

Twenty-four-hour duration of effect of intranasal corticosteroids for seasonal allergic rhinitis symptoms: Clinical evidence and relevance

Lawrence M. DuBuske, M.D.

ABSTRACT

Background: Seasonal allergic rhinitis (SAR) symptoms are often most severe and/or disruptive during overnight and morning hours, resulting in cognitive/performance impairments and reduced quality of life throughout the following day. Surveys of allergy patients and health care practitioners reveal a common perception that intranasal steroids (INSs), many of which are dosed q.d., fail to adequately relieve symptoms for a full 24 hours. This review assessed whether perceptions of the 24-hour duration of action of INSs correspond with duration of action documented in clinical literature.

Methods: SAR clinical trial literature of the last 5 years was reviewed to identify studies of INSs incorporating morning instantaneous (A.M. NOW) or instantaneous assessments of 24-hour duration of action.

Results: In numerous placebo-controlled trials of INSs in patients with SAR, treatment was associated with significantly greater improvements in A.M. NOW symptoms from baseline versus placebo. For congestion, this is noteworthy, because patients often cite this symptom, especially in the morning, as the most bothersome symptom. Comparison of A.M. NOW and daily scores suggests minimal drop in efficacy at 24 hours postdose. In several studies, INS treatment was found superior to intranasal or oral antihistamines in A.M. NOW symptom improvement.

Conclusion: Once-daily INSs have potential for effective 24-hour symptom relief; however, there is an apparent disconnect between these findings and patient/physician perceptions. This discrepancy may be explained, in part, by less-than-ideal treatment adherence among "real-world" patients versus subjects treated in clinical trials. Proactive counseling can encourage proper INS use and help maximize treatment benefits.

(Am J Rhinol Allergy 26, 287–292, 2012; doi: 10.2500/ajra.2012.26.3770)

Seasonal allergic rhinitis (SAR) is a common, chronic condition with potential for substantial morbidity and impact on quality of life. The self-reported prevalence of SAR or perennial AR symptoms in the United States was recently given as 30.2%, corresponding to almost 90 million persons.¹ Conservative estimates suggest a worldwide prevalence of >500 million, and incidence appears to be rising.² Direct and indirect costs are high and continue to increase.³ Nonetheless, approximately one of eight affected individuals in the United States seeks medical advice and treatment for these conditions, suggesting substantial underdiagnosis, self-treatment, mild symptoms, or even poor access to health care.^{3,4}

Almost one-half of patients with AR report greatest symptom severity in the morning, with nasal congestion the most commonly experienced complaint on awakening. In most patients, the presence of morning symptoms affects their emotions and behavior throughout the day.⁵

Given these issues, greater attention is being given to evaluating the 24-hour duration of action of allergy medications dosed q.d. in the morning, in an effort to determine whether high levels of symptom relief are maintained through the night and until the next morning dose. Clinical studies of AR treatments now frequently include subjective efficacy assessments at the 24-hour time point, just before the next scheduled dose. Morning instantaneous (A.M. NOW) or A.M. NOW symptom severity ratings immediately before dosing provide

an assessment of drug effectiveness at that moment, ~23.75 hours after the previous dose.

The SAR clinical trial literature of the last 5 years was reviewed to identify studies of intranasal steroids (INSs) incorporating A.M. NOW or A.M. instantaneous assessments of 24-hour duration of action. Search terms "budesonide," "fluticasone furoate," "fluticasone propionate," "mometasone furoate," and "triamcinolone," paired with "A.M. NOW" and "A.M. instantaneous," yielded articles on fluticasone furoate, mometasone furoate, and ciclesonide. This review of the identified literature assessed the 24-hour duration of action of INS agents, which are widely used for SAR, to determine whether perceptions of duration of action correspond with duration of action documented in the clinical literature.

RELEVANCE OF 24-HOUR DURATION OF EFFECT

In recent years, pharmaceutical advances have produced oral and intranasal allergy treatments that can be administered q.d. to improve patient convenience and adherence. An Internet-based survey conducted in 2005 asked 1000 adult patients with AR in the United States about disease characteristics and patterns as well as treatment preferences and satisfaction/dissatisfaction.⁵ Approximately two-thirds of respondents indicated it was very important for an allergy medication to sustain efficacy from dose to dose, provide relief all day and into the next morning, and let them awaken with good symptom control. However, up to one-third of patients in the Allergies in America survey cited a perceived lack of 24-hour symptom relief as a reason for discontinuing treatment.⁶ Thus, the q.d. dosing of many allergy products, intended to improve adherence through convenience, may actually lead to nonadherence or even treatment disruption if the patient does not experience or perceive sufficient continued relief between doses. These concerns are especially relevant given the relatively greater burden of AR symptoms during the overnight/morning periods.

