Chapter 19

The Use of Glucocorticoids in the Treatment of Acute Asthma Exacerbations

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1. Introduction

1.1. Pathophysiology of asthma and acute asthma exacerbations: Brief overview

Asthma is a chronic respiratory disease that is prevalent worldwide. It is considered as a major cause of morbidity and a main contributor to the high health care expenditure especially in developed countries (Subbarao et al, 2009). There are two major pathological features in asthmatics' airways, inflammation and hyperresponsiveness. These features are interrelated but not totally dependent on each other. Airway inflammatory changes include increased airway mucus secretions, airway wall edema, inflammatory cellular infiltrates, epithelial cell damage, smooth muscle hypertrophy, and submucosal fibrosis (Bergeron et al, 2009). The cellular infiltrates are mainly composed of eosinophils, neutrophils, mast cells, lymphocytes, basophils and macrophages. The ratio of these cells may widely vary between patients pointing to asthma heterogeneity (Holgate, 2008). Overall, asthma can be divided into eosinophilic, neutrophilic, and pauci-granulocytic phenotypes. The eosinophilic phenotype is characterized by predominant eosinophilic infiltration of the airways. Patients tend to be allergic, have asthma triggered by exposure to allergens and tend to respond well to glucocorticoids. The neutrophilic phenotype is characterized by predominant neutrophil infiltration of the airways. Patients tend to have severe, more aggressive, poorly controlled asthma, or acute asthma triggered by viral infection. They usually do not respond to glucocorticoids as good as the eosinophilic type. In the pauci-granulocytic phenotype neutrophils and eosinophils are almost absent (Holgate, 2008).

Triggers of acute asthma exacerbation include allergens like pollens, animal dander, dust mites and mold; viral respiratory tract infections; irritants like smoke and dust; cold air and exercise. When pollens, for instance, are inhaled by an allergic individual, the allergenic protein is taken up by antigen presenting cells (dendritic cells) in the airway. It is then presented to naïve T-helper (Th) cells that develop into Th2 cell phenotype. These cells respond by secreting Th2 cytokines like IL-4 and IL-13 that cause allergen specific B-cells to

switch from IgM producing to IgE producing cells. These cytokines could also contribute to epithelial cell damage, increased mucus secretion and airway hyperresponsiveness. Th2 cells also secrete IL-5 that stimulates eosinophil development, release from the bone marrow and their recruitment to the site of inflammation. IgE antibodies bind to their receptors on the surface of mast cells. Cross linking of adjacent IgE molecules leads to degranulation and release of mediators like histamine and tryptase that are key to features of immediate hypersensitivity reaction. Activation of mast cells and eosinophils will also stimulate the synthesis and release of lipid derived mediators like prostaglandins and cysteinyl leukotrienes that are very potent bronchoconstrictors. Moreover, activation of eosinophils leads to the release of mediators like eosinophil cataionic protein and major basic protein, which can cause airway epithelial cell damage and submucosal fibrosis. New evidence suggests that Th1 cells contribute to chronic changes in the airways including epithelial cells damage and smooth muscle cells activation. Regulatory T cells (Treg) inhibit Th2 cells by secreting IL-10 and tansforming growth factor β (TGFβ). Also, antigen specific Th17 cells were found to play an important role in neutrophilic airway inflammation and the process of airway remodeling (fixed changes to the airway) through the secretion of IL-17A and IL-17F (figure 1). This is a very quick overview, but many other changes take place during this process that are beyond the scope of this chapter.

