New treatment options in allergic rhinitis: patient considerations and the role of ciclesonide

**Abstract:** Allergic rhinitis (AR) is a chronic inflammatory respiratory disease affecting 5%-50% of the worldwide population and its prevalence is increasing (Herman 2007). In addition, AR is associated with asthma and other co-morbidities such as conjunctivitis and sinusitis. The main symptoms are nasal congestion, rhinorrhea, sneezing, itching, and post-nasal drainage induced after allergen exposure by an IgE-mediated inflammation of the membranes lining the nose. AR is not a life-threatening disease, but it has been shown to have a significant impact on quality of life. The Allergic Rhinitis and its Impact on Asthma (ARIA) guidelines propose a classification of AR in intermittent and persistent, each graded as mild or moderate-severe, and provide a stepwise approach to the treatment. Inhaled steroids and antihistamine are the main tools in AR therapy but more safe and effective drugs are, however, needed. Inhaled steroid ciclesonide appears to be safe and effective.

**Keywords:** ciclesonide, allergic rhinitis, asthma, quality of life.

The burden of allergic rhinitis: the patient’s perspective

Allergic rhinitis is a global health problem that causes major illness and disability worldwide. Allergic rhinitis (AR) affects social life, sleep, school, and work. The economic impact of allergic rhinitis is often underestimated because the disease does not induce elevated direct costs. The indirect costs are, however, substantial. It is now recognized that allergic rhinitis comprises more than the classical symptoms of sneezing, rhinorrhea, and nasal obstruction. It is associated with impairments in how patients function in day-to-day life (Kirmaz et al 2005). It has been known for a long time that having an allergic reaction causes significant fatigue and mood changes (Marshall et al 2002), some impairment of cognitive function (Marshall et al 2000; Kremer et al 2002), and depression and anxiety (Cuffel et al 1999; Bavbek et al 2002). Impairment of quality of life, and work and school performance is common, particularly in patients with severe symptoms. These aspects of quality-of-life impairment in AR should be quantified using two types of tools for HRQL assessment – generic and specific questionnaires (Meltzer 2001; Gerth Van Wijk 2003; Leong et al 2005).

The available treatments

Current pharmacology treatment for AR includes antihistamines, decongestants, anticholinergic agents, intranasal cromolyn, leukotriene modifiers and inhaled steroids. The Allergic Rhinitis and its Impact on Asthma (ARIA) guidelines (ARIA 2007) suggest a stepwise approach to AR treatment.

In mild intermittent rhinitis, oral or intranasal anti-H1, intranasal decongestants, and oral decongestants (not in children) are suggested. For moderate-severe intermittent rhinitis and mild persistent rhinitis, the suggested options (not in preferred order)
are oral or intranasal anti-H1, oral anti-H1 + decongestant, intranasal CS, and chromones.

Moderate-severe persistent rhinitis requires intranasal CS as a first line treatment and, in case of major blockage, to add short course of oral CS or decongestant; if symptoms persists it should be useful to add oral anti-H1 (± decongestants) and or ipratropium.

In accordance with ARIA guidelines (ARIA 2007), therapy with intranasal corticosteroid is recommended as first-line prescription treatment in all the cases of AR with the exception of mild intermittent. Specific immunotherapy represents the unique treatment able not only to improve symptoms and quality of life but also to modify the disease progression.

The new treatment options
Monoclonal anti-IgE antibody
The recombinant, humanized, monoclonal anti-IgE antibody (omalizumab) forms complexes with free IgE, blocking its interaction with mast cells and basophils, and lowering (ARIA 2007) free IgE levels in the circulation (Holgate et al 2005). In a large pivotal trial, omalizumab decreased serum-free IgE levels and provided clinical benefit in a dose-dependent fashion in patients with seasonal allergic rhinitis (Linna et al 1992; Kaliner 2004). In adults and adolescents, omalizumab was found to decrease all nasal symptoms and to improve RQLQ in patients with rhinitis induced by birch and ragweed pollens as well as in those with sensitization to outdoor allergens (Adelroth et al 2001; Chervinsky et al 2003). Moreover, the treatment was safe and well tolerated (Berger et al 2003; Nayak et al 2003). The clinical benefit of treatment with omalizumab is associated with an anti-inflammatory effect on cellular markers in blood and nasal tissue (Plewako et al 2002; Bez et al 2004) as well as with a reduction in mast cell FcεRI expression and function (Beck et al 2004). Omalizumab inhibits allergen challenge-induced nasal response (Hanf et al 2004).

