

Managing moderate-to-severe paediatric asthma: a scoping review of the efficacy and safety of fluticasone propionate/salmeterol

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ABSTRACT

Background Fluticasone propionate/salmeterol xinafoate (FP/SAL) is an inhaled corticosteroid (ICS) and long-acting β_2 -agonist (LABA) combination, indicated for the regular treatment of children (aged >4 years) with asthma that is inadequately controlled with ICS monotherapy plus as-needed short-acting β_2 -agonists, or already adequately controlled with ICS/LABA.

Objective Compared with the adult population, fewer clinical studies have investigated the efficacy of FP/SAL in paediatric patients with moderate and moderate-to-severe asthma. In this review, we synthesise the available evidence for the efficacy and safety of FP/SAL in the paediatric population, compared with other available therapies indicated for asthma in children.

Eligibility criteria A literature review identified randomised controlled trials and observational studies of FP/SAL in the paediatric population with moderate-to-severe asthma.

Sources of evidence The Medline database was searched using PubMed (<https://pubmed.ncbi.nlm.nih.gov/>), with no publication date restrictions. Search strategies were developed and refined by authors.

Charting methods Selected articles were screened for clinical outcome data (exacerbation reduction, nocturnal awakenings, lung function, symptom control, rescue medication use and safety) and a table of key parameters developed.

Results Improvements in asthma outcomes with FP/SAL include reduced risk of asthma-related emergency department visits and hospitalisations, protection against exercise-induced asthma and improvements in measures of lung function. Compared with FP monotherapy, greater improvements in measures of lung function and asthma control are reported. In addition, reduced incidence of exacerbations, hospitalisations and rescue medication use is observed with FP/SAL compared with ICS and leukotriene receptor antagonist therapy. Furthermore, FP/SAL therapy can reduce exposure to both inhaled and oral corticosteroids.

Conclusions FP/SAL is a reliable treatment option in patients not achieving control with ICS monotherapy or a different ICS/LABA combination. Evidence shows that FP/SAL is well tolerated and has a similar safety profile to FP monotherapy. Thus, FP/SAL provides an effective option for the management of moderate-to-severe asthma in the paediatric population.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Fluticasone propionate/salmeterol xinafoate (FP/SAL) is indicated for the regular treatment of children (aged >4 years) with asthma. Clinical efficacy data are more limited in paediatric patients compared with the adult population.

WHAT THIS STUDY ADDS

⇒ We conducted a rigorous literature review of the efficacy and safety of FP/SAL in the paediatric population considering a variety of asthma outcomes including hospitalisation, rescue medication use and exercise-induced bronchoconstriction.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ Our review reinforces FP/SAL as a reliable and safe alternative to treat asthma in different situations in appropriate paediatric patients, providing potential corticosteroid-sparing effects when used in a step-up strategy.

INTRODUCTION

Asthma is a chronic, heterogeneous disease affecting approximately 262 million people worldwide,¹ characterised by chronic airway inflammation, bronchoconstriction, and airway hyper-responsiveness triggered by allergens and environmental factors.²

Asthma is the most common chronic disease in the paediatric population,³ and its prevalence is increasing.² According to the European Lung Foundation, approximately one in three people will be diagnosed with asthma between the ages of 5 and 80 years, with many patients being diagnosed before the age of 20 years.⁴

Parents can underestimate their child's asthma severity and overestimate their level of asthma control.⁵ In a global survey of parents of children/adolescents with asthma, 73% considered their child's asthma to be mild or intermittent, despite 35% reporting severe

exacerbations, requiring oral corticosteroids (OCSs) or hospitalisation, at least once per year.⁵ When assessed with the Childhood Asthma Control Test (C-ACT), 40% of children/adolescents had scores indicating inadequate control, and 85% had incompletely controlled asthma as defined by the Global Initiative for Asthma (GINA).⁵

Paediatric asthma is one of the top 10 causes of disability-adjusted life years in children aged 5–14 years and has a considerable societal burden.⁶ High levels of absenteeism from school are reported for children with asthma, inhibiting academic achievement and social interaction.⁶

