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ASTHMA STATUS: AN EVALUATION OF THE CURRENT PROGRESS IN RESEARCH AND COST CONTROL OF THE ASTHMA EPIDEMIC

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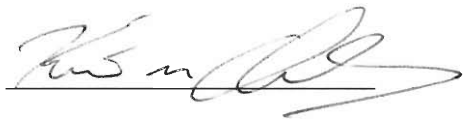

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ABSTRACT

A simple yet disturbing trend has been noted in the past two decades regarding not only the prevalence of asthma among the population, but also of the increase in healthcare costs for everybody involved in asthma care, especially the patients. There are many hypotheses regarding this tremendous increase in both the numbers of individuals affected by asthma and of the unfortunate rapidly rising healthcare coverage costs for proper patient care. This IQP provides a thorough evaluation of the current literature and issues surrounding the asthma epidemic.

INTRODUCTION AND BACKGROUND

Asthma is a chronic respiratory inflammatory disease that is characterized by difficulty in breathing, wheezing, and a tight feeling in the chest. However, many common respiratory diseases can display many or all of these characteristics. Therefore the diagnosis of asthma by many physicians is often wrong or too late to provide early intervention with asthma drugs (Heal Asthma). Asthma has been a problem for much of society for the past 50 years but only recently has asthma become a genuine global epidemic that currently affects over 150 million people per year and continues to grow (Cleland, et al, 2003). Within the past 25 years, a steady increase in the deaths arising from asthma symptoms has become a public concern (NIH).

Asthma symptoms are not identical between individuals and can vary widely in severity. This further complicates treatment but allows for a clear division of asthma patients into three categories: 1) Mild, 2) Moderate, and 3) Severe. Each of these categories require different levels of control of symptoms and have been described in great detail by the 1997 NIH Published Guidelines for the Treatment of Asthma (NIH). This 153 page document is the rule for

physicians and researchers investigating asthma. The goal of these guidelines is to aid both physician and patient understanding about asthma as well as to provide suggestions for its treatment.

Asthma involves the inflammation of the airways constricting airflow into the lungs. Many different cells (including T lymphocytes, mast cells, and eosinophils) play a role in the pathogenesis of asthma but many other factors such as secondary messengers and signaling mediators are also involved. Although many of the players in asthma pathogenesis are identified, still much speculation and argument exists regarding the true cause of asthma (Umetsu, et al. 2002). Currently there are two debated methods for the cause of asthma: 1) Genetic Pre-disposition and 2) The Hygiene Hypothesis.

Many researchers believe that asthma is a genetic polymorphic disease that cannot be avoided for those who are already pre-disposed. Although many of the players in asthma result from dysfunctional, mutated species (such is the prevalence of the β2-adrenoceptor where 75% of asthmatics display one of nine possible mutations (Fenech, Hall, 2002)), not all asthma individuals show mutations and asthma has actually been noted to lapse in certain individuals over time (Heal Asthma). Therefore, genetic pre-disposition cannot account for the entirety of asthma cases or its rapid increase in prevalence worldwide.

To account for aspects of asthma that genetic pre-disposition cannot define, other researchers have identified a new theory termed the Hygiene Hypothesis. The hypothesis suggests that due to improved hygiene in developed countries as well as improved healthcare systems, sectors of society have become less susceptible to infections that may prevent the asthma phenotype (Umetsu, et al. 2003). This idea parallels already drawn conclusions from antibiotic resistance already seen within society. It is also supported by research demonstrating

that asthma is a T_h2 cell driven response. T_h2 cells cause "immunity memory" as well as being more involved in the adaptive immunity of the body. Worldwide prevalence statistics also support this idea, having the largest proportions of asthmatics residing in industrialized societies (Figure 1). The debate over the cause of asthma may last forever, but treatment for symptoms cannot.

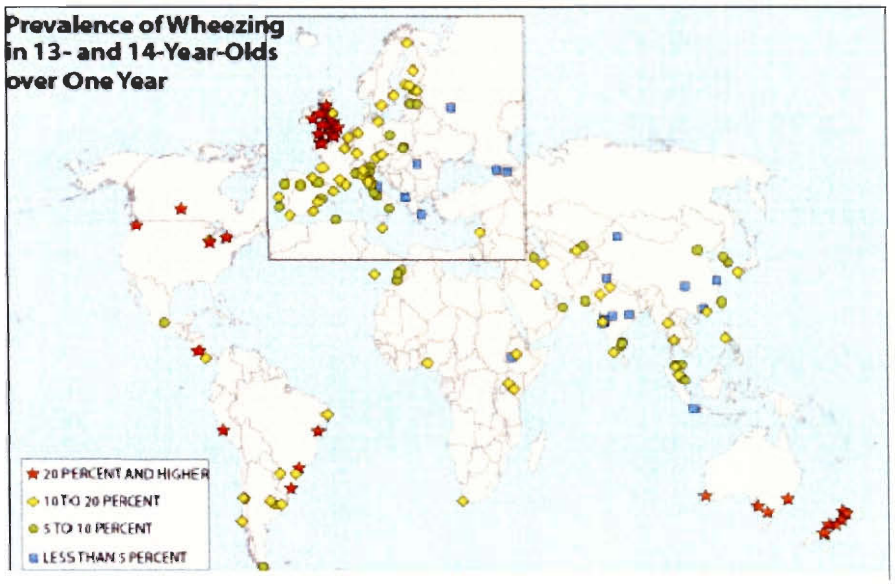

Figure 1: Worldwide Asthma Prevalence.
The more industrialized countries of the show greater proportions of asthmatic than less industrialized countries.

Figure Courtesy of Heal Asthma.com

To combat asthma, many different types of medications have been developed that target the different cellular causes of asthma symptoms. These medications range from β2-adrenoceptor agonists that provide long-term (12 hr) symptom control, to corticosteroids that reduce airway inflammation in asthma patients and reverse damage caused by this inflammation (O'Connell, 2003). But even with the advent of new, very efficacious medications such as the new IgE monoclonal antibody, Xolair® from Genetech, all of these medications have one thing in common; they are not cures of the disease. The cure for asthma may be far in the future, or

may never be seen because of its complications and many players implicated in the pathogenesis of the disease. Though not cures, the newer technologies and newer medications have provided asthma patients with a brighter, more symptom free life.

Even with the many medications available to asthma patients, the current epidemic shows no signs of slowing, nor do the deaths yearly from asthma decrease (NIH). Consequently, there must be another underlying cause that affects the life of asthma patients. It has been shown that many patients improperly use their medication devices or simply do not take their medications either from forgetfulness or unsurity of medication effects (Clark, Partridge, 2002). It has been estimated that less than 50% of patients properly use their medication and take medications in a timely manner (Leung, Nelson, 2001). This level of un-compliance is unacceptable for control and further aggravates the situation.

It is relatively easy to see how much of an impact asthma has on society when over 150 million individuals worldwide and an estimated 15 million Americans suffer from asthma (Cleland, et al. 2003). Estimates for asthma costs range between 2 and 5 percent of the American disease budget accounting for nearly 13 billion dollars of expenditure per year (Cisternas, et al. 2003). This type of rampant expense for one disease needs to be halted and re-explored for ways of decreasing the burden of asthma.

This IQP is designed to address both the current treatment strategies and the cost of asthma. To perform such a tremendous task, the current literature was reviewed and evaluated. The first goal of this IQP is to establish a firm understanding into the design and usage of the currently marketed asthma drugs. This understanding will help to develop ideas into why the asthma epidemic costs society to such a great extent. The second goal of this IQP is to develop and suggest methods to alleviate the burden of asthma on both the individual and society. By

utilizing the literature and making reasonable assumptions, maybe a new idea to relieve asthma pressures will develop.

ASTHMA TARGETS

Many different approaches have been employed by pharmaceutical companies and independent researchers in the discovery of both new targets for asthma research and the re-development of old, established targets for asthma research. The primary targets for asthma medications have traditionally focused on cellular actions and receptors (Wong, Pang, 2004: Fenech, Hall, 2002). Only until recently have newer non-related targets such as kinases and cytokines been highly explored for their therapeutic value in asthma.

Glucocorticoid Receptor (GR)

Steroidal medications for asthma have long been the stable for asthma control. These medications are known for their potent anti-inflammatory characteristics and can be very useful for treatment. The glucocorticoid receptor (GR) and its ligands, glucocorticoids, are located within the cytoplasm of many cell types, especially those cells implicated in asthma.

Glucocorticoids (GC) are responsible for regulating homeostasis within the body and to minimize the upregulation of pro-inflammatory mediators (O'Connell, 2003). These molecules are free to diffuse into cells and bind to their receptor GR where upon binding, they allow for receptor translocation into the nucleus and bind AP-1 and NF-κB. This effectively counteracts the effects of pro-inflammatory cytokines (Adcock, et al. 2002: Zhang, et al. 2000: O'Connell, 2003). The receptor complex, however, relies upon specific binding locations termed GREs (Glucocorticoid Receptor Elements) that are randomly located throughout the chromosome. After binding to their respective signal sequence they promote the further synthesis of GC's, continuing the repression of inflammatory molecule synthesis. Because of this GC amplification

and loss of elements implicated in inflammation, the GR/GC complex is a well-studied, well-defined, and highly sought after target for asthma medications.

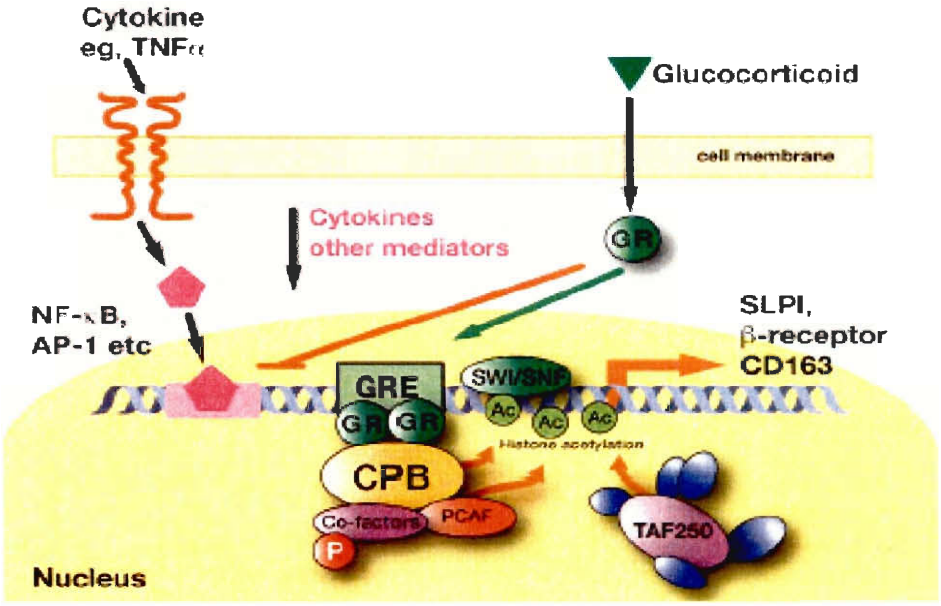

Figure 2: GC/GR Mechanism of Action.
Glucocorticoids free diffuse through the cell membrane, bind to their GR and are translocated to the nucleus. Upon translocation, they bind to regulatory elements (GRE) and downregulate pro-inflammatory cytokine translocation.

