Available online at www.sciencedirect.com

ScienceDirect

journal homepage: www.elsevier.com/locate/mjafi

Review Article

Refractory asthma – An old disorder: Novel approaches for effective control

Lt Gen B.N.B.M. Prasad, SM, VSM

Director General Hospital Services (Armed Forces), O/o DGAFMS, Ministry of Defence, 'M' Block,
New Delhi 110001, India

ARTICLE INFO

Article history:

Received 6 January 2016

Accepted 25 April 2016

Available online 24 June 2016

Keywords:

Refractory asthma

Triggers

Phenotypes

Therapeutic options

Targeted therapy

ABSTRACT

Bronchial asthma is an inflammatory disorder of airways characterized by hyper-responsiveness to a wide range of triggers and is associated with variable airflow obstruction that remits spontaneously or with the treatment. Several phenotype of asthma not responding to the currently acceptable standard therapy of high dose inhaled gluco-corticosteroids along with long acting β_2 agonists come under the purview of refractory asthma. This condition is a heterogeneous and complex disease that requires a multi-disciplinary approach to identify accurately various sub-phenotypes to enable improved understanding of the pathogenesis and development of effective management strategies including use of novel methods and targeted therapy.

© 2016 Published by Elsevier B.V. on behalf of Director General, Armed Forces Medical Services.

Bronchial asthma is an inflammatory disorder of airways characterized by hyper-responsiveness to a wide range of triggers and is associated with variable airflow obstruction that remits spontaneously or with the treatment. It is a common condition affecting both sexes and all age groups, more often children and young adults with an approximate prevalence of 300 million globally. It is a heterogeneous condition wherein both environmental and genetic factors have been implicated as causative factors. Being an anti-inflammatory condition of airways, inhaled corticosteroid therapy has been established as a standard along with β_2 -agonists for symptomatic relief of airway obstruction.¹

Refractory asthma

Even maximal inhaled therapy does not ensure adequate control in approximately 5% of asthmatics, which encompass

a variety of sub-phenotypes of asthma not responding to the currently acceptable standard therapy of high-dose inhaled gluco-corticosteroids along with long-acting β_2 -agonists.² These cases, variously called as difficult-to-treat asthma, corticosteroid-dependent asthma, “problematic” asthma, “poorly controlled” asthma and refractory asthma, need to be differentiated, investigated and corrected for any mechanism that may be aggravating asthma.^{3,4}

Triggers

Significant number of cases labelled as severe or difficult-to-control asthma do not suffer from severe refractory asthma since control is possible by addressing the triggering factors that include poor compliance to treatment, inappropriate inhalation techniques and continued exposure to environmental triggers. Presence of co-morbidities, such as obesity,

E-mail address: shashirekhak@rediffmail.com.

<http://dx.doi.org/10.1016/j.mjafi.2016.04.006>

0377-1237/© 2016 Published by Elsevier B.V. on behalf of Director General, Armed Forces Medical Services.

rhinosinusitis, allergic bronchopulmonary aspergillosis (ABPA), gastroesophageal reflux and chronic infection, should be evaluated and treated. The role of hormonal abnormalities, especially in females, should be investigated and treated if considered to be a precipitating factor. Infection due to mycoplasma pneumoniae or chlamydia can trigger asthma and appropriate antibiotic therapy helps in improving asthma control. Intake of common drugs like aspirin and beta blockers^{5,6} can make asthma control worse and should be omitted. In the Indian context, underlying ABPA is observed to be present in 39% of acute severe asthma cases admitted to intensive care units.⁷ In tuberculosis (TB) endemic areas, ABPA is often misdiagnosed as TB. Early recognition of this condition in asthma is extremely important for initiating appropriate therapy and to prevent progression of the disease to irreversible bronchiectasis and lung fibrosis. Aspergillus hypersensitivity is the first step in the pathogenesis of ABPA and has a very high (51%) prevalence in acute asthma cases. Thus, routine screening, for all patients of asthma, by Aspergillus skin testing is required for detection of hypersensitivity.⁷

Phenotypes – newer insights

It is important to identify phenotypes of true refractory asthma. Three distinct phenotypes of severe refractory asthma with different clinical and physiological features have been identified by unsupervised cluster analysis, as shown in Table 1.^{8–13} Further, based on sputum eosinophilia, severe asthma has been categorized under three sub-types: early onset severe atopic asthma with eosinophilia, late onset asthma among males with severe persistent eosinophilic airway inflammation and late onset asthma in female obese cases without eosinophilia. Bronchial biopsy has given more insight in to heterogeneous nature of the condition with some showing eosinophilic inflammation while others having neutrophilic airway inflammation. Antibiotic therapy with macrolides may help in those with neutrophilic asthma. Unpredictable and chaotic lung functions have been observed in some asthmatics who are labelled as cases of brittle asthma, which is a rare form of severe asthma with a wide variation of peak expiratory flow (PEF) despite heavy dose of steroids, and these patients are prone to very serious and often, life-threatening attacks.

