CURRENT ASPECTS IN THE TREATMENT OF BRONCHIALASTHMA

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ABSTRACT

Asthma is increasing in prevalence worldwide and results in significant health care resources. Although many patients are suffering from asthma can be adequately treated with inhaled corticosteroids, an important number of patients are required additional therapy there are several number of options are available. In further minority of patients may develop severe persistent asthma which remains difficult to manage despite current pharmacological therapies. In this literature we emphasized current therapies viz. cytokine modulators Anti-TNF agents, $Beta_2$ agonist, Immune and Gene therapy beside that other drug delivery system which are used in Asthma and several outlines of directions which may progress the management of asthma in the future.

Keywords: Cytokine Modulators, Anti-TNF agents, $Beta_2$ agonist, Immune therapy, Gene therapy, Antisense therapy & drug delivery.

INTRODUCTION

Bronchial Asthma is a chronic inflammatory disease of the airways that causes periodic attacks of coughing, wheezing shortness of breath, and chest tightness. Asthma is also associated with mast cell, eosinophils and T-lymphocytes. Mast cells are the allergy causing cells that release chemical substance like histamine. Histamine is the substance that causes nasal stuffiness and dripping in cold or hay fever, constriction of airways in Asthma and itchy areas in a skin allergy. Eosinophils are a type of white blood cell associated with allergic disease.

T-lymphocytes are also white blood cells associated with allergy and inflammation. According to the CDC more than 22 million Americans, Including 6.5 million children under18 years suffer from asthma today.

Allergy also plays an important role in many asthma cases but not in all. Allergies are strongly linked to bronchial asthma and to other respiratory diseases such as chronic sinusitis, middle ear infection, and nasal polyps.

Several types of Asthma are present under which allergic asthma is very well known common type of asthma.

About 90% of kids with childhood asthma have allergies compared with about 50% of adults. Inhaling specific substances are called allergens bring on the asthma symptoms associated with allergic asthma. Nearly everyone with asthma (Allergic or non-allergic) gets worse after exercising in cold air or after inhaling any type of smoke dust, fumes and sometimes strong smells.

Another type is exercise induced Asthma is asthma that triggered by vigorous or prolonged exercise or physical exertion. Most people with chronic asthma experience symptoms of asthma during exercise. However there are many people without chronic asthma who develop symptoms only during exercise.

In exercised-induced asthma the muscle bands around the airways are sensitive to these changes in temperature and humidity and react by contracting which narrows the airways. This results in symptoms of exercised include asthma, which include (a) coughing with asthma (b) Tightening of chest (c) Shortness of breath when exercising.

The symptoms of exercised induced asthma generally started within 5-20 minutes after the start of exercise or 5 to 10 minutes after brief exercise has stopped.

Second class of asthma is called cough-variant asthma, severe coughing with asthma is the predominant symptom. There can be other causes of cough such as post nasal drip, chronic rhinitis, sinusitis, or GERD or heart burn. Asthma is a serious cause of cough that is common today. Cough-variant asthma is very under diagnosed and under treated. Asthma triggers for cough variant asthma are usually respiratory infections and exercise.

In Briefly Asthma is a chronic respiratory disease characterized by excessive mucus production, inflammation and constriction of the airways. Genetic and environmental factors contribute in initiation and progression of asthma.

The Global Initiative for Asthma was created to increase awareness of asthma among health professionals, public health authority and the general public to improve prevention and management through a concerted worldwide effort. [1]

Various research studies indicates that airway hyper responsiveness is important in the pathogenesis of asthma and the level of airway hyper responsiveness usually correlates with the clinical severity of asthma.[2]

CYTOKINE MODULATORS AS NOVEL THERAPIES FOR BRONCHIAL ASTHMA

Cytokines play a critical role in orchestrating and perpetuating inflammation in asthma airways and several specific cytokine and chemokine inhibitors are now in development for the treatment of asthma.

Leukotrienes are derived from the cell membrane phospholipids arachidonic acid and are members of a larger group of molecules known as eicosanoids. It is possible to inhibit the production of leukotrienes by inhibiting their synthesis or antagonizing their receptor the [cys LT_1 receptor].