Figure Adapted From Adcock et al. 2002.

The question arises however, if many cells contain GR/GC complexes, and every person's immune cell subsets of eosinophils transcribe GCs, why do some people develop respiratory inflammation like asthma while others do not? Fenech and Hall (2002) have shown that this may be due to genetic polymorphisms within susceptible asthmatic patients. There are five currently known mutations within the GR (Koper, 2002). Although evidence for the link between these mutations and asthma phenotypes are weak, data suggest that a single amino acid substitution (Val641 → Asp641) may exhibit a decreased affinity for GC and ultimately a decreased response to their effects on inflammation. Two other mutations (Val729 → Ile729 and Asn363 → Ser363) have also shown decreased affinity for dexamethasone (a synthetic GC), but have not been further characterized or implicated in the asthma phenotype (Fenech, Hall, 2002).

Because of the pool of knowledge generated for GRs and GCs as well as their prevalence in eosinophil populations that are routinely considered players in asthma development (Zhang, et al, 2000), GRs and GCs will remain an asthma target for some time. The research required for the development of new, steroidal medications that utilize the GR in some manner remains as a top choice for future drug development due to ease of costs and production as well as its effectiveness in controlling inflammation within airways.

β2-adrenoceptors

Before the advent of even steroidal medications, early treatment of asthma relied on the SABA or Short Acting β2 Agonist inhaler. These drugs target a group of receptors collectively named β2-adrenoceptors that are found on the surface of airway smooth muscle cells such as vascular endothelium and alveolar walls (Fenech, Hall, 2002). β2-adrenoceptors are G-proteins and activate adenylate cyclase via a GTP coupled inner membrane surface reaction that ultimately increases cAMP (Cyclic Adenosine MonoPhosphate) resulting in smooth muscle relaxation via activation of PKA and inactivation of myosin-actin interactions (Adcock, et al. 2003). Relaxation of airway smooth muscle cells implies a less stressed area and therefore a decrease in localized inflammation, diminishing asthma symptoms.

Nine single base mutations have been identified and characterized in the β2-adrenoreceptor. Five of these mutations are degenerate and have no detectable functional changes in the receptor while three others demonstrate in vivo functional changes that may help to elucidate the function of this receptor in asthmatic patients. The receptor is 413 amino acids in length and is imbedded within the membrane by seven transmembrane domains, creating 3 extracelllular domains with an N-terminus and 3 intracellular domains with a C-terminus

(Fenech, Hall, 2002). Two of the mutations (Arg16 → Gly16 and Gln27 → Glu27) lie on the N-terminus extracellular region of the receptor while the third (Thr164 → Ile164) is actually located within an transmembrane helical segment (Fenech, Hall, 2002: Reihsaus, 2003).

The mutation of Arg16 results in a receptor that is much more easily downregulated and therefore not as active as the wild-type species. This downregulation also results in less expressed β2-adrenoreceptors on the cell surface. The Gln27 mutation greatly decreases desensitization the receptor to its agonist as well as increasing resistance to receptor downregulation and therefore may be a great target for asthma medications that create sensitivity and lose potency after use (this has been a common problem among medications targeted for β2-adrenoreceptors). The final transmembrane mutation results in decreased affinity for ligand and a reduced functionality to phosphorylate adenylate cyclase and cause signal transduction.

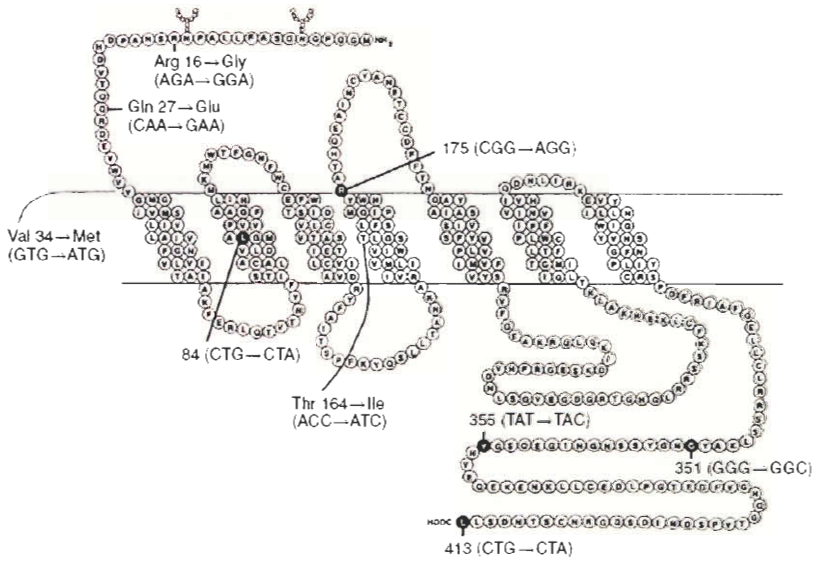

Figure 3: The β2-Adrenoceptor Mutations
Mutations are described in the text. Degenerate mutations are black
Figure Adapted from Fenech et al. 2002

Although the β2-adrenoreceptors have long been targets for asthma medications, it has only been recently that research has linked these receptors to GRs. Early studies have suggested that β2-adrenoreceptors may aid in regulation of GRs and create long half-lives for both chemicals in the body.

Tyrosine Kinases

Kinase inhibition of any kind in any disease is a newly, highly desirable trait for developing specific medications and reducing side effects. Tyrosine kinases are important proteins in all cells but may have more specific roles in immune cells such as T_h2 and T_h1 cells. A great deal research has been dedicated to the characterization of novel tyrosine kinase targets in these cells. Many of these kinases such as Src family kinases (Src, Lck, Fyn, etc…) are well studied. Only recently have newer, more specific kinases such as Tec family kinases (Tec, Itk, Btk, etc…) and JAK/Stat kinases been explored for their roles in asthma.

Because many of these kinases are novel, many of the on-going projects and developments for medications by pharmaceutical companies are proprietary and therefore restricted from public access. However, the understanding behind the research can be understood and applied to evaluate tyrosine kinases as reasonable asthma targets.

Kinase inhibition relies on the natural specificity of enzymes in the body for their substrates as well as their individually specific ATP binding pockets. This creates the opportunity to develop incredibly specific inhibitors of desired targets without having much undesirable inhibition of other proteins. These targets must be chosen wisely and with knowledge of its pathway to avoid complications. Currently, asthma is believed to be primarily a T_h2 cell predominate disease (Wong, Pang, 2004). Because of this, many kinase targets for asthma are believed to be only in T_h2 cells or at least located within T_h2 cells (Corry, 2002). Therefore the Tec family kinases and JAK/Stat family kinases are currently the most sought after targets.

ITK (Inducible T cell Kinase) is a Tec family kinase that is believed to be only in T_h2 cells (Mueller, August, 2003). Activation of the TCR (T-Cell Receptor) on T_h2 cells results in

activation of not only Tec family kinases, but also many others such as Src and Syk. Unfortunately many of these activated kinases phosphorylate and activate many other proteins and therefore are indispensable for cell growth and development (Wong, Pang, 2004). Preliminary research however, shows that ITK seems to not be involved in cell growth or differentiation and therefore may be a good target for kinase inhibited asthma relief. ITK is a very novel discovery in the Tec family and much debate has occurred since its discovery on both its structure and function (Mueller, August, 2003). Consequently, there are still mixed reviews on what consequences occur during the loss of ITK function in T_h2 cells.

Activation of ITK affects the regulation of many of the required cytokines and their production from T_h2 cells. Induction of Ca^{2+} is a major contribution to cytokine production and it has been shown (Fowell, 2002) that knock-out Itk mice are deficient in many T_h2 cytokines and cytokine production. IL-4, which is required by B-cells for IgE Ab switching is produced by activating the Tec family pathway containing ITK. Decreased IL-4 in vivo would result in a less susceptible allergy immune response and therefore may be useful in asthma treatment (Mueller, August, 2003). More importantly than the loss of IL-4 in asthma treatment would be the loss of IL-5, a T_h2 cytokine that is responsible for eosinophil recruitment to the lungs (Lee, 2000). Because eosinophils are attributed to not only the cause of asthma but also its future development and progression, reduction of eosinophils in lung tissue could potentially have a dramatic affect for the better in asthma treatment.

Due to Itk's prevalence in T_h2 mediated cytokine production, it represents an asthma target that could potentially be one of the best therapies to date. Itk's loss of function would result in less inflammation, less eosinophil infiltration into lungs, as well as a reduction in asthma allergy stimulus; all major concerns for asthma and all treated by different medications.

Jak/Stat (Janus Kinases) also represent a class of tyrosine kinases that may be good targets in future asthma research. In mammals, there are currently four characterized Jaks, Jak1/2/3 and Tyk2 (Imada, Leonard, 2000). Janus kinases are responsible for relaying messages from receptor bound proteins to the nucleus to control cytokine production. More specifically, these kinases activate downstream elements termed STATs, which bind to localized areas of the chromosome and regulate cytokine production (Imada, Leonard, 2000). The most studied of these relationships is the Jak3/Stat 6 relationship. Jaks have been implicated not only in asthma, but other diseases such as SCID (Severe Combined Immuno-Deficiency), which further describes their role in leukocyte cytokine signaling (Aringer, et al. 1999).

