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COMPREHENSIVE ASSESSMENT OF ICS

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ABSTRACT

Chronic obstructive pulmonary disease is a progressive inflammatory disease of the lung characterized by chronic bronchitis, airway thickening and emphysema. Pulmonary inflammation is prominent in chronic obstructive pulmonary disease and corticosteroids are generally used in controlling the inflammation. The inflammation in chronic obstructive pulmonary disease is dominated by neutrophilic infiltration, with an increased numbers of macrophages and CD8 T lymphocytes; neutrophilic infiltration is not as responsive to steroids as the eosinophilic inflammation seen in asthma. Current guidelines highlight the fact that for chronic obstructive pulmonary disease patients uncontrolled by bronchodilator monotherapy, the use of a combination therapy is recommended. The combination of long acting beta agonists and inhaled corticosteroids is the most common in use for both chronic obstructive pulmonary disease and asthma. Inhaled corticosteroids and long acting beta agonists combination products have been shown to improve lung function, symptoms, and health status, and they reduce exacerbations in patients with moderate to severe chronic obstructive pulmonary disease . A more recently published retrospective analysis of veterans treated with tiotropium revealed that inhaled corticosteroids and long acting beta agonists and long acting muscarinic antagonists therapy was associated with a 40% reduction in mortality compared with treatment with inhaled corticosteroids plus long acting beta agonists. The adverse effects from the use of inhaled corticosteroids in patients with Chronic obstructive pulmonary disease, most notably severe pneumonia results in excess deaths**.**

KEYWORDS: Glucocorticoid receptor; Nuclear factor-κB; Inflammatory gene; Histone deacetylase; Eosinophil, Epithelial cell; Inhaled corticosteroids; Inflammation; Pneumonia.

INTRODUCTION

Chronic bronchitis, airway thickening, and emphysema are all features of the progressive inflammatory lung disease, chronic obstructive pulmonary disease (COPD). COPD is expected to become the most significant disease for doctors to treat because it is the third-leading cause of mortality worldwide and has a sharply rising trend in global prevalence.[1,2] Understanding the basic pathophysiology of COPD will be very helpful in diagnosing and treating the condition in emergency situations. Persistent inflammation and an imbalance in oxidant-antioxidant activity that results in oxidative stress are two significant and mutually non-exclusive mechanisms implicated in the pathogenesis of COPD.[3]

Since smoking cigarettes causes COPD almost everywhere in the world, stopping smoking and treating nicotine addiction should be the top priorities in the fight against COPD. However, COPD medication therapy costs far more than quitting smoking.[1]

In COPD, pulmonary inflammation is common, and corticosteroids are typically administered to treat the inflammation.[4]

Anti-inflammatory medicines, such as inhaled corticosteroids, have little to no impact on the rate of lung function loss[5,6] but they may lessen the frequency of exacerbations, especially when used in conjunction with an inhaled long-acting beta-agonist.[7] According to retrospective investigations, inhaled corticosteroids decrease the death rate in COPD patients, and the addition of a long-acting beta-agonist may enhance this benefit.[8] These medications are now commonly administered to COPD patients in high doses, with many of them receiving the daily equivalent of 1000 g of fluticasone.[9]

The only medications that can successfully suppress the characteristic inflammation in asthmatic airways, even at extremely low doses, are inhaled corticosteroids (ICS), also known as glucocorticoids, glucocorticoids, or

steroids), which are by far the most effective medications used in the treatment of asthma. In contrast, ICS has a poor clinical outcome and is mainly ineffective at controlling pulmonary inflammation in COPD. Long-acting 2-agonists (LABA) are frequently combined with inhalers that contain ICS to treat both COPD and asthma.[10]

It is evident that ICS is the mainstay of treatment for asthma because it lowers airway inflammation, airflow restriction, and symptoms.[11]

However, in COPD, the function of ICS is more debatable, primarily because the pattern of inflammation is different. With an increased number of macrophages and CD8 T cells, neutrophilic infiltration dominates the inflammation in COPD, yet it is less sensitive to drugs than the eosinophilic inflammation found in asthma.[12]

The Cochrane collaboration examined the usage of ICS in COPD and came to the conclusion that while using this may result in fewer exacerbations and probably a slower rate of FEV1 loss, these benefits must be balanced against higher risks of pneumonia and local adverse effects.[13]

Molecular Mechanisms in the Pathogenesis of COPD

The tiny airways and alveoli are most commonly affected by COPD, which is a chronic inflammatory disease of the airways that progresses over time. Persistent inflammation and an imbalance in oxidant-antioxidant function that results in oxidative stress are two significant and mutually non-exclusive processes linked to the pathophysiology of COPD. The inflammatory cells in COPD do not react to steroids, in contrast to asthma inflammation, which is predominantly composed of eosinophils and mast cells that are responsive to steroids. Neutrophils, macrophages, and lymphocytes are the principal inflammatory cells in COPD. These inflammatory cells go on to generate a variety of inflammatory mediators, such as cytokines, chemokines, and chemoattractants, which continue the inflammation and set off an uncontrollable chain of events. By producing chemoattractants including leukotriene B4 (LTB4) and interleukin-8 (IL-8), neutrophils further entice neutrophils to the area.[14]

