

## Progress of three kinds of treatment for asthma

Pengbo Gao<sup>1, \*, †</sup>, Chenyi Zhou<sup>2, †</sup>

<sup>1</sup>Beijing International Bilingual Academy, Beijing, China

<sup>2</sup>School of Nanjing Foreign Language School, Nanjing, China

\*Corresponding author: 2024egao@biba-student.org

†These authors contribute equally.

**Abstract.** Asthma is chronic inflammatory airway disease and may be induced by both genetic factors and epigenetic factors. Asthma has no particularly typical symptoms, and these symptoms include cough, expectoration, suffocation, chest tightness and even breathing difficulties. Drugs for asthma treatment are divided into rescue treatment and maintenance treatment, rescue treatments are for people with mild symptoms of asthma which means the frequency of onset does not exceed two times a week while maintenance treatments with inhalable drugs that deal with inflammation are for all other patients that suffer severely and to increase control. As in recent years, the population with asthma has shown to be increasing worldwide over time, the importance and necessity of understanding the mechanism of asthma and its main treatment methods and principles are also increasing. This article mainly focused on three types of most commonly seen maintenance treatment for asthma, including glucocorticoid, theophylline and leukotriene receptor antagonist.

**Keywords:** asthma; treatment; mechanism.

### 1. Introduction

Asthma generally refers to bronchial asthma. Bronchial asthma is a heterogeneous disease characterized by chronic airway inflammation involving multiple cells. The origins of asthma can be divided into two groups, and they are genetics and epigenetics, respiratory infections, especially infections of virus at a young age and allergies caused by exposure to poor air conditions. Among all of these factors, It is well known that genetics are deeply involved in asthma, with the approximal rate of inheritance between 35% to 95%. The 17q21 locus has been consistently identified across the human genome in searching for the genetic differences between people with and without asthma. Epigenetic factors refer to characteristics in DNA that manipulate the expression of genes but are not controlled by the sequence itself. For example, Histone modifications and RNA modification. In theory, other factors, like the response to different vitamins, microorganisms, change in diet and emotional stress also contributes to the development of asthma [1]. The risk of getting asthma also varies in people who were born in different seasons. Research has shown that people who were born in summer, especially those with their birthdays in June, have a significantly increased risk of asthma, in comparison with people who have a winter birth [2]. As children, boys have an increased prevalence of asthma while as adults it is vice versa. Males with Non-allergic asthma are more likely to be cured in adulthood [3], but females, especially those obese ones are more likely to suffer from non-allergic asthma. For women, fluctuations in sex hormones in childhood levels off during puberty [4]. The symptoms of asthma can be triggered by some kinds of potential mechanisms that are always related to airway inflammation and airway remodeling. Asthma symptoms like shortness of breath, cough, chest tightness, and wheezing are non-specific. Different types of asthma include late-onset asthma, occupational asthma and cough-variant asthma.

As for the treatment for asthma, the primary prevention job should be done among high-risk populations; and the secondary prevention job is avoiding exposure to allergens and timely vaccination; in addition the education about asthma knowledge received by patients can all be considered as immunotherapy. Drugs include two kinds: one for rescue treatment another for maintenance treatment. Rescue treatments are for patients with asthma who have mild Intermittent

symptoms no more than twice a week. A maintenance treatment is using inhaled anti-inflammatory and other drugs for all the other patients to increase control. The severity of chronic symptoms should be taken into account while choosing the right treatment [5]. The most common maintenance treatments that exist today include Glucocorticoid, leukotriene receptor antagonist and theophylline. Glucocorticoids inhibit the inflammatory response in asthmatics by increasing the transcription of anti-inflammatory genes and decreasing the transcription of inflammatory genes [6]. Leukotriene receptor antagonists are a new kind of drugs for the treatment of asthma, which can be taken in tablet forms. Their unique mechanism of action triggers the function bronchodilators and anti-inflammatory effects, which indirectly help to treat asthma [7]. Theophylline is a commonly used drug for the treatment of asthma by down-regulating the function of inflammatory cells and immune cells in animals with inflamed airway.

