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Review Article

Recent trends and directions in the rationalization of pharmacotherapy of bronchial asthma: Probing for alternatives

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Abstract
Although tremendous progress has been made in the understanding of Bronchial Asthma (BA) over the past decade, asthma remains a frequently encountered challenging condition for the physicians in the health care locale**.** Inflammation is distinguished as the most important event in the pathogenesis and the knowledge that asthma is an inflammatory disorder has become elementary to our explanation of asthma; this has broadened the perspective for the treatment of BA. However, bronchodilators and corticosteroids are still the mainstay of asthma treatment over the decades. The introduction of superior derivatives of corticosteroids and beta agonists, the choice, safety, duration of action and ease of delivery have enhanced progressively. Surrogated anti - inflammatory agents have been used in severe disease, but have been limited by adverse effects. The introduction of new agents affecting leukotrienes synthesis and action provides an alternative strategy but it needs to be confirmed on a large subset of population of asthmatics. In fact, the past decade has been witnessed by a proliferation of scientific information and a widespread addition of anti-inflammatory therapy to improve asthma outcomes along with the recommended therapies. In this context, there has been much advancement in the available pharmacologic panorama for both chronic and acute therapy and the development and approval of novel medications. Yet, many controversies abound this disorder, and further fundamental developments in novel therapeutics are imminent.
This review of asthma for the practicing clinician will summarize these developments and their implications in treatment of BA

Key words: Bronchial Asthma (BA), Pharmacotherapy, Review, Novel Drugs

Although tremendous progress has been made in the understanding of Bronchial Asthma (BA) over the past decade, asthma remains a frequently encountered challenging condition for the physicians in the health care locale. Although the 1980s and 1990s have seen an increase in asthma morbidity and mortality, the most recent data indicates a static phase of this trend[1,2]. There is a disparity in the understanding of asthma. To the patient, asthma means episodes of wheezing, shortness of breath and chest tightness that can interfere with daily activities and sleep. To parents of asthmatics, it may mean administering multiple medications on a regular basis and the institution of environmental control measures that may be a difficult task. From the point of view of the pathologist, it means the presence of bronchial smooth muscle hypertrophy, mucous hyper secretion and airway inflammation resulting from the airway hyper responsiveness to a range of chemical (histamine), microbiologic (viruses), physical (exercise) and immunologic (allergens) stimuli. For the clinician, it insinuates developing a therapeutic plan for maximizing compliance of the patient and disease control, while minimizing any potential adverse effects for the patient.

Remarkable progress has been made in the understanding of pathogenesis of asthma by virtue of invasive research tools such as bronchoscopy, bronchoalveolar lavage, airway biopsy, and measurement of airway gases, although the aetiology of airway inflammation remains obscure.

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The knowledge that asthma is an inflammatory disorder has become elementary to our explanation of asthma; this has broadened the perspective for the treatment of BA. In fact, the past decade has been witnessed by a proliferation of scientific information and a widespread addition of anti-inflammatory therapy to improve asthma outcomes along with the recommended therapies. In this context, there has been much advancement in the available pharmacologic panorama for both chronic and acute therapy and the development and approval of novel medications. Yet, many controversies abound this disorder, and further fundamental developments in novel therapeutics are imminent. This review of asthma for the practicing clinician will summarize these developments and their implications in treatment of BA.

Important pathophysiological feature of Asthma

A rational approach to pharmacotherapy of asthma depends on an understanding of its pathogenesis. An aberrant immune response associated with allergy underlies the extrinsic asthma in young patients. In contrast, in intrinsic asthma is seen in a large number of cases who acquire asthma and in this, no immunological basis is suggested. An airway inflammation remains a characteristic of the disease. There may be coexistence of these conditions in patients.

In the classic allergic model, asthma is mediated by reaginic (IgE) antibodies bound to mast cells in the airway mucosa. On exposure to an antigen, antigen-antibody reaction on the surface of mast cells triggers an immediate/ release of preformed mediators, like histamine, proteases and (NF-κβ) from, the cells granules, and initiate a rapid synthesis of cell-membrane derived lipid mediators, such as prostaglandins ($PGD_2/PGF_{2\alpha}$), leukotricnes (C4 and D4) and platelet activating factor (PAF) which are released within minutes following an antigen-antibody reaction.. Thus causing muscle contraction and vascular leakage.

