

PHENOTYPES

Glucocorticoid-resistant asthma: more than meets the eye

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Abstract

Introduction: For decades glucocorticoids have been considered as the gold standard for the treatment of asthma. We present a case report of typical glucocorticoid-resistant asthma and current consensus in definitions of "severe refractory", "difficult" and "glucocorticoid-resistant" asthma. **Methods:** Full-text papers and abstracts were identified on the basis of a comprehensive literature search primarily in MEDLINE (1966 to June 2012) but also in the Cochrane Central Register of Controlled Trials database. **Results:** Glucocorticoid-resistant asthmatics are a small subset of patients who pose noteworthy diagnostic challenges while contributing disproportionately to health care costs. Recognition of various asthma phenotypes has aided in characterizing groups with severe asthma and given a better understanding of its pathophysiological process. The molecular mechanism of glucocorticoid action is complicated and several pathways have been identified to explain drug resistance, which in turn is crucial for drug development. Tobacco smoking appears to be the single most important contributor of glucocorticoid resistance. We present the emerging and promising concepts in the management of glucocorticoid-resistant asthma, which mainly include drugs targeting specific molecules, receptors, inflammatory cells or immune processes. **Conclusion:** The challenges in making a diagnosis of glucocorticoid-resistant asthma may contribute to underestimating its prevalence and impact on patient care. Considerable progress has been made in identifying distinct phenotypes and mechanisms of glucocorticoid resistance; therefore the future of new drug development in management of asthma is promising.

Keywords

Asthma, poorly controlled, refractory, severe, glucocorticoids

History

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Introduction**Case**

A 35-year-old Puerto Rican male, with no significant past medical history, developed recurrent episodes of acute onset shortness of breath and wheezing in the setting of bacterial/viral upper respiratory tract infections and/or cigarette smoking requiring emergency care and systemic glucocorticoids. He had a 40-pack-year tobacco smoking and a 20-year daily marijuana use history, both of which were active. He had a family history of asthma, had worked as a mechanic and a plumber in the past and had a guinea pig, a cat, a fish and 5 cockatiels for pets. His pulmonary function tests (PFTs) initially showed moderate airflow obstruction with no significant bronchodilator response. Routine laboratory tests were significant only for peripheral eosinophilia. Chest X-ray revealed a linear right mid lung opacity suggestive of scarring.

Based on his presenting clinical features and age, the initial working diagnosis was asthma/COPD overlap syndrome and he was started on inhaled glucocorticoid and albuterol.

However, he remained symptomatic with poor control despite aggressive step-up therapy of glucocorticoid, anti-cholinergic, long and short acting β -agonist inhalers, leading to an expanded evaluation for alternate causes and contributors of intermittent dyspnea and wheeze: His HIV and tuberculin skin test were negative; TSH, immunoglobulin E levels, alpha-1-antitrypsin and ACE levels were within normal limits. D-dimer, rheumatoid factor, ANA, ANCA and anti-GBM were negative. There was no evidence of atopy to common local indoor and outdoor aeroallergens. Antibodies for Aspergillus, Filaria and Schistosoma were negative but were positive for Strongyloides. Stool was negative for ova and parasites. Computed Tomography of the Thorax showed tracheal and bilateral lower lobe endo-bronchial debris. Trans-thoracic Echocardiography showed mild right ventricular dilation with normal systolic function.

Despite quitting tobacco and marijuana use, giving away his pets, and taking a standard 2-week course of Ivermectin for Strongyloides patient's symptoms worsened requiring chronic prednisone. Repeat PFTs revealed worsening of lung function with FEV1 declining from 2.28 to 1.16 L in 7 months. Frequency of hospital admissions increased, and it was noted that his symptoms and peripheral eosinophilia improved with intravenous glucocorticoids but not with oral glucocorticoids. Due to the refractory nature of his symptoms despite intensive therapy and absence of other contributors

