Chapter

Inhaled Corticosteroids: Benefits and Risks

Hanaa Shafiek

Abstract

Airway diseases, mainly asthma and chronic obstructive pulmonary diseases (COPD), are frequently treated with inhaled corticosteroids (ICS). ICS are considered as the cornerstone of asthma management, however, in COPD the picture is different and ICS are indicated in special circumstances. The benefits of ICS are well documented in controlling disease symptomatology. But, still there are side effects of using ICS, especially the risk of pneumonia and bacterial colonization of the airways. In this chapter, I will explore the change in the use of ICS in asthma and COPD, the indications of ICS, the benefits of ICS and its drawbacks, and how we could modify our practice in order to avoid the side effects of ICS.

Keywords: airway inflammation, asthma, chronic obstructive pulmonary disease, inhaled corticosteroids types, complications

1. Introduction

Systemic Corticosteroids (SC) are synthetic analogs of the naturally occurring steroid hormones produced by the cortex of the adrenal gland that is administrated by oral or injectable routes. The SC hormones have glucocorticoid and mineralocorticoid properties with varying degrees. The most important is the glucocorticoids which are predominantly involved in metabolism and have immunosuppressive, anti-inflammatory, and vasoconstrictive effects. SC is widely prescribed in medicine including respiratory medicine as in airway diseases, sarcoidosis, interstitial lung diseases, pulmonary eosinophilic diseases and others [1]. Since the 1950s, SC has been proven to be an effective therapy for persistent asthma [2, 3], however, they have various side effects.

The first pressurized metered-dose inhaler (pMDI) as a bronchodilator for asthma, was introduced in 1956 namely non-selective beta-2-agonists isoprenaline and adrenaline that was associated with rapid relief of asthma symptoms [4]. In the 1960s, there was an epidemic of asthma deaths in Britain thought to be caused by the high use of inhaled bronchodilators [5, 6] and so delayed in seeking medical advice, even if not proved, resulted in suspending the use of inhaled isoprenaline that was replaced later by salbutamol, the selective short-acting beta-2-agonist, and increase the use of SC [4]. By the early 1970s, inhaled beclomethasone dipropionate started to develop as 1st inhaled corticosteroid (ICS) and placebo-controlled studies confirmed

the value of ICS therapy in asthma [7–9]. Afterward, ICS became the cornerstone of asthma management and various substitutes and forms were introduced in pulmonary medicine.

2. Mechanisms of ICS

ICS have glucocorticoids effects that suppress the ongoing inflammatory process through gene transcription mechanisms [10, 11]. Glucocorticoids act by binding to glucocorticoid receptors (GRs) in the cytoplasm resulting in their activation and translocation in the nucleus to produce their anti-inflammatory effects through various molecular effects.

Corticosteroids switch off various activated inflammatory genes that encode cytokines, chemokines, inflammatory enzymes and proteins as the anti-inflammatory proteins secretory leukoprotease inhibitor, and mitogen-activated protein kinase phosphatase-1 (MKP-1) which inhibits MAP kinase pathways [12, 13]. The nuclear GR interacts with coactivator molecules as CREB-binding protein resulting in the activation of proinflammatory transcription factors, nuclear factor-κB (NF-κB) and activator protein-1, in the airways and so reduces histone acetyltransferase activity [10, 14]. Also, activated GR recruits histone deacetylase-2 (HDAC2) to the activated inflammatory gene complex which reverses histone acetylation resulting in the suppression of all nuclear-activated inflammatory genes [15].

Further, ICS increase the gene transcription encoding β_2-receptors, resulting in increased expression of β_2-receptors on the cell surface of the airways [16, 17] which protect against the β_2-receptors tolerance after long-term use. Moreover, ICS may enhance the β_2-receptors coupling to G-proteins that promote β_2-agonist effects and reverse its uncoupling in response to some inflammatory mediators as interleukin-1β through G-protein coupled receptor kinase stimulation [18]. β_2-Agonists also increase the translocation of GR to the nucleus after its activation thus enhancing corticosteroids' anti-inflammatory effects through synchronized interactions [19, 20].

On the other hand, ICS have cellular effects by reducing the numbers of various inflammatory cells mainly eosinophils, mast cell, T-lymphocytes and dendritic cells through either inhibiting the recruitment of these cells in the airways or their survival [21]. Moreover, ICS restore the airway epithelial cell integrity thus inhibiting the transcription of inflammatory genes thus suppressing mucosal inflammation and eosinophilic recruitment into the airways that is associated with airway hyperreactivity [22, 23].

3. Types of ICS

Nowadays, there are eight different ICS molecules available. These are: beclomethasone dipropionate (BMD) which is the first known ICS, budesonide (BUD), ciclesonide (CC), flunisolide, fluticasone propionate (FP), fluticasone furoate (FF), triamcinolone acetonide (TA) and mometasone furoate (MF). The difference between these molecules is lipophilia with greater GR affinity and longer duration of action; as fluticasone furoate is the most lipophilic (i.e., high potency) and beclomethasone dipropionate the lowest [24].

The various ICS have also different pulmonary bioavailability (i.e., within the airways) and oral bioavailability (i.e., in the systemic circulation) [25]. Negligible oral bioavailability due to high first-pass metabolism is found for FF, FP, MF and CC and so fewer side effects [24]. Three factors are expected to affect the efficacy of an ICS: the potency (the lower inhaled dose occupied the same number of GRs), the delivered dose (the device efficiency) and airway residency duration. FF, FP, MF and CC have greater residency duration in the airways which allows one daily dose; however, twice daily is considered better [26, 27]. **Figure 1** shows the relationship between ICS dose and its affinity to GR, whereas FF has both the higher GR affinity with the lowest dose compared to triamcinolone acetonide and flunisolide [28].

