Demographic and clinical patterns of severe asthma in the Middle East

Mohamed Abuzakouk, Omar Khaled Hassan Attia Ghorab, Bassam Mahboub¹, Ashraf Alzaabi², Mateen Haider Uzbeck, Mohsen Nasir, Zaid Zoumot, Deepa Grandon, Yaser Abu El Sameed, Rajae Namas³, Ali Saeed Wahla, Jeffrey Chapman, Khaled Saleh, Fulvio Salvo, Govinda Saicharan Bodi, Irfan Shafiq

Abstract:

BACKGROUND: Severe asthma is a major burden on health-economic resources; hence, knowing the epidemiology of these patients is important in planning and provision of asthma care. In addition, identifying and managing the comorbidities helps improve symptoms and reduce associated morbidity and mortality.

OBJECTIVES: Epidemiology of difficult asthma has not been well studied in the Middle East, so in this study, we present the demographic and clinical characteristics of severe asthma in the United Arab Emirates (UAE).

METHODS: We retrospectively reviewed the notes of severe asthma patients attending three tertiary care hospitals between May 2015 and December 2019. Data on baseline demographics, asthma characteristics, treatment, and comorbidities were collected.

RESULTS: We reviewed the notes of 458 patients (271 females and 187 males) that fulfilled the 2019 Global Initiative for Asthma guidelines for the diagnosis of severe asthma. The mean age was 47.7 (standard deviation 17.2) years. Males had significantly higher asthma control test scores (17.9 vs. 16, \(P = 0.01\)) and mean blood eosinophils (0.401 vs. 0.294, \(P <0.01\)) than females. The most common comorbidity observed was allergic rhinitis (52.2%) followed by gastroesophageal reflux disease (27.1%). In total, 109 (23.8%) patients were on biological therapies with most patients being on omalizumab and dupilumab (29 and 18 patients, respectively). Most patients were nonsmokers (97.2%), and majority were of TH2-high phenotype (75.7%).

CONCLUSIONS: In this first report of severe asthma characteristics in the UAE, we found a pattern of female preponderance and most patients having a Th2-high phenotype. The findings are likely to help optimize asthma care in the region in the era of biologic therapies.

Keywords: Airflow obstruction, allergic asthma, asthma, asthma epidemiology, severe asthma epidemiology, Th1/Th2

Asthma is a chronic lung disease characterized by airway inflammation and hyper-responsiveness affecting almost 300 million people worldwide. Asthma can be classified as mild, moderate, or severe, based on the intensity of treatment required to achieve asthma control. Severe asthma is defined as asthma that requires treatment with high-dose inhaled corticosteroids (ICS) to maintain good control or as asthma that is poorly controlled despite the use of maximal optimized therapy and treatment of contributory factors. Severe asthma is reported to affect about 5%-10% of asthmatics. It is important to differentiate severe asthma from difficult-to-treat asthma, which is defined as asthma that is poorly controlled due to correctable factors such as environmental allergens, comorbidities, poor medication compliance, and incorrect inhaler technique. While severe asthma is
less prevalent than milder asthma severities, it remains a major cause of morbidity[4] and mortality[5,6] worldwide. In addition, it is associated with a major socioeconomic,[7] psychological,[8] and treatment[9] burden.

The clinical characteristics and phenotypes of severe asthma patients have been previously reported from various parts of the world,[10‑12] and this knowledge has been particularly important for the development and application of novel biological therapies. In addition, severe asthma registries can be used for genetic profiling to help identify individuals who are genetically predisposed to severe asthma. Difficult asthma phenotypes, including patients with severe asthma, have not been well studied in the Middle Eastern populations. The United Arab Emirates (UAE) has no official severe asthma registry and as yet no published data describing the characteristics of these patients. Undoubtedly, it is necessary to understand local epidemiology and clinical characteristics of severe asthma to make better-informed local guidelines and treatment decisions. Therefore, we took the initiative to examine the demographic and clinical variables of severe asthma in a local population attending three tertiary care hospitals in the UAE between May 2015 and December 2019.

