REVIEW ARTICLE

Modern approaches in asthma management: Revolutionizing severe asthma treatment with biologics

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Abstract

There have been advancements in the management of asthma among adults over the last two decades. The type 2 processes of airways inflammation and the use of type 2 biomarkers fractional expired nitric oxide and eosinophils have been further illuminated owing to such advancements. Moreover, epithelial cells are appearing as noteworthy elements for inflammation via the production of alarmins to start the local injury along with downstream pathways. Five new biologics have revolutionised severe asthma therapy apart from omalizumab, which are mepolizumab, benralizumab, reslizumab, dupilumab and tezepelumab. These biologics prevent the exacerbations significantly, thereby sparing the use of systemic corticosteroids and their adverse effects. For both rescue and maintenance therapies, the available guidelines prove the efficacy of inhaled corticosteroids and long-acting beta-2 agonists, like formoterol. Future guidelines ought to incorporate phenotype/endotype-focussed management to acquire further precision-directed therapy.

Keywords: Asthma management, Phenotype/endotype, T2 inflammation and biologics, Adult asthma treatment.

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Introduction

There have been fundamental changes in asthma management in the last two decades. For establishing individualised targetted therapy with disease-modifying anti-asthmatic drugs (DMAADs), proper assessment and phenotyping are necessary now. Asthmatic patients are frequently handled in secondary care by primary care clinicians or non-respiratory experts, yet the execution of asthma treatment guidelines in such facilities is a challenge as easy-to-understand and concise guidelines are needed for clinical practice. In this connection, a practical guide to manage asthma has been identified as having four elements; dual asthma assessment (A2), basic determinants (B), detection and management of comorbidities (C), and phenotype-specific, personalised targetted therapy with DMAADs (D). This has been titled the A2BCD guidelines, in which A2 includes diagnosis and phenotype, asthma control, and impending risks); B includes education, regular physical activity, self-management practice, and evading asthma triggers; C includes comorbidities with asthma, like obesity, chronic rhinosinusitis and sleep apnoea; and D includes phenotype-specific, personalised targetted therapy with DMAADs along with personalised inhalation arrangements built on inhaled corticosteroids (ICSs), leukotriene modifiers, allergen immunotherapy and biologics.[1,2]

There has been a major revolution for asthma assessment and management in the last two decades. Some new management approaches have been recommended for mild asthma, while amendments have been mostly suggested for severe asthma cases. Although severe asthmatics represent a smaller subgroup of asthma cases,[3] it denotes an elevated disease burden and escalated morbidity disproportionally, which has boosted investigations and improvement for their care. The heterogeneity of asthma has been acknowledged for long, and has been highlighted for further explorations. Clinical and molecular asthma phenotypes are characterised well, and the processes are now known better, resulting in recognition of novel biomarkers.[4,5] This progress has made asthma management more targetted, and has allowed development and utilisation of biologics for particularly severe asthma cases.[6] The vital principles for asthma management must be taken care of in spite of the availability of new therapies, like the evaluation of comorbid conditions, the effect of environmental exposures, and compliance with treatment to achieve disease control.[7]

The current narrative review was planned to explore the available literature on the subject in order summarise what a personalised strategy to asthma management entails that has transformed this critical area in a fast-moving world.

Methods and Results

The literature was electronically searched on PubMed database for review articles using key words, including

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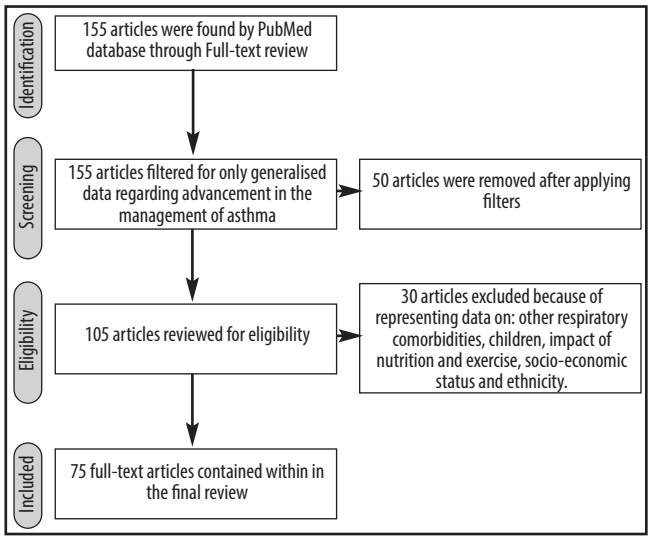