ICS could be delivered by pressurized metered-dose (pMDI) inhaler, dry-powder (DPI) inhaler and nebulization which are expected to influence the ICS dose. The great difference between the devices is the size of respirable particles emitted that are generally <5 μm [29]. DPI and pMDI (with drugs dissolved in chlorofluoro-carbon "CFC") usually emit particles between 3 and 5 μm, however, pMDI with drugs dissolved in hydrofluoroalkane (HFA) emits ultrafine particles of about 1 μm which allow high delivery of ICS in low-mid doses with high lung deposition. **Table 1** compares the low-, mid- and high-doses of ICS of different molecules and devices. Regarding fluticasone, according to the manufacturer's summary of Product Characteristics, FF 100 μg once daily is approximately equivalent to FP 250 μg twice daily [35]. The devices nowadays are many, especially those designed to deliver the DPI either pre-metered or device-metered (**Figure 2**) [36].

In addition, the GINA guidelines has published equivalent doses of different ICS molecules (**Table 2**) [37].

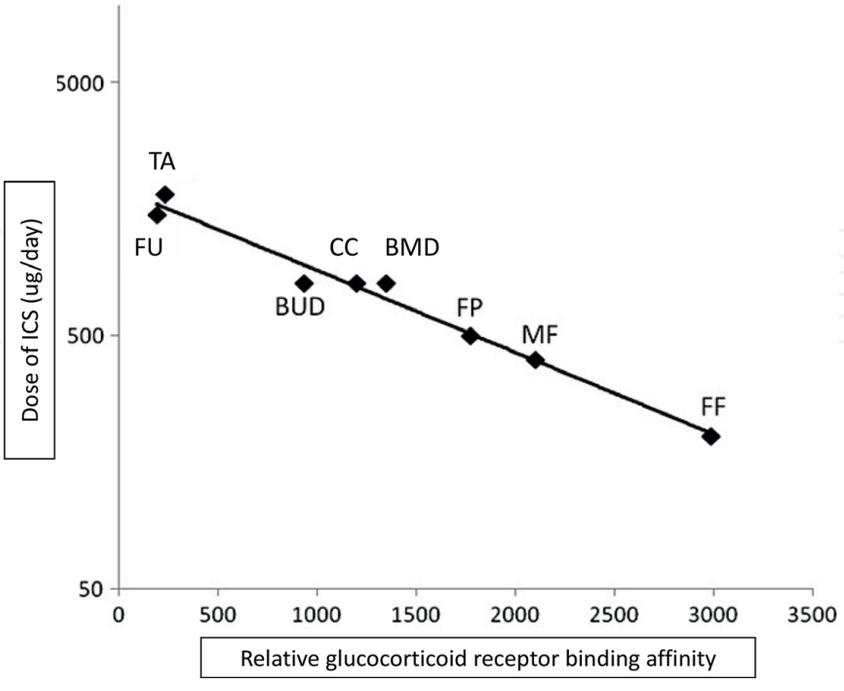

Figure 1.
Relationship between the dose of ICS and relative glucocorticoid receptor binding affinity [28].

ICS molecule	Age	Low-dose	Mid-dose	High-dose
Beclomethasone HFA/pMDI	0–4 years	NA	NA	NA
	5–11 years	80–160 μg	160–320 μg	>320 μg
	≥12 years	80–240 μg	240–480 μg	>480 μg
Budesonide DPI	0–4 years	NA	NA	NA
	5–11 years	180–400 μg	400–800 μg	>800 μg
	≥12 years	180–600 μg	600–1200 μg	>1200 μg
Fluticasone HFA/pMDI	0–4 years	176 μg	176–352 μg	352 μg
	5–11 years	88–176 μg	176–352 μg	>352 μg
	≥12 years	88–264 μg	264–440 μg	>440 μg
Fluticasone DPI	0–4 years	NA	NA	NA
	5–11 years	100–200 μg	200–400 μg	>400 μg
	≥12 years	100–300 μg	300–500 μg	>500 μg
Mometasone DPI	0–4 years	NA	NA	NA
	5–11 years	NA	NA	NA
	≥12 years	200 μg	400 μg	>400 μg
Budesonide nebulized (solution inhalation)	0–4 years	0.25–0.5 mg	0.5–1 mg	>1 mg
	5–11 years	0.5 mg	1 mg	2 mg
	≥12 years	NA	NA	NA