Elastic lung tissue is harmed by proteolytic enzymes secreted by neutrophils, including elastase, proteinase-3, cathepsin G, cathepsin B, and matrix metalloproteinases (MMP).[14]

Macrophages release a variety of proteinases, particularly MMPs with tremendous elastolytic potential, such as MMP-2, MMP-9, MMP-12, and MMP-14, and elastolytic cysteine proteinases like cathepsin K, L, and S. They also release reactive oxygen species, which attract and activate various inflammatory cells.[15] Alveolar epithelial cells may undergo apoptosis when CD8+ lymphocytes release granzyme B and perforin, and CD4 lymphocytes might cause an autoimmune reaction to lung tissue.[16] Additionally, oxidative stress has been linked to a number of clinical alterations associated with COPD, including oxidative inactivation of antiproteases and surfactants, mucus hypersecretion, membrane lipid peroxidation, alveolar epithelium damage, modification of extracellular matrix, apoptosis, decreased elastin and collagen synthesis, fragmentation of these skeletal proteins, and steroid insensitivity.[17]

Mechanism of Action of ICS

The main effects of glucocorticoids result from activation of certain glucocorticoid receptors (GCR), which are present in the cytoplasm of the majority of mammalian cell types. The relationship between histone deacetylase-2 (HDAC2) and nuclear factor kappa B (Nf-kB), a crucial transcription factor, is another way that the GCR affects the inflammatory processes in COPD. During inflammation, Nf-kB is elevated in many different cell types and stimulates the production of genes that cause inflammation. The GCR is able to bind to Nf-kB and inhibit its function as a pro-inflammatory molecule thanks to HDAC2-mediated deacetylation.[18] An area of focus in COPD treatment right now is HDAC2 regulation.[19]

Inhibition of monocyte activities such as chemotaxis, bactericidal activity, and the generation of interleukin (IL)-1 and TNF by corticosteroids results in peripheral blood monocytopenia and immune system suppression.[20] Use of corticosteroids could lead to an increase in the spread of TB due to their immunosuppression.[21]

In addition, corticosteroids prevent T cell activation, which reduces proliferative responses and cytokine production. They also cause T cells to be redistributed out of circulation, which results in peripheral lymphocytopenia.[22]

There are numerous anti-inflammatory actions of corticosteroids that are cell-and tissue-specific and have been well-documented. The inactive glucocorticoid receptor complex is bound by the corticosteroid after it enters the cell cytoplasm. As a result, the DNA-binding activity of the active glucocorticoid receptor at the glucocorticoid response element sequence stimulates the synthesis of anti-inflammatory proteins (transactivation) while inhibiting transcription and synthesis of several proinflammatory cytokines (transrepression). The majority of corticosteroids' harmful systemic effects are also caused by transactivation. Additionally, corticosteroids decrease the generation of inducible nitric oxide and the quantity of T lymphocytes, dendritic cells, eosinophils, and mast cells in the airways.[23]

A thorough examination of the effects of corticosteroids is outside the purview of this article. However, corticosteroids often have two beneficial effects for COPD: they may change the transcription of

inflammatory genes[24,25] and they might modify β2-adrenoceptor activity.[26]

The anti-inflammatory effect is the one that has drawn the most attention. Glucocorticoid receptors are corticosteroids' primary targets (GRs). The majority of the dormant GRs are found in the cytoplasm of the cell and are surrounded by multichaperone proteins. After entering through the cell membrane, the corticosteroid molecule binds to the GR via the corticosteroid-binding domain. As a result, the receptor protein undergoes a conformational change that enables the chaperone proteins to separate and a functional corticosteroid-GR complex to form. Following the formation of a dimer, this complex travels from the cytosol to the cell's nucleus where it binds to particular DNA sequences known as glucocorticoid response elements that are located in the promoter region of target genes. This results in cofactor activation and changes in the transcription of anti-inflammatory or proinflammatory genes. Transactivation is the word for the entire process.[27]

As an alternative, the active corticosteroid-GR complex can directly interact with intracellular transcription factors like activating protein-1 or nuclear factor-B through a protein-protein interaction in order to reduce the proinflammatory processes that are mediated by these factors. Histone deacetylases (HDAC) are recruited during this process, and chromatin structure is altered.[28] A disease can cause a relative corticosteroid resistance state if it can prevent HDAC recruitment and/or activity.[29] Another significant effect of corticosteroids is their ability to alter β2-adrenoceptor activity, which may guard against tolerance and desensitization, stop inflammation-induced receptor uncoupling and downregulation, and improve receptor responsiveness.[26]

