Effect of micronized cellulose powder on the efficacy of topical oxymetazoline in allergic rhinitis

Anna Valerieva, M.D.,[1] Todor A. Popov, M.D., Ph.D.,[1] Maria Staevska, M.D.,[1] Tanya Kralimarkova, M.D.,[1] Elena Petkova, M.D.,[1] Elitsa Valerieva, M.D.,[1] Tihomir Mustakov, M.D.,[1] Tsvetelina Lazarova, M.D.,[1] and Vasil Dimitrov, M.D.,[1] and Martin K. Church, Ph.D., D.Sc.[2]

ABSTRACT

Background: *Defective nasal barrier function is implicated in allergic rhinitis, which results in persistent inflammation and clinical symptoms, among which congestion plays a prominent role. In searching ways to improve the efficacy of nasally applied drugs in this condition, we tested the hypothesis that hydroxypropylmethylcellulose (HPMC), known as a mucoprotective agent, could enhance the efficacy of a decongestant (oxymetazoline nasal spray, 0.05%) by "sealing" it to the mucosa.*

Methods: *This double-blind placebo-controlled study was conducted with 40 patients (mean age, 35 years; 23 women) with persistent allergic rhinitis. The patients were randomized to receive 1 puff of oxymetazoline, followed by 1 puff of either HPMC or lactose powder (placebo) twice a day for 7 days and then only oxymetazoline rescue medication for another week. Peak inspiratory nasal flow (PNIF) was measured for 360 minutes after oxymetazoline and HPMC or placebo insufflation on days 1 and 8, and at a single point on day 15. Symptoms assessments involve visual analog scales and total nasal symptom scores.*

Results: *HPMC significantly enhanced oxymetazoline-increased PNIF at days 1 ($p = 0.042$) and 8 ($p = 0.006$). Baseline PNIF was greater in the HPMC group at day 15 ($p = 0.014$), indicative of further reduced nasal congestion. All nasal symptoms improved in both groups at day 8, but only the HPMC group showed further amelioration at day 15. Rescue medication was smaller in the HPMC group between days 8 and 15.*

Conclusion: *HPMC enhances decongestion through mucoadhesion but may also be augmenting the mucosal barrier in allergic rhinitis, which explains the carryover efficacy of oxymetazoline for a week after its discontinuation.*

Clinical Trial Registration: clinicaltrials.gov identifier: NCT01986582.

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To express symptoms of allergy, an individual must have both an atopic disposition and defective barrier function. The recognition of the importance of barrier function is relatively recent, derived from studies of atopic dermatitis in which abnormalities in the epidermal epithelium allow enhanced allergen penetration to induce immunoglobulin E sensitization and subsequent symptoms.[1–3] These observations stimulated the development of topical emollients as safe and inexpensive therapies.[4,5] Defective barrier function has also been implicated in the bronchi in asthma,[6] in the eye in allergic conjunctivitis,[7] and in the nose in allergic rhinitis.[8–16] The nasal epithelium is a highly regulated and impermeable barrier sealed by tight junctions.[9] Dysregulation of the tight junctions would allow increased allergen penetration to cause acute and chronic symptoms of allergic rhinitis.

The Allergic Rhinitis and its Impact on Asthma guidelines[17] recommend primarily pharmacologic therapies, *viz*. H_1 antihistamines and intranasal corticosteroids and decongestants for the treatment of allergic rhinitis. Whereas, procedures aimed at increasing barrier function provide a potential alternative safe therapy, research into these is in its infancy. The agent under investigation in this article is an inert dry hydroxypropyl-methylcellulose (HPMC) powder (NoAl; Nasaleze, Isle of Man, U.K.). Methylcellulose derivatives possess different ratios of hydroxypropyl to methoxyl substitution that determine their properties, such as viscosity, hydrophilicity, and gelling behavior when dissolved in water. The characteristics of the particular HPMC product here have been specifically tailored for intranasal delivery for the treatment of allergic rhinitis. Initial clinical trials have shown HPMC to be effective in both seasonal[18–20] and perennial[21] allergic rhinitis. Studies have concluded that it is safe and well tolerated,[22,23] and a review has been dedicated to the topic.[24]