There is no perfect and uniform standard for asthma diagnosis. Diagnosis is based on probability and one needs to consider specific symptoms and variable limitations. Since asthma is heterogeneous, symptoms on some patients might not be detected [4]. Asthma symptoms, which are non-specific, include shortness of breath, cough, chest tightness, and wheezing. Therefore, recording a medical history is vital to differentiate the symptoms between asthma and a differential diagnosis. For example, exiratory wheezing can be heard during auscultation of asthma, while constant lack of wheezing when having symptoms should suggest another diagnosis. And with all these different underlying mechanisms, some phenotypes of asthma are possibly not easily distinguished from each other. Eczema, rhinitis, or food allergy, a family history of asthma is commonly associated with childhood-onset allergic asthma, and wheezing or coughing is associated with viral respiratory infections. Non-allergic asthma can occur in different periods of one's life, and it may also appear when one has a viral respiratory infection. Airway inflammation is not regarded as a mandatory feature of asthma because it has variable symptoms and variable airflow limitation, which is not consistent with the existing accepted definition of asthma.

To let researchers understand the mechanism and background of the current existing treatments for asthma, this article summerised three types of most commonly seen maintenance treatment for asthma, including glucocorticoid, theophylline and leukotriene receptor antagonist.

## **2. Three type of treatments**

### **2.1. Glucocorticoid**

Glucocorticoids (GC) are a very important class of regulatory molecules in the body, which play an important regulatory role in the development, growth, metabolism, and immune function of the body, During most of pregnancy, fetal serum glucocorticoids are relatively low, but they increase significantly several weeks before labour. Their widely known function is to promote the differentiation and to improve the lungs. Inhalable glucocorticoids used to treat asthma have become one of the most commonly used treatments [6]. Glucocorticoid is a type of hormone that represent a group of extremely potent anti-inflammatory agent used to cope with inflammation. Having been first fully extracted in 1940s, the first synthetic glucocorticoids were actually developed in late 1950s as drugs to treat rheumatoid arthritis.

### **2.2. Mechanism of glucocorticoid**

Glucocorticoids can only exert their affects after they bind to glucocorticoid receptor (GR) (May also bind to regions on DNA that are less well known and manipulate promoters that do not contain sequences of GRE) which are located in the cytoplasm of the target cells. So far, one type of GR has been identified to bind with glucocorticoids (Fig 1). Glucocorticoids activate GR to control the transcription of specific genes in the target cells.