Similar outcomes were seen in a group of COPD patients with virus-associated exacerbations; ICS users had decreased IFN expression and mucus hypersecretion together with a larger acute decline in lung function than ICS nonusers, indicating that these outcomes are likely to be clinically significant. Notably, in a mouse model of rhinovirus infection, these effects could be reversed by the administration of recombinant IFN- β.[30]

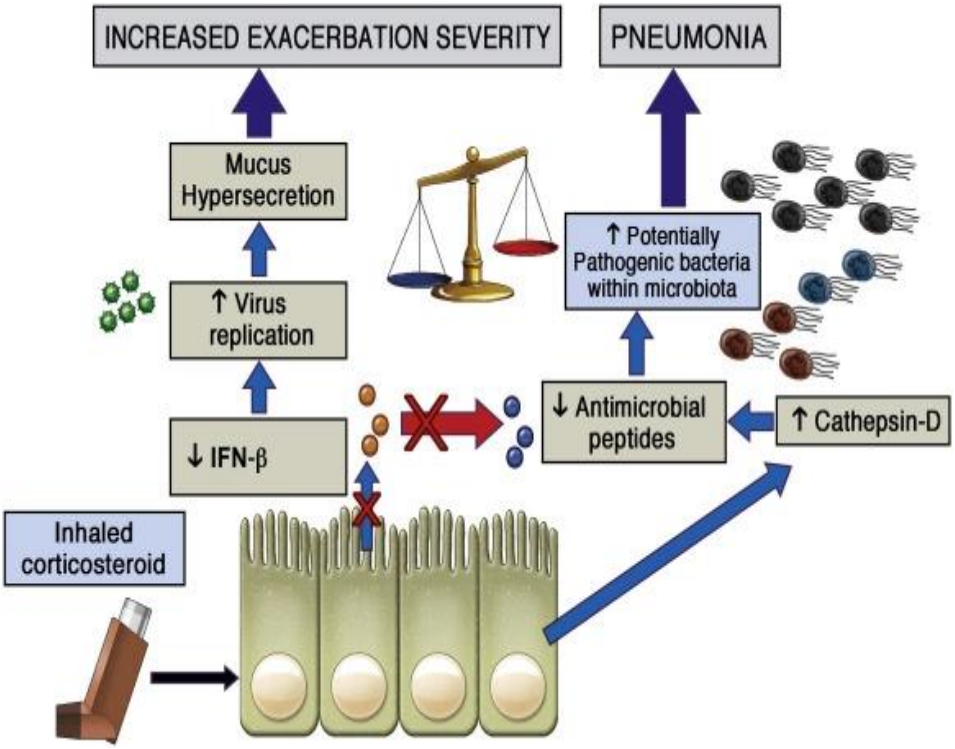

Figure 1: Mechanisms of ICS impairment of host immunity.

Corticosteroid administration using inhalation reduces systemic absorption and negative effects while delivering anti-inflammatory properties. Endobronchial biopsy-detected airway inflammation is reduced by ICS alone or in conjunction with a LABA[31,32,33] Histone acetyltransferase activity is inhibited by corticosteroids, which increase the activity of histone deacetylase (HDAC2). This results in chromatin compaction and the suppression of gene expression.[34]

An explanation for why ICS should be given along with bronchodilators comes from molecular mechanisms. Corticosteroids can inhibit or reverse the down-regulation (tachyphylaxis) of β2-adrenoreceptors in response to agonists[36,37] and up-regulate β2-adrenoreceptors in the body.[35]

Theophylline activates HDAC2, which could enhance corticosteroid action by amplifying its effects alone or in conjunction with corticosteroids.[38-48]