Methods

Subjects
We performed a retrospective chart review of all patients diagnosed with severe asthma according to the 2019 Global Initiative for Asthma (GINA) guidelines[3] attending Cleveland Clinic Abu Dhabi (Abu Dhabi), Rashid Hospital (Dubai), and Zayed Military Hospital (Abu Dhabi), between May 2015 and December 2019. Patients were included if they had at least three visits to the asthma clinic, with the visits being at least 1 month apart, were on high-dose ICS with optimal inhaler technique, showed good compliance with medication, and had good control of the contributing/exacerbating factors. Patients with asthma-chronic obstructive pulmonary disease overlap syndrome and deceased patients were excluded. We identified a total of 604 patients that met the inclusion/exclusion criteria, of whom 458 were Emirati citizens and were used to form the cohort for the current analysis.

Study variables
The medical records of all participants were reviewed by a study team comprised of one or two researchers at each study site. Apart from basic demographic information, the Asthma Control Test (ACT) scores, fractional exhaled nitric oxide (FeNO) levels, eosinophil counts, and total immunoglobulin E (IgE) levels were also recorded. Comorbidities including body mass index, cigarette smoking, allergic rhinitis, hypertension, gastroesophageal reflux disease (GERD), hyperlipidemia, diabetes, obesity, obstructive sleep apnea (OSA), nasal polyps, thyroid disease, bronchiectasis, depression, anxiety, osteoporosis, food allergy, eczema, and malignancies were documented.

Statistical analysis
Descriptive statistics were used to summarize the characteristics of the cohort. Comparisons of categorical baseline characteristics in the cohort were performed using Pearson’s Chi-squared test. Comparisons of continuous baseline characteristics were performed using Welch’s two-sample t-test. We considered a p-value less than 0.05 to be statistically significant in our study.

Results

Baseline characteristics
A total of 604 patients fulfilled the 2019 GINA guidelines for the diagnosis of severe asthma. Among these, 458 patients (75.8%) were Emirati citizens, whereas 146 patients (24.2%) were expatriates. Since our objective is to study the demographics of the local Arab population, the expatriates were excluded from the analysis. Among the 458 patients, there were 271 females (59.2%) and 187 males (41%) [Table 1]. The mean ± standard deviation age for females was higher than that for males (50.2 ± 16.6 years vs. 44.2 ± 17.4 years, P = 0.002), with a range between 14 and 92 years.

Age of asthma onset was available for 241 patients, of these 111 patients (46.1%) reported having been diagnosed with asthma in childhood, whereas 130 patients (53.9%) were diagnosed as adults.

Information about asthma phenotype, i.e., allergic versus nonallergic was available for 242 patients. Out of those, 148 patients (61.2%) were labeled as having allergic asthma and 35 patients (14.5%) suffered from eosinophilic asthma. Together these two groups made up the Th2 high phenotype (75.7%). The rest of the patients in the cohort (24.3%) were nonallergic/Th2 low phenotype.

We carried out statistical comparisons of asthma characteristics between males and females and identified significant differences in ACT scores and mean blood eosinophil count [Table 2]. A significantly higher mean ACT score and eosinophil count was observed in males compared to females (17.9 vs. 16, P = 0.01) and (0.401 vs. 0.294, P < 0.01), respectively. The mean IgE and FeNO levels were not significantly different across genders.

Comorbidities and modifiable risk factors
The most frequent comorbidity observed was...
allergic rhinitis (52.2%), followed by GERD (27.1%), hypertension (26.9%), hyperlipidemia (26.0%), diabetes (25.3%), obesity (20.3%), OSA (14.0%), nasal polyps (11.1%), thyroid disease (9.6%), bronchiectasis (5.5%), eczema (3.9%), food allergy (3.7%), depression (3.5%), anxiety (3.5%), and osteoporosis (3.1%). Sixty-two patients (13%) had a history of past/present smoking. We analyzed the difference between genders in terms of comorbidities and found that GERD and depression were significantly more common in females while nasal polyps and eczema were more prevalent among males [Table 3].

Biological therapy
A total of 109 (23.8%) patients were receiving biological therapy for the treatment of severe asthma. The breakdown of the data according to the biological agents showed 56 (51.4%) patients on omalizumab, 29 (26.6%) patients on dupilumab, 18 (16.5%) patients on benralizumab, and 6 (5.5%) patients on mepolizumab.

Malignancy
Thirteen patients (2.8%) had a history of malignancy; the most common malignancies were breast, lung, and thyroid cancer, each found in three patients. Colon cancer was found in two patients, and bladder cancer and prostate cancer were each found in one patient.