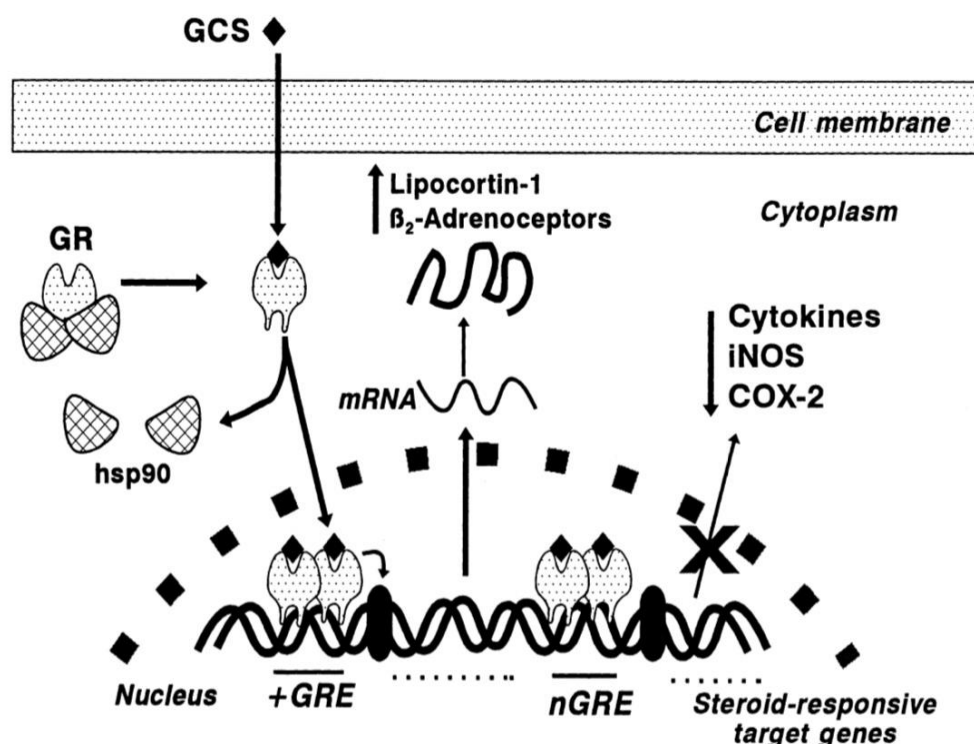


Fig.1 Mechanism of GC [6].

There are about 10 to 100 genes that are directly regulated by steroids in every cell. Other genes present in cells are indirectly regulated by interacting with other transcription factors. The speed at which DNA is being transcribed changes accordingly, therefore repressing or inducing the gene. GR may make a direct interaction with other transcription factors, which bind to each other in a manner called leucine zipper interactions. This is vital when it comes to determining the responsiveness of steroid. Glucocorticoid's main effect is to suppress the airway when patients are experiencing a sudden airway pressure or block.

Glucocorticoids inhibit inflammation through accelerating formation of proteins that are anti-inflammatory. Accumulation of Lipo portion 1 caused by the steroids is also immensely beneficial to the suppression of inflammation due to the properties of the recombinant lipo cortin 1. In the epithelial cells of the airway, glucocorticoids increases the formation of secretory leukocyte protease inhibitor as well. Evidence also shows that the increase of the formation of one type of IjB, IjB-a, found in mono nuclear cells and lymphocytes. The synthesis of this substance deactivates NF-jB, an inhibitor of interleukin 10, produced by macrophages in human lungs as an anti-inflammatory substance [7].

### 2.3. Side effects of glucocorticoids in asthma

Although glucocorticoids are very commonly used in asthma, they have side effects. most major organ systems are involved in the glucocorticoid associated side effects. Side effects may lead to gastrointestinal, musculoskeletal, endocrine, cardiovascular, neuropsychiatric, ocular, dermatological and other diseases.

Since glucocorticoid largely reduces the effect of osteoplast on the metabolism of bones, this will in time result in a decrease in the synthesis of bone. Once glucocorticoid treatment is initiated, the process of rapid bone loss begins, and this happens mainly in the first six months. What's more, myopathy is also a disease that can be caused by glucocorticoid therapy [8].

Hyperglycemia is also a possible side effect. This induction can be explained by increase of liver gluconeogenesis, inhibition of the consumption of glucose in adipose tissue, and glucocorticoid-induced changes in the functions of receptors. Dyslipidemia can also be caused by the therapy of glucocorticoid. This involves very low density lipoproteins' increase in formation, and the accumulation of free fatty acids in the liver.

Other side effects include weight gain, growth and adrenal suppression, hypertension, etc. Which are all much related to the destruction of the homeostasis inside the human body [9].

## 2.4. Theophylline

Theophylline is a substance that is derived from tea. Since the effectiveness of theophylline as a useful therapy for curing asthma has been proved in the 1970s, the official use of theophylline has started ever since. After that, theophylline has gradually become one of the leading therapies to treat asthma. As an anti-asthma drug, the substance has anti-inflammatory, immunomodulatory and bronchoprotective effects [10].