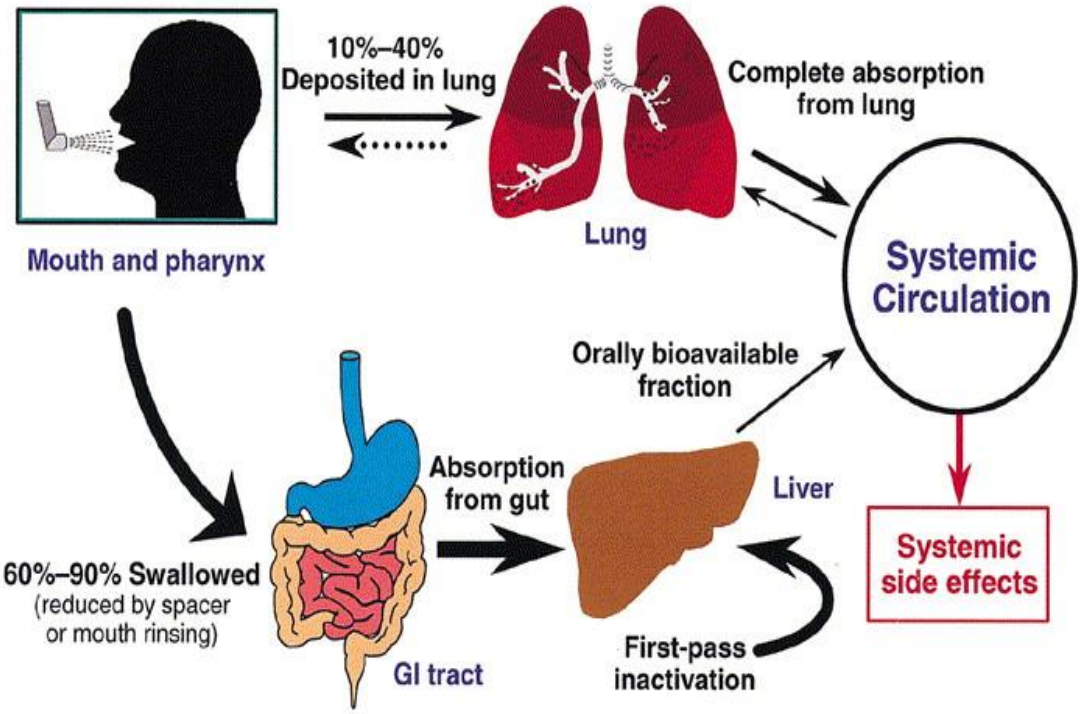

Figure 2: The fate of inhaled corticosteroid.[40]

ICS Combination Therapy

According to current guidelines, the use of combination therapy is advised for COPD patients whose symptoms are not managed by bronchodilator monotherapy.[41]

Bi-therapy [Inhaled Glucocorticoids (ICS)/LABA]

The most common treatment for COPD and asthma is a combination of LABA and ICS.[41]

When given along with ICS, LABAs have greater physiological and clinical effects,[42] which have a positive impact on patient outcomes.

In patients with moderate to severe COPD, ICS and LABA combination products have been found to improve lung function, symptoms, and health status, and they also decrease exacerbations.[43,46]

The combination treatment (salmeterol and fluticasone propionate) improved spirometric values and improved health status, lowering the annual rate of exacerbations from 1.13 to 0.85 (P 0.001 for all comparisons with placebo).[9]

The combined regimen considerably reduced the risk of exacerbations compared to each of its individual components, and these advantages were complemented by long-lasting enhancements in FEV1 and health status.[9]

Future large, prospective trials should be used to further examine the potential for a 17.5% reduction in the risk of death and a potential 2.6 percentage point reduction in the risk of death among patients receiving salmeterol + fluticasone propionate compared to placebo. Our data support the use of salmeterol with fluticasone propionate in the clinical therapy of COPD until such trials are finished.[9]

Combining several classes of bronchodilators, such as an inhaled anticholinergic with a b β2-AR agonist, this may be more beneficial than using just one type of drug in terms of improving lung function, alleviating symptoms, and lowering the risk of side effects.[47–49]

However, ICS/LABA did not reduce the number of severe exacerbations, all-cause mortality, respiratory mortality, or cardiovascular mortality when compared to LABA alone, according to the findings of a recent meta analysis.[50] The meta-analysis revealed that the increased prevalence of pneumonia came at the expense of the better FEV1 obtained with IC/LABA compared to LABA monotherapy.

This is in contrast to a prior analysis of the same database, which discovered that ICS/LABA combination therapy was superior to LABA monotherapy for reducing exacerbation frequency.[51]

Tiotropium takes longer (5 minutes) to start working than formoterol, although both drugs have equal effects on bronchodilation over a 12-hour period.[52]

According to a recent study by Rabe and colleagues, using two agents from different bronchodilator classes is preferable to using a bronchodilator plus an ICS.[53] The salmeterol/fluticasone combo was compared to tiotropium plus formoterol (SFC). After six weeks, the group taking tiotropium with formoterol had significantly higher 12-hour FEV1 AUC, FVC AUC, peak FEV1 and FVC, and all of these measurements were higher.

The frequency of ocular or bone side effects was comparable. Patients taking medications containing fluticasone propionate were more likely to have pneumonia reported as an adverse event (19.6% in the combination-therapy group and 18.3% in the fluticasone group) than patients receiving placebo (12.3%, P 0.001 for comparisons between these treatments and placebo).[9]

Triple Therapy [Inhaled Glucocorticoids (ICS)/LABA/LAMA]

A rationale for using anticholinergic/corticosteroid combination therapy is emerging from in vitro investigations that reveal a relationship between corticosteroids and muscarinic receptors.[54]

Three studies comparing the efficacy of "triple therapy" (tiotropium, salmeterol, and fluticasone) to the three individual medications demonstrate that 113–115 FEV1, inspiratory capacity (IC), and airway conductance were all significantly higher in the triple combination compared to tiotropium monotherapy and SFC (salmeterol fluticasone combination).[55]

According to research by Perng et al., Tiotropium can enhance FVC, FEV1, IC, and SGRQ in patients with severe COPD who are already receiving treatment with a LABA/ICS combination.[56]

Tiotropium monotherapy, tiotropium plus salmeterol, and tiotropium plus SFC were all examined by the Canadian Respiratory Clinical Research Consortium in association with the Canadian Thoracic Society. The proportion of patients experiencing an exacerbation, which served as the study's main endpoint and it did not change significantly across the three groups. However, when compared to tiotropium monotherapy, tiotropium SFC improved lung function, disease-specific quality of life, and decreased hospitalization for COPD exacerbations and all-cause hospitalizations.[57]

In contrast to ICS + LABA therapy, ICS + LABA + LAMA therapy was related to a 40% reduction in mortality, according to a more recent retrospective review of veterans treated with tiotropium.[58] Future clinical trials should examine the clinical impact of such an interaction.