In the late phase of BA, cytokines, synthesized from T-helper (Th-2) cells and granulocyte/ macrophage colony- stimulating factor (GM-CSF), TNF-interleukins (Il-1,3,4,5,6 and 8), macrophage - inflammatory protein (MIP-1) and tissue growth factor (TGF) produce more sustained bronchoconstriction, cellular infiltration of the airway mucosa and mucus hyper secretion that occurs 2-8 hours later . Basically, all these mediators account for the inflammatory response but how bronchoconstriction is produced remains obscure but thought to be due to altered smooth muscle behaviour along with airway all swelling and secretion (intraluminal). However, it is now proposed that the beneficial effects of corticosteroid therapy may result from their inhibition of cytokines which are paramount mediators in the bronchial tree.

In intrinsic asthma, the antigen-challenge model does not explain fully its pathogenesis. In this group of B A, viral respiratory infections may lead to severe exacerbations of asthma rather an exposure to allergens. In idiopathic asthma, bronchospasm can be provoked by non-antigenic environmental stimuli such as, exercise, cold air, sulfur di-oxide and rapid respiratory manoeuvres ushering to ‘non-specific’ "bronchial hyper reactivity".

Thus, to approach the BA therapy, the following pathophysiological aspect should be considered:

1. Chronic inflammation of the airway is to be ascertained for the diagnosis, prevention, and management of the disease irrespective of severity of BA.
2. Airway inflammation can cause airway hyper responsiveness, airflow limitation, respiratory symptoms, and disease progression.
3. Airflow limitation due to acute bronchoconstriction, airway oedema, mucous plug formation and, airway remodelling may be the consequence of inflammation.
4. There is also a genetic susceptibility especially in atopics for the development an Ig E-mediated response to common aero factors causing BA.

These characteristics of the disease have moved us towards the recognition of the inflammation as a hall mark of asthma. Thus, ablating inflammation with considering underlying pathogenesis is the mainstay of in progress advances for the therapeutic interventions in BA.

Novel Pharmacotherapeutic Agents in BA

1. Bronchodilator Drugs:

a) Newer β_2 - adrenoceptor agonists

β_2 -Adrenergic drugs are the most potent and rapidly acting bronchodilators in clinical use today[3]. Their availability in multiple forms: short, intermediate, and long acting drugs and a wide variety of delivery systems (metered dose inhalers MDIs), give them wide clinical versatility. Until recently, all available inhaled β_2-agonists had a short duration of action. The development of newer long-acting inhaled β_2-agonists Salmeterol and Formoterol imparts new approach for asthma control. These drugs provide 12 hours of effective and sustained bronchodilation following a single administration[4]. Salmeterol

produces better symptom control and improved lung function compared with regular use of salbutamol[5].

The development of tolerance to the bronchoprotective effect of salmeterol is now recognized as a major concern[5]. It has been observed that the regular use of twice- daily inhaled salmeterol for 4 weeks produced bronchorelaxation against the airway challenge, however, the bronchodilation and symptomatic control was maintained even on long term treatment with these newer agents[7]. The long term use of β_2-agonists has been associated with a down regulation of pulmonary β_2 adrenergic receptors and recent studies showed concomitant administration of corticosteroids with β_2 -agonist initiates the up regulation of β adreno receptors[8].

In a double-blind study of patients with uncontrolled asthma despite regular treatment with inhaled corticosteroids, the addition of formoterol yielded marked symptomatic control in comparison with the higher doses of inhaled steroids, thus it was evident that the combination was more effective in reducing the number of exacerbations[9]. Other studies also support this emergent evidence that addition of a long acting β_2-agonist to low or moderate dosage inhaled corticosteroids provides equal or better control of asthma than a higher dosage of inhaled corticosteroids, with fewer adverse effects[10-12]. There is a possibility that long acting β_2-agonists either alone or in combination with a corticosteroid might replace the use of short acting β_2-agonists for the management of BA.

b) Theophylline

The importance of theophylline as a therapeutic agent in the treatment of BA has waned as greater efficacy of inhaled adrenoreceptor agonists and steroids for acute asthma and chronic asthma has been established, but its low cost is an important forethought in developing countries where health care resources are limited.