**All doses are per day.*

Table 1.
Comparison between ICS molecules classified by doses [30–34].*

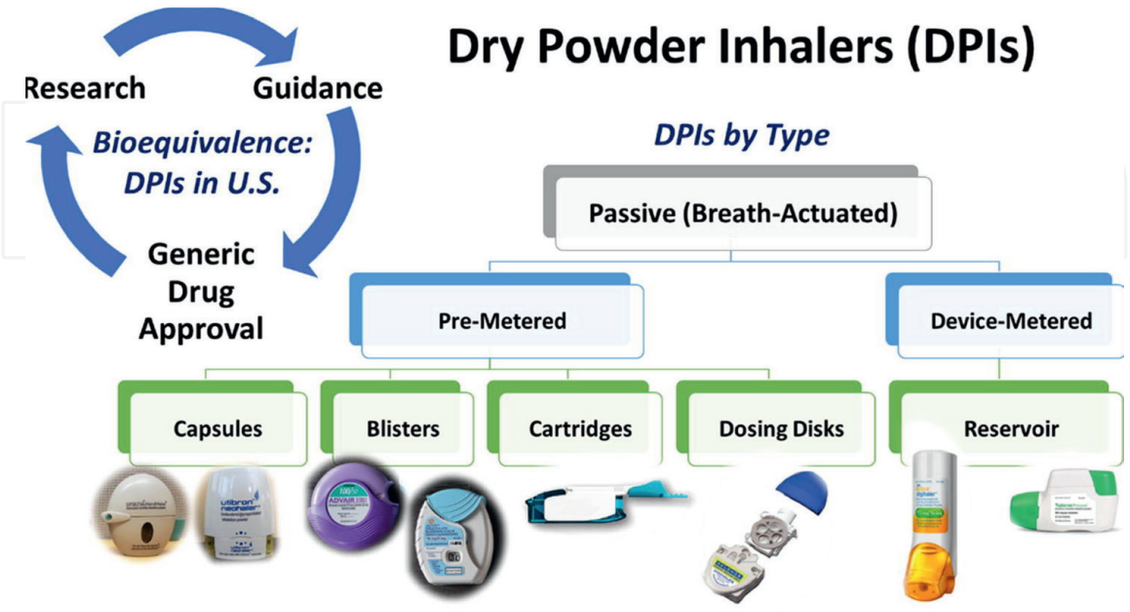

Figure 2.
Classifications of drug powder inhalers (DPI) [36].

ICS molecule	Age	Low-dose	Mid-dose	High-dose
Beclomethasone HFA/ pMDI	5–11 years	100–200 μg	>200–400 μg	> 400 μg
	≥12 years	200–500 μg	> 500–1000 μg	>1000 μg
Budesonide (DPI, pMDI, standard particle or HFA)	5–11 years	50–100 μg	>100–200 μg	>200 μg
	≥12 years	200–400 μg	>400–800 μg	>800 μg
Fluticasone furoate DPI	5–11 years	50 μg		NA
	≥12 years	100 μg		200 μg
Fluticasone propionate (DPI, pMDI, standard particle or HFA)	5–11 years	50–100 μg	100–200 μg	>200 μg
	≥12 years	100–250 μg	250–500 μg	>500 μg
Mometasone (pMDI, standard particle or HFA)	5–11 years	100	200	5–11 years
	≥12 years	200–400 μg		>400 μg
Ciclosonide pMDI /HFA	5–11 years	80	>80–160	>160
	≥12 years	80–160	>160–320	>320

Table 2.
Comparison between ICS molecules classified by doses as published in GINA guidelines.

4. Clinical uses and benefits of ICS

4.1 Asthma

ICS are considered as the cornerstone treatment for the management of asthma in all ages. ICS are the first line of therapy for persistent asthma with a starting low-dose that to be increased according to the level of control of the disease including the addition of other types of inhalers such as long-acting- β_2-agonist (LABA) and/or long-acting muscarinic antagonists (LAMA) in a step-wise approach [37]. In addition, in the latest GINA guidelines [37], low-dose ICS in combination with formoterol (a LABA inhaler) was approved as a reliever instead of short-acting β_2-agonist (SABA) as salbutamol that was associated with a decrease risk of severe exacerbations and is called the anti-inflammatory reliever.

Moreover, it is recommended the addition of low-dose ICS in the management of mild asthma. Juniper et al. showed that the use of low-dose ICS in mild asthma was associated with less symptoms and improvement of lung function up to being asymptomatic over several months of therapy [38]. Further, Pauwels et al. reported a reduction in asthma exacerbations among mild asthmatics treated with low-dose ICS [39]. Recent GINA guidelines recommend the use of low-dose ICS or low-dose ICS-formoterol as a reliever for mild asthma to decrease the risk of severe asthma exacerbation based on various studies [40–42]. Medium to high dose ICS are recommended for persistent asthma according to the step-wise approach of GINA guidelines [37]. ICS are also related to improvement in lung function in asthmatic children and adults [43, 44] owing to the switch-off of the chronic inflammatory process by ICS in asthma. Further, many studies showed that regular ICS use provides significant protection and reduces the risk of mortality, severe exacerbation and hospitalization of asthma population [39, 45, 46].