Discussion
The scarcity of data on severe asthma not only in the UAE, but also in the Middle East as a whole necessitated this retrospective review in which we evaluated the demographic and clinical characteristics of patients with severe asthma in the UAE’s local Arab population and compared our data with previously published international cohorts. One of the earliest reports of asthma prevalence in the UAE stated that asthma affects about 13.6% of children in the UAE.[14] However, there is a variation in the asthma prevalence rates recently reported in the UAE; one report suggested that asthma affects at least 9.8% of the total UAE population,[15] another report estimated that it affects 13% of the population[16] and a third report estimated that asthma affects 4.9% of the population.[2] The variation in prevalence rates may be due to the different methodologies used in each of the studies, where asthma definitions have differed from one study to another. With this in mind, it is sensible for us to estimate the asthma prevalence in that the UAE is about 8%–9%, similar to that found in Kuwait (9.5%) and Saudi Arabia (8.3%).[2] The economic burden of asthma care

Table 1: Comparison of severe asthma characteristics between different studies

|                      | Current study | Wang et al.[13] | Kim et al.[16] | Novelli et al.[12] |
|----------------------|--------------|-----------------|----------------|-------------------|
| Number of patients   | 458          | 4990            | 489            | 72                |
| Age (years), mean±SD | 47.7±17.2    | 55.0±15.9       | 62.3±14.0      | 59.1±11.1         |
| Male/female          | 187/271      | 2029/2957       | 220/269        | 25/47             |
| Percentage females   | 59.2         | 59.3            | 54.9           | 65.3              |
| Percentage nonsmokers| 97.2         | 94.1            | 87.7           | 94.5              |
| Blood eosinophils    | 0.34±0.420   | 0.42±0.660      | 0.28±0.365     | 0.136             |
| Blood IgE (IU/mL), mean±SD | 627.7±2049.7 | 466.0±736.0    | 275.9±415.9    |                   |
| FeNO (ppb), mean±SD  | 36.8±35.6    | 41.1±28.4       | 22.4           |                   |
| ACT score, mean±SD   | 16.7±5.7     | 16.5±5.9        | 19             |                   |

FeNO=Fractional exhaled nitric oxide, SD=Standard deviation, ACT=Asthma control test, IgE=Immunoglobulin E

Table 2: Comparison of asthma characteristics between males and females

|                | Males |                | Females |                |
|----------------|-------|----------------|---------|----------------|
| ACT score, mean±SD | 17.9±5.1 | (n=87)         | 16±6.0  | (n=143)        |
| Mean serum IgE (IU/mL), mean±SD | 641.5±869 | (n=118)       | 615.7±2682.7 | (n=137)        |
| Mean blood eosinophils (10^9/L), mean±SD | 0.401±0.457 | (n=132)    | 0.29±0.338  | (n=161)        |
| FeNO (ppb), mean±SD | 41.7±44.5 | (n=23)        | 34±29.8  | (n=41)         |

FeNO=Fractional exhaled nitric oxide, SD=Standard deviation, ACT=Asthma control test, IgE=Immunoglobulin E

Table 3: Comorbidities according to gender

| Comorbidity         | Total | Males (%) | Females (%) | P     |
|---------------------|-------|-----------|-------------|-------|
| Allergic rhinitis   | 239   | 38.5      | 61.5        | 0.287 |
| GERD                | 124   | 31.5      | 68.5        | 0.013 |
| Hypertension        | 123   | 36.6      | 63.4        | 0.265 |
| Hyperlipidaemia     | 119   | 37        | 63          | 0.319 |
| Diabetes            | 116   | 36.2      | 63.8        | 0.238 |
| Obesity             | 93    | 36.6      | 63.4        | 0.345 |
| OSA                 | 64    | 35.9      | 64.1        | 0.395 |
| Nasal polyps        | 51    | 56.9      | 43.1        | 0.013 |
| Thyroid             | 44    | 25        | 75          | 0.024 |
| Bronchiectasis      | 25    | 44        | 66          | 0.738 |
| Eczema              | 18    | 61.1      | 38.9        | 0.070 |
| Food allergy        | 17    | 52.9      | 47.1        | 0.291 |
| Depression          | 16    | 12.5      | 87.5        | 0.020 |
| Anxiety             | 16    | 31.3      | 68.7        | 0.437 |
| Osteoporosis        | 14    | 21.4      | 78.6        | 0.136 |

OSA=Obstructive sleep apnoea, GERD=Gastroesophageal reflux disease

Annals of Thoracic Medicine - Volume 16, Issue 2, April-June 2021
in the emirate of Abu Dhabi was reported to be around 29 million USD in 2014; however, with increasing use of biologics in the severe asthma subgroup, this cost is likely to increase significantly.