Low- and middle-income countries often carry a higher burden of asthma.⁷ Over half of Latin American countries have reported a higher prevalence of childhood asthma (>15%) than the USA (9.3%).⁷ In the Asthma Insights and Reality in Latin America (AIRLA) Survey of parents of children with asthma in 11 Latin American countries, 2.6% of children met all GINA criteria for asthma control, with 68% of children reporting limitation in their activities and 58% reporting absence from school, due to asthma.⁸

Paediatric asthma also has substantial economic costs.⁹ The US Medical Expenditure Survey 2007–2013 reported total asthma-related annual healthcare expenditure of US\$5.92 billion for school-aged children.⁹

Clinical recommendations: moderate and moderate-to-severe paediatric asthma

Children and adolescents with mild, moderate and severe asthma are primarily managed with inhaled corticosteroid (ICS) therapy, based on international treatment recommendations.² For children (aged 6–11 years), the GINA 2022 report recommends adding a long-acting β_2 -agonist (LABA) to low-dose or medium-dose ICS as the step 3/4 controller option with as-needed short-acting β_2 -agonists (SABAs) or, alternatively, maintenance and reliever therapy (MART) with very low or low-dose ICS/formoterol (ICS/FORM).² For adolescents (aged ≥ 12 years old), GINA proposes two treatment tracks at step 3/4: ICS/FORM as MART (track 1) or low-/medium-dose ICS/LABA with as-needed SABA (track 2).²

Fluticasone propionate/salmeterol xinafoate: maintenance therapy for paediatric asthma

Fluticasone propionate (FP) is a synthetic corticosteroid with glucocorticoid activity.¹⁰ Salmeterol xinafoate (SAL) is a selective LABA with a bronchodilator effect lasting >12 hours.¹⁰ FP/SAL is a fixed-dose combination inhalation agent approved for use in children (aged 4–11 years).^{11–14}

FP/SAL is indicated for the regular treatment of children and adolescents (aged ≥ 4 years) with asthma, where use of a combination product is appropriate (ie, asthma not adequately controlled with ICS monotherapy and as-needed SABA, or already adequately controlled with ICS/LABA).¹¹ In Europe, the licensed dosage of FP/SAL

delivered to a child (aged 4–11 years) from an inhaler is 100 μg FP and 50 μg SAL two times per day.¹¹ Adolescents (aged >12 years) may be prescribed one inhalation of 100, 250 or 500 μg FP two times per day in combination with 50 μg SAL two times per day.¹¹ FP/SAL can be delivered as a pressurised metered-dose inhaler (pMDI) or as a dry powder inhaler (DPI). Licensed dosages may vary between countries.

Compared with the adult population, limited clinical efficacy data are available for FP/SAL in children with moderate and moderate-to-severe asthma. This review aims to synthesise the available evidence of efficacy and safety by:

- ▶ Identifying publications relating to FP/SAL in children and adolescents (aged 4–16 years) with moderate and moderate-to-severe asthma.
- ▶ Discussing the efficacy of FP/SAL as step-up treatment from ICS monotherapy versus ICS (particularly high-dose ICS), leukotriene receptor antagonists (LTRAs) and other available comparators.
- ▶ Assessing outcomes including symptom control, exacerbation reduction, lung function, nocturnal awakenings and rescue medication use.
- ▶ Examining evidence relating to the safety and tolerability of FP/SAL.

METHODS

Publications investigating FP/SAL treatment in children and adolescents (aged 4–16 years) with moderate-to-severe asthma were reviewed in June 2022. Literature published in the Medline database was searched using PubMed (<https://pubmed.ncbi.nlm.nih.gov/>), with no publication date restrictions. Specific search strings are presented in online supplemental table 1. Reference lists of relevant publications were reviewed to identify potential studies not found in the database search.

Publications were screened and selected based on inclusion of:

- ▶ Information relating to treatment with FP/SAL in the paediatric population with moderate-to-severe asthma.
- ▶ Data comparing FP/SAL with other comparators. The literature search did not exclude any comparators (including other ICS/LABA combinations); however, targeted searches were conducted for comparators of greatest clinical relevance (placebo, high-dose and low-dose ICS monotherapy, and LTRA).