Several drugs have been investigated extensively in clinical trial of asthmatic patients and are now available for prescription use in the management of asthma.

These drugs include one enzyme inhibitor Zileuton, Zafirlukast and Montelukast. Antileukotrienes have been shown to inhibit effectively allergen induced early and late responses, airway hyper- responsiveness and allergen induced airway inflammation.

They are also effective in attenuating exercise-induced broncho-constriction and acetylsalicylic acid induced asthmatic responses. In clinical trials anti-leukotrienes improve broncho-constriction, reduce symptom, reduce rescue β_2-agonist use and may reduce severe asthma exacerbations. Anti-leukotrienes are a new class of drugs; therefore, the total patients exposure, which needs to be known to evaluate safety fully, is limited. Anti-leukotrienes are the first new class of novel and effective therapy for asthma in more than 20 years. They have been shown to have a beneficial effect in the treatment of both induced and spontaneously occurring asthma.

While encouraging different results have been obtained

from clinical trials of anti-leukotrienes there are no guidelines for the optimal clinical use of anti-leuko trienes in asthma treatment Inhibition of IL-4 with soluble IL-4 receptors has shown promising early results in asthma.

Anti- IL-5 antibody is very effective at inhibiting peripheral blood and airway eosinophils but does not appear to be effective in symptomatic asthma.

Inhibitory cytokines, Such as IL-10, Interferons and IL-12 are less promising because systemic delivery produces intolerable side effects. Inhibition of TNF-α may be useful in severe asthma. Many chemokines are involved in the inflammatory response of asthma, and small molecule inhibitors of chemokine receptors are in development. CCR3 antagonists are now in clinical development for the treatment of asthma, because so many cytokines are involved in asthma, drugs that inhibit the synthesis of multiple cytokines may prove to be more useful.

Several such classes of drug are now in clinical development and the risk of side effects with these non-specific inhibitors may be reduced by the inhaled route of delivery.

STRATEGIES FOR INHIBITING CYTOKINES

There are a number of possible approaches to the inhibition specific cytokines.[3,4] These include drugs that inhibit cytokine synthesis (Glucocorticoids, tacrolimus, lymphocyte (Th_2- Selective inhibitors), humanized blocking antibodies to cytokines or their receptors, soluble receptors that modulate secreted cytokines, low molecular, weight receptor antagonists and drugs that block the signal transduction pathways activated by cytokine [3].

Conversely, there are cytokines that themselves suppress the allergic inflammatory process and these may have therapeutic potential in asthma and COPD. [5,6]

INHIBITION OF THE Th_2 CYTOKINES

Th_2 cytokines may play an important role in the pathophysiology of allergic diseases including asthma. They may be useful therapeutic targets in the future management of allergic diseases, and several approaches to inhibiting these cytokines are now being tested in clinical trials or are in active development. [7]

Th_2 cells are involved in the regulation of the IgE immune response and local allergic inflammation which underlie allergic diseases. Various cytokines produce and released by Th2 cells play important roles in the development of many allergic diseases including asthma and the exacerbations of their disease states. Therefore targeting of Th2 cell derived cytokines is a rational therapeutic strategy for the treatment of asthma. Corticosteroids and immune suppressive agents can potently inhibit Th_2 cytokine mediated responses, but have no selectivity for Th_2 cells: they also exert pharmacological activity against cells other than inflammatory cells, there by potentially causing adverse side effects. However suplatast tosilate is the only specific Th_2 cytokine inhibitor that can be used clinically and it has been used widely in Japan as a maintenance drug in the treatment of asthma. Th_2 type cytokines particularly interleukin 5, together with granulocyte-macrophage colony stimulating factor and IL-3, orchestrate the eosinophils response in asthma.

Eosinophils are believed to be prime pro-inflammatory effectors cells causing bronchial damage, which in turn, leads to chronic asthma symptoms. Although many cells may secrete cytokines all of which influence eosinophils differentiation, survival and function, the TH2 type T cell is seen as having a central role since it is capable of direct antigen recognition. The putative driving antigen for asthmatic inflammation may be allergen although other antigen (i.e. viral epithelial) are also positive candidates. Although T-cells also influence the synthesis of IgE-IgE mediated.