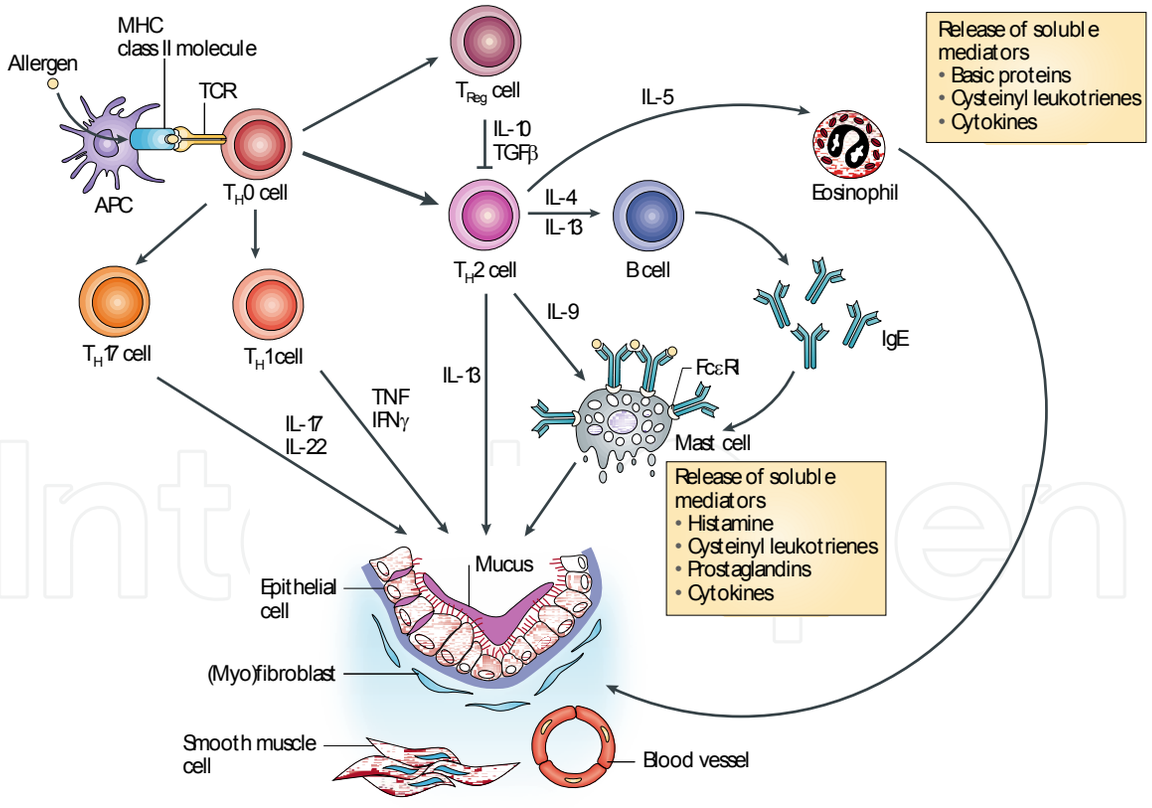

Figure 1. Major immunopahtologic processes that take place in the bronchial airways of patients with asthma. Please see the text for detailed description. FcεRI, high-affinity receptor for IgE; IFNγ, interferon-γ; TCR, T-cell receptor; TNF, tumour-necrosis factor. Reprinted by permission from Macmillan Publishers Ltd: Nature Reviews Immunology. Stephen T. Holgate and Riccardo Polosa. Treatment strategies for allergy and asthma. Vol. 8(3):Page 220, Copyright 2008.

The most common cause of acute asthma exacerbation in both adults and children, but more in children, is viral respiratory tract infections. Viruses may be responsible for up to 80% of wheezing episodes in children and 50-75% of episodes in adults (Jackson et al, 2011b). Many viruses can cause exacerbation of asthma symptoms, the most important and most common is rhinovirus (Khetsuriani et al, 2007). Respiratory syncycial virus and influenza virus also cause significant proportion of exacerbations. The pathology of virally induced asthma exacerbation is more related to the airway epithelial cells which, in response to infection secret chemokines like IL-8 and CCL-5 that can attract inflammatory cells including neutrophils and lymphocytes and augment allergic inflammation (Gern & Busse, 2002). This finding is supported by epidemiological observations that allergen sensitization and respiratory viral infections can synergize to cause asthma exacerbation (Green et al, 2002). Children who are atopic are more likely to have virally induced wheezing and respiratory distress than non-atopic children (Jackson et al, 2011a).

1.2. Treatment of acute asthma exacerbation: general overview

Acute asthma exacerbations are defined as "episodes of progressive increase in shortness of breath, cough, wheezing, or chest tightness, or some combination of these symptoms" (EPR3, 2007; GINA, 2011). Most recently an expert group formed by the NIH agreed to define acute asthma as "a worsening of asthma requiring the use of systemic corticosteroids to prevent a serious outcome" (Fuhlbrigge et al, 2012). Acute exacerbation of asthma symptoms is a common complication of the disease. The frequency in which exacerbations happen vary widely depending on the severity of disease (Moore et al, 2007), the degree of control with prophylactic medications (Peters et al, 2007), and exposure to triggers. In a multicenter study from the US (Pollack et al, 2002) the admission rate of all comers to the ER with acute asthma was 23%. On the other hand, a European study showed that only about 7% of all patients with acute asthma exacerbation required hospitalization (Rabe et al, 2000). We have a similar experience in Saudi Arabia where about 8% of all asthmatics with acute exacerbation are hospitalized, but if we look at only the severe group the rate goes up to 40% (unpublished data). These epidemiological data underscores the importance of effective treatment of asthma exacerbations and their prevention.

Patients with acute asthma exacerbation usually present with increasing cough, and dyspnea. On examination patients may have increased respiratory rate, retractions (accessory respiratory muscle use), wheezing, oxygen desaturation on pulse oxymetry and, in more severe cases, inability to speak, silent chest, with reduced respiratory lung volumes, cyanosis and change in mental status. Asthma exacerbations can be classified as mild, moderate, or severe based on the level of severity of the signs and symptoms as illustrated in Table 1. (Adams et al, 2011)

Different asthma scoring systems have been developed to assess the severity of asthma exacerbations more objectively, which is more useful for research purposes. An example is shown in table 2. (Qureshi et al, 1998). This scoring system is becoming more widely used because of its high reliability and objectivity.

Severity	Mild	Moderate	Severe
PEFR*	≥ 70%	40-69%	<40%
Speech	Sentences	Phrases	Words
Mental Status	Anxious	Agitated	Distressed
Accessory muscle use	No	Sometimes	Commonly
Oxygen saturation	≥ 95%	90-95%	<90%

Table 1. General classification of asthma severity. * PEFR: Peak Expiratory Flow Rate

Other frequently used scoring systems in the literature include; the Pulmonary Index Score (Scarfone et al, 1993) (table 3), and to a lesser degree the Preschool Respiratory Assessment Measure (PRAM) (Ducharme et al, 2008)(table 4), and the Pediatrics Asthma Severity Score (PASS) (Gorelick et al, 2004) (table 5).

