ABSTRACT

Background: To date, several studies conducted to assess the role of genetics in the pathophysiology and treatment of asthma. Objectives: However, the findings were not consistent and remain uncertain. Thus, it is the need of the hour to assess the recent literature, observe limitations and finally propose future research directions in this field. Methodology: The relevant literature published in the English language was retrieved by using different electronic databases including Cochrane Library, Web of Science, PubMed, Ovid, EMBASE, and MEDLINE. Results: Leukotriene modifiers, β-adrenergic receptor agonists, and inhaled corticosteroids are the three most important classes. Data suggested that the heterogeneity in the treatment response among asthma patients is partly due to genetic factors. Conclusion: Large-scale genetic investigations can be improved by using the high throughput technologies that could have promising potential for personalized treatment of asthma, which in turn will minimize side effects, better therapeutic outcomes, and finally lead to more cost-effective care.

Keywords: Asthma, Pharmacogenomics, Treatment, Genetics.
INTRODUCTION

Asthma is a pathological condition that is characterized by narrow and inflamed airways, leading to bronchial hyper-responsiveness and airflow obstruction (1). It is a heterogeneous disease that can be either non-allergic or allergic. There are different endotypes of asthma that remain poorly characterized. Its endotypes classification is mainly based on the predominant T helper (Th) type inflammation. Low T-helper 2 asthma is more heterogeneous but less common as compared to high T-helper 2 asthma. Low T-helper 2 asthma is characterized by the involvement of the Th17, Th1, paucygranulocytic and neutrophilic inflammation. On the other hand, high helper 2 asthma is characterized by the central role of Immunoglobulin E (IgE), eosinophilia, and Th2-driven inflammation (2). The Th17 and Th1 are associated with steroid-resistant asthma but the Th2, natural killer T (NKT) cells, and CD8+T cells are associated with eosinophilic recruitment (3).

Clinical manifestations of asthma include breathing difficulty, coughing, wheezing, and shortness of breath (1). One of the well-recognized clinical characteristic is ‘allergic triad’ which is defined as association between allergic rhinitis, asthma, and atopic dermatitis (4). In fact, up to 80% of asthmatic patients also show the symptoms of allergic rhinitis, while 40% of patients having allergic rhinitis develop concomitant asthma (5). It is reported that clinically, epidemiologically, and in accordance with the pathophysiologic system; allergic rhinitis and asthma are commonly linked to each other and may share the genetic etiology which provides more insights into the molecular mechanisms of asthma (6), even though there is an illustration of discrepancy (7).

The affected patients are mostly children showing a family history of these diseases. Various studies report suggested that food allergy and atopic dermatitis mostly build up in new-born’s leading to asthma and in childhood development to allergic rhinitis known as ‘atopic march’ (8). The current data demonstrate more incidences of allergic disease and asthma than ever before and it not only has created health concerns for people of all ages belonging to different localities but also leads to a serious economic impact on the healthcare system (9). Moreover, whether allergic disorders and asthma have a shared origin or a discrete cause remains an open subject. The recent literature reports revealed that worldwide 300 million individuals are affected by asthma and anticipated an increase in this number by 400 million more patients by 2025 (10). In Pakistan, there is great variation in reported asthma prevalence ranging from 4.3% to 31.58% (11).

Asthma is a multifactorial disorder involving a complex interaction between various genetic and environmental factors. It is noticed that asthma at young age engrosses genetic and multiple environmental (tobacco, smoke, air pollution, life style including urbanization and bacterial infections) contributors (11, 12). Asthma susceptibility has a strong genetic background predictable about more than 50% which is further proved by the genome-wide association studies (GWAS) and candidate gene association studies (13). More than 61 loci were reported to associate with asthma including the 17q locus (14). Some of the genes responsible for the development of asthma include GSDML, TSLP, IL33, ORMDL3, and HLA region genes which were confirmed by the GWAS studies (15). Single nucleotide polymorphisms [SNPs] in IL-4, IL-13, IL-10, CD14, TBXA2R, 17q21, and ADAM33 are found to be associated with asthma (16, 17).

This narrative review was planned to provide streamlined information regarding the role of genetic factors, and updated information on the pathophysiology and treatment of asthma.

METHODOLOGY

All the information was searched through different electronic databases such as MEDLINE, Google Scholar, PubMed, and EMBASE, etc., without any time limit. Following MeSH terms and keywords were used for data retrieval: ‘asthma’, ‘genetics’, ‘treatment for asthma’, and ‘prevalence and diagnosis of asthma’. Articles published in the English language were considered eligible for final analysis. The literature with inadequate information or that does not follow the objectives of this review was excluded from the final analysis. The following article types: research articles, meta-analyses, systematic reviews, and original articles were considered eligible for final evaluation.
RESULTS AND DISCUSSION
In the initial screening, a total of 63 articles were shortlisted, and after applying our study inclusion criteria, a total of forty articles proceeded further.

