https://doi.org/10.33591/sfp.48.6.uc3

MIXED SEVERE EOSINOPHILIC AND ALLERGIC ASTHMA

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SFP2022; 48(6): 68-74

INTRODUCTION

Patient Profile and Medical History

The patient is a 71-year-old Chinese male. He is a non-smoker and retired police officer who was diagnosed with asthma at the age of 45. His medical history includes hyperlipidaemia, benign prostatic hyperplasia and well-controlled type 2 diabetes mellitus. He also has chronic rhinosinusitis without nasal polyposis and allergy to contrast media. His common triggers are environmental irritants – predominantly smoke and haze, but not aero-allergens such as house dust mite and animal dander. He has no pets at home, and has no exposure to second-hand smoke.

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At Presentation

He was referred to the difficult asthma clinic (DAC) because of frequent exacerbations and poor symptom control. He experienced symptoms of cough and shortness of breath with wheezing.

Over the past 12 months, he has had 11 acute asthma exacerbations requiring systemic corticosteroid bursts – two exacerbations requiring hospital admissions, six exacerbations requiring emergency department visits, and three exacerbations that were managed in primary care. His Asthma Control Test score was 19, suggesting poorly-controlled asthma. He was prescribed treatment with Seretide (25/250) at two puffs twice daily and montelukast. He claimed adherence to his asthma controllers and his last metered dose inhaler (MDI) with spacer technique check three months prior to DAC visit was deemed to be good.

On examination, he was overweight with a body mass index (BMI) of 26.2. Clinical features of cushingoid habitus were absent with no oral candidiasis detected. Clinical examination revealed clear lung fields. No wheeze was present. He has had persistent hoarseness of voice for many years.

Investigations Spirometry

Table 1. Pulmonary assessment

	2014	2019	2020
Pre FEV1	1.73 L (73%)	1.43 L (71%)	1.39 L (62%)
Pre FVC	2.57 L (76%)	2.53 L (86%)	2.25 L (80%)
Pre FEV1/ FVC	67%	57%	61%
Post FEV1	1.92 L (81%)	1.57 L (77%)	1.51 L (67%)
Post FVC	2.8 L (83%)	2.79 L (95%)	2.29 L (81%)
Post FEV1/ FVC	69%	56%	66%
TLC	-	99%	-
RV/TLC	-	47%	-
FENO (ppb)	-	86	106

FENO = fractional exhaled nitric oxide
FEV1 = forced expiratory volume in 1 second
RV = residual volume
TLC = total lung capacity
ppb = parts per billion

Full Blood Count (FBC)
Haemoglobin 16.2 g/dL
Total white 8 x 103/uL
Platelet 270 x 103/u
Absolute eosinophil 0.7 x 103/uL
Total serum IgE 215 IU/mL
ANCA profile: Anti-MPO and Anti-PR3 negative

Skin-prick test positive to:

- House-dust mites
  - o Blomia tropicalis (8 mm)
  - o Dermatophagoides pteronyssinus (5 mm)
- Dog fur (4 mm)

Imaging

His chest X-ray was normal and high-resolution computed tomography (HRCT) of the thorax revealed nonspecific bronchial wall thickening and band atelectasis (refer to **Figure 1**) in the lower zone of his right lung. No emphysema, mosaic attenuation, nodules, or consolidation were detected.