Another effect of HPMC may also be considered. A reduction in rhinorrhea will slow down the clearance from the nose of locally applied drugs, thus prolonging

From the [1]Clinic of Allergy and Asthma, Medical University of Sofia, Sofia, Bulgaria, and [2]Department of Dermatology and Allergy, Allergie-Centrum-Charité, Charité, Universitätsmedizin Berlin, Berlin, Germany

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Address correspondence to Todor A. Popov, M.D., Clinic of Allergy and Asthma, Medical University of Sofia, 1, Georgi Sofiyski St., 1431 Sofia, Bulgaria

E-mail address: ted.popov@gmail.com

their contact time and, theoretically, improving their efficacy. This possibility has been tested previously when administering intranasal xylometazoline with a different mucoadhesive agent in patients with perennial allergic rhinitis.[25] The results showed that the decongestant-mucoprotective agent combination had a greater and longer-lasting effect on nasal congestion and caused fewer adverse effects than decongestant alone. We attributed these effects at the time to the ability of HPMC to act as a mucoadhesive agent.

This article describes an initial double-blind study to substantiate the hypothesis that a combination of a mucoprotective agent with pharmacologic therapy will enhance the effectiveness of the latter. The pharmacologic agent that was chosen was oxymetazoline nasal spray, a potent agonist of α_1- and α_2-adrenergic receptors with an almost instantaneous onset of action and proven benefits in the management of nasal congestion.[26,27]

METHODS

This was a double-blind, randomized, parallel group, one-center study of patients with moderately severe–to–severe persistent allergic rhinitis by comparing treatment with nasal decongestant (oxymetazoline) immediately followed by nasally applied HPMC or placebo. The study was performed out of the pollen season, between November 2013 and January 2014. The study's objectives and protocols were approved by the local investigational review board (University Hospital "Alexandrovska," Medical University Sofia, Sofia, Bulgaria; reference 344/09/10/2013). All participants gave signed informed consent, and the study was conducted in accordance with the current standards for good clinical practice.

Forty patients with a confirmed clinical history of persistent moderate-to-severe allergic rhinitis (17 men and 23 women; age 35 years [18÷49 years], mean [range]) were enrolled in the study. The sample size of 20 patients per group was calculated based on the 20% effect size, with a power of 80% and a level of significance of 0.05 (2-tailed) by using as proxy our previous work,[26] in which we measured nasal resistance for our sample size calculation. To be included in the trial, patients needed to have active moderately severe–to–severe persistent symptoms of allergic rhinitis with prominent congestion. Inclusion criteria also were a positive skin-prick test (wheal >3 mm diameter) to at least one of a panel of perennial allergens, including *Dermatophagoides pteronyssinus, Dermatophagoides farinae,* feathers mixture, cockroach, cat, dog, *Cladosporium, Penicillium, Aspergillus, Alternaria* (Stallergenes, SA, Antony, France). Exclusion criteria encompassed individuals with seasonal allergic rhinitis or nasal polyposis, patients with serious chronic comorbidities, with flu-like symptoms during the past 30 days, pregnant or lactating women, and individuals unable to give informed consent were excluded.