Variable	Asthma score		
	1 point	2 points	3 points
Respiratory rate (breaths/min)			
2-3 years	≤ 34	35 - 39	≥ 40
4-5 years	≤ 30	31 - 35	≥ 36
6-12 years	≤ 26	27 - 30	≥ 31
>12 years	≤ 23	24 - 27	≥ 28
Oxygen saturation (%)	> 95 with room air	90 - 95 with room air	<90 with room air or supplemental oxygen
Auscultation	Normal breathing or end-expiratory wheezing	Expiratory wheezing	Inspiratory and expiratory wheezing, diminished breath sounds, or both
Retractions	None or intercostal	Intercostal and substernal	Intercostal, substernal, and supraclavicular
Dyspnea	Speaks in sentences or coos and babbles	Speaks in partial sentences or utters short cries	Speaks in single words or short phrases or grunts

Table 2. Asthma severity score (Qureshi et al). Score interpretation: Mild asthma 5-7, Moderate 8-11, Severe 12-15

In patients with mild asthma exacerbation, inhaled β2-agonists like albuterol (salbutamol) is usually sufficient to resolve symptoms. The dose can be repeated 3 times every 15-20 minutes. Levalbuterol, the (R)-enantiomer of albuterol is the effective form of the drug, but clinical trials did not show any advantage of using it over albuterol in terms of efficacy or side effects (Kelly, 2007). Most patients with mild asthma exacerbation will not require systemic glucocoricoids. However, it is recommended that patients who take them regularly or patients who fail initial treatment with albuterol should be given systemic glucocorticoids.

Score	0	1	2	3
Respiratory Rate* (breaths/min)	< 30	31-45	46-60	> 60
Wheezing	None	End expiration	Entire expiration	Inspiration and expiration without stethoscope
Inspiratory / Expiratory Ratio	5/2	5/3 - 5/4	1/1	<1/1
Accessory Muscle Use	0	+	++	+++

Table 3. Pulmonary Index Score. * For patients aged 6 years or older: <20 = 0; 21-35 = 1; 36-50 = 2; >50 = 3

Signs	0	1	2	3
Suprasternal retractions	Absent		Present	
Scalene muscle contraction	Absent		Present	
Air entry*	Normal	Decreased at bases	Widespread decrease	Absent/minimal
Wheezing*	Absent	Expiration only	Inspiratory and expiratory	Audible without stethoscope/silent chest with minimal air entry
O_2 saturation	≥95%	92%-94%	<92%	

Table 4. The Preschool Respiratory Assessment Measure (PRAM). *If asymmetric findings between right and left lungs, the most severe side is rated.

Current guidelines recommend that patients with mild-moderate or moderate exacerbation should receive 3 doses of inhaled or nebulized β2-agonist every 15-20 minutes in the first hour (Camargo et al, 2003). Additional doses may be repeated in the next 2-3 hours every 30-60 minutes. All those patients should be treated with systemic glucocorticoids at a dose of 2mg/kg or a maximum dose of 80 mg early in the course of management as it takes at least 4 hours to start working (Rowe et al, 2004). Doses more than 80 mg will not confer any additional benefit. Systemic glucocorticoids were found to speed resolution of symptoms, decrease the rate of admission and decrease the rate of relapse if administered for 3-5 days after the acute exacerbation. More detailed discussion about the use of systemic glucocoricoids in the treatment of acute asthma can be found below in section 2.1.

Clinical Finding	Definition	0	1	2
Wheezing	High-pitched expiratory sound heard by auscultation	None or mild	Moderate	Severe wheezing due to poor air exchange
Air entry	Intensity of inspiratory sounds by auscultation	Normal or mildly diminished	Moderately diminished	Severely diminished
Work of breathing	Observed use of accessory muscles, retractions, or in-breathing	None or mild	Moderate	Severe
Prolongation of expiration	Ratio of duration of expiration to inspiration	Normal or mildly prolonged	Moderately prolonged	Severely prolonged
Tachypnea	Respiratory rate above normal for age	Absent	Present	
Mental status	Observation of the child's state of alertness	Normal	Depressed	

Table 5. The Pediatrics Asthma Severity Score (PASS)

Patients with severe asthma exacerbation should obviously be treated more aggressively. High dose inhaled (8-12 puffs) or nebulized β2-agonist should be given every 15-20 minutes at least in the first hour, which could be repeated for up to 4 hours then as required. The data are conflicting whether continuous nebulization using β2-agonist is superior to intermittent nebulaization or not (Camargo et al, 2003; Rodrigo & Rodrigo, 2002). Practically, continuous high dose nebulization could be used for the first hour and then intermittent nebulization thereafter as required. Ipratropium bromide has been shown to decrease the rate of hospitalization and shorten the stay in the emergency room in patients with severe or moderate to severe asthma exacerbation in many clinical trials (Qureshi et al, 1998; Rodrigo & Castro-Rodriguez, 2005; Zorc et al, 1999). Therefore, it is recommended to add it to each treatment of β2-agonist at least in the first hour of therapy. Its use in patients after admission to the hospital was not shown to make a difference. Systemic steroids should be used as mentioned in patients with moderate exacerbation. Other treatment modalities may be considered like magnesium sulfate and helium oxygen (heliox) therapy in the more severe and non-responsive patients. Subcutaneous or intravenous β2-agonists (Travers et al, 2002), intravenous aminophylline (Parameswaran et al, 2000), intravenous montelukast (Camargo et al, 2010; Morris et al, 2010), or oral montelukast added to standard therapy in the ER (Todi et al, 2010) were not shown to be helpful in the treatment of patients

with severe asthma exacerbation and therefore are not recommended. Moreover, oral montelukast given to patients post discharge for 5 days was also shown not to be helpful (Schuh et al, 2009).