PERCEPTIONS OF INS DURATION OF EFFECT

INSs have been shown to be among the most effective nasal congestion treatments and, as a class, have been a recommended first-line intervention for AR for >10 years.^{2,7–10} Results from trials, meta-analyses, and systematic reviews suggest that INSs are superior to

From the Division of Allergy and Immunology, Department of Internal Medicine, George Washington University School of Medicine, Washington, D.C. and Immunology Research Institute of New England, Gardner, MA
Funded by Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc., Whitehouse Station, NJ

L. DuBuske received research grants from Merck, Boehringer Ingelheim, Novartis, Genentech, Alson, Allergy Therapeutics; consultant for Sunovion, Merck, Novartis, Ista, Allergy Therapeutics, AstraZeneca, Lypanosis, GlaxoSmithKline; lecturer from GlaxoSmithKline, Novartis, Merck, Sunovion, Allergy Therapeutics, UCB, Alcon
Address correspondence and reprint requests to Lawrence DuBuske, M.D., George Washington University Medical Faculty Associates, Allergy, Suite 200, 2300 M Street, Washington, D.C. 20037

E-mail address: ldubuske@aol.com

Copyright © 2012, OceanSide Publications, Inc., U.S.A.

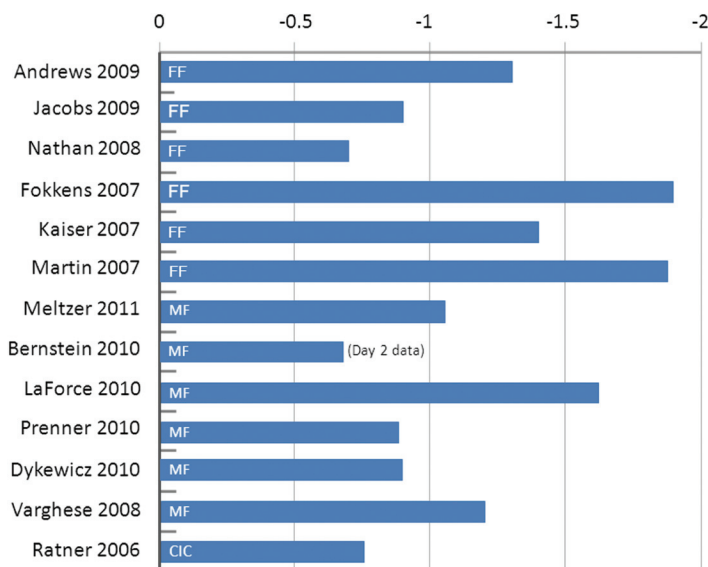


Figure 1. Treatment differences in mean A.M. NOW TNSS scores, INS versus placebo, in subjects with SAR. Although direct comparison of studies is challenging due to variations in design, results illustrate consistency of effect across INSSs. All studies were of 2-week duration, with the exception of the Varghese study, which was an 8-day chamber study (see text for further detail).^{23–35} All versus placebo, $p < 0.05$. A.M. NOW, morning instantaneous; CIC, ciclesonide; FF, fluticasone furoate; INS, intranasal corticosteroid; MF, mometasone furoate; SAR, seasonal allergic rhinitis; TNSS, total nasal symptom score.

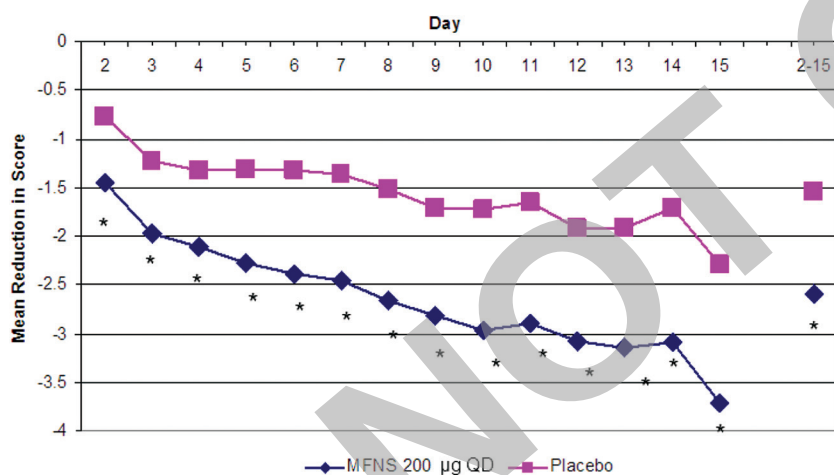


Figure 2. Significantly greater improvement in A.M. NOW TNSS was seen in subjects treated with mometasone furoate nasal spray at 200 µg q.d. ($n = 344$) versus placebo ($n = 340$). The benefit vs placebo was significant by day 1 and on each subsequent day of the study³⁰ ($*p < 0.001$ versus placebo). A.M. NOW, morning instantaneous; MFNS, mometasone furoate nasal spray; TNSS, total nasal symptom score.

oral and intranasal antihistamines for relieving AR symptoms, particularly nasal complaints.^{11–16} Most widely used INSs are labeled for q.d. dosing (budesonide/Rhinocort Aqua, ciclesonide/Omnaris, fluticasone furoate/Veramyst, fluticasone propionate/Flonase; mometasone furoate/Nasonex, and triamcinolone/Nasacort AQ).^{17–22} However, many physicians and patients perceive INSs as providing inadequate 24-hour symptom relief. In the Allergies in America survey, 48% of patients indicated that their prescription nasal spray loses efficacy over 24 hours, an opinion shared by sizable numbers of responding health care professionals.⁶

CLINICAL STUDY EVIDENCE FOR INS DURATION OF EFFECT

A primary assessment to evaluate 24-hour duration of effect for q.d. medications dosed in the morning is patient-rated A.M. NOW (also called A.M. instantaneous). Historically, SAR study designs rarely incorporated A.M. NOW efficacy evaluations, focusing on efficacy ratings over periods of time (*i.e.*, daytime or nighttime periods). The A.M. NOW rating is a relatively new outcome of interest; thus, most relevant study data represent only the newer INS compounds.