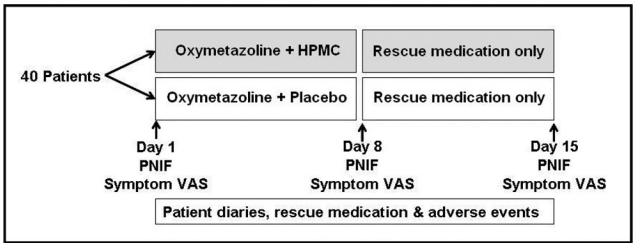

Figure 1. *Study protocol.*

The duration of the study for each individual was 15 days (Fig. 1). At enrollment, the patients were randomized at a 1:1 ratio by following a computer-generated sequence to be treated twice daily for 7 days with either 1 puff of oxymetazoline 0.05% nasal spray (Afrin, Schering Plough, Saint Clair, France), followed by either 1 puff of HPMC powder (NoAl, Nasaleze International Ltd., Douglas, Isle of Man, United Kingdom) (test treatment) or lactose powder from identically looking plastic bottles used as placebo (placebo treatment). During the following week, no regular treatment was given, and only puffs of oxymetazoline were allowed as rescue medication. The patients kept daily diaries of symptoms and rescue medication, and formal clinical assessments were made on days 1, 8, and 15. Peak nasal inspiratory flow (PNIF) was the objective assessment of the study. PNIF was measured by using a PNIF meter (In-Check Nasal; Clement Clarke International Ltd., Harlow, Essex, U.K.) on day 1 immediately before drug administration and at 1, 2, 5, 15, 30, 60, 120 180, 240, 300, and 360 minutes afterward. Similar measurements of PNIF were made on day 8, and a single measurement was taken on day 15.

A subjective assessment by patients of their symptoms was documented at their regular visits and daily in their diaries. During visits, overall discomfort due to allergic rhinitis symptoms was recorded on a 10-cm visual analog scale (VAS), which ranged from "no nasal symptoms" at 0 cm to "worst nasal symptoms ever" at 10 cm. The patients also rated, in their diaries, their stuffiness, rhinorrhea, itching, and sneezing by a symptom score between 0 (none) and 3 (worst). From this, the total nasal symptom score was calculated. The use of rescue medication and adverse events between days 8 and 15 were extracted from the patients' diaries.

Statistical Analyses

PNIF values were normally distributed, and differences within groups were analyzed by using Student's *t*-test for paired data and between groups by using the Student's *t*-test for unpaired data. Because the number of times that the patients resorted to rescue medication was not normally distributed, these results are given as median (25–75 percentiles), and group differences were assessed by using the Mann-Whitney *U* test. All tests

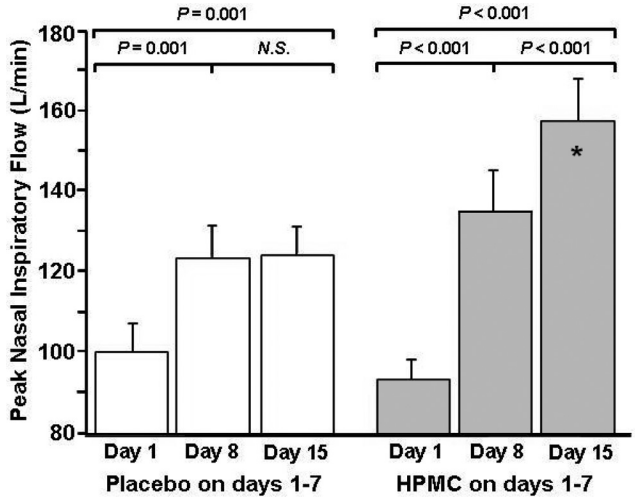

*Figure 2. Baseline PNIF values at days 1, 8, and 15. Each group contains results from 18 individuals. Significance values were calculated by using the Student's t-test for paired data. *The baseline PNIF of the patients treated with HPMC at 15 days was significantly ($p = 0.014$) higher than that of patients treated with placebo. This value was calculated by using the Student's t-test for unpaired data.*