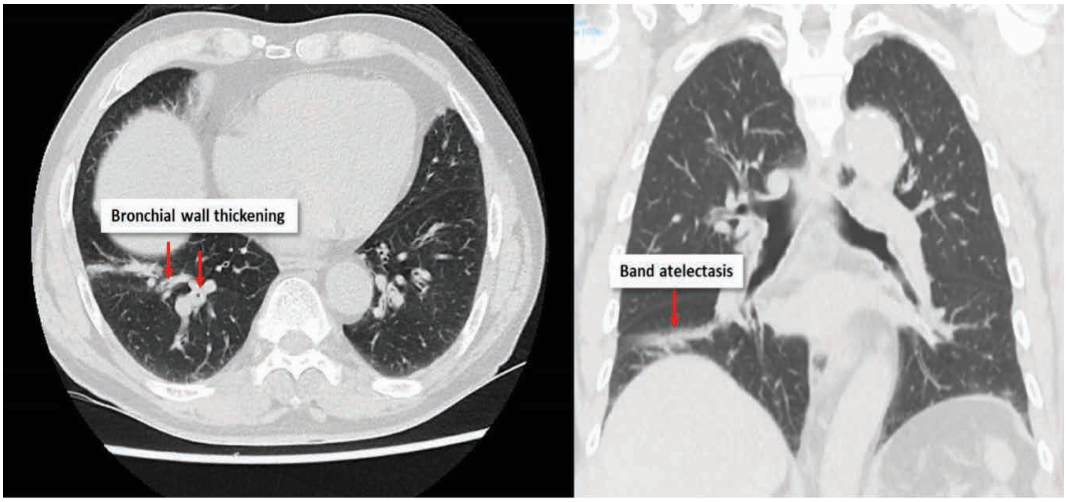

Figure 1. Thorax HRCT scan of the patient

Treatment and Management

At the DAC, a systematic assessment was performed to evaluate for other potential contributory factors to poor asthma control. Comorbidity screening was performed for the following conditions: chronic rhinitis, gastroesophageal reflux (GERD), obstructive sleep apnoea (OSA), vocal cord dysfunction (VCD), dysfunctional breathing (DB), depression, and anxiety. Objective determination of medication adherence was based on pharmacy refills.

Questionnaires used for comorbidity screening:

- OSA: STOP-Bang Questionnaire[1]
- VCD: Pittsburgh Vocal Cord Dysfunction Index[2]
- Dysfunctional breathing: Nijmegen questionnaire[3]
- Depression: Patient Health Questionnaire (PHQ-9)[4]
- Anxiety: Generalised anxiety disorder (GAD-7)[5]

Outcomes of Systematic Assessment

He tested negative for OSA, VCD, DB, depression, and anxiety. His pharmacy refill for the past six months was 100 percent and inhaler technique was good. Bone mineral density (BMD) testing showed osteoporosis (T-score -3), and his repeat FBC unexpectedly showed marked increase in absolute blood eosinophil to 15 x 103/uL.

As subsequent FBC still showed hypereosinophilia, a haematology consultation and further investigations were obtained. He tested negative for autoimmune screen (ANA and repeat ANCA) and there were no parasites in stool culture. Bone marrow testing was not performed.

He was referred to the ear, nose, and throat (ENT) specialist in view of hoarseness of voice, history of CRSsNP, and cough. A nasoendoscopy returned the following results: minimal mucous in left middle meatus, no nasal polyps, the presence of bilateral arytenoid fold oedema, and CRSsNP and laryngopharyngeal reflux.

Following his evaluation, he was started on calcium supplements and bisphosphonates. Intranasal steroids and

douche, as well as a trial of proton pump inhibitor, were commenced. He had no systemic symptoms during this period of time and his subsequent FBC showed decreasing eosinophil trending back to baseline (refer to **Figure 2**). Hence, the haematologist's impression was that of reactive eosinophilia. Once a haematological malignancy was excluded, the decision was made to commence an anti-interleukin-5 (anti-IL5) biologic, benralizumab.