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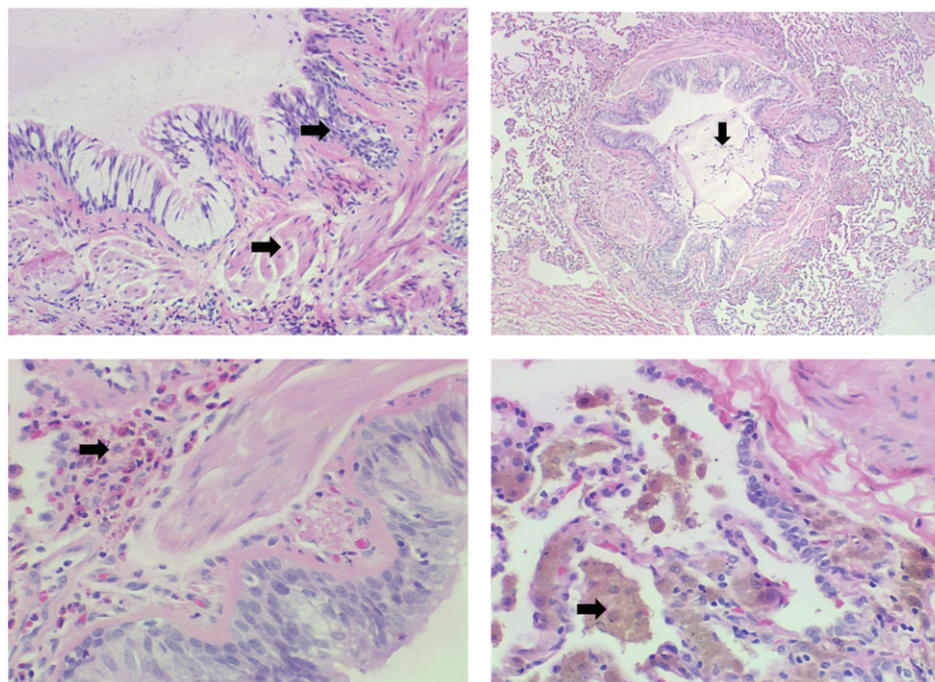


Figure 1. Lung biopsy showing features of asthma: mucous stasis, goblet cell hyperplasia, basement membrane thickening and smooth muscle hypertrophy with eosinophilic infiltrates and hemosiderin laden macrophages (H and E stain, 10 $\times$, 25 $\times$ and 100 $\times$ magnification).

based on clinical and serologic evaluation, he was taken for open lung biopsy, which showed dilated terminal bronchioles associated with mucous stasis, prominent goblet cell hyperplasia, basement membrane thickening and smooth muscle hypertrophy with variable infiltrate of eosinophils; highly suggestive of asthma (Figure 1). While hypereosinophilic syndromes and smoking related lung injury were in the differential diagnosis, the patient's age, ethnicity, eosinophilic airway inflammation without emphysematous changes on lung biopsy in spite of smoking cessation, and his response pattern to glucocorticoids, lead to the leading diagnosis of glucocorticoid-resistant asthma.

Glucocorticoid-resistant asthma: definition

In 2010, the international consensus statement from the Innovative Medicine Initiative (IMI) attempted to delineate "problematic", "difficult" and "severe refractory" asthma. Figure 2 illustrates the different subsets of asthma based on the definitions. The term "problematic severe asthma" includes patients with asthma and asthma-like symptoms that remain uncontrolled despite the prescription of high-intensity asthma treatment. This is a broad term and includes both "difficult" and "severe refractory asthma". "Difficult asthma" is defined as uncontrolled asthma despite the prescription of high intensity asthma treatment due to factors that contribute to poor or inadequate control (Table 1). "Severe refractory asthma" is reserved for patients with asthma for whom despite: (1) exclusion of alternative diagnoses, (2) treatment of comorbidities, (3) removal of known trigger factors (if possible) and (4) treatment adherence is confirmed, poor asthma control persists with frequent (>2) severe exacerbations per year on high intensity treatment or dependence on continuous systemic glucocorticoid that puts the patient at significant risk of serious adverse effects of treatment [1–3].

A proportion of the true "severe refractory asthma" patients who do not have adequate response to the standard treatment of glucocorticoids or require such high doses that they develop severe side effects are diagnosed with glucocorticoid-resistant asthma (SRA). Clinically it is defined as having FEV1 <75% of predicted with failure to improve by 15% after having an adequate dose and duration of glucocorticoid therapy (40 mg/day of prednisone for 2 weeks) [4].

The objective of this case presentation and targeted review is to summarize the clinical, molecular and diagnostic features of glucocorticoid-resistant asthma. We will also discuss some emerging concepts in the management of SRA.

Methods

Full-text papers and abstracts were identified on the basis of a literature search primarily in MEDLINE (1966 to June 2012) but also in the Cochrane Central Register of Controlled Trials database. The terms used for the electronic search by section were as follows:

- Epidemiology and diagnostic limitations: Severe asthma/or/refractory asthma/or/glucocorticoid-dependent asthma/AND/epidemiology/or/incidence/or/prevalence/or/diagnosis
- Mechanisms: Severe asthma/or/refractory asthma/or/glucocorticoid-dependent asthma/AND/mechanisms; glucocorticoids/or/glucocorticoids/AND/mechanisms; glucocorticoids/or glucocorticoids/AND/resistance/AND/asthma/or refractory asthma/or/severe asthma
- Emerging concepts: Severe asthma/or/refractory asthma/or/glucocorticoid-dependent asthma/AND/therapy/or/azathioprine/or/cyclosporin/or/TNF/or/etanercept/or/infliximab/or/gold/or/methotrexate/or/omalizumab/or/targeted therapy/or/interleukins/or/cytokines.