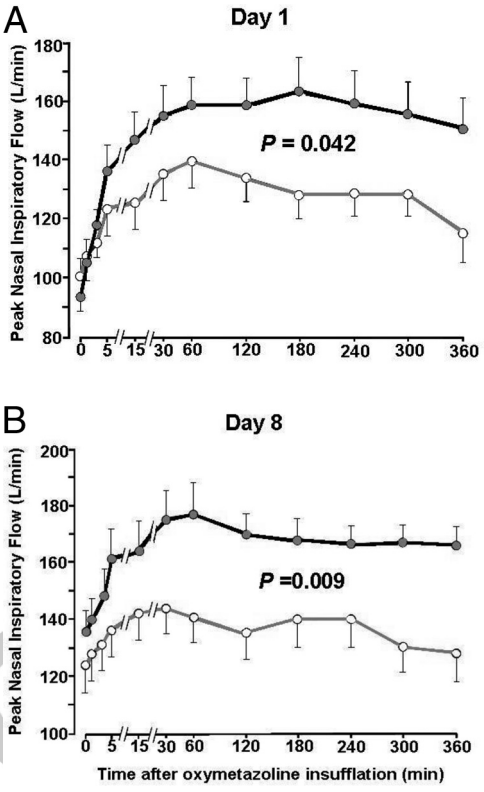

Figure 3. PNIF values after insufflation of oxymetazoline on (A) day 1 and (B) day 8. The solid dots are the patients treated with HPMC and the open dots are those treated with placebo. Each group contains results from 18 individuals. Significance values were calculated by using the Student's t-test for unpaired data.

were 2-tailed, and the threshold for statistical significance was set to $p < 0.05$.

RESULTS

Of the 40 patients recruited into the study, two dropped out from the test-treatment group, one for noncompliance and the other for headache; and two dropped out from the placebo group, one for concomitant disease and the other for a severe reaction to a cat. The remaining 36 patients completed all three visits and were included in the final analysis. Shown in Fig. 2, are the baseline PNIF values before oxymetazoline insufflation at the start of the study (day 1), after 7 days of treatment with HPMC or placebo (day 8), and after a further 7 days of only rescue medication (day 15). The results in the HPMC group showed a 26% increase ($p < 0.001$) in PNIF at day 8 and a further 21% increase ($p < 0.001$) at day 15. The total increase in PNIF between days 1 and 15 was 53% ($p < 0.001$). In the placebo group, there was a 24% in PNIF ($p < 0.001$) at day 8 but no further increase at day 15. There was no significant difference between groups on days 1 and 8, but the PNIF of the HPMC group was 26% greater ($p = 0.014$) than that of the placebo group on day 15.

The changes in PNIF after insufflation of oxymetazoline on days 1 and 8 are shown in Fig. 3. On both days, the effects of oxymetazoline were greater in patients also inhaling HPMC compared with placebo. On day 1, the area under the curve for the 360 minutes of observations for oxymetazoline was 20% greater in patients who received HPMC compared with those who received placebo (56,366 ± 14,910 sq. units versus 46,818 ± 12,080 sq. units; $p = .042$). On day 8, the area under the curve for oxymetazoline was 23% greater in the HPMC group than in the placebo group (60,855 ± 13,691 sq. units versus 49,350 ± 11,211 sq. units; $p = 0.009$).

The VAS assessments by patients on days 1, 8, and 15 of nasal congestion, rhinorrhea, itching/sneezing, and total nasal symptoms are shown in Table 1. In the placebo group, there were significant improvements in nasal congestion, rhinorrhea, and total nasal symptoms at day 8 but little or no further improvement thereafter. In the HPMC-treated group, there were similar improvements in these parameters at day 8. However, in this group, these improvements appeared to continue up to day 15. With total nasal symptoms, the improvement between days 8 and 15 was statistically significant ($p = 0.006$). There were no statistically significant differences between the groups. A similar pattern of results was obtained from analysis of the patients' diaries on days 1, 8, and 15 of the study. Of special mention is nasal itching/sneezing. With this symptom, there was no significant improvement in the placebo group. However, in the HPMC-treated group, there were significant improvements, of 56% ($p = 0.012$) and

Table 1 **The VAS assessments by patients on days 1, 8, and 15 of nasal congestion, rhinorrhea, itching/sneezing, and total nasal symptoms**

