

Inhaled Corticosteroids Safety and Adverse Effects in Patients with Asthma



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Asthma is a common inflammatory airway disease for which the most commonly used controller medications are inhaled corticosteroids (ICS). Asthma control is difficult to achieve in individuals with severe asthma, which comprise 5% to 10% of individuals with asthma, even with high doses of ICS and other anti-inflammatory drugs. In this clinical context, the adverse effects of ICS (including hypothalamic-pituitary-adrenal axis suppression, reduction in growth velocity, osteoporosis, diabetes, and respiratory infections) become more probable and impacting on the quality of life of severe asthmatics. We here summarize the evidence of ICS-related adverse effects, particularly in patients with asthma. The possibility of using biologic agents earlier for severe asthma has the potential to prevent or reduce the occurrence of corticosteroid-related adverse effects, and also reduce corticosteroid-related costs. © 2018 American Academy of Allergy, Asthma & Immunology (J Allergy Clin Immunol Pract 2018;6:776-81)

Key words: Asthma; Inhaled corticosteroids; Safety; Side effects; Biologics

Inhaled corticosteroids (ICS) have been the cornerstone of asthma treatment since their introduction to the market at the end of the 1970s.¹ They have reduced asthma mortality and morbidity by suppressing airway inflammation and therefore diminishing asthma symptoms, improving lung function, reducing bronchial hyperresponsiveness, and lowering the

exacerbation rate.^{1,2} However, despite the efficacy of ICS as a class, some patients may have drug-related adverse effects, including mild acute symptoms such as dysphonia and thrush, or severe symptoms that may raise the issue of continuing, stopping, or modifying the ICS dose.³

Adverse effects to ICS are a relevant issue as the long-term goals of asthma management are not only achieving symptom control and maintaining normal activity levels, but also minimizing the future risk of exacerbations, fixed airflow limitation, and adverse effects.^{1,4-6}

The risk of systemic adverse effects has been concerning to physicians and patients,^{1,4,6} (Figure 1) leading some patients to have suboptimal adherence to prescribed medication with resulting poor disease control, increased visits to the emergency room or hospitalizations, and increased disease-related health care costs.⁷ The risk of ICS adverse effects is particularly relevant in severe asthmatics, accounting for approximately 5% to 10% of all patients with asthma, who require high doses of ICS and consume around 50% of the asthma-related costs.^{3,6,8} With the increased knowledge about asthma as a heterogeneous disease and its underlying immunological mechanisms and the subsequent development of new biologic drugs, the individualization of asthma treatment and the beginning of a “personalized medicine” era may offer a more specific therapeutic approach with reduced adverse effects from corticosteroids.²

The aim of this review article is to summarize the evidence regarding the main adverse effects of ICS, particularly in asthmatics and those with the most severe spectrum of disease.

SYSTEMIC BIOAVAILABILITY OF ICS

The amount of an ICS reaching the systemic circulation is the sum of the drug available after absorption across lung and nasal mucosa, plus the gastrointestinal tract absorption of swallowed drug that escapes hepatic first-pass inactivation, and is distinct for each ICS molecule/device.^{5,9}

Pharmacokinetic and pharmacodynamics parameters of ICS, such as rate of systemic clearance, volume of distribution, half-life, accumulation, protein binding property, and first-passage liver metabolism, contribute to the overall systemic exposure; other relevant factors are the glucocorticoid molecule administered, the inhaler device used, the particle size, the aerosol formulations, the dose and amount of drug that is actually delivered to the lungs and absorbed.^{1,5,10}

Relative ICS potencies are mometasone > fluticasone propionate > ciclesonide > beclomethasone monopropionate (active form of beclomethasone dipropionate) > budesonide⁹; potency is one of the major determinants of the relative comparable doses that are reported in Table I. It is important to remark that a

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This article has been supported by “ARMIA (Associazione Ricerca Malattie Immunologiche e Allergiche).”

Conflicts of interest: The authors declare that they have no relevant conflicts of interest.

Received for publication October 23, 2017; revised January 13, 2018; accepted for publication January 18, 2018.

Available online February 3, 2018.