Study types were limited to randomised controlled trials (RCTs) and observational studies. Publications not stratifying results for adult and paediatric populations were excluded. Studies including patient ages above 4–16 years were not excluded, but only results for patients aged <18 years were considered. Studies including the off-label use of FP/SAL were also excluded. Selected articles were screened for clinical outcome data (exacerbation reduction, nocturnal

awakenings, lung function, symptom control, rescue medication use and safety).

Patient and public involvement

There was no patient or public involvement in this research.

RESULTS

Screening identified 18 RCTs (N=11384) and 4 observational studies (N=1.1 million) including patients aged 4–17 years with moderate-to-severe asthma. A scoping review of all key outcomes was determined as the best approach for this article. A list of 20 selected studies and their key outcomes is presented in online supplemental table 2; 2 studies were not reported here as further analysis showed that study drugs were used outside of their licensed indications. Although studies of FP/SAL versus any comparators which met the criteria were included, the discussion focuses on those comparators of greatest clinical relevance (high-dose and low-dose ICS monotherapy, and LTRA).

Pharmacodynamics and pharmacokinetics: FP/SAL

The pharmacokinetic (PK) and pharmacodynamic (PD) profiles of FP and SAL are well established in adults and children.^{15–17} Negligible oral bioavailability (<1%) is reported for FP.^{11 18 19} Inhaled absolute bioavailability varies between 5% and 11%.¹¹ FP also has a high relative glucocorticoid receptor affinity.²⁰

Concurrent therapy versus combination therapy

The PK properties of FP and SAL are similar whether they are administered separately or in combination. No systemic PK/PD interactions exist between the two therapies given together.^{17 21} Data on the PK/PD profile of combination FP/SAL are limited in the paediatric population. In a randomised study, 257 children (aged 4–11 years) with asthma who remained symptomatic on ICS alone (beclomethasone dipropionate (BDP), budesonide (BUD) or flunisolide 400–500 µg/day, or FP 200–250 µg/day) received FP/SAL 100/50 µg two times per day either in combination or as two inhalers administered concurrently.²² Adjusted mean morning and evening peak expiratory flow (PEF) improved through 12 weeks using both regimens (by 33 L/min and 29 L/min for the FP/SAL combination and 28 L/min and 25 L/min for concurrent therapy) and treatment groups were found to be clinically equivalent.²²

Clinical outcomes

Asthma control

Comparative evidence: FP/SAL versus ICS

Achieving asthma control and reducing symptom burden and limitation of daily activities are key when managing childhood asthma. A small number of studies have shown

improvements in asthma control with FP/SAL versus ICS alone in this population.^{23–25}

In the multicentre, double-blind VIAPED RCT of children (aged 4–16 years), FP/SAL (100 µg/50 µg two times per day) gave 8.7% more symptom-free days and 8.0% more reliever-free days compared with FP monotherapy (200 µg two times per day) over 8 weeks following a 14-day run-in period with FP (100 µg two times per day).²⁶ Another double-blind RCT of children (aged 4–11 years) with asthma judged as ‘not-controlled’ for 2/4 weeks of the run-in period reported that 75% of patients treated with FP/SAL (100/50 µg) achieved a well-controlled week by week 4, while 75% of patients in the FP group (200 µg two times per day) achieved a well-controlled week by week 6.²⁴ A ‘well-controlled week’ was defined as no nocturnal awakenings/exacerbations, emergency department (ED) visits or treatment-related adverse events (AEs) and having ≥2 of: symptoms on <3 days, SABA use on <3 days and daily morning PEF ≥80% predicted.²⁴

Three studies report similar benefits of FP/SAL, FP or FP/FORM on asthma symptom/sleep disturbance scores, SABA use, nocturnal awakenings or asthma control days.^{23 24 26} In the paediatric population, significant improvements in lung function with ICS/LABA versus ICS monotherapy do not necessarily translate to improvements in symptoms and exacerbations, in contrast to the adult population²³; differences in interpretation of lung function results or unreliable subjective reports from paediatric patients may contribute to this anomaly.²³

