

REVIEW

Efficacy of fluticasone furoate nasal spray vs. placebo for the treatment of ocular and nasal symptoms of allergic rhinitis: a systematic review

G. J. Rodrigo¹ and H. Neffen²

¹Departamento de Emergencia, Hospital Central de las Fuerzas Armadas, Montevideo, Uruguay and ²Unidad de Medicina Respiratoria, Hospital de Niños 'O. Alassia', Santa Fe, Argentina

Clinical & Experimental Allergy

Summary

Background Although previous data suggest that intranasal fluticasone furoate (FF) improves ocular symptoms of allergic rhinitis (AR), it presents serious limitations that question its results and conclusions. Therefore, an independent systematic review with meta-analysis is required to confirm and clarify the magnitude of the effect of FF.

Methods This review compared the efficacy of intranasal FF to placebo on ocular and nasal symptoms in patients with AR. Primary outcomes were reflective and instantaneous total ocular symptom scores (rTOSS and iTOSS), and reflective and instantaneous total nasal symptom scores (rTNSS and iTNSS). Secondary outcomes included the assessment of response to therapy, quality of life (QoL), and adverse effects.

Results Sixteen trials (5348 patients) were selected. Seven studies included seasonal AR patients and nine studies, perennial AR patients. Intranasal FF significantly improved rTOSS and iTOSS scores compared with placebo in patients with seasonal (weighted mean difference [WMD] -0.54 , 95% CI, -0.70 to -0.37 , and -0.59 , 95% CI, -0.76 to -0.43) and perennial AR (-0.33 , 95% CI, -0.31 to -0.05 , and -0.38 , 95% CI, -0.69 to -0.07). Intranasal FF was also significantly more effective in improving rTNSS and iTNSS scores in seasonal (WMD -1.14 , 95% CI, -1.57 to -0.72 , and -1.32 , 95% CI, -1.64 to -1.01) and perennial AR patients (-0.83 , 95% CI, -1.08 to -0.59 , and -0.90 , 95% CI, -1.33 to -0.48). Finally, there were greater improvements in response to therapy and QoL with a favourable safety profile.

Conclusions and Clinical Relevance Intranasal FF showed a consistent ocular and nasal efficacy along with improvement in QoL in AR patients. This review provides significant evidence that treatment with FF nasal spray at a dose of 110 mcg once daily is effective in relieving ocular and nasal symptoms in adolescents and adults with AR.

Correspondence:

Gustavo J. Rodrigo MD, Departamento de Emergencia, Hospital Central de las Fuerzas Armadas, Av. 8 de Octubre 3020, Montevideo 11600, Uruguay.
E-mail: gurodrig@adinet.com.uy

Introduction

Allergic rhinitis (AR) is a chronic disease of the nasal mucosa induced by IgE-mediated inflammation following exposure of the nasal mucosal membranes to one or more allergens [1]. AR is a highly prevalent condition that represents an enormous global health burden. It is estimated that at least 500 million individuals have AR, constituting a frequent reason for attendance at a primary care setting. AR is clinically defined as a symptomatic condition with nasal (congestion, rhinorrhoea, sneezing, and itching) and ocular (redness, watery eyes, itching, and burning) symptoms. Both of these symptoms are reported by more than 70% of patients [2], and are particularly prominent in those with seasonal allergic rhinitis (SAR). In

perennial allergic rhinitis (PAR), ocular symptoms are less intense but are a continuous reaction related to exposure to perennial allergens such as house dust mites [3].

AR treatment includes allergen avoidance, pharmacotherapy, and immunotherapy. Intranasal corticosteroids (INS) are recommended for the treatment of AR in adults and children [4]. They are significantly more effective than oral [5] or intranasal antihistamines [6] and anti-leukotrienes [7], and equal to the combination of anti-histamines plus anti-leukotrienes [8]. However, there is inconsistent evidence of the effect of INS on ocular symptoms [9, 10].

Fluticasone furoate (FF) is a new topical, intranasal, enhanced-affinity trifluorinated corticosteroid with potent anti-inflammatory activity and low systemic

exposure [11]. The drug was licensed for the treatment of both SAR and PAR. It is available in a nasal spray formulation, as an aqueous suspension of micronized FF for topical administration to the nasal mucosa by means of a metering, atomizing spray pump. Data from a recently published review suggested that intranasal FF shows a specific effect on ocular symptoms of AR [12]; however, it poses serious limitations that question its results and conclusions: (a) although it contains an explicit statement of objectives, materials and methods, it synthesizes data based only on *P*-values (the number of positive studies that shows a statistically significant improvement of ocular symptoms was compared with the number of negative studies that exhibits significantly worse or not significant changes in ocular symptoms); (b) consequently, it is not possible to estimate the magnitude and clinical significance of the effect size; (c) the review did not include unpublished studies comparing intranasal FF with placebo; and (d) it was sponsored (as well as all individual studies included) by the pharmaceutical industry. Consequently, we performed an independent systematic review with meta-analysis to confirm and clarify the magnitude and clinical significance of the effect of intranasal FF.

Methods

Search strategy and selection criteria

We identified studies from MEDLINE, EMBASE (January 1980–October 2010), and the Cochrane Controlled Trials Register (CENTRAL) (third quarter 2010) databases using the following Medical Subject Headings, full text, and keywords ('fluticasone furoate' or 'GW685698X' and 'rhinitis' or 'hay fever' or 'allergic' or 'season' or 'perennial' or 'pollen' or 'mite'). Also, we performed a search of relevant files from the GlaxoSmithKline clinical trials database (<http://www.gsk-clinicalstudyregister.com>). Trials published solely in abstract form were excluded because the methods and results could not be fully analysed.

The specific inclusion criteria were as follows: (1) children (aged ≤ 12 years) and adolescents-adults (aged > 12 years) with AR (SAR or PAR): the diagnosis must have been confirmed by the clinical history or the allergen identified, and sensitivity proven by positive skin prick test); (2) administration of topical FF at any dose over any period of time compared with a placebo; (3) trials with other co-interventions were excluded (INS, antihistamines, anti-leukotrienes); (4) randomized (parallel group) placebo controlled trials without language restriction (cross-over designs were excluded); and (5) primary outcomes: mean change in daily reflective total ocular symptom score (rTOSS), calculated from the average of the AM and PM score; mean change from baseline over the entire treatment period in AM pre-dose instantaneous

total ocular symptom score (iTOSS); mean change from baseline throughout treatment period in daily reflective nasal symptom score (rTNSS) calculated as an average AM and PM score; and mean change from baseline throughout treatment period in AM pre-dose instantaneous total nasal symptom score (iTNSS). Secondary outcomes measures included: individual nasal and ocular symptoms, overall evaluation of response to therapy, quality of life (QoL) (assessed using the Rhinoconjunctivitis Quality of Life Questionnaire [RQLQ]) [13], and adverse events. A serious adverse event was defined as any untoward medical occurrence that at any dose results in death, is life-threatening, requires inpatient hospitalization, or results in persistent or significant disability/incapacity [14].