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2213-2198

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<https://doi.org/10.1016/j.jaip.2018.01.025>

Abbreviations used

COPD- Chronic obstructive pulmonary disease

HPA- Hypothalamus-pituitary-adrenal

ICS- Inhaled corticosteroids

TB- Tuberculosis

higher drug potency does not necessarily correspond to higher efficacy, as potency is the amount of drug that is needed to produce a given effect, whereas efficacy refers to the maximum effect that it can produce regardless of dose.

Therefore, even small amounts of ICS can be systemically absorbed and produce adverse effects, particularly in patients using high ICS doses.⁹

ICS AND HYPOTHALAMIC-PITUITARY-ADRENAL-AXIS SUPPRESSION

When ICS were first used, it was thought that associated adrenal suppression would be rare. Although the prevalence rate of adrenal crisis after ICS therapy is not known, it is not so rare for pediatricians and endocrinologists to find cases of adrenal crisis associated with ICS in their clinical practice.¹²⁻¹⁷ Some researchers showed that not only the prolonged use of high doses of any kind of ICS is associated with greater risk,⁵ but also moderate and even low doses can lead to adverse effects.^{18,19}

In a recent meta-analysis,²⁰ the prevalence of adrenal insufficiency in asthmatics using ICS ranged from 2.4% (low dose) to 21.5% (high dose), and according to treatment duration from 1.4% (<28 days) to 27.4% (>1 year). In addition, adrenal suppression can persist for prolonged periods after corticosteroid discontinuation, including ICS (around 6 to 9 months).¹⁹⁻²¹

Adrenal suppression is a condition characterized by the inability to produce adequate amounts of cortisol that is critical during periods of physiological stress.¹⁴ The clinical presentation of adrenal insufficiency varies with degree and rate of adrenal function loss, as well as with the degree of stress the patient is exposed to, and on whether mineralocorticoid production is preserved or not.¹² The adrenal crisis after complete suppression of hypothalamic-pituitary-adrenal (HPA)-axis function is a serious adverse effect of ICS use.^{5,13}

Outcomes from some studies suggest that low-medium ICS doses may disturb basal cortisol secretion, a marker of adrenal suppression, in adults and children, but the clinical relevance is still unclear.⁵ A systematic review of the literature by Zöllner¹³ showed that, given a correct dose and duration, all ICS (100% of risk in treated patients) would cause HPA-axis suppression, at least biochemically. In chronic secondary adrenal insufficiency (eg, ICS-caused HPA-axis suppression), the clinical presentation (weakness, dizziness, abdominal pain, headache, poor growth, or weight loss) is not specific. These signs can easily be overlooked or misinterpreted. Orthostatic hypotension is a well-known sign, but pediatricians caring for asthmatic children on ICS are unlikely to be actively looking for this sign on a routine basis.^{12,14}

The symptoms of adrenal crisis include hypotension, acute hypoglycemia (often leading to seizures), decreased consciousness, and even coma. Adrenal suppression-induced hypoglycemia may also remain unrecognized, leading to significant morbidity and even mortality.¹⁴

Endogenous cortisol can be substituted by ICS, masking HPA-axis suppression. If the patient is exposed to stress (eg, infection, injury, burn, or surgery), the cortisol requirement may overcome the supply of the exogenous steroid, precipitating acute adrenal insufficiency. Abruptly stopping high-dose ICS can have the same effect.¹²

Despite the availability of a variety of tests assessing cortisol levels, there isn't a single test sensitive enough to detect low levels of HPA-axis suppression caused by ICS.⁵ Basal and dynamic adrenal function assessments, testing the integrity of the axis, are available but not commonly employed.^{12,22} The gold standard adrenal function tests are those evaluating the entire HPA-axis after adrenocorticotrophic hormone (ACTH) stimulation. However, they suffer from large variations in the execution and usually are expensive.^{12,19,21} Therefore, it is not uncommon that ICS-related adverse effects due to HPA-axis effects are unrecognized or not reported.¹³

As an alternative, some investigators have suggested the combined use of regular examinations to optimize control and for following up of HPA-axis integrity,⁵ increasing safety in the management of asthmatic patients, but also entailing more frequent consultations and increased examination-related expenses. Therefore, routine dynamic assessment of HPA-axis function in all patients using ICS may be prohibitive, considering the workload and cost implications; assessment of basal serum cortisol concentration may be helpful in determining which patients should be further studied for HPA-axis integrity.¹⁹