Symptom	Baseline VAS, (mean ± SE)	VAS (mean ± SE); % Reduction at 8 days	VAS (mean ± SE); % Reduction at 15 days
Congestion			
Placebo	56.6 ± 4.9	43.6 ± 5.7; 23 $p = 0.04$	47.2 ± 5.8; 17 N.S.
HPMC	65.0 ± 4.1	42.6 ± 6.4; 35 $p = 0.004$	36.2 ± 6.7; 44 $p < 0.001$
Significance of difference between groups		N.S.	N.S.
Rhinorrhea			
Placebo	51.9 ± 7.7	43.6 ± 5.7; 39 $p = 0.003$	47.7 ± 5.8; 23 $p = 0.04$
HPMC	59.7 ± 6.2	37.9 ± 6.9; 36 $p = 0.012$	32.5 ± 7.3; 46 $p = 0.013$
Significance of difference between groups		N.S.	N.S.
Itch/sneezing			
Placebo	27.7 ± 7.1	24.3 ± 5.9; 12 N.S.	21.2 ± 5.6; 23 N.S.
HPMC	32.8 ± 7.0	14.3 ± 4.5; 56 $p = 0.012$	8.5 ± 3.0; 74 $p = 0.013$
Significance of difference between groups		N.S.	N.S.
Total symptoms			
Placebo	68.4 ± 5.1	39.6 ± 5.8; 42 $p < 0.001$	41.7 ± 5.7; 39 $p < 0.001$
HPMC	70.2 ± 5.2	43.7 ± 6.0; 38 $p = 0.002$	34.2 ± 6.5 51% ($p < 0.001$)
Significance of difference between groups		N.S.	N.S.

SE = standard error; N.S. = not significant.
Significance values within groups were calculated by using the Student's t-test for paired data and between groups by using the Student's t-test for unpaired data.

74% ($p = 0.013$) at days 8 and 15, respectively. Also, the improvement between days 8 and 15 was statistically significant ($p = 0.02$). However, the differences between the treatment groups failed to reach statistical significance, mainly because of the number of patients who gave low itch/sneezing scores at all times (Fig. 4).

The median (25–75 percentiles) numbers of times the patients resorted to escape medication, puffs of oxymetazoline, during days 8–15 of the study were 8.5 (1–15.5) for the HPMC group and 16 (11.5–16) for the placebo group. There was a wide variability between the patients, which precluded the difference between groups being statistically significant ($p = 0.076$). However, 13 of the 18 patients who received placebo on days 1–7 took more than 2 puffs of oxymetazoline per day compared with only five patients treated with HPMC ($p = 0.04$, Fisher exact test). Adverse events were mild and infrequent. In the HPMC group, two patients had headache, two had intermittent coughing, one had common cold symptoms, and one had dysmenorrhea. In the placebo group, three patients had headache and one had flu-like symptoms. None of the events were persistent or considered to be drug related.

DISCUSSION

The primary objective of this study was to substantiate the hypothesis that a combination of a mucoprotective and mucoadhesive agent with pharmacologic therapy will enhance the effectiveness of the latter. This objective was achieved with the finding that an area under the curve for 6 hours of observations after oxymetazoline insufflation was significantly greater on the first and eighth days of HPMC therapy compared with placebo. In addition, there was a trend for continual improvement of rhinitis symptoms in the week after HPMC treatment but not in those who received placebo.

There are two possible mechanisms by which HPMC may act to enhance the effects of oxymetazoline therapy. The first is a purely physical one. Because HPMC