Data abstraction and assessment of risk of bias

This systematic review was performed according to the PRISMA guidelines (Preferred Reporting Items for Systematic reviews and Meta-Analyses) [15]. Titles, abstracts, and citations were independently analysed by all reviewers. From full text, they independently assessed all studies for inclusion based on the criteria for population intervention, study design, and outcomes. After obtaining full reports about potentially relevant trials, they assessed eligibility. The authors were independently involved in all stages of study selection, data extraction, and risk of bias assessment. The latter was assessed using the Cochrane risk of bias tool consisting of five domains: adequacy of randomization, concealment of allocation, blinding of patients, incomplete outcome data, and selective outcome reporting [16]. Disagreements were resolved by consensus. In case of multiple published or unpublished reports for a particular study, data from the most recent version were extracted.

Data analysis

For continuous outcomes, the weighted mean difference (WMD) with the 95% confidence intervals (CIs) was calculated. Binary outcomes were pooled using common relative risks (RRs) and 95% CIs. If pooled effect estimates were significantly different between groups, we calculated the number needed to treat for benefit (NNTB) or for harm (NNTH). Heterogeneity was measured by the I^2 test [17]. Values below 40% represent unimportant heterogeneity, between 40% to 60%, moderate, and 60% to 100%, substantial heterogeneity [16]. Because selected studies differed in the mixes of participants (by participant age and duration of symptoms), there may be different effect sizes underlying different studies. Consequently, a random-effects meta-analysis was performed to address this variation across studies in all outcomes [18]. We evaluated the publication bias by visual inspection of funnel plots and using the Egger test [19]. A predefined sensitivity

analysis of the primary outcomes (i.e., rTOSS and rTNSS) was conducted on the basis of the statistical model: fixed vs. random-effects. Additionally, as a priori subgroup analysis, we explore the influence of the following factors: the age of patients (children vs. adolescents and adults), and duration of symptoms (SAR vs. PAR). Subgroups were compared using the interaction test [20]. $P \leq 0.05$ (using a two-tailed test) was considered significant. Meta-analysis was performed using the Review Manager 5.0.25 software (Copenhagen, Denmark; The Nordic Cochrane Centre, The Cochrane Collaboration, 2010).

Results

Sixteen trials (5348 patients) fulfilled the criteria for inclusion in this review. Of them, seven studies [21–26] included SAR patients ($n = 2.589$) (one publication [24] presented two independent trials), and nine studies [27–35], PAR patients ($n = 2.759$) (Fig. 1). Three studies were unpublished [33–35]. Cumulative exposure to study drug (patient-years) was 741 for intranasal FF (38.8 for SAR patients and 702 for PAR patients) and 338 for placebo (39 for SAR patients and 299 for PAR patients). Patients were included if they had an iTNSS score ≥ 6 , an instantaneous symptom score for congestion ≥ 2 , an rTNSS ≥ 5 –6, and an rTOSS score ≥ 4 (only in trials with SAR patients). Intranasal FF was administered for 2 weeks in all studies with SAR patients and for 2–54 weeks (median 6 weeks) in studies with PAR subjects (Table 1). Patients had SAR to grass, ragweed, or mountain cedar pollen, all confirmed by skin prick tests. Intranasal FF was administered at a dose of 110 mcg daily in all studies. Additionally, some studies included different doses of intranasal FF [23, 26, 28, 33–34] or compared intranasal FF with an antihistamine [24]. For the purpose of this analysis, we selected an intranasal FF dose of 110 mcg daily (included in all studies) to make a comparison with the placebo. Thirteen studies included adolescents and adults (≥ 12 years) [21–25, 27, 29–31, 33–35], and three paediatric participants [26, 28, 32]. All trials were sponsored by the pharmaceutical industry. Regarding the risk of bias, only one study met the five selected markers, (Table 2) [25]; both the sequence generation and the allocation concealment were unclear in the remaining studies.

Primary outcomes

Patients with AR (SAR and PAR) that received intranasal FF significantly showed improvements in ocular symptoms (daily rTOSS and AM pre-dose iTOSS scores) compared with the placebo (Fig. 2 and Table 3). Accordingly, intranasal FF patients demonstrated significant improvements for individual ocular symptoms (itching/burning, tearing/watering, and redness). There was no evidence of publication bias on visual examination of the funnel plot,

and on the Egger test in both variables for SAR ($\beta = -0.30$, $P = 0.56$, and $\beta = 0.23$, $P = 0.96$) and PAR patients ($\beta = 0.96$, $P = 0.18$, and $\beta = 0.06$, $P = 0.96$). Post hoc sensitivity analysis showed that the statistical model did not influence the effect size. Thus, for rTOSS score, we found identical WMDs (95% CI) using the random or fixed models for SAR and PAR patients. Finally, although SAR patients showed higher improvements in ocular symptoms than PAR patients, they were not significantly different (rTOSS, $P = 0.20$, and iTOSS $P = 0.24$). We could not explore the influence of age due the low number of paediatric studies.

Regarding nasal symptoms, SAR and PAR patients receiving intranasal FF had significantly higher improvements from baseline in rTNSS and iTNSS scores than those receiving placebo (Table 3). The first comparison showed substantial statistical heterogeneity; on the contrary, the comparison involving patients with PAR showed an unimportant to moderate grade of heterogeneity. There was no evidence of publication bias on visual examination of the funnel plot, or on the Egger test in both variables for SAR ($\beta = -0.16$, $P = 0.72$, and $\beta = 0.06$, $P = 0.89$), and PAR patients ($\beta = -0.18$, $P = 0.70$, and $\beta = 0.89$, $P = 0.12$). Again, the statistical model used did not influence the effect size. Thus, for rTNSS score we found no difference with the use of random or fixed models ([WMD] -1.14 , 95% CI, -1.57 to -0.72 vs. -1.07 , 95% CI, -1.25 to -0.88 , $P = 0.77$, for SAR patients, and -0.83 , 95% CI, -1.08 to -0.59 vs. -0.84 , 95% CI, -1.03 to -0.64 , $P = 0.99$ for PAR subjects). Consistently with these data, intranasal FF showed significantly greater reductions in individual nasal symptoms than placebo in daily reflective symptoms of congestion, rhinorrhoea, itching, and sneezing (all $P < 0.001$). Finally, although the improvement in nasal symptoms was higher in SAR patients, there were no significant differences compared with PAR patients (rTNSS, $P = 0.12$, and iTNSS, $P = 0.18$). Again, the subgroup analysis exploring the influence of age could not be performed due to the low number of paediatric studies.