Step-up therapy: FP/SAL versus high-dose ICS and ICS+LTRA

The efficacy of FP/SAL compared with high-dose ICS monotherapy is a key consideration for step-up therapy, as long-term use of high-dose ICS has been associated with increased risk of local and systemic side effects.²⁷ Evidence comparing high-dose ICS with ICS/LABA is limited in the paediatric population²⁸; however, FP/SAL is reported to have efficacy equal to or greater than double-dose FP (200 µg two times per day) in measures of symptom control in children with moderate asthma.^{24 26 29}

For children aged 6–11 years, the stepwise GINA recommendations also indicate that ICS+LTRA may be considered as an alternative controller option to ICS/LABA at step 3, although evidence supporting this approach is limited.² It should be noted that LTRAs have been associated with neuropsychiatric AEs and LTRA prescription should consider all benefits and risks, with the provision of patient counselling.^{2 30}

The most appropriate step-up therapy for paediatric patients (aged 6–17 years) with asthma uncontrolled on low-dose ICS was investigated in a crossover RCT based on a composite of exacerbations, asthma-control days and forced expiratory volume in 1 s (FEV₁).³¹ While each of the step-up treatments improved responses, step-up to FP/SAL 100/50 µg was significantly more likely to provide a better response than step-up of ICS dose to

FP 250 µg (relative probability, 1.7; 95% CI, 1.2 to 2.4) or step-up to FP 100 µg+LTRA (relative probability, 1.6; 95% CI, 1.1 to 2.3).³¹ Although these data support the GINA recommendation for ICS/LABA as preferred step-up controller medication for children, several characteristics, including race, Asthma Control Test score and presence of eczema may affect the treatment response.³¹ Many children had a best response to LTRA step-up, so regular monitoring and adjustment of each child's therapy is important before stepping up further.³¹

FP/SAL can provide similar benefit to high-dose FP while reducing corticosteroid exposure.²⁹ An RCT of 158 children (aged 6–16 years) with moderate asthma, symptomatic on moderately dosed ICS monotherapy, reported the efficacy of FP/SAL (100/50 µg two times per day) as equal to doubling the dose of FP (200 µg two times per day) in terms of symptom control.²⁹ Mean-adjusted difference in symptom-free days between FP and FP/SAL over 10 weeks was 0.4% (95% CI, –9.1% to 9.9%) in the intention-to-treat analysis, showing negligible difference between treatments and non-inferiority for FP/SAL.²⁹

Non-inferiority of FP/SAL (and potential superiority) to double-dose FP monotherapy has been recognised in the GINA step 3 recommendations.² GINA also recommends low-dose ICS/FORM as MART in track 1 at step 3/4 for children (aged 6–11 years),² although evidence for the efficacy of ICS/FORM as MART versus FP/SAL in this cohort is lacking.

Step-down of FP/SAL

Step-down of therapy can be considered once good asthma control has been achieved, in order to prescribe the minimum effective treatment while maintaining symptom and exacerbation control.² This can minimise the cost of treatment and risk of potential side effects.²

A Japanese RCT demonstrated that in 121 children (aged 5–15 years) with asthma controlled by FP/SAL (200 µg per day) for at least 12 weeks, step-down of therapy to halve the dose of FP/SAL to 25/50 µg two times per day and/or switching to FP (100 µg two times per day) resulted in the same high level of asthma control.^{32–33}

Exacerbations and hospitalisations

Regular dosing with FP/SAL treats underlying inflammation in paediatric asthma, reducing the risk of asthma-related ED visits and hospitalisations versus treatment with ICS monotherapy and LTRA.^{34–36}

A large, retrospective, observational study of healthcare claims showed that following treatment with FP/SAL in the summer, the incidence of asthma-related ED visits in the fall was reduced from 5.4% to 3.4% (adjusted OR, 0.60; 95% CI, 0.54 to 0.67) and hospitalisations was reduced from 1.3% to 0.7% (OR, 0.49; 95% CI, 0.39 to 0.61).³⁴ This suggests that administration of FP/SAL throughout the summer prevents worsening of asthma in the fall, with an estimated number needed to treat of 50 to prevent one ED visit and 167 to prevent one hospitalisation.³⁴

