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Fluticasone Furoate: A Once Daily Preparation in Patients with Persistent Asthma

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Article Info

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Abstract

Asthma affects approximately 240 million people worldwide. It is characterised by an allergic pattern of smooth muscle constriction and airway inflammation, and if chronic, the inflammation can lead to structural changes and fixed airflow obstruction. Bronchodilators relieve the bronchoconstriction, while inhaled corticosteroids reduce the airway inflammation. This paper reviews fluticasone furoate (FF), a novel inhaled corticosteroid with 24-hour duration of action. It is a synthetic fluorinated corticosteroid with agonist activity at the glucocorticoid receptor (GRE). It is reported to have a fast association and slow dissociation from the GRE compared to other ICSs. FF has been found to have a greater lung retention time than all other ICS preparations which may contribute to the extended duration of anti-inflammatory action. FF has extensive first pass hepatic metabolism resulting in a low gastrointestinal bioavailability which is consistent with the findings for other ICS preparations. FF, however, will pass from the lung into the systemic circulation and therefore an adverse profile similar to all ICS is likely, but long term data are needed.

FF has demonstrated treatment efficacy for asthma between 100μg and 200μg alone, but in combination with the long-acting beta agonist, vilanterol (FF/VIL 200μg/50μg OD) there were further improvements in lung function relative to monotherapy. There is an increased risk of pneumonia identified in patients with airways disease in associated with ICS preparations and surveillance will be required to determine if this also applies to FF. Once daily therapy, such as FF, may improve compliance and could hopefully be translated into further improvements in asthma-related outcomes.

Introduction

Asthma is estimated to affect over 240 million people worldwide[1]. It is a heterogeneous disease, defined by symptoms which include wheeze, shortness of breath, chest tightness and cough. Asthma varies in intensity and over time, being characterised by variable expiratory airflow obstruction and inflammation.

Th2 asthma is caused characteristically by an allergic pattern of inflammation in the airways, involving initial sensitization to allergens, infiltration by antigen presenting cells such as dendritic cells, inflammatory cells (eosinophils and T-helper 2 (Th2) cells) and IgE priming of mast cells[2, 3, 4]. Less commonly, an alternate pathway has been described that can contribute to the development of low-Th2 asthma. These factors include infection-related elements, Th1 and Th17 immunity; non-Th2 associated smooth-muscle changes and the development of neutrophilic inflammation include hypertrophy and hyperplasia of airway smooth muscle cells, fibrosis, angiogenesis, and hyperplasia of mucus-secreting cells[3, 5]. Chronic inflammation can lead to structural changes and fixed airflow obstruction.

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Oral corticosteroid therapy has proved efficacious for the treatment of asthma for many decades. To mitigate against some of the systemic side effects, inhalational therapy was a logical, effective solution. This coupled with the fact that asthma pathology is largely confined to the airways of the lungs has made inhaled corticosteroid (ICS) therapy the gold standard method for anti-inflammatory drug delivery[6, 7].

Glucocorticoids are the most effective anti-inflammatory treatment in asthma and switch off multiple activated pro-inflammatory genes[8]. Treatment with inhaled corticosteroids has been demonstrated, through histological specimens, to produce a reduction in mast cells, eosinophils, T lymphocytes and dendritic cells in the mucosa and submucosa; reduced goblet hyperplasia and epithelial-cell injury and decreased vascularity. However, neutrophilic inflammation is less likely to respond to ICS. No other drug class to date has demonstrated a greater effect in preventing adverse asthma-related outcomes than ICS[9].

In those with poorly controlled asthma, it is estimated that this is due to poor adherence with preventative therapy in more than half of the patients, at least to some degree[10]. Over-confidence and misuse of inhaled β_2-adrenergic therapy have also been shown to increase the risk of hospitalisation in asthmatics[11, 12].

Fluticasone furoate (FF) is a novel inhaled corticosteroid with 24-hour duration of action with proven efficacy morning and evening[13]. This paper reviews the literature supporting the use of FF as a once daily maintenance treatment of asthma in adults and adolescents over the age of 12. A once daily inhaled corticosteroid could potentially improve compliance with medication and therefore reduce the risk of poor asthma-related outcomes associated with poor adherence[1,14].