Traditionally, theophyllines has multiple mechanisms producing bronchodilatation but among these significant are via phosphodiestrase (PDE) inhibition inhibiting synthesis of cAMP or cGMP and inhibition of adenosine receptors directly or by hampering enzyme adenyl cyclases. The recent studies indicate that it possesses an additional anti-inflammatory effect[13]. It reduces the infiltration of pro-inflammatory cells into bronchial epithelium as well as reduces the expression of cytokines (IL-4, IL-5) that are involved in the activation of lymphocytes. Regular use of theophylline reduces the population of T-lymphocytes in the bronchial epithelium[14].

Though the comparative study of inhaled salmeterol and oral theophylline in the treatment of moderate to severe asthma suggests, salmeterol is more effectual for symptomatic relief, with fewer adverse effects than theophylline[15,16]. But, β_2-agonists do not produce suppression of underlying inflammatory reaction and are prescribed with other agents such as inhaled corticosteroids. Regular theophylline might provide an alternative but the role of the anti-inflammatory effect in asthma is yet to be defined copiously.

A single undivided evening dose of theophylline in asthmatic patients with nocturnal symptoms can be as effective as twice daily administration providing a better control in the morning that is at a phase of amplified requirement due to circadian rhythm variations[17]. New reports state that high dosage inhaled budesonide and low dosage budesonide plus theophylline in patients with moderate asthma produced comparable improvement in lung function in both groups but the low dose steroid with theophylline were well tolerated[18]. This suggests that the addition of theophylline to low dose of inhaled corticosteroid in suitable patients may provide an immunomodulation and a reserve for increasing the dose of corticosteroid in uncontrolled asthma, limiting the adverse effects of steroids[19].

Present clinical guidelines for the management of asthma recommend the use of theophylline as an additional bronchodilator if patient remain symptomatic with moderate-to-high dosage inhaled corticosteroids[20].

Unfortunately, theophylline may produce a number of dose related adverse effects. Gastrointestinal symptoms may be intolerable to some patients, even well within the usual therapeutic drug levels. Serum levels of theophylline may be markedly affected by a number of pathological as well as physiological variables, including age, diet, disease states, and drug interaction, this contributes to the complexity of using it as concomitant medication[21,22].

In the light of current substantiation, the anti-inflammatory effect may revolutionize the status of theophylline as an adjuvant for control of BA.

c) Anticholinergics

Inhaled anticholinergic agents (e.g. ipratropium bromide and tiotropium bromide) are available and may produce bronchodilatation by reducing intrinsic cholinergic tone of the airway. In clinical trials of asthma, there has been little evidence to support their use in long term management as there is a lot of interindividual discrepancy in response to these drugs[23]. In patients with COPD, however, these agents have been shown to be more effective

particularly tiotropium bromide due to its 24 hour duration of action. In general, these drugs are less potent than β_2-agonist and have a slow onset of action to attain maximal effect, i.e. 30-60 minutes. In a small number of patients with acute exacerbation of BA, ipratropium bromide enhanced the bronchodilatation produced by nebulised albuterol[24]. Anticholinergics have also been effective in treating asthma exacerbations resulting due to intolerance to β_2 agonists.

2. Anti-inflammatory drugs for BA:

a) Glucocorticosteroids

Glucocorticosteroids are the most potent anti-inflammatory agents existing for the treatment of asthma[25]. Their efficacy is related to numerous factors including attenuation in inflammatory response of polymorphonuclear cells, stabilization of vascular leakage, a decrease in mucus production, and an increase in β-adrenergic response. Glucocorticosteroids exert their effect on various cells by binding to intracellular glucocorticosteroids receptors, which regulate transcription of certain target genes controlling the phenomenon of atopy[26].