Janus kinases are tyrosine kinases that display unique phosphorylation sequences when compared to the other ten tyrosine kinase families (Aringer, et al. 1999). They remain constitutively bound to their receptors and are completely dependent upon this receptor to phosphorylate key residues near the N-terminus of the protein to become fully active. Although many studies have been tried to determine the importance of each subunit of the Jak protein,

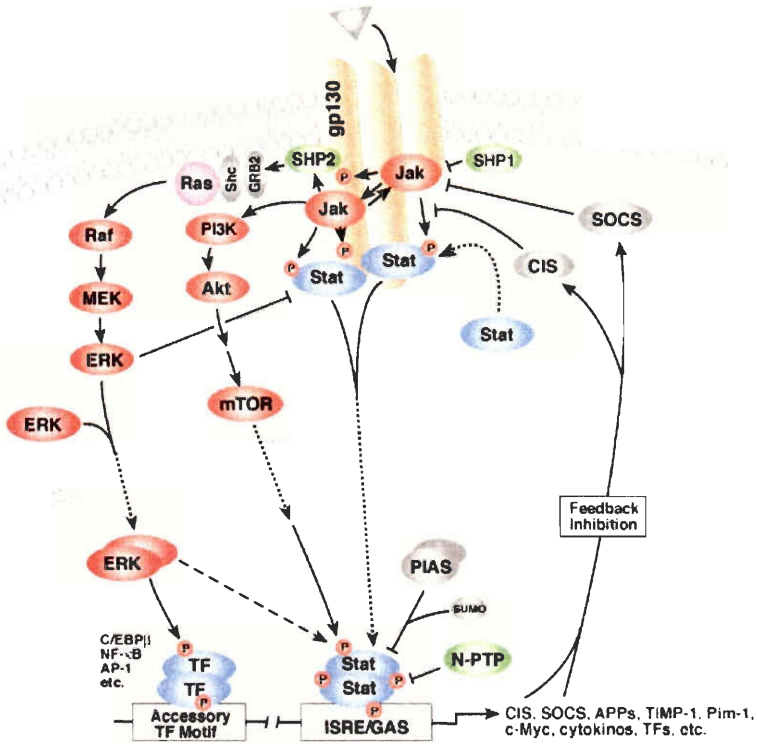

Figure 4: The JAK/Stat Signaling Pathway

Janus Kinases (Jaks) are constitutively bound to their receptors and required phosphorylation from these receptors for full activation. Jaks are responsible for downstream phosphorylation of Stats that regulate cellular functions.

Figure Courtesy of Cell Signaling Technology, 2004.

very little success has been noticed. One major discovery however, is the belief that the second domain of the protein (JH2 domain) is necessary for interferon signaling and may be a possible target for future drug development (Aringer, et al. 1999: Imada, Leonard, 2000).

Although the Jak/Stat pathway may seem like the ultimate target since it is involved in many aspects of cytokines trafficking and their signaling, this pathway is limited in its therapeutic value by its involvement in many of the leukocyte signaling pathways (Aringer, et al. 1999). JAK3 is required by leukocytes for growth and development, which involves many other signaling pathways other than the Jak/Stat pathway. Inhibition of Jaks may create undesirable effects on other kinase pathways and cause loss of interest in the pathway for future drug discovery due to uncontrollable side effects.

Leukotrienes

Although first described in 1937, leukotrienes have only recently been linked to asthma and remain the only non-related, not previously explored option for asthma therapy (Bryan, et al. 2000). Leukotrienes (LTs) are a family of eicosanoid lipid mediators that are extremely potent chemotaxis agents used by leukocytes (Haeggstrom, Wetterholm, 2002: Yopp, et al. 2003). Today, leukotrienes are subdivided into five categories, A_4, B_4, C_4, D_4 and E_4. Leukotrienes LTA_4, LTC_4, LTD_4, and LTE_4 all contain cysteine groups from bound glutathione (Haeggstrom, Wetterholm, 2002: Yopp, et al. 2003). LTB_4 is synthesized in a different manner than its cysteinyl counterparts and does not contribute to inflammation or bronchoconstriction seen in asthmatics (Yopp, et al. 2003).

Cysteinyl LTs however, play major roles in recruitment of leukocytes and are synthesized primarily by eosinophils, creating inflammation and further propagating the asthma phenotype

(Fenech, Hall, 2002: Haeggstrom, Wetterholm, 2002). Since all LTs (even LTB_4) are synthesized from a primary LTA_4 molecule by an enzyme termed 5-LO (discussed later), initial attempts were made to reduce the plasma levels of LTA_4 and reduce overall LT levels in the body. However, LTA_4 experiences a short half-life within the body and is quickly hydrolyzed to LTB_4 or conjugated to glutathione (LTC_4, LTD_4, LTE_4) (Haeggstrom, Wetterholm, 2002). With this said, recently marketed pharmaceuticals such as zileuton (Abbott Pharmaceuticals), zafirlukast (AstraZeneca), montelukast (Merck) that target leukotriene synthesis or receptor binding, target other cysteinyl LTs and 5-LO rather than LTA_4 (Vianna, Martin, 1998).

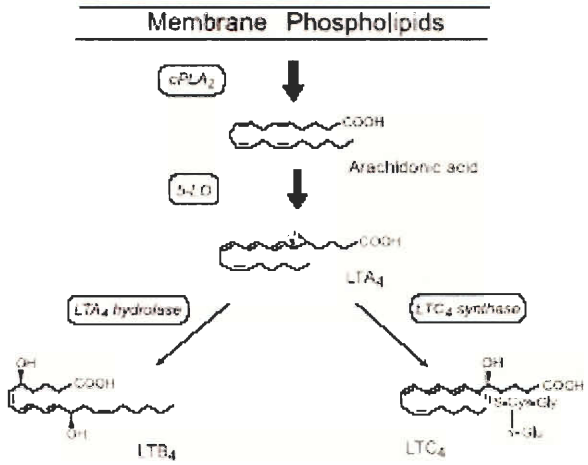

Figure 5: LT Synthesis Pathway
Synthesis of any LT begins with the conversion of Arachindonic Acid. After the formation of LTA_4, both LTB4 and the all of the cysteinyl LTs are synthesized via different means. LT receptors are in parentheses.

Figure Courtesy of Haeggstrom, et al. 2003.

Leukotriene synthesis involves 4 primary enzymes, each converting their substrate to a different LT. 5-LO is an enzyme responsible for the initial conversion of Arachidonic Acid (AA) to LTA_4. Because of its importance in the initial steps of LT synthesis, it represents a great target for asthma prevention. Not only would LTA_4 not be synthesized, but also all other cysteinyl LTs involved in asthma inflammation and eosinophil recruitment would be inhibited as well. Unfortunately, 5-LO is expressed in many cell types and is constitutively express as a housekeeping gene in many cells including eosinophils (Haeggstrom, Wetterholm, 2002). This has been hypothesized that the loss of LTA_4 conversion could also cause significant other

undesirable effects on local cellular structure and still cause inflammation of surrounding tissues in other manners (Vianna, Martin, 1998). Consequently, this does not solve the problem of excess LTs. Fenech (2002) suggests that chromosomal polymorphism may be a contributing factor to LT imbalances since 35% asthmatic patients show a variant 5-LO allele within their genome.

Inhibition of 5-LO and possibly other enzymes involved in the synthesis of LTs is not the only method currently being explored by pharmaceutical companies for asthma therapy, nor is it the more popular of the methods. LT receptor antagonists have marketed by pharmaceutical companies for many years as anti-asthma drugs (Fenech, Hall, 2002). These targets are the membrane receptors for all of the cysteinyl LTs (except LTA_4) and result in competition for receptor binding. Since these targets remain relatively new to the science community and are currently being explored as asthma targeting options, this field of therapy represents a novel asthma therapy not involving a typical asthma inhaler device.

Cytokines and Chemokines

Many cytokines and chemokines such as IL-4, IL-5, IL-10, IL-13 and CCR3 and CCR4 have been implicated in asthma pathogenesis (Bryan, et al. 2000). Cytokines are important signaling molecules created by cells to sense outside environmental stimuli as well as to create stimuli for other cells. For instance, IL-4 is responsible for inducing B-cell IgE production but is primarily produced by activated T-cells (Bryan, et al. 2000). Inhibition of cytokine and chemokine signaling is one of the newest ideas in research for suitable asthma drug targets and has taken off remarkably over the past decade.

To better understand cytokine and chemokine inhibition, comprehension of how these molecules work is needed. Cytokines are small peptide sequences produced by cells that bind to their receptors (although binding cross-talk is believed to be extensive (Wong, Pang, 2004)), and create a stimulus for another cell to perform a particular action. It is much too involved to make peptide sequences similar to interleukin molecules so therefore research has been focused at the receptor level rather than the signaling molecules themselves (Bryan, et al. 2000). Chemokines are a type of cytokine but are larger in size and are used for cell chemotaxis and homing to particular areas (Corry, 2002). They are named by the number and spacing of conserved cysteine residues at their amino terminus (Wong, Pang, 2004).

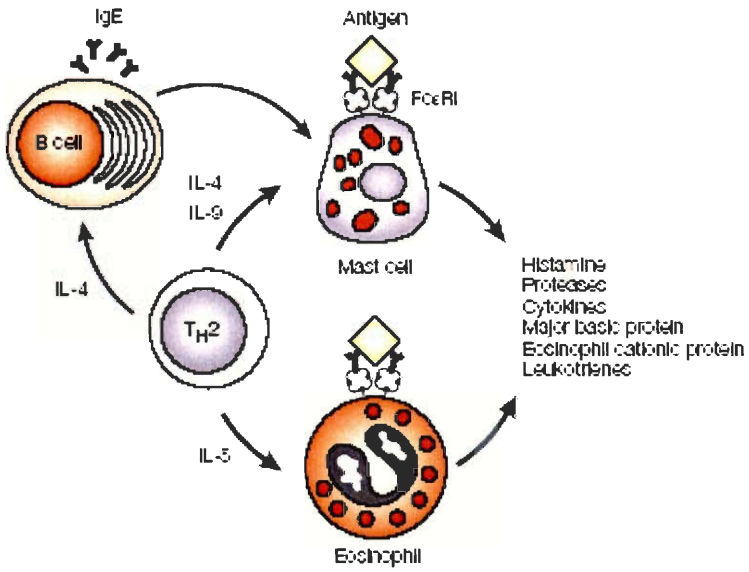

Figure 6: T_h2 Cytokine Effects and Production
Schematic representation of T_h2 cytokine release. IL-4 and IL-5 both play significant roles in asthma pathogenesis. See text for more information.

Figure Adapted from Corry, 2002.

The two major cytokines involved in asthma pathogenesis are IL-4 and IL-5, both of which are transiently controlled by IL-13 (Wong, Pang, 2004). IL-4 binds to its receptor, IL-4R, and further activates tyrosine signaling cascades, specifically the Jak3/Stat6 cascade. Both B-cell IgE production and T_h2 cell development are dependent upon the proper binding and subsequent signaling of IL-4 (Corry, 2002). Production of IgE results in a hypersensitivity to airborne allergens and aids in creating an atmosphere for allergic asthma development. Preventing IL-4 from binding to IL-4R would alleviate hypersensitivity and return the body to homeostasis in respect to IgE synthesis.