Treatment
Extensive research has been conducted to develop consistent strategies for the prevention and management of asthma around the world but this aim is not been completely achieved yet. There is no cure for asthma, however, the current therapies proved to be effective in the management of this disease and the main focus is to select those therapeutic interventions that possess minimum side effects (18). The reaction to medicines is different even in patients with the same clinical characteristics. The study of the response of drugs that is related to variations in human genome characteristics is termed pharmacogenomics (19). The three main types of asthma medications—β2-agonists, leukotriene modifiers, and inhaled corticosteroids have been linked to a long range of genes through GWAS research. Additionally, a recent integrative, systems-level approach reveals a promising prospect in the pharmacogenomics of asthma. However, making this discipline directly relevant to patients we are still a long way away. And for its clinical relevance, there is a need for a combination of different approaches like integrative omics technologies combined with the polygenetic technique that may help in the field of precision medicine or pharmacogenomics (20, 21).

Bronchodilators
For relief and to prevent bronchoconstriction, bronchodilators are used. Novel approaches are reported in this therapy like the introduction of long-acting β-agonist (LABA) including salmeterol and formoterol. Their effect lasts for more than 12 hours. These drugs and corticosteroids perform the same functions and the most useful therapy is considered as fixed combination inhalers (LABA plus corticosteroids). Many new long-acting β-agonists (ultra LABA) are appropriate for only one dose daily and show a duration of action of more than 24 hours (22). The mode of action of muscarinic antagonists has the para-sympathetic activity which mediates both the release of mucus into the airway lumen through stimulation of muscarinic receptors and bronchial smooth muscle contraction while the mechanism of action of b2-agonists involves the binding of B2 agonists to the B2 adrenergic receptors (B2AR), which are present in airway smooth muscle thus by the activation of protein kinase A it finally results in phosphorylation of various smooth muscle relaxation mediating targets such as calcium-dependent potassium channels and myosin light chain kinase (23).

Corticosteroids
Inhaled corticosteroids (ICS) are the key therapy against inflammation in asthma. There are systemic side effects for all presently available ICS (24). Dissociated steroids are assumed to be good therapy for asthma due to their inhibition effect on the inflammatory gene expression and mitogen-activated protein kinase [MAPK] signalling (25). The recent advances in genome-wide technologies revealed the various novel DNA binding sequence bound by the glucocorticoid receptor and unexpected types of glucocorticoid receptor protein to protein interactions which leads to novel anti-inflammatory mechanisms (26). Another research study conducted by Toubi and Vadasz reported that the anti-leukotrienes and inhaled corticosteroids have a limited effect on angiogenesis and remodeling. However, Semaphorin3A (sema3A) administration in mouse models provides evidence of its promising role as a therapeutic tool for asthma as it inhibits angiogenesis and regulatory roles in all the stages of the immune response (27).
70% of glucocorticoids are present in the form of free circulating glucocorticoids while the remaining is protein bound (28). For the anti-inflammatory effects, glucocorticoids have both genomic and non-genomic modes of action. Glucocorticoid receptors (GR) exist in the form of two isoforms one is the GRα isoform and the other is GR beta which is non-functional and rare (29). Both heat shock proteins mainly HSP70 and HSP90 dissociate GRα after its binding to GRα which results in the translocation of this active GR ligand complex into the nucleus. It encodes anti-inflammatory proteins such as glucocorticoid-induced leucine zipper (GILZ) and mitogen-activated protein kinase phosphatase-1 (MKP-1). The synthesis of pro-inflammatory cytokines is inhibited by the process of transrepression (30).
Cytokines modulators
Cytokines play an important role in the pathophysiology of chronic inflammation, so considered to be crucial targets to be blocked in asthma. To date, there is various targeting type 2 cytokines are reported that are summarized in Table 1 (31). Inhibition of particular cytokines can be done by using different possible approaches. These include drugs that inhibit cytokine synthesis or inhibition of signal transduction pathway, or it may be due to the humanized blocking antibodies to cytokines.

Cytokine blockade
The Th2 cytokines IL-4, and IL-13, play a central role in the pathogenesis of asthma, which is an initiator for class switching and activator of chemotaxis IgE in asthmatic patients. In asthma, there is evidence of significant clinical efficacy of Dupilumab a human monoclonal antibody that concurrently stops signalling of IL-4 and IL-13 (32). A study conducted in 2017 by Yancey et al reported that mepolizumab significantly reduced the emergency room visit (P < .001) and rate of exacerbations requiring hospitalization (P = .004) versus placebo (33).