In another retrospective, observational cohort study of pharmacy claims, after matching for ICS, OCS and hospitalisation/ED visit history, incidence of asthma-related hospitalisations and ED visits were significantly lower for children who started FP/SAL (3.5%) than those who started ICS+LTRA (5.7%) with a 96% lower risk of asthma-related hospitalisation.³⁶

Rescue medication use

FP/SAL is highly effective and clinically equivalent in paediatric patients when administered via the DPI Diskus or pMDI.³⁷ In an RCT of children with asthma aged 4–11 years receiving BDP, BUD, flunisolide (up to 500 µg/day) or FP (up to 200 µg/day), patients who switched to FP/SAL either via Diskus or pMDI experienced the same increase in median percentage of medication-free days to 99%, following a 2-week run-in with ICS.³⁷

A retrospective, observational study of healthcare claims of 9192 children aged 4–17 years found that those treated with FP, LTRA, ICS+SAL and ICS+LTRA were 14%, 22%, 32% and 83%, respectively, more likely to fill a prescription for SABA therapy compared with those treated with FP/SAL.³⁸ Children treated with FP/SAL were also less likely to receive an additional SABA prescription during the post-index period.³⁸

Step-up therapy: FP/SAL versus high-dose ICS

FP/SAL effectively reduces exacerbation risk and rescue medication use in paediatric patients versus higher doses of ICS monotherapy, although the evidence for improvement in lung function is limited.^{24–26 29}

In children aged 4–11 years with asthma, previously treated with ICS (FP 100 µg two times per day for a 4-week run-in period), the proportion achieving 100% rescue medication-free days through week 12 has been reported as 29% (43 of 150) for those randomised to FP/SAL (100/50 µg) compared with 19% (29 of 153) for those randomised to double-dose FP monotherapy.²⁴

In an RCT of 158 children (aged 6–16 years) with moderate asthma who were symptomatic on moderate doses of ICS monotherapy during a 4-week run-in period, the percentage of days with SABA use decreased from 38% to 22% with FP/SAL (100/50 µg two times per day) treatment. This was not significantly different to FP (200 µg two times per day) treatment, with which SABA use decreased from 35% to 20%.²⁹

Exercise

Exercise-induced bronchoconstriction (EIB) is an important consideration for the management of paediatric asthma, because physical activity levels are high among children and adolescents,³⁹ and exertion is a major precipitating factor for asthma symptoms.⁴⁰ FP/SAL produces greater protection from EIB than FP alone and could be used as a regular controller in children with persistent EIB who are not adequately controlled on ICS monotherapy.^{40 41}

Comparison of lung function following exercise challenge was investigated in an RCT of 248 paediatric patients (aged 4–17 years) with persistent asthma, receiving daily ICS before the study, and switched to either FP (100 µg two times per day) or FP/SAL (100/50 µg two times per day) with albuterol as needed.⁴⁰ By week 4, maximal decline in FEV₁ following exercise challenge was significantly better with FP/SAL (9.5%) than with FP alone (12.7%); 64% of the FP/SAL treatment group had a <10% decrease in FEV₁ compared with 47% of the FP treatment group.⁴⁰ Additionally, 14% of patients receiving FP/SAL had a ≥20% decrease in FEV₁, vs 20% of patients receiving FP.⁴⁰

Corticosteroid ‘bursts’

Sparing corticosteroid exposure in children with asthma is an important consideration. Adverse drug reactions have been reported in children (aged 28 days–18 years) following short courses of OCS, with the most frequent reactions being vomiting, behavioural changes, sleep disturbances and increased susceptibility to infection.⁴² OCS bursts in children with mild-to-moderate asthma have also been associated with dose-dependent reduction in bone mineral accretion over a period of years, with increased risk of osteopenia in boys.⁴³ Attention to corticosteroid exposure should also include high-dose ICS in light of concerns about long-term ICS use in children.²⁷