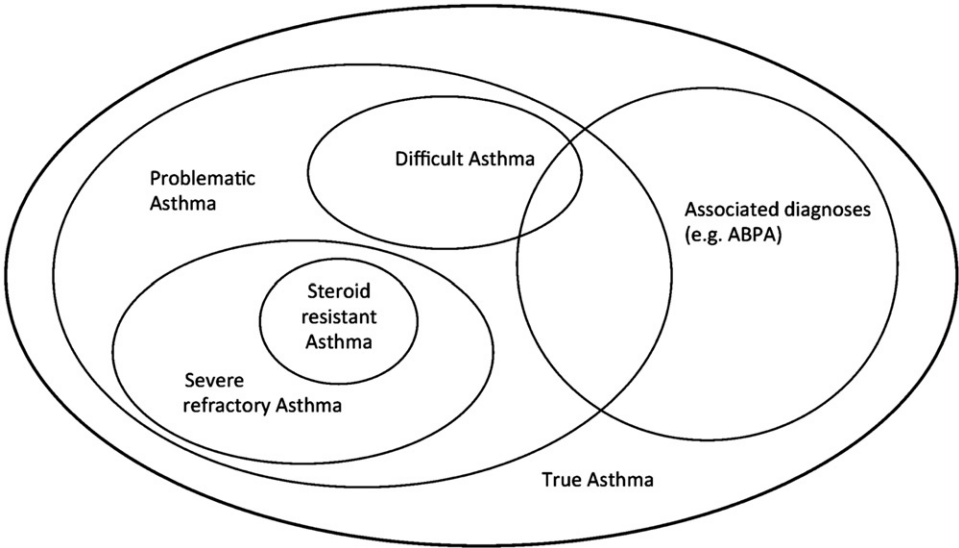


Figure 2. Venn diagram showing various subsets of asthma. Interpretation of definitions provided in the international consensus statement of the Innovative Medicine Initiative (IMI) [1,2].

Table 1. Factors that may contribute to poor or inadequate control of asthma symptoms [3,12].

Psychosocial
Poor compliance/adherence to therapy
Psychiatric diseases such as bipolar and schizophrenia
Inadequate medical facilities
Poor access to medical facilities
Co-morbidities
Obesity
Obstructive sleep apnea
Vocal cord dysfunction
Gastro-esophageal reflux disease
Rhino-sinusitis
Viral respiratory tract infections
Misdiagnosis
Medications
Inadequate treatment
Poor inhaler techniques
Environmental
Continued exposure to allergens such as pet dander, dust mites
Indoor/outdoor pollution such as cigarette smoke
Genetic factors

We limited our search to titles of human studies published in English. Randomized control trials, crossover trials, observation studies such as cohort, case–control, nested case–control trials, systematic reviews and book chapters were included in the search.

Results and discussion

Glucocorticoid-resistant asthma: epidemiology and diagnostic limitations

Over the past decade, the prevalence of asthma has increased from 7.3% to 8.4% in USA and in 2010 an estimated 25.7 million people carried this diagnosis [5]. Approximately 5–10% of these patients are reported to have severe or difficult to treat asthma [6]. This group alone accounts for 2 million emergency room visits and 500 000 hospitalizations per year [5]. The impact of asthma on health care is enormous with an estimated 50 billion dollars in incremental (asthma-

attributable) direct costs in 2007, much of which is applied to individuals with severe disease [7]. Due to this burden on health care, a tremendous amount of effort has been put in characterizing the group of patients with severe refractory asthma with reasonable success [8]. Female gender, obesity, smoking and poor socioeconomic status are some of the factors associated with severe asthma and poor response rate to treatment [9]. Puerto Rican Hispanics, not only have the highest prevalence of 16.6% in USA [10], but also have a 2- to 4-fold increased risk of mortality from asthma [11]. The Severe Asthma Research Program (SARP) has phenotyped severe asthmatics on the basis of clinical presentation, onset of symptoms and type of airway inflammatory cells. Patients with “early onset” severe asthma are more likely to have higher IgE levels, history of atopic dermatitis, reversible airway obstruction and air trapping compared to “late onset” severe asthmatics [12]. Based on the type of inflammatory cells in the bronchoalveolar lavage (BAL), induced sputum and endobronchial biopsies, eosinophilic predominant, neutrophilic predominant and pauci-inflammatory phenotypes have been identified. Distinct histopathological patterns found in these groups may account for the differences in treatment response. Patients with persistent eosinophilic inflammation are clinically worse with frequent exacerbations and poorer prognosis compared to the other phenotypes [12,13]. Asthma being a heterogeneous disease, it is hoped that phenotyping patients will give us a better understanding of the pathophysiological processes involved which in turn could individualize therapy and help identify new ones.