## 2.5. Mechanism of theophylline

Theophylline exerts inhibition on cells that have immune or inflammatory functions inside the body of a patient with inflammation in the airways. In people who have allergic asthma, it decreases the relative increase in the obstruction of the airways and the sensitivity and responsiveness of airways to histamine, a very important factor in the inflammatory response and stimulation of bronchial smooth muscle contraction

In people who have mild asthma, theophylline decreases respond to histamine, allergen, methacholine, adenosine, distilled water and sulfur dioxide in the airways. While the decreased amount is comparatively little for the bronchoconstrictors, the airways can be completely inhibited of responding to these substances. Therefore providing a good control over chronic asthma. By decreasing hydrolysis of nucleotides controlled by phosphodiesterase, theophylline raises the concentration of cyclic nucleotides in the smooth muscle of the airways, thus relaxing the smooth muscle located in the airways and in the pulmonary arteries. While anti-inflammatory actions are most likely caused by the deactivations of the type IV isoenzymes, Theophylline's effects of protecting the bronchus against antigen and leukotriene D4 induced constriction seem to be carried out through a molecular mechanism, Where the inhibition of phosphodiesterase or receptors is not commonly seen.

Theophylline induces apoptosis in neutrophils by reducing the anti-apoptotic protein Bcl-2 and induces the apoptosis of t-lymphocytes. Theophylline also inhibits the enzyme poly polymerase-1, which is activated by oxidative stress, this leads to the reduction of the levels of NAD and an eventual death of the cell caused by lack of energy [11].

When in extremely low Theophylline concentrations (~5mg/L), HDACs are activated, particularly when their activity is reduced because of oxidative stress. Theophylline prevents the degradation and loss of inhibitory I- $\kappa$ B $\alpha$  and the transport ion of transcription factors into the nucleus, this cause the expression of inflammatory genes involved in the development of asthma to decrease [12]

To sum up, Theophylline helps relax the smooth muscle of the bronchial airways, helps air easily flow and also smooth the pulmonary blood vessels and to reduces airway responsiveness to allergens and therefore helps with asthma [10].

## 2.6. Side effects of theophylline

One of the main limitations of theophylline is that it has high chance and frequency of side effects when used at regular doses. The most commonly seen adverse reactions are nausea and vomiting, headache, gastroesophageal reflux which may be caused by the inhibition of PDE, and increased acid secretion. Diuresis may be caused by adenosine receptor antagonism. Due to Theophylline's unique characteristics, Over obtaining can also cause seizures, arrhythmia and GI effects. It also causes stomach pain, trouble sleeping, diarrhea, irritability, restlessness, nervousness, and shaking [11-12].

## 2.7. Leukotrienes Modifier

During acute asthma attacks which usually caused by allergens and exercise. There is a symptom that is happening fast and obvious which is bronchoconstriction. This symptom is usually viewed as patients being hard to breathe and having asphyxia [13]. This symptom is caused by a substance in

the human body called Leukotrienes. Leukotrienes is a type of substance in the human body that has a relationship with eosinophils which will cause these symptoms [13]. During asthma, the leukotrienes will be produced and attracted the eosinophils into bronchioles [13]. In bronchioles, they will also produce more leukotrienes to attract more eosinophils [13]. In the end, this will increase the swelling of the lung lining [13]. The leukotrienes will also cause the mucus inside the bronchioles which makes the fluid inside the lungs easier to accumulate [13]. Therefore, Leukotrienes modifiers have invited that function to block typical leukotriene receptors on the bronchial tissues and reduce the potential possibility of symptoms that are caused by leukotrienes. Leukotrienes Modifiers are also called leukotriene receptor antagonists. One Most used Leukotrienes Modifiers in modern life is called Montelukast [13]. Montelukast is been approved for medical use in 1998 [14]. Is one of the leukotriene receptor antagonist drugs. However, leukotriene receptor antagonist drugs are only can be used for asthma prevention instead of emergency uses [14].