Figure: Literature search and selection of studies for analysis.

asthma management, advancement in asthma management, asthma phenotype and endotype, along with the use of as Boolean operators. The search filters applied were: free full text, review, English, humans, and adults.

Of the 105 articles identified, 75(71.4%) were included in the final review based on the provision of comprehensive information regarding asthma phenotype and endotype, management of asthma, and advanced management of asthma. The focus was on articles published from 2011 onwards, but some articles published in 1995, 1999, 2001, 2002 and 2009 were also included to represent the originality (Figure).

Mechanism of disease and therapy targets (asthma phenotypes and endotypes)

The progress in understanding potential processes of asthma development and its exacerbation has resulted in the recognition and creation of stimulating opportunities for therapeutic intervention. The findings from the preceding couple of years are considered most intriguing, splitting them on the basis of immune elements implied in the process or therapy.[8] Asthma is considered a heterogeneous disease.[9,10] There are variations in terms of clinical presentation, physiological assessments and response to therapy among asthmatic patients. The characterisation of asthma via phenotyping is necessary to make asthma groups more homogeneous and to individualise the therapy. This specifically relates to severe asthma cases because several therapies are target specific subgroups.[7]

A phenotype comprises visible properties of a single person or group owing to the interaction of genes and environment. Numerous phenotypes of asthma have been recognised via clustering studies[4,11,12] and have been associated with particular molecular pathways.[13,14] The most frequent phenotypes of asthma include early-onset allergic asthma, late-onset eosinophilic asthma, neutrophilic asthma, obesity-related asthma and exercise-induced asthma.[15] Endotypes are the subgroups within the phenotype, specified by discrete pathophysiological processes. Endotypes focus on the aetiology and pathophysiology of illnesses, and are the main therapeutic targets. The knowledge about asthma endotypes is still developing.[16] The phenotyping and endotyping target specific mechanisms that are essential to the development of novel biologics for treating severe asthma. In this regard, biomarkers have been proposed, but there is much more to be done in this area. It is established for severe asthma now that there are two central airway inflammatory pathways: the type 2 (T2) high and the T2 low.[17] The former pathway activates T lymphocytes into T-helper 2 cells, leading to eosinophilic inflammation. The latter pathway is not clearly explained, but neutrophils have an association.[18] Allergic severe asthma liked to immunoglobulin E (IgE) and eosinophilic asthma in T2 severe asthma are the ones responsive to peculiar treatment with anti-IgE and anti-interleukin-5 (IL5) cytokine, respectively.[19] However, there is much to be established regarding non-T2 severe asthma treatment.[7]

Management of asthma

The standard guidelines and pharmacological treatment of asthma cases have been updated in the last couple of years.[8] Updated National Asthma Education Prevention Programme (NAEPP) guidelines were released in December 2020, notifying suggestions about the occasional use of ICSs and the as-per-need usage of budesonide-formoterol as sole maintenance and reliever treatment.[20] The guidelines encompassed a review of bronchial thermoplasty, for which the efficacy and safety on long-term basis had been unidentified before. However, it was observed in a research that the efficacy of bronchial thermoplasty with an adequate safety for patients lasted a decade or more.[21]