While the success in severe asthma research has been encouraging, it has only compounded the challenge of identifying the subgroup of patients with SRA. Recently American Thoracic Society released a clinical practice guideline acknowledging measurement of fractional nitric oxide in exhaled breath (FeNO) as a non-invasive, quantitative test to detect the presence of eosinophilic airway inflammation and possibly predict glucocorticoid responsiveness [14]. However, as there are no tests otherwise available

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to definitively diagnose SRA, it is considered a diagnosis of exclusion.

The following features of managing difficult asthma can contribute to delay in attributing disease severity to glucocorticoid refractoriness:

- (1) Asthma-like symptoms are non-specific and seen in patients with systemic diseases other than asthma such as hypereosinophilic syndromes, Churg Strauss Syndrome (currently also referred to as allergic granulomatosis and angiitis), congestive heart failure, sarcoidosis and cryptogenic organizing pneumonia. An open lung biopsy, which has minor but non-trivial morbidity, is needed for the diagnosis of a majority of these conditions [15].
- (2) Co-existence of asthma with vocal cord dysfunction, sinusitis and gastro-esophageal reflux disease is well documented. Treatment of these co-morbidities is often difficult as it requires patient commitment for additional treatment and behavioral modification [15].
- (3) Known and unknown genetic and environmental factors contribute to the persistence of asthma symptoms despite maximal therapy [15].
- (4) Glucocorticoid resistance may vary over time, as shown in a small study of severe asthmatics [16]. This could complicate the diagnostic work up for SRA.
- (5) Cases of proven glucocorticoid-resistant asthma on chronic prednisone that are refractory to the systemic adverse effects of glucocorticoids have been documented. This raises the question of localized pulmonary resistance versus generalized systemic resistance [17].

We therefore recommend that patients with spontaneous, frequent and severe exacerbations with no abatement of asthma symptoms or poor quality of life despite maximal standard therapy and progressive development of glucocorticoid-related side effects should raise the suspicion of SRA. This is particularly important as there is increasing evidence suggesting an under appreciation of the prevalence of SRA. A retrospective study of 164 patients suggested that SRA is quite common (25%) among adolescents with severe asthma evaluated at a national referral center [18]. The Gaining Optimal Asthma Control (GOAL) study also estimated that in a controlled environment inhaled or oral corticosteroid therapy is clinically effective in ~70% of the asthmatics in the general population [19]. Recognition of SRA is critical as the management may vary with potential discontinuation of glucocorticoids and β -Agonists (as discussed below – “Mechanisms of Glucocorticoid Resistance”) in order to prevent further adverse effects.

Mechanism of action of glucocorticoids

Glucocorticoids (GC) exert their pro and anti-inflammatory effects by both gene induction and gene repression (Figure 3). The process begins with the molecules binding to free intracellular glucocorticoid receptors (GR). Two GR isomers (α and β) have been described. GR β is known to have a dominant negative effect on GR α through the formation of GR α /GR β heterodimers. Recent evidence suggests that there may be up to 8 different isomers each varying in their affinity to glucocorticoid molecules and transcriptional regulation [20]. This GC-GR molecule causes dissociation

of molecular chaperones such as heat shock proteins (hsp 70 and hsp 90), which in turn allows the ligand to bind to the complex to activate it. Specific importins then transport the activated complex into the nucleus. The ligand directs two activated GRs (homodimers) to specific Glucocorticoid Response Elements (GRE) on DNA [21].

Gene induction occurs with recruitment and activation of several transcriptional factors, coactivator proteins including Glucocorticoid Receptor Coactivator-1 (SRC-1), cyclic AMP response element-binding protein (CREB) and CREB binding protein (CBP) which constitutes the transcriptional complex that initiates gene transcription [21]. Certain chromatin modifiers such as SWItch/Sucrose NonFermentable (SWI/SNF) and RNA Polymerase II also participate by facilitating transcription of mRNAs that encode for several pro-inflammatory molecules such as SLP-1 (Secretory leucocyte protease inhibitor), MKP-1 (mitogen-activated protein kinase phosphatase 1), CD163 and B2 Adrenoceptor [21] via post-translational core histone enzymatic modification such as acetylation, methylation, phosphorylation or ubiquitination [22].