Mechanism are seen as playing a secondary role only in atopic subjects where they may be responsible for acute short lived symptoms superimposed on the chronic ongoing cell mediated inflammatory disease.

ROLE OF ANTI-TNF AGENTS IN BRONCHIAL ASTHMA

It has been that recruitment of neutrophils and eosinophils associated with allergic condition is mediated via TNF-α. TNF-α is released in allergic responses, from mast cells and macrophases via IgE dependnt mechanisms Anti-TNF-α therapy may be useful as a gluco corticoid Sparing asthma therapy. Anti-TNF-α therapy may be effective in the treatment of certain allergic conditions including Jarisch-Herxheimer reaction. Asthma is regarded as a Th_2 type disorder especially when associated with atopy. However, TNF-α production is increased in severe corticosteroid dependent asthma. Improvements in clinical and physiological measures of asthma following 12 weeks treatment with etanercept were observed in an open label uncontrolled clinical study.

Etanercept treatment was associated with improvement in asthma symptoms, lung function and bronchial hyper responsiveness. However further long term RcTs are required to establish the status of anti TNF therapy in refractory bronchial asthma and allergic conditions. [8,9,10]

TNF-α is stored in granules and is known to be released during allergic responses from both mast cells and macrophages via IgE-dependent mechanisms. [11]

Besides mast cells and macrophases many other cell types that appear to play a contributory role in the pathogenesis of asthma are also a significant source of TNF-α including eosinophils, [12] epithelial cells [13] and neutrophils. [14]

In addition, T-cells from asthmatic airways constitutively produce large amounts of TNF-α both the protein and mRNA levels. [15]

TNF-α mRNA is more frequently expressed in the airways of asthematic subjects than normal subjects and increased release of this cytokine has been shown from BAL (Broncho alveolar lavage) cells of asthmatic subjects. [16]

LPS (Lipopoly Saccharide) inhalation by mild asthmatic subjects induces TNF-α secretion in to BAL fluid and is associated with increased airway reactivity. [17,18]

In addition, after allergen challenge, TNF-α is found to be increased in BAL fluid of asthmatic subjects, and their peripheral blood monocytes generate more of this cytokine. [19, 20]

TNF-α is known to be implicated in the proliferation and activation of sub epithelial basement membranes. [21]

TNF-α is known to be implicated in the proliferation and activation of subepithelial fibroblasts thus contributing to development of fibrosis below the bronchial basement membrane of the epithelial layer and to tissue remodeling in general. [22,23]

Moreover, airway epithelial cells also secrete mucus when stimulated with TNF-α.[24] TNF-α is also likely to have a more integrated role in airway remodeling, since it appears to modulate the EGFR dependent stress and repair response that occurs as a result of the inflammatory response that is associated with airway epithelial injury.[25]

The current goal of translational research in asthma is to develop biological agents based on clucidation of specific immune mechanisms and to develop drugs that can intervene the events felt to be critical in the pathophysiology of asthma. For e.g. omalizumab is the most currently approved recently available immunotherapy.

It is a humanized monoclonal antibody that specifically binds and blocks free circulating IgE. The success of omalizumab in treating asthma has opened possibilities

for the development of novel therapies for asthma.

TNF-α is a pro-inflammatory cytokine that has been implicated in many aspects of the airway pathology in asthma. Evidence is emerging to suggest that it may play an important role in severe refractory disease. The development of novel TNF-α antagonist has allowed us to test rote of this cytokine in vivo. Several studies demonstrated an improvement in asthma quality of life, lung function, airway hyper responsiveness (AHR) and a reduction in exacerbation frequency in patients treated with TNF-α therapy.