Secondary outcomes

At the end of treatment, patients rated their overall response to therapy significantly better in the intranasal FF group compared with the placebo group (Table 4). The percentage of patients reporting significant/moderate improvement was 52% in the intranasal FF group compared with 34% in the placebo group for SAR patients (NNTB = 5, 95% CI, 4–7), and 56% vs. 42% for PAR patients (NNTB = 7, 95% CI, 5–13). Compared with the placebo, the intranasal FF group experienced a significant improvement in the overall RQLQ score (-1.92 points vs. -1.22 in SAR patients, and -1.67 points vs. -1.2 points in PAR patients, respectively (all $P = 0.0001$).

Regarding safety, there was no significant difference between intranasal FF and placebo in the incidence of

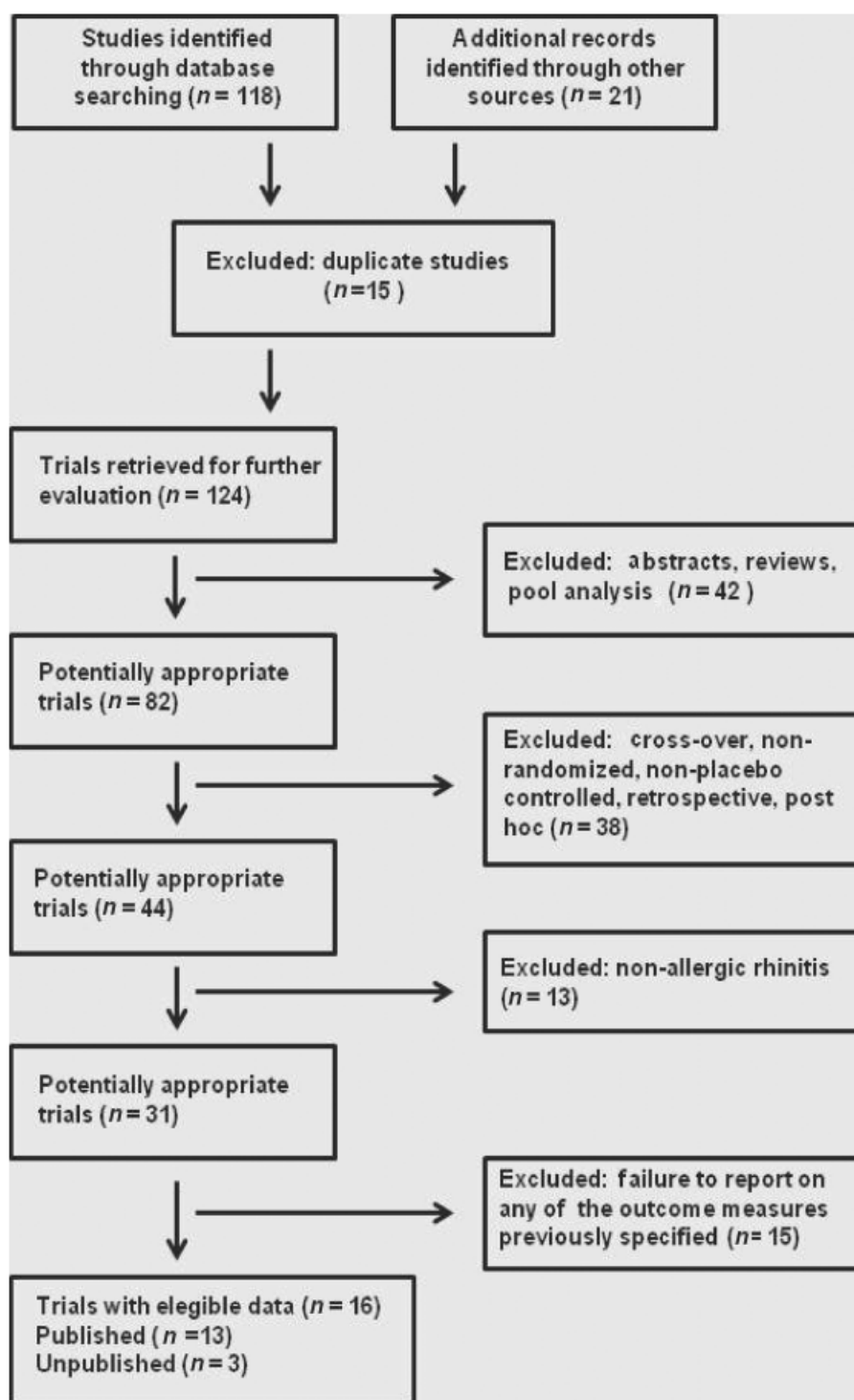


Fig. 1. Flowchart for identification of eligible studies.

early withdrawals in both SAR (3.9% vs. 5.9%, $P = 0.1$) and PAR patients (16.0% vs. 14.2%, $P = 0.22$). Moreover, there was no difference in the rate of patients reporting withdrawals due to adverse effects between the intranasal FF and placebo groups in SAR (0.46% vs. 1.08%, $P = 0.16$) and PAR patients (3.27% vs. 2.55%, $P = 0.77$). In the same

way, the incidence of adverse effects (20.1% vs. 17.9% for SAR patients, and 55.7% vs. 46.8% for PAR patients) and serious adverse effects (0% vs. 0.5% for SAR patients, and 1.9% vs. 1.1% for PAR patients) were similar in both groups. Headache was the most commonly reported adverse effect (4.8% vs. 3.4%, $P = 0.07$ for SAR patients, and