IL-5, although acting in the same manner as IL-4 by binding its membrane bound receptor and further activating numerous tyrosine kinase pathways (such as the Lyn and Syk pathways as well as stimulating Jak2 and Stat5), is not involved in hypersensitivity. Rather, IL-5 is important in eosinophil differentiation and may hold the key to preventing eosinophilia (excess eosinophil populations in the lungs), which is a key contributor in airway inflammation and asthma pathogenesis (Wong, Pang, 2004: Zhang, et al. 2000: Bryan, et al. 2000: Vianna, Martin, 1998). IL-5 binding to its eosinophil membrane bound receptor activates the cell and promotes the release of many basic proteins and histamines that damage and alter osmolarity of certain areas of the respiratory tract, while over-activating and stimulating others in a cascade style release of other, potentially more damaging proteins (Wong, Pang, 2004). The altered expression of different areas of the respiratory tract, with increasing numbers of activated eosinophils creates inflammation in localized tissues and ultimately difficulty in breathing and irreversible damage, two major diagnosis factors in clinical asthma (Creticos, 2003).

Other cytokines such as IL-10 and IL-18 are involved in the balance between Th1 and Th2 cells within the body. Disruptions in these cytokines can lead to an over-expression of one type of cell over another and create diseases such as asthma that are dependent upon this cell balance.

Because many chemokines and chemokine receptors are cell specific, they represent a new asthma target that could potentially be used in the treatment of asthma. Chemokines are required by both Th1 and Th2 cells but each has their own specific set of receptors allowing for cell specific chemotaxis (Wong, Pang, 2004). Chemokine receptors are members of the seven transmembrane GPCR family. Their activation mimics cytokine receptor activation and signaling by triggering the activation of downstream kinase cascades leading to cellular

activation and recruitment (Wong, Pang, 2004). One such receptor CCR3 is found on both T_h2 cells and eosinophils and represents the best target for drug discovery since both cells are implicated in asthma pathogenesis.

CURRENT ASTHMA DEVICE DESIGN AND FUNCTION

With the overabundant information available for asthma targets and newer, more specific targets routinely being discovered, it becomes necessary to identify current medications used by the asthma community against these defined targets. This chapter will review the past, currently used, and future developments of prescription pharmaceuticals used in asthma treatment as well as giving the reader an insight into device design and drug formulation.

Nearly 15 million people in the United States alone suffer from asthma related symptoms (Dhand, 2000) and more than 60% of these patients use the typical, everyday asthma inhaler. The asthma inhaler has undergone extensive evolution over the last few decades. It has evolved rapidly from an inconvenient, over-sized, non-transportable nebulizer device, to a more convenient, small, transportable pressurized metered-dose inhaler (pMDI). Recently, newer dry powder formulations, using a Dry Powder Inhaler (DPI) device have been examined as alternatives to the pressurized pMDI canisters in response to chlorofluorocarbon (CFC) restrictions and global warming concerns (Dhand, 2000: Dalby, Suman, 2003).

The cornerstone of any disease management program, including asthma, relies on the ability to deliver a drug to a specific location. In the case of asthma, this is difficult as inhalation of a drug is the best means of delivery. Inhalation therapy has major drawbacks and concerns about not only drug delivery, but cost effectiveness, ease of operation, oropharyngeal deposition, and side effects (Dalby, Suman, 2003) as well.

Figure 7. A Typical pMDI

Pressurized Metered Dose Inhalers (pMDIs)

pMDIs are the earliest and most extensively used inhaler devices for the treatment of asthma (Buck, 2001). The medication of choice for these devices must be in powder form and mixed with a propellant to ensure accurate measured doses with each use (Dhand, 2000). Its design is simple, yet requires extensive knowledge of propellant and drug properties to ensure proper lung deposition.

The medication and propellant are placed under pressure in a small canister. When used, a precise, pre-determined volume of medication/propellant is forced from the canister through the device, and administered to the patient. At such high forced pressures and high expiratory flow rates from the device, as much as 90% of the drug may deposit in the oropharynx resulting in a mere 10% deposition of drug into the lungs (Dhand, 2000). This rate of drug delivery is unacceptable for true control of asthma symptoms and add-on technologies and experimentation with different propellants have increased lung deposition (Dalby, Suman, 2003).

Differences in propellants have caused havoc for the pharmaceutical industry since the 1987 Montreal Protocol banning the usage of CFCs (Newman, Busse, 2002). Before the Montreal Protocol, the most widely used propellant for asthma inhalers were CFCs. Recently, these have been replaced with new, more environmentally friendly propellants, hydrofluoroalkane (HFA)-134a and 227. These propellants are not only safe for patient use, but

do not harm the ozone layer and may provide better drug deposition to the lungs for numerous reasons (Dalby, Suman, 2003).

Drug deposition to the lungs relies on many factors including drug particle size, the solution the drug is dissolved in, as well as the forced expiratory rate (pressure) of the drug when it is expelled from the canister. It has been shown (Leach, 2003, Dhand, 2000) that pMDIs using HFA as a propellant and containing drugs solubilized in ethanol, can produce extremely fine particles, further increasing drug deposition. Finer particle size may also aid in deposition of the drug to lung capillaries and other tight junctions that large CFC propelled propellants cannot obtain (Dhand, 2000). This could create more effective treatment options and reduce the number of times a drug must be taken during a single day.

Equally as important as particle size, is the expiratory flow rate of the drug from the canister. Extremely high velocities (such as those from CFC canisters and many generic drugs) promote deposition of the drug in locations other than that of the lungs. HFA propellants do not require as high of pressures in the canister and therefore do not have the same high expiratory flow rates as many other propellants (Barry, 2002). Before the advent of HFA propellants, devices known as spacers were used. These devices are still used (even with HFA propellants at times) to reduce the velocity of the drug before reaching the oropharynx.

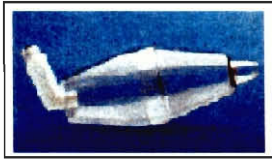

Figure 8. A Typical Spacer Device

Spacers

Spacers can range from numerous designs such as tubular extensions and bags, to more sophisticated valve controlled devices. They attach to almost every type and design inhaler and usually hold and slow the drug/propellant before passing the patients lips. However, spacers are usually bulky and cumbersome causing improper use or in some cases, no use at all (Buck,

2001). Spacers also alter the deliver of any pMDI drug when used properly. The extra "space" that spacers provide before the drug is administered to a patient can contribute to better drug deliver in many ways. By slowing the velocity of the drug, less inappropriate deposition occurs. Also, many spacers contain valves or other types of controls (Dhand, 2000) that allow for drug inhalation over an extended period of time. It has been shown (Dhand, 2000: Dalby, Suman, 2003: Buck, 2001) that >50% pulmonary drug deposition can be obtained with proper spacer use.

Proper spacer choice for particular inhaler designs and medication designs should be taken into consideration before any patient should use spacer devices. Charge buildup on the interior walls of the spacer may contribute in markedly decreased levels of drug effectively inhaled since the drug may bind to the sides of the spacer and remain un-inhaled (Barry, 2002). This can be overcome by not washing the spacer after use but may result in other, more detrimental effects such as bacterial buildup within the spacer.

Inherent properties of the drug and solution can also play a major role in the efficacy of the drug for asthma treatment. Barry and Bryon have demonstrated with the help of many pharmaceutical companies, that the drug suspension within the canister will undergo separation over time. Drug and suspension separation results in inaccurate doses of the inhaled drug. For this reason, many physicians urge their patients to vigorously shake their pMDIs before use to prevent inaccurate inhalations. Separation also results in leakage of the propellant from the canister (Barry, 2002) again yielding inaccurate doses of the medication.

Although pMDIs have many technical issues to face in both design and patient use, they remain the staple for asthma inhalation therapy. This is primarily due to their low cost in both manufacturing and purchasing (Buck, 2001). Most inhaled asthma medications are preparations for the pMDI type devices.

Dry Powder Inhalers (DPIs)

Figure 9. Two Typical DPI Designs: The Diskus and Turbuhaler

In the early 1970's, new thoughts into inhaler design were tried by GlaxoSmithKline (GSK) in an attempt to reduce the large proportion of drug being deposited in the oropharynx (Newman, Busse, 2002). The early design that GSK developed (Rotahaler) was breath actuated, meaning that the drug was dispelled from the device by the force of breath of the patient, not of a pressurized propellant. Ideally, this method of inhalation is far superior to that of the pMDI because no propellant is needed (reducing environmental concerns) and patient inhalation does not have to be coordinated to propellant expulsion (Buck, 2001: Dhand, 2000). Since GSK's Rotahaler design, the design of DPI devices has evolved greatly.

DPI medications can be formulated in two ways: 1) pure drug or 2) drug mixed with an inactive incipient (such as glucose or lactose) (Newman, Busse, 2002). By mixing the drug with substances such as lactose, the typical inhaler medication taste can be reduced promoting use of the drug. But this is not the only reason, nor the most important reason, for mixing the drug with other substances. Typically, DPI preparations have particle sizes <5 uM (Newman, Busse, 2002) and with such small particle sizes, static charges in the air and on the device can interfere with drug delivery. By attaching the smaller drug particles to larger lactose/glucose molecules, the drug is better delivered and suffers from less static interference (Newman, Busse, 2002: Dhand, 2000). Pure drug formulations overcome this problem by creating aggregates of the drug, creating larger particles, and reduced static interference (Newman, Busse, 2002: Dhand, 2000: Barry, 2002). Promising new technologies in drug particle design to potentially reduce the

density of drug particles have been explored. These less dense particles would be better able to penetrate deep into the lungs and treat asthma more effectively (Newman, Busse, 2002).

Akin to pMDIs, DPI devices are metered but in a slightly different fashion. The early devices created were single-dose and required refilling with a new blister pak containing medication after each use (Newman, Busse, 2002). Recently, most new DPI technology has been focused on multi-dosing devices that can be discarded after all of the contained doses are used. Unlike pMDIs however, DPI devices are all designed differently and all work in different ways. Primarily, multi-dose devices work by twisting or opening the device. This opens the single-dosage blister pak within the reservoir and sets up the device for use. Only after the patient has inhaled deeply using the device, is the device closed causing resealing of the reservoir and making another blister pak available for the next use (Newman, Busse, 2002: Barry, 2002: Buck, 2001: Dhand, 2000). Single-dose devices are similar to multi-dose devices but do not contain a blister pak reservoir. Therefore, removal of the used blister paks and replacement with new, unused medication is required.