INHALED CORTICOSTEROIDS AND REDUCTION IN GROWTH VELOCITY

ICS may have potential adverse effects on growth velocity,^{1,5} and this is the most common family worry about ICS adverse effects, leading to poor adherence.²³

Glucocorticoids are known to interfere with many key mediators involved in growth; they inhibit growth hormone secretion and activity, collagen synthesis, adrenal androgen production, insulin-like growth factor 1 bioactivity, osteoblast activity, and acceleration of chondrocyte apoptosis; they also downregulate hepatic and growth plate growth hormone receptor expression.^{1,9,24}

The majority of ICS show a systemic activity by means of a decrease in growth velocity, resulting in a linear growth reduction of 0.5 to 3.0 cm (approximately 1 cm on average) during the first few years of therapy (particularly in the first year); the type of inhaled glucocorticoid and the delivery method are crucial factors for this adverse effect^{1,5,25-27}; in particular, a recent systematic review and meta-analysis highlighted that daily doses of inhaled beclomethasone 400 mcg and mometasone 200 mcg were significantly associated with reduction in growth velocity, while more conflicting are the reported results on inhaled budesonide.²⁶

The ICS-dose-dependent effect on growth seen in the first few years of administration in prepubertal children generally persists as lowered adult height.²⁵ Moreover, long-term ICS use (>12 months) is associated with slight reduced growth velocity and final adult height in treated children.²⁶⁻²⁸

Only ciclesonide 40 to 160 µg/day showed no effect in some studies, revealing pharmacokinetic and pharmacodynamic characteristics of high efficacy with low risk for systemic exposure,⁵ but a Cochrane review advised that further longer-term and superiority studies are required to verify benefits and risks of

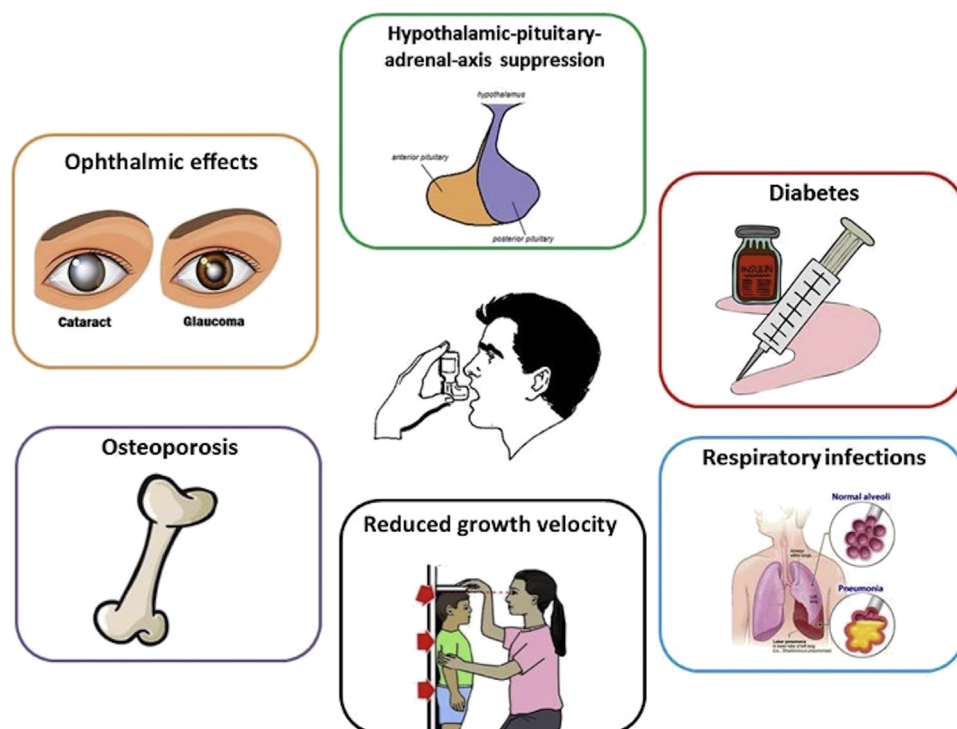


FIGURE 1. Common adverse effects related to the chronic use of inhaled corticosteroids.