Some of these cases have almost normal lung function with intermittent severe exacerbations due to swift and unpredictable fall in lung functions, with a high risk of mortality. These cases categorized as Type 2 Brittle Asthma often do not respond well to steroids and are treated effectively by

sub-cutaneous epinephrine. On the other hand, Type 1 Brittle Asthma has frenzied variations in lung functions in spite of appropriate therapy. These cases may require OCS and continuous infusion of β_2 -agonists.

A pan European study, using an innovative systems biology approach, is being conducted for finger printing refractory asthma phenotypes by integration of patient-reported outcomes, non-invasive (exhaled air, sputum and blood), and invasive (bronchial biopsies) data, in an effort to target the pathway of asthma pathogenesis.³

Therapeutic options

As per current guidelines (Global Initiative for Asthma, National Asthma Education and Prevention Programme and the British Thoracic Society), the treatment of patients with severe asthma comprises high-dose inhaled corticosteroids combined with long-acting β_2 -agonists (LABAs) and/or additional controller medications.^{1,14} Most of the cases of refractory asthma are corticosteroid-dependent requiring maintenance treatment with oral corticosteroids. Some cases of refractory asthma showing poor response to 40 mg corticosteroid administered daily for 2 weeks need to be

Table 2 – Treatment approaches for the spectrum of refractory asthma.

S. No	Approaches
1	Optimizing bronchodilatation Tiotropium and salmeterol are comparable and both are superior to doubling ICS dose for improving lung function and asthma control. Tiotropium is superior to salmeterol in improving evening PEF and pre-bronchodilator FEV1. The currently recommended treatment approach is addition of tiotropium to ICS/LABA treatment for significant improvement in lung function, as measured by FEV1 over 24 h.
2	Reducing airway smooth muscle Bronchial thermoplasty, a therapeutic procedure to heat the airways by using radio frequency energy (65 °C), reduces the volume of airway smooth muscle in the treated airways. Three bronchoscopies, spaced several weeks apart, are required for a complete treatment.
3	Reducing airway inflammatory cell number and/or activity (use of biological agents) Anti-IgE therapy; omalizumab; targeting Th2 response; anti-IL5 (mepolizumab and reslizumab); anti-IL13 (lebrizumab); anti-IL4 (dupilumab).
4	Macrolide prophylaxis Immunomodulatory and anti-inflammatory effects along with antibacterial effects of macrolides are well known. Maintenance treatment with macrolides, such as azithromycin, has been proven to be effective.

Treatment approaches: summary

Optimizing bronchodilatation, reducing airway smooth muscle, reducing airway inflammatory cell number and/or, activity, use of macrolide antibiotics.

Table 1 – Phenotypes of refractory asthma.

1	Early onset severe allergic asthma with very low forced expiratory volume in 1st second (FEV1).
2	Late onset non-atopic steroid-dependent eosinophilic asthma with fixed airways obstruction, aspirin sensitivity and rhinosinusitis.
3	Older obese females with late onset asthma and reduced lung function.

labelled as corticosteroid-resistant asthma, an extremely uncommon condition affecting less than 1 in 1000 patients. The impaired anti-inflammatory action of corticosteroids among these patients may be due to molecular abnormalities. Corticosteroid-dependent asthma on the other hand has reduced steroid responsiveness requiring daily oral steroids above 15 mg per day to remit symptoms. Various approaches have been summarized in Table 2.

Targeted therapy

In addition to elimination of triggers and optimizing conventional drug therapy, targeted therapy based on asthma phenotypes should be the main focus while managing severe asthma. IgE plays an important role in the pathogenesis of early onset severe allergic asthma^{15,16} and can be targeted by a safe and effective anti-IgE agent like omalizumab, which reduces the exacerbation rate, inhaled gluco-corticosteroid dosage and need for rescue medications.^{15,16} There are only few case reports to substantiate clinical improvements following therapy with omalizumab in ABPA, not well controlled by steroids and antifungal therapy.¹⁷