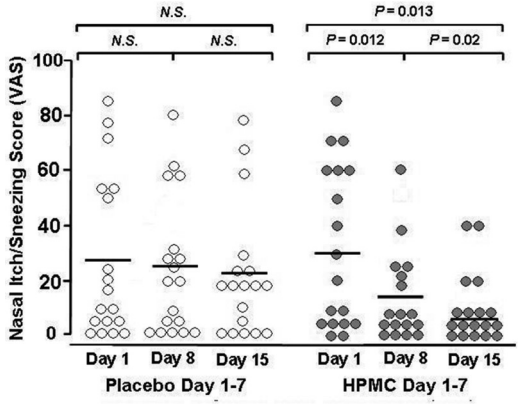

Figure 4. Nasal itch/sneezing VAS scores on days 1, 8, and 15 of the study. The solid dots are the patients treated with HPMC, and the open dots are those treated with placebo. Each group contains results from 18 individuals. Significance values were calculated by using the Student's t-test for paired data. There were no statistically significant differences between the groups.

was insufflated immediately after oxymetazoline, the formation of a gel layer above the decongestant would be likely to reduce its clearance from the nasal mucosa and thereby increase its effectiveness. Such effect would occur even with the first dose, as was seen on day 1 of the study. This was actually the starting point of our reasoning when planning the study. The second mechanism would be for HPMC to create an improved barrier to allergen penetration into the nasal mucosa. In the longer term, it would reduce the inflammatory events of the mucosal barrier thereby reducing nasal reactivity.[28–30] This activity is evidenced particularly by the increased baseline PNIF, an index of nasal congestion,[31] up to 15 days in the HPMC-treated group.

Nasal congestion is recognized to be the most important symptom in terms of impact on quality of life.[32,33] We have identified it as the prominent symptom that motivates patients to seek medical advice.[34] We also were aware that, in real life, people are driven by the discomfort due to a "stuffy nose" to buy over-the-counter decongestants to alleviate their discomfort oblivious of any consequences.[35–37] We reasoned that choosing the "decongestant" design to improve the benefits HPMC uses as a mucoadhesive agent, we could achieve longer intervals between the oxymetazoline applications.

In designing this study, we were cognizant of the Allergic Rhinitis and its Impact on Asthma guidelines recommendation[17] that nasal decongestants should be given only in short courses because, when used for more than 10 days, these lead to rebound congestion and rhinitis medicamentosa[38,39] However, doubt has been cast on the validity of this recommendation because neither the cumulative dose of nasal decongestants nor time period needed to initiate rhinitis medicamentosa has been conclusively determined.[40] Furthermore, the 2010 revision of the Allergic Rhinitis and its Impact on Asthma guidelines[17] grades the evidence related to the application of decongestants in allergic rhinitis as weak and lists this issue as unmet need for future research. In our study, we could find no evidence of rebound congestion or rhinitis medicamentosa after usage of oxymetazoline for 7 days and even 15 days if rescue usage is taken into consideration.

The primary subjective assessments of rhinitis symptoms were made by using VAS. Extensively investigated and validated in allergic rhinitis, VAS has been shown to correlate significantly with disease severity and quality of life.[41] In addition, it has been proven useful in the assessment of the effect of pharmacotherapies on symptoms.[42] Nasal congestion, rhinorrhea, and total nasal symptoms all improved in both groups at 8 days but continued to improve only in the HPMC group thereafter. Further evidence that individuals in the HPMC group felt better in the 8–15 day period was their smaller usage of rescue medication compared with the placebo group. Particular mention should be made of itching/sneezing, which was greatly improved by HPMC but not by oxymetazoline alone. Unfortunately, the study was powered for identifying statistical differences between the objective measurements of PNIF rather than the more variable subjective VAS assessments. Consequently, although there were definite trends for patients having less-severe symptoms when taking HPMC, differences between the groups failed to reach statistical significance.

As one might expect of a proof-of-concept study, our work has limitations related to the small sample size and the short duration of the observation. Furthermore, one might question the lack of a study arm with HPMC alone: initially we focused on the potential of HPMC as a mucoadhesive agent and did not anticipate the longer-lasting benefits, which we registered in the week after the discontinuation of treatment. Consequently, our work raised questions, which now need to be addressed by further research:

- Is the synergy offered by HPMC also valid for the other nasal symptoms? The answer to this question requires different study designs.
- Is the synergy offered by HPMC also valid for the other nasally applied drugs? This is a tantalizing possibility because it opens the door for increased effectiveness of drugs for local treatment, such as antihistamines, nasal corticosteroids, antimuscarinic agents, and combining these under the gelatinous HPMC mucosal cover.