DPI devices do have limitations and, as with any other devices, suffer from design flaws that require remodeling. Resistance of the device is the primary concern of DPI devices. Resistance is how forcefully a patient must inhale to completely inhale the powder medication from the blister pak (Dhand, 2000). Patients that suffer from severe asthma or simply do not have the lung capacity to inhale extremely deeply (such as young children and the elderly) may not obtain the full dose of the medication and therefore would not be effectively treating their condition. Furthermore, although the device is breath actuated, accidental breathing into the device can destroy the reservoir and require a new device or blister pak for proper usage (Barry, 2002: Newman, Busse, 2002).

Because the medication within the device is a dry powder, DPIs are more susceptible to environmental factors than pMDIs. Humidity and ambient temperature can greatly affect the particle size of the device by creating aggregates of medication rather than fine particle size. DPIs also required the device to be completely level before use (Dhand, 2000: Bryan, et al. 2000). This increases the chance that all of the medication will be properly inhaled as well as assuring that the reservoir remain undisturbed.

Generally speaking, DPIs work as efficiently or better than most pMDI devices when used correctly (Barry, 2002: Dhand, 2000). DPIs have consistently been tested against their pMDI counterparts and even with different device designs, have shown no statistical differences under controlled studies (Barry, 2002). However, it is worth noting that because of their ease of use, many pMDI devices have undergone formulation switching and been adapted to the DPI design (Leung, Nelson, 2001: Barry, 2002).

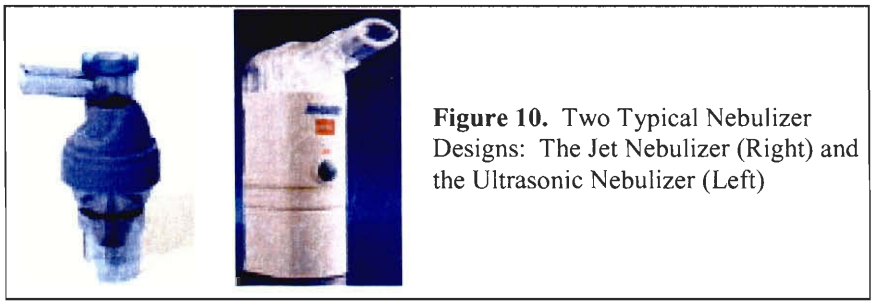

Figure 10. Two Typical Nebulizer Designs: The Jet Nebulizer (Right) and the Ultrasonic Nebulizer (Left)

Nebulizers

Nebulizer devices have long been a common technique of drug administration to patients suffering from any respiratory distress. Over the last few decades, with the invention of pMDIs and other more technologically advanced systems of inhalation drug delivery, nebulizers have been pushed to a last resort for severe asthma conditions. Nebulizers work by aerosolizing a drug solution and allowing the patient to breathe the aerosol for an extended amount of time (usually 1 hr or more) (Dhand, 2000). These devices work in many different ways but their overall design remains relatively constant.

There are basically two distinct classes of nebulizers: 1) jet nebulizers and 2) ultrasonic nebulizers. Jet nebulizers work by compressing a gas and passing it through a small hole termed a Venturi. This creates a vacuum from the expansion of the gas, which draws the drug solution through a capillary tube. As the solution passes through the tube, the stream is fragmented into small particles that can then be inhaled by the patient (Dhand, 2000: O'Callaghan, Barry, 1997). Larger droplets that cannot be completely aerosolized impact baffles and the nebulizer walls, and fall back to the initial solution to repeat the nebulization process. Ultrasonic nebulizers work in a different way than jet nebulizers. Ultrasonic vibrations of a piezoelectric crystal vibrate the drug solution into droplets that aerosolize from the surface of reservoir. Again, not all particles are small enough to be properly inhaled or pass through the nebulizer device and are collected and returned to the drug reservoir (O'Callaghan, Barry, 1997: Le Brun, et al. 2000). Evolution of the nebulizer device has been extensive over the decades but still suffers from many setbacks.

The science of nebulization is the oldest technique for the treatment of asthma and is therefore inherently limited by its technology. Aerosol particle size can be nearly ten times that seen within a typical pMDI. This raises the issue of pulmonary drug deposition. Because it is impossible to create uniformly sized particles during nebulization, upwards of two-thirds of the medication may not be delivered due to improper particle size (O'Callaghan, Barry, 1997). The larger droplets will be deposited within the oropharynx while the smaller droplets may simply be exhaled and never enter the bronchial tubes (LeBrun, et al. 2000).

The intrinsic design of nebulizers causes many problems that cannot be overcome by technological advances in nebulization science. The drug solution has the most influential role in nebulization. Its characteristics will determine not only the effective droplet size during nebulization, but also how effectively the drug will be administered to the patient. A maximum

of 50% of drug can be aerosolized in a nebulizer with 2 mL of initial drug solution (O'Callaghan, Barry, 1997). This computes to less than 50% of the drug being utilized by the patient while inhaling since non-uniformity exists for droplet size. Although increases in volume result in a larger percentage of the drug being released as an aerosol, increases in volume also substantially increase the time of drug administration. Unfortunately, increases in initial drug concentration are not viable options either since nebulization naturally causes increases in drug concentration due to evaporation of the drug solvent (Dalby, Suman, 2003: O'Callaghan, Barry, 1997). Extremely high concentrations of drug released as aerosol cannot only cause respiratory irritation, but also may cause incorrect dosages that can lead to significant breathing problems (O'Callaghan, Barry, 1997).

There are three other significant factors that are involved determining the effectiveness of nebulization of a solution: 1) Viscosity and Surface Tension, 2) Temperature, and 3) Solution charges. Solutions that have low surface tension will not stick to baffles and the walls of the reservoir and can be readily be returned to an aerosol quickly. This can potentially increase the percentage of drug that becomes an aerosol and will enhance the level of drug that the patient inhales. Solution viscosity creates huge problems in nebulization, creating longer nebulization times and decreased output (O'Callaghan, Barry, 1997). The temperature of the solution can also affect both the surface tension and viscosity of the solution and is therefore an important characteristic to note in nebulization. Because the drug solvent is slowly evaporated, the temperature of the solution may fall upwards of ten degrees, increasing viscosity and surface tension (O'Callaghan, Barry, 1997). To solve this problem, many newly designed nebulizers have heating systems that warm the solution as it evaporates (LeBrun, et al. 2000: O'Callaghan, Barry, 1997).

Because of the rapid evolution of inhaler technology and the desire to create new medication that do not require extensive treatment times for asthma, the nebulizer and its drug solutions have all but been abandoned. In an asthmatic episode, it is crucial for technicians to return normal breathing patterns to the patient quickly. This can readily be accomplished with quick inhalers, but long nebulization times are far too inefficient to be of any benefit. Due to the lack of interest and inherent detrimental properties of nebulization compared to pMDI and DPI devices, most new medications marketed today are never released as nebulizer solutions (Le Brun, et al. 2000: O'Callaghan, Barry, 1997). These devices are useful however for administration of medications to the elderly and children, who cannot coordinate their breathing and may benefit from the extended inhalation time given by nebulization.

CURRENTLY MARKETED ASTHMA DRUGS

Now that a thorough understanding of how drug targets are decided upon and how to effectively administer novel drugs to patients is recognized, this review will shift to a brief overview of the currently marketed asthma drugs that have been shown to be effective relievers of asthma symptoms.

Short-Acting and Long-Acting β2-Agonists (Albuterol, Salmeterol, Formoterol)

Short-acting β2-agonists (SABAs) have long been regarded as the first step of asthma prevention. Discovered in the 1960's as potent relievers of asthma symptoms (and known about long before), SABAs have remained a consistent step in asthma control (Busse, 1996). Albuterol consists of two racemic species (chemical species that have the same chemical formula but different chiral centers and therefore reflect light differently and act in different ways). Only the R-enantiomer has been shown to be predominantly involved in bronchodilation (Mitra, 1998).

SABA inhalation is very fast acting but also very short in duration. Bronchodilation can begin within five minutes after inhalation and can continue for about six hours afterwards (Busse, 1996). Due to its fast acting nature, medications such as albuterol are used in emergency asthma episodes. Albuterol exists in both nebulizer forms as well as inhaler forms and is the cornerstone of asthma treatment.

Few side effects have been noted with albuterol during its reign atop the asthma treatment ladder. The primary concern has been tolerance to the drug. It has been shown (Busse, 1996) that patients who continually take SABAs such as albuterol, although developing tolerance to the drug, seem to not undergo diminishing FEVs (Forced Expiratory Volume). Therefore, although patients may not see increases in asthma control with increased dose or dose frequency, asthma

control usually does not fall with continual usage. Lately, with the elucidation of new adrenergic receptors, new concerns about SABA overdosing have surfaced. Albuterol as well as many other SABAs can cross react with β1-receptors (another adrenergic receptor located within heart muscle). Because asthma mortality has increased over the years, speculation has surfaced that SABAs may possibly be reacting with β1-adrenergic receptors as a side effect of over-dosing (Busse, 1996). This has yet to be proven for any type (both short and long acting) of β2 agonist medications currently marketed today. Albuterol is marketed under many different names and brands including Proventil®

Figure 11: The Proventil® pMDI

Long acting β2-agonists (LABAs) have become a prime example of the evolution of asthma medications. The first of these new medications was salmeterol. Developed to control nocturnal asthma symptoms as well as to provide a more convenient means of daily control for patients, salmeterol provides continual control of asthma symptoms in excess of 12 hours (Johnson, et al. 1993: Leung, Nelson, 2001). Salmeterol is also one of the first asthma drugs specifically designed for its purpose.

Salmeterol

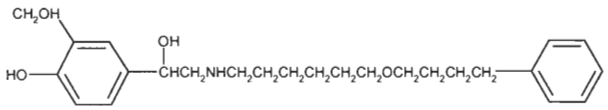

Figure 12. The Structure of Salmeterol

Salmeterol contains both hydrophilic and hydrophobic regions in its structure that give it the dual ability to bind to the adrenergic receptor. Although its true binding mode has yet to be

elucidated it is believed that salmeterol hydrophilic head binds to the Asp113 residue while the long hydrophobic side chain is buried deep within the hydrophobic transmembrane domains of the receptor (Johnson, et al. 1993). The binding of the long chain may facilitate prolonged binding of the molecule to the receptor permitting long lasting therapy. Salmeterol's structure also permits its high selectivity with a binding affinity to the β2-adrenergic receptor of 53 nM (Johnson, et al. 1993), almost 50 times more selective than albuterol.