## 2.8. Mechanism

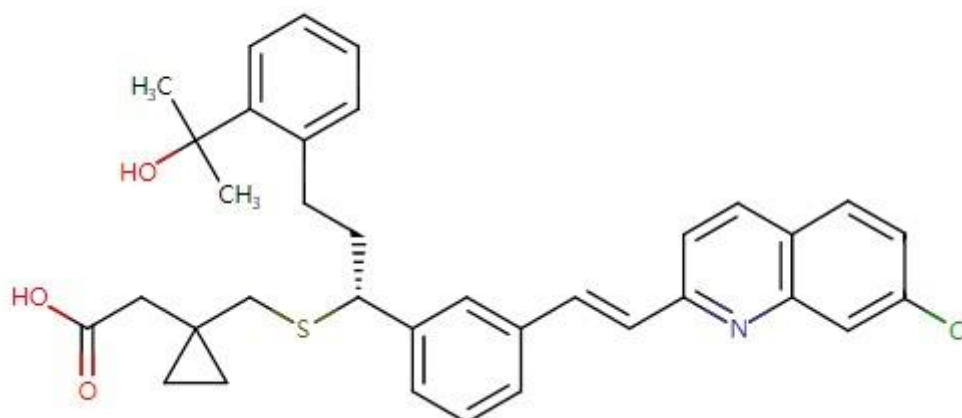
As in the mechanism way, leukotrienes Modifiers are used to block specific leukotrienes receptors that are producing more leukotrienes to attract eosinophils to cause breathing problems for patients. In a specific view. The leukotrienes Modifiers will work as two specific inhibitors each will have different functions. One, use to block leukotriene synthesis by using enzyme inhibition. Second, is used to distribute the leukotrienes in the human body to bind to their receptors [15].

The first inhibitor's function will be to produce a substance that can block the formation of leukotriene substances like 5-lipoxygenase and [15] one of the inhibitors will bind to the active side of the enzyme that will synthesize the leukotriene A4 (the substance that can trigger the synthesis of leukotrienes B4 which is the substance that acts one of the main roles of asthma [16].) which the inhibitor name is 5-lipoxygenase inhibitor [15]. The 5-lipoxygenase inhibitor also can be represented as zileuton, this inhibitor is useful in preventing the action of 5-lipoxygenase's translocation and synthesis of Leukotriene A4 which can trigger Leukotrienes B4 synthesis. However, the specific inhibitor of the 5-lipoxygenase activating protein is still in the process of developing stage. As this type of inhibitor has been invented, it will contain a better effect on blocking the synthesis of Leukotriene B4 in the human body [15].

The second type inhibitor, it's function is to compete with the cysteinyl leukotrienes function in the body which is more focused on leukotriene D4 receptor Cys-LT1 [15]. This type of receptor will cause patients' bronchial smooth-muscle to contract, which is opposite to the Cys-LT2 that will cause contraction of the pulmonary-vein [15]. The inhibitor will be chosen to bind with the CysLT type 1 receptor which assists in inhibiting the symptoms caused by CysLTs like LTD4, LTE4, and others. These inhibitors were been approved been disappointed in the treatment of asthma in the early studies due to they are lack of potency and specificity in treating asthma. However, the new receptor antagonists are having a better effect which shifts the leukotriene D4 dose-response curve to the right around 100 times [15]. As a supplement, these receptors of leukotriene D4 also works well for blocking the Leukotrienes C4 and E4 which are the other two substance that can increase the symptom of asthma [15]. At the global level most use drugs of cysteinyl leukotriene-receptor antagonists are Montelukast, Zafirlukast, and Prankast [13].

## 2.9. Side Effect

Due to the fact that inhibitor of 5-lipoxygenase activating protein are still in the development stage, following passage will be more focus on side affect of cysteinyl leukotriene-receptor antagonists, and it's most used type of drug Montelukast. Montelukast contain the chemical formula:  $C_{35}H_{36}ClNO_3$  and structure will be in the following Fig 2.