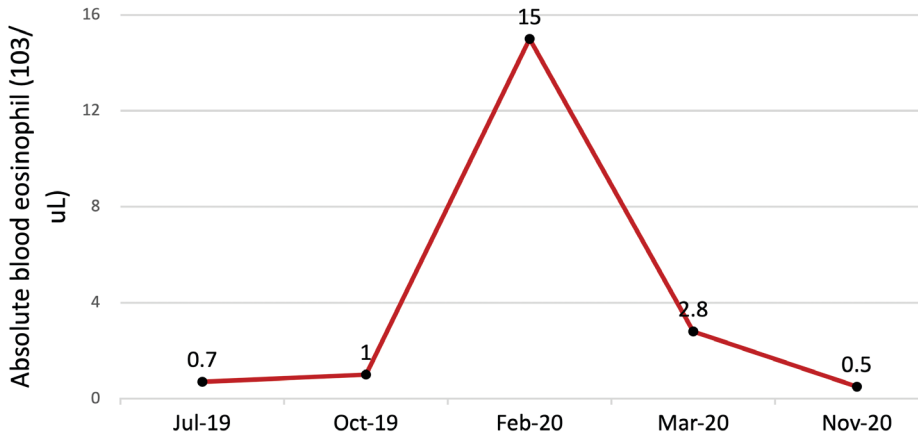

Figure 2. Full blood count results

CASE DISCUSSION

Diagnosis of Severe Asthma

He fulfilled the criteria for difficult-to-treat asthma when he presented to the clinic as his asthma was uncontrolled despite Global Initiative for Asthma (GINA) step 5 treatment.[6,7] It is important to first confirm the diagnosis of asthma, as well as identify and address possible contributory factors such as nonadherence, poor inhaler technique, and/or comorbidities.[8] Only a subset of difficult asthma patients are found to have "biologically" severe asthma after such careful evaluations.[9] It is this group of patients with severe asthma in whom asthma therapy should be escalated.

He had objective evidence of obstructive airflow obstruction on spirometry, with near significant bronchodilator response. The absence of a significant smoking history and HRCT thorax findings also made asthma the most likely diagnosis for his obstructive airway disease. Neither suboptimal medication adherence nor inhaler technique appeared to be contributory factors to his poor asthma control. His main asthma-related comorbidities were chronic rhinosinusitis (CRS) and gastroesophageal reflux disease (GERD), as indicated by evidence of laryngopharyngeal reflux on nasoendoscopy. As his asthma remained uncontrolled despite treatment of these comorbidities, a diagnosis of severe asthma was made and escalation of asthma treatment was deemed appropriate.

Asthma Phenotype

Ascertaining the inflammatory phenotype is the next step once a decision is made to escalate asthma therapy. Patients can be broadly categorised as having type 2 high or type 2 low inflammation. Type 2 high inflammation is typified by the secretion of cytokines such as interleukin (IL) 4, 5, and 13, and recognised clinically as allergic and/or eosinophilic asthma.[10] The converse is true for type 2 low inflammation.

Our patient demonstrated type 2 high inflammation and was considered to be both eosinophilic (raised blood eosinophils and fractional exhaled nitric oxide [FENO]) and allergic (raised total serum immunoglobulin E [IgE]) and sensitisation to allergens). Although systemic corticosteroids are highly effective in suppressing type 2 inflammation, they are not the preferred step-up therapy due to their side effect profile. This is particularly relevant in our patient who had DM and osteoporosis. Biologics would be most appropriate therapy for this patient.

Biologics Treatment Options for Mixed Allergic and Eosinophilic Asthma Patients

There are currently four biologics available in Singapore for severe asthma: omalizumab (anti-IgE), mepolizumab (anti-IL-5), benralizumab (anti-IL5Ra), and dupilumab (anti-IL4Ra). Omalizumab is indicated for patients with severe persistent allergic asthma, while mepolizumab, benralizumab, and dupilumab are indicated for patients with severe eosinophilic asthma.[11] As observed in real-world studies, there is a group of "overlap" patients who are eligible for both anti-allergic and anti-eosinophilic biologics.[12] Our patient fell into this "overlap" group. There are some studies showing the biologics' efficacy in overlap patients (refer to **Figures 3 and 4**).[17,28]