Table 1. Characteristics of the studies included

Trial	Design	Participants	Duration of protocol (wk)	Intervention	Outcomes
Fokkens [21]	M,R,DB,PC,PG	N = 285 (53% female, 47% male); mean age 30.1 y (12–65 y) with SAR (grass)	2	FF 110 mcg OD vs. placebo OD (Nasal spray)	Daily rTNSS Mean change from baseline: iTNSS, rTOSS, RQLQ Evaluation of response to therapy Safety
Kaiser [22]	M,R,DB,PC,PG	N = 299 (60% female, 40% male); mean age 35.0 y (12–74 y) with SAR (ragweed)	2	FF 110 mcg OD vs. placebo OD (Nasal spray)	Mean change from baseline daily rTNSS Mean change from baseline: iTNSS, rTOSS, RQLQ Evaluation of response to therapy Safety
Martin [23]	R,DB,PC,PG	N = 255 (66% female, 34% male); mean age 39.0 y (≥ 12 y) with SAR (mountain cedar)	2	FF 110 mcg OD vs. placebo OD (Nasal spray)	Mean change from baseline daily rTNSS Mean change from baseline: iTNSS, rTOSS, RQLQ Evaluation of response to therapy Safety
Andrews [24] (Study 1)	M,R,DB,PC,PG	N = 625 (69% female, 31% male); mean age 37.8 y (> 12 y) with SAR (mountain cedar)	2	FF 110 mcg OD vs. placebo OD (Nasal spray)	Mean change from baseline in nighttime symptoms score Mean change from baseline in daily rTNSS, iTNSS, rTOSS, iTOSS and RQLQ Safety
Andrews [24] (Study 2)	M,R,DB,PC,PG	N = 453 (64% female, 36% male); mean age 34.4 y (> 12 y) with SAR (ragweed)	2	FF 110 mcg OD vs. placebo OD (Nasal spray)	Mean change from baseline in nighttime symptoms score Mean change from baseline in daily rTNSS, iTNSS, rTOSS, iTOSS and RQLQ Safety
Jacobs [25]	M,R,DB,PC,PG	N = 302 (63% female, 37% male); mean age 37.6 y (12–75 y) with SAR (mountain cedar)	2	FF 110 mcg OD vs. placebo OD (Nasal spray)	Mean change from baseline in daily rTNSS Mean change from baseline: iTNSS, rTOSS, RQLQ Evaluation of response to therapy Safety
Meltzer [26]	M,R,DB,PC,PG	N = 370 (42% female, 58% male); mean age 8.0 y (2–11 y) with SAR (seasonal allergens)	2	FF 110 mcg OD vs. placebo OD (Nasal spray)	Mean change from baseline in daily rTNSS and iTNSS Evaluation of response to therapy Safety
Rosenblut [27]	M,R,DB,PC,PG	N = 806 (51% female, 49% male); mean age 32.4 y (12–77 y) with PAR	54	FF 110 mcg OD vs. placebo OD (Nasal spray)	Adverse effects Mean change from baseline in daily rTNSS and iTNSS Evaluation of response to therapy Safety
Máspero [28]	M,R,DB,PC,PG	N = 373 (56% female, 44% male); mean age 7.6 y (2–12 y) with PAR	12	FF 110 mcg OD vs. placebo OD (Nasal spray)	Mean change from baseline in daily rTNSS Mean change from baseline in iTNSS Evaluation of response to therapy Safety
Nathan [29]	M,R,DB,PC,PG	N = 302 (63% female, 37% male); mean age 36.7 y (> 12 y) with PAR	4	FF 110 mcg OD vs. placebo OD (Nasal spray)	Mean change from baseline in daily rTNSS Mean change from baseline in iTNSS, and RQLQ

Table 1. continued

Trial	Design	Participants	Duration of protocol (wk)	Intervention	Outcomes
Patel [30]	M,R,DB,PC,PG	N = 99 (52% female, 48% male); mean age 36 y (12–62 y) with PAR	6	FF 110 mcg OD vs. placebo OD (Nasal spray)	Evaluation of response to therapy Safety Change from baseline (expressed as a ratio) in 24 h SC weighted mean Safety
Vasar [31]	M,R,DB,PC,PG	N = 302 (56% female, 44% male); mean age 37.1 y (12–77 y) with PAR	6	FF 110 mcg OD vs. placebo OD (Nasal spray)	Mean change from baseline in daily rTNSS, iTNSS, and RQLQ Evaluation of response to therapy Safety
Tripathy [32]	M,R,DB,PC,PG	N = 112 (50% female, 50% male); mean age 6.2 y (2–11 y) with PAR	6	FF 110 mcg OD vs. placebo OD (Nasal spray)	Change from baseline (expressed as a ratio) in 24 h SC weighted mean. Safety
GSK FFR100650 [33]	M,R,DB,PC,PG	N = 159 (29% female, 71% male); mean age 30 y (> 12 y) with PAR	2	FF 110 mcg OD vs. placebo OD (Nasal spray)	Mean change from baseline in daily rTNSS, and RQLQ Safety
GSK FFR100652 [34]	M,R,DB,PC,PG	N = 291 (48% female, 52% male); mean age 32 y (> 12 y) with PAR	2	FF 110 mcg OD vs. placebo OD (Nasal spray)	Mean change from baseline in daily rTNSS, and RQLQ Safety
GSK FFR111439 [35]	M,R,DB,PC,PG	N = 315 (32% female, 68% male); mean age 38.5 y (> 12 y) with PAR	4	FF 110 mcg OD vs. placebo OD (Nasal spray)	Mean change from baseline in daily rTNSS, iTNSS, rTOSS, and RQLQ Safety

DB, double blind; FF, fluticasone furoate; iTOSS – instantaneous iTNSS, instantaneous total nasal symptom score; M, multicenter; OD, once daily; PAR, perennial allergic rhinitis; PC, placebo controlled; PG, parallel group; R, randomized; RQLQ, Rhinoconjunctivitis Quality of Life Questionnaire; rTNSS, daily reflective nasal symptom score; rTOSS, reflective total ocular symptom score; SAR, Seasonal allergic rhinitis; SC, serum cortisol; y, years.

Table 2. Risk of bias of the eligible studies

Source	Sequence generation	Allocation concealment	Data collection blinded	Complete outcome data	Selective outcome reporting
Fokkens [21]	B	B	Yes	Yes	Yes
Kaiser [22]	B	B	Yes	Yes	Yes
Martin [23]	B	B	Yes	Yes	Yes
Andrews [24] (Study 1)	B	B	Yes	Yes	Yes
Andrews [24] (Study 2)	B	B	Yes	Yes	Yes
Jacobs [25]	A	A	Yes	Yes	Yes
Meltzer [26]	B	B	Yes	Yes	Yes
Rosenblut [27]	B	B	Yes	Yes	Yes
Máspero [28]	B	B	Yes	Yes	Yes
Nathan [29]	B	B	Yes	Yes	Yes
Patel [30]	B	B	Yes	Yes	Yes
Vasar [31]	B	B	Yes	Yes	Yes
Tripathy [32]	B	B	Yes	Yes	Yes
GSK FFR100650 [33]	B	B	Yes	Yes	Yes
GSK FFR100652 [34]	B	B	Yes	Yes	Yes
GSK FFR111439 [35]	B	B	Yes	Yes	Yes

A, adequate; B, unclear.