**Fig. 2** Structure of Montelukast [14].

Even though Montelukast is one of the most used Leukotrienes Modifiers it's side effects can be a problem. Including Body aches, cough, difficulty of breathing, fever, headache, loss of voice, pain, stomach pain, runny nose, trouble swallowing, voice change, and many others [17]. However, Montelukast also has several psychological side affect including anxiety, attempts suicide, dream abnormalities, drowsiness, Churg–Strauss syndrome, and many others [18]. These psychological in the final lead to further psychological problems for patients [18].

### 3. Future development

Even though the treatment for asthma mentioned above are well established, each of them still contains several side effects and disadvantages that can cause different problems to patients as small and big problems for societies.

As in the first treatment for Glucocorticoids, even though is a well-established and emergency medicine for most asthma patients, You still can take it too much each time in the short term and long term. Glucocorticoids are still a type of hormone therapy that contain several serious problems and risks. The two main problems created by long-term or excessive taking of Glucocorticoids are Cushing's syndrome and the risk of cancer. Cushing's syndrome is a type of syndrome that is caused by loss of muscle tissue which is one of the problems created by excess and long-term use of Glucocorticoids [19]. This can cause patients to start gaining fats while creating further health concerns including diabetes, high blood pressure, thin skin, and many others [19]. Each of these side effects can cause further extra treatment fees and increase the economic burdens for patients and patients' families. Another one is cancerous [19]. This could lead to also increase in economic burdens for patients' families in increasing the health check fee but also lead the patients to a high risk of disease that have a high rate of dying.

Theophylline treatment is usually having a very specific patient area and specific medication restrictions for patients who are using it. Theophylline toxicity can be like other methylxanthines that will cause gastrointestinal distress, insomnia, and tumor, and also increase the rate of vomiting cardiac arrhythmias, hypotension, and other many side effects. These side effects are all caused by over using the drugs. And as mentioned above theophylline is only used for immunomodulatory, anti-inflammatory, and bronchoprotective effects. Therefore, it can not be used as an emergency as hypersensitivity happened to a patient [20]. In the long term, future for further development of Theophylline it may have to lower its toxicity that is capable of all ages patients won't have to set restrictions for some age patients that use this therapy, which can give them better way and treatments to get better in the asthma treatment process.

As the top mentioned, A extreme side effect of Leukotrienes Modifier specially Montelukast will somehow affect a patient's mental health. This side effect created a huge impact on society.

According to the research these years, there is a close relationship between patients using Montelukast with depression and committing suicide. Even though this type of side effect is well known for Montelukast, this medicine are still one of the major medicine for Leukotrienes Modifier that use between not only asthma patients but also people with allergic rhinitis and other patients with any disease that are related to allergy [18]. If in the future these side effects are not been decrease or disappear, the growth of asthma and allergic disease patients. This side effect can cause a huge problem. Leukotrienes Modifier as a whole is having as similarity problems with Theophylline in that they are only for preventing the risk of having asthma again instead of full treatments for asthma or emergency usage [15]. In an emergency, these type of medicine will still be less effect than hormone treatment which can save patients life during hypersensitivity [15].

#### 4. Conclusion

As the compare of these 3 types of treatments are used most in preventing asthma symptoms and stopping the emergency symptoms of asthma. There will be a full treatment to heal asthma through chemical therapy way. Therefore, the possible way of future development can be focusing on how to apply chemical therapy in patients with allergic agents that cause asthma happened. For each development that has been mentioned above. Glucocorticoids have to decrease the side effect to let patients less pain or bad feeling after they use the drugs. Theophylline can focus on the way to reduce its toxicity that is able to use in a wider range of patients group. Leukotrienes Modifiers are more focuses on reducing the mental health side effect in the future of the patients due to they are the other most used chemical therapy that will be used in asthma instead of Glucocorticoids.

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