ROLE OF β2 AGONISTS IN ASTHMA

Salmeterol and Formoterol are long acting beta agonists (LABAS) that produce bronchodilation that can last up to 12 hours. They are useful for control of nocturnal asthma and have been found to be particularly useful in combination therapy with inhaled corticosteroids in adults who are inadeque controlled with inhaled corticosteroids alone, Althrogh salmeterol and formoterol are well established effective treatment for asthma in combination with corticosteroids, recent studied have questioned whether the use of either of these medications alone, or in higher doses might contribute to the development of serious asthma exacerbations. Although patients treated with the combination of salmeterol and fluticasone had improved forced expiratory volume in 1second (FEV1) and peak flow measurements after 3 months of therapy compared with ICS alone, the addition of salmeterol to fluticasone was not associated with any increases in airway inflammation in the biopsy, Specimens, bronchoalveolar lavage or bronchial washings. Therefore long acting beta agonists might not increase airway inflammation when used in combination with an inhaled corticosteroid Beta-2 agonists donot reduce inflammation or airway responsiveness but severe as bronchodilators, relaxing and opening constricted airways during an acute asthma attack. They are used alone only for patients with mild and intermittent asthma. Patients with more severe cases should use them in combination with other agents.

Specific shart acting β_2 agonists include the following:

Albuterol called salbutamol outside the U.S. is the standard short acting beta 2 agonist in America.

Other similar β_2 agonists are isoproterenol, metaproternol, terbutaline and bitolterol.

ISO- etharine is available in nebulizers. Newer β_2 agonists, including levalbuterol have more specific action than the standard agents. Studies have indicated that levalbuterol is an effective as albuterol with fewer side effects. Short acting bronchodilators are generally administered through inhalation and are effective for three to six hours. They relieve the symptoms of acute attacks, but they do not control the underlying inflammation.

If asthma continues to worse with the use of these agents, then patients should discuss conticosteroids or other drugs to treat underlying inflammation.

ROLE OF IMMUNOTHERAPY FOR ASTHMA

It is currently perceived that there is an asthma epidemic.[26] In north America allergic diseases affects approximately 20% of the population and the third and fifth leading causing of chronic disease in children and adult, respectively.[27] while current therapies include allergen avoidance and medications such as antihistamines, leukotrienes receptor antagonists and corticosteroids for almost 100 years, vaccination or immunotherapy has been practiced to control the development of allergic symptoms that occur on control with allergen. Asthma is characterized in large part by an abnormally polarized Th-2 type immune response, often specific for innocuous allergens.

This results in an inflammatory response that has been hypothesized to be responsible for the persistent to be responsible for the persistent changes of airway

remodeling. This proposal is now being questioned with more attention paid to the active epithelial mesenchymal trophic unit that is activated during tissue injury and repaid. The damage lung epithelium expresses increased levels of arginase, which reduces bronchodilatory and anti-proliferative nitric oxide (No) and promotes the release of aminoacides and polyamines regulating smooth muscle remodeling. The airway smooth muscle itself actively participates in the process through the secretion of chemokine and cytokines. [28,29,30]

While the mechanisms of action of immunotherapy were initially unknown in the last 40 years, the immunopathology of allergic disease has become better understood and this has allowed the development of new forms of immunotherapy that target specific molecules involved in the causation of diseases such as asthma. In addition, the use of classical immunotherapy has become more sophisticated with the introduction of alternative methods of administration and new forms of allergen.

Therefore, immunotherapy in asthma may now include subcutaneous immunotherapy, sublingual immunotherapy (SLIT), treatment with specific monoclonal antibodies against IgE, TNF, IL-5, TLR-9 Vaccines, cytosine phosphorothioate guanosine (CPG) allergen conjugates, allergen peptide vaccines, and even vaccines generating autologous antibodies to specific cytokines such as TNF and IL-5.

The importance of immunotherapy in asthma lies not only in its ability to modify ongoing disease processes but also in its potential to prevent progression of allergic disease.

Specific allergen immunotherapy is an effective treatment of allergic asthma. Advantages of immunotherapy compared with most pharmacotherapies include modification of the natural history of allergic disease reduction of need for chronic medication and treatment of both upper and lower airway disease simultaneasly. Improvements in immunotherapy occurred in the later portion of the twentieth century because of enhanced understanding of immunotherapy mechanism, of action, recognition of the dose effect and improved quality and consistency of allergen vaccines.

Purified inhibitors of specific mediators of the allergic response, products of biotechnology will probably lead to improvement of immunotherapy of asthma in the twenty first century.