17.8% vs. 14.4% $P = 0.33$ for PAR patients). The most common drug-related adverse effect was epistaxis, which occurred at an incidence of 8.1% in the intranasal FF group (2.8% in SAR patients and 12.5% in PAR patients)

and 4.1% in the placebo group (2.5% in SAR patients and 5.7% in PAR patients). There was a significant difference only for PAR patients (NNTH = 15; 95% CI, 11–21). On the contrary, the frequency of nasopharyngitis did not differ

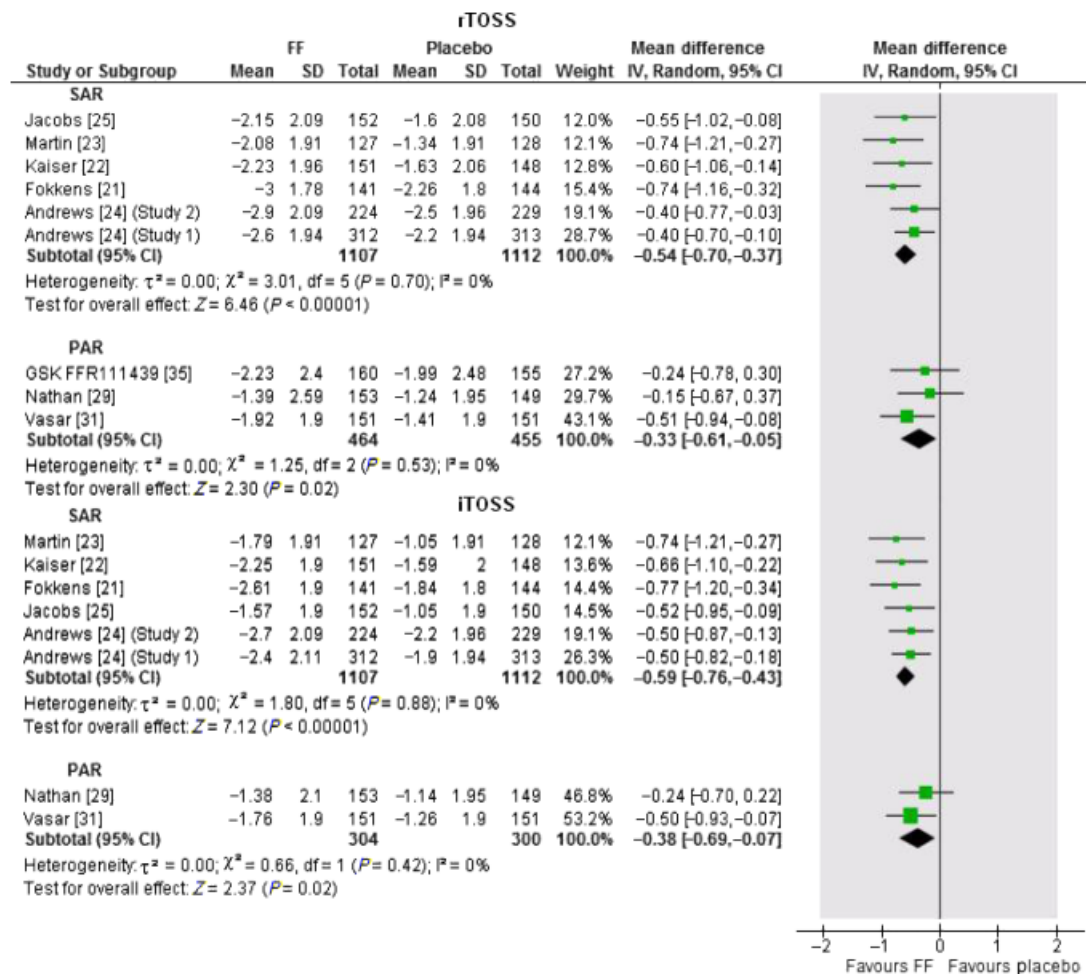


Fig. 2. Forest plots showing pooled weighted mean differences (with 95% confidence intervals) for daily reflective total ocular symptoms score (rTOSS) and instantaneous total nasal score (iTOSS) of eligible studies comparing intranasal fluticasone furoate (FF) with placebo.

between intranasal FF and placebo. Two studies of 6 weeks of duration found that serum cortisol change from baseline (as a ratio) in 24 h was similar for intranasal FF and placebo in children [32] and adults [30] with PAR. Finally, no clinically relevant findings or changes in vital signs and ECG assessments were observed during all trials.

Discussion

To our knowledge, this is the first systematic review performed exclusively to explore the efficacy and safety of intranasal FF against placebo in patients with AR. The results of this review suggest that the administration of FF 110 mcg once daily via a nasal spray significantly improved nasal symptoms (congestion, rhinorrhoea, sneezing, and itching) in adolescents and adults with SAR and PAR, compared with the placebo. A striking finding was the consistent efficacy of intranasal FF on reducing ocular symptoms (itching/burning, tearing/watering, and redness) in both SAR and PAR patients. Although the improvement in nasal and ocular symptoms was higher in

SAR patients, there was no significant statistical difference compared with PAR patients. These conclusions cannot be extrapolated to paediatric population because the experience of intranasal FF for AR is limited to one trial with SAR patients [26], and two trials with PAR children [28, 32]. Meltzer et al. [26] found that in patients aged 6–11 years, intranasal FF 110 mcg once daily significantly improved rTNSS and iTNSS scores compared with placebo. In the same way, Máspero et al. [28] reported that intranasal FF at doses of 110 or 55 mcg once daily in children 2–11 years was beneficial for both rTNSS and iTNSS scores compared with placebo. The third study [32] only explored the effects of intranasal FF on the hypothalamic–pituitary–adrenal axis. Thus, new studies are required to assess the efficacy and safety of intranasal FF in children.