INS versus Placebo

Several placebo-controlled studies were identified in which A.M. NOW symptom ratings were used to evaluate the 24-hour duration of

effect of fluticasone furoate,^{23–28} mometasone furoate,^{29–34} or ciclesonide.³⁵ Figure 1 depicts changes from baseline in mean A.M. NOW scores for total nasal symptom score (TNSS) in studies rating four individual nasal symptoms (congestion, rhinorrhea, sneezing, and itching) on a scale of 0 (none) to 3 (severe), with TNSS the sum of these four scores (maximum possible TNSS = 12). In every study, INS treatment was associated with significantly greater improvement from baseline in A.M. NOW assessments versus placebo, with mean improvement versus placebo ranging from 0.7 to 1.9. These data provide consistent evidence of significant, measurable INS activity 24 hours postdosing. Figure 2 illustrates day-by-day differences in A.M. NOW TNSS ratings from a 2-week study comparing q.d. mometasone furoate nasal spray (MFNS) and placebo. Beginning on day 1 and on each subsequent study day, MFNS treatment was significantly superior to placebo 24 hours after the previous day's dose.³⁰ Figure 3 depicts changes from baseline in patient-reported daily reflective TNSS (rTNSS) and A.M. NOW TNSS scores, indicating little change in patient-perceived benefits over the 24-hour dosing interval and suggesting duration of action throughout this period.^{23–28}

A.M. NOW TNSS was a secondary end point in a recent report of pooled results from two studies evaluating MFNS versus placebo. The majority of the 684 subjects had moderate-to-severe congestion and SAR.²⁹ Subjects receiving MFNS ($n = 344$) showed a 1.04-point difference versus placebo ($n = 340$) in least squares mean change from baseline for

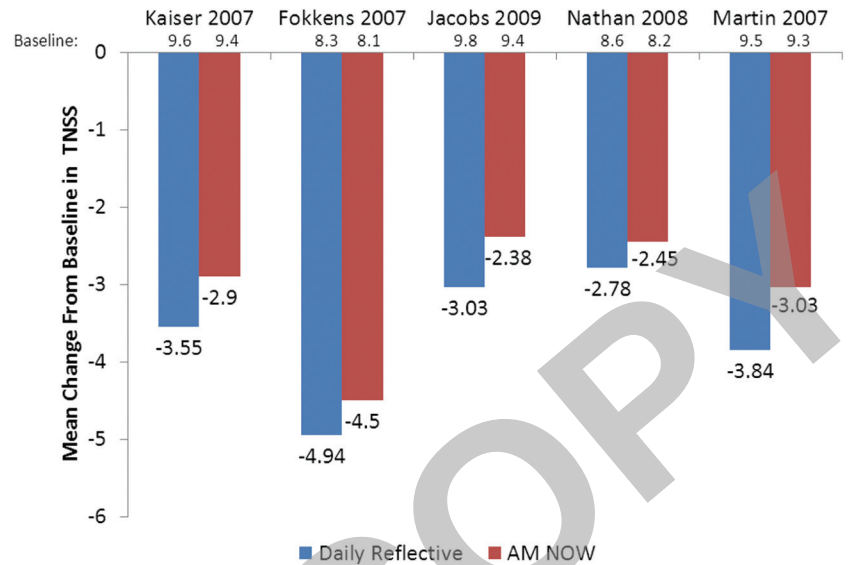


Figure 3. Changes from baseline in patient-reported daily rTNSS and A.M. NOW TNSS scores in studies with intranasal corticosteroids. Data imply minimal difference in patient-perceived benefit over the 24-hour dosing interval.^{24–28} A.M. NOW, morning instantaneous; TNSS, total nasal symptom score.

Table 1 Changes from baseline in A.M. NOW congestion severity scores (0 = none to 3 = severe) among SAR subjects using INS vs subjects using placebo spray

Study	INS	Treatment Duration (wk)	Change from Baseline, A.M. NOW Congestion (SE)		
			INS	Placebo	p Value
Kaiser 2007 ²⁷	FF	2	−0.65 (0.05)	−0.34 (0.05)	<0.001
Martin 2007 ²⁸	FF	2	−0.7 (0.05)	−0.3 (0.05)	<0.001
Fokkens 2007 ²⁶	FF	2	Data points not provided		<0.001
Nathan 2008 ²⁵	FF	4	−0.62 (0.06)	−0.46 (0.06)	0.035
Lanier 2010 ⁴¹	MF	2	−0.66	−0.44	<0.05
Meltzer 2011 ²⁹	MF	2	−0.60	−0.36	<0.001

Source: Refs. 25–29 and 41.