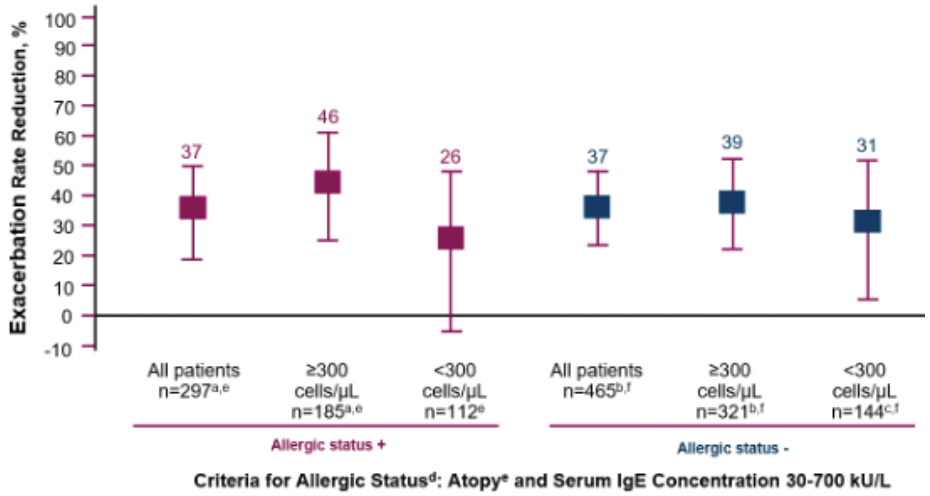

Figure 3. Benralizumab demonstrated exacerbation reductions independent of allergic status[28]

[a]Nominal p=0.0002

[b]Nominal p<0.0001

[c]Nominal p=0.0257. Results are descriptive.

[d]Adapted from criteria similar to those for patients who might qualify for omalizumab treatment.

[e]Atopy (by Phadiatop test) and serum IgE concentration of 30-700 kU/L criteria.

[f] Did not meet atopy and IgE 30-700 kU/L criteria.

Note: Data are from the pooled adult intention-to-treat population from the high-dosage ICS/LABA treatment cohorts of the SIROCCO and CALIMA studies. Estimates were calculated by using a negative binomial model, with adjustment for study code, treatment, region, oral corticosteroid use at time of randomisation, and prior exacerbations. The log of each patient's corresponding follow-up time was used as an offset variable in the model to adjust for patients having different exposure times during which the events occurred. Error bars are 95 percent confidence interval.

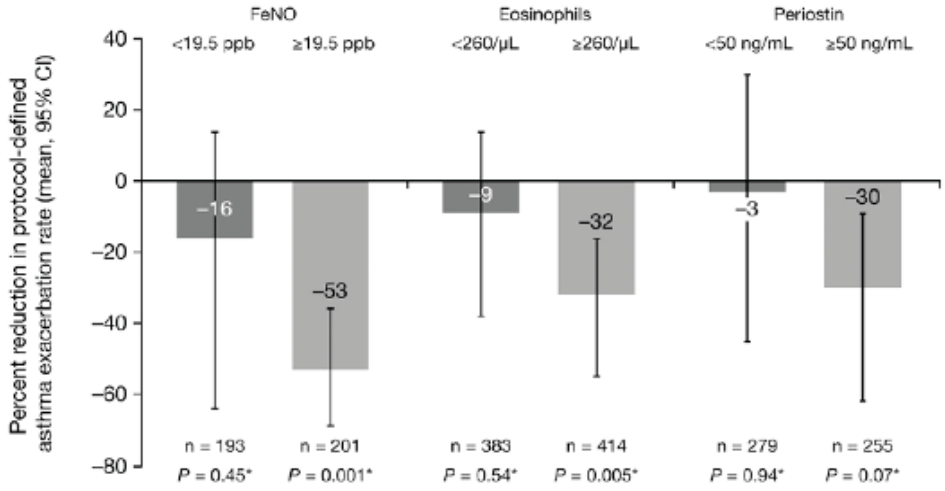

Figure 4. Omalizumab reduced exacerbation in severe allergic asthma with eosinophilia[17]
*Exacerbation reduction P values

It is important to note that the eligibility criteria for biologics are not always predictors of treatment response, as illustrated by the poor predictive value of total serum IgE for Omalizumab response.[13] There is, as yet, no single biomarker to predict treatment response for each biologic, but decision-making algorithms have been proposed.[14,15] In addition, various clinical considerations may also aid clinicians in choosing a suitable biologic.[16] Factors to consider include age, markers predicting response, effect of biologic on asthma outcomes (exacerbations, symptoms, lung function, corticosteroid-sparing effect), comorbid conditions, safety, dosing regime, and cost (refer to **Table 2 on page** 74).