The last couple of years have also led to stimulating awareness about the distinctive functions of ICS and long-acting beta2-agonist (LABA) treatments. For instance, Wechsler et al. revealed that about 50% of African-American children having uncontrolled asthma had a better response to an enhanced ICS dose compared to African-American youngsters and adults having a better response to LABA add-on.[22] As-per-need use of budesonide-formoterol was studied by O'Byrne et al., who found that it decreased the interim probability of severe exacerbations after one day of enhanced usage in mild

asthma.[23] In another research, Weinstein et al. reported that the adding up of formoterol to mometasone furoate maintenance therapy did not raise the risk of asthma-linked events and minimised the probability of exacerbations.[24] It was found by a study a once-daily dosing of ICS and LABA made lung function better at week 26 over ICS-alone therapy, with once-daily elevated dose not being inferior to the usual twice-daily dose of ICS-LABA in improving forced expiratory volume in 1 second (FEV1).[25]

Furthermore, several benefits in the field of biologics have been reported. A study by Busse et al. reported that upon administration for a couple of years, benralizumab had safety and tolerability profiles similar to those detected over a year in Efficacy and Safety Study of Benralizumab Added to High-dose Inhaled Corticosteroid Plus LABA in cases with Uncontrolled Asthma (SIROCCO) and the Efficacy and Safety Study of Benralizumab in Adults and Adolescents Inadequately Controlled on Inhaled Corticosteroid Plus Long-acting β2 Agonist (CALIMA) studies. Also, eosinophil depletion on long-term benralizumab did not result in further adverse outcomes. Enhancements in efficacy measures displayed in former primary randomised controlled trials were sustained, including exacerbation rate, asthma symptoms and lung function.[26] In the Safety Extension Study to Evaluate the Safety and Tolerability of Benralizumab in Asthmatic Adults and Adolescents on Inhaled Corticosteroid Plus LABA (BORA) study, benralizumab was found to be safe and effective in dosage of 30mg every 4 or 8 weeks for 3 years to treat asthma in 86 adolescent cases.[27] Khatri et al. reported the safety and efficacy of long-term mepolizumab in severe eosinophilic asthma without the induction of neutralising antibodies.[28]

The Food and Drug Administration (FDA) has approved many biologics for clinical use, but investigations are continuing for other novel treatments. Menzies-Gow et al. studied cases with severe, uncontrolled asthma who received tezepelumab, a human monoclonal antibody (mAb) that inhibits thymic stromal lymphopoietin. They found that the cases had less exacerbations with improved lung function, control of asthma, and quality of life compared to those who took placebo.[29] A prostaglandin D2 (PGD2) receptor antagonist, fevipiprant, was studied by Brightling et al. in phase 2 clinical trial on asthmatics30, revealing decreased sputum eosinophils and increased lung function. These studies could not demonstrate a statistically significant decline in asthma exacerbations when adjusted for various analyses, but displayed regular and reasonable decline in the exacerbations rates.[30] The discipline of allergy and immunology is persistent in gathering further data on the first FDA-permitted biologic omalizumab to treat severe asthma. A comparison on the outcomes from the Observational Study of the Use and Safety of Xolair (omalizumab) during Pregnancy (Expect) was conducted by Namazy et al. The cohort managed with omalizumab was contrasted from a disease-matched group of pregnant females who were not administered omalizumab. Any enhanced risk of major congenital anomalies amid pregnant females who were subjected to omalizumab treatment was not observed.[31]