A.M. NOW = morning instantaneous; FF = fluticasone furoate; INS = intranasal steroid; MF = mometasone furoate; SAR = seasonal allergic rhinitis.

days 2 through 15 ($p < 0.001$) A.M. NOW TNSS, indicating a sustained 24-hour effect from medication taken the previous day.

Almost all of the studies depicted in Fig. 1 were 2-week double-blind trials conducted in “real-life” conditions during allergy seasons. The exception was an 8-day environmental exposure chamber (EEC) study of MFNS, mimicking allergen conditions on peak pollen days while minimizing the exposure variability of field trials.^{34,36} In that study, 310 subjects with SAR assessed NOW TNSS on day 1 with continual ragweed exposure in the EEC every half hour for 1.5 hours before randomization and dosing, and during the 6 hours after dosing. A randomly selected subgroup ($n = 155$) then received 7 days of treatment with MFNS or placebo, and then rated NOW TNSS severity again before EEC entry on day 8 (22 hours postdose) and every 30 minutes for 4 hours in the EEC (up to 26 hours postdose). Subjects using MFNS reported significantly less severe TNSS versus those using placebo at 24 hours after dosing (7.21 versus 8.41; $p = 0.2$) and as long as 26 hours after dosing (7.50 versus 8.62; $p = 0.3$). Studies using an EEC are of particular importance in determining onset of action; the early onset of action of MFNS shown by acoustic rhinometry in this study preceded subjective improvement, indicating clinical relevance in terms of patient expectations of symptom relief after dosing.³⁶ Similar results were seen in in patients receiving fluticasone furoate or placebo over 8 days in an EEC study in 59 patients with history of grass pollen AR,³⁷ indicating that even in the simulated environment of an EEC, INSs offered sustained, effective relief.

Congestion-Specific Data. Congestion, routinely implicated as the most prevalent and bothersome SAR symptom, is considered largely responsible for associated sleep disruption.^{38–40} Thus, prolonged congestion relief is highly desirable. In placebo-controlled studies reporting A.M. NOW congestion scores, changes from baseline were consistently, significantly greater with INS versus placebo, implying sustained and measurable congestion relief even 24 hours after dosing (Table 1).^{25–29,41} The least robust difference was reported at the end of the one 4-week study, the others being 2 weeks in duration. This may reflect the inherent seasonal dynamics of SAR and potential variability in allergen exposure over time. Congestion was a primary end point in the pooled studies of 684 patients mentioned previously.²⁹ A.M. NOW congestion findings in these studies suggest that MFNS continued to be significantly superior to placebo 24 hours after dosing, with significantly greater changes from baseline versus placebo on days 2 through 15 (0.24-point difference; $p < 0.001$), 2 through 8 (0.21 points; $p < 0.001$), and 9–15 (0.29 points; $p < 0.001$).

Another report of pooled results from five 15-day studies evaluated 24-hour efficacy of MFNS.³³ In the studies, in which 1812 total subjects with symptomatic SAR were randomly assigned to MFNS or placebo, a single daily dose of MFNS was associated with rapidly and significantly improved nasal congestion/stuffiness and TNSS, as shown by A.M. NOW symptom scores. The difference in least squares mean decrease from baseline in A.M. NOW scores was evident as early as day 2 (nasal congestion/stuffiness, -0.28 versus -0.19 for MFNS and

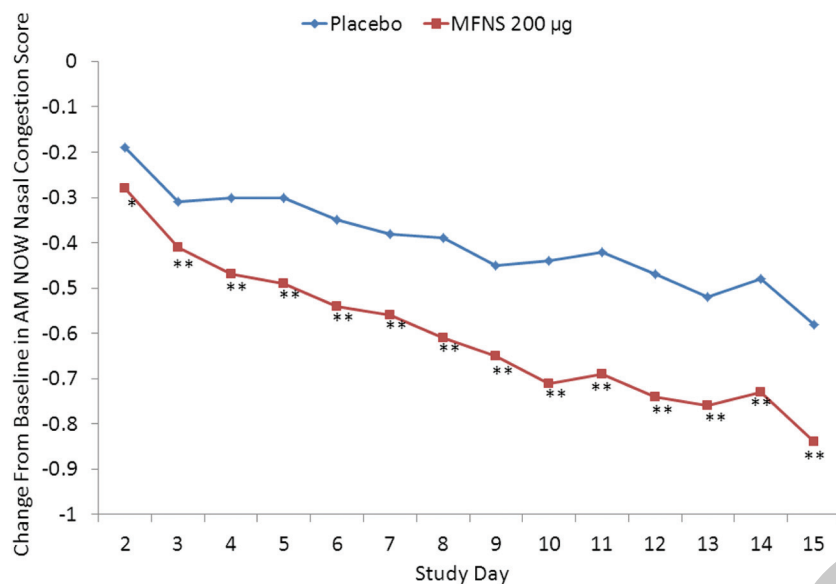


Figure 4. Least squares mean change in A.M. NOW nasal congestion score, days 2–15, in 1812 subjects receiving MFNS ($n = 912$) or placebo ($n = 900$)³³ (* $p = 0.01$ versus placebo; ** $p < 0.001$ versus placebo). A.M. NOW, morning instantaneous; MFNS, mometasone furoate nasal spray.