TABLE I. Comparative daily dosages of inhaled corticosteroids¹¹

Drug	Comparative daily dosages (μ g)					
	Low		Medium		High	
	Child (5-11 y)	Adult (≥ 12 y)	Child (5-11 y)	Adult (≥ 12 y)	Child (5-11 y)	Adult (≥ 12 y)
Beclomethasone dipropionate						
HFA-MDI	80-160	80-240	>160-320	>240-480	>320	>480
Budesonide						
DPI	180-400	200-600	>400-800	>600-1200	>800	>1200
Nebules	500	UK	1000	UK	2000	UK
Ciclesonide						
HFA-MDI	80-160	160-320	>160-320	>320-640	>320	>640
Flunisolide						
CFC-MDI	500-750	500-1000	>1000-1250	>1000-2000	>1250	>2000
HFA-MDI	160	320	320	>320-640	≥ 640	>640
Fluticasone propionate						
HFA-MDI	88-176	88-264	>176-352	264-440	>352	>440
DPI	100-200	100-300	>200-400	300-500	>400	>500
Mometasone furoate DPI	110	220	220-440	440	>440	>440
Triamcinolone acetonide CFC-MDI	300-600	300-750	>600-900	>750-1500	>900	>1500

CFC-MDI, Chlorofluorocarbon-propelled metered-dose inhaler; DPI, dry-powder inhaler; HFA-MDI, hydrofluoroalkane-propelled metered-dose inhaler; UK, unknown.

ciclesonide before recommending it as standard clinical practice.^{24,29,30}

Some studies showed that ICS have minor and short-term effects on growth and very mild but potentially persistent long-term effects. However, the few studies that followed the patients through final height attainment found a minor effect on final height of 1 cm mean reduction.^{17,23,31} Longer-term trials (>1 year) are required to provide a fair comparison of the long-

term safety of different ICS dose options.³¹ Reduced linear growth in a child with asthma taking ICS should lead to a critical re-evaluation of the child's medication regimen.²³

INHALED CORTICOSTEROIDS AND OSTEOPOROSIS

Several factors are identified as capable of interfering with bone mass content: gender, nutrition, genetic predisposition,

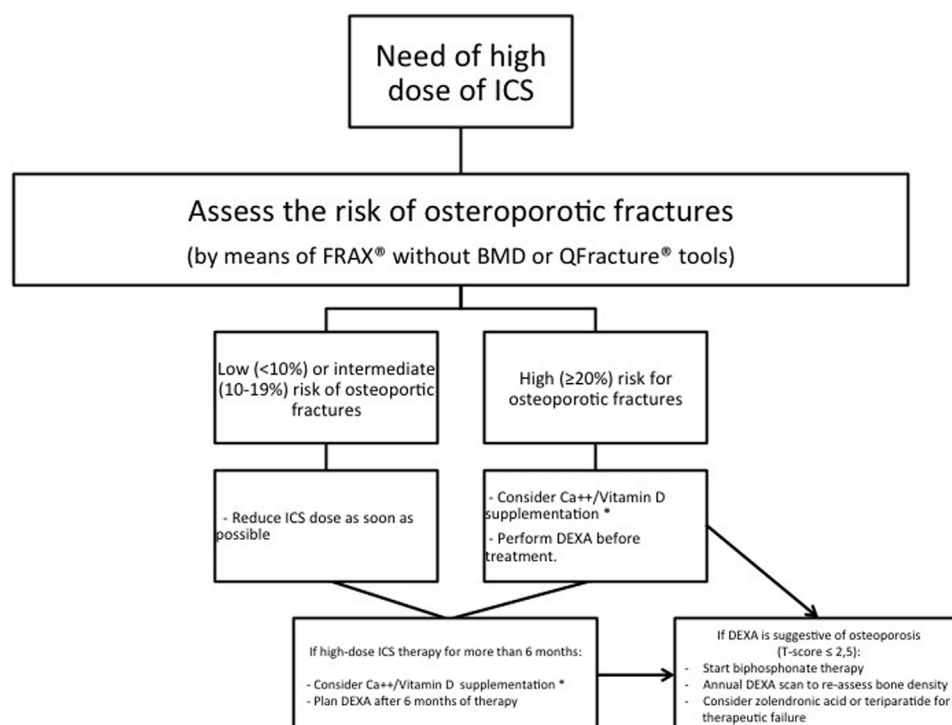


FIGURE 2. Proposed management of patients requiring high doses of inhaled corticosteroids depending on their personal risk of osteoporotic fractures. *To maintain, through diet or supplementation, a total daily calcium intake of 800 mg to 1200 mg daily and vitamin D of 800 to 2000 units daily. *BMD*, Bone mineral density; *DEXA*, dual X-ray absorptiometry, *ICS*, inhaled corticosteroids.