Side effects of ICS

The effectiveness of ICS has already been proven in short-and long-term studies in adults and kids, although there are still worries regarding adverse effects, especially in kids and when using large inhalation doses. Several negative effects have been identified.[59]

Acute exacerbations are frequent among COPD patients.[60,61] Specific symptoms and indicators, including increased dyspnea, a productive cough with changed sputum, and fever, may be caused by exacerbations. Alternative symptoms include malaise, fatigue, insomnia or sleepiness, and depression, which are less specific. Even though such exacerbations are linked to deteriorated lung function, only 50% of all exacerbations are thought to be reported to doctors.[61]

Local side effects

- Dysphonia
- Oropharyngeal candidiasis
- Cough
- Pneumonia (COPD patients)

Systemic side effects

- Adrenal suppression
- Growth suppression
- Bruising
- Osteoporosis
- Cataracts
- Glaucoma
- Metabolic abnormalities (Glucose, Insulin, Triglycerides)
- Psychiatric disturbances

Local side effects

Steroids may cause side effects because of the local deposition of the ICS in the oropharynx. However, the incidence of complaints is based on the dosage, frequency of administration, and delivery method. It was anticipated that individuals using fluticasone propionate or the combo regimen would see an increase in oropharyngeal side effects.[9]

Over 50% of individuals using MDI may experience dysphonia, the most prevalent complaint, which is hoarseness of the voice. The use of spacers does not significantly diminish dysphonia, however dry powder devices may have a smaller impact. Laryngeal muscular myopathy may cause dysphonia, which is treatable when the medication is stopped.[62] Most people do not have any issues, although vocalists and lecturers may find it to be incapacitating. In some patients, especially the elderly, oropharyngeal candidiasis (thrush) may be an issue with concurrent oral corticosteroids and more than twice daily dosage.[63] Large volume spacers counteract this local side effect by lowering the amount of ICS that accumulates in the oropharynx.

Infections

There is no proof that ICS, even in large dosages, makes asthmatic patients more susceptible to infections in the lower respiratory tract, such as tuberculosis. Recent large controlled studies have demonstrated that high doses of ICS, whether administered alone or in conjunction with a LABA, lead to increased diagnosis of pneumonia by physicians,[13,51] and this has been confirmed in an epidemiological investigation of pneumonia-related hospital admissions among COPD patients.[64] Uncertainty surrounds the cause of pneumonia in COPD, but it appears to be treated with FP more frequently than with budesonide.[65]

ICS can decrease monocyte chemotaxis, bactericidal activity, interleukin (IL)-1 and tumour necrosis factor production, as well as T-cell activation[66,67] which increases the risk of respiratory infections like pneumonia,[9] oropharyngeal candidiasis[68, 69,70] mycobacterial[71, 72] and upper respiratory tract infections (URTIs).

Pneumonia

Pneumonia is more likely to develop in people with COPD.[73,74,75]

According to the 3-year TORCH and 2-year INSPIRE studies, fluticasone (1000 mg per day) increases the risk of pneumonia by 64% and 94%, respectively[76,77]

Patients receiving trial drugs containing fluticasone propionate in TORCH had the highest risk of pneumonia among those with a FEV1[76] diagnosis of pneumonia.[9]

Patients with COPD who use ICS run a higher risk of developing severe pneumonia. Two trials testing a lower dose of fluticasone (500 g per day) for 1 year likewise discovered nearly a twofold greater incidence of pneumonia at 1 year with fluticasone, indicating that the risk is particularly significant to the dose associated with fluticasone.[78,79,80]

Another study comparing salmeterol/fluticasone to tiotropium, Investigating New Standards for Prophylaxis in Reduction of Exacerbations (INSPIRE), likewise found an increase in pneumonia.[81]

A recent study of a new LABA/ICS combination containing fluticasone furoate, however, reported an increase of eight pneumonia deaths, seven of which occurred in the group receiving the higher-than-recommended dose of this medication, indicating that fluticasone itself may be particularly problematic.[82]

A recent meta-analysis, however, did not exonerate budesonide[83]