In conclusion, our proof-of-concept study demonstrated that micronized HPMC powder enhances the decongestant effect of nasal oxymetazoline in patients with allergic rhinitis. It also showed that 1 week of such regular combined treatment reduced nasal con-

gestion in these patients, and this effect carries over for another week after its discontinuation. Thus, HPMC appears to be a safe and inexpensive adjunct to the therapy of allergic rhinitis.

REFERENCES

1. Palmer CN, Irvine AD, Terron-Kwiatkowski A, et al. Common loss-of-function variants of the epidermal barrier protein filaggrin are a major predisposing factor for atopic dermatitis. Nat Genet 38:441–446, 2006.
2. Brough HA, Santos AF, Makinson K, et al. Peanut protein in household dust is related to household peanut consumption and is biologically active. J Allergy Clin Immunol 132:630–638, 2013.
3. Leung DY, and Guttman-Yassky E. Deciphering the complexities of atopic dermatitis: Shifting paradigms in treatment approaches. J Allergy Clin Immunol 134:769–779, 2014.
4. Pacha O, and Hebert AA. Treating atopic dermatitis: Safety, efficacy, and patient acceptability of a ceramide hyaluronic acid emollient foam. Clin Cosmet Investig Dermatol 5:39–42, 2012.
5. Simpson EL, Chalmers JR, Hanifin JM, et al. Emollient enhancement of the skin barrier from birth offers effective atopic dermatitis prevention. J Allergy Clin Immunol 134:818–823, 2014.
6. Xiao C, Puddicombe SM, Field S, et al. Defective epithelial barrier function in asthma. J Allergy Clin Immunol 128:549–556, 2011.
7. Hughes JL, Lackie PM, Wilson SJ, et al. Reduced structural proteins in the conjunctival epithelium in allergic eye disease. Allergy 61:1268–1274, 2006.
8. Soyka MB, Wawrzyniak P, Eiwegger T, et al. Defective epithelial barrier in chronic rhinosinusitis: The regulation of tight junctions by IFN-gamma and IL-4. J Allergy Clin Immunol 130:1087–1096, 2012.
9. Kojima T, Go M, Takano K, et al. Regulation of tight junctions in upper airway epithelium. Biomed Res Int 2013:947072, 2013.
10. Frieri M. Inflammatory issues in allergic rhinitis and asthma. Allergy Asthma Proc 26:163–169, 2005.
11. Capetandes A, Horne NS, and Frieri M. Dermatophagoides extract-treated confluent type II epithelial cells (cA549) and human lung mesenchymal cell growth. Ann Allergy Asthma Immunol 95:381–388, 2005.
12. Frieri M. Asthma concepts in new millennium-update in asthma pathophysiology. Allergy Asthma Proc 26:83–88, 2005.
13. Frieri M. Advances in understanding allergic asthma. Allergy Asthma Proc 28:614–619, 2007.
14. Frieri M, and Capetandes A. The effect of enantiomers of beta agonists on myofibroblast-derived vascular endothelial growth factor and other matrix components in the presence of dust mite extract. Allergy Asthma Proc 29:182–188, 2008.
15. Frisella PD, Silverberg J, Joks R, and Frieri M. Transforming growth factor-beta. A role in the upper airway and rhinosinusitis: *D. pteronyssinusi* induced apoptosis with pulmonary alveolar cells. Am J Rhinol Allergy 25:231–235, 2011.
16. Frieri M. Asthma linked with rhinosinusitis. An extensive review. Allergy Rhinol (Providence) 5:41–49, 2014.
17. 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.
18. Josling P, and Steadman S. Use of cellulose powder for the treatment of seasonal allergic rhinitis. Adv Ther 20:213–219, 2003.