New inhaled steroids
The relative efficiency of this treatment compared to H1-antihistamines and intranasal glucocorticosteroids needs to be established and a thorough cost/efficacy analysis should be performed.

New inhaled steroids such as ciclesonide, appear to be promising. Ciclesonide, administered as an inactive parent compound that is metabolized by endogenous esterases in the upper and lower airways to the pharmacologically active metabolite, has shown to be effective, safe and, accordingly to once-daily administration, liked by patients.

From available glucocorticosteroids to ciclesonide
The goals of corticosteroid therapy are to maximize efficacy, minimize potential systemic adverse effects, and improve patient adherence. Factors that will potentially improve adherence to treatment and differentiate the inhaled corticosteroids are dosing, regimen, patient preference and cost-effectiveness (Dupclay and Doyle 2002; Herman 2007).

The commercially available inhaled corticosteroids (ICS) for AR treatment are beclometasone dipropionate (BDP), budesonide (BUD), flunisolide (FLU), fluticasone propionate (FP), mometasone furoate (MF), and triamcinolone acetonide (TA); most of these are also available as nasal sprays for the treatment of AR. There is no longer any doubt about their effectiveness in both asthma and rhinitis. Since ICS are widely used in both adults and children, the issue of safety and the risk/benefit ratio assumes a primary importance (Passalacqua et al 2000).

Treatment with glucocorticosteroids is the most efficacious medication for AR. The rationale for therapy using glucocorticosteroids can be summarized by their anti-inflammatory action and by their capacity to reduce nasal mucosa hyperreactivity (ARIA 2007). These medications are effective in improving all symptoms caused by allergic reaction to nasal and bronchial mucosa. For this reason, ICS are the most appropriate first-line treatment, as they are more effective than any other treatment (Berger et al 2005; Bhatia et al 2005; ARIA 2007).

Mechanism of action of ICS
ICS are widely used and prescribed in both adults and children, usually in long-term treatments. Therefore, the safety of these drugs is of some importance for both general practitioners and specialists. The mechanism of action of glucocorticosteroids is directed to specific nuclear receptors, which induce and modulate the transcription of specific target genes. These genes encode for cytokines, lipocortin-1, endothelin, b-adrenoceptors, iNOS, endopeptidases, and so on. Several transcription factors are involved in this mechanism (Carson-Jurica et al 1990; Munk et al 1990; Funder 1993; Barnes and Adcock 1993; Smith and Toft 1993; Barnes 1996). ICS exert their clinical and anti-inflammatory actions depending on a wide range of variables, including the status of the nasal and bronchial wall (Laitinen 1994; Barnes 1995; Kraft et al 1996), the pharmacodynamic-pharmacokinetic properties of the drug (Andersson and Ryrfeldt 1984; English et al 1994; Miller-Larson et al 1994; Lipworth 1995; Johnson 1996), the delivery system (Brown et al 1990; Selroos and Halme 1991;

Side-effects
The occurrence and severity of these side-effects depend, as mentioned above, upon a large number of variables, including the characteristics of the drug (lipophilicity, pharmacokinetics, and pharmacodynamics) and the mode of administration (for example, dose, delivery system, coordination).

Intranasal corticosteroids are highly effective; nevertheless, they are not completely devoid of systemic effects. Thus, care has to be taken, especially in children, when prescribing long-term treatments.

According to the available controlled studies, some effects on the hypothalamic-pituitary-adrenal axis (HPAA) and bone metabolism are detectable with high doses of ICS. Indeed, the effects on the HPAA and bone metabolism are measurable only by means of biochemical parameters; their clinical significance is still unknown and probably extremely small compared to the benefit achieved. Exogenous steroids, through negative feedback, suppress corticotrophin secretion, thus leading to adrenal cortex atrophy and to subsequent decrease of cortisol secretion; in fact long-term treatment with oral corticosteroids may result in significant suppression of the HPAA. The free urinary cortisol over 24 h appears to be a practical and reliable index of HPAA interaction, since it provides a global evaluation of the adrenal function, and is not influenced by circadian changes in cortisol blood levels, but it is difficult to demonstrate its clinical counterpart and its clinical significance: in the controlled studies, no sign or symptom of adrenal failure was described.