Ocular symptoms of allergy can be particularly upsetting for the patient, and often difficult to treat. Data from narrative reviews advocate that not all INS are equal regarding ocular symptoms of AR [10, 11]. Moreover, it has been suggested that only FF nasal spray shows a consistent specific effect on ocular symptoms of SAR

Table 3. Analysis of primary outcomes (intranasal fluticasone furoate vs. placebo)

SAR						PAR				
Outcome	References	N	WMD			References	N	WMD		
			(95% CI)	P	I ² %			(95% CI)	P	I ² %
Mean change from baseline in rTOSS	[21–25]	2219	–0.54 (–0.70 to –0.37)	0.0001	0	[28, 30, 34]	919	–0.33 (–0.61 to –0.05)	0.0001	0
Mean change from baseline in iTOSS	[21–25]	2219	–0.59 (–0.76 to –0.43)	0.0001	0	[28, 30]	604	–0.38 (–0.69 to –0.07)	0.02	0
Eye itching/Burning	[21, 22, 25]	886	–0.20 (–0.29 to –0.11)	0.0001	0	[28, 30]	604	–0.14 (–0.27 to –0.01)	0.05	52
Eye tearing/watering	[21, 22, 25]	886	–0.22 (–0.31 to –0.13)	0.0001	0	[28, 30]	604	–0.11 (–0.21 to –0.01)	0.03	0
Eye redness	[21, 22, 25]	886	–0.21 (–0.30 to –0.12)	0.0001	0	[28, 30]	604	–0.11 (–0.19 to –0.09)	0.02	59
Mean change from baseline in rTNSS	[21–26]	2589	–1.14 (–1.57 to –0.72)	0.0001	80	[26–28, 30, 32–34]	2539	–0.83 (–1.08 to –0.59)	0.0001	32
Mean change from baseline in iTNSS	[21–26]	2589	–1.32 (–1.64 to –1.01)	0.0001	62	[27–28, 30, 34]	1244	–0.90 (–1.33 to –0.48)	0.0001	52
Rhinorrhea	[21–23, 25]	1141	–0.35 (–0.48 to –0.22)	0.0001	50	[28, 30, 32–33]	1054	–0.20 (–0.32 to –0.07)	0.002	63
Nasal congestion	[21–23, 25]	1141	–0.31 (–0.40 to –0.23)	0.0001	60	[28, 30, 32–33]	1054	–0.16 (–0.24 to –0.09)	0.001	27
Nasal itching	[21–23, 25]	1141	–0.31 (–0.39 to –0.22)	0.0001	72	[28, 30, 32–33]	1054	–0.22 (–0.30 to –0.14)	0.0001	64
Sneezing	[21–23, 25]	1141	–0.39 (–0.48 to –0.31)	0.0001	46	[28, 30, 32–33]	1054	–0.25 (–0.32 to –0.18)	0.0001	52

iTNSS, instantaneous total nasal symptom score; iTOSS, instantaneous total ocular score; PAR, perennial allergic rhinitis; rTNSS, daily reflective nasal symptom score; rTOSS, daily reflective ocular symptom score; SAR, seasonal allergic rhinitis; WMD, weighted mean difference.

[10, 11]. Thus, data from clinical trials of other INS show that the effects on ocular symptoms are inconsistent (no significant differences, significant differences without reaching the predefined threshold of >0.5 for ocular symptoms or even negative effects). However, more recent literature supports the positive effects on ocular symptoms of other INS, suggesting a class effect [36–38]. Inconsistent efficacy across trials might be the result of variations in different factors: trial design, heterogeneity of patients enrolled (SAR or PAR patients), different baseline ocular symptom score (studies with mild ocular symptoms might not exhibit sufficient baseline symptoms to show a statistically significant effect), or different methods of assessing ocular symptoms (variable, categorical or visual scales, patient or physician-rated scoring systems). Finally, other possible reason for which older studies may not have consistently shown a positive effect for ocular symptoms is that those studies did not focus on the ocular domain of allergy symptoms, but combined all symptoms into a single component of the total non-nasal symptom score [39].

This systematic review has demonstrated that intranasal FF exhibits efficacy against ocular symptoms in patients with SAR and PAR. In particular, intranasal FF showed a clinically significant benefit (mean differences from base-

line in rTOSS and iTOSS >0.5) in patients with SAR. In these patients, the results were consistent across different allergy seasons and different geographical locations. Concerning PAR patients, the review demonstrated significant differences between intranasal FF and placebo for rTOSS and iTOSS scores; however, these benefits did not reach the predefined threshold. This analysis included very homogeneous studies with a minimum ocular symptom score as an inclusion criterion (SAR trials), and showed that intranasal FF had consistent positive effects on ocular symptoms (including different types of AR, and allergens). The fact that ocular symptoms tend to be less severe in patients with PAR than in those with SAR [3], might account for the observed results (in the placebo group, SAR patients showed greater improvements in rTOSS and iTOSS scores compared with PAR patients in the same group). It is presumed that the effect of intranasal FF on ocular manifestations of AR is related to the effects of decreased inflammatory mediators that prime nasal neurogenic tissue and initiate the nasal-ocular reflex [40].

Additionally, this study demonstrated that topical FF was effective for treating nasal symptoms of SAR and PAR patients. Statistical and clinical significant improvements from baseline with intranasal FF compared with placebo

Table 4. Analysis of secondary outcomes (Fluticasone furoate vs. placebo)

Outcome	SAR					PAR				
	References	N	Measure (95% CI)	P	I ² %	References	N	Measure (95% CI)	P	I ² %
Mean difference in RQLQ	[21–25]	2219	WMD = −0.68 (−0.80 to −0.56)	0.0001	0	[28, 30, 34]	919	WMD = −0.51 (−0.76 to −0.22)	0.0001	44
Response to treatment (significant or moderate improvement)	[21–23, 25–26]	1511	RR = 0.64 (0.57 to 0.72)	0.0001	0	[27–28, 30]	869	RR = 0.75 (0.63 to 0.8)	0.0007	33
Early withdrawals	[21–26]	2589	RR = 0.67 (0.41 to 1.09)	0.10	40	[26–34]	2444	RR = 0.89 (0.73 to 1.08)	0.22	0
Withdrawals due to AEs	[21–26]	2589	RR = 0.51 (0.20 to 1.30)	0.16	0	[26–34]	2444	RR = 0.89 (0.43 to 1.85)	0.75	29
AEs	[21–26]	2589	RR = 1.12 (0.92 to 1.35)	0.26	30	[26–34]	2444	RR = 1.09 (0.97 to 1.21)	0.10	29
Serious AEs	[26]	370	RR = 0.33 (0.01 to 8.04)	0.50		[27–29, 31–32]	1895	RR = 1.52 (0.64 to 3.64)	0.35	0
Headache	[21–26]	2589	RR = 1.42 (0.97 to 2.07)	0.07	0	[27–31, 33–35]	2647	RR = 0.92 (0.77 to 1.09)	0.33	0
Epistaxis	[21–26]	2589	RR = 1.12 (0.66 to 1.89)	0.67	11	[27–31, 33–35]	2647	RR = 1.68 (1.16 to 2.45)	0.007	26
Nasopharyngitis	[21–26]	2589	RR = 1.47 (0.62 to 3.49)	0.39	0	[27–31, 33–35]	2647	RR = 1.06 (0.85 to 1.32)	0.62	0
SC change from baseline in 24 h (ratio)						[30, 32]	198	WMD = 0.01 (−0.06 to 0.08)	0.78	0

AEs, adverse effects; FF, fluticasone furoate; PAR, perennial allergic rhinitis; RR, relative risk; RQLQ, Rhinoconjunctivitis Quality of Life Questionnaire; SAR, seasonal allergic rhinitis; SC, serum cortisol; WMD, weighted mean difference.

were observed in daily rTNSS and iTNSS. A significant difference was also demonstrated for each of the individual nasal symptoms (rhinorrhea, sneezing, and nasal itching).