Children (aged 4–17 years) treated with FP/SAL are significantly less likely ($p \leq 0.009$) to have received a prescription for OCS compared with those receiving LTRA, ICS+SAL and ICS+LTRA.³⁸ FP/SAL can be also prescribed for patients who fail to gain adequate symptom control while taking ICS, minimising the risk of systemic effects from high-dose ICS and OCS ‘bursts’.⁴⁴

Lung function

Clinically significant improvements in lung function have been observed with FP/SAL treatment in children aged 4–11 years with documented history of asthma receiving ICS.³⁷ In a 12-week study, morning PEF (\pm SE) from baseline improved by 37.7 \pm 3.1 L/min and 38.6 \pm 3.0 L/min with FP/SAL via Diskus or pMDI, respectively.³⁷

Comparative evidence: FP/SAL versus ICS

Lung function improvements with FP/SAL are superior to those achieved with FP monotherapy in children, and similar to FP/FORM.^{23 24} An RCT of 512 children (aged 5–11 years) with persistent asthma, inadequately controlled with ICS alone (≤ 500 µg/day FP or equivalent) or controlled with an ICS/LABA combination (≤ 200 µg FP or equivalent), investigated the change in FEV₁ from baseline to 2 hours post-dose.²³ Although the primary comparison was FP/FORM versus FP monotherapy, results suggested that mean change in FEV₁ over 12 weeks was greater with FP/SAL (100/50 µg two times per day: 0.22 L; 95% CI, 0.18 to 0.26) than with FP alone (100 µg two times per day: 0.15 L; 95% CI, 0.11 to 0.19).²³

Other lung function endpoints (forced expiratory flow, PEF) showed improvements pre-dose and 2 hours post-dose for FP/SAL versus FP monotherapy.²³

An RCT of 24 children aged 4–11 years with moderate-severe asthma demonstrated that lung function improvement was superior with FP/SAL (100 µg/50 µg two times per day) versus high-dose FP (200 µg two times per day), measured using specific airway resistance (sR_{aw}), a potentially more applicable measure than FEV₁ or PEF for young children. After 6 weeks of treatment, children who were taking daily BDP or equivalent (200–800 µg) and switched to FP/SAL had a 19% greater reduction in sR_{aw} (95% CI, 3% to 32%) than those switched to higher-dose FP.²⁵

Step-up therapy: FP/SAL versus high-dose ICS

Limited evidence is available in paediatric patients comparing lung function improvements with FP/SAL versus higher doses of ICS monotherapy.^{24–26 29 31} One RCT directly compared FP/SAL (100/50 µg two times per day) with double-dose FP (200 µg two times per day) to assess effect on morning PEF over 12 weeks in 321 children (aged 4–11 years) with asthma previously treated with ICS (BDP 400 µg/day or equivalent). After demonstrating non-inferiority of FP/SAL to high-dose FP for mean change in morning PEF, the treatment difference between treatment groups of 7.6 L/min (95% CI, 1.7 to 13.5) showed that FP/SAL was superior to FP.²⁴

In the VIAPAED Study, FP/SAL was non-inferior to high-dose FP for change from baseline in mean morning PEF after 8 weeks of therapy ($p < 0.0004$).²⁶ In the intention-to-treat population, mean morning PEF was higher with FP/SAL than FP monotherapy (+8.6 L/min; 95% CI, 1.3–infinity).²⁶

Safety

Safety studies are especially critical in the paediatric population, to avoid risks to this vulnerable group.⁴⁵ Absence of safety data may lead to overdosing and resultant AEs or underdosing and undertreatment.⁴⁵ Specific safety concerns for FP/SAL relate to the effect of ICS on statural growth, the potential of LABA monotherapy to increase the risk of asthma-related death in adults and risk of asthma-related hospitalisation in paediatric patients.^{11 29 46}