Oral corticosteroids may induce osteoporosis and increase the risk of fractures in adult patients, reducing intestinal calcium absorption and enhancing its renal excretion; these actions result in compensatory secretion of parathormone, bone resorption, and increased activity of osteoclasts. Secondly, corticosteroids inhibit osteoblastic activity and the synthesis of osteocalcin. Thirdly, steroids reduce the synthesis of adrenal cortex-derived oestrogens. This last finding partly explains the increased risk of osteoporosis in postmenopausal women.

Although certain effects of ICS on bone metabolism are detectable, they are evident only by means of laboratory assessment, when high doses are used. In general, experimental evidence does not support an increased risk of osteoporosis or pathologic fractures in either adults or children. No change in bone density was detectable in adult patients taking ICS at high dosages (BUD or BDP >800 mg/day) for up to 18 months.

Some data suggest that high doses of ICS can affect short-term growth in children, but this effect is certainly less significant than that due to uncontrolled asthma. Growth retardation was seen only in children taking oral steroids. The available data suggest that short-term growth may be affected by high doses of ICS, but speed of growth and stature seem to depend strictly on the degree of asthma control. However this potential systemic side-effect imposes cautious use in children: the lowest effective dose must be used, and stature should be regularly monitored.

No significant effect on glucose metabolism has been shown for ICS, even with high doses. An increase in neutrophil counts in the peripheral blood of patients taking ICS has been noted. Some local side-effects have also been described. Since local application of corticosteroids may cause dermal atrophy, the possibility of mucosal atrophy and epistaxis by long-term use of intranasal steroids has been thoroughly investigated. Furthermore, the data indicated that some of the adverse events such as irritation, crusting, itching, and stinging may be due to the propellant used in older formulations rather than to the active drug.

Cutaneous side-effects may be of some relevance in the elderly, such as skin thinning and increased capillary fragility, especially in women, using high doses of ICS for long periods. Neurologic and ocular adverse events have to be considered anecdotal. In pregnant women, when indicated, ICS should be used at the lowest effective dose. BDP, for which more data are available, should be preferred; nevertheless, no actual teratogenicity in men has ever been reported. No specific study has been conducted on ICS and lactation (Passalacqua et al 2000).

Ciclesonide
Double blind, placebo-controlled studies on budesonide (Creticos et al 1998; Andersson et al 2000; Day et al 2000, 2001), fluticasone propionate (Nathan et al 1991; Dolovich et al 1994; LaForce et al 1994 Foresi et al 1996), mometasone furoate (Bronsly et al 1997; Berkowitz et al 1999a, b; Gawchik et al 2003), and triamcinolone acetonide (Munk et al 1996; Settipane et al 2002) have shown that once-daily administration of these ICS are well tolerated and more effective than placebo in the treatment of seasonal AR (SAR) and perennial AR (PAR) (Herman 2007).
Ciclesonide is a new-generation corticosteroid with previously demonstrated efficacy in the treatment of asthma when delivered through a metered-dose inhaler. Ciclesonide is also currently in clinical development as an intranasal formulation for use in the treatment of AR.

**Pharmacodynamics and pharmacokinetics**

The ciclesonide molecule has a chiral center in the acetal side chain. The two epimers of the compound are clearly different in their receptor affinities and metabolism rates. The R-epimer has a considerably higher binding affinity to the glucocorticoid receptor as compared to the S-epimer, and therefore only R-epimer is developed for clinical use (Schmidt et al 1999).

Ciclesonide is administered as an inactive parent compound that is metabolized by endogenous esterases in the upper and lower airways to the pharmacologically active metabolite desisobutyryl-ciclesonide (des-CIC). In vitro studies in rat lung have shown that esterification of des-CIC, working as a pool of active drug, may lead to durable anti-inflammatory activity (Dietzel et al 2001; Nave et al 2005; Wingertzahm et al 2005; Ratner et al 2006a).

Advantages of on-site activation include targeted activation in the lung, minimal systemic adverse effects, and minimal oropharyngeal side effects (Ukena 2005).

Low oral bioavailability (oral bioavailability of des-CIC is approximately 1%), high protein binding (99%) and high hepatic clearance (396 L/h) contribute to the favorable safety profile of ciclesonide.