Structure

The chemical composition of FF is $C_{27}H_{29}F_3O_6S$ and is demonstrated below (Figure 1). It can be administered as a single agent via the inhalational route or in combination with a long acting β_2- agonist (LABA) [15]. It is a synthetic fluorinated corticosteroid with agonist activity at the glucocorticoid receptor (GRE).

Fluticasone propionate (FP) is a well-established ICS for the treatment of asthma[9]. Although FF and FP are structurally related, they are chemically and pharmacologically distinct. They share no common metabolites nor are they metabolised to fluticasone, acting not as pro-drugs but as distinct drug molecules[16]. Differences between FF and FP were shown using x-ray crystallography demonstrating the ester derived from FF occupying a discreet pocket on the glucocorticoid receptor more fully than FP[17]. This suggests higher affinity of FF for both lung and nasal tissue[18].

Efficacy

Pre-clinical Studies

The pharmacological properties of FF were examined *in vitro* and *in vivo* models of respiratory inflammatory disease (i.e. asthma and chronic obstructive pulmonary disease (COPD)). The potency of FF activity on the glucocorticoid response element (GRE) was examined
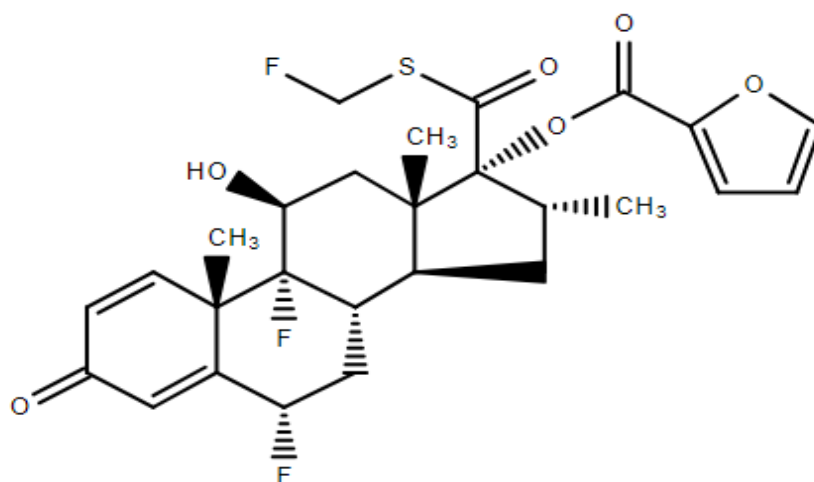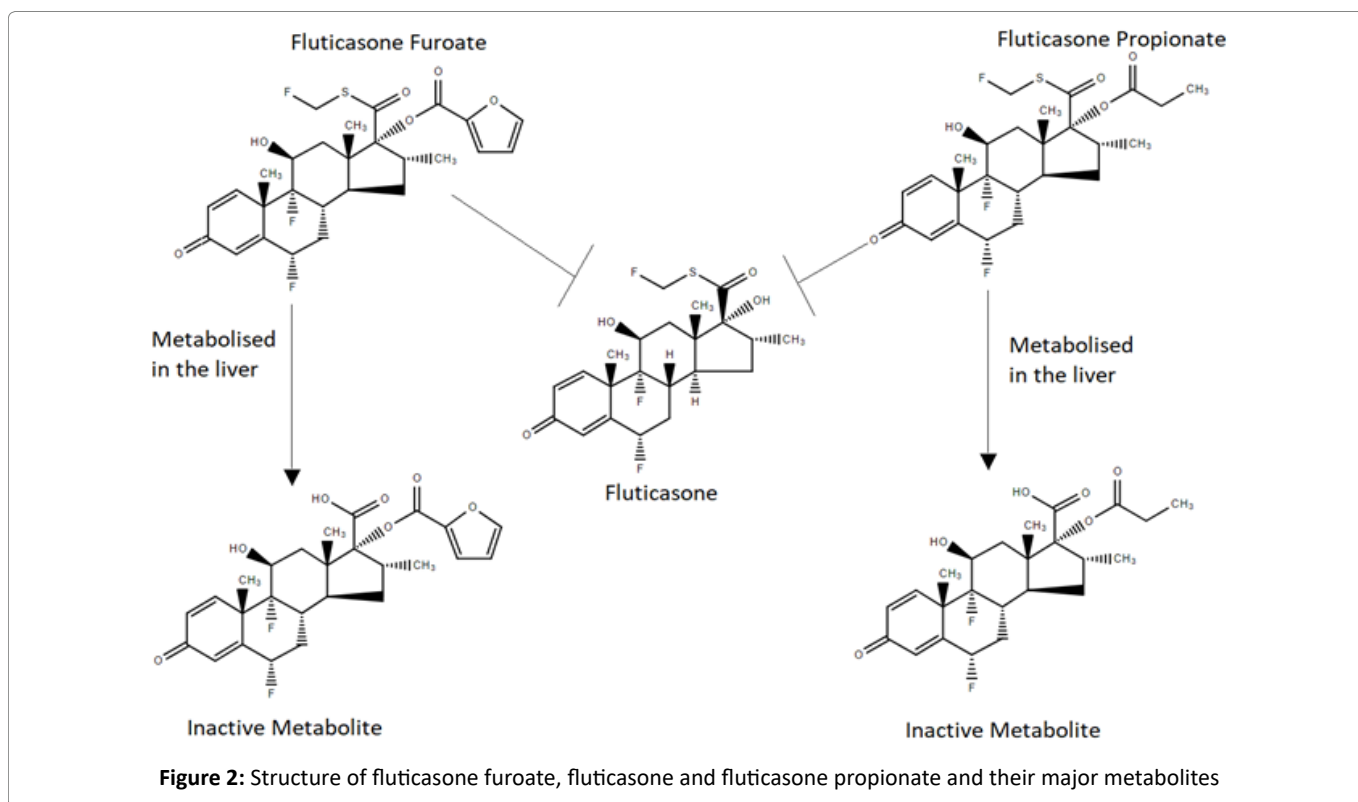