endocrine factors, and physical activities.³² Women are more prone for developing osteoporotic fractures, and up to 40% of postmenopausal women suffer such a fracture in their lifetime.³³ Severe asthma, for which high ICS doses are required that may interfere with bone metabolism, is more common in females over 50 years old, making osteoporosis and osteopenia an important clinical problem in women with asthma.

Glucocorticoids reduce bone mineralization and increase bone resorption by direct actions on osteoblasts and osteoclasts associated with decreasing bone mineral density^{22,33}; this may lead to osteoporosis and subsequent pathological fractures, which has a substantial impact on patients' quality of life (particularly older individuals), and frequently is a direct cause of death. The estimated annual cost related to osteoporotic fractures exceeds \$18 billion in the USA.^{33,34}

Although the systemic bioavailability of ICS is claimed to be minimal, such effects tend to occur in a significant number of ICS users, especially among those who receive moderate-to-high doses.^{32,33,35,36} Sasagawa et al³⁴ found a significant deterioration of bone status in female ICS users over a duration of 6 months: this kind of patient may be at a similar risk as with low-dose systemic corticosteroid.

ICS therapy during childhood, a critical time for bone development, could adversely affect bone mass and may predispose asthmatic children to osteoporosis during adulthood.^{5,33} However, in a recent study by Gray et al,³⁷ systemic corticosteroids, but not ICS, were significantly associated with increased odds of fracture in the pediatric asthma population. Kapadia et al¹⁷ suggest that children receiving high-dose ICS are at risk for diminished bone mineral density (BMD) if they also

have concomitant risk factors (eg, frequent oral corticosteroids, malnutrition, chronic diseases, etc).

Regarding use in adult asthmatics, long-term ICS use may result in BMD reduction possibly leading to an increase in fractures⁵: a meta-analysis including observational studies in older chronic obstructive pulmonary disease (COPD) and asthmatic patients found an increased fracture risk among those using high ICS doses.³⁸

Moreover, a 10% decrease in the baseline BMD increases the costs for ICS use over a prolonged period.³⁹

For all these reasons, the bone health of patients using ICS should be carefully monitored to avoid loss of bone density, leading to osteoporosis and a related increase in the cost of care.

Currently, there are no validated recommendations or scientific societies consensus for the management of patients with high risk of ICS-induced bone loss. However, considering the above-reported evidence of potential ICS-adverse effects on bone homeostasis, we propose to adapt a modification of the American College of Rheumatology 2010 recommendations for the prevention and treatment of systemic glucocorticoid-induced osteoporosis⁴⁰ as described in Figure 2. In particular, we propose to assess the risk of osteoporotic fractures by means of tools such as FRAX (<http://www.shef.ac.uk/FRAX/>)⁴¹ or QFracture (<http://www.qfracture.org/>)⁴²; the latter may have the advantage to be used for patients aged more than 30 years (whereas FRAX is for people aged more than 40 years) and to include, as risk factors, the presence of asthma and oral corticosteroid treatment. We suggest to approach patients depending on the assessed level of osteoporotic fractures risk (Figure 2).

INHALED CORTICOSTEROIDS AND DIABETES

Glucocorticoids may cause hyperglycemia by 2 main mechanisms: increased liver gluconeogenesis and decreased insulin sensitivity in several tissues.^{17,43} As with oral corticosteroids, ICS use has also been associated with an increased risk of developing diabetes and also worsening glycemic control in patients with known diabetes.^{40,44}

Suissa et al⁴⁵ found that ICS use was associated with a 34% increase in the risk of incident diabetes, particularly in patients taking high ICS doses (fluticasone propionate ≥ 1000 mcg). In addition, they found an increased risk of worsening of diabetes in ICS-treated patients on oral hypoglycemic agents¹⁰; in these patients, ICS initiation or dosage increase may require changes to their diabetes medications regimen. The association of ICS use with high serum glucose levels in diabetic patients seems to be dose-dependent.¹⁷

Asthmatic children using long-term ICS (for at least 6 months) have been reported to have an increase in average serum glucose levels,⁴⁶ and Lelii et al⁴⁷ diagnosed a transient symptomatic hyperglycemia in a child with recurrent wheezing and no predisposing factor for poor glucose tolerance, who was treated with fluticasone propionate only.