Unfortunately, long term administration of oral glucocorticosteroids, may result in multiple adverse effect, including hypothalamic-pituitary-adrenal axis suppression, osteoporosis, posterior sub capsular cataract, hyperglycaemia, hypertension, dermal thinning and strial, avascular necrosis of bone and growth retardation[27,28]. The oral preparations of steroids are now gradually replaced by the inhaled corticosteroids thus minimizing risks as well as systemic adverse effects on long term use[29,30]. Many patients can be maintained on a low dosage of inhaled corticosteroid, providing effective symptom control with no adverse effects.

Although inhaled corticosteroids when used in recommended doses have minimal adverse effects (with the exception of oral candidiasis when oral hygiene is suboptimal), recent studies have relighted trepidation about the long term effects of these compounds on growth in children[31]. The issue of growth in children who are atopic and/or have asthma is further complicated by the fact that both conditions appear to delay the onset of puberty[32]. The studies have demonstrated that on treatment with inhaled beclomethasone dipropionate, no significant association between its use and the adverse effects of diminished stature could be demonstrated. Thus there is no clinical evidence depicting that glucocorticosteroids therapy is coupled with growth impairment at higher doses or when prescribed for longer durations or in severe cases of B A. A few authors however raise vigilance regarding the doses beyond 800mg/day of beclomethasone as well of others steroids at appreciable high doses should be judged for the effects on growth in children. Conventionally, inhaled corticosteroids are administered twice daily. The effectiveness of once daily administration has been studied, initially with conflicting results[33, 34]. Conversely, a recent study with a large sample size established that once-daily administration of inhaled flunisolide was as effective as twice daily administration[35].

The question of whether the dosage of inhaled corticosteroids should be increased during an upper respiratory tract infection has not been responded adequately. The current British Thoracic Society (BTS) guidelines on asthma[36] recommend increasing dose of steroids in URI, till the results of controlled trials are available. Early control of symptoms is supportive for the patients and inhaled corticosteroids should be started at a higher dosage until control is achieved and then the dosage should be reduced in a stepwise fashion to the lowest needed to control the symptoms[37].

Oral corticosteroids remain useful in acute exacerbation and as continuous therapy for some patients with severe asthma. A few patients have asthma that is partially or completely corticosteroid resistant and in such cases the long-term or high dosage corticosteroids may not demonstrate the useful effects[38]. There is some preliminary evidence that early use of inhaled corticosteroids as anti inflammatory agents in asthma may limit to prevent the evolution of irreversible obstruction secondary to structural changes from prolonged inflammation[39]. The epithelial disruption and inflow of inflammatory cells are reduced by corticosteroids but there is less evidence of an effect on sub epithelial fibrosis and airway remodelling.

The inhaled steroids do not offer a curative strategy and the extensive doses of inhaled steroids can result in adrenal insufficiency. A minority of patients especially with severe asthma demonstrate resistance to the effect of corticosteroid treatment despite good compliance. The mechanism for this is not clear and confronts a therapeutic challenge for use of steroids.

b) Mast cell stabilizer: Cromolyn and nedocromil

Cromolyn sodium and nedocromil sodium, administered by metered-dose inhaler, are impressively safe medications that inhibit inflammatory cell activation and mediator release, early and late allergen-induced bronchoconstriction

and airway hyper responsiveness[40,41]. They are effective in both adult[41] and pediatric[42] patients presenting with persistent asthma. The mechanism of action of these agents may be related to their effects on airway epithelial chloride channels[43].