Chronic rhino-sinusitis should be identified and appropriately treated in cases of late onset non-atopic asthma with fixed airflow limitation.^{18,19} Asthma control with low-dose systemic gluco-corticosteroid therapy is often required for cases having persistent eosinophilia.²⁰ Ultrafine inhaled corticosteroids have been tried for achieving adequate drug deposition in small airway to control its inflammation, a feature of this asthma phenotype.²¹ Targeting eosinophils by an anti-interleukin (IL)-5 agent, namely mepolizumab, has been found to improve asthma control, reduce exacerbation and improve quality of life in those with sputum eosinophilia and poor control with high doses of inhaled steroids.²² A blunted response to steroids has been seen in late onset obese female preponderant asthma. Asthma aggravating co-morbidities like gastro-oesophageal reflux disease and sleep-disordered breathing are commonly observed in this phenotype, warranting specific therapy for better asthma control.^{23,24} Weight reduction is an effective adjunct, as it improves pulmonary function and reduces airway hyper-responsiveness, thus facilitating asthma control and quality of life.²⁵ Bariatric surgery may offer benefit to morbidly obese cases.²⁶ Improved asthma control and quality of life in these cases has been seen by treatment of sleep-disordered breathing with continuous positive airway pressure.²⁷ In symptomatic cases with gastroesophageal reflux disease, proton-pump inhibitors are recommended²⁸ for improving asthma control.

In the last few years, several biological pathways have been shown to play a significant role in asthma pathogenesis and are being targeted for improved asthma control. Newer innovative experimental therapies include the following: Daclizumab, a humanised IgG1 monoclonal antibody against IL-2R chain of activated lymphocytes, which has been shown to improve asthma scores and pulmonary function; and antibodies against IL-13, namely lebrikizumab and tralokinumab, which have shown to improve pulmonary function without any significant effect on exacerbation rate or symptoms.^{29–31}

Alternate therapy

Several non-pharmacological therapies have been tried in treating severe asthma. Bronchial thermoplasty by radio-frequency ablation of airway smooth muscle has shown improvement in pulmonary function, airway hyper-responsiveness, asthma-related quality of life and symptom scores.³² As per few reports, patients with severe refractory asthma, irrespective of the phenotype, who are uncontrolled at sea level despite maximum recommended dose of medications, have shown improved asthma control by a periodic rehabilitation programme at high altitude. The benefits offered by high altitude climate are well known, such as the following: decreased exposure to allergens and air pollution; reduced gas density lowering the effort of breathing; stress relief and immuno-modulatory effect of high exposure to UV light.³³

Conclusion

Refractory asthma, a heterogenous and complex disease, requires a multi-disciplinary approach to identify accurately various sub-phenotypes to enable improved understanding of the pathogenesis and development of effective management strategies.

Conflicts of interest

The author has none to declare.

REFERENCES

1. Global Strategy for Asthma Management and Prevention. Global Initiative for Asthma (GINA); 2015. <http://ginasthma.org/gina-report-global-strategy-for-asthma-management-and-prevention/> [accessed 05.03.16].
2. Reinier RLW, Elisabeth HB. Severe refractory asthma: an update. *Eur Respir Rev.* (September)2013;(September).
3. Bel EH, Sousa A, Fleming L, et al. Diagnosis and definition of severe refractory asthma: an international consensus statement from the Innovative Medicine Initiative (IMI). *Thorax.* 2011;66:910–917.
4. Bousquet J, Mantzouranis E, Cruz AA, et al. Uniform definition of asthma severity, control, and exacerbations: document presented for the World Health Organization Consultation on Severe Asthma. *Allergy Clin Immunol.* 2010;126:926–938.
5. Heaney LG, Conway E, Kelly C, et al. Predictors of therapy resistant asthma: outcome of a systematic evaluation protocol. *Thorax.* 2003;58:561–566.
6. Murphy AC, Proeschal A, Brightling CE, et al. The relationship between clinical outcomes and medication adherence in difficult-to-control asthma. *Thorax.* 2012;67:751–753.
7. Agarwal R. Allergic bronchopulmonary aspergillosis. *Chest.* 2009;135:805–826.
8. Moore WC, Bleecker ER, Curran-Everett D, et al. Characterization of the severe asthma phenotype by the National Heart, Lung, and Blood Institute's Severe Asthma Research Program. *J Allergy Clin Immunol.* 2007;119:405–413.