The primary mechanism of gene repression appears to be due to suppression of transcription factors such as Nuclear factor- κ B (NF- κ B) and Activator Protein-1 (AP-1). NF- κ B, a cytoplasmic protein, is activated by an array of extracellular stimuli including interleukins, cytokines, viruses and lipopolysaccharide. Activated NF- κ B recruits the co-factors p65/p50 heterodimers, translocates to the nucleus and binds to NF- κ B response elements on DNA and initiates transcription of several pro-inflammatory genes including cytokines, chemokines, cell-adhesion molecules, complement factors and cyclooxygenase 2. These pro-inflammatory factors are repressed by GR-GC complex, eliciting transcription of NF- κ B and AP-1 inhibitors such as I κ B α and glucocorticoid inducible leucine zipper (GLIP). GR-GC complex can also directly suppress NF- κ B and cofactors such as p65 and inactivate RNA Polymerase II by dephosphorylation [20,21]. Gene repression is a complicated process and several other mechanisms have been described which is beyond the scope of this review.

Mechanism of glucocorticoid resistance

Several potential mechanisms have been identified that contribute to glucocorticoid resistance. These can be broadly categorized into Extrinsic and Intrinsic factors as shown in Table 2. As, multiple mechanisms can co-exist in a patient, defining the contribution of these different mechanisms is an area of active investigation.

Intrinsic factors

Leung et al. showed that glucocorticoid-resistant asthmatics have a higher concentration of GR β instead of GR α in their peripheral circulating cells. Cytokine induced alternate splicing of the pre-messenger RNA likely results in production of these GR β , which negates the proinflammatory activity of glucocorticoids [23].

Sher et al. showed that a significant amount of glucocorticoid resistance is due to cytokine (IL-2 and IL-4) induced reduction in GR binding affinity in addition to reduction in