Reported adverse effects for cromolyn are increased cough and wheeze, dermatitis, myositis and gastroenteritis[44]. And nedocromil include nausea, vomiting, sore throat, throat irritation, cough and headache[45]. Initial increase in wheeze and cough produced by these drugs can be prevented by inhaling β_2- agonist before cromolyn/nedocromil treatment. But the effects produced by these agents are inferior to inhaled low dose steroids and the long term potential effects on BA are lacking. This needs to be probed further.

c) Antileukotriene drugs

Leukotrienes are important pro-inflammatory mediators of asthma. Like prostaglandins these eicosanoids are derived from the metabolism of membrane phospholipids within the alveolar macrophages, eosinophils, mast cells and neutrophils[46]. Antileukotriene drugs have been shown to improve pulmonary function in patients with chronic stable asthma[47]. The actions of leukotrienes can be blocked in two ways, i.e. by blockade at their receptors or inhibition of their synthesis. The addition of these agents to the treatment of asthma provides the first group agents that target specific steps in the inflammatory pathway rather than the general anti-inflammatory effect of corticosteroids. There are 2 types of leukotrienes receptor - those for leukotrienes B4 and those for cysteinyl leukotrienes. In human airways, leukotrienes C4, D4 and E4 all activate cysteinyl leukotrienes (CysLT) receptor[48]. Early studies using leukotrienes receptor antagonists were disappointing, but the newer agents have proved to be more effective. Their effects on asthma induced by exercise and allergen have been promising[49]. Montelukast and zafirlukast are the first leukotrienes receptor antagonists, licensed for clinical use in the UK in exercise induced asthma.

Montelukast is used to treat persistent asthma in paediatric age group. The drug has a rapid onset of action and produces an early improvement with in a day of initiation with it, in lung function and reduction in the requirement of β_2-agonists[50]. Zileuton, a 5 lipoxygenase inhibitor has also attributed to the desired clinical effects in BA. Early studies with it were disappointing, but these agents serve an important role in aspirin or NSAIDs induced asthma which occurs due to over activation of leukotrienes pathway. Off these agents Zileuton is least prescribed because of requirement of four times daily dosing and occasional liver toxicity.

The overall effect of these groups of drugs is less than inhaled steroids but they are equally effective in reducing frequency of exacerbations. Promising results are evident in patients complying poorly with inhaled steroids and exercise induced asthma and asthma induced by cold air[51]. Clinical trials have shown that the addition of montelukast in patients on high dose of inhaled steroids lead to decrease in the requirement of dose of inhaled steroids without loss of asthma control[53,52]. Affirmative effects have been dictated their addition to inhaled corticosteroids in poorly controlled patients of asthma. They may provide an early anti-inflammatory treatment in milder disease. However, addition of leukotrienes antagonist to existing therapies needs to be fully addressed. The relative effectiveness of these drugs in comparison with inhaled steroids and long acting β agonists is lacking and focused.

d) Anti-immunoglobulin (Ig-E) monoclonal antibodies

IgE has a vital role in the development of asthma in atopics and suppression of IgE is therefore a potential target in management of BA. In animal models anti-IgE antibodies reduce serum IgE, cytokine production and pulmonary eosinophil infiltration mediated by helper T-cells by preventing IgE dependent allergen presentation. A monoclonal anti-IgE antibody, Omalizumab, has been studied in patients of asthma. Compared with placebo omalizumab, given as a subcutaneous injection at doses titrated to serum IgE levels, it resulted in improved symptom control, fewer exacerbations and greater reduction in inhaled corticosteroids doses with no apparent adverse effects[55, 54]. Many studies and clinical trials show a reduction of early and late phase bronchoconstriction responses by anti IgE therapies but more work is needed to asses their place in treatment of asthma[56].

e) Monoclonal antibody to interleukin - 5

Interleukin-5 is responsible for the maturation and release of eosinophils which play an important role in the pathophysiology of BA. To monoclonal antibodies to IL-5 are current under investigation. A recent report showed that anti-interleukin-5, SB-240563 was able to reduce eosinophilia after allergen challenge when given intravenously but had no affect on early or late phase or on air way hyper responsiveness[57,58].

f) Humanized Recombinant interleukin-12

IL-12 is derived from macrophages, it suppress eosinophlic inflammation via modulation of T-lymphocyte. But the clinical effectiveness of recombinant interleukin-12 in patients of mild asthma has been disappointing and yielded toxic and adverse effects. Thus, its role in future is limited[58].