The mean age of our severe asthma cohort was 47.7 ± 17.2, which is lower than the three studies we used for comparison [Table 1]. However, data from the Severe Asthma Research Program (SARP) registry reported a mean age of 37 years which is considerably lower than our cohort. This heterogeneity in the age of difficult asthma is interesting, being as high as 62.3 in Korea as reported by Kim et al. and as low as 37 in SARP, and it highlights that the care needs for these patient populations may be significantly different in the different parts of the world.

In our study, almost 54% of the patients had adult onset asthma. It has been reported that age of onset affects the response of severe asthma patients to biological therapy. Patients with adult onset usually respond better to anti-interleukin 5 (IL-5) or anti IL-5 receptor therapy, whereas patients with childhood onset disease respond better to anti-IgE therapy. Our cohort was the youngest cohort compared to cohorts from other global studies, and therefore, this could explain why more than half (51.4%) of our patients receiving biological therapy for severe asthma were on anti-IgE therapy (Omalizumab).

We observed a female predominance of 59% in our patient cohort which was no different from the studies we used for comparison. Although our observation is for severe asthma, it is well-known that females dominate all asthma severity groups. It has been suggested that sex hormones in females contribute to worse asthma symptoms compared to males, and animal studies have shown that oestrogen increased Th2-mediated airway inflammation, while androgens reduced it. This is a significant finding as it not only provides an explanation for the difference in asthma prevalence, onset, and severity between males and females, but also offers opportunities for further studies to be carried out to assess the difference in inflammatory pathways between males and females and potentially consider hormonal therapy for asthma.

In this study, we found that males had significantly higher mean blood eosinophil count and ACT scores than females (P < 0.01 and P = 0.01, respectively); this is in concordance with the previously reported data. This is an interesting observation firstly as previous studies have reported no gender-based differences in asthma control, and secondly because females in our cohort were older and more obese, which are parameters associated with worse asthma control.

Allergic rhinitis was the most prevalent comorbidity in our cohort (52.2%) as observed in other severe asthma cohorts. Allergic rhinitis is well known to coexist with asthma and according to some authors more than 80% of asthmatics have a diagnosis of allergic rhinitis. In addition, the presence of allergic rhinitis is thought to be associated with increased asthma severity. This connection between allergic rhinitis and asthma is not surprising as the “united airway disease” theory suggests that the upper and the lower airway are functionally a singular unit and the inflammatory allergic disorders in one are bound to have similar effects on the other. Hence, it is not surprising that treatment of allergic rhinitis with nasal corticosteroids and the leukotriene receptor antagonists also seems to reduce asthma exacerbations and asthma-related respiratory symptoms.

Similar to other cohorts, GERD was the second most common co-morbidity observed in our patients (27.1%), and it is known to be more prevalent among asthmatics compared to the general population. We also observed a statistically significant difference in the prevalence of GERD between females and males (68.5% vs. 31.5%, respectively, P = 0.013). This finding has been reported in two other studies previously and is possibly due to the effect of estrogen on the lower esophageal sphincter; however, the mechanism is not entirely clear.

Anxiety and depression were each present in 3.5% of the patients. Previously, Kim et al. had reported a somewhat similar prevalence of anxiety and depression in their study which was 1.7% and 3.7%, respectively. We also observed a significant difference in the prevalence of depression between males and females with a female preponderance (females 87.5%, males 12.5%, P = 0.02) which is in accordance with a higher prevalence of depression in women in the general population.

These findings are important as depression is reported to be a risk factor for developing asthma, and both anxiety and depression are associated with poor asthma control.