The future of immunotherapy including other immunomodulation of allergic asthma is promising, asthma is an inflammatory disease characterized by the presence of cells eosinophils most cells basophils and CD^{25+} T- lymphocytes in the airway walls. There is close interaction between these cells, because of the activity of cytokines which have a variety of communication and biological effector properties.

Chemokines attract cells to the site of inflammation and cytokines activate them, resulting in inflammation and damage to the mucosa,[31] with chronicity of the process, secondary changes occur such as thickening of the basement membrane and fibrosis.[32]

An immunological reaction to allergen is the initiating events of airway in many cases of asthma. [33]

Continued exposure to allergen results in chronic inflammation. Current therapy aims to suppress this inflammation with inhaled corticosteroids, sodium cromoglycate or nedocromil sodium, all of which interfere with the cellular and cytokine interactions by diverse mechanisms, but do not address the initiating events in allergic asthma. By withdrawing the allergen or altering the immune response to allergen, it is theoretically possible to control the allergic trigger of asthma.

Immunotherapy leads to a reduction in mediator release from mast cells in vitro, alterations in lymphocytes subsets, and a down regulation of IL-4 production from

T-Cells. [34]

Several studies have shown a reduction in inflammation and a decrease in bronchial hyper-responsiveness after immunotherapy. [35,36,37]

Immunotherapy should not be regarded as an alternative to established forms of preventive therapy, as recommended by the National Asthma Campaign. [38]

A systematic cost benefit analysis of immunotherapy has not been undertaken.

ROLE OF GENE-THERAPY IN THE MANAGEMENT OF ASTHMA

Asthma affects one child in 7 in some societies, and approximately 15 milion individuals worldwide. [39]

Five asthma genes or gene complexes have now been identified by positional cloning including ADAM33, PHF11, DPP10, GRPA and SPINK5. [40,41,42,43,44]

The functions of all of these genes are obscure, but the expression of DPP10, GRPA and SPINK5 in terminally differentiating epithelium suggests that they deal with threat or damage from the external environment. [45]

Many of the genes identified by candidate gene studies may also exert their effects within the cells that make up the mucosa. These include IL-13 which modifies mucus production.

FcåRI-β which modifies the allergic trigger on mast cells and microbial pattern recognition receptors of the innate immune system. [45] It is also to be hoped that genetic finding may help identify the environmental factors that protect against asthma. To become relevant to clinical asthma, potential asthma susceptibility genes now need to be tested in cases and controls with different manifestations of disease severity and in representative population samples with different environmental risk factors. Several of the asthma susceptibility genes so far identified potential targets for asthma therapy.

Polymorphisms may also predict the response to asthma therapy. A positive association between common arginine-16 variants in the β-adrenergic receptor gene and the responsiveness of asthmatic patients to β-adrenergic agonists is particularly interesting. [46]

It is not known whether these differences in response represent a failure of β-agonists in individuals carrying the arginine-16 genotype, or whether therapy in these individuals will be adequate with an upward adjustment of dose.

A proportion of individuals with severe intractable asthma do not respond to inhaled steroids. It is possible that these individuals also carry mutations in some of the genes that control the anti-inflammatory response of steroids. They pathway are not completely understood, and it is yet known if genetic testing will be helpful in these circumstances.

ROLE OF ANTISENSE GENE THERAPY STRATEGIES IN THE TREATMENT OF ASTHMA

Asthma triggered by allergen exposure is a chronic pulmonary disease primarily affecting the airway inflammation and reversal obstruction.

In allergic asthma a common feature appears to be a polarization of T-lmphocyte function, highlighted by a predomainance of $CD4^+$ Tcells producing IL-4, IL-5, IL-13 and IL-10. Enhanced secretion of these cytokine results in IgE synthesis eosinophilic lung inflammation, goblet cell hyperplasia, and mucus hyper production. This polarization to a Th_2 predominant response in association with reduced Th1 cytokine production is postulated to underlie the patho-biology of allergic asthma. In association with Th2 immunity and IgE production, most cell and basophil activation is also increased.