Although our patient had raised total serum IgE and allergic sensitisation, he had late-onset asthma and did not report worsening of symptoms to allergens. Our impression was that his asthma was not allergy-driven, hence the decision to choose an anti-eosinophilic biologic rather than an anti-IgE agent. Some typical eosinophilic characteristics are OCS dependence, nasal polyps, frequent exacerbation, and late onset.

Dupilumab was not preferred in this patient due to concerns over hypereosinophilia. Our patient would be expected to respond well to both mepolizumab and benralizumab as he had raised blood eosinophil and CRS (both of which are predictors of response to mepolizumab and benralizumab). The decision to select one biologic over the other was based on patient preference.

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LEARNING POINTS

- **Not all patients with difficult-to-treat asthma require escalation of asthma treatment. Escalation of treatment should only be considered after confirming asthma diagnosis and addressing possible contributory factors, i.e., patients with severe asthma.**
- **Assessment of inflammatory phenotype is the next step once the patient is diagnosed with severe asthma. Patients can be broadly categorised as having type 2 high or type 2 low inflammation.**
- **Having allergen sensitisation may not necessarily indicate that a patient has an allergic disease. It is important to check for allergic symptoms to allergens as well as the presence of other atopic conditions.**
- **Determining the treatment option for mixed allergic and eosinophilic asthma patients includes consideration of age, biomarkers, intended treatment outcomes, co-existing medical conditions, safety, dosing regime and patient preference can help in the selection of a biologic (refer to Table 2).**

Table 2. Considerations for selecting biologic agent

	Omalizumab[17,18]	**Mepolizumab**[19-22]	**Benralizumab**[23-25]	**Dupilumab**[26,27]
Age	≥6 years	≥12 years	≥18 years	≥12 years
Some identified response predictors	FENO ≥19.5 ppb Blood eosinophil ≥260/uL	Higher blood eosinophil Nasal polyposis	Higher blood eosinophil Nasal polyposis	Higher blood eosinophil Nasal polyposis
Effect on exacerbations	Reduce by approximately 25%	Reduce by approximately 50%	Reduce by approximately 50%	Reduce by approximately 50%
Effect on symptoms	Some improvement	Some improvement	Some improvement	Some improvement
Effect on lung function (Difference compared to placebo)	Improve FEV1 by approximately 100 ml	Improve FEV1 by approximately 100 ml	Improve FEV1 by approximately 100 ml	Improve FEV1 by approximately 150-200 ml
Corticosteroid-sparing effect	No available RCT data	Yes	Yes	Yes
Utility in other comorbid conditions	FDA-approved for chronic idiopathic urticaria RCT evidence for CRS and ABPA	Higher blood eosinophil RCT evidence for CRSwNP	RCT evidence for CRSwNP	FDA-approved for CRSwNP and atopic dermatitis
Dosing regime	S.C every 2-4 weeks depending on total serum IgE and body weight	SC 100 mg Q4w	SC 30 mg Q4w for first 3 doses then SC 30 mg Q8w	SC initial dose of 400 mg (two 200 mg injections) followed by 200 mg given every other week. Or an initial dose of 600 mg (two 300 mg injections) followed by 300 mg given every other week.

ABPA = allergic bronchopulmonary aspergillosis
CRS = chronic rhinosinusiti
EGPA = eosinophilic granulomatous polyangiitis
FDA = Food and Drug Administration
FENO = fractional exhaled nitric oxide
FEV1 = forced expiratory volume in 1 second
HES = hypereosinophilic syndrome
RCT = randomised controlled trial
IgE = immunoglobulin
EQ4W = dosing every 4 weeks
Q2w = dosing every 2 weeks
SC = subcutaneous
CRSwNP = chronic rhinosinusitis with nasal polyps