β2-agonists can be delivered via a nebulizer or by metered dose inhaled (MDI) with a holding chamber. An MDI dose of 4-8 puffs depending on age is equivalent to a nebulized dose of 2.5-5 mg of albuterol (Cates et al, 2006). Nebulizer is preferable in cases of severe symptoms when patients are unable to use the MDI effectively or if other nebulized medications are needed to be mixed with albuterol at the same time or if the patient is requiring oxygen supplementation. Oxygen therapy should be given to maintain saturation ≥ 90% in adults and ≥95% in pregnant women or children.

Patients who maintain normal oxygen saturation, have no or minimal wheezing on chest auscultation, and have no or mild intercostal retractions can be discharged home after 1 hour of assessment on no additional medications in the emergency room. However, these patients should have a step up in their maintenance medications to prevent relapse. Patients who fail to achieve improvement after 4 hours of treatment should be admitted to the hospital for further aggressive therapy.

1.3. Introduction and evolution of glucocorticoids in the management of asthma: Historical background

Shortly after the discovery of the structure of adrenal steroid hormones, Hench and his colleagues examined using cortisone to treat arthritis in 1949. The effect was remarkable and that work won the Nobel Prize the next year. It also started a series of trials of corticosteroids in various inflammatory conditions. The first use of corticosteroid to treat acute asthma exacerbation occured in 1956 (Subcommittee on clinical trials in asthma, 1956). Development of corticosteroids that have less mineralocorticoid activity, like prednisone, and later those that have no mineralocorticoid activity, like dexamethasone, made glucocorticoids more attractive therapies to use in asthma. In 1972, Clerk et. al. showed for the first time that inhaled beclomethasone was effective in the management of asthma with less adverse effects than systemic steroids (Clark, 1972). Numerous reports came afterwards describing the efficacy of oral prednisone and prednisolone, intravenous methylprednisolone and inhaled glucocorticoids (IGC) like triamcinolone, budesonide, and fluticasone in the management of asthma. Table 3 shows some common systemic glucocorticoids and their relative potency.

Preparation	Potency relative to hydrocortisone	Relative sodium retention potency	Biological half life (h)
Hydrocortisone	1	1	8-12
Prednisone/Prednisolone	4	0.8	12-36
Methylprednisolone	5	0.5	12-36
Dexamethasone	25	0	36-72

Table 6. Common types of systemic glucocorticoids and their relative properties

1.4. Adverse effects of glucocorticoids

There are many adverse effects that may result from the use of oral or IGC in the treatment of asthma especially in high doses. I will summarize here the most pertinent ones.

a. Suppression of the hypothalamic-pituitary-adrenal axis. Soon after the commencement of high dose oral glucocorticoids adrenal suppression may be noticeable. It also occurs with longer use of lower doses. IGC can also be systemically absorbed in their active form through particle deposition in the orophaynx or the lungs (particles deposited in the stomach usually undergo first pass hepatic metabolism where they are deactivated). High doses of IGC, more than 400 mcg of becloemthasone and 200 mcg of fluticasone or budesonide per day, could cause systemic adverse effects especially in children (Gulliver & Eid, 2005). Patients who undergo a stressful situation like major surgery should receive systemic steroid coverage to avoid symptoms of adrenal crises. These symptoms include lethargy, vomiting, change in mental status, and electrolyte disturbances. The hypothalamic-pituitary-adrenal axis can be evaluated by measuring early morning cortisol level.
b. Osteoporosis. A common and serious complication of prolonged oral or high dose IGC therapy. Patients on such treatment, especially women and those with limited physical activity or who are taking medications that increase vitamine D metabolism in the liver, should undergo bone densitometry evaluation because this complication cannot be detected clinically. In one specialized center in the US, 40% of adolescent females admitted with severe asthma had osteopenia (Covar et al, 2000).
c. Growth suppression. Glucocorticiods have been consistently shown to suppress growth in children. This seems to be independent from the growth suppression caused by the disease itself (Covar et al, 2000). The degree of growth suppression may reach 1 cm especially in the first year after starting IGC treatment. However, children eventually reach their expected height as adults (Agertoft & Pedersen, 2000; Sharek & Bergman, 2000).
d. Ophthalmologic adverse effects. Long-term administration of oral glucocorticoids or high doses IGC can lead to the development of posterior capsular cataract (Cumming et al, 1997). Some patients may need lens replacement surgery. Another ophthalmic complication is glaucoma that also may result from prolonged therapy with high dose IGC (Garbe et al, 1997). However, short-term treatment for less than 2 years or the use of moderate doses of IGC was found to be safe (Li et al, 1999; Pelkonen et al, 2008).
e. Local adverse effects: Chronic use of IGC can be associated with the development of oral thrush (candidiasis), which could be minimized by washing the mouth with water after the inhalation. It may also be associated with hoarseness of voice and dysphonia due probably to laryngeal edema. These effects can be managed by changing the mode of inhalation (e.g: from dry powder inhaler to MDI) and the use of a holding chamber.
f. Other adverse effects: These include immune suppression, metabolic changes like hyperglycemia, acne, hirsutism, skin thinning, delayed wound healing, myopathy, psychosis or mood changes.