Salmeterol as well as other LABAs and SABAs have routinely undergone stringent testing for side effects and asthma related deaths. In a 1996 salmeterol study, 17% of African Americans taking the drug in the study displayed abnormally high secondary side effects that required either ventilation or resulted in death (Wooltorton, 2003). Salmeterol was also linked (although no study has proven) to increased heart rates and possible increases in risk of heart attack. The latter of these questions is very puzzling as salmeterol has in-vitro been studied to show no discernable affinity for β1 adrenergic receptors and has the highest selectivity of all of the β2-agonists on the market. The drug has not been pulled from the market albeit health risk concerns and continues to undergo routine FDA studies (Lueng, Nelson, 2001). Salmeterol is now marketed by GSK as Serevent® and as part of the combinational therapy Advair®.

Figure 13. The Serevent® DPI

Figure 14. The Advair® DPI

Formoterol

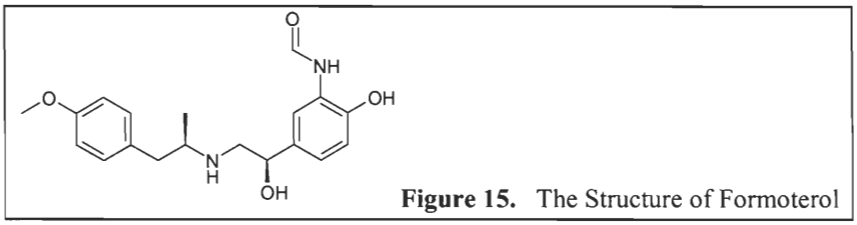

Figure 15. The Structure of Formoterol

Although formoterol is considered a LABA, its method of action, and time for bronchodilation is more like SABAs. Analogous to the SABA, albuterol, formoterol has a rapid effect on bronchodilation, working within 2-5 min after inhalation (Anderson, 1993). This gives formoterol a distinct advantage over salmeterol in that it can be used for rapid bronchodilation in asthma emergencies. With a 12-hour duration of efficacy, formoterol displays a definite advantage over albuterol and is equally as efficacious as salmeterol. Because of its relative unusual characteristics, formoterol has become the choice for many physicians for distinct types of asthma such as Exercise Induced Asthma (Ferrari, 2002).

Formoterol is a N-substituted phenylethanolamine (many of the other SABAs and LABAs are non-substituted phenylethanolamines). As with other β2-agonists, it also exists as a racemic form and like salmeterol, its R-enatiomer has been shown to be the major constituent of action (Anderson, 1993). Formoterol has also been tested for tolerance among individuals taking the maximum recommended dosage per day and has yet to display significant results showing patient tolerance (Anderson, 1993).

More importantly, life-threatening side effects like those seen in the 1996 salmeterol clinical study (Wooltorton, 2003), have not been noticed or not been documented within the current literature. Although the β2-receptor binding affinity for formoterol is slightly less than that of salmeterol (8.1 nM to 1.7 nM respectively), its affinity for the receptor is still high and displays no selectivity towards β1-adrenergic receptors (Johnson, 1993: Anderson, 1993).

Formoterol is marketed by AstraZeneca as Oxis® or as part of the combinational therapy Symbicort®.

Figure 16. The Oxis® DPI

Figure 17. The Symbicort® DPI

Corticoid Steroid Medications (Fluticasone Propionate, Budesonide)

Currently the best medications on the market to combat inflammation associated with asthma are the corticoid steroids (Creticos, 2003: Jenkins, et al. 2000). Inhaled Corticoid Steriods (ICS) have been shown to reverse permanent airway remodeling, fix airflow obstruction, and prevent other asthma symptoms resulting from continual airway inflammation (Leung, Nelson, 2001). Many of these benefits however are time constrained in that the earlier a patient receives ICS medications in their therapy routine, the more they are likely to benefit from it (Leung, Nelson, 2001: Selroos, 2001). There are two generations of ICS drugs. The first generation drugs (such as beclomethasone and triamcinolone) are more naturally occurring steroids and do not contain lipophilic substitutions (O'Connell, 2003: Staresinic, Sorkness, 2000). The level of lipophilicity and the characteristics of the substitution determine the clinical efficacy of the drug as well as its specificity (O'Connell, 2003). The second-generation drugs, which are used much more today in the treatment of asthma, are very lipophilic and are usually substituted with groups like acetyl side chains or halogens. Both budesonide and fluticasone propionate are second-generation drugs.

Fluticasone Propionate (FP)

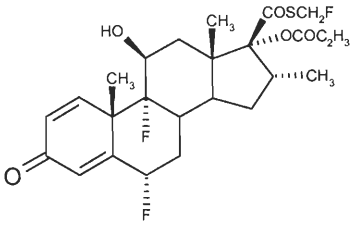

Figure 18. The Structure of FP

Fluticasone propionate (FP) was discovered in 1981 by GSK and was first used as a topical cream before being investigated in the treatment of asthma. In the mid-1990's, the drug was introduced to the asthma community as a pMDI (Hovione). FP has long been regarded as one of the best ICS medications available. It is available in a large variety of strengths and has undergone numerous studies into its effect of asthma.

FP is designed for patients with mild to severe asthma and works by interfering with the glucocorticoid receptor molecules within target cells (Jenkins, et al. 2000). It has also been shown to provide greater control with a smaller microgram dose than many of the other ICS medications including budesonide. Only recently however have ICS medications been incorporated into combinatorial medications that include the actions of LABAs. It is well known that corticoid steroids induce B2 adrenorecepter transcription (Jenkins, et al. 2000: Adcock, et al. 2002) and therefore, by administering both ICS and LABAs together in a single medication (such as Advair® or Symbicort®) greater efficacy has been noted in the treatment of daily asthma symptoms (Leung, Nelson, 2001: Jenkins, et al. 2000: Creticos, 2003). FP is marketed by GSK as Flovent® or as part of the combinatorial therapy Advair®.

Figure 19. The Flovent® pMDI

Figure 20. The Advair® DPI

Budesonide

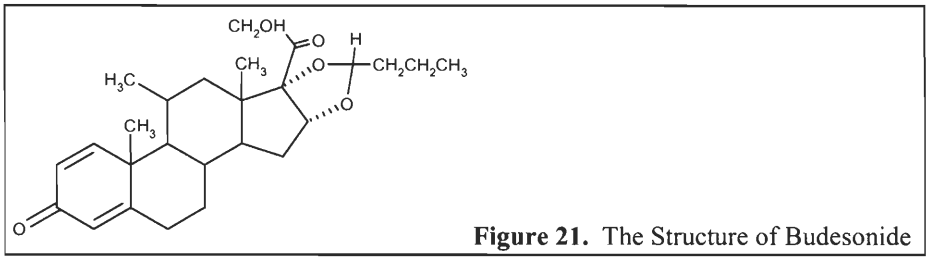

Figure 21. The Structure of Budesonide

Budesonide (BUD), another very potent ICS medication, has routinely been used in asthma treatment since the early-1990's as well (Buhl, 2003: Zetterstrom, et al. 2002). BUD undergoes an esterification process within the cell that enables it to remain efficacious longer than FP (O'Connell, 2003). The process starts when unbound BUD forms ester bonds with long-chain fatty acids within the cell. As these chains are hydrolyzed into smaller fragments, small proportions of BUD are released as well. By forming bonding partners with long-chain fatty acids, the local concentration of BUD is maintained permitting extended release of the steroid throughout the cell (O'Connell, 2003).

BUD has been shown to decrease eosinophil levels within the brochials as well as enhancing synthesis of anti-inflammatory mediators and inflammatory cell apoptosis (O'Connell, 2003). Another unique quality of BUD is its ability to be used at variable microgram concentrations over time enabling greater control of asthma symptoms (Buhl, 2003). All of the other ICS, including FP, required a continued steady dose at a single concentration to maintain asthma control, whether or not conditions wean or worsen. However, although BUD may appear to be the best choice ICS for most asthma conditions, it requires double the microgram concentration of FP to reach the same level of control. BUD is marketed under many names by AstraZeneca such as Rhinocort® and Pulmicort® or as part of the combinatorial therapy Symbicort®

Figure 22. The Pulimicort® DPI

Figure 23. The Symbicort® DPI

Although ICS medications have been substantiated as great sources of asthma control, they can potentially incur detrimental effects on patients such as disrupting normal child growth, altering bone density, and even aid in cataract formation and glaucoma (Staresinic, Sorkness, 2000). However, many studies have been performed on both first and second generation ICS (Staresinic, Sorkness, 2000: O'Connell, 2003: Buhl, 2003) resulting in no substantial changes in bone density, no significant increases in eye problems, nor have any published studies demonstrated negative effects on child growth and development. Many patients and physicians also worry about the potential that ICS medications may hide asthma related inflammation (Leung, Nelson, 2001). There are no published studies that show that ICS medications are involved in hidden inflammation and these worries seem unnecessary. It has routinely been proven that incorporation of ICS into an asthma therapy regimen greatly increases patient wellbeing (Jenkins, et al. 2000: Leung, Nelson, 2001).

Leukotriene Receptor Antagonists/Inhibitors (Zafirlukast, Montelukast, Zileuton)

Leukotriene Receptor Antagonists (LTRAs) are the newest agents routinely prescribed to asthma patients. These drugs, discovered in the late 1990's, act by blocking cysteinyl leukotrienes from binding to their required receptors, ultimately reducing inflammation and eosinophil recruitment (Vianna, Martin, 1998: Yopp, et al. 2003). Although LTRAs have been

licensed as first step medications they remain untested compared to many of the current asthma treatments such as ICS therapy due to their recent introduction into asthma therapy (Vignola, 2003: Vianna, Martin, 1998: Creticos, 2003). LTRAs have become a mainstay for the treatment of mild, non-persistent asthma.

Zafirlukast and montelukast are the two most potent LTRAs currently marketed today. Unlike their asthma treatment counterparts, both of these medications come in an easy to take oral pill form and do not exist in an inhaler design. Patients are required to take 2-4 pills daily with each pill providing asthma protection for upwards of 12 hours. The pill form of medication also enables patients who cannot coordinate breathing to actuation with a pMDI device to take medications that aid in symptom relief.