Figure 1: Fluticasone furoate ($C_{27}H_{29}F_3O_6S$)

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Figure 2: Structure of fluticasone furoate, fluticasone and fluticasone propionate and their major metabolites

and compared with other available ICS (e.g. mometasone furoate (MF); budesonide (BUD) and ciclesonide (CIC). The GRE is found in many target pro-inflammatory genes that respond to glucocorticoids. FF displayed the highest potency when compared with other corticosteroids tested by GRE binding, with a relative receptor affinity 1.7 times that of FP and 1.3 times that of MF. FF has also been shown to have increased affinity when compared to other available corticosteroids (dexamethasone and FP) on the GRE. MF demonstrated lower tissue binding compared with FF and FP[19]. FF has been found to be have greater lung tissue retention time than all other ICS preparations: FF > MF ≥ FP >triamcinolone acetonide (TAA) > BUD ≥ (des-CIC) > FLU ≥Beclomethasone (BMP) [20].

In an assay of lipopolysaccharide-stimulated tumour necrosis factor (TNF-alpha) release from peripheral blood mononuclear cells and transrepression nuclear factor- κB (NF-κB) reporter assays using a human lung epithelial cell line the anti-inflammatory effects of FF have been studied. Again, FF was compared with FP, MF, BUD and CIC. FF showed the highest potency of all the corticosteroids tested, with MF demonstrating a similarly high potency in the NF-κB assay. This study also demonstrated that FF had the largest cellular accumulation and the slowest rate of efflux relative to other clinically used glucocorticoids[18]. Additionally, *in vitro,* the rate of transport of FF out of the cells in the basal aqueous layer was slower than the other glucocorticoids, again consistent with retention of FF in respiratory tissues, which has been described. This

is thought likely to contribute to an extended duration of anti-inflammatory action[19].

Clinical Research studies

A Phase 0 study looking at metabolism and disposition of FF in 5 healthy male adults indicated systemic exposure from oral preparations had extensive first pass hepatic metabolism resulting in very low gastrointestinal bioavailability (recorded as 1.6%) which is consistent with the findings for other ICS preparations[21]. Systemic availability of budesonide after oral administration was found to be approximately 10%[22]. Interestingly, a study assessing the effect of systemic absorption of FP on adrenal glucocorticoid secretion via urinary cortisol in 28 asthmatic patients demonstrated that FP is likely to induce a decrease in nocturnal cortisol secretion in those with less severe airway obstruction, demonstrating variability of systemic bioavailability and possibly the effect being secondary to the amount of peripheral drug lung deposition in the target population[23]. No data have been published for FF in this regard.

