)	93.4 (80.0-110.5)	79.9 (63.9-94.5)	79.4 (60.0-98.5)	85.5 (70.0-100.8)	<0.001
Serum positive allergy test, n (%)	11 (47.8)	16 (53.3)	7 (50.0)	34 (50.7)	0.922
Current blood eosinophil count, cells/μ1, median (interquartile range)	200 (100.0-308.0)	342 (231.5-602.5)	500 (400.0-800.0)	300 (188.0-508.5)	0.007
Total serum IgE, median (interquartile range)	145.0 (49.0-400.0)	94.3 (26.0-256.3)	109.0 (28.0-473.0)	117.5 (29.4-360.5)	0.327
ACQ7 score, median (interquartile range)	0.7 (0.4-1.3)	1.1 (0.7-2.0)	2.1 (1.4-3.1)	1.1 (0.7-2.1)	<0.001

Group 1, patients with mild-moderate asthma; group 2, patients with difficult-to-treat asthma on long-acting muscarinic antagonists and/or high dose inhaled corticosteroids; group 3, patients with severe asthma on biologic agent (omalizumab/mepolizumab). FEV1, forced expiratory volume in 1 sec; ACQ7, Asthma Control Questionnaire 7; OCS, oral corticosteroid.

Patients with mild to moderate asthma had significantly higher FEV1% of predicted compared to patients with difficult to treat asthma and those on biologic agent (93.4% vs. 79.9% and 79.4%, respectively, P<0.001, Fig. 1). Approximately half of the patients had positive serum allergy test (50.7%), median eosinophil count was 300 (108-508.5) cells/mcl and median total IgE level was 117.5 (29.4-360.5) IU/ml. Finally, median ACQ7 score was 1.14 (0.7-2.1), with patients from group 2 and group 3 presenting higher ACQ7 scores compared to group 1 patients as expected 1.1 (0.7-2) and 2.1 (1.4-3.1) vs. 0.7 (0.4-1.3) respectively, P<0.001, Fig. 2).

Patient treated with biologic agent. Both Tables III and IV show the characteristics of patients who were treated with a biologic
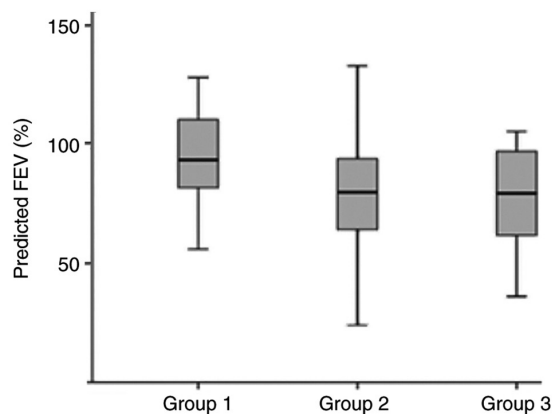
Figure 1. Predicted FEV1 (%) in each group of patients with asthma. Group 1, patients with mild-moderate asthma; group 2, patients with difficult-to-treat asthma on long-acting muscarinic antagonists and/or high dose inhaled corticosteroids; group 3, patients with severe asthma on biologic agent (omalizumab/mepolizumab). FEV1, forced expiratory volume in 1 sec.
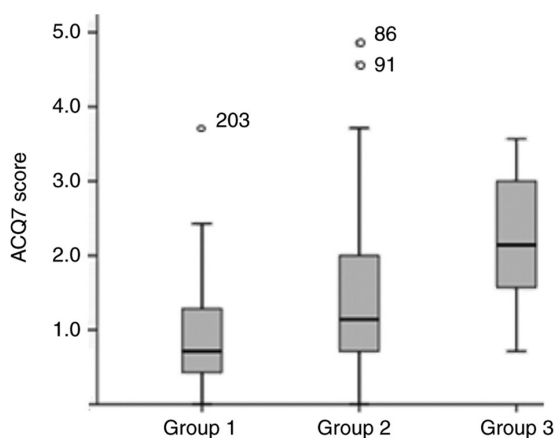

Figure 2. ACQ7 score in each group of patients with asthma. Group 1, patients with mild-moderate asthma; group 2, patients with difficult-to-treat asthma on long-acting muscarinic antagonists and/or high dose inhaled corticosteroids; group 3, patients with severe asthma on biologic agent (omalizumab/mepolizumab). ACQ7, Asthma Control Questionnaire 7.

agent after their initial assessment any time during their follow up (totally 86 patients, 32%). A total of 32 asthma patients were given omalizumab, whereas 54 were treated with mepolizumab and 13 of the latter were previously on omalizumab and had switched due to poor response. 48% of the patients were already on high dose inhaled corticosteroids and LABA and 52% were prescribed add on treatment with LAMA. 10% of patients on biologic agents received maintenance treatment with oral steroids. As demonstrated, there are no significant differences between the groups treated with a different biologic agent.