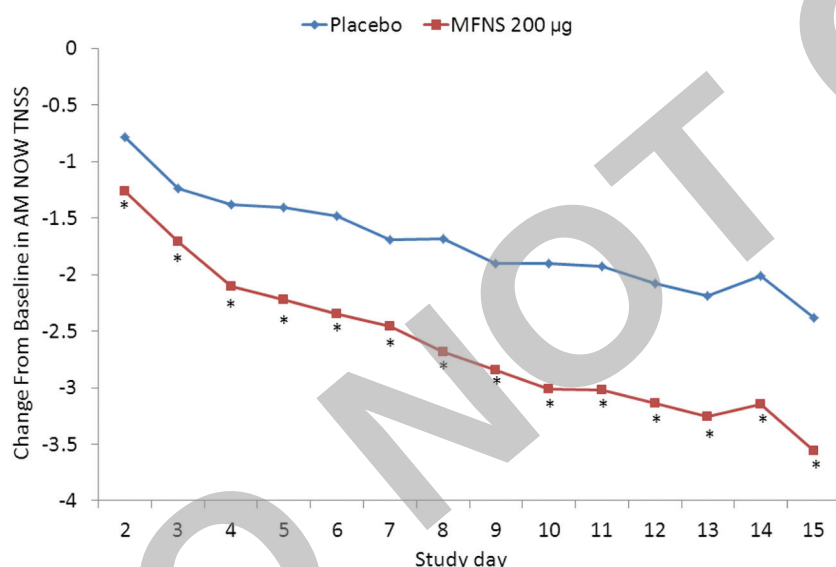


Figure 5. Least squares mean change in A.M. NOW TNSS, days 2–15, in 1812 subjects receiving MFNS ($n = 912$) or placebo ($n = 900$)³³ (* $p < 0.001$ versus placebo). A.M. NOW, morning instantaneous; MFNS, mometasone furoate nasal spray; TNSS, total nasal symptom score.

placebo, respectively, $p = 0.01$; TNSS, -1.26 versus -0.78 for MFNS and placebo, respectively, $p < 0.001$) and continued to be significant daily, suggesting 24-hour efficacy in alleviating nasal SAR symptoms over 15 days of treatment (Figs. 4 and 5). A meta-analysis including seven studies of fluticasone furoate versus placebo in SAR patients ($n = 2589$) evaluated 24-hour duration of action with NOW TNSS scores.⁴² Patients receiving fluticasone furoate showed a weighted mean difference from baseline of -1.32 versus placebo over 2 weeks. These reports consistently show superior benefit of INS versus placebo at relieving nasal symptoms in patients with SAR at the 24-hour time point.

A.M. versus P.M. rTNSS Scores. One study reported comparative A.M. and P.M. rTNSS scores with various doses of q.d. fluticasone furoate nasal spray.²⁸ Over weeks 1–2 of treatment, least squares mean changes in A.M. and P.M. rTNSS scores, respectively, for each dosing cohort were $55 \mu\text{g}$, -3.5 and -3.6 ; $110 \mu\text{g}$, -3.7 and -4.0 ; $220 \mu\text{g}$, -3.2 and -3.2 ; and $440 \mu\text{g}$, -3.9 and -4.1 . Although no statistical analysis was conducted, numerical differences between treatment effect over the first and second 12-hour postdosing windows were not dramatically different.

A.M. NOW versus Daily Reflective Scores. NOW scores represent how the patient is feeling at the moment; individual studies sometimes define NOW as referring to the last 5, 10, 15, or 30 minutes; reflective scores pertain to symptoms recollected over a 12-hour period. Comparisons between INS and placebo A.M. NOW symptom scores provide a good snapshot of treatment effectiveness 24 hours after the prior dose. However, this assessment can not evaluate INS efficacy maintained over the entire 24-hour period. To investigate this concept, A.M. NOW symptom scores, indicating perceived benefit at the clinical “trough,” just before the next dose, can be compared with daily reflective scores, which capture the patient’s retrospective impression of treatment effectiveness over the entire dosing period, generally measured b.i.d. If INS treatment effectiveness does wane over 24 hours, as patients asserted in survey data, one could expect daily reflective symptom scores to be markedly higher than the A.M. NOW evaluation at the end of the dosing interval. Figure 3 presents a comparison of daily rTNSS and A.M. NOW TNSS score changes from baseline.^{24–28} Although daily reflective score reductions are consistently numerically greater than A.M. NOW reductions, the magnitude of treatment efficacy at the end of 24 hours was ~80–90% of the

efficacy for the entire 24-hour period, suggesting minimal loss in perceived symptom improvement at 24 hours.