2. Clinical evidence of the effect of glucocorticoids in acute asthma

2.1. Systemic glucocorticoids

Systemic glucocorticoids given early in the course of treatment of acute asthma exacerbations in the emergency room were overall shown to be effective and are recommended by different asthma guidelines like GINA and EPR3. Littenberg et al. initially showed that they decrease hospital admission rate (Littenberg & Gluck, 1986). Five subsequent studies had, however, conflicting results. Rodrigo & Rodrigo reviewed all these six studies and concluded that there was no improvement in hospital admission rate or lung function (Rodrigo & Rodrigo, 1999). They, however, reported a trend of improvement in lung function only with medium or high doses systemic glucocorticoids. So data in terms of lung function are more encouraging (Fanta et al, 1983; Lin et al, 1999). In terms of effect on exacerbation relapse after discharge from the emergency room, most studies showed less relapse with systemic glucocorticoids (Schneider et al, 1988; Subcommittee on clinical trials in asthma, 1956) although others did not (Rodrigo & Rodrigo, 1994). One important issue with all these studies is the low number of patients recruited. Almost all had subject number less than 100 per study and all were performed in adults. On the other hand, Krishnan et al recently reviewed 9 published studies in the use of systemic glucocorticoids in acute asthma in adults and concluded "systemic corticosteroids provide clinically meaningful benefits in patients presenting with acute asthma" (Krishnan et al, 2009). In children, more limited data showed benefit of systemic steroids used early in the emergency room with decreased rate of admission (Scarfone et al, 1993). A Cochrane database review by Rowe et al showed decrease rate of admission in patients with acute asthma with the use of systemic glucocorticoids in adults and children especially those with severe asthma and those not currently receiving steroids (Rowe et al, 2001).

There is no significant difference in efficacy of systemic glucocorticoids at doses above 60-80 mg/d or 2 mg/kg/d in regards to pulmonary function, rate of admission, or length of stay in the hospital. For example, Marquette et al compared 1 mg/kg/d to 6 mg/kg/d methylprednisolone in 47 adults hospitalized with severe acute asthma and found no benefit of the high dose over the low dose (Marquette et al, 1995). Manser et al performed a systematic review of randomized controlled studies of patients with acute severe asthma comparing different doses of glucocorticoids with a minimum follow up of 24 hours. They divided the different doses used in the trials included into 3 groups as equivalent dose of methylprednisolone in 24 hours; low dose (≤80 mg), medium dose (>80 mg and ≤360 mg), and high dose (>360 mg). Nine trials were included with a total of 344 adults. They found no difference between the different doses (Manser et al, 2001).

Studies also showed no difference in efficacy between oral or intravenous administration or in their onset on action. Fifty-two adults with severe acute asthma were treated with either IV hydrocortisone or PO prednisolone. There was no difference in their peak flow measurements 24 hours after admission (Harrison et al, 1986). Ratto et al compared four different doses of methylprednisolone; 160 or 320 mg given orally, or 500 or 1000 mg given IV in four divided doses in adults with acute asthma and found no difference in their FEV_1,

days of hospitalization (Ratto et al, 1988). In children oral prednisolone was found equivalent to IV methylprednisolone in regards to patients' length of hospital stay (Becker et al, 1999). In addition, oral treatment was cost saving. GINA and the EPR3 guidelines prefer oral administration because it is less invasive except in patients with absorption problems or those who are not able to take orally due to the severity of their respiratory distress or because they are vomiting.

Prescribing oral glucocorticoids for the treatment of acute asthma exacerbations for longer than 5 days was not found to provide any additional benefit (Hasegawa et al, 2000; Jones et al, 2002). In children, a single dose of dexamethasone 0.6 mg/kg (max. 18 mg) was found to be equivalent to prednisolone 2 mg/kg/d in two divided doses for 5 days in terms of symptoms resolution (Altamimi et al, 2006). There is also no benefit from using a dose taper over fixed-dose regimen (Krishnan et al, 2009). Because of poor compliance on oral prednisone after discharge from the emergency, intramuscular injection of methylprednisolone was studied as an alternative but was not found superior, plus there was an evidence of injection-site adverse reaction (see last reference).

2.2. Inhaled glucocorticoids

IGC were studied in the treatment of acute asthma in 4 contexts: as compared to placebo, as compared to systemic glucocorticoids, as add on therapy to systemic steroids for up to few weeks after discharge from the ER, or as add on therapy to systemic steroids in the ER only.

In the first context, a review that looked at 8 randomized and blinded studies comparing the efficacy of IGC to placebo in acute asthma exacerbation suggested that IGC are superior to placebo especially when given at high doses (> 1mg of budesonide or fluticasone) and to patients with severe exacerbations (Rodrigo, 2006). It is important to note that those studies were quite heterogeneous in terms of the severity of asthma in recruited patients, the dose and frequency of IGC administered, and in the outcome measures that included clinical symptoms, pulmonary function, oxygen saturation, admission rate, or relapse rate. A recent study found that preemptive use of high dose fluticasone (750 mcg BID) at the onset of an upper respiratory tract infection in children with recurrent virus induced wheezing and continuing it for 10 days, reduced the use of rescue oral glucocorticoids (Ducharme et al, 2009).