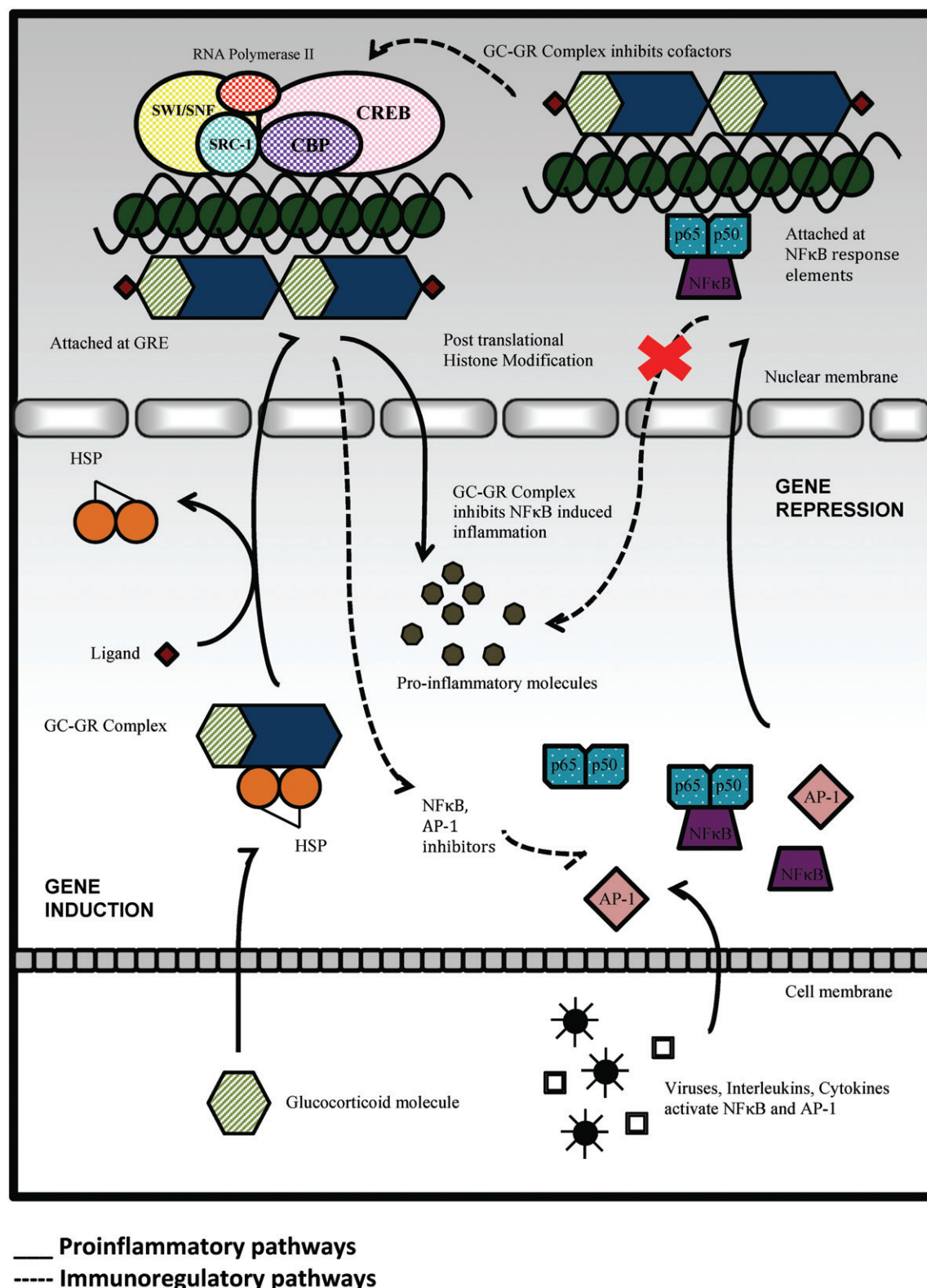


Figure 3. Mechanism of glucocorticoids at the molecular level. GC: glucocorticoid molecule, GR: glucocorticoid receptor, NF-κB: nuclear factor-κB, AP-1: activated protein-1, HSP: heat shock proteins, p65 and p50: Cofactors, GRE: glucocorticoid response elements on the DNA, SRC-1: steroid receptor coactivator-1, CREB: cyclic AMP response element-binding protein, CBP: CREB binding protein, SWI/SNF: SWItch/Sucrose NonFermentable.

number of GRs. T-cells with glucocorticoid resistance showed normal activity when incubated with glucocorticoids for 48 h in culture media. However cells incubated in IL-2 and IL-4 rich culture media continued to show the defect [24]. Irusen et al. also showed that cytokines IL-2 and IL-4 can cause activation

of p38 mitogen-activated protein kinases (p38MAPK), which in turn phosphorylates glucocorticoid receptors, reducing the ligand binding affinity and ultimately causing glucocorticoid resistance. Ligand binding affinity was normalized with the addition of a p38MAPK inhibitor [25,26]. Translocation of

Table 2. Mechanisms of glucocorticoid resistance.

Intrinsic factors
Cytokine induced suppression of glucocorticoid activity
Reduction in number of glucocorticoid receptors
Differential action and predominance of glucocorticoid receptor β
Altered affinity of ligand to the glucocorticoid receptor
Impaired nuclear translocation of glucocorticoid receptors
Reduced histone deacetylase activity over expression of AP-1, NF- κ B
Predominant neutrophilic inflammation
Extrinsic factors
Interactions between smoking and glucocorticoid action
Interaction between β agonists and glucocorticoid receptors
Inflammation in small airways
Severe inflammation eventually leading to remodeling

AP-1: activated protein-1, NF- κ B: nuclear factor- κ B.

phosphorylated GC into the nucleus may be impaired due to abnormal interactions with Importin α [25,27]. Inflammatory cytokines such as tumor necrosis factor α (TNF- α) can cause over expression of AP-1 and NF- κ B, and cause alterations in GR-GRE binding and cause resistance to glucocorticoid action [28].

Cosio et al. found a decreased histone acetylase activity in alveolar macrophages and polymorphonuclear leukocytes from patients with severe asthma compared to milder asthma. Post-translational histone acetylation is vital for production of several pro-inflammatory molecules especially MKP-1, which inactivates p38MAPK. This is likely another mechanism of glucocorticoid resistance [29].

Wenzel et al. [30] found that patients with severe asthma had increased concentrations of neutrophils, and a high molecular weight, pro-inflammatory isoform of matrix metalloproteinase-9 (MMP-9) in their BAL fluid [31]. Native inhibitors of MMP-9 (including TIMPs) and glucocorticoid poorly inhibit this particular isoform of MMP-9, contributing to resistance [32].

Extrinsic factors

In spite of clear evidence associating tobacco smoking with increased severity of asthma and accelerated decline in lung function [33,34], ~25% of asthmatics in USA continue to smoke [35]. The role of tobacco smoke exposure in glucocorticoid resistance was first established by Chalmers and Pedersen [36,37] when they showed that asthmatic smokers treated with glucocorticoid inhalers had less improvement in symptoms and lung function than asthmatic non-smokers. Several hypotheses have been suggested to explain this finding. Significant impairment in muco-ciliary function in smokers causes excess mucous deposition along the airways. This barrier, along with inflammation-induced airway permeability in asthmatics reduces the effective concentration of the glucocorticoid drug particles within the inflammation in the airways [38,39]. BAL fluid of smoking asthmatics has an increased proportion of neutrophils and CD8+ lymphocytes and a relative decrease in the number of eosinophils as compared to non-smoking asthmatics. This alteration in inflammatory pattern likely contributes to glucocorticoid resistance as eosinophils are considered as the primary glucocorticoid-responsive cells in asthmatic airway inflammation [39,40]. In addition, smoking has been linked to several previously described intrinsic factors that

cause glucocorticoid resistance such as reduction in the number of GRs, increasing the dominance of glucocorticoid receptor β , altering ligand affinity, impaired nuclear translocation, reduced histone deacetylase activity and over expression of NF- κ B and AP-1 [35]. Given the multitude of ways in which cigarette smoking can induce glucocorticoid resistance, it appears to be the single most important factor contributing to the same.