Improvement in the management of severe asthma

The treatment of severe asthma was generally restricted to the use of ICS in high dose with LABAs. Upon failure, other agents, like theophylline or anti-cholinergics, could be added which are of limited value. Thus, lots of patients were given oral corticosteroids (OCS) for maintenance per year, or administered with many courses of high-dose OCS, leading to increased morbidity due to asthma.[32] The short-acting β2 agonists (SABA) are generally employed for rescue therapy (relievers) except for regular budesonide-formoterol treatment; it may be used as a reliever, too.[12] Non-compliance to maintenance therapy or abuse of SABA require monitoring, otherwise severe asthma events can be the consequences.[33] The exploration towards hetero-geneity of asthma improved the understanding about the underlying pathophysiology of the disease, and led to the development and marketing of new therapies and rational use of current therapies. Hence, when the therapeutic schemes are optimised in severe asthma, this can reduce morbidity and socioeconomic liabilities.[7] Even though suggestions on recent approaches are more targetted and personalised, established on clinical phenotypes, an optimised individualised medication is still not available.[6,34] Individualised medication or precision medicine is the therapy beset to the requirements of individuals grounded on biomarkers, genetic, phenotypic, or psychosocial features that differentiate a certain case from others having same clinical signs and symptoms.[35] Several new medications targeting the eosinophilic part of inflammatory asthma phenotypes are available, but novel treatments for non-eosinophilic asthma are required to be developed. Even though investigating and targetting 'treatable traits' employing suitable intervention are progressively been used to assess individual patients, there is a lack of proper biomarkers.[36,37]

Selection of biologics

The present guidelines suggest phenotyping the cases fully when asthma remains uncontrolled by optimal treatment involving ICS and a LABA in high dose so as to opt for the next appropriate approach.[10,38-40] If a patient's phenotype indicates an eosinophilic inflammation, several biologic agents are there to be chosen for therapy. Among them,

omalizumab, an anti-IgE mAb, is the first choice for allergic asthma since early 2000s, that acts on allergic pathways via different processes.[42,43] This agent lowers exacerbations and hospitalisations, and has an OCS-sparing activity.[44,45] It is permitted for use in children aged 6-12 years. Anti-IgE antibody ligelizumab is under investigation, binding with higher affinity to IgE compared to omalizumab, and exhibiting preliminary beneficial results. But its commercial availability is indeterminate.[46]

More biological agents have been approved for asthma which target the IL-5 pathway. It is the main cytokine in the T2 eosinophilic pathway. Mepolizumab and reslizumab target the interleukin itself, and benralizumab targets its receptor.[47] Mepolizumab is a human mAb whose initial studies displayed enhancement to biologic parameters only.[48] Due to improved targetting of the proper population, more studies were conducted that revealed advantages of the antibody in decreasing severe exacerbations especially, and also the requirement for OCS.[49-51] Another humanised mAb is reslizumab that acts on eosinophilic asthma, and is used as an intravenous preparation. It has also exhibited reduction in asthma exacerbations, even though the research involving this agent recruited patients having increased eosinophil counts (400 cells/microliter at the minimum).[52-56] The IL-5 receptor is also targetted by benralizumab, inducing a cytotoxic impact on eosinophils, and hence eliminating them completely. The trials with this biologic revealed a reduction in asthma exacerbation rate and OCS.[57,58] For mepolizumab and benralizumab, long-term safety and efficacy have been reported.[59,60]

Another human mAb is bupilumab that targets the IL-4 receptor. IL-4 is a functional receptor shared for IL-4 and IL-13, and dupilumab seems to be inhibiting both the signalling pathways. This agent demonstrated a decline in severe exacerbations and need for OCS.[61,62] Two other agents, namely lebrikizumab and tralokinumab, solely inhibit IL-13, but could not display any benefits in severe asthma, although they target the same pathway.[63] Tezepelumab is a human mAb with thymic stromal lymphopoietin (TSLP) actions. TSLP also participates in the T2 inflammation pathway. It is a component of epithelial-derived cytokines group, known as 'alarmins'. Tesepelumab is an investigational agent, but has exhibited beneficial outcomes in asthmatics patients.[64] More agents are also under research that aim at inhibiting alarmins like IL-33.[65]