Therefore, serum glucose levels in ICS-treated asthma, particularly among those with diabetes, should be closely monitored.^{17,48}

INHALED CORTICOSTEROIDS AND OPHTHALMIC EFFECTS

Although the use of systemic corticosteroids increases the risk for cataracts, it has been difficult to establish a definitive link between ICS therapy and cataract formation. There have been conflicting data reported: some studies have shown minimal risk of ICS-related posterior subcapsular cataract development in asthmatic children, whereas the risk seems to be greater in adult patients.^{22,43} Ophthalmic effects may vary depending on individual susceptibility and timing of drug exposure.²²

Ernst et al⁴⁹ found a significant association between ICS use among elderly patients and an increased risk of cataracts, including severe forms requiring surgery. Although the excess risk was small, it was present even at 500 μ g/day of beclomethasone dipropionate or an equivalent dose of other ICS.

An increased risk of increased ocular hypertension or open-angle glaucoma related to ICS use has been reported.^{5,22,43} Gartlehner et al⁵⁰ conducted a meta-analysis that revealed a modest risk of cataracts and open-angle glaucoma. It was largely attributable to high dosage (with significantly higher odds ratios for cataract at dosage higher than 1000 mcg/day of fluticasone equivalents, and for glaucoma at dosage of at least 1500 mcg of flunisolide or 1600 mcg of other ICS) and long duration of ICS use.

Although there are limitations in the literature,⁵⁰ most studies suggest that patients on long-term ICS need to have their ocular pressure regularly monitored.^{5,22,43}

INHALED CORTICOSTEROIDS AND RESPIRATORY INFECTIONS

There are several studies demonstrating the suppression of cell-mediated immunity by oral corticosteroids. Thus far it is uncertain whether ICS do the same. Case reports have suggested

that ICS may cause a recurrence of viral infections and atypical infections, particularly tuberculosis.^{43,51}

Several clinical trials and observational studies demonstrated a higher risk of pneumonia in patients with COPD while using ICS, but other studies have reported opposite results.^{10,52-57} Increased incidence of pneumonia is the most serious potential adverse effect observed in these patients.¹⁰ Although there are few and discordant studies in asthmatic patients using ICS, there is some evidence that this adverse effect may occur, particularly in patients taking high doses of ICS.^{10,51,56} Few studies evaluate the severity of pneumonia in relation to ICS use: Sibila et al⁵¹ have related a higher severity of pneumonia with the need for hospitalization to prior out-patient use of ICS. They also found a higher incidence of antimicrobial-resistant pathogens. Further studies are needed to confirm these data, which are different from the results of some others studies.⁵⁵

Tuberculosis (TB) infection or re-activation may be another relevant adverse effects of corticosteroid use. A meta-analysis conducted by Ni et al⁵⁸ found that using ICS (>500 μ g/day fluticasone) could increase the risk of mycobacterium or TB in patients with chronic respiratory diseases, even if the mechanism is still unclear. ICS have also been shown to re-activate latent infection of *Mycobacterium tuberculosis* in patients with prior pulmonary TB.^{59,60} However, more large-scale, well-designed, high-quality studies are required to confirm these findings.

CONCLUSIONS

In conclusion, the use of ICS in children and adults with asthma is associated with potential adverse effects. Children and adults with severe asthma are at greatest risk of adverse effects and the risk increases with the administered dose; this is why many severe asthmatics may experience several harmful adverse effects that negatively affect their quality of life. We therefore suggest that in this subset of asthmatic patients and others with relevant ICS-related adverse effects, biological agents (which are able to significantly reduce the use of glucocorticosteroids)⁶¹⁻⁶³ should be promptly and preferentially used (provided that good adherence to treatment has been checked and achieved), and stepping down of ICS dose should be considered as soon as patients improve on biologic therapy (at least after 3 months of control of asthma).

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