When IGCs were compared with systemic glucocorticoids in randomized and blinded studies the data were more controversial. Some studies reported superiority of systemic steroids in reducing admission rate (Schuh et al, 2000), some reported equal efficacy in relation to admission rate as well (Lee-Wong et al, 2002; Levy et al, 1996; Scarfone et al, 1995), and some reported clear superiority of IGC (Devidayal et al, 1999; Rodrigo, 2005). A study compared high dose fluticasone in the ER and for 5 days post discharge to systemic glucocorticoids in the same period in patients with mild to moderate asthma found that oral steroids lead to faster improvement in FEV_1 at 4 hours in the ER and less relapse rate at 48 hours post discharge (Schuh et al, 2006). One recent study showed that in patients who were given systemic glucocorticoids plus IGC post discharge from the ER, stopping the systemic

glucocorticoids after 1 week resulted in rebound in the level of exhaled NO 2 weeks post discharge despite continuing IGC with no effect on the use of rescue medications or on FEV_1 (Khoo & Lim, 2009). GINA guideline state that "IGC are effective as part of therapy for asthma exacerbations….and can be as effective as oral glucocorticoids at preventing relapses"(GINA, 2011), while the EPR3 guidelines state that "high doses of IGC may be considered in the ER, although current evidence is insufficient to permit conclusions about using IGC rather than oral systemic corticosteroids in the ER"(EPR3, 2007).

When IGC were used as add on therapy to systemic glucocorticoids in the ER and continued after discharge for few weeks, Rowe et al found decrease in relapse rate when 1600 mcg/d budesonide for 21 days was added to a course of 50 mg/d prednisone for 7 days as compared to placebo (Rowe et al, 1999). On the other hand, Brenner et al found no difference in the peak expiratory flow rate between high dose flunisolide used for 24 days added to prednisone 40 mg/d for 5 days as compared to placebo (Brenner et al, 2000). A systematic review of ten trials concluded no benefit of adding inhaled to systemic glucocorticoids in reducing the relapse rate of acute asthma (Edmonds et al, 2000).

There are few randomized and blinded studies examining only the short-term effect of IGC in the ER as add on therapy to systemic glucocorticoids plus other standard acute asthma therapy. One study looked at the addition of high dose beclomethasone versus placebo to methylprednisolone in 60 adults and found no difference in FEV_1 or symptoms between the two groups (Guttman et al, 1997). One study looked at the addition of budesonide nebulizations to methylprednisolone in a population of 26 children with moderate asthma (Nuhoglu et al, 2005) and found no difference in the primary outcome of pulmonary index score but there was an improvement in the PEFR in the budesonide group compared to placebo. However, the patient number included is very small and PEFR is generally not reliable in young children. The two other randomized and blinded studies that were larger and more rigorous examined the effect of adding 2 mg of budesonide nebulization to prednisone in children with moderate to severe asthma (Sung et al, 1998; Upham et al, 2011). In the study by Sung et al, 44 children with moderate to severe asthma were included. Both groups had no difference in the pulmonary index score. In the Upham et al study, 180 children with moderate to severe asthma were included. There was no difference in the asthma score (adopted form (Qureshi et al, 1998)) at 2 hours after intervention or in the admission rate or time to discharge from the ER between the two groups. Collectively, all these studies, although small in subjects number, indicate that the addition of IGC to systemic steroid is not helpful in patients with moderate to severe acute asthma. We are conducting a larger study that will hopefully shed more light on that question, the results of which should be available quite soon.

3. A brief overview of the use of glucocorticoids in asthma prophylaxis

3.1. Inhaled glucocorticoids

IGCs are the main stay of asthma management. They were shown to very consistently change many of the pathologic inflammatory features of asthma in the lung airways. They

lead to decrease cellular infiltrates including T-lymphocytes, mast cells, eosinophils, and macrophages. Also, epithelial damage, goblet cell hyperplasia, and vascular blood flow significantly decreases with IGC therapy (Fanta, 2009). Consistent with the histological changes, clinical changes are observed. Compliant use of IGC is associated with decreased airway hyperresponsiveness and improved asthma symptomatology (CAMP, 2000; Haahtela et al, 1991). Most patients will also have improved lung function demonstrated by increased FEV_1. In addition, the risk of patients' hospitalization from asthma exacerbations is decreased by up to 50% (Donahue et al, 1997). Moreover, the risk of death from asthma is decreased, an effect that is dependent on the patients' compliance on IGC and the duration of their use (Suissa et al, 2000).

It is important here to note several points. First, the local anti-inflammatory effect of IGC usually plateaus after reaching low to moderate dosages, except probably for the most severe patients. However, the other systemic effects of IGC increase steeply after exceeding the low to moderate dose (Szefler et al, 2005). Therefore, efforts should be made to maintain patients on the lowest possible dose of IGC and, in cases of inappropriate response, long acting beta-agonists (LABA) or leukotriene receptor antagonists (LTRA) or both should be added before doubling the dose of IGC (Fanta, 2009). Second, there is great heterogeneity among asthmatics in their response to IGC. This variability can be attributed to several factors, most importantly are genetic variations between individuals (Lima et al, 2009). Third, multiple studies have shown that IGC therapy over the years do not change the natural history of the disease or prevent decline in lung function. They may have little effect on some features of remodeling but not all of them. Also, IGC, even when used in high risk infants who are very likely to develop asthma, were not able to prevent its development (Murray, 2008).