INS versus Intranasal Antihistamine

Once-daily fluticasone propionate was compared with a b.i.d. intranasal antihistamine (olopatadine) in a 2-week, double-blind trial.⁴³ A.M. and P.M. NOW symptom severity scores were recorded, and averages were provided for all NOW assessments (A.M. and P.M.); A.M. NOW assessments were not tracked separately. Comparative NOW findings between the two treatments are of interest. At the end of the 2-week treatment period, percentage changes from baseline in NOW TNSS were -48.8% (q.d. INS) and -45.3% (b.i.d. olopatadine nasal spray). The reduction in average NOW congestion scores with INS ($n = 65$) was almost double that observed with olopatadine ($n = 65$; -30.21% versus -16.49% , respectively). Percent changes from baseline in runny nose were similar between groups (-38.80% versus -38.45%). Numerically greater improvement in itchy nose was seen with INS (-42.57%) versus olopatadine (-30.20%). Conversely, reduction from baseline in average NOW sneezing score was greater with olopatadine (-55.23% ; INS, -42.88%). None of these changes was statistically significant. Thus, q.d. INS treatment provided benefit at least similar to that of b.i.d. intranasal antihistamine. Although a separate report of the A.M. NOW scores would have been informative, it can be surmised that any substantial tapering of INS effect at the end of 24 hours would have led to lower average NOW scores overall.

INS versus Oral Antihistamine

Two double-blind, placebo-controlled studies compared fluticasone furoate nasal spray ($110\text{ }\mu\text{g}$) with oral fexofenadine (180 mg) and placebo, each given q.d. in the morning for 2 weeks, in patients with SAR.²³ These studies were designed to evaluate the effects of treatment on allergy-related nighttime sleep disturbance. Each morning, patients completed a validated nighttime symptoms questionnaire, answering questions on a scale of 0 (no effect) to 3 (severely affected): "How difficult was it to get to sleep last night because of your nose symptoms?" "How many times did your nose symptoms wake you up last night?" and "How severe was your stuffy nose when you woke up?" The sum of these scores comprised the "nighttime symptoms score." Individual symptoms were also rated instantaneously each morning on a zero-to-three scale. Baseline predose NOW TNSS scores were similar among treatment groups in both studies. At the end of each 2-week study, mean changes from baseline in predose A.M. NOW TNSS scores were significantly greater for INS versus oral antihistamine (study 1 treatment difference, -1.1 , $p < 0.001$; study 2 treatment difference, -1.5 , $p < 0.001$); fexofenadine failed to show superiority to placebo in predose TNSS scores. Changes from baseline in mean nighttime symptom scores and mean nighttime rTNSSs over 2 weeks of treatment were significantly greater with INS versus oral antihistamine or placebo (all, $p < 0.001$). In contrast, oral antihistamine was not superior to placebo even in changes in nighttime symptom scores or mean nighttime rTNSSs. These data suggest that the 24-hour duration of effect of q.d. INS treatment was statistically superior to oral antihistamine.

INS versus Decongestant

A blinded, randomized, placebo-controlled study evaluated MFNS ($200\text{ }\mu\text{g}$) and intranasal decongestant (oxymetazoline 0.05%), in combination and as monotherapy, versus placebo in patients with SAR.⁴¹ (INS versus placebo data from this study are included in the Table 1.) Combination therapy was evaluated with two different doses of oxymetazoline. Patients received MFNS q.d. plus oxymetazoline 1 spray/nostril daily, MFNS q.d. and oxymetazoline 3 sprays/nostril q.d., MFNS only q.d., oxymetazoline only 2 sprays/nostril b.i.d., or placebo. Baseline symptoms were similar among treatment groups.

Over days 2–15, both combination treatments and MFNS monotherapy all showed significantly greater reductions from baseline versus placebo in A.M. NOW congestion scores (-0.78 , -0.77 , -0.66 , and -0.44 for MFNS plus 1 spray oxymetazoline, MFNS plus 3 sprays oxymetazoline, MFNS monotherapy, and placebo respectively; $p \leq 0.002$ for each of the three active treatments versus placebo). Change from baseline for oxymetazoline monotherapy (-0.55) in A.M. NOW congestion did not reach statistical significance versus placebo.

Translating Clinical Trial Evidence into Improved Patient Care

The data reviewed here suggest that q.d. INS treatment of SAR symptoms has sustained and measurable efficacy extending until the next dose. However, as discussed earlier, patient survey data have indicated a high level of dissatisfaction with regard to INS duration of effect. One explanation for this discrepancy could be a difference in adherence between a strictly controlled clinical trial environment and in real-world settings. In an online survey, only 20% of allergy patients reported using their prescription medication according to their physician's instructions.⁴⁴ In the same survey, 29% of INS users reported using their medication only when symptoms were bothersome. An earlier United Kingdom survey noted that approximately two-thirds of allergy patients experiencing unsatisfactory symptom control with both an INS and an oral antihistamine were not using their medication as recommended.⁴⁵

Results from the Allergies in America survey indicated that many physicians and other health care providers doubt the duration of INS effect. Almost one-half of otolaryngologists, a fourth of allergists, and more than one-third of primary care physicians felt that INSs do not provide 24-hour symptom relief.⁶ Given the contrary clinical study evidence, it is possible that such perceptions are fostered by feedback from patients failing to use INSs properly and/or consistently. Health care professionals can maximize the success of treatment by thoroughly counseling patients on the expected benefits of INSs and stressing the importance of regular administration. Patients motivated to adhere closely to their prescribed regimen and who anticipate high efficacy will likely maximize their treatment outcome.