Other therapies

In case high-dose ICS and LABA could not control asthma and biological therapy is not suitable for the asthma patients either due to asthma inflammatory phenotype, individual's predilections or local guidelines, some alternatives are available for symptom alleviation. Macrolide treatment may be tried in persistent uncontrolled or symptomatic severe asthmatic patients as per recent guidelines.[7] Research has revealed a considerable decline in moderate to severe exacerbation of asthmatics with least adverse events, but this is not so for children due to lack of efficacy observed in a study in which the therapy was terminated.[65] Long-acting muscarinic antagonists (LAMAs) prevent acetylcholine-mediated bronchoconstriction as they antagonise M3-receptors competitively in the airways, thereby achieving bronchodilatation. The preliminary reports were from investigations that employed tiotropium soft mist inhalers the use of which is endorsed by various guidelines, with further studies and meta-analyses presenting an enhancement in lung function upon use as an aide in severe asthmatics. Its action to decrease the exacerbations is uncertain.[66,67] Lastly, majority guidelines incorporate bronchial thermoplasty in specialised centres as a management alternative for chosen severe asthma cases. This caution owes to the risk of asthma exacerbations (post-procedural) related to the interventional procedure. The studies have shown a durable decline in exacerbations, betterment of symptoms and quality of life of patients, but with partial advantage in lung function.[68,69] Asthma therapy should be decreased to obtain the minimal effective dose of ICS once the patient gets good control, as specified by symptom assessment and exacerbations. Each decline should be established as a remedial trial, and the asthma patient should be instructed to resume the previous dose in case of worsening of the symptoms.[70]

Education for self-management

Regardless of asthma severity, all asthma patients should have an individual 'Asthma Action Plan', describing the symptoms of control worsening or an exacerbation, and how to cope with them through self-management. The peak flow values may be added as they can help some patients who are poor percipients of symptoms. It has been reported that patients were 36% less often hospitalised if they received education on self-management compared to those who did not receive it.[71]

Immunotherapy

A role for immunotherapy may be present in some selected allergic asthma patients, like either subcutaneous or sublingual immunotherapy (SLIT) administration of an exogenous aeroallergen to which sensitisation is shown by an individual so as to decrease the IgE-mediated allergic responses related to asthma and rhinitis.[72] Registered treatments that have efficacy for asthma in Australia incorporate house dust mite and grass pollen SLIT with the option of treatment frequently directed by the allergy

expert.[73,74] Immunotherapy can impair asthma symptoms, and in patients with optimised asthma control, it should be directed under supervision.[74]

Individualised asthma management

Asthma management should be stratified and tailored specifically when severe. The basis of a patient-focussed approach, learnt by an understanding of inflammatory pathways, is designed by perceptions of joint decision-making involving the clinician and the patient to set therapeutic aims, and applied pharmacotherapy, like as-per-need preventer medicine, bearing in mind the 'treatable traits' of asthma and endotyping/ phenotyping of severe asthma.[75]

The current narrative review has limitations as it used PubMed as the only search database. They may limit the generalisability of the findings as the data may not fully represent the broader population or encompass all relevant variables. This was done because PubMed has access to millions of citations and articles from numerous reputable journals, and is one of the biggest and most well-known databases for scientific literature. Additionally, most of the publications listed in PubMed's index undergo peer review, guaranteeing that the data being accessed is reliable and of the highest quality. Furthermore, because trends and results can change over time, the lack of a specified timeframe for the literature search could have induced temporal biases. As a result, the current findings should be interpreted cautiously, and further studies should be conducted to validate these findings using a variety of data sources.

Conclusion

Asthma is a heterogenous illness requiring optimal management through understanding of the miscellaneous drivers of immune pathways, together with step-by-step titration of treatments that are designed individually for the patients and their symptoms. Significant advancements in the control of severe asthma have been seen due to phenotyping/endotyping asthma with the aid of biomarkers and biologics, targeting specific immune pathways. This has stimulating potential for forthcoming treatments. Noteworthy modifications to proposed management have ensued in recent years, and a more personalised strategy to asthma management has transformed this area in the fast-moving world.

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SZ: Concept, supervision, development, literature review, structured content and finalised the article.
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FZ: Data collection, reviewing relevant references, editing and refinement.
VZ: Writing, drafting, prepared the tables and figures and ensured citation accuracy.
SN: Review, proofreading, coherence of arguments, revision and final approval.