The imbalance between Th2 and Th1 immunity in allergic asthma has promoted several therapeutic initiatives to restore the balance. These have included interfering with IL-4 or IL-5 and their receptors, prevention of the accumulation of eosinophils and targeting downstream mediators.

Many these approaches have failed to significantly improve outcomes for patients with the disease. The reasons are not immediately obvious, but do include the possibility that the reagents used could not fully eliminate the biologic activity of the target protein or sustain such effects in vivo.

USE OF ANTI-SENSE OLIGO NUCLEOTIDES IN ASTHMA

On newer approach involves the use of antisense oligonucleotides. Each sequence on the DNA provides a blue print for the production of a specific protein. In order to produce a protein DNA must transmit its information to messenger RNA (mRNA) the sense strand. An anti-sense drug is the exact opposite, a mirror image of a specific sense strand.

Anti-sense olignucleotides are short synthetic DNA molecules, designed to attach or interact with the mRNA encoding a specific targeted protein.

Tradition drug attack proteins but because proteins are large complex structures produced in large quantities, traditional drugs must disable every copy of the protein.

Antisense is an attractive option because each mRNA molecule produces large quantities of a single protein.

Antisense technology by attaching to a single mRNA started responsible for producing a single protein, mat be a much more efficient way of eliminating unwanted proteins. In addition, antisense drug only binds with its exact opposite it is highly specific.

However as simple and elegant as it appears the use of antisense drugs have not translated in to clinical reality at least not yet. The anti-sense drugs must be the right size to achieve specificity for the right piece of RNA, but stable enough to avoid ribonuclease cleavage. They must also be small enough to reach and penetrate target cells. Phosphorous analogues of anti-senes oligonucteotides are often used to increase resistance to nucleases but as such may trigger side effects. Anti-sense oligonucleotides can be delivered intravenously, S.C. or by inhalation. Infact the presence of surfactant in the lung may facilitate the entry of anti-sense oligonucleotides into cells.

In most cases the half-life of these drugs in around 24 hours, implying a requirement for regular administration. As it patients to allergic asthma some of current anti-sense targets being explored include stem cell factor, adenosine receptor, beta chain of IL-3, IL-5 and granulocytes mecrophase colony stimulating factor (GM-CSF), CCR3, IL-4R alpha chain, STAT 6, GATA-3 and SKY.

The lung represents an ideal organ to target with antisens oligonucleotides, given that its large surface area and the surfactant that is present could facilitate the cellular absorption of the oligonucleotides. This facilitation by surfactant may be enhanced during allergic inflammation as surfactant levels have been shown to increase in parallel to the inflammatory response.

ANTISENSE TARGETS

GATA-3: It is a pleiotropic transcription factor expressed in Tcells, mastcells and basophils. This factor has been shown to be essential for the delelopment of the earliest progenitor Tcells and is expressed selectively in Th2 but not Th1 cells.

The function of GATA-3 on Th2 cytokine gene promotes position it as a potentially important target. In asthmatics GATA-3 mRNA expression is increased in the airways. In vitro GATA-3 expression in IL-4 producing T cells could be suppressed by an anti-sense phosphorothioate oligonucleotides. This sets the stage for determining if this stategy could be effects in vivo.

In a murine model of allergen induced airway/ inflammation and hyperresponsiveness, GATA-3 anti-senese oligonucleotides were given by intranasal administration prior to challenge of sensitized mice. [47]

Intrapulmonary blockade of GATA-3 expression in this way resulted in a marked reduction of lung inflammation, including the prevention of accumulation of eosinophils, Th2 cytokine production, as well as a reduction in airway hyper-responsiveness such data suggest that lung delivery of an anti-sense DNA can be effective in this case targeting GATA-3 to selectively suppress the production of lung inflammation and airway hyper responsiveness. There is now a high probability that all the genes encoded in the human genome will have been sequenced by the year 2005, resulting in a massive increase in the identification of noval therapeutic targets. The use of new genomic sequence information in conjugation with anti-sense oligo nucteotides is one means by which the gene products playing the most important roles in multifactorial disease such as asthma can be identified.