Discussion

In the present study we presented a Greek difficult to treat asthma registry. The main findings of this study were the differences observed among the 3 groups in certain clinical, physiological and immunological factors such as late onset asthma, lung function, IgE, blood eosinophils and ACQ7 scale. Severe uncontrolled asthma treatment in daily clinical

practice poses a great challenge to the pulmonologists. New strategies have been approved the recent years, implemented within a stepwise approach, taking into consideration relevant phenotypic characteristics of individuals and specific biomarkers (17,18).

Asthma prevalence is high in Greece and it imposes a high economic burden on society and the healthcare system with both direct and indirect costs (19,20). As such asthma should be recognized as a priority disease in health care policies and detailed asthma registries should exist. It is the respiratory physicians' responsibility to make 'visible' a disease that has until now been mostly 'invisible' (21) and this is something we may have achieved through our study.

Severe asthma in Europe is heterogeneous in both clinical characteristics and treatment. The European Respiratory Society Severe Heterogeneous Asthma Research collaboration, Patient-centered (SHARP) Clinical Research Collaboration was the first study to compare characteristics of patients in European severe asthma registries and treatments before starting biological therapies. It is very important to achieve harmonization of severe asthma databases across Europe (22). For example, the Portuguese Severe Asthma Registry is a national web-based disease registry of adult and pediatric severe asthma patients. It collects evidence on severe asthma in Portugal and aims at improving the healthcare delivery of severe asthma and supporting collaborative research projects (23).

As we showed in our registry, patients with severe asthma were on high dose inhaled corticosteroids and/or oral steroids. A recent German study showed that 33.6% of asthma patients treated with high dose inhaled corticosteroids/long-acting β agonists received additional oral corticosteroids. In addition, those patients had higher prevalence of other underlying disorders and more steroid side effects (24). In our registry patients on biologics received maintenance oral corticosteroids in a lesser degree (10%).

Patients with severe asthma in our cohort generally benefit from visits to our asthma clinic because of the optimization of their treatment, which may include the initiation of biologic agents after the necessary step by step characterization approach (25). We emphasized on avoidable risk factors, such as lack of education, that lead commonly to uncontrolled asthma and frequent Emergency Department visits (26). The precise asthma diagnosis in our asthma outpatient clinic is essential as it is widely accepted that asthma diagnosis is confirmed only in two third of asthma cases referred to tertiary specialists (27).

Approved biologics targeting IL-5/IL-5R, IL-4/IL-13, and IgE have shown significant reduction in exacerbations rate and other asthma outcomes such as lung function, oral corticosteroid use and quality of life in appropriately selected patients (28-32). 15% of patients in our cohort with an indication to receive a biologic agent switched from omalizumab to mepolizumab. However, further understanding is needed on how and when to switch from one biological therapy to another (32). A simple algorithm on switching possibilities in case that the physicians' initial choice is proven not to be the best has been recently suggested by a Greek expert group (33). Moreover, the clinical approach for choosing an initial biologic, the assessment of response to biologics, and the process of troubleshooting and adjusting biologic

Table III. Characteristics of patients with asthma on biologic agent.

Characteristics	Biologic agent			Total (n=86)	P-value
	Omalizumab (n=32)	Mepolizumab (n=41)	Omalizumab to mepolizumab (n=13)		
Age, years, median (interquartile range)	56 (47.5-64.0)	59 (48.5-67.5)	56 (48.5-62.0)	57 (48.8-60.0)	0.636
Sex					0.712
Male, n (%)	11 (34.4)	14 (34.1)	6 (46.2)	31 (36.0)	
Female, n (%)	21 (65.6)	27 (65.9)	7 (53.8)	55 (64.0)	
Smoking status					0.076
Non-smoker, n (%)	21 (70.0)	22 (53.7)	6 (46.2)	49 (58.3)	
Ex-smoker, n (%)	4 (13.3)	17 (41.5)	5 (38.5)	26 (31.0)	
Current smoker, n (%)	5 (16.7)	2 (4.9)	2 (15.4)	9 (10.7)	
Pack-years[a], median (interquartile range)	0.0 (0.0-15.3)	7.0 (1.5-30.0)	37.5 (22.5-58.8)	5.0 (0.0-30.0)	0.001
BMI, median (interquartile range)	30.1 (25.7-35.1)	29.7 (25.0-33.9)	28.1 (24.8-33.2)	29.3 (25.4-34.7)	0.820

[a]Calculated by multiplying the number of packs of cigarettes smoked per day by the number of years the person smoked. BMI, body mass index.