g) Interleukin 4 antagonists

Interleukin 4 is another cytokine targeted for novel asthma therapies. A nebulised IL-4 is under investigation. Preliminary results depicted that this drug was well tolerated and may reverse the deterioration in lung function seen on withdrawing corticosteroids. However, more studies are required for exploration of their role in BA[60, 59].

h) Selective phosphodiestrase (PDE) inhibitors

There has been a close association with bronchodilation of theophylline and phospodiestease inhibition. However, evidence accumulated in the early 1990s points to an anti-inflammatory action of this compound at sub-bronchodilator doses due to PDE inhibition. This provoked a remarkable resurgence of interest in theophylline and the invention of so called 'second generation' "**PDE inhibitors" for** potent smooth muscle relaxation and supplementary anti allergic and/or anti-inflammatory properties without complications of receptor down regulation and increased bronchial reactivity[61].

PDE 4 appears to be the isoform directly involved in the airway action of methylxanthines. More selective inhibitors of PDE4 are developed in an effort to reduce the toxicity while maintaining therapeutic efficacy of theophylline. Several combined PDE III/IV inhibitors have been developed and their clinical effects are currently being studied[62]. Evidence, so far shows that they have some anti-inflammatory effect but a disadvantage is their short duration of action and adverse effect especially nausea and vomiting. PDE-IV inhibitors have shown promising results in clinical trials. These trials have suggested that some of these drugs suppress the late asthmatic reaction (LAR) through anti-inflammatory effect. PDE-IV inhibitors suppress a diverse range of functional responses across many cell types implicated in the pathogenesis of asthma[63]. The adverse effect profile of PDE-IV inhibitors (nausea, vomiting and gastric acid secretion) has prompted the need to develop second generation compounds with fewer adverse effect but maintained therapeutic efficacy. The second generation compounds include **Piclamilast and rolipram**. Initial clinical results with these drugs have been encouraging especially in patients of chronic obstructive pulmonary disorder[64].

i) Alternative Treatment in BA- Corticosteroid-sparing agents

A few patients on bronchotherapy either show resistance to steroids or are difficult to manage with high dose of steroids, thus showing poor symptom control. This subgroup of patients could profit from early intervention with alternate asthma therapies for better control and reduction in adverse effects of corticosteroids[64].

I. **Methotrexate:** The mechanism of action for the antiasthmatic effect is unclear. It has shown to inhibit leukotrienes mediated neutrophil chemo taxis, macrophage and monocyte activation, lymphocyte proliferation and antibody formation[66,65]. Of the 11 perspective clinical trials in steroid dependent asthma only eight studies significant reduction in their placebo group[67,77]. The significance of current data is limited by small number of patients, high drop outs and short duration of study period. The hepatotoxic, G I, constitutional adverse effects and activation of underlying disease and the pulmonary hypersensitivity reactions induced by it, might impound it's use in patients[78,79,80].

II. **Cyclosporin:** It has been proposed to possess immunomodulatory effect and anti inflammatory action in asthma by inhibiting mucosal inflammation caused by activated T-lymphocytes. It reduces the synthesis and release of inflammatory mediators from mast cells and basophils and decreases B cell IgE synthesis and release. It reduces production of oxidant enzymes and interleukins[81]. In clinical trials it has shown to block the late asthmatic response and eosinophillic mediated response after allergen challenge[82-85]. There are three clinical reports with cyclosporine but benefit with reduction of steroid dose was observed in only one trial[86]. But its use is limited by toxicity. The possibility of using cyclosporine as an inhaled preparation is likely to be explored further.

III. **Gold:** Gold has been tried in BA because of it s immunomodulatory effects. It decrease phagocytosis of polymorphic nuclear cells following antigen challenge, inhibits lysosomal enzyme release, inhibits antibody production and complement activation[88, 87]. Three randomized trials have examined efficacy of gold in asthmatics. Though, it showed substantial response as compared to placebo but there were high drop outs due to intolerable adverse effects[87, 89, 91].

IV. **Others:** Troleandomycin (macrolide), sirolimus, Heparin, Furosemide, Intravenous inmmunoglobulins and Dapsone are being studied but experience is limited because of toxicity and doubtful efficacy[92].