The prevalence of nasal polyposis in the Middle East including the UAE has not been previously reported. In our patient population, nasal polyposis was present in 11.1% of the total cohort while Wang et al. reported the prevalence of nasal polyposis to be 7.3%. Nasal polyposis has been reported to be associated with greater asthma severity; however, we did not observe a significant difference in ACT scores between asthma patients with and without nasal polyps (P = 0.5). Interestingly, we observed a significant difference in the prevalence of nasal polyposis between males and females (P = 0.013), where males had a higher
prevalence (56.9% vs. 43.1%, \( P = 0.013 \)) which is in concordance with previously reported data.\textsuperscript{[40]}

The choice of biologics for the treatment of asthma is expanding and phenotyping difficult asthma is the necessary first step in deciding the need and the choice of biologic therapy. Omalizumab is an anti-IgE monoclonal antibody that is approved by the Food and Drug Agency (FDA) in the treatment of moderate-to-severe allergic asthma.\textsuperscript{[41]} Mepolizumab (anti-IL5), Benralizumab (anti-IL5R), and Dupilumab (anti-IL4) are FDA approved for the treatment of severe eosinophilic asthma.\textsuperscript{[42,43]} Allergic asthma is well known to be the most common asthma phenotype worldwide,\textsuperscript{[42]} and in our cohort as well, asthma was predominantly allergic (61.2%). Wang \textit{et al.} suggested that early onset asthma combined with high IgE levels predisposes patients to develop allergic asthma later on.\textsuperscript{[13]} Our cohort had the higher mean blood IgE levels than the compared studies [Table 1], and almost 50% of the patients were diagnosed with asthma during childhood, therefore, our findings support this suggestion by Wang \textit{et al.} On the other hand, nonallergic asthma is suggested to be defined by late disease onset combined with lower IgE levels, as seen in one study.\textsuperscript{[43]} The patients who were identified as having nonallergic asthma in our study were predominantly diagnosed in adulthood and had a lower mean blood IgE compared to patients with allergic asthma; however, the difference in mean blood IgE levels was not statistically significant.

Our study is focused on the Emirati population and completely excludes the expatriate population. The genetic makeup of Emiratis could be different to the expatriate population, which would reflect on the prevalence of the different severe asthma phenotypes. The UAE government provides its citizens with a good quality health-care system administered by its Federal Ministry of Health, and this may explain the low prevalence of severe asthma in the country. In addition, while our study measures the prevalence of severe asthma across three major health-care centers in the UAE, the figure we report is not conclusive, as there may be patients receiving asthma care elsewhere in the country. Moreover, data on the prevalence of comorbidities among UAE nationals is not available; therefore, we were not able to determine whether the comorbidities we identified were truly raised in the Emirati population with severe asthma.

**Conclusion**

In summary, our study is the first to report the demographics, clinical phenotypes and treatment variables in a large cohort of Emirati patients diagnosed with severe asthma. Our findings provide important information regarding the understanding of the disease in the region and highlight the need for establishing a national registry to identify the true prevalence and help improve the management of severe asthma in the UAE.

**Financial support and sponsorship**
Nil.

**Conflicts of interest**
There are no conflicts of interest.

**References**

1. Dharmage SC, Perret JL, Custovic A. Epidemiology of asthma in children and adults. Front Pediatr 2019;7:246.
2. Chung KF, Wenzel SE, Brozek JL, Bush A, Castro M, Sterk PJ, \textit{et al.} International ERS/ATS guidelines on definition, evaluation and treatment of severe asthma. Eur Respir J 2014;43:343-73.
3. GINA-2019-main-Pocket-Guide-wms.pdf. Available from: https://ginasthma.org/wp-content/uploads/2019/04/GINA-2019-main-Pocket-Guide-wms.pdf. [Last accessed on 2020 Mar 15].
4. Nordon C, Grimaldi-Bensouda L, Pribil C, Nachbaur G, Amzal B, Thabut G, \textit{et al.} Clinical and economic burden of severe asthma: A French cohort study. Respir Med 2018;144:42-9.
5. Gupta RP, Mukherjee M, Sheikh A, Strachan DP. Persistent variations in national asthma mortality, hospital admissions and prevalence by socioeconomic status and region in England. Thorax 2018;73:706-12.
6. Majeed H, Moore GWK. Influence of the Scandinavian climate pattern on the UK asthma mortality: A time series and geospatial study. BMJ Open 2018;8:e020822.
7. Kerkhof M, Tran TN, Soriano JB, Golam S, Gibson D, Hillyer EV, \textit{et al.} Healthcare resource use and costs of severe, uncontrolled eosinophilic asthma in the UK general population. Thorax 2018;73:116-24.
8. Foster JM, McDonald VM, Guo M, Reddel HK. ‘I have lost in every facet of my life’: The hidden burden of severe asthma. Eur Respir J. 2017;50:1700765.
9. Volmer T, Effenberger T, Trautner C, Buhl R. Consequences of long-term oral corticosteroid therapy and its side-effects in severe asthma in adults: A focused review of the impact data in the literature. Eur Respir J 2018;52:1800703.
10. Kim MH, Kim SH, Park SY, Ban GY, Kim JH, Jung JW, \textit{et al.} Characteristics of adult severe refractory asthma in Korea analyzed from the severe asthma registry. Allergy Asthma Immunol Res 2019;11:43-54.
11. Gibson PG, McDonald VM. Management of severe asthma: Targeting the airways, comorbidities and risk factors. Intern Med J 2017;47:623-31.
12. Novelli F, Bacci E, Latorre M, Seccia V, Bartoli ML, Cianchetti S, \textit{et al.} Comorbidities are associated with different features of severe asthma. Clin Mol Allergy 2018;16:25.
13. Wang E, Wechsler ME, Tran TN, Heaney LG, Jones RC, Menzies-Gow AN, \textit{et al.} Characterization of severe asthma worldwide: Data from the international severe asthma registry. Chest 2020;157:790-804.
14. Bener A, Abdulkazzaq YM, Debuse P, al-Mutawwba J. Prevalence of asthma among Emirates school children. Eur J Epidemiol 1994;10:271-8.
15. Mahboub BH, Al-Hammadi S, Rafique M, Sulaiman N, Pawankar R, Al Redha AI, \textit{et al.} Population prevalence of asthma and its determinants based on European Community Respiratory Health Survey in the United Arab Emirates. BMC Pulm Med 2018;18:31.
Abuzakouk, et al.: Severe asthma demographics in the Middle East