Zafirlukast

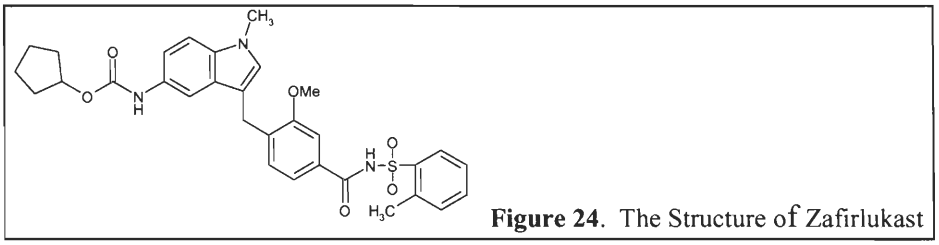

Figure 24. The Structure of Zafirlukast

Zafirlukast is a synthetically derived CysLT type 1 receptor antagonist that protects patients by blocking LTD_4 and LTE_4 binding (Vianna, Martin, 1998: Merck: AstraZeneca). These cysteinyl LTs are known to be involved in bronchoconstriction. Therefore, clinical trials have shown that zafirlukast is able to reverse LT induced bronchoconstriction (Vianna, Martin, 1998: AstraZeneca). Zafirlukast has also been shown to create eosinophilic conditions that can exaggerate certain symptoms of severe asthma. For this reason, zafirlukast provides better support and therapy for mild to moderate asthma symptoms rather than severe symptoms. Zafirlukast and is marketed by AstraZeneca as Accolate®.

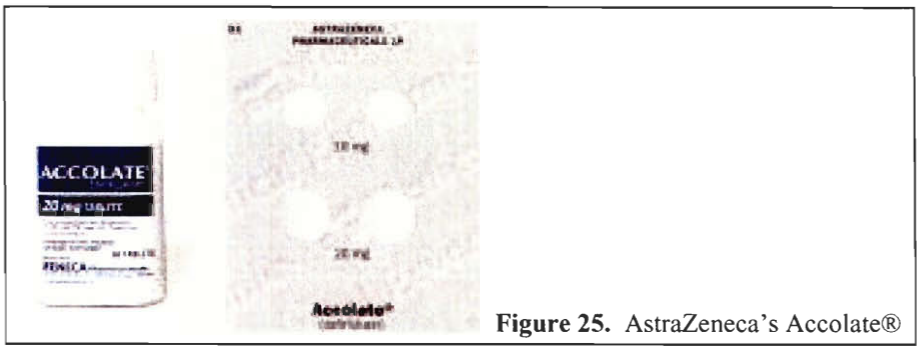

Figure 25. AstraZeneca's Accolate®

Montelukast

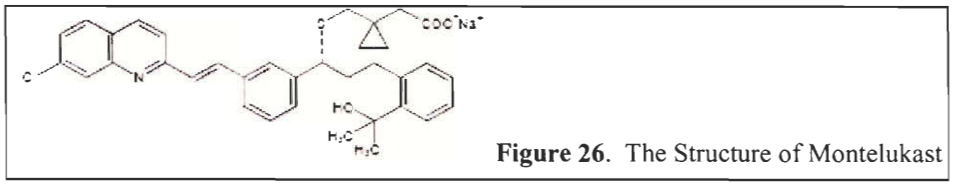

Figure 26. The Structure of Montelukast

Montelukast is also involved in treatment of bronchoconstriction. It however, is a LTD_4 only inhibitor and has no cross-reactivity with other LT species (Merck: Vignola, 2003). Montelukast is also synthetically derived antagonist of the CysLT type 1 receptor but due to its specificity in only blocking one of the many LT species, it is not as potent as zafirlukast. Montelukast also is not meant to be a monotherapy at any time and should be added to an asthma treatment regimen involving B2-agonists and/or ICS medications. Montelukast is marketed by Merck as Singulair®.

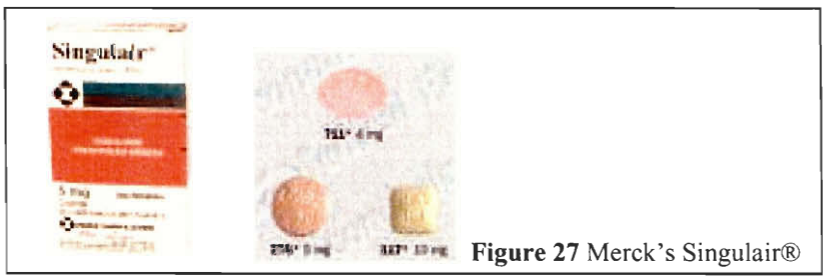

Figure 27 Merck's Singulair®

Zileuton

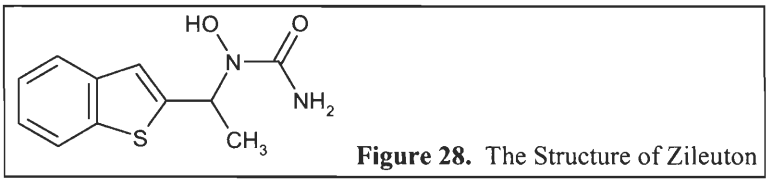

Figure 28. The Structure of Zileuton

The only currently market LT synthesis inhibitor is Abbott Laboratories' zileuton. This drug is designed to target the 5-LO enzyme in the 5-LOX pathway of LT synthesis (see Targets pg) (Vianna, Martin, 1998). Because zileuton inhibits the 5-LO enzyme, both the formation of cysteinyl LTs (LTC_4, LTD_4, and LTE_4) and LTB_4 are inhibited (Yopp, et al. 2003). This prevents not only bronchoconstriction, but hinders recruitment of neutrophils and eosinophils to inflammatory areas (Abbott) and therefore neutralizes two major causes of asthma symptoms, inflammation and eosinophilia. Zileuton is taken as a tablet like both zafirlukast and montelukast but at much higher microgram concentrations and clinical trials have been effective, reducing asthma symptoms and bronchoconstriction better than with the usage of just a LABA (Abbott: Vianna, Martin, 1998). New drugs similar to zileuton are currently undergoing FDA clinical trials in various stages and may provide future relief of asthma symptoms. Zileuton is marketed by Abbott Laboratories as Zyflo®.

Figure 29. Abbott Laboratories' Zyflo®

Unfortunately, these new LTRAs and other LT inhibitors have not undergone the extensive screenings that many of their therapeutic partners have. This is primarily because of their late introduction into the asthma community but can also be partially attributed to their

relative un-extensive use as compared to both B2-agonists and ICS medications. All LT medications suffer from many side effects including eosinophilia and elevated liver enzymatic activities (Merck: AstraZeneca: Abbott). Preliminary research indicates that though these medications are effective in asthma treatment, many future studies need to be performed to evaluate their contribution to not only to liver damage, but to other possible indications as well.

ASTHMA COSTS – DIRECT AND INDIRECT

There exists much debate within the scientific community about the true burden of asthma on both the economy as a whole and by a per person basis. There are many types of costs to asthma patients as well as their families, friends and employers. These types of costs are direct (those costs that can be exactly quantified) and indirect (those costs which are more obscure and harder to quantify). It's the combination of these costs that affect not only asthma patients and their direct surroundings, but also every other individual whether in increased healthcare premiums or work related issues.

Direct Costs

Direct costs of asthma are much easier to describe and much easier to understand than the indirect cost consequences of asthma. Direct costs encompass both medical and non-medical related issues to asthma patients such as prescription medicine costs, hospitalization, and other items that may allow for greater asthma control such as humidifiers and hypoallergenic pillows (Cisternas, et al. 2003: Birnbaum, et al. 2002). Indirect costs are much less defined and consist primarily of work/school related losses, workplace/school limitations, and other lesser important things such as transportation costs to hospitals and decreased enjoyment in routine activities.

With upwards of 130 million asthmatics worldwide and an estimated 15 million within the United States (Birnbaum, et al. 2002: Cleland, et al. 2003)), it is very easy to see that this epidemic can wage havoc on any economy. In the United States alone, it has been estimated that asthma accounts for 2-5% of the economic cost of all diseases with a staggering 13 billion dollars in cost (Birnbaum, et al. 2002: Cleland, et al. 2003). With an average cost of

approximately 5,000 dollars per asthmatic, there is incentive to develop new costing techniques and better asthma control (Cisternas, et al. 2003).

Although grossly underestimated but highly important in lowering the costs of asthma are proper understanding of the disease by physician intervention and proper teaching of inhaler technique. Many patients forget to take medications timely or simply stop taking medications on symptom free days. By providing information to patients about their condition and better enforcing adherence to asthma control regimens, costs other than that of medication could potentially be dramatically reduced (Cisternas, et al. 2003: Clark, Partridge, 2002). One study has even gone as far as to text-message teenagers on their cell phones to remind them to take medications. Patients rely not only upon themselves for asthma care and maintenance, but are part of a ring in which they are invariably linked to family, friends, physicians, and even to business practices and government policies (Clark, Partridge, 2002). This ring is a better way for patients to envision themselves and their condition to more effectively control everyday asthma symptoms. However, in real world situations asthma care culminates in proper use of medications and medication cost.

It has been shown (Numata, et al. 2002: Epstein, et al. 2001), that the teaching time for both children and adult asthma patients is more than the simple one-minute demonstration from the family physician. Learning to properly use a pMDI device takes time even for those already experienced with other devices since asthma inhalers are not standardized devices. As described earlier in the medications section of this paper, there are many steps in proper usage of asthma inhalers and these steps differ between devices. Numata (2002) recommends continual reinforcement of proper technique in the use of pMDI devices. This reinforcement fortifies proper technique to both children and adults and can substantially increase asthma control.

Teaching should not stop with pMDI devices however. Epstein has shown that many patients poorly understand how to use Turbuhaler, a DPI device. Improper use of any asthma inhaler can lead to exacerbations, hospitalizations, and an obvious waste of medication.

With rising costs of all prescription medications, asthmatic patients suffer tremendously to obtain required drugs to maintain their control and quality of life. On average, medical costs are responsible for 85% of an individual's expenditure to treat their symptoms (Cisternas, et al. 2003). Surprisingly however, prescription costs for asthmatics and non-asthmatics are equivalent when viewed from the perspective of the employer rather than employee. When viewed in this manner, prescription medications only account for approximately 25% of a typical employers cost for an asthmatic worker (Birnbaum, et al. 2002). Many studies however have been performed to evaluate why asthma patients have tremendously high medication costs when compared to non-asthmatic individuals. One such study has focused on the early intervention of budesonide/formeterol (Symbicort®, AstraZeneca) in asthma treatment (Sullivan, et al. 2003).