Even if the case fatality rate is the same once hospitalised, more pneumonia deaths will occur in COPD patients using ICS since more of them are admitted with severe pneumonia. Our findings from a large database study of almost 24 000 pneumonias, in which patients receiving high doses of ICS equivalent to 1000 µg fluticasone propionate had a 70% greater risk of pneumonia hospitalisation resulting in death within 30 days[64] and a recent study of vilanterol/fluticasone furoate, in which eight pneumonia deaths occurred in those receiving fluticasone furoate, highlights this.[82]

Using a huge population-based cohort of over 160 000 COPD patients followed for up to 18 years, we discovered that ICS treatment is significantly linked to a 69% increased risk of severe pneumonia that is deadly or requires hospitalization. Fluticasone significantly enhanced this risk, doubling the rate, and it was dose-dependent, with daily dosages of 1000 g of fluticasone being linked to a 122% increase. The risk with budesonide was significantly lower, increasing by 17%, and there was no dose-response impact. After quitting the usage of ICS, these increased hazards vanished after a short period of time.[78]

A team of researchers conducted a significant prospective cohort analysis in a medical administrative database and discovered an overall 70% increase in pneumonia requiring hospitalisation (rate ratio (RR) 1.70, 95% confidence interval (CI) 1.63-1.77), with the highest risk (RR 2.25, CI 2.07-2.44) reported in patients who received a daily fluticasone-equivalent dose of less than 1000 µg.[64]

An aggravation of COPD was the most frequently reported adverse event. Patients taking a study drug containing fluticasone propionate had a significantly higher chance of having pneumonia reported as an adverse event over the course of the 3-year study: the probability was 19.6% in the combination-therapy group, 12.3% in the placebo group, 13.3% in the salmeterol group, and 18.3% in the fluticasone group (P 0.001 for the comparison between the combination-therapy and fluticasone groups and the placebo group). Eight pneumonia-related deaths occurred among study participants who were getting combination therapy, compared to seven in the placebo, nine in the salmeterol, and thirteen in the fluticasone groups.[9]

Tuberculosis

The chance of getting active tuberculosis in patients with respiratory illnesses is elevated, and this increased risk is made worse by the administration of large doses of ICS.[84]

In a country with an intermediate TB burden, the use of ICS raises the chance of developing TB. Patients who utilise large doses of ICS may acquire TB, and clinicians should be aware of this possibility.[85]

In this nested case-control analysis, we demonstrated that ICS use raised the chance of developing TB in a country where the incidence of the disease was 97 cases per 100

000 people in 2010. Patients with COPD and patients with asthma were both found to have an increased chance of developing TB when using ICS.[85]

Prednisone dosages as low as 7.5 mg per day were found to enhance the risk of TB.[86]

Consequently, a cohort of 427 648 people with respiratory problems headquartered in Canada revealed an elevated risk of TB development among ICS users.[87]

The use of ICS could raise the chance of developing TB, according to analysis of a larger cohort made up of 853 439 new users of inhaled respiratory medicine in South Korea, a nation with a medium TB burden.[85]

Based on a subgroup analysis of OCS users, it was found that using ICS in addition to OCS did not accelerate the development of TB. The Canadian study also supports this finding.[87]

One study revealed that, in every analysis, OCS use exceeding a cumulative dose of 1680 mg of hydrocortisone equivalents was related to a higher risk of TB development among inhaler users.[85]

Viral infections

Long-term ICS use enhances URTI risk, including coronavirus, rhinovirus, and respiratory syncytial virus. The relationship appears more consistent with FP and is particularly significant in patients taking large ICS dosages.[88]

In patients with COPD using ICS, the incidence of influenza was not significantly elevated, according to a meta-analysis of 26 trials; however, when only FP studies were taken into account, there was a statistically significant difference.[72]

Candidiasis

Patients who received ICS/LABA had considerably higher probabilities of developing oral thrush than those who received LABA alone, according to an observational, matched cohort research, with a dose-dependent effect for FP/ SAL.[70]

Additionally, RCTs have shown that ICS increases the risk of oropharyngeal candidiasis (OR 2.65 (2.03-3.46)).[13]

Systemic Side Effects

The systemic impact of an inhaled corticosteroid will range from patient to patient depending on their specific responses to the corticosteroid as well as the dose given to the patient, the site of administration (gastrointestinal tract and lung), the delivery method, and other variables. According to recent research, patients with more severe asthma get fewer systemic effects from inhaled corticosteroids, possibly because less of the drug reaches the lung periphery.[89,90]

The amount of medication absorbed into the systemic circulation determines how an ICS will affect the body as a whole. 80–90% of the dose from an MDI that is inhaled settles in the oropharynx before being ingested and then absorbed from the gastrointestinal system. When oral bioavailability is low, as it is with FP, the use of a high volume spacer device significantly lowers oropharyngeal deposition and, thus, the systemic effects of ICS. However, this effect is less significant. Mouthwashing and dumping the fluid can reduce systemic effects of dry powder inhalers in a manner similar to this. Therefore, to lessen systemic absorption, all patients utilising a daily dose of less than 800 mg of an inhaled corticosteroid should either use a spacer or mouthwash. 10% of an MDI penetrates the lung on average. 10% of an MDI enters the lung, and this portion, which is thought to have a therapeutic impact, may be absorbed into the bloodstream. The amount of the inhaled dose that reaches the lungs increases as less of the ICS is deposited in the oropharynx. Increased systemic absorption is consequently brought on by more effective delivery to the lungs, but this is counterbalanced by a decrease in the dose required for the best control of airway inflammation.[9]