3.2. Systemic glucocorticoids

Systemic glucocorticoids are only occasionally used for long-term asthma control. There use is limited to the most severe patients who are difficult to control using other common modalities (EPR3, 2007). This is due to their side effects that can be very serious as stated above. The side effects are dose and duration dependent. Prolonged low dose therapy (<7.5 mg prednisone-equivalent in adults/day) is usually associated with mild adverse effects. Moderate doses (7.5 mg – 30 mg/day) are usually associated with significant adverse effects, and high doses (30 mg – 100 mg) may be associated with serious adverse effects (Stahn & Buttgereit, 2008).

4. Mechanism of action of glucocorticoids in asthma

Discussion of the mechanism of action of glucocorticoids in asthma is beyond the scope of this chapter and was recently reviewed (Alangari, 2010). Glucocorticoids act either by altering the rate of transcription of certain genes at the DNA level or through non-genomic pathways. Some of these effects could lead to the desirable anti-inflammatory action and some may result in adverse reactions.

4.1. Genomic action

The main mechanism whereby glucocorticoids deliver their anti-inflammatory action involves genomic action. This mechanism entails binding of glucocorticoids to their cytoplasmic receptors forming complexes that then translocate to the nucleus, where they either homo-dimerize then bind to their glucocorticoid response elements (GRE) in the DNA, or bind to different transcription factors (protein-protein interaction) as monomers (Ito et al, 2006; Lowenberg et al, 2008). Because of this, the genomic action of glucocorticoids takes at least 4 hours to start showing an effect and the duration of action is also prolonged and may exceed 24 hours.