Autopsy studies have shown structural changes in both small and large airways in fatal asthma cases compared to patients who died from causes other than asthma [41]. This finding has been validated in surgical lung specimens and transbronchial biopsies as well [42,43]. While introduction of hydrofluoroalkane propellants and smaller drug particles in metered-dose inhalers has improved delivery of glucocorticoids into the lungs, it is still not entirely clear if sufficient quantities are reaching the small airways [44]. This could explain apparent glucocorticoid resistance and lack of improvement in symptoms in some asthmatic patients.

Goleva et al. showed low levels of tissue inhibitor of metalloproteinase (TIMP-1) in the BALs of SRA patients. A rise in the MMP-9/TIMP-1 ratio promotes proteolytic activity in airways contributing to chronic airway remodeling [45]. Thus glucocorticoid resistance can worsen respiratory symptoms by causing irreversible airway damage, which is unresponsive to bronchodilators or inhaled glucocorticoid.

Excess inhaled β 2-Agonist usage has been strongly associated with asthma mortality in the past [46]. Thomas et al. [47] showed that increasing inhaled corticosteroid dose lead to reduced asthma exacerbations and hospitalizations compared to step up therapy with long acting β 2-Agonists alone. This may be due to alteration in bronchial glucocorticoid responsiveness by β 2-Agonists, which by activating transcription factors such as CREB can inhibit GR-GC interaction with corresponding GRE sites on the DNA [17,48]. The relationship between glucocorticoids and Long-acting β 2-Agonists (LABA) appears to be complicated, as Rider et al. [49] also showed that LABAs could potentially negate the inflammatory cytokine induced suppression of GRE dependent transcription when combined with glucocorticoids. Further research in this area is therefore warranted.

Current and emerging concepts in management of glucocorticoid-resistant asthma

Based on current guidelines, glucocorticoids are accepted as first-line treatment for persistent asthma requiring controller medication. Glucocorticoid-resistant asthmatics can respond to glucocorticoids but often at higher dosage than glucocorticoid-responsive patients, often leading to treatment-limiting adverse effects. Advanced drug delivery systems such as ultrafine hydrofluoroalkane (HFA)-134a propelled pressurized metered-dose inhalers allow for improved inhaled glucocorticoid drug delivery to the smaller airways [50]. Ciclesonide is a novel inhaled corticosteroid with unique pharmacokinetics that is currently being studied for its use in SRA. It is a prodrug and is converted to its active metabolite desisobutyl-ciclesonide only in the airways. It has been shown to have fewer local and systemic side effects such as thrush, dysphonia and osteoporosis, cataracts, growth

Table 3. Alternate and emerging drugs for treatment of glucocorticoid-resistant asthma.

Glucocorticoids: Inhaled ciclesonide, unique pharmacokinetics, prodrug, metabolized in the airway epithelial cells, minimal systemic toxicity [51]
Glucocorticoid sparing agents: Usage limited by side effects
Cyclosporine [52]
Gold [52]
Methotrexate [53,54]
Anti-Ig E: Omalizumab, reduces frequency of asthma exacerbations and emergency room visits [55,56]
Cytokines and cytokine inhibitors: Modulation of cytokines playing an important role in SRA and inflammation
TNF- α [57,58]
Interferon α [60]
Mutated anti-IL-4 blocking IL-4R α subunit (Pitrakinra) [63]
Anti-IL-5 (mepolizumab) [61,62]
Anti-IL-9 [57]
Anti-IL-13 (lebrikizumab) [65]
Intravenous immunoglobulin: Reduces glucocorticoid requirements but does not improve lung function [59]
Chemokine receptor antagonists [21,66]
CXCR1/2 directed against neutrophils
CCR3 directed against eosinophils
CRTH2 directed against eosinophils and Th2 cells
Miscellaneous [21,67]
MAPK inhibitors
AP-1 inhibitors
NF- κ B inhibitors
IL-10 secreting T regulatory cell inducers

TNF: tumor necrosis factor, IL: interleukin, AP-1: activated protein-1, NF- κ B: nuclear factor- κ B, MAPK: mitogen-activated protein kinases.

reduction and adrenal suppression, respectively [51] (Table 3).