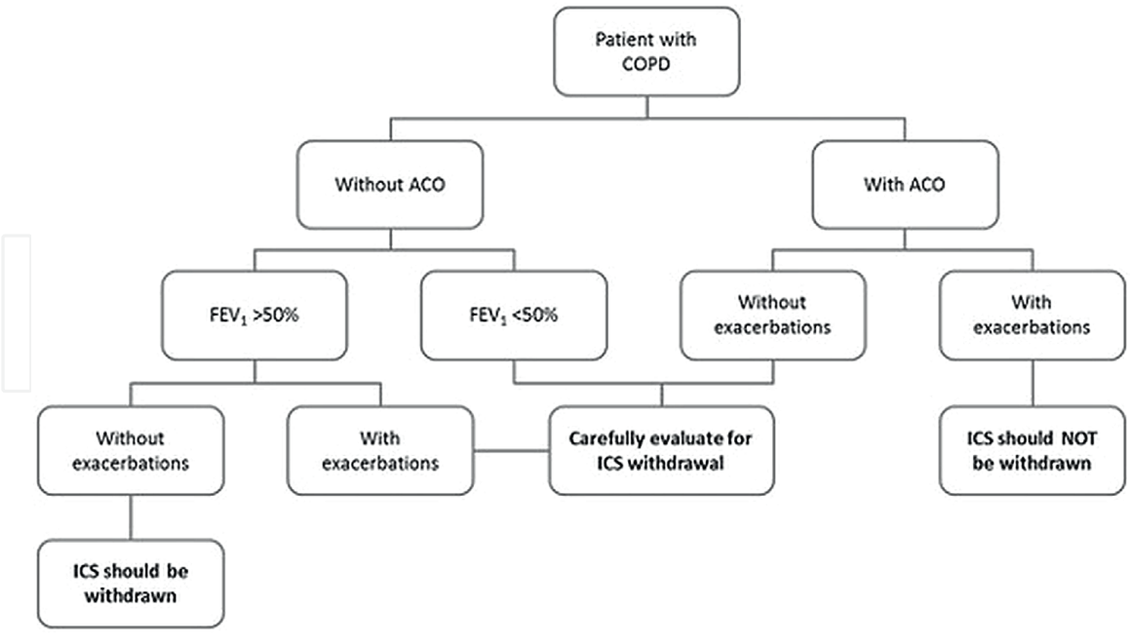

Figure 3.
Algorithm for ICS withdrawal in COPD [54].

4.2 Chronic obstructive pulmonary disease (COPD)

The use of ICS is controversial in COPD medications. The response to ICS in COPD patients is less than asthma population [47] which reflects the resistance of airway inflammation to ICS secondary to the reduction of HDAC2 [48, 49]. According to Global Initiative Lung Disease (GOLD) guidelines of COPD [50], ICS are indicated in frequent COPD exacerbator phenotype (i.e., those who had ≥2 exacerbations/year required OCS or ≥ 1 exacerbation need hospitalization) or COPD patients with blood eosinophilia ≥300 cells/μL [51]. Also, the Spanish guidelines of COPD, recommended the use of ICS in asthma-COPD overlap (ACO) who are patients with criteria of asthma and COPD with blood eosinophil counts >300 cells/μL and/or a post-bronchodilator response of >400 mL and 15% in FEV_1 [52]. A meta-analysis of important studies in COPD reported that ICS withdrawal did not result in a significant increase in COPD exacerbations risk [53]. Miravitlles et al. proposed an algorithm for the withdrawal of ICS in COPD patients based on FEV_1% predicted and exacerbation history [54]. **Figure 3** summarizes this algorithm [54].

5. Risks and complications of ICS

5.1 Local effects

ICS are associated with some local side effects, despite being not serious but could be associated with discontinuation of therapy. Hoarseness of the voice or dysphonia is the most common local side effect that occurs in about 50% of ICS users. It is a reversible side effect of drug withdrawal that is attributed to myopathy of laryngeal muscles [55]. Oropharyngeal candidiasis is the second most common side effect, despite being more in the elderly population, a percentage of ICS users complaint of it

which is related to poor inhalation technique and high doses of ICS. The use of spacers is associated with decreasing these side effects [37, 56].

Importantly, ICS are associated with an increased risk of pneumonia. Patients with COPD, older patients, active smokers, low body mass index <25 kg/m^2, patients with a history of exacerbations or pneumonia, and/or severe airflow limitation are associated with a higher risk of pneumonia on ICS use [57, 58]. In a meta-analysis, both inhaled fluticasone and budesonide were associated with a significant risk of pneumonia [59] that could be related to the use of a high dose of ICS alone or in-combination with bronchodilator [60]. Further, ICS use was associated with a specific bacterial infection in a subset of the severe COPD population. Shafiek et al. [61] found that ICS dose could be associated with *Pseudomonas aeruginosa* infection in the severe COPD population. This could be explained on the basis of impaired recognition of *P. aeruginosa* and activity of alveolar macrophages secondary to altered expression of Toll-like receptor 2 and various cytokine production in COPD patients receiving ICS [62]. On the other hand, O'Byrne et al. found that budesonide, as an ICS, was not associated with increased risk of pneumonia in asthmatic patients [63]. However, Qian et al. found that ICS use is associated with increased risk of pneumonia in asthma population with a risk of 1.44/1000 asthmatics/year [64].

A recent meta-analysis showed that ICS in high doses of fluticasone is associated with an increased risk of non-tuberculous mycobacteria in chronic respiratory diseases, and also may be associated with tuberculosis, especially in COPD patients [65].

5.2 Systemic effects

The use of ICS is less associated with systemic side effects compared to OCS. However, long-term ICS use is associated with an increased risk of bone fractures in patients with COPD which was reported to be up to 27% in a meta-analysis of various RCTs and observational studies with fluticasone or budesonide therapy [66]. Although bone density is less in patients taking high-dose of ICS, interpretation is confounded by the fact that these patients are also taking intermittent courses of OCS [21]. Further, osteoporosis is strongly correlated to COPD due to various lifestyle risk factors such as poor physical inactivity and smoking, vitamin D deficiency and COPD-associated inflammation [67].

Hypothalamic–pituitary–adrenal axis suppression is associated mainly with OCS for weeks even with short courses, but with ICS the results of the studies are inconsistent as often the patients have also been taking courses of OCS [68]. Increased risk of new-onset diabetes or diabetes progression has been reported in ICS users which was about 34% and is more among high doses ICS users and COPD [69]. Further, cataracts [70] and glaucoma [71] have been reported as side effects of high doses of ICS.

6. Conclusions

The introduction of ICS in respiratory medicine is crucial and modifies the management of diseases. ICS are good anti-inflammatory medication. ICS can effectively replace OCS in the control of chronic obstructive respiratory diseases, especially asthma. However, ICS has still side effects, especially in high doses; despite being less than OCS, it is associated with some morbidity that should be well controlled and managed.

Conflict of interest

I declare that I have no conflicts in relation to the current work.