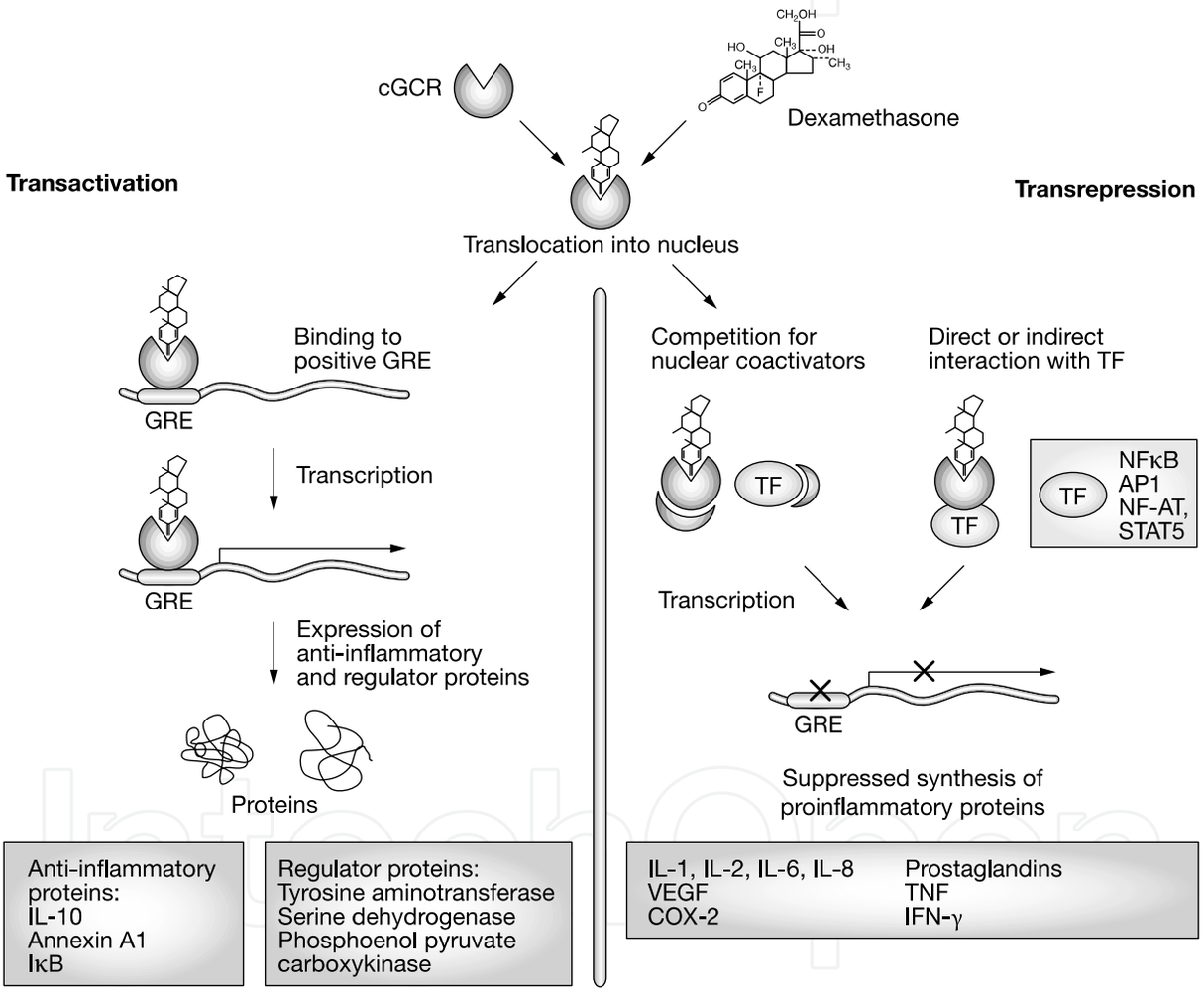

Figure 2. The genomic effect of glucocorticoids is in the form of transactivation or transrepression. In transactivation, the transcription of genes encoding certain anti-inflammatory or regulatory proteins is upregulated, while in transrepression the transcription of certain genes encoding proinflammatory proteins is up regulated. Abbreviations: AP1, activator protein 1; cGCR, cytosolic glucocorticoid receptor; COX-2, cyclooxygenase 2; GRE, glucocorticoid response element; IkB, inhibitor of NFkB; IFNγ interferon IL, interleukin; NF-AT, nuclear factor of activated T cells; NFkB, nuclear factor kB; STAT5, signal transducer and activator of transcription 5; TF, transcription factor; TNF, tumor necrosis factor; VEGF, vascular endothelial growth factor. Reprinted by permission from Macmillan Publishers Ltd: Nature Reviews Rheumatology. Cindy Stahn and Frank Buttgereit. Vol. 4(10):Page 529, copyright 2008.

Binding of glucocorticoid receptors to their GRE activates the transcription of certain genes encoding anti-inflammatory proteins, like IL-10 and IkB, and regulatory proteins. This process is called *transactivation* (figure 2). Some of the glucocorticoids adverse effects like glaucoma and hyperglycemia are mediated through this pathway (Schacke et al, 2002). On the other hand, binding of glucocorticoid receptors to pro-inflammatory transcription factors like nuclear factor kappa B (NFkB) or activator protein 1 (AP-1), or their competition for nuclear coactivators; down regulates the transcription of certain genes encoding pro-inflammatory proteins like IL-1, IL-2, IL-6, and TNF. This process is called *transrepression* (De Bosscher et al, 2003) (figure 2). Most of the desired genomic actions of glucocorticoids in asthma are mediated through this pathway.

4.2. Non-genomic action

Non-genomic action of glucocorticoids includes all actions that do not directly alter gene expression and are not blunted by inhibitors of gene transcription (Losel & Wehling, 2003). This mode of action is characterized by its rapid onset (seconds to minutes) and short duration (60-90 min). These actions are dose dependent (Wanner et al, 2004). There are four types of non-genomic action of glucocorticoids (Alangari, 2010). Firstly, acting through the inhibition of the extraneuronal monoamine transporter-mediated uptake of norepinephrine. Asthmatic patients have increased blood flow in their airways (Kumar et al, 1998). IGC were shown to decrease blood flow in the airways within few minutes. This effect will last for 90 minutes only and therefore, cannot be explained by the genomic action (Kumar et al, 2000; Mendes et al, 2003). The proposed mechanism is that IGCs by a topical effect can block the extraneuronal monoamine transporter on the membrane of vascular endothelial cells, preventing their uptake of norepinephrine and thus making it more available in the synaptic cleft (Horvath & Wanner, 2006). Secondly, in high doses, glucocorticoids can induce physiochemical changes in the cell membrane by directly incorporating into the membrane. This can result in immune cell suppression (Buttgereit & Scheffold, 2002). Thirdly, glucocorticoids may interact with membrane bound GRs on mononuclear cells. These receptors are variants of cytosolic GRs and can mediate inhibition of Lck/Fyn kinases down stream form the T-cell receptor leading to immune suppression (Lowenberg et al, 2005; Lowenberg et al, 2007). Lastly, few in vitro studies showed that some protein components associated with GRs complex, which are released upon GR ligation can inactivate cytosolic phospholipase 2 and therefore inhibit the production of arachidonic acid and downstream components like prostaglandins and leukotriens (Croxtall et al, 2000; Croxtall et al, 2002). However this action was not shown to be of clinical significance.

5. Future directions and recommendations

We have seen through this chapter that glucocorticoids play an extremely important role in the current prophylactic treatment of patients with persistent asthma, in the treatment of acute asthma exacerbations post discharge from the ER and possibly in the acute management in the ER. The introduction of IGC has revolutionized the way we manage

asthma and it seems that those medications will stay with us for a long while. Further research is greatly needed to shed more light on the use of IGC in the ER in patients coming with acute asthma exacerbation and on the safety of dispensing oral glucocorticoids for home use in case of asthma exacerbation. Training physicians to follow asthma management guidelines as well as education of patients and their families cannot be over emphasized and will save a lot of money.

Our improved understanding of the tertiary structure of glucocorticoids and their receptors and their mechanisms of action has led to the discovery and development of selective glucocorticoid receptor modulators (SGRM). Those are new agents that have the transrepression but little or no transactivation properties of glucocorticoids, which means that those compounds could deliver the desired anti-inflammatory action of glucocorticoids while avoiding most of their adverse effects (De Bosscher et al, 2010). Still under investigation, those agents could hold a lot of promise in the future. Moreover, it was recently shown that simultaneous activation of GRα and peroxisome proliferator-activated receptor alpha (PPARα), which are cytosolic receptors with many immunomodulatory functions and multiple natural ligands, can block the GRE mediated transactivating effects of glucocorticoids while potentiating their anti-inflammatory effects in mice (Bougarne et al, 2009). If this holds true in humans, combination therapy of a glucocorticoid and a PPARα agonist could be very promising.

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