Significant systemic consequences from high doses of ICS have includes pneumonia, glaucoma, cataracts, adrenal suppression, rapid bone turnover, and diabetes.[91,92,93,94,64,95]

Ocular hypertension or open-angle glaucoma risk, is increased by the prolonged treatment of high dosages of inhaled glucocorticoids. This finding shows that intraocular pressure monitoring may be necessary for these patients.[91]

Adrenal suppression

By decreasing the formation of corticotrophin (ACTH), which in turn decreases the adrenal gland's ability to secrete cortisol, corticosteroids may suppress the hypothalamic-pituitary-adrenal (HPA) axis. How much HPA is suppressed depends on the amount, duration, frequency, and timing of corticosteroid therapy. Evidence for the systemic effects of an inhaled corticosteroid can be found in measurements of HPA axis function. A morning plasma cortisol test, a 24-hour urinary cortisol test, or a plasma cortisol profile over 24 hours can all be used to quantify basal adrenal cortisol release. Other tests assess the HPA response following stimulation with metyrapone and insulin or tetracosactrin, which assesses the reserve of adrenal hormones (which measure the response to stress).[9]

Numerous studies have been conducted on the HPA axis in asthmatic patients using ICS, but the outcomes have been inconsistent because the trials were frequently uncontrolled and the patients were also receiving courses of oral corticosteroids (which may affect the HPA axis for weeks).[96]

Although the findings are still well within the normal range, BDP, budesonide, and FP at high doses by conventional MDI (>1600 g daily) cause a dose-related drop in morning blood cortisol levels and 24 h urine cortisol. However, BDP or budesonide dosages of 2000 g per day, however, have minimal impact on the 24 hour urine cortisol excretion when a large volume spacer is utilised. Similar results from stimulation studies of HPA axis function indicate that corticosteroid dosages of 1500 g or less have no consistently negative effects. At high dosages (> 1500 g daily), budesonide and FP have a less significant impact than BDP on the HPA axis function at high dosages. With dosages of BDP of 800g or less, no suppression of urinary cortisol is observed in children. When plasma cortisol has been measured in investigations. In studies where plasma cortisol levels were monitored frequently, dosages of inhaled BDP of as little as 400 g per day significantly reduced cortisol peaks, albeit this doesn't seem to be dose-related in the 400-1000 g range. However, it is uncertain if these effects have any clinical significance.[9]

Bone metabolism

Corticosteroids cause a decrease in bone mass through direct effects on bone formation and resorption as well as indirect effects on the pituitary-gonadal and HPA axes, intestinal calcium absorption, renal tubular calcium reabsorption, and secondary hyperparathyroidism.[97]

There were no data indicating that long-term use of ICS is linked to an increased risk of fractures, despite the well-known effects of oral corticosteroids on osteoporosis and an elevated risk of vertebral and rib fractures. In order to evaluate how ICS affects bone mass, bone densitometry has been used. Despite evidence that individuals receiving high doses of ICS have lower bone density, interpretation is complicated by the fact that these patients are also receiving intermittent bouts of oral corticosteroids.[9]

The short-term effects of ICS on bone metabolism have been evaluated using a variety of biochemical indicators because changes in bone mass happen relatively slowly. Plasma levels of bone-specific alkaline phosphatase, serum osteocalcin, or procollagen peptides have all been used to evaluate bone development. Urine hydroxyproline following a 12-hour fast, urinary calcium excretion, and urinary pyridinium cross-link excretion can all be used to measure bone resorption. Acute and transient dose-related suppression of serum osteocalcin has been found with BDP and budesonide when given by standard MDI in various investigations. However, ICS, even at dosages up to 2,000 g daily, has no meaningful impact on calcium excretion.[9]

At comparable doses, budesonide consistently has less of an impact than BDP, and only BDP, at large doses, causes a rise in urine hydroxyproline. However, even doses of 2,000 g per day of either BDP or budesonide had no impact on plasma osteocalcin concentrations when a large volume spacer is used. Even with intermittent regimens of oral corticosteroids, ICS (BDP > 1,000 g daily) does not increase urinary pyridinium and deoxypyridinoline cross-links, a more precise and consistent indicator of bone and collagen degradation. The net effect on bone turnover must be taken into consideration, hence it is crucial to track changes in markers of both bone creation and bone breakdown. There is no clear evidence that ICS makes fractures more common. There has been no evidence that long-term high-dose ICS treatment alters bone density in a predictable way. In fact, increasing movement in older people may result in an increase in bone density.[9]

However, a systematic study reported no increase in fractures or decrease in bone mineral density in COPD patients receiving ICS for up to 3 years.[13]

Connective tissue effects

Due to an inhibitory effect on dermal fibroblasts, oral and topical corticosteroids cause telangiectasiae, easy bruising, and skin thinning. This is likely due to a loss of extracellular ground substance inside the dermis. There have been reports of increased skin bruising and purpura in individuals using large doses of inhaled BDP, however it is unknown how often these people take intermittent oral corticosteroids. Elderly patients are more likely to experience easy bruising in conjunction with ICS, and there are no reports of this issue in minors.[98] Different ICS and long-term prospective investigations with objective measurements of skin thickness are required.