Author details

Hanaa Shafiek
Alexandria Faculty of Medicine, Alexandria University, Alexandria, Egypt

*Address all correspondence to: whitecoat.med@gmail.com

References

[1] Sethi GR, Singhal KK. Pulmonary diseases and corticosteroids. Indian Journal of Pediatrics. 2008;**75**(10):1045-1056. Epub 2008/11/22. DOI: 10.1007/s12098-008-0209-0

[2] Carryer HM, Koelsche GA, Prickman LE, Maytum CK, Lake CF, Williams HL. The effect of cortisone of bronchial asthma and hay fever occurring in subjects sensitive to ragweed pollen. The Journal of Allergy. 1950;**21**(4):282-287. Epub 1950/07/01. DOI: 10.1016/0021-8707(50)90059-1

[3] CONTROLLED trial of effects of cortisone acetate in chronic asthma; report to the Medical Research Council by the subcommittee on clinical trials in asthma. Lancet. 1956;**271**(6947):798-803. Epub 1956/10/20

[4] Crompton G. A brief history of inhaled asthma therapy over the last fifty years. Primary Care Respiratory Journal. 2006;**15**(6):326-331. Epub 2006/11/10. DOI: 10.1016/j.pcrj.2006.09.002

[5] Speizer FE, Doll R, Heaf P, Strang LB. Investigation into use of drugs preceding death from asthma. British Medical Journal. 1968;**1**(5588):339-343. Epub 1968/02/10. DOI: 10.1136/bmj.1.5588.339

[6] Inman WH, Adelstein AM. Rise and fall of asthma mortality in England and Wales in relation to use of pressurised aerosols. Lancet. 1969;**2**(7615):279-285. Epub 1969/08/09. DOI: 10.1016/s0140-6736(69)90051-8

[7] Cameron SJ, Cooper EJ, Crompton GK, Hoare MV, Grant IW. Substitution of beclomethasone aerosol for oral prednisolone in the treatment of chronic asthma. British Medical Journal. 1973;**4**(5886):205-207. Epub 1973/10/27. DOI: 10.1136/bmj.4.5886.205

[8] Hodson ME, Batten JC, Clarke SW, Gregg I. Beclomethasone dipropionate aerosol in asthma. Transfer of steroid-dependent asthmatic patients from oral prednisone to beclomethasone dipropionate aerosol. The American Review of Respiratory Disease. 1974;**110**(4):403-408. Epub 1974/10/01. DOI: 10.1164/arrd.1974.110.4.403

[9] Vilsvik JS, Schaanning J. Beclomethasone dipropionate aerosol in adult steroid-dependent obstructive lung disease. Scandinavian Journal of Respiratory Diseases. 1974;**55**(3):169-175 Epub 1974/01/01

[10] Barnes PJ. How corticosteroids control inflammation: Quintiles prize lecture 2005. British Journal of Pharmacology. 2006;**148**(3):245-254. Epub 2006/04/11. DOI: 10.1038/sj.bjp.0706736

[11] Rhen T, Cidlowski JA. Antiinflammatory action of glucocorticoids--new mechanisms for old drugs. The New England Journal of Medicine. 2005;**353**(16):1711-1723. Epub 2005/10/21. DOI: 10.1056/NEJMra050541

[12] Clark AR, Martins JR, Tchen CR. Role of dual specificity phosphatases in biological responses to glucocorticoids. The Journal of Biological Chemistry. 2008;**283**(38):25765-25769. Epub 2008/06/11. DOI: 10.1074/jbc.R700053200

[13] Barnes PJ. Corticosteroid effects on cell signalling. The European Respiratory Journal. 2006;**27**(2):413-426. Epub 2006/02/03. DOI: 10.1183/09031936.06.00125404

[14] Barnes PJ, Adcock IM, Ito K. Histone acetylation and deacetylation: Importance in inflammatory lung diseases. The European Respiratory Journal. 2005;**25**(3):552-563. Epub 2005/03/02. DOI: 10.1183/09031936.05.00117504

[15] Ito K, Barnes PJ, Adcock IM. Glucocorticoid receptor recruitment of histone deacetylase 2 inhibits interleukin-1beta-induced histone H4 acetylation on lysines 8 and 12. Molecular and Cellular Biology. 2000;**20**(18):6891-6903. Epub 2000/08/25. DOI: 10.1128/mcb.20.18.6891-6903.2000

[16] Mak JC, Nishikawa M, Barnes PJ. Glucocorticosteroids increase beta 2-adrenergic receptor transcription in human lung. The American Journal of Physiology. 1995;**268**(1 Pt 1):L41-L46. Epub 1995/01/01. DOI: 10.1152/ajplung.1995.268.1.L41

[17] Baraniuk JN, Ali M, Brody D, Maniscalco J, Gaumond E, Fitzgerald T, et al. Glucocorticoids induce beta2-adrenergic receptor function in human nasal mucosa. American Journal of Respiratory and Critical Care Medicine. 1997;**155**(2):704-710. Epub 1997/02/01. DOI: 10.1164/ajrccm.155.2.9032216

[18] Mak JC, Chuang TT, Harris CA, Barnes PJ. Increased expression of G protein-coupled receptor kinases in cystic fibrosis lung. European Journal of Pharmacology. 2002;**436**(3):165-172. Epub 2002/02/23. DOI: 10.1016/s0014-2999(01)01625-9

[19] Usmani OS, Ito K, Maneechotesuwan K, Ito M, Johnson M, Barnes PJ, et al. Glucocorticoid receptor nuclear translocation in airway cells after inhaled combination therapy. American Journal of Respiratory and Critical Care Medicine. 2005;**172**(6):704-712. Epub 2005/04/30. DOI: 10.1164/rccm.200408-1041OC