Several trials have studied the efficacy of cortico-glucocorticoid-sparing drugs in severe asthmatics. Hydroxychloroquine, Colchicine, Azathioprine and Troleandomycin have failed to show any benefit. Cyclosporine and gold showed some benefit however their usage has been limited by side effects [52]. Two randomized placebo-controlled studies in glucocorticoid dependent asthmatics have shown methotrexate to have a significant glucocorticoid sparing effect with patients having fewer exacerbations and acceptable side effects [53,54]. As patients vary in their response to drugs, usage of methotrexate warrants close monitoring of side effects and continual evaluation of its benefit.

Omalizumab, anti-immunoglobulin IgE monoclonal antibody, is one of the newer drugs to be approved for usage in severe persistent asthma patients with specific allergen sensitivity to perennial aeroallergen(s). A meta-analysis of 7 studies showed that omalizumab significantly reduced the number of asthma exacerbations and emergency room visits by 38% and 47%, respectively, in severe persistent asthmatics [55]. Domingo et al. [56] recently showed that it could even have some corticoglucocorticoid sparing effect in this group of individuals. These results however have not been validated with large randomized trials.

Tumor necrosis factor alpha (TNF- α) is involved in several pathways of asthma pathophysiology including inflammatory cell recruitment, airway hyper-responsiveness and airway remodeling. Inhibition of TNF- α would therefore interrupt multiple mechanisms similar to glucocorticoids [57]. Initial studies involving infliximab, etanercept, adalimumab and golimumab have shown conflicting results in respiratory function improvement, exacerbations and hospital admissions, while raising a concern over the safety of their usage [58].

Several small studies in glucocorticoid-dependant asthmatic patients showed that adjunctive administration of Intravenous Immunoglobulin (IVIG) might have a glucocorticoid sparing effect and reduce hospital admissions without improving lung function. These results, however, were not validated by randomized control trials and currently it is not recommended in the management of severe asthma [59].

Modulation of cytokines, which play an integral role in glucocorticoid resistance, is emerging as the key to treatment of SRA. Several newer drugs are currently in trials and show promise. A 10 patient study by Simon et al. showed dramatic improvement of asthma symptoms with Interferon α . This improvement has been attributed to establishment of a correct Th1/Th2 balance and the induction of the anti-inflammatory IL-10 gene [60]. Mepolizumab, an anti-IL-5 molecule that inhibits eosinophilic inflammation, in a randomized controlled study in patients with severe glucocorticoid-unresponsive eosinophilic asthma showed significant decrease in severe exacerbations with a corticoglucocorticoid sparing effect [61,62]. Pitrakinra, a mutated IL-4 receptor antagonist, has shown the ability to block IL-4R α subunit thereby inhibiting the inflammatory action of IL-4 and IL-13 in in-vitro studies [63]. Similarly, anti-IL-9 and anti-IL-13 (lebrikizumab) are currently being studied in phase II and III trials and being developed for the treatment of severe persistent asthma [57]. Periostin, induced by IL-13 in bronchial epithelial cells and implicated in sub-epithelial fibrosis, has shown potential to be a biomarker for guiding asthma management, especially in suitability of IL-13 blockade [64]. A recently published randomized double-blinded placebo controlled study showed that lebrikizumab improves baseline FEV1 significantly more in severe asthmatics with higher serum periostin levels compared to patients with lower levels [65].

There has been increasing interest in chemokine receptor antagonists, such as those directed against neutrophils

(CXCR1/2), eosinophils (CCR3, CRTH2) and Th2 cells (CRTH2) to reduce airway inflammation and thereby airway remodeling [21,66]. Several therapies such as MAPK, AP-1 and NF- κ B inhibitors, IL-10 secreting T regulatory cell inducers, are also being developed for the treatment of glucocorticoid-resistant asthma [21,67].

Conclusions

The challenges in making a diagnosis of glucocorticoid-resistant asthma may contribute to underestimating its prevalence and impact on patient care. These patients are usually included in the group of asthmatics with severe refractory asthma, a significant percentage of who are on oral glucocorticoid. In glucocorticoid-resistant asthmatics, glucocorticoid make little difference in the inflammatory processes in the hyperactive airways and only lead to serious systemic adverse effects of the same. It is therefore important to consider this diagnosis in patients with persistent symptoms in spite of optimal high intensity treatment. Asthma is a heterogeneous, complicated disease and considerable progress has been made in identifying distinct phenotypes and mechanisms of glucocorticoid resistance. The future of new drug development in management of asthma is therefore promising and it is our hope that by targeting specific receptors and molecules involved in the pathophysiological processes, an alternative or corticoglucocorticoid-sparing agent will be available.

Author contributions

Dr. Divya Reddy takes full responsibility for the content of the manuscript.

Dr. Frederic Little has made substantial contributions to concept, design, oversight and drafting of the manuscript.

Both Drs. Reddy and Little provide approval of the submitted version for the purpose of publication.

All the authors who have contributed significantly to the manuscript have been enlisted.

Declaration of interest

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