A real-world evaluation of severe asthmatics referred for bronchial thermoplasty

Dear Editor,

Difficult-to-treat asthmatics are those requiring steps 4 or 5 treatment as per the Global Initiative for Asthma (GINA) guidelines.[1] Difficult-to-treat asthma is encountered in about 17% of asthmatics, and has several contributing factors, including incorrect diagnosis, incorrect inhaler technique, comorbid illnesses, and others.[1] After adequately addressing these factors, asthmatics requiring steps 4 or 5 are labeled severe asthma (<5%).[1,2] Current guidelines recommend biologicals for severe asthma patients with evidence of type-2 inflammation, while bronchial thermoplasty (BT) is generally reserved for the remaining.[1,3,4] As the studies on BT have included subjects regardless of type-2 inflammation, the proportion of patients truly eligible for BT in the real-world setting remains unclear. Moreover, all data on severe asthma are from developed countries. To our knowledge, there is no published data on this issue from the developing world.

We performed a retrospective analysis of subjects with difficult-to-treat asthma referred for BT to our institute between November 2018 and March 2020. The institutional ethics committee approved the study protocol. We were granted a consent waiver as the analysis was performed on anonymized patient data (NK/6300/Study/568). Our main objective was to determine the proportion of subjects with severe asthma eligible for BT.[5]

We performed a detailed review of the subject's diagnosis, exacerbation and treatment history, and the level of asthma control. We labeled uncontrolled asthma and difficult-to-treat asthma as per the GINA guidelines.[1,2] We further corrected factors contributing to poor asthma control (inhaler technique, compliance, exposure to tobacco smoke and other pollutants, drugs, and comorbidities). All modifiable risk factors and comorbidities were adequately addressed, and the treatment of asthma was optimized (increase in the dose of inhaled corticosteroid [ICS], the addition of long-acting muscarinic antagonist [LAMA] or-beta-agonist [LABA], leukotriene-antagonist, or methylxanthines). We followed the subjects for at least 6 months and categorized those with uncontrolled asthma despite these measures as severe asthma.

We further performed eosinophil count, serum total IgE, and high-resolution computed tomography (HRCT) of the chest in those with severe asthma. We considered subjects with peripheral blood eosinophil count ≥150/μL and serum total IgE >30 IU/mL eligible for anti-Th2 and anti-IgE therapies, respectively.[1] We considered subjects with severe asthma eligible for BT if they remained symptomatic despite >1000 μg beclomethasone dipropionate equivalent of ICS and a second controller medication (LABA, LAMA, leukotriene antagonist, or methylxanthine). We did not consider BT in those with age >65 years, forced expiratory volume in 1 sec (FEV1) <35% predicted, anticoagulation therapy, implantable cardioverter-defibrillator or a pacemaker, bronchiectasis, or emphysema on HRCT chest.

During the study period, we evaluated 48 subjects with difficult-to-treat asthma for BT [Table 1]. The

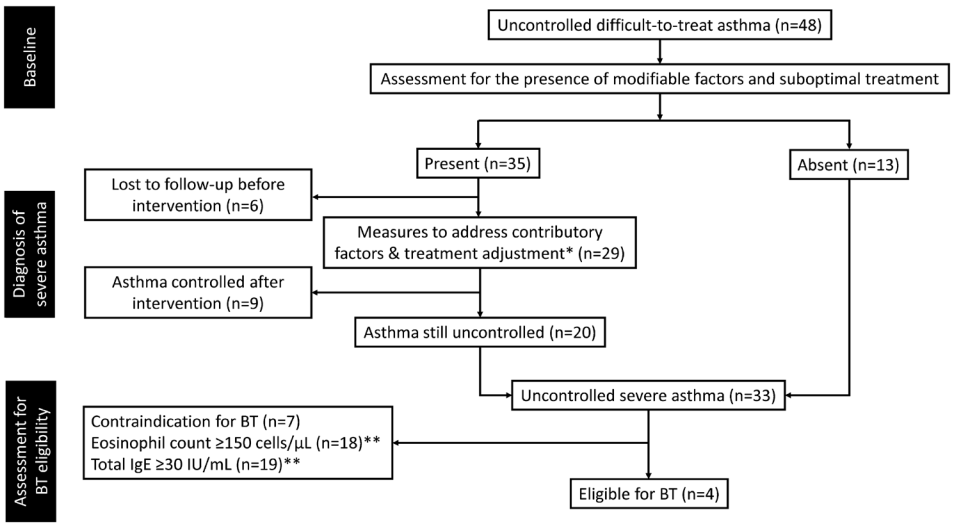

Figure 1: Flowchart describing the diagnosis of severe asthma and assessment for bronchial thermoplasty in subjects with uncontrolled difficult-to-treat asthma. Measures to address contributory factors and optimization of treatment included the following: improvement of treatment adherence ($n = 13$), correction of inhaler technique ($n = 2$), optimization of therapy ($n = 17$), addition of long-acting muscarinic antagonist ($n = 9$), increase in the dose of inhaled corticosteroid ($n = 8$), the addition of leukotriene-antagonist ($n = 7$), and addition of methylxanthine ($n = 3$). More than one measure could have been performed in each subject. **Either eosinophil count ≥150/μL or total IgE ≥30 IU/mL was observed in 22 subjects. BT: Bronchial thermoplasty

Table 1: Baseline characteristics of subjects with difficult-to-treat asthma (*n*=48)