[20] Roth M, Johnson PR, Rüdiger JJ, King GG, Ge Q, Burgess JK, et al. Interaction between glucocorticoids and beta2 agonists on bronchial airway smooth muscle cells through synchronised cellular signalling. Lancet. 2002;**360**(9342):1293-1299. Epub 2002/11/05. DOI: 10.1016/s0140-6736(02)11319-5

[21] Barnes PJ. Inhaled corticosteroids. Pharmaceuticals (Basel). 2010;**3**(3):514-540. Epub 2010/03/08. DOI: 10.3390/ph3030514

[22] Ketchell RI, Jensen MW, Lumley P, Wright AM, Allenby MI, O'Connor BJ. Rapid effect of inhaled fluticasone propionate on airway responsiveness to adenosine 5′-monophosphate in mild asthma. The Journal of Allergy and Clinical Immunology. 2002;**110**(4):603-606. Epub 2002/10/10. DOI: 10.1067/mai.2002.128486

[23] Erin EM, Zacharasiewicz AS, Nicholson GC, Tan AJ, Neighbour H, Engelstätter R, et al. Rapid effect of inhaled ciclesonide in asthma: A randomized, placebo-controlled study. Chest. 2008;**134**(4):740-745. Epub 2008/04/12. DOI: 10.1378/chest.07-2575

[24] Daley-Yates PT. Inhaled corticosteroids: Potency, dose equivalence and therapeutic index. British Journal of Clinical Pharmacology. 2015;**80**(3):372-380. Epub 2015/03/27. DOI: 10.1111/bcp.12637

[25] Duse M, Santamaria F, Verga MC, Bergamini M, Simeone G, Leonardi L, et al. Inter-society consensus for the use of inhaled corticosteroids in infants, children and adolescents with airway diseases. Italian Journal of Pediatrics. 2021;**47**(1):97. DOI: 10.1186/s13052-021-01013-8

[26] Woodcock A, Bleecker ER, Busse WW, Lötvall J, Snowise NG,

Frith L, et al. Fluticasone furoate: Once-daily evening treatment versus twice-daily treatment in moderate asthma. Respiratory Research. 2011;**12**(1):160. Epub 2011/12/23. DOI: 10.1186/1465-9921-12-160

[27] Boulet LP, Cowie RL, Negro RD, Brett W, Gold M, Marques A, et al. Comparison of once- with twice-daily dosing of fluticasone propionate in mild and moderate asthma. Canadian Respiratory Journal. 2000;**7**(3):239-247. Epub 2000/07/21. DOI: 10.1155/2000/464639

[28] Electronic Medicines Compendium. Datapharm Communications Limited AahwmouelaM

[29] Daley-Yates P, editor Relationship between pharmacokinetic and aerodynamic particle size distribution properties for inhalers containing corticosteroids. Respiratory Drug Delivery; 2014

[30] Liu T, Han M, Tian F, Cun D, Rantanen J, Yang M. Budesonide nanocrystal-loaded hyaluronic acid microparticles for inhalation: In vitro and in vivo evaluation. Carbohydrate Polymers. 2018;**181**:1143-1152. Epub 2017/12/20. DOI: 10.1016/j.carbpol.2017.11.018

[31] Miyazaki Y, Aruga N, Kadota K, Tozuka Y, Takeuchi H. Improved respirable fraction of budesonide powder for dry powder inhaler formulations produced by advanced supercritical CO(2) processing and use of a novel additive. International Journal of Pharmaceutics. 2017;**528**(1-2):118-126. Epub 2017/06/07. DOI: 10.1016/j.ijpharm.2017.06.002

[32] Kobayashi Y, Asako M, Yamamoto T, Yasuba H, Tomoda K, Kanda A. Replacement of SFC-DPI with SFC-MDI exhaled through the nose improves eosinophilic chronic rhinosinusitis in patients with bronchial asthma. International Journal of Clinical Pharmacology and Therapeutics. 2017;**55**(1):89-94. Epub 2016/11/24. DOI: 10.5414/cp202633

[33] Sher LD, Yiu G, Sakov A, Liu S, Caracta CF. Fluticasone propionate and fluticasone propionate/salmeterol multidose dry powder inhalers compared with placebo for persistent asthma. Allergy and Asthma Proceedings. 2017;**38**(5):343-353. Epub 2017/06/24. DOI: 10.2500/aap.2017.38.4069

[34] Cloutier MM, Baptist AP, Blake KV, Brooks EG, Bryant-Stephens T, DiMango E, et al. 2020 focused updates to the asthma management guidelines: A report from the National Asthma Education and prevention program coordinating committee expert panel working group. The Journal of Allergy and Clinical Immunology. 2020;**146**(6):1217-1270. Epub 2020/12/08. DOI: 10.1016/j.jaci.2020.10.003

[35] Available from: https://northeast.devonformularyguidance.nhs.uk/formulary/chapters/3.-respiratory/corticosteroid-inhaler-preparations-equivalent-beclometasone-bdp.

[36] Newman B, Babiskin A, Bielski E, Boc S, Dhapare S, Fang L, et al. Scientific and regulatory activities initiated by the U.S. food and drug administration to foster approvals of generic dry powder inhalers: Bioequivalence perspective. Advanced Drug Delivery Reviews. 2022;**190**:114526. DOI: 10.1016/j.addr.2022.114526

[37] Global initiative for asthma. Global Strategy for Asthma Management and Prevention AN, 1, 2021. Available from: https://ginasthma.org/wp-content/

uploads/2021/05/GINA-Main-Report-2021-V2-WMS.pdf.