**Clinical trials**

**Administration and dosage**

The intranasal administration of ciclesonide at recommended doses results in negligible serum concentrations of ciclesonide. However, the known active metabolite (des-ciclesonide) is detected in the serum of some patients after nasal inhalation of ciclesonide.

In healthy adults treated for 2 weeks with 50–800 µg of ciclesonide nasal spray daily (n = 6 in each treatment group), the peak serum concentrations of des-ciclesonide in all subjects were found to be below 30 pg/mL. Among those treated with 800 µg and 400 µg daily, 100% and 67% had detectable levels of des-ciclesonide, respectively. With daily doses of 200 µg or less, detectable serum levels of des-ciclesonide were not observed.

In pediatric subjects treated with 25–200 µg of ciclesonide nasal spray daily, serum concentrations of des-ciclesonide were less than 45 pg/mL, with the exception of one value of 64.5 pg/mL. In a 12-week study, in children aged from 6 to 11 with perennial allergic rhinitis, des-ciclesonide was detected in 50% of subjects treated with 200 µg and in 5% of those treated with 100 µg ciclesonide nasal spray daily. In a 6-week study, in children aged from 2 to 5 with perennial allergic rhinitis, des-ciclesonide was detected in 41%, 22%, and 13% of subjects treated with 200 µg, 100 µg, and 25 µg ciclesonide nasal spray daily, respectively.

Following intravenous administration of 800 µg of ciclesonide, the volumes of distribution of ciclesonide and des-ciclesonide were approximately 2.9 L/kg and 12.1 L/kg, respectively. The percentage of ciclesonide and des-ciclesonide bound to human plasma proteins averaged ≥99% each, with ≤1% of unbound drug detected in the systemic circulation. Des-ciclesonide is not significantly bound to human transcortin.

Des-ciclesonide undergoes further metabolism in the liver to additional metabolites mainly by the cytochrome P450 (CYP) 3A4 isozyme and to a lesser extent by CYP 2D6. The full range of potentially active metabolites of ciclesonide has not been characterized. After intravenous administration of 14C-ciclesonide, 19.3% of the resulting radioactivity in the plasma is accounted for by ciclesonide or des-ciclesonide; the remainder may be a result of other, yet, unidentified multiple metabolites.

Following intravenous administration of 800 µg of ciclesonide, the clearance values of ciclesonide and des-ciclesonide were high (approximately 152 L/h and 228 L/h, respectively). 14C-labeled ciclesonide was predominantly excreted via the feces after intravenous administration (66%) indicating that excretion through bile is the major route of elimination. Approximately 20% or less of drug related radioactivity was excreted in the urine. The relative glucocorticoid receptor binding affinity of des-CIC is 100-fold greater than that of ciclesonide. Des-ciclesonide has anti-inflammatory activity with affinity for the glucocorticoid receptor that is 120 times higher than the parent compound. (ALTANA Pharma 2006).

**Intranasal formulation**

Ciclesonide for intranasal use is formulated in a hypotonic suspension, which has been shown in preclinical in vivo models to provide enhanced tissue uptake when compared with a traditional isotonic formulation. In addition, the intranasal formulation of ciclesonide is preserved with potassium sorbate rather than benzalkonium chloride, which is used in many intranasal steroids (INSs). Benzalkonium chloride is believed to interfere with mucociliary transport and can lead
to the development of hypersensitivity, rhinitis medicamentosa, and neutrophil dysfunction.

Furthermore, benzalkonium chloride has a bitter taste that might compromise patient adherence (Graf 1999; Bernstein 2000; Ratner et al 2006b).

**Efficacy and safety of ciclesonide**

The once-daily intranasal administration of 200 µg of ciclesonide was shown to be effective for the treatment of seasonal AR, as demonstrated by a statistically significant improvement from baseline compared with that seen in the placebo group in the primary efficacy variable of the average of morning and evening reflective TNSSs (total nasal symptom score) over days 1–14. Interestingly, although inhaled steroid products are typically perceived as having the greatest effect on nasal congestion, this study demonstrated that ciclesonide nasal spray showed a similar magnitude of effect on all four components of the TNSS, namely nasal congestion, rhinorrhea, nasal itching, and sneezing. Although no direct head-to-head trials between ciclesonide and other products have been performed to date, the indirect comparison across studies suggests that the treatment-effect size observed between ciclesonide and placebo is larger than that generally seen with montelukast, as well as nonsedating oral histamines, such as desloratadine, in the treatment of seasonal allergic rhinitis (Salman and Lorber 2002; Nasonex 2003). Additionally, the magnitude of effect observed in this study appears comparable with what had been previously demonstrated with mometasone in trials using a similar measurement scale (Dykewicz et al 2003).