Variable	Results
Age (years), mean (SD)	47.1 (13.3)
Women	25 (52.1)
Duration of asthma (years), mean (SD)	16.4 (12.4)
Duration of asthma >10 years	21 (43.8)
Spirometry, mean (SD)	
FVC (L)	2.2 (0.6)
FVC% predicted	74.2 (19.1)
FEV1 (L)	1.2 (0.5)
FEV1% predicted	50.4 (18.3)
ICS daily dose (μg) BDPE, mean (SD)	887.5 (209.0)
ICS daily dose ≥1000 μg BDPE	37 (77.1)
Other controllers*	
LABA	48 (100.0)
LAMA	22 (45.8)
Leukotriene antagonist	27 (56.3)
Methylxanthines	14 (29.2)
Maintenance OCS	3 (6.3)
Omalizumab	2 (4.2)
Comorbidities*	19 (34.5)
Bronchiectasis	5 (10.4)
Rhinosinusitis	5 (10.4)
Cardiac disease	3 (6.3)
Obesity	3 (6.3)
ABPA	2 (4.2)
GERD	1 (2.1)
Chest wall deformity	1 (2.1)
Patients requiring ≥20 CS pulses for asthma exacerbation in the previous year	14 (29.2)
Patients requiring ≥1 hospitalization for asthma exacerbation in the previous year	8 (16.7)

*Each subject may have more than one condition/option. All data are provided as *n* (%), unless specified otherwise. ABPA: Allergic bronchopulmonary aspergillosis, BDPE: Beclomethasone dipropionate equivalent, FEV1: Forced expiratory volume in 1 s, FVC: Forced vital capacity, GERD: Gastroesophageal reflux disease, ICS: Inhaled corticosteroid, LABA: Long-acting beta agonist, LAMA: Long-acting muscarinic antagonist, OCS: Oral corticosteroid, SD: Standard deviation

mean (standard deviation [SD]) age of the study population (52.1% women) was 47.1 (13.3) years. The mean (SD) duration of asthma was 16.4 (12.4) years, with 43.8% of subjects having the disease for >10 years. The mean (SD) percentage predicted forced vital capacity, and FEV1 was 74.2 (19.1) and 50.4 (18.3). The mean (SD) dose of daily ICS was 887.5 (209.0) μg with 77.1% on ≥1000 μg beclomethasone dipropionate equivalent. LABA (100.0%), leukotriene-antagonist (56.3%), and LAMA (45.8%) were the other controllers. Bronchiectasis (10.4%) and rhinosinusitis (10.4%) were the most common comorbidities.

Among the 48 subjects in our study, we instituted measures to address modifiable risk factors and adjusted asthma therapy in 29 (60.4%) subjects [Figure 1]. These measures included improvement in treatment adherence ($n = 13$, 27.1%), adjustment of therapy ($n = 17$, 35.4%), and correction of the inhaler technique ($n = 2$, 4.2%). The addition of LAMA ($n = 9$, 18.8%) and increase in ICS dose ($n = 8$, 16.7%) were the most common treatment adjustments. We could achieve asthma control in nine (18.8%) subjects after these measures. Finally, we diagnosed 33 subjects (68.8%) with severe asthma.

Seven of the 33 subjects with severe asthma had contraindications for BT (bronchiectasis [$n = 3$], FEV1 predicted <35% [$n = 3$], and age >65 [$n = 1$]). Of the remaining 26 subjects, eosinophil counts or total IgE were available for 23 subjects. We observed an eosinophil count ≥150/μL or total IgE ≥30 IU/mL in 22 subjects (eosinophil count ≥300/μL and total IgE ≥30 IU/mL in 19 subjects) (indicating them as candidates for treatment with biologicals). Finally, only four (12.1%) of the 33 subjects with severe asthma were eligible for BT.

Our experience has a few learning points. First, identifying and correcting modifiable factors and optimizing asthma therapy led to significant improvement in a considerable proportion of difficult-to-treat asthmatics even at tertiary referral centers. Hence, we should routinely institute these measures before initiating other therapies. Second, many patients with severe asthma are not eligible for BT due to bronchiectasis and poor lung function. The prevalence of bronchiectasis can be as high as 35% in patients with severe asthma.[6] Finally, after excluding subjects who are candidates for biological therapies, only a small proportion of patients remain eligible for BT. When comparing BT or anti-Th2 therapies in severe asthma, the evidence is far more robust for the latter.[7] Hence, it is crucial that we meticulously phenotype asthma before subjecting the patient to BT.[8,9]

Our study has a few limitations. Ours is a single-center, retrospective study with a small sample size. The proportion of patients with poor inhaler technique was low (<5%) in our study, not reflecting the real-world scenario. We are a referral center, and we carefully check the inhaler technique in the first visit itself. Further, we did not identify any subject with allergic bronchopulmonary aspergillosis or severe asthma with fungal sensitization in the study population. We routinely screen asthmatics for *Aspergillus* sensitization before referral to a severe asthma specialist. We also did not perform fractional exhaled nitric oxide measurements due to logistical reasons. Finally, our study was restricted to the initial therapy selected for severe asthma. Hence, we cannot comment on the proportion of patients eligible for BT after failing to respond to biologicals.

In conclusion, in a real-world scenario, only a small proportion of severe asthmatics remain eligible for BT as initial therapy after managing modifiable factors, adjusting asthma therapy, excluding subjects with contraindications, and identifying patients suitable for biological therapy.

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Conflicts of interest
There are no conflicts of interest.

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