[38] Juniper EF, Kline PA, Vanzieleghem MA, Ramsdale EH, O'Byrne PM, Hargreave FE. Effect of long-term treatment with an inhaled corticosteroid (budesonide) on airway hyperresponsiveness and clinical asthma in nonsteroid-dependent asthmatics. The American Review of Respiratory Disease. 1990;**142**(4):832-836. Epub 1990/10/01. DOI: 10.1164/ajrccm/142.4.832

[39] Pauwels RA, Pedersen S, Busse WW, Tan WC, Chen YZ, Ohlsson SV, et al. Early intervention with budesonide in mild persistent asthma: A randomised, double-blind trial. Lancet. 2003;**361**(9363):1071-1076. Epub 2003/04/04. DOI: 10.1016/s0140-6736(03)12891-7

[40] O'Byrne PM, FitzGerald JM, Bateman ED, Barnes PJ, Zhong N, Keen C, et al. Inhaled combined budesonide-Formoterol as needed in mild asthma. The New England Journal of Medicine. 2018;**378**(20):1865-1876. Epub 2018/05/17. DOI: 10.1056/NEJMoa1715274

[41] Bateman ED, Reddel HK, O'Byrne PM, Barnes PJ, Zhong N, Keen C, et al. As-needed budesonide-Formoterol versus maintenance budesonide in mild asthma. The New England Journal of Medicine. 2018;**378**(20):1877-1887. Epub 2018/05/17. DOI: 10.1056/NEJMoa1715275

[42] Hardy J, Baggott C, Fingleton J, Reddel HK, Hancox RJ, Harwood M, et al. Budesonide-formoterol reliever therapy versus maintenance budesonide plus terbutaline reliever therapy in adults with mild to moderate asthma (PRACTICAL): A 52-week, open-label, multicentre, superiority, randomised controlled trial. Lancet. 2019;**394**(10202):919-928. Epub 2019/08/28. DOI: 10.1016/s0140-6736(19)31948-8

[43] Agertoft L, Pedersen S. Effects of long-term treatment with an inhaled corticosteroid on growth and pulmonary function in asthmatic children. Respiratory Medicine. 1994;**88**(5):373-381. Epub 1994/05/01. DOI: 10.1016/0954-6111(94)90044-2

[44] Selroos O, Pietinalho A, Löfroos AB, Riska H. Effect of early vs late intervention with inhaled corticosteroids in asthma. Chest. 1995;**108**(5):1228-1234. Epub 1995/11/01. DOI: 10.1378/chest.108.5.1228

[45] Suissa S, Ernst P, Benayoun S, Baltzan M, Cai B. Low-dose inhaled corticosteroids and the prevention of death from asthma. The New England Journal of Medicine. 2000;**343**(5):332-336. Epub 2000/08/03. DOI: 10.1056/nejm200008033430504

[46] O'Byrne PM, Barnes PJ, Rodriguez-Roisin R, Runnerstrom E, Sandstrom T, Svensson K, et al. Low dose inhaled budesonide and formoterol in mild persistent asthma: The OPTIMA randomized trial. American Journal of Respiratory and Critical Care Medicine. 2001;**164**(8 Pt 1):1392-1397. Epub 2001/11/13. DOI: 10.1164/ajrccm.164.8.2104102

[47] Suissa S, Barnes PJ. Inhaled corticosteroids in COPD: The case against. The European Respiratory Journal. 2009;**34**(1):13-16. Epub 2009/07/02. DOI: 10.1183/09031936.00190908

[48] Barnes PJ. Role of HDAC2 in the pathophysiology of COPD. Annual Review of Physiology. 2009;**71**:451-464. Epub 2008/09/27. DOI: 10.1146/annurev.physiol.010908.163257

[49] Adcock IM, Cosio B, Tsaprouni L, Barnes PJ, Ito K. Redox regulation of histone deacetylases and glucocorticoid-mediated inhibition of the inflammatory response. Antioxidants & Redox Signaling. 2005;**7**(1-2):144-152. Epub 2005/01/15. DOI: 10.1089/ars.2005.7.144

[50] The Global Initiative for Chronic Obstructive Lung Disease (GOLD). The 2023 global strategy for the diagnosis m, and prevention of chronic obstructive pulmonary disease (COPD). Available at: https://goldcopd.org/2023-gold-report-2/.

[51] Venkatesan P. GOLD COPD report: 2023 update. The Lancet Respiratory Medicine. 2023;**11**(1):18. Epub 2022/12/04. DOI: 10.1016/S2213-2600(22)00494-5

[52] Miravitlles M, Alvarez-Gutierrez FJ, Calle M, Casanova C, Cosio BG, López-Viña A, et al. Algorithm for identification of asthma-COPD overlap: consensus between the Spanish COPD and asthma guidelines. Eur Respir J. 2017;**49**(5). Epub 2017/05/04. DOI: 10.1183/13993003.00068-2017

[53] Nadeem NJ, Taylor SJ, Eldridge SM. Withdrawal of inhaled corticosteroids in individuals with COPD--a systematic review and comment on trial methodology. Respiratory Research. 2011;**12**(1):107. Epub 2011/08/16. DOI: 10.1186/1465-9921-12-107

[54] Miravitlles M, Cosío BG, Arnedillo A, Calle M, Alcázar-Navarrete B, González C, et al. A proposal for the withdrawal of inhaled corticosteroids in the clinical practice of chronic obstructive pulmonary disease. Respiratory Research. 2017;**18**(1):198. Epub 2017/12/01. DOI: 10.1186/s12931-017-0682-y