RECENT DEVELOPMENT OF DRUG DELIVERY SYSTEMS FOR THE TREATMENT OF ASTHMA

Aerosol delivery of anti-asthmatic drugs such as corticosteroids is ideal from the stand point of maximizing local effects in the lung as well as minimizing systemic side effects compared with oral therapy. [48]

Prototype aerosol inhalers of beclometasone and beta stimulants utilized chlorofluoro carbon (CFC) as carriers in the form of pressurized metered dose inhalers (PMDIS) and showed their beneficial effects. [49]

The third group of delivering devices of anti-asthma drugs is nebulizers, which are specially useful in children and emergency rooms. [50]

There are a variety of devices such as pneumatic jet, nebulizers ultrasonic nebulizers, and mesh nebulizers. Newer nebulizer designs have been developed including breath-enhanced breath actuated or have acrosol storage base to minimize aerosol loss during exhalation.

NOVEL DOSAGE FORM FOR THE TREATMENT OF ASTHMA

Nanosurfactants for the treatment of asthma

The smooth muscle constriction and mucosal edema associated with asthma may be due to poor functions of the airway surfactant. Surfactant maintains low airway resistance and potency of aleveolar and conducting airways. In case of inflammation plasma proteins affects the patency of the airways causing increased airway resistance. Research have developed protein free, nano-sized airway surfactant therapy that can be used as an adjuvant for the treatment of asthma. The formulation is resistant to plasma proteins and can reverse the plasma protein induced increased airway resistance. The invented surfactant (with and without drugs) achieved 100% airway potency as tasted in a capillary surfactometer model of airways. Addition of this surfactant as a replacement may thus be a novel method of adjuvant therapy in asthma.

Inhated corticosteroids (ICS) are used for long term management of asthma. Clinical effects of ICSs depends on the time the drug resides in the lung therefore increased drug residence time improved asthma therapy. It has been proposed that nano particles could escape clearance mechanisms in the lung and adhere strongly to the lung surface, leading to increased residence time. There are two main barriers to this approach, first nano particles cannot deposit in the lung and instead they are exhaled.

Second the particles must be formulated to release drug slowly in order to take advantage of the increased residence time, Triamcinolone acetonide (TA) and polymer, poly-lactide co-glycolide (PLGA), were

formulated into nano particles.

Nano particles will be spray dried with lactose to form microspheres able to deposit within the lung on inhalation particles deposit in the pulmonary airways nano particle will de-aggregate and adhere to the pulmorlary epithelium and provide sustained release of TA.

Most of the steroid inhalers when prescribed by the physician at the usual dose have an immeasurable effect on the body. Some potential effects include the suppression of the hypothalamus (in the brain) and the adrenals (above the kidneys).

These glands are involved in our bodies response to stress. Measurement of their function is a very sensitive way of determining the impact inhaled steroids may have on the body. When function of these glands is suppressed than the many side effects seen with oral steroids may also occur. The most common side effect of inhaled steroids is oral candidiasis.

CONCLUSION

Bronchial Asthma is a chronic inflammatory disease. People are suffering from asthma experience reactions including coughing, wheezing and tightness in their chest. This combination of reactions restricts breathing as the airways become inflamed and obstructed. Mild episodic asthma is due primarily to bronchial smooth muscle constraction where as moderate to severe sustained asthma is largely due to chronic inflammation of the bronchi with the presence of such white cells as eosinophils, neutronphils and mononuclear cells.

These cells contribute products that inflame the airways. There are several treatment of options are available both pharmacological and non-pharmacological. Inhaled corticosteroids therapy are used for long term management of asthma.

Several cytokine and chemokine inhibitors are now in development for the treatment of asthma.

Inhibitor of Th_2 cytokines also play a major role in the allergic diseases like asthma. Anti-TNF-α therapy may be beneficial effects as a glucocorticoid sparing asthma therapy several bronchodilators and β_2 agonist are useful in the short term management of the asthma. Immunotherapy also play the major role in preventing the mediator release from the most cell therefore it reduces the inflammation and bronchial hyperesponsiveness protein free nano-sized airway surfactant therapy that can be used as an adjuvant for the treatment of asthma. Though research are on going but researcher are hoped that genetic findings may be useful to identity the environmental factors that protect against asthma.

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