Table IV. Asthma parameters of patients on biologic agent.

Parameters	Biologic agent			Total (n=86)	P-value
	Omalizumab (n=32)	Mepolizumab (n=41)	Omalizumab to mepolizumab (n=13)		
Asthma onset					0.151
Early, n (%)	5 (26.3)	5 (14.3)	0 (0.0)	10 (15.4)	
Late, n (%)	14 (73.7)	30 (85.7)	11 (100.0)	55 (84.6)	
Maintenance OCS, n (%)	0 (0.0)	5 (14.7)	2 (22.2)	7 (10.0)	0.149
Exacerbations in prior year, median (interquartile range)	2.5 (0.8-6.3)	1.5 (1.0-3.0)	4 (3.0-6.5)	2.5 (1.0-4.3)	0.162
Predicted % FEV1, median (interquartile range)	67.2 (53.8-92.5)	76.6 (62.1-86.3)	65.6 (43.1-78.2)	75.6 (56.6-85.4)	0.384
Serum positive allergy test, n (%)	8 (88.9)	6 (42.9)	4 (66.7)	18 (62.1)	0.082
Current blood eosinophil count, cells/μl, median (interquartile range)	300 (150-550)	375 (125-636)	100 (65-550)	321 (100-563)	0.532
Total serum IgE, median (interquartile range)	365.5 (115.8-571.3)	99.5 (20.1-429.3)	337.0 (46.1-1,705.5)	277.0 (31.2-538.5)	0.150
ACQ7 score, median (interquartile range)	2.3 (1.1-3.4)	2.1 (1.3-2.8)	2.9 (2.0-3.4)	2.2 (1.3-3.2)	0.438

FEV1, forced expiratory volume in 1 sec; ACQ7, Asthma Control Questionnaire 7; OCS, oral corticosteroid.

treatment for those patients with suboptimal responses are discussed in the recent literature (34).

Super-responders (upper 25% of ACQ5 responders) were found to have a higher T2 disease burden and fewer comorbidities at baseline in The Australian Mepolizumab Registry (8). We recently participated, as one of the specialized asthma clinics in Greece, that in patients with severe eosinophilic asthma, 1 year of treatment with mepolizumab was safe and resulted in significant reduction of the annual exacerbation rate, reduction (or even discontinuation) of the needed dose of OCS, and improvements of asthma control and lung function (35).

Our study has both strengths and limitations. An important limitation is the retrospective nature of the study making the lack of a large amount of information and missing data, a common phenomenon in real-life studies. Additionally, it was a single-center study, however, the only one in the island of Crete, which also could carry bias. The strengths are that

it provides real life data regarding a lot of aspects of asthma management in a large group of Cretan patients for a period of several years. As such it yields more precisely the reality of the daily management of these patients. Furthermore, it analyses a large group of severe asthma patients on biologic treatment for asthma. Such studies are unfortunately limited in our country, so, we hope that we add important information about the best clinical and holistic approach for our patients, in the era of the biologics in the severe asthma patients.

The majority of the patients included had severe asthma. Particularly those on biologic treatment were on high dose ICS or/and oral steroids while commonly presented with allergic rhinitis and nasal polyposis. Our study demonstrates the importance of a detailed assessment in expert asthma centers for uncontrolled asthmatic patients for precise identification of severe disease and timely initiation of targeted therapy.

Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Authors' contributions

KMA, DAS and NT were responsible for designing the study, writing the manuscript, approving the data analysis and reviewing the manuscript. KMA, KK and NT confirm the authenticity of all the raw data. MB, KK, AT and DI were responsible for collecting the data, performing data analysis and writing the manuscript. VS, CC and SM acquired and analyzed the daya. GP, IL and IM were involved in the study design, conception and interpretation of data. ES acquired and analyzed the data. All authors have read and approved the final manuscript.

Ethics approval and consent to participate

The present study was approved by the ethics committee of University General Hospital Heraklion (Heraklion, Greece; approval no. 404A-9751). This study was conducted in a retrospective manner, and thus the need for consent was waivered by the ethics committee of University General hospital Heraklion.

Patient consent for publication

All identifying information has been removed, public interest considerations outweigh the potential harm.

Competing interests

DAS is the Editor-in-Chief for the journal, but had no personal involvement in the reviewing process, or any influence in terms of adjudicating on the final decision, for this article. The other authors declare that they have no competing interests.

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