[55] Williamson IJ, Matusiewicz SP, Brown PH, Greening AP, Crompton GK. Frequency of voice problems and cough in patients using pressurized aerosol inhaled steroid preparations. The European Respiratory Journal. 1995;**8**(4):590-592 Epub 1995/04/01

[56] Toogood JH, Jennings B, Greenway RW, Chuang L. Candidiasis and dysphonia complicating beclomethasone treatment of asthma. The Journal of Allergy and Clinical Immunology. 1980;**65**(2):145-153. Epub 1980/02/01. DOI: 10.1016/0091-6749(80)90200-6

[57] Vogelmeier CF, Criner GJ, Martinez FJ, Anzueto A, Barnes PJ, Bourbeau J, et al. Global strategy for the diagnosis, management, and prevention of chronic obstructive lung disease 2017 report: GOLD executive summary. Archivos de Bronconeumología. 2017;**53**(3):128-149. Epub 2017/03/10. DOI: 10.1016/j.arbres.2017.02.001

[58] Crim C, Dransfield MT, Bourbeau J, Jones PW, Hanania NA, Mahler DA, et al. Pneumonia risk with inhaled fluticasone furoate and vilanterol compared with vilanterol alone in patients with COPD. Annals of the American Thoracic Society. 2015;**12**(1):27-34. Epub 2014/12/10. DOI: 10.1513/AnnalsATS.201409-413OC

[59] Singh S, Loke YK. Risk of pneumonia associated with long-term use of inhaled corticosteroids in chronic obstructive pulmonary disease: A critical review and update. Current Opinion in Pulmonary Medicine. 2010;**16**(2):118-122. Epub 2009/11/21. DOI: 10.1097/MCP.0b013e328334c085

[60] Yang IA, Fong KM, Sim EH, Black PN, Lasserson TJ. Inhaled corticosteroids for stable chronic obstructive pulmonary disease. Cochrane Database of Systematic Reviews. 2007;**(2)**:Cd002991. Epub 2007/04/20. DOI: 10.1002/14651858.CD002991.pub2

[61] Shafiek H, Verdú J, Iglesias A, Ramon-Clar L, Toledo-Pons N, Lopez-Causape C, et al. Inhaled corticosteroid dose is associated with Pseudomonas aeruginosa infection in severe COPD. BMJ Open Respir Res. 2021;**8**(1). Epub 2021/10/08. DOI: 10.1136/bmjresp-2021-001067

[62] Cerón-Pisa N, Shafiek H, Martín-Medina A, Verdú J, Jordana-Lluch E, Escobar-Salom M, et al. Effects of Inhaled Corticosteroids on the Innate Immunological Response to Pseudomonas aeruginosa Infection in Patients with COPD. Int J Mol Sci. 2022;**23**(15). Epub 2022/07/29. DOI: 10.3390/ijms23158127

[63] O'Byrne PM, Pedersen S, Carlsson LG, Radner F, Thorén A, Peterson S, et al. Risks of pneumonia in patients with asthma taking inhaled corticosteroids. American Journal of Respiratory and Critical Care Medicine. 2011;**183**(5):589-595. Epub 2010/10/05. DOI: 10.1164/rccm.201005-0694OC

[64] Qian CJ, Coulombe J, Suissa S, Ernst P. Pneumonia risk in asthma patients using inhaled corticosteroids: A quasi-cohort study. British Journal of Clinical Pharmacology. 2017;**83**(9):2077-2086. Epub 2017/04/21. DOI: 10.1111/bcp.13295

[65] You Y, Ni Y, Shi G. Inhaled corticosteroids and mycobacterial infection in patients with chronic airway diseases: A systematic review and meta-analysis. Respiration. 2022;**101**(10):970-980. Epub 2022/08/24. DOI: 10.1159/000525980

[66] Loke YK, Cavallazzi R, Singh S. Risk of fractures with inhaled corticosteroids in COPD: Systematic review and meta-analysis of randomised controlled trials and observational studies. Thorax. 2011;**66**(8):699-708. Epub 2011/05/24. DOI: 10.1136/thx.2011.160028

[67] Lehouck A, Boonen S, Decramer M, Janssens W. COPD, bone metabolism, and osteoporosis. Chest. 2011;**139**(3):648-657. Epub 2011/03/03. DOI: 10.1378/chest.10-1427

[68] Barnes PJ, Pedersen S, Busse WW. Efficacy and safety of inhaled corticosteroids. New developments. American Journal of Respiratory and Critical Care Medicine. 1998;**157**(3 Pt 2):S1-S53. Epub 1998/04/01. DOI: 10.1164/ajrccm.157.3.157315

[69] Suissa S, Kezouh A, Ernst P. Inhaled corticosteroids and the risks of diabetes onset and progression. The American Journal of Medicine. 2010;**123**(11):1001-1006. Epub 2010/09/28. DOI: 10.1016/j.amjmed.2010.06.019

[70] Wang JJ, Rochtchina E, Tan AG, Cumming RG, Leeder SR, Mitchell P. Use of inhaled and oral corticosteroids and the long-term risk of cataract. Ophthalmology. 2009;**116**(4):652-657. Epub 2009/02/27. DOI: 10.1016/j.ophtha.2008.12.001

[71] Garbe E, LeLorier J, Boivin JF, Suissa S. Inhaled and nasal glucocorticoids and the risks of ocular hypertension or open-angle glaucoma. Journal of the American Medical Association. 1997;**277**(9):722-727 Epub 1997/03/05