Cataracts

There are multiple case reports reporting cataracts in specific ICS patients, and long-term use of oral corticosteroids increases the incidence of posterior subcapsular cataracts.[99] In a recent cross-sectional investigation, no cataracts were seen on slit-lamp examination in individuals aged 5 to 25 years taking either inhaled BDP or budesonide, even in those receiving 2,000 mg per day for more than 10 years.[100] Additionally, it has been found that patients using extremely high doses of inhaled corticosteroids have a risk of developing glaucoma.[91]

An epidemiological study revealed an increase in cataracts, which affect an older population more frequently.[62] The frequency of ocular or bone side effects was the same.[9]

It iss important not to emphasize how ICSs' ophthalmological side effects, such as glaucoma and intraocular pressure, affect the eyes.[101]

After 6 weeks of twice-daily fluticasone propionate treatment versus inhaled placebo in patients with well-controlled open-angle glaucoma and ocular hypertension, we found no clinically significant rise in IOP.[102]

Even at high current and cumulative dosages, there was no increase in risk with ICS when analysing cases of glaucoma requiring medication.[102]

Patients who received ICS/LABA Bi-therapy had considerably higher probabilities of developing oral thrush than those who received LABA alone, according to an observational, matched cohort research, with a dose-dependent effect for FP/ SAL.[70]

Growth

Numerous research have looked into the possibility that ICS can inhibit growth, which has been a source of special concern. Asthma has been linked to delayed puberty onset and a slowing of development velocity, which is more obvious with more severe disease. Asthma itself (like with other chronic diseases) may have an impact on the growth pattern.[103] These kids, however, seem to grow more slowly, so their final height is normal.

Since oral corticosteroid courses are a confounding factor, it is challenging to determine how the effects of ICS on growth in cross-sectional studies due to the influence of asthma on growth. Longitudinal investigations have shown that ICS does not significantly affect statural growth at doses up to 800 µg per day and for up to five years of treatment.[100]

Even at higher doses and for a longer period of time, inhaled BDP had no effect on statural height, according to a meta-analysis of 21 studies with more than 800 children,[104] and a large study of asthmatics treated with ICS during childhood found no difference in statural height compared to children without asthma.[105]

Another long-term follow-up study revealed that corticosteroids had no impact on children's final height who were treated over a number of years.[106] Even a small dose of an oral corticosteroid (prednisolone 2.5 mg) is sufficient to completely restrict the growth of the lower leg, according to short-term growth measures (knemometry). While there is some suppression reported with 800 mg and 400 mg BDP, inhaled budesonide up to 400 mg has no impact. Since modest doses of oral corticosteroids elicit severe suppression even when they have little influence on ultimate height, the link between knemometry readings and final height is questionable.[106]

Psychiatric effects

Numerous reports of psychiatric disruption following ICS have been made, including emotional instability, euphoria, despair, aggression, and insomnia. Eight such individuals have been reported thus far, indicating that this is extremely uncommon and that a causal relationship with ICS is typically not established.[10]

Pregnancy

Despite the lack of any controlled research, ICS appears to be safe during pregnancy based on considerable clinical experience. There is no proof that ICS has any negative effects on pregnancy, delivery, or the foetus.[107] It is crucial to understand that poorly managed asthma may raise the risk of perinatal mortality and stunt intrauterine growth. Therefore, better asthma management with ICS may lessen these issues.[10]

CONCLUSION

ICS was previously approved for first-line therapy for COPD patients with airflow obstruction and frequent exacerbations and was used to reduce symptoms in patients with COPD. The indication of ICS is an important issue in COPD management. The use of ICS in dual and/or triple therapy in COPD has been shown to reduce exacerbation and improve symptoms. ICS use is associated with a number of benefits, particularly in asthma, whereas their use in COPD may induce disruption of antimicrobial responses via a range of mechanisms. These effects may promote more severe viral infections and pneumonia in these patients. The adverse effects from the use of ICS in patients with COPD, most notably severe pneumonia results in excess deaths. Blood eosinophil levels would be taken into account in further withdrawal and initiation of ICS. The introduction of fixed dual long-acting bronchodilator therapy has changed the pattern of inhaler prescriptions for patients with COPD: prescriptions of ICS are rapidly being replaced by those of LAMA/LABA.

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