The major route for metabolism of fluticasone furoate in humans is mediated primarily by Cytochrome P450 3A4 (CYP3A4). FF is converted by hydrolysis of the S-fluoromethyl carbthioate group to metabolites with significantly reduced corticosteroid activity. FF is also known to be a substrate of P-glycoprotein[24]. A repeat dose CYP3A4 drug interaction study was performed in healthy

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subjects with FF/VIL (200µg/25µg) and a strong inhibitor of CYP3A4, ketoconazole 400µg. The administration of both of these agents lead to an increase in the area under the curve$_{(0-24)}$ and maximal plasma concentration (Cmax) by 36% and 33% respectively. This subsequently led to a 27% reduction in serum cortisol, which could potentially lead to an increase in adverse events [24]. A Phase I study of FF and FP in 24 healthy male subjects showed the half-life (t1/2) for inhaled FF was longer than the estimated half-life for intravenous (IV) FF (17–24 h vs 14 h, respectively), in contrast, the half-life for FP was similar whether inhaled or given intravenously (11 and 14 h, respectively). This would suggest that FF is exhibiting absorption rate-limited pharmacokinetics following inhalation. The time for 90% absorption from the lung was also measured and found to be significantly longer for FF (20–30 h) than for FP (8 h), indicating a more prolonged lung retention time thus implying drug persistence with once-daily administration[25].

A 24-week placebo and active-controlled randomised trial was undertaken in 2013. The authors concluded FF 100 µg vs FP 250 µg showed similar improvements in lung function vs placebo (FEV$_1$ pre-dose +146ml [p=0.009] and +145ml [p=0.011])[26].

The following year, a 24-week multi-centre international, double blind, double dummy, parallel group Phase III study compared placebo vs FF 50µg and FP 100µg BD in 350 patients. This demonstrated that FF 50 µg once daily dosing was not as effective as FP 100 µg BD (evening trough FEV$_1$ +37ml [p=0.43] and +102ml [p=0.03]) [27]. The lower dose (50ug) is not commercially available as a consequence.

Investigation into differences between ethnicities has been undertaken with FF. Statistically significant differences in systemic absorption have been demonstrated between Caucasians and East Asian patients using both high dose (800µg) and low dose (200µg) FF. Adjusting for weight East Asian compared with Caucasian subjects appeared to have FF retained in their lung for a longer duration 29.1-30.8hr vs 21.4hr respectively)[28]. However, dose adjustments were deemed unnecessary because there had been no associated clinically significant effect on serum cortisol.

A study published in 2016 has also shown FF as an effective step-down agent from combination ICS/LABA to a single ICS monotherapy. A multicentre randomised control trial (RCT) assessed 430 Japanese asthma patients. This involved run in with ICS/LABA (FF/Vilanterol - VIL) in well-controlled asthmatics. This study demonstrated that step down to FF 100µg maintained similar control as compared with FP 100µg BD and FP 250µg BD with asthma control maintained at 89.5%, compared with 78.2% and 83.1% respectively[29]. The study was not powered to detect treatment differences nor did the study mention if these differences were statistically significant.

In addition, the combination of FF/VIL has been examined. A Phase III study with both FF/VIL and FF alone demonstrated improvements in lung function relative to placebo at doses of 100µg/25µg, and 100µg respectively[30]. High doses of the vilanterol combination (FF/VIL 200µg/50µg OD) show significant improvements in lung function relative to FF 200µg OD and FP 500µg BD with significant improvements in symptomatic end points compared with FF alone (p<0.001) and a trend towards a significant difference relative to FP (p=0.067) in regards to rescue-free 24 hour periods[31].

A systematic review assessed 31 studies and it concluded once daily FF/VIL was comparable with twice daily ICS/LABAs in improving lung function and patient reported symptom scores in asthmatics[32]. A similar review by Gray et al. concluded the FF/VIL combination demonstrated improvements in lung function and asthma control in addition to a similar side effect profile when compared with FP/salmeterol[15].

Of interest, an observational study performed in 40 patients used a slightly lower dose of FF/VIL at 92/22µg OD compared with BMP/formoterol (F) 100/6µg BD[33]. Significant improvements in asthma control and nocturnal symptoms, in addition to improved stability in lung function, were seen with BMP/F[33]. Mean FEV$_1$ in the BMP/F group was found to be 78% at third visit and 79.1% at the final assessment compared with 74.5% and 75.8% in the FF/VIL group[33], thus highlighting the importance of more robust head to head studies comparing different combination inhalers at equivalent commercially available doses.