3. New Developments under Investigation: Specific Targeted approach

These agents are newly developed compound, many of which are in their Phase II and III clinical development stage. All these agents specifically target sides for bronchodilation or inhibition of inflammatory mediators.

a. Anti-tryptase therapies:

Tryptase, a protease released by mast cells cause bronchoconstriction (55). Some in vitro studies show the efficacy of anti-tryptase agents and further work on these agents to establish their role as antiasthmatic agent is required[93, 94].

b. Anti-CD4 therapies:

CD4 + lymphocytes play an important role in inducing airway hyper-responsiveness through eosinophilic airway inflammation. These cells produce cytokines (IL-3, IL-4 and IL-5) that are involved in the inflammatory cascade in asthma. The anti CD4 therapy might avert the generation of cytokines and can be looked forward as the new target therapy in asthmatics. The safety of these agents has to be ascertained before their introduction for BA intervention[95].

c. Immunotherapy:

The challenging with extracts of various allergens (such as pollens or moulds) to which the patient is sensitive is performed with the intention of attenuating the inflammatory element of the disease. Peptide immunotherapy involves the down regulation of T cells through the injection of T-cell reactive peptides from defined allergens. These peptides lack Ig-E- binding activity and thus can verge the Ig-E mediated adverse effects[95]. The clinical effectiveness of immunotherapy in asthma is still debated. In most cases, similar or better results can be achieved more safely with simple drug therapy.

d. BCG:

Intranasal administration of extract of mycobacterium bovis - Bacillus Calmette Guerin (BCG) has been demonstrated to suppress airway eosinophilia in a model of atopic asthma and suggests its potential as a useful therapeutic agent in the treatment of atopic asthma[95].

Proposed targets Accosts:

a. Other Cytokine Antagonists:

With the increasing evidence that airway inflammation is mediated by cytokines such as IL-4 and IL-5, drugs preventing the release of cytokines may reduce chronic inflammation in asthma.

b. Neurokinin antagonists:

As tachykinins are responsible for airway inflammation, its receptor antagonists may be effective but further evaluation to determine their therapeutic effects is required[96].

c. Platelet Activating Factor (PAF) antagonist:

(PAF) is mediator, which is implicated in airway inflammation. Most trials of PAF antagonist have shown disappointing results in the treatment of chronic asthma[97].

d. Vaccines For Asthma- a dream to pursue:

It is possible to affect the allergic response by DNA immunization. Intramuscular inoculation with plasmid DNA encoding a specific antigen (gene vaccination) induces antibody and cytotoxic T-lymphocyte responses. Among other effects, gene vaccination mediates a fall in total and specific IgE levels and suppresses eosinophilic lung infiltration after antigen challenge. Much work still needs to be done on this novel approach to modulating the allergic response[98].

e. Asthma genetics:

Polymorphisms in the GPRS (G protein- related receptors for asthma) gene on chromosome 7p have now also been associated with asthma, airway hyperresponsiveness and allergic predisposition in children[99], confirming prior findings in adults of the gene's impact on asthma susceptibility and allergy[100]. New therapies of the near future include genetic screening for 'at risk' individual targeted gene therapy and possible immunization.

Conclusion

There have been many unswerving that have highly developed our understanding of pathogenesis of asthma and its management. Inflammation is distinguished as the most important event in the pathogenesis. However, bronchodilators and corticosteroids are still the mainstay of asthma treatment over the decades. The introduction of superior derivatives of corticosteroidss and beta agonists, the choice, safety, duration of action and ease of delivery have enhanced progressively. Surrogated anti - inflammatory agents have been used in severe disease, but have been limited by adverse

effects. The introduction of new agents affecting leukotrienes synthesis and action provides an alternative strategy but it needs to be confirmed on a large subset of population of asthmatics. The multifaceted approach attacking different targets leading to pathogenesis of BA would govern a better control of the disease. However, unmitigated management of the asthma improving the patient compliance and preserving the sensitivity to drugs in use will remain a significant confrontation but with the new advances further queries would be unravelled.

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