FP/SAL (100/50 µg or 250/50 µg two times per day) has a similar safety profile to FP (100 µg or 200 µg two times per day) and carries similar risk of serious asthma-related events.⁴⁷ In the prospective VESTRI trial of 6208 children (aged 4–11 years) who required daily maintenance treatment and had a history of asthma exacerbation in the previous year, FP/SAL (100/50 µg or 250/50 µg) did not increase the risk of serious asthma-related events (death, endotracheal intubation or hospitalisation) compared with FP monotherapy (100 or 250 µg).⁴⁷ The HR for a serious asthma-related event with FP/SAL versus FP monotherapy was 1.28 (95% CI, 0.73 to 2.27), demonstrating

non-inferiority.⁴⁷ Asthma-related hospitalisations were the only reported serious asthma-related events, at a rate of ~1.5 per 100 patient-years (consistent with the known rate of hospitalisations among children aged 5–14 years⁴⁸), with no deaths or asthma-related intubations.⁴⁷

Other studies have demonstrated a similar safety profile and rate of associated AEs with FP/SAL compared with FP alone^{23 29 44}; nasopharyngitis is the most common AE for both treatments.²³

Similar effects on statural growth are noted for FP and FP/SAL.²⁹ In three studies in children (aged 4–11 years), urinary/serum cortisol levels remain within normal limits with no evidence of hypothalamic–pituitary–adrenal axis suppression following administration of FP (100 µg two times per day) or FP/SAL (50/100 µg two times per day) in the studies that assessed cortisol levels.^{22 37 44}

DISCUSSION

FP/SAL evidently improves the burden of asthma in the paediatric population with moderate and moderate-to-severe asthma, versus ICS monotherapy and LTRA, owing to the reduced exacerbation/hospitalisation risk and improvements from baseline in lung function, nocturnal awakenings, rescue medication-free days and asthma control experienced with FP/SAL treatment. FP/SAL can also be beneficial in reducing OCS ‘bursts’, as it improves asthma control, reduces exacerbations and can minimise the need for OCS use.^{2 49 50} FP/SAL is well tolerated and shares a similar safety profile to FP monotherapy in paediatric patients^{23 29 44}; and while no evidence of growth retardation or cortisol suppression was reported in the studies that assessed them, relatively few studies assessed these key safety measures in paediatric populations.^{22 37 44 51}

Limitations

Conclusions that can be drawn from this review are restricted by the narrow evidence base in the paediatric population and the limitations of the studies presented. For example, studies without a placebo arm cannot properly assess absolute clinical effects of individual treatments,^{24 25 29 44 52 53} and open-label, non-blinded trials carry a risk of bias that may affect subjective measures of efficacy.³² The studies identified generally had short durations (4–12 weeks) which may be considered insufficient to gather meaningful data.^{22–26 32 37 40 44 52} In addition, a range of outcome measures are reported, making comparisons across studies difficult.

Some RCTs also reported small sample sizes with limitations in representative subgroup analyses.^{25 32} Observational healthcare claim studies have limited accuracy within patient records and cannot confirm whether dispensed medications were used correctly.^{34 38}

CONCLUSIONS

FP/SAL is recommended by national asthma guidelines in several countries for treatment step-up in paediatric

patients.^{49 50} Positive efficacy outcomes and reported equivalence to high-dose FP support these recommendations.^{26 29} Children treated with FP/SAL are expected to be less likely to receive additional OCS for asthma exacerbations/ED visits, because FP/SAL improves asthma control compared with other therapies; however, the need for OCS may vary with asthma severity and phenotype.³⁸

In conclusion, FP/SAL is a reliable alternative to ICS step-up in appropriate paediatric patients with moderate and moderate-to-severe asthma not controlled with low-dose ICS, and provides potential corticosteroid-sparing effects when used in a step-up strategy. Since FP/SAL is a key therapy considered for paediatric asthma, treatment plans should be tailored to each child and their suitability for step-up to FP/SAL should be regularly assessed. However, further studies of FP/SAL in paediatric asthma, including comparison with ICS/FORM as MART and low-dose ICS monotherapy, would be beneficial to establish stronger evidence to aid physicians in clinical decision-making and improve management of childhood asthma.

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