19. Emberlin JC, and Lewis RA. A double blind, placebo controlled trial of inert cellulose powder for the relief of symptoms of hay fever in adults. Curr Med Res Opin 22:275–285, 2006.
20. Aberg N, Ospanova ST, Nikitin NP, et al. A nasally applied cellulose powder in seasonal allergic rhinitis in adults with grass pollen allergy: A double-blind, randomized, placebo-controlled, parallel-group study. Int Arch Allergy Immunol 163:313–318, 2014.
21. Emberlin JC, and Lewis RA. A double blind, placebo-controlled cross over trial of cellulose powder by nasal provocation with Der p1 and Der f1. Curr Med Res Opin 23:2423–2431, 2007.
22. Traini D, Scalia S, Adi H, et al. Polymer coating of carrier excipients modify aerosol performance of adhered drugs used in dry powder inhalation therapy. Int J Pharm 438:150–159, 2012.
23. Caccavo D, Cascone S, Lamberti G, et al. Controlled drug release from hydrogel-based matrices: Experiments and modeling. Int J Pharm 486:144–152, 2015.
24. Bouic PJD. A review of the efficacy and safety of nasaleze in the prevention and management of allergic rhinitis. Open Allergy J 1:1–4, 2008. http://benthamopen.com/contents/pdf/TOALLJ/TOALLJ-1-1.pdf
25. Tzachev CT, Mandajieva M, Minkov EH, and Popov TA. Comparison of the clinical efficacy of standard and mucoadhesive-based nasal decongestants. Br J Clin Pharmacol 53:107–109, 2002.
26. Haenisch B, Walstab J, Herberhold S, et al. Alpha-adrenoceptor agonistic activity of oxymetazoline and xylometazoline. Fundam Clin Pharmacol 24:729–739, 2010.
27. Baroody FM, Brown D, Gavanescu L, et al. Oxymetazoline adds to the effectiveness of fluticasone furoate in the treatment of perennial allergic rhinitis. J Allergy Clin Immunol 127:927–934, 2011.
28. Wachs M, Proud D, Lichtenstein LM, et al. Observations on the pathogenesis of nasal priming. J Allergy Clin Immunol 84:492–501, 1989.
29. Naclerio RM, Bachert C, and Baraniuk JN. Pathophysiology of nasal congestion. Int J Gen Med 3:47–57, 2010.
30. Klimek L, and Pfaar O. Allergic rhinitis. Immunological and neurogenic mechanisms [in German with English abstract]. HNO 59:1191–1197, 2011.
31. Rujanavej V, Snidvongs K, Chusakul S, and Aeumjaturapat S. The validity of peak nasal inspiratory flow as a screening tool for nasal obstruction. J Med Assoc Thai 95:1205–1210, 2012.
32. Stewart M, Ferguson B, and Fromer L. Epidemiology and burden of nasal congestion. Int J Gen Med 3:37–45, 2010.
33. Stull DE, Vernon MK, Canonica GW, et al. Using the congestion quantifier seven-item test to assess change in patient symptoms and their impact. Allergy Asthma Proc 29:295–303, 2008.
34. Popov TA, Kralimarkova TZ, Staevska MT, and Dimitrov VD. Characteristics of patient population seeking medical advice for nasal symptoms in Bulgaria. Ann Allergy Asthma Immunol 108:232–236, 2012.
35. Mehuys E, Gevaert P, Brusselle G, et al. Self-medication in persistent rhinitis: Overuse of decongestants in half of the patients. J Allergy Clin Immunol Pract 2:313–319, 2014.
36. Dokuyucu R, Gokce H, Sahan M, et al. Systemic side effects of locally used oxymetazoline. Int J Clin Exp Med 8:2674–2678, 2015.
37. Montastruc F, Montastruc G, Taudou MJ, et al. Acute coronary syndrome after nasal spray of oxymetazoline. Chest 146:e214–e215, 2014.
38. Graf P. Long