CONCLUSIONS

Although almost one-half of surveyed patients with AR perceive that their INS treatment loses efficacy over the course of the day or night, clinical studies have consistently shown that these agents continue to provide relief superior to placebo 24 hours after dosing. In clinical trials, A.M. NOW ratings of symptom severity 24 hours after INS administration have been only slightly lower than daytime reflective scores measuring efficacy over the initial 12-hour postdosing interval, suggesting little drop off in benefit at the end of the dosing interval. To date, studies have not reported specific analyses comparing INS benefit during various intervals within the postdosing 24-hour period; such data would be of great interest. A small number of studies comparing duration of effect of INSs with q.d. oral or b.i.d. intranasal antihistamines have found INSs to be at least similar in the degree of A.M. NOW symptom improvement, and congestion A.M. NOW scores have been better with INSs versus these comparators.

In summary, existing clinical data suggest that INSs offer a high level of 24-hour symptom relief, especially congestion, with q.d. dosing, but there is an apparent disconnect between these findings and survey responses expressing dissatisfaction with INS duration of effect. Primary care physicians can serve an important function by stressing dosing adherence and proper use of INSs for patients to experience the greatest potential benefit from their INS treatment regimen.

ACKNOWLEDGMENTS

Medical writing and editorial assistance were provided by Sandra Westra, Pharm.D., and Rina Kleege, M.S., of AdelphiEden Health Communications, New York, NY.