Nasal and ocular symptoms were assessed in a reflective and instantaneous manner in all trials. Reflective scores indicated how a patient was feeling during the previous 12 h and were recorded in the morning (AM) and evening (PM). Instantaneous scores represented patients' symptoms at the time of assessment (immediately before taking the next dose each day) and provided a measure of 24-hour duration of action. In addition to the improvement in reflective scores, there was also a significant improvement in instantaneous scores, confirming that a once-daily dosing is effective for the entire 24-hour period.

The reductions in ocular and nasal symptoms were associated with an improvement in the QoL questionnaire RQLQ, and with a significant higher percentage of patients reporting significant/moderate improvements, indicating a significant degree of patient-perceived benefit (five SAR patients and seven PAR patients would need to be treated in order to achieve a benefit). Additionally, the improvement in overall RQLQ score exceeded the minimally important difference in both SAR and PAR patients (≥ 0.5) [41].

The use of intranasal FF at 110 mcg once daily was associated with a favourable safety profile. Hence, patients treated with intranasal FF presented similar numbers of early withdrawals, adverse effects, and serious adverse effects compared with placebo patients. Mild-to-moderate headache and epistaxis were the most common drug-related adverse effect. Only PAR patients that received intranasal FF showed a significant increase in the rate of epistaxis compared with placebo (12.5% vs. 5.7%, $P < 0.007$). Fifteen patients would need to be treated with intranasal FF to present one adverse effect. On the contrary, no increased risk of epistaxis was found in SAR patients (2.8% vs. 2.5%). Although limited to a few studies, there was no evidence suggestive of impairment of hypothalamic-pituitary-adrenal axis function. Finally, no clinically relevant findings in vital signs or ECG assessments were observed.

This review met most of the methodological criteria suggested for systematic reviews [15]. All studies were randomized, double-blind, and placebo controlled. However, only one out of 16 trials reported an appropriate sequence generation, and an adequately concealed allocation [25]. Regarding consistency, the meta-analysis of the majority of outcomes showed unimportant or moderate statistical heterogeneity. Moreover, there was no evidence

of publication bias. Most participants were adolescents and adults with SAR, and only three trials recruited paediatric participants. Although results from these three trials were similar to those reported for adults and adolescents, further studies on exclusively SAR and PAR paediatric population are necessary.

In conclusion, this systematic review shows that in adolescents and adults with AR, intranasal FF nasal spray at a dose of 110 mcg once daily, is effective in improving ocular and nasal symptoms. Significant benefits in QoL and in the degree of patient-perceived benefit were also demonstrated. These improvements were clinically significant and associated with a safe therapeutic profile.

Acknowledgements

Role of authors.

Dr. Rodrigo: (1) has made substantial contributions to the conception and design, acquisition of data, analysis and interpretation of data; (2) has drafted the submitted article and revised it critically for important intellectual content,

and (3) has provided final approval of the version to be published.

Dr. Neffen: (1) has made substantial contributions to the conception, design, and interpretation of data, (2) has revised the article critically for important intellectual content, and (3) has provided final approval of the version to be published.

Conflict of Interests: Dr. Rodrigo has participated as a lecturer and speaker in scientific meetings and courses under the sponsorship of Boehringer Ingelheim, Glaxo-SmithKline, AstraZeneca, Dr. Esteve SA, and Merck Sharp & Dome. Dr. Neffen has participated as a lecturer and speaker in scientific meetings and courses under the sponsorship of Schering Plough, GlaxoSmithKline, Novartis, and AstraZeneca.

Funding Source: The funding for this study came from the salary of Dr. Rodrigo. No sponsorship from institutions or the pharmaceutical industry was provided to conduct this study.

References

- Bousquet J, Khaltaev N, Cruz AA *et al.* Allergic rhinitis and its impact on asthma (ARIA) 2008 update (in collaboration with the World Health Organization, GA LEN and AllerGen). *Allergy* 2008; **63**: 8–160.
- Canonica GW, Bousquet J, Mullol J, Scadding JK, Virchow JC. A survey of the burden of allergic rhinitis in Europe. *Allergy* 2007; **62** (Suppl 85):17–25.
- Ciprandi G, Cirillo I, Vizzaccaro A *et al.* Seasonal and perennial allergic rhinitis: is this classification adherent to real life? *Allergy* 2005; **60**:882–7.
- Brozek JL, Bousquet J, Baena-Cagnani CE *et al.* Allergic rhinitis and its impact on asthma (ARIA) guidelines: 2010 revision. *J Allergy Clin Immunol* 2010; **126**: 466–7.
- Weiner JM, Abramson MJ, Puy RM. Intranasal corticosteroids vs. oral H1 receptor antagonists in allergic rhinitis: systematic review of randomised controlled trials. *BMJ* 1998; **317**:1624–9.
- Yañez A, Rodrigo GJ. Intranasal corticosteroids vs. topical H1 receptor antagonists for the treatment of allergic rhinitis: a systematic review with meta-analysis. *Ann Allergy Asthma Immunol* 2002; **89**:479–84.
- Rodrigo GJ, Yañez A. the role of antileukotriene therapy in allergic rhinitis: a systematic review of randomized trials. *Ann Allergy Asthma Immunol* 2006; **96**: 779–86.
- Wilson AM, O'Byrne PM, Parameswaran K. Leukotriene receptor antagonists for allergic rhinitis: a systematic review and meta-analysis. *Am J Med* 2004; **116**: 338–44.
- Wallace DV, Dykewicz MS, Bernstein DI *et al.* The diagnosis and management of rhinitis: an updated practice parameter. *J Allergy Clin Immunol* 2008; **122**:S1–84.
- Keith PK, Scadding GK. Are intranasal corticosteroids all equally consistent in managing ocular symptoms of seasonal allergic rhinitis? *Curr Med Res Opin* 2009; **25**:2021–4.
- Scadding GK, Keith PK. Fluticasone furoate nasal spray consistently and significantly improves both the nasal and ocular symptoms of seasonal allergic rhinitis: a review of the clinical data. *Expert Opin Pharmacother* 2008; **9**: 2707–15.
- Kariyawasam HH, Scadding GK. Seasonal allergic rhinitis: fluticasone propionate and fluticasone furoate therapy evaluated. *J Asthma Allergy* 2010; **3**: 17–26.
- Juniper EF, Guyatt GH. Development and testing of a new measure of health status for clinical trials in rhinoconjunctivitis. *Clin Exp Allergy* 1991; **21**: 77–83.
- International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use. Clinical safety data management: Definitions and standards for expedited reporting. Available at: <http://www.ich.org/LOB/media/MEDIA436.pdf>. Accessed June 24, 2010.
- Liberati A, Altman DG, Tetzlaff J *et al.* The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate health care interventions: explanation and elaboration. *Ann Intern Med* 2009; **151**:W1–30.
- Higgins JPT, Green S editors. Cochrane Handbook for Systematic Reviews of Interventions 5.0.2 [updated September 2009]. Available at: <http://www.cochrane-handbook.org>. Accessed June 24, 2010.
- Higgins JPT, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. *BMJ* 2003; **327**:557–60.
- Borenstein M, Hedges LV, Higgins JPT, Rothstein HR. *Introduction to meta-analysis*. Chichester (West Sussex): John Wiley & Sons, Ltd, 2009.
- Egger M, Davey Smith G, Schneider M, Minder C. Bias in meta-analysis detected by a simple, graphical test. *BMJ* 1997; **315**:629–34.
- Altman DG, Bland JM. Interaction revisited: the difference between two estimates. *BMJ* 2003; **326**:219.