Abuzakouk, et al.: Severe asthma demographics in the Middle East

Annals of Thoracic Medicine - Volume 16, Issue 2, April-June 2021

177

2012;12:4.

16. Alzaiabi A, Alseiari M, Mahboub B. Economic burden of asthma in Abu Dhabi: A retrospective study. Clinicoecon Outcomes Res 2014;6:445-50.

18. Cunningham AS. Eosinophil counts: Age and sex differences. J Pediatr 1975;87:426-7.

19. Bleecker ER, Wechsler ME, FitzGerald JM, Menzies-Gow A, Wu Y, Hirsch I, et al. Baseline patient factors impact on the clinical efficacy of benralizumab for severe asthma. Eur Respir J 2018;52:1800936.

20. Fuseini H, Newcomb DC. Mechanisms driving gender differences in asthma. Curr Allergy Asthma Rep 2017;17:19.

21. Shah R, Newcomb DC. Sex bias in asthma prevalence and pathogenesis. Front Immunol 2018;9:2997.

22. Bittner JJ, Halberg F, Hamerston O. Sex difference in eosinophil counts in tail blood of mature B1 mice. Science 1957;125:73.

23. Dursun AB, Kurt OK, Bayiz H, Ozkan E, Cakaloglu A, Karasoy D. Does gender affect asthma control in adult asthmatics? Chron Respir Dis 2014;11:83–7.

24. Novosad S, Khan S, Wolfe B, Khan A. Role of obesity in asthma control in patients on regular medication. J Clin Diagn Res 2016;10:OC31-5.

25. Bousquet J, Khaltaev N, Cruz AA, Denburg J, Fokkens WJ, Togias A, et al. Allergic Rhinitis and its Impact on Asthma (ARIA) 2008 update (in collaboration with the World Health Organization, GA(2)LEN and Allergen). Allergy 2008;63 Suppl 86:8-160.

26. Salvin RG, Cannon RE, Friedman WH, Palitang E, Sundaram M. Sinusitis and bronchial asthma. J Allergy Clin Immunol 1980;66:250-7.

27. Meynane Jahromi A, Shahabi Pour A. The Epidemiological and Clinical Aspects of Nasal Polyps that Require Surgery. Iran J Otorhinolaryngol 2012;24:75-8.

28. FDA. Omalizumab Prescribing Information. Available from: https://www.accessdata.fda.gov/drugsatfda_docs/label/2016/103976s5225lbl.pdf. [Last accessed on 2020 Mar 15].

29. Arbes SJ Jr., Gergen PJ, Vaughn B, Zeldin DC. Asthma cases attributable to atopy: Results from the Third National Health and Nutrition Examination Survey. J Allergy Clin Immunol 2007;120:1139-45.

30. Jones TL, Neville DM, Chaunah AJ. Diagnosis and treatment of severe asthma: A phenotype-based approach. Clin Med (Lond) 2018;18:s36-40.