The dosing posology was also assessed from the data of total nasal symptom score in another randomized, double-blind, parallel-group, placebo-controlled, multicenter clinical trial (Ratner et al 2006b), which suggested that once-daily morning dosing is appropriate for ciclesonide nasal spray, and which could theoretically lead to increased compliance compared with drugs that are dosed twice or more daily.

In a multicenter, double-blind, randomized, placebo-controlled, 2-week safety and efficacy dose-ranging study, ciclesonide nasal spray (25–200 µg/day) was administered once daily for 14 days showing to be safe and effective in the treatment of SAR. Intranasal administration at doses of 100–200 µg/day was associated with dose-related improvements in nasal symptom relief compared with placebo and the 200 µg/day dose was numerically superior to 100 µg/day dose (Ratner et al 2006a).

Evidence supporting the 200 µg/day dose of ciclesonide nasal spray as the starting and maximum doses in adult patients was obtained from a post hoc test demonstrating that there is a dose-dependent increase in efficacy and the 200 µg/day dose of ciclesonide is the most effective dose studied for the amelioration of symptoms associated with SAR (Ratner et al 2006a).

Another study evaluated the efficacy and safety of intranasal ciclesonide, 200 µg once-daily, for the treatment of perennial allergic rhinitis (PAR). In this double-blind, randomized, placebo-controlled study, patients with at least 2 years history of rhinitis received ciclesonide (n = 238) or placebo (n = 233) once daily for 6 weeks. In controlling daytime and nighttime, twice daily, nasal symptoms of PAR (runny nose, itchy nose, sneezing, and nasal congestion), ciclesonide was demonstrated to be superior to placebo. The comparable improvements in the morning and in the evening reflective TNSS observed in this study support the rationale for a once-daily dosing regimen of ciclesonide in the treatment of PAR.

Ciclesonide, 200 µg once daily, was well tolerated in adult and adolescent patients with PAR and it was associated with a significant reduction in correlated total nasal symptoms. Moreover, the frequency of adverse events in patients in ciclesonide group was similar to that of placebo. Ciclesonide treatment improved one measure of quality of life and was delivered with the convenience of once-daily dosing (Meltzer et al 2007).

The efficacy and safety of ciclesonide in the treatment of allergic rhinitis have also been investigated in a double-blind, randomized, placebo-controlled, crossover trial involving 24 subjects who were symptom free at the time of the study. A dose of 200 µg/nostril was administrated for 7 days. Subjective symptoms of obstruction, itching, and rhinorrhea improved from day 2 of treatment, and rhinal airflow showed significant improvement from day 5. Excellent tolerance at both local and systemic levels was seen (Meltzer and Derendorf 2006). These data confirmed the results of previous clinical trials (Ratner et al 2004; Nave et al 2006; Meltzer et al 2007). Results from ciclesonide clinical trials in allergic rhinitis are summarized in Table 1.

**Ciclesonide and HPAA**

Several studies have evaluated the potential suppressive effects of ciclesonide on HPAA function by measuring both sensitive and clinically relevant markers.

In a placebo-controlled, randomized, double-blind, 4-period changeover equivalence study of healthy volunteers, ciclesonide (640 µg/day) was administered once daily, in the morning or evening, or half-dosed twice daily, to evaluate
its effect on cortisol excretion and circadian serum cortisol rhythm. Patients were hospitalized after 6 days of ciclesonide treatment to measure 24-hour serum cortisol levels across the seventh day of treatment.

The 24-hour cortisol profiles obtained after ciclesonide treatment were equivalent to those observed in the placebo control group, because no significant difference was seen in cortisol amplitude and acrophase (time to maximum). These results suggest that ciclesonide at a dose of up to 640 µg/day does not disrupt cortisol production or the normal diurnal rhythm of endogenous cortisol secretion, regardless of the time of administration.

This lack of effect that ciclesonide has on HPAA function has been repeatedly demonstrated in several additional short-term safety and efficacy trials and long-term safety studies at doses that are therapeutically effective.