9. Holguin F, Bleecker ER, Busse WW, et al. Obesity and asthma: an association modified by age of asthma onset. *J Allergy Clin Immunol.* 2011;127:1486–1493.
10. Gibeon D, Chung KF. The investigation of severe asthma to define phenotypes. *Clin Exp Allergy.* 2012;42:678–692.
11. Moore WC, Meyers DA, Wenzel SE, et al. Identification of asthma phenotypes using cluster analysis in the Severe Asthma Research Program. *Am J Respir Crit Care Med.* 2010;181:315–323.
12. Siroux V, Basagana X, Boudier A, et al. Identifying adult asthma phenotypes using a clustering approach. *Eur Respir J.* 2011;38:310–317.
13. Sutherland ER, Goleva E, King TS, et al. Cluster analysis of obesity and asthma phenotypes. *PLoS ONE.* 2012;7:e36631.
14. Barnes PJ. Severe asthma: advances in current management and future therapy. *J Allergy Clin Immunol.* 2012;129:48–59.
15. Busse W, Corren J, Lanier BQ, et al. Omalizumab, anti-IgE recombinant humanized monoclonal antibody for the treatment of severe allergic asthma. *J Allergy Clin Immunol.* 2001;108:184–190.
16. Rodrigo GJ, Neffen H, Castro-Rodriguez JA. Efficacy and safety of subcutaneous omalizumab vs placebo as add-on therapy to corticosteroids for children and adults with asthma: a systematic review. *Chest.* 2011;139:28–35.
17. van der Ent CK, Hoekstra H, Rijkers GT. Successful treatment of allergic bronchopulmonary aspergillosis with recombinant anti-IgE antibody. *Thorax.* 2007;62:276–277.
18. Mascia K, Haselkorn T, Deniz YM, et al. Aspirin sensitivity and severity of asthma: evidence for irreversible airway obstruction in patients with severe or difficult-to-treat asthma. *J Allergy Clin Immunol.* 2005;116:970–975.
19. Ragab S, Scadding GK, Lund VJ, et al. Treatment of chronic rhinosinusitis and its effects on asthma. *Eur Respir J.* 2006;28:68–74.
20. tenBrinke A, Zwinderman AH, Sterk PJ, et al. “Refractory” eosinophilic airway inflammation in severe asthma: effect of parenteral corticosteroids. *Am J Respir Crit Care Med.* 2004;170:601–605.
21. Hauber HP, Gotfried M, Newman K, et al. Effect of HFA-flunisolide on peripheral lung inflammation in asthma. *J Allergy Clin Immunol.* 2003;112:58–63.
22. Pavord ID, Korn S, Howarth P, et al. Mepolizumab for severe eosinophilic asthma (DREAM): a multicentre, double-blind, placebo-controlled trial. *Lancet.* 2012;380:651–659.
23. Sabate JM, Jouet P, Merrouche M, et al. Gastroesophageal reflux in patients with morbid obesity: a role of obstructive sleep apnea syndrome? *Obes Surg.* 2008;18:1479–1484.
24. Mosen DM, Schatz M, Magid DJ, et al. The relationship between obesity and asthma severity and control in adults. *J Allergy Clin Immunol.* 2008;122:507–511.
25. Stenius-Aarniala B, Poussa T, Kvarnstrom J, et al. Immediate and long term effects of weight reduction in obese people with asthma: randomised controlled study. *BMJ.* 2000;320:827–832.
26. Dixon AE, Pratley RE, Forgione PM, et al. Effects of obesity and bariatric surgery on airway hyperresponsiveness, asthma control, and inflammation. *J Allergy Clin Immunol.* 2011;128:508–515.
27. Alkhalil M, Schulman ES, Getsy J. Obstructive sleep apnea syndrome and asthma: the role of continuous positive airway pressure treatment. *Ann Allergy Asthma Immunol.* 2008;101:350–357.
28. Mastroradarde JG, Anthonisen NR, Castro M, et al. Efficacy of esomeprazole for treatment of poorly controlled asthma. *N Engl J Med.* 2009;360:1487–1499.
29. Busse WW, Israel E, Nelson HS, et al. Daclizumab improves asthma control in patients with moderate to severe persistent asthma: a randomized, controlled trial. *Am J Respir Crit Care Med.* 2008;178:1002–1008.
30. Corren J, Lemanske RF, Hanania NA, et al. Lebrikizumab treatment in adults with asthma. *N Engl J Med.* 2011;365:1088–1098.
31. Piper E, Brightling C, Niven R, et al. A phase II placebo-controlled study of tralokinumab in moderate-to-severe asthma. *Eur Respir J.* 2013;41:330–338.
32. Khatri SB, Gildea TR. In: Mehta AC, Jain P, eds. In: *Bronchial Thermoplasty for Severe Asthma in Interventional Bronchoscopy – A Clinical Guide.* Springer (India) Private Ltd.; 2015:189–200 [Indian reprint].
33. Rijssenbeek-Nouwens LH, Bel EH. High-altitude treatment: a therapeutic option for patients with severe, refractory asthma? *Clin Exp Allergy.* 2011;41:775–782.