- 21 Fokkens WJ, Jogi R, Reinartz S *et al.* Once daily fluticasone furoate nasal spray is effective in seasonal allergic rhinitis caused by grass pollen. *Allergy* 2007; **62**:1078–84.
- 22 Kaiser HB, Naclerio RM, Given J, Toler TN, Ellsworth A, Philpot EE. Fluticasone furoate nasal spray: a single treatment option for the symptoms of seasonal allergic rhinitis. *J Allergy Clin Immunol* 2007; **119**:1430–7.
- 23 Martin BG, Ratner PH, Hampel FC *et al.* Optimal dose selection of fluticasone furoate nasal spray for the treatment of seasonal allergic rhinitis in adults and adolescents. *Allergy Asthma Proc* 2007; **28**:216–25.
- 24 Andrews CP, Martin BG, Jacobs RL *et al.* Fluticasone furoate nasal spray is more effective than fexofenadine for nighttime symptoms of seasonal allergy. *Allergy Asthma Proc* 2009; **30**:128–3.
- 25 Jacobs R, Martin B, Hampel F, Toler W, Ellsworth A, Philpot E. Effectiveness of fluticasone furoate 110 mg once daily in the treatment of nasal and ocular symptoms of seasonal allergic rhinitis in adults and adolescents sensitized to mountain cedar pollen. *Curr Med Res Opin* 2009; **25**:1393–401.
- 26 Meltzer EO, Lee J, Tripathy I, Lim J, Ellsworth A, Philpot E. Efficacy and safety of once-daily fluticasone furoate nasal spray in children with seasonal allergic rhinitis treated for 2 wk. *Pediatr Allergy Immunol* 2009; **20**:279–86.
- 27 Rosenblut A, Bardin PG, Muller B *et al.* Long-term safety of fluticasone furoate nasal spray in adults and adolescents with perennial allergic rhinitis. *Allergy* 2007; **62**:1071–7.
- 28 Máspero JF, Rosenblut A, Finn A, Lim L, Wu W, Philpot E. Safety and efficacy of fluticasone furoate in pediatric patients with perennial allergic rhinitis. *Otolaryngol-Head Neck Surg* 2008; **138**:30–7.
- 29 Nathan RA, Berger W, Yang W *et al.* Effect of once-daily fluticasone furoate nasal spray on nasal symptoms in adults and adolescents with perennial allergic rhinitis. *Ann Allergy Asthma Immunol* 2008; **100**:497–505.
- 30 Patel D, Ratner P, Clements D, Wu W, Faris M, Philpot E. Lack of effect on adult and adolescent hypothalamic-pituitary-adrenal axis function with use of fluticasone furoate nasal spray. *Ann Allergy Asthma Immunol* 2008; **100**:490–6.
- 31 Vasar M, Houle PA, Meltzer EO *et al.* Fluticasone furoate nasal spray: effective monotherapy for symptoms of perennial allergic rhinitis in adults/adolescents. *Allergy Asthma Proc* 2008; **29**:313–21.
- 32 Tripathy I, Levy A, Ratner P, Clements D, Wu W, Philpot E. HPA axis safety of fluticasone furoate nasal spray once daily in children with perennial allergic rhinitis. *Pediatr Allergy Immunol* 2009; **20**:287–94.
- 33 GlaxoSmithKline. Trial number FFR100650. Available at: <http://www.gsk-clinicalstudyregister.com/files/pdf/3441.pdf> (Accessed 26 June 2010).
- 34 GlaxoSmithKline. Trial number FFR100652. Available at: <http://www.gsk-clinicalstudyregister.com/files/pdf/20723.pdf>. Accessed June 26, 2010.
- 35 GlaxoSmithKline. Trial number FFR111439. Available at: <http://gsk-clinicalstudyregister.com/files/pdf/20746.pdf>. Accessed June 26, 2010.
- 36 Bernstein DI, Levy AL, Hampel FC *et al.* Treatment with intranasal fluticasone propionate significantly improves ocular symptoms in patients with seasonal allergic rhinitis. *Clin Exp Allergy* 2004; **34**:952–7.
- 37 Bielory L. Ocular symptom reduction in patients with seasonal rhinitis treated with the intranasal corticosteroid mometasone furoate. *Ann Allergy Asthma Immunol* 2008; **100**:272–9.
- 38 Prenner BM, Lanier BQ, Bernstein DI, Shekar T, Teper A. Mometasone furoate nasal spray reduces the ocular symptoms of seasonal allergic rhinitis. *J Allergy Clin Immunol* 2010; **125**:1247–53.
- 39 Bielory L. Intranasal corticosteroids reduce ocular symptoms of allergic rhinitis as a class effect. *J Allergy Clin Immunol* 2008; **121**:538–9.
- 40 Naclerio RM, Pinto J, deTineo M, Baroody FM. Elucidating the mechanism underlying the ocular symptoms associated with allergic rhinitis. *Allergy Asthma Proc* 2008; **29**:24–8.
- 41 Juniper EF, Guyatt GH, Griffith LE, Ferrie PJ. Interpretation of rhinoconjunctivitis quality of life questionnaire data. *J Allergy Clin Immunol* 1996; **98**:843–5.