The unique molecular patterns are named endotypes which have broad implications for therapeutic intervention through the characterization of endotypes which proves helpful in severe asthmatic patients (34). The choice largely depends on patient factors in the absence of endotypes. In asthma cellular and molecular components are better described through mechanistic studies. The ad on therapy for asthma is omalizumab which is directed against immunoglobulins IgE (35).

Anti-IgE therapy
Omalizumab a monoclonal antibody that blocks IgE is currently used in the treatment of severe asthmatic patients. Due to its high cost, it has been opted for cautiously, especially for low-income patients (36). In an allergic person, re-exposure or a cross-reactive antigen results in the consequent aggregation of surface FceRI due to cross-linking of nearby FceRI-bound IgE. When the aggregation of FceRI is adequate duration and strength, it causes the secretion of biologically active products by triggering basophils and mast cells to begin complex signalling events. After antigen and IgE-induced mast cell degranulation, mediators are released they induce a response termed an immediate hypersensitivity reaction and which in the airways, causes enhanced secretion of mucus, contraction of the airway smooth muscle, and increased vascular permeability (37).

Mast cell inhibitors
In the early 1960s cromones (cromolyn sodium) were introduced into clinical medicine, which showed efficient results in case of allergens but is not considered good for long-term actions as it has a short half-life. The cromones mechanism of action is not ascertained. Although two recent modes of action revealed that it works by stabilizing the mast cell one is the GRP35-mediated mechanism and the other is the anti-inflammatory loop Anx-A1 which reciprocally inhibits the mast cell activation (38). There is further extensive progress in the development of c-kit inhibitors.

Immunotherapy
The key asthma treatment involves variations in the immune cells; as a result, the long-term cure is achieved but some adverse effects are also associated with this therapy. To control asthma subcutaneous injection against allergens is not very efficient and this also produces a risk of anaphylaxis. In allergic patients, extracts of house dust mites with sublingual immunotherapy have shown some better efficiency but still more studies are required to confirm the efficacy (39).

A new class of peptide therapy that is tested through clinical trials across a range of allergens proves beneficial. This class of peptide therapy is called specific T cell epitope peptide therapy for allergic diseases (40). Many other advances include the use of CpG oligodeoxynucleotides [ODNs] or other non-pathogenic bacteria that targets the toll-like receptors (TLR)-9 (41).

CONCLUSION
From the current review, we concluded that well-designed observational studies or randomized controlled trials are now compulsory to ascertain how each patient responds to pharmacogenetics predictors of treatment response. Therefore, for many clinical practices routine, the implementation of pharmacogenomics into clinical practice remains a far-off challenge in the future.
Table 1. Type 2 cytokines targeting in asthma (31)

<table>
<thead>
<tr>
<th>Cytokines</th>
<th>Therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Targeting type 2 cytokines</strong></td>
<td></td>
</tr>
<tr>
<td>Thymic stromal lymphopoietin</td>
<td>Tezepelumab</td>
</tr>
<tr>
<td>IL-4Ra</td>
<td>Dupilumab</td>
</tr>
<tr>
<td>IL-5Ra</td>
<td>Benralizumab</td>
</tr>
<tr>
<td>IL-5</td>
<td>Mepolizumab and Reslizumab</td>
</tr>
<tr>
<td>IL-13</td>
<td>Lebrikizumab, Tralokinumab</td>
</tr>
<tr>
<td><strong>Targeting non-type 2 cytokines</strong></td>
<td></td>
</tr>
<tr>
<td>IL-17Ra</td>
<td>Brodalumab</td>
</tr>
<tr>
<td>IL-1β</td>
<td>Canakinumab and Anakinra</td>
</tr>
<tr>
<td>IL-18</td>
<td>GSK1070806</td>
</tr>
<tr>
<td>IL-6R</td>
<td>Tocilizumab</td>
</tr>
<tr>
<td>IL-23</td>
<td>Ustekinumab and Risankizumab</td>
</tr>
<tr>
<td>TNF</td>
<td>Infliximab, Golimumab and Etanercept</td>
</tr>
<tr>
<td>CXCR2</td>
<td>Navarixin and Danirixin</td>
</tr>
</tbody>
</table>

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DECLARATIONS

Authors’ Contributions
MFS and MUG contributed to study concept, study design and data collection. AF and SA contributed in data analysis and interpretation. MA and FIA did the literature review and critically reviewed the manuscript. All the authors read and approved the final manuscript.

Ethical Approval
Not applicable

Conflict of Interest
The authors declared no conflict of interest among them.

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