REFERENCES

- Nathan RA, Meltzer EO, Derebery J, et al. The prevalence of nasal symptoms attributed to allergies in the United States: Findings from the burden of rhinitis in an America survey. *Allergy Asthma Proc* 29:600–608, 2008.
- 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, GA²LEN and AllerGen). *Allergy* 63(suppl 86):8–160, 2008.
- Blaiss MS. Allergic rhinitis: Direct and indirect costs. *Allergy Asthma Proc* 31:375–380, 2010.
- Malone DC, Lawson KA, Smith DH, et al. A cost of illness study of allergic rhinitis in the United States. *J Allergy Clin Immunol* 99:22–27, 1997.
- Long AA. Findings from a 1000-patient internet-based survey assessing the impact of morning symptoms on individuals with allergic rhinitis. *Clin Ther* 29:342–351, 2007.
- Naclerio RM, Hadley JA, Stoloff S, et al. Patient and physician perspectives on the attributes of nasal allergy medications. *Allergy Asthma Proc* 28(suppl 1):S11–S17, 2007.
- van Cauwenberge P, Bachert C, Passalacqua G, et al. Consensus statement on the treatment of allergic rhinitis. *Allergy* 55:116–134, 2000.
- Dykewicz MS, and Fineman S (Eds). Diagnosis and management of rhinitis: Complete guidelines of the Joint Task Force on Practice Parameters in Allergy, Asthma, and Immunology. *Ann Allergy Asthma Immunol* 81:478–518, 1998.
- Brozek JL, Bousquet J, Baena-Cagnani CE, et al. Allergic Rhinitis and its Impact on Asthma (ARIA) guidelines: 2010 Revision. *J Allergy Clin Immunol* 126:466–476, 2010.
- Scadding GK, Durham SR, Mirakian R, et al. BSACI guidelines for the management of allergic and non-allergic rhinitis. *Clin Exp Allergy* 38:19–42, 2008.
- Weiner JM, Abramson MJ, and Puy RM. Intranasal corticosteroids versus oral H₁ receptor antagonists in allergic rhinitis: Systematic review of randomised controlled trials. *BMJ* 317:1624–1629, 1998.
- Yanez A, and Rodrigo GJ. Intranasal corticosteroids versus topical H₁ receptor antagonists for the treatment of allergic rhinitis: A systematic review with meta-analysis. *Ann Allergy Asthma Immunol* 89: 479–484, 2002.
- Hampel FC, Ratner PH, Van Bavel J, et al. Double-blind, placebo-controlled study of azelastine and fluticasone in a single nasal spray delivery device. *Ann Allergy Asthma Immunol* 105:168–173, 2010.
- Di Lorenzo G, Pacor ML, Pellitteri ME, et al. Randomized placebo-controlled trial comparing fluticasone aqueous nasal spray in monotherapy, fluticasone plus cetirizine, fluticasone plus montelukast and cetirizine plus montelukast for seasonal allergic rhinitis. *Clin Exp Allergy* 34:259–267, 2004.
- Anolik R, and Mometasone Furoate Nasal Spray With Loratadine Study Group. Clinical benefits of combination treatment with mometasone furoate nasal spray and loratadine vs monotherapy with mometasone furoate in the treatment of seasonal allergic rhinitis. *Ann Allergy Asthma Immunol* 100:264–271, 2008.
- Benninger M, Farrar JR, Blaiss M, et al. Evaluating approved medications to treat allergic rhinitis in the United States: An evidence-based review of efficacy for nasal symptoms by class. *Ann Allergy Asthma Immunol* 104:13–29, 2010.
- AstraZeneca LP. Rhinocort Aqua prescribing information. Revised 12/2010. Wilmington, DE; 2004.
- Altana Pharma US, Inc. Omnaris prescribing information. Revised 10/2011. Florham Park, NJ; 2009.
- GlaxoSmithKline. Veramyst prescribing information. Revised 10/2011. Research Triangle Park, NC; 2009.
- GlaxoSmithKline. Flonase prescribing information. Revised 8/2007. Research Triangle Park, NC; 2004.
- Schering Corp. (now Merck & Co.). Nasonex prescribing information. Revised 1/2011. Kenilworth, NJ; 2009.
- sanofi-aventis U.S., LLC. Nasacort prescribing information. Revised 11/2010. Bridgewater, NJ; 2006.
- 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* 30:128–138, 2009.
- Jacobs R, Martin B, Hampel F, et al. Effectiveness of fluticasone furoate 100 µg 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* 25:1393–1401, 2009.
- 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* 100: 497–505, 2008.
- 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* 62:1078–1084, 2007.
- Kaiser HB, Naclerio RM, Given J, et al. Fluticasone furoate nasal spray: A single treatment option for the symptoms of seasonal allergic rhinitis. *J Allergy Clin Immunol* 119:1430–1437, 2007.
- 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* 28:216–225, 2007.
- Meltzer EO, Shekar T, and Teper AA. Mometasone furoate nasal spray for moderate-to-severe nasal congestion in subjects with seasonal allergic rhinitis. *Allergy Asthma Proc* 32:159–167, 2011.
- Bernstein DI, van Bavel JH, Shekar T, et al. Once-daily mometasone furoate nasal spray provides effective 24-hour relief of nasal congestion in subjects with moderate-to-severe seasonal allergic rhinitis. *J Allergy Clin Immunol* 125(Suppl 2): Abstract 177, 2010.
- LaForce CF. Duration of action of mometasone furoate nasal spray in seasonal allergic rhinitis: A double-blind, placebo-controlled study. *Ann Allergy Asthma Immunol* 100(Suppl 1): Abstract 90, 2008.
- Prenner BM, Lanier BQ, Bernstein DI, et al. Mometasone furoate nasal spray reduces the ocular symptoms of seasonal allergic rhinitis. *J Allergy Clin Immunol* 125:1247–1253.e5, 2010.
- Dykewicz M, Spector S, Shekar T, et al. Once-daily mometasone furoate nasal spray provides relief of nasal symptoms of seasonal allergic rhinitis 24 hrs after dosing. *Ann Allergy Asthma Immunol* 107(Suppl 1): Abstract 119, 2010.
- Varghese S, Patel D, Patel P, et al. Duration of action of mometasone furoate nasal spray in subjects with symptoms of seasonal allergic rhinitis induced in an environmental exposure chamber. *J Allergy Clin Immunol* 122:S54, 2008.
- Ratner PH, Wingertzahn MA, van Bavel JH, et al. Effectiveness of ciclesonide nasal spray in the treatment of seasonal allergic rhinitis. *Ann Allergy Asthma Immunol* 97:657–663, 2006.
- Salapatek AM, Patel P, Gopalan G, et al. Mometasone furoate nasal spray provides early, continuing relief of nasal congestion and improves nasal patency in allergic patients. *Am J Rhinol Allergy* 24:1–6, 2010.
- Zieglmayer P, Zieglmayer R, Bareille P, et al. Fluticasone furoate versus placebo in symptoms of grass-pollen allergic rhinitis induced by exposure in the Vienna Challenge Chamber. *Curr Med Res Opin* 24:1833–1840, 2008.
- Craig TJ, McCann JL, Gurevich F, et al. The correlation between allergic rhinitis and sleep disturbance. *J Allergy Clin Immunol* 114: S139–S145, 2004.
- Young T, Finn L, and Kim H; University of Wisconsin Sleep and Respiratory Research Group. Nasal obstruction as a risk factor for sleep-disordered breathing. *J Allergy Clin Immunol* 99:S757–S762, 1997.
- Meltzer EO, Munafo DA, Chung W, et al. Intranasal mometasone furoate therapy for allergic rhinitis symptoms and rhinitis-disturbed sleep. *Ann Allergy Asthma Immunol* 105:65–74, 2010.
- Lanier BQ, Meltzer EO, Gates D, et al. Onset and duration of action of concomitant administration of mometasone furoate nasal spray with oxymetazoline nasal spray versus either drug alone and placebo in subjects with seasonal allergic rhinitis. *J Allergy Clin Immunol* 125(Suppl 1): Abstract 173, 2010.
- Rodrigo GJ, and Neffen H. Efficacy of fluticasone furoate nasal spray vs. placebo for the treatment of ocular and nasal symptoms of allergic rhinitis: A systematic review. *Clin Exp Allergy* 41:160–170, 2011.
- Kaliner MA, Storms W, Tilles S, et al. Comparison of olopatadine 0.6% nasal spray versus fluticasone propionate 50 µg in the treatment of seasonal allergic rhinitis. *Allergy Asthma Proc* 30:255–262, 2009.
- Shedden A. Impact of nasal congestion on quality of life and work productivity in allergic rhinitis. *Treat Respir Med* 4:439–446, 2005.
- White P, Smith H, Baker N, et al. Symptom control in patients with hay fever in UK general practice: How well are we doing and is there a need for allergen immunotherapy? *Clin Exp Allergy* 28:266–270, 1997. □

Copyright of American Journal of Rhinology & Allergy is the property of OceanSide Publications Inc. and its content may not be copied or emailed to multiple sites or posted to a listserv without the copyright holder's express written permission. However, users may print, download, or email articles for individual use.