FP has not demonstrated a clear dose-response curve with regards to lung function. A meta-analysis of seven studies in 2431 adolescents and adults with moderate to severe asthma demonstrated no therapeutic benefit of FP at doses higher than 200µg/day[34]. FF has a similarly flat dose-response curve. In an 8-week multicentre, randomised, double-blind Phase III study with 627 patients, incremental dosing of FF to 800µg did not show a dose relationship nor an improvement beyond 200µg for FEV$_1$, but there were significant improvements above baseline[35]. budesonide, by comparison, has shown a dose-dependent response when using commercially available inhalers[36, 37]. Single maintenance and reliever therapy (or 'SMART)' has been described with this ICS preparation in combination with the LABA, formoterol[38].

FF has demonstrated clinical efficacy at both 100µg and 200µg, which are now the commercially licensed inhaled doses[39]. Patients were randomised to either 100µg or 200µg FF and improvements in lung function were seen in both groups. Greater improvements in FEV$_1$ with the higher dose were noted at week 24, the end of the study period, however, this failed to reach significance (77ml 95% CI

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-39, 192)[40]. A similar study in 598 patients demonstrated a dose-response effect when comparing doses of 25µg, 50µg, 100µg and 200µg FF. Significant increases in FEV_1 were observed versus baseline for 50µg, 100µg and 200µg FF which were clinically significant (>200ml) in the FF 100µg and 200µg arms (p < .05 vs placebo) [41].

The efficacy of once daily dosing compared with a twice daily regimen was also investigated. The higher dose of 200µg taken in the evening was compared with a 100µg BD regimen of FF. The study in 190 individuals demonstrated non-inferiority of once daily administration to twice a day dosing[42]. A further study randomised 575 individuals to one of four treatment arms of either placebo, 100µg in the morning or evening or a higher dose of 250µg FF. Completion rates were high, but lower, as expected, in the placebo arm. Significant improvements in lung function were demonstrated in all active treatment arms, combined with a reduction in asthma symptoms (difference in PEF vs placebo 19.2L/min, 15.9L/min and 24.6L/min respectively [p<0.001]). All measures of symptoms – rescue medication, symptom-free nights & days, met statistical significance (p<0.001)[43].

An integrated safety and efficacy analysis study pooled data from 14 Phase II and Phase III studies and demonstrated FF efficacy compared with placebo[44].

Despite MF having reportedly less specificity for the glucocorticoid receptor[45], this ICS preparation has proved efficacious with once daily dosing also[46]. No head to head comparisons of this or other ICS preparations with once-daily FF have been undertaken.

Adverse event profile

FF has a low oral bioavailability due to limited absorption and extensive first pass metabolism, therefore any drug swallowed is thought unlikely to produce significant systemic side effects in most circumstances[47]. However, inhaled FF will pass from the lung into the systemic circulation and therefore an adverse profile similar to all ICS needs to be considered.

ICS related side effects are mainly due to either local deposition in the oropharynx or systemic absorption via the lung and the effect they have on the hypothalamic-pituitary-axis (HPA). Studies to demonstrate the effect on the HPA largely involve screening tests demonstrating a reduction the 24-hour urinary cortisol (UC) or performing a 24-hour integrated measurement of plasma cortisol levels which are impractical and challenging to achieve in an outpatient setting[48].

Due to these issues, the side effect profile of FF is routinely studied using the rates of oropharyngeal candidiasis and, as mentioned, a reduction in total 24-hour UC levels.

Oropharyngeal candidiasis demonstrates a dose dependent relationship with FF, occurring in 1% to 4% of patients taking doses up to 400µg[35, 43, 49, 50] which increases to 12% when inhaling 800µg FF per day[35].

Urinary cortisol suppression has been reported for FF in a variable manner. No clinically significant difference in 24hr UC compared with placebo using doses up to 400µg OD has been seen[35, 43, 49, 50]. However, doses at 800µg of FF vs placebo indicated UC suppression[35]. Daily doses of FF 200µg had statistically significant reductions of UC compared to placebo as did FP 100µg BD (ratio 0.75 p < 0.001 and 0.84 p = 0.02, respectively). No effects on urinary free-cortisol were recorded in the study [42]. Additionally, another study found similar suppression of UC relative to placebo with a lower dose of FF 100µg OD and a higher dose of FP 250µg BD[26]. Differences in the patient characteristics (e.g. weight, concurrent medication) would likely explain the variability seen as well as measurement methods between the studies.