Although research has shown that asthma patients desire to control their asthma with as few medications as possible, the newer combinatorial therapies such as Symbicort® have higher per unit costs than many other asthma medications (Sullivan, et al. 2003: Buhl, 2003). However, medications such as Symbicort® have been proven to enhance asthma symptom control over time and thus reduce other cost types such as hospitalization (Sullivan, et al. 2003: Buhl, 2003: Zetterstrom, et al. 2002). Consequently, early ICS intervention can decrease asthma symptoms and therefore create fewer cost complications such as emergency room visits, dramatically decreasing the overall cost of the patient to society. This type of savings can also be attributed to many of the newer, more potent asthma treatments that reduce symptoms and reduce overall costs.

Medication costs however are a double-edged blade and must be taken into consideration very carefully. Early asthma treatment utilizes many older, more routinely used medications that do not display the efficacy of today's newer drugs. As shown by Horn, et al. (2001), patients taking older dated medications such as albuterol on a routine basis without substitution with newer drugs, demonstrated statistically higher drug costs than patients who routinely take the newer market drugs. This can be attributed to actual asthma control. Patients will more frequently use older medications to obtain the same level of control that patients using newer medications taken less frequently use (Horn, et al. 2001). This results in a quicker usage of inhalers and subsequent refilling of prescriptions sooner than when using newer drugs. Therefore, although many HMOs encourage physicians to prescribe older, less expensive medications over the newer, more expensive ones, in actuality all parties accumulate more cost because of poor control and more frequent refilling of prescriptions (Horn, et al. 2001: Cisternas, et al. 2003).

Although medication costs are the primary concern for many asthma patient expenses, other more subtle causes of increased asthma expenditures should be observed. In particular, hospitalization and emergency room visit costs can greatly affect an individuals overall expenditure. An estimated 1.5 million hospital visits were charged to asthma related conditions in 2002, with 30% of those stays requiring expensive treatments such as nebulisation therapy (HIP). Hospitalization accounts for an average of 15% of an asthmatic's cost of treatment and can vary greatly upon the severity of daily symptoms (Cisternas, et al. 2003: Cleland, et al. 2003). It has been shown that increased severity of asthma distorts the overall costs of patients. Rather than having their primary expense for medications, they are subject to increased proportions of their budget being spent for hospital stays and emergency room visits (Cleland, et

al. 2003). Medical costs are the largest component of employer costs for asthma patients (Birnbaum, et al. 2002). Hospital stays and emergency room visits raise insurance premiums for companies which in turn, raises costs for employers. Healthcare requirements for asthmatic workers are statistically higher than non-asthmatic workers. However, the largest proportion of employer expenditure for asthmatic workers lies within their indirects costs.

Indirect Costs of Asthma

Although indirect costs of asthma may be harder to define, they are equally as important in deciding the true cost of asthma as direct costs. Work/school loss from asthma symptoms accounts for 16% of the yearly costs to employers (Birnbaum, et al. 2002). This figure however is only based on wage replacement costs and not loss in production. Although indirect costs may not initially appear to be equally as important as direct costs to individual asthma patients, it has been shown that indirect costs can attribute to twice the level of expenditure than direct costs (Cleland, et al. 2003). Asthma is the number one cause of workforce disability and the fifth most common cause of workplace limitation (Cleland, et al. 2003). Upwards of 2,000 dollars can be lost per year by the average asthma worker for just loss of work time. This does not account for decreased productivity or decreased hours of work per day that many asthma patients endure (Cisternas, et al. 2003), nor does it account for a total loss (death) of the individual to family members.

Analogous to direct costs, indirect costs to asthma patients are determined primarily by the level of severity of their symptoms. As shown by Cisternas (2003), mild asthmatics display very low indirect costs when compared to sever asthmatics (~10x decrease). This is because mild asthma is easier to treat and therefore less likely to cause work/school loss during the year.

This greater expenditure not only results from work/school loss, but from other costs as well such as hypoallergenic materials and other costly outpatient procedures used to subdue severe symptoms.

Chronic diseases such as asthma require lifetime treatment and a lifetime of patience and understanding by the patient about their condition. Unfortunately along with chronic diseases comes chronic expenditures that will continue for the lifetime of the disease. This type of thinking has only recently been incorporated into the evaluation of the costs of asthma and must be thoroughly considered before continued analysis of asthma costs.

CONCLUSIONS

Asthma is a disease that affects individuals from all ages, infants to grandparents. Because of its extent of prevalence within society today, measures need to be taken now to further treatment options and to begin initiatives to determine ways of stopping its rampage across the globe. Many different approaches are being utilized by researchers and physicians globally to alleviate the symptoms of asthma. These approaches must start first with the identification of the triggers and targets of asthma. Currently, there are effectively six different targets for asthma ranging from receptors and kinases, to secondary signaling molecules and cytokines.

This IQP has described the many different research options available for asthma treatment and has come to the conclusion that they are all equal. But this statement must be taken extremely cautiously and must be better defined. Each asthma target represents a potential cure for a different clinical symptom of asthma. Early treatment of asthma has relied on the development of drugs without known function or design (i.e. naturally occurring compounds). These compounds were soon discovered to be agonists of the β2-adrenoreceptor complex and were termed SABAs for their rapid relief of asthma symptoms. However, asthma is not an hourly disease and must be treated at all times. With this concept came the specific design of agonists of the β2-adrenoreceptor that would give longer lasting symptom control. These LABAs have now been elevated to the most used asthma therapy worldwide (Johnson, 1993) and can provide all day symptom relief for certain patients.

Although symptoms were reduced in some asthmatic patients, other types of symptoms such as inflammation went unattended to. To combat asthma inflammation, glucocorticoids and their receptors have been explored and are now the best targets for the treatment of inflammation

seen in asthma patients (Jenkins, et al. 2000). Although prevalent in all cells within the human body, direct assault with medications in the respiratory tract has shown that the glucocorticoid receptor can be utilized to reduce inflammation only in the areas exposed to the inhaled drug. Because inflammation of the airways is the largest problem for asthmatics, many other types of drugs such as Leukotriene Receptor Antagonists have been developed as an alternative means to steroid medications. Though new as asthma targets, leukotrienes have been shown to play a large role in propagating further inflammation.

With the advent of newer technologies, newer, more sophisticated targets have emerged for the treatment of asthma. Tyrosine kinase and cytokine inhibition, as well as specific Ab to combat asthma have become the most promising newly developed targets for the treatment of asthma. Genetech's new drug Xolair®, and Anti-IgE (an antibody that prevents IgE binding and subsequent release of histamines and other inflammatory agents), represents the newest asthma drug on the market and is the first of its kind. Promising new therapeutics such as Xolair® and under development at many of the leading pharmaceutical companies and will be the future of asthma therapy.

Although drugs have been utilized for many of the major contributors to asthma exacerbations, this still does not explain why this author considers all of these treatments equivalent. This statement implies that each drug will aid in asthma control equally when in fact they do not. Instead, this statement is meant to mean that each drug will give particular patient classes (i.e. mild/moderate/severe asthma) their desired level of control by utilizing combinations of these drugs, therefore making them equal in their control of different asthma conditions.

Until new drugs are made from newly discovered, promising targets, patients must continue to use their traditional inhaler devices and the traditional medications. The asthma

inhaler has undergone extensive evolution since the invention of the nebuliser in the mid-1900's. Today, the asthma inhaler is a quick, easy to use device that can deliver measurable amounts of medication directly into the lungs and provide superior asthma control. But its not the inhaler that determines the quality of asthma control. The medication contained within determines the true control of symptoms. β2-agonists and ICS medications are the most prescribed medications today for asthma treatment (Leung, Nelson, 2001). This is because they deliver a level of acceptable control for most asthma patients and can be adjusted accordingly to the severity of the disease. But even with their efficacy, different drugs within the same class can dramatically differ in their abilities to control asthma symptoms.

This IQP has reviewed many of the popular medication classes used today and has found many differences between similar class medications. LABAs such as salmeterol and formoterol, though providing long-lasting control, act in entirely different ways in their quickness to alleviate symptoms as well as their duration of control. This type of discrepancy can also be seen within ICS class medications such as budesonide and fluticasone propionate. Though both have identical targets (the glucocorticoid receptor), these two medications function in more diverse ways than the most popular LABAs both in their method of action and their duration. Newer LTRAs however are much more identical in their actions than their counterparts which may help to explain their slight differences in efficacy between medications. These medications still require time and effort to evaluate for their role in asthma care.

But even with the amazing new medications marketed today, asthma still persists and still kills. Care to re-evaluate symptoms and identify asthma warnings by both patient and physician are constantly required and will remain so since asthma is for a lifetime. Proper

teaching by physicians of devices as well as instruction to patients about the triggers and causes of asthma may help to alleviate the asthma epidemic.

More of a concern to most about the current asthma epidemic is its cost to both society and to individuals. Asthma affects an average of 15 million American citizens yearly and costs the economy roughly 13 billion dollars a year in treatment (Dhand, 2000: Cleland, et al. 2003). With so many people affected and such a huge burden on society, the time is now to develop strategies to combat asthma.

Suggestions have been widespread by the public and the government on ways to reduce the cost of asthma. These have ranged from reduce medicinal costs to "Asthma Awareness Month." So far, none of these options have worked. Reduced medicinal costs only reflect back to the pharmaceutical companies that produce them and lower revenues, ultimately culminating in layoffs and mergers that displace workers and cost money in other aspects of society. Awareness of asthma is a great idea, but simply being aware that asthma exists is not sufficient to reduce the staggering burden of asthma on society.

This author has unfortunately come to the conclusion that there is very little that can be done within today's society to combat the overwhelming prevalence and cost of asthma. As an asthmatic, this author knows the costs of medicines and healthcare premiums and can sympathize with those who have much more severe symptoms and spend much of their money to treat their symptoms. Newer, more efficacious medications have made a substantial difference on the impact of asthma and in some cases have been shown to reduce overall asthma costs (Clark, Partridge, 2002). These medications are a small way to reduce costs in asthma but are by no means a method to reduce the prevalence of asthma.

With no cure in sight, and the difficulty in developing a cure for asthma, due to its numerous causes and vastly difference symptoms, the only hope is to maintain the crisis at hand. Until a cure for asthma is developed, the rising costs of asthma care and its burden on society will continue to linger. Although the stress for asthmatic individuals has been alleviated with newer medication that allow them a full and eventful life without worry of exacerbations, the stress is squarely placed upon others to develop more sophisticated treatments and to maintain costs.

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