Overall, the observations from these studies demonstrate that treatment with ciclesonide in adults appears to achieve comparable efficacy with a currently available ICS treatment while also reducing systemic activity, as evaluated by basal cortisol excretion on HPAA stimulation. Since all ICSs deposited in the lungs enter the systemic circulation at some stage in the drug’s life-cycle, the lack of effect on HPAA function with ciclesonide may be due to its unique

<table>
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<tr>
<th>Author (year)</th>
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<td>Ratner (2006b)</td>
<td>SAR</td>
<td>DBPCR</td>
<td>327</td>
<td>28 days</td>
<td>Efficacy, safety, tolerably</td>
<td>“Intranasal ciclesonide was superior to placebo in relieving nasal symptoms in[...].confirm the dose range-finding study and support the efficacy of ciclesonide in AR”</td>
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<td>Nave (2006)</td>
<td>SAR</td>
<td>DBPCR</td>
<td>48</td>
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<td>“The low systemic exposure and favorable safety profile support the continued clinical development”</td>
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<tr>
<td>Ratner (2006a)</td>
<td>SAR</td>
<td>DBPCR</td>
<td>145</td>
<td>14 days</td>
<td>Efficacy, safety</td>
<td>“200 µg appears to be the optimal dose studied for reducing the symptom of SAR while maintaining an acceptable safety profile”</td>
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<td>ALTANA Pharma (2006)</td>
<td>SAR PAR</td>
<td>4DBPCR</td>
<td>1524 in 3 trials</td>
<td>3 trials: 2–6 weeks 1 trial: 1 year</td>
<td>Efficacy, safety, tolerably</td>
<td>“The results showed that patients treated with 200 µg once daily exhibited statistically significantly greater decreases in total nasal symptom scores than placebo treated patients. Measures of efficacy were also generally supportive”</td>
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Abbreviations: AR, allergic rhinitis; DBPCR, double blind, placebo-controlled, randomized trial; PAR, perennial allergic rhinitis; SAR, seasonal allergic rhinitis.
pharmacologic characteristics: the low levels of systemically available pharmacologically active desisobutyryl-ciclesonide, in addition to rapid elimination and low oral bioavailability, may account for the lack of clinically relevant effect that ciclesonide has on HPAA function, as evaluated by both basal cortisol concentration measurements and dynamic stimulation tests (Meltzer and Derendorf 2006).

Adverse effects
In a phase I, single center, randomized, double-blind, placebo-controlled, multiple-dose, modified sequential design study, healthy volunteers or asymptomatic subjects with a history of seasonal allergic rhinitis were randomized to receive ciclesonide or placebo via intranasal pump spray for 14 days. As expected, intranasal ciclesonide (50–800 µg/day) administration was generally safe and well tolerated in both healthy volunteers and asymptomatic subjects with SAR. An increase in the dose of ciclesonide did not correlate with an increase in adverse event frequency and the incidence of treatment-emergent adverse events was comparable between healthy volunteers and subjects with SAR. The data are consistent with earlier findings in a 7-day trial of ciclesonide nasal spray delivered via a pressurized metered-dose inhaler versus placebo in subjects with allergic rhinitis, wherein the frequency of treatment-emergent adverse events was low and no local or systemic side-effects were reported (Nave et al 2006).

A total of 134 treatment-emergent adverse events was reported by 41 participants (out of a total of 100 participants). The most common adverse effects were headache (11%), fatigue (7%), and rhinitis (7%). The majority of adverse events (97%) were mild in intensity. The frequency of adverse events was comparable among healthy volunteers and asymptomatic subjects with SAR. The most common adverse events considered by the investigator to be possibly or probably related to study medication were nose congestion, headache, and rhinorrhea. No adverse events were considered to be definitely related to the study medication. No serious adverse event was reported (Nave et al 2006).

Conclusions
Ciclesonide nasal spray provided substantial symptom relief, as measured by patients and physicians. Intranasal administration of ciclesonide was well tolerated, with an overall incidence rate of adverse events comparable with that of placebo. The demonstrated efficacy and favorable safety and tolerability profile of ciclesonide suggest that ciclesonide nasal spray is an effective treatment option for patients with AR (Ratner et al 2006b).

These findings, in conjunction with the observed clinical efficacy of ciclesonide, may suggest that ciclesonide has an improved therapeutic profile and safety compared with some other currently available ICS treatments and, therefore, the potential to ameliorate adherence rates and therapeutic outcomes (Meltzer and Derendorf 2006).

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