Pooled data from 8 studies found no difference between FF and FP with respect to cortisol reduction in terms of clinically relevant doses (100µg & 200µg) [51].

Other potential long term adverse drug reactions and complications include osteoporosis, increased risk of mycobacterial infections, cataracts, hypertension, and diabetes mellitus are likely to occur. Currently, no direct data exist to further quantify the risk of these expected side effects with this drug versus the risks with other inhaled corticosteroids. FF is likely to be a more potent ICS[19], and therefore extra care may need to be taken with the drug to avoid systemic side effects.

The well documented risk of ICS causing an increase in pneumonia in COPD patients by the TORCH[52] and FLAME[53] studies provoked interest into whether this effect was translated in the asthmatic population. A Canadian study which identified 1928 pneumonia cases in over 150, 000 patients using ICS suggesting an increased risk of pneumonia associated with current use of ICS [RR 1.83; 95% confidence interval (CI) 1.57, 2.14][54]. To date there do not appear to be data to suggest that this signal has been investigated for FF. Further work is needed to assess risk in asthmatics, especially as the recent IMPACT[55], Salford Lung Study[56] and Summit[57] studies all showed that COPD patients using an ICS, in these instances FF, was again associated with an increased pneumonia risk.

Drug Delivery

FF is inhaled using the ELLIPTA® dry powder inhaler (DPI) device[39]. The ELLIPTA® multi-dose inhaler has been developed for the delivery of inhaled medication in patients with airways disease with demonstrated efficacy at different flow rates – 30, 60 and 90L/min[58]. In addition, this device has been shown to be less prone to inhaler errors in patients with COPD[59]. Both asthma and COPD

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patients also showed a preference to the ELLIPTA® DPI device when compared with the other inhalation devices tested[59].

Discussion

Fluticasone furoate is a novel inhaled corticosteroid with a long lung retention time and fast association and slow dissociation from the glucocorticoid receptor compared to other ICS[19]. Thomas and colleagues demonstrated that either evening or morning doses of FF at a dose of 100 μg produced similar improvements in lung function compared with placebo[13]. The pharmacological profile of FF has been demonstrated in multiple preclinical and clinical studies with 24-hour duration of action, making it an acceptable option for once daily dosing.

FF has demonstrated non-inferiority to FP and is therefore an alternative to this ICS twice daily medication. Budesonide and mometasone may be more desirable ICS preparations given the fact that FF, like FP, has not been demonstrated to have a dose-response effect. Nevertheless, FF at low dose has demonstrable efficacy and could be used for many patients with persistent asthma uncontrolled by short acting β2-agonists alone, and the lowest effective dose should be used in accordance with the GINA guidelines[1]. In addition, FF has not been identified as a candidate for 'SMART' therapy in asthmatics, used with other ICS preparations.

Further studies are required investigating the comparison of FF versus the other ICS drugs currently available. FF appears to show improved specificity compared with MF with regards to the GRE, this and the long lung retention may support once daily ICS preparation. MF has shown improved adherence with once daily dosing[46]. A large Cochrane review was undertaken in 2010[60] which compared multiple different ICS preparations, but unfortunately since the introduction of FF no large scale meta-analysis or RCT has been undertaken comparing FF with other ICS.

Currently, its side effect profile does not present additional concern that would lead physicians to consider the medication more hazardous than other ICS preparations but with a long retention time, other side effects may be recognised later. Adverse effects including oropharyngeal candidiasis and adrenal suppression are likely to be associated with higher doses of FF. The FF adverse profile appears similar to other ICS preparations. There is an increased risk of pneumonia identified in patients with airways disease with the use of some ICS preparations and as it is likely to be a class effect, this will need to be observed in large scale studies to identify whether FF also demonstrates this signal.

It is recognised that personality traits and beliefs about medicine will directly affect adherence to asthma treatment, however, ease of administration also plays a significant role[61]. Once daily therapy, such as FF could hopefully be translated into further improvements in asthma-related outcomes in the future, however, to date the evidence for this over twice daily dosing is currently lacking.

Conflict of interests

Professor Paul S. Thomas has been a principal investigator for trials in asthma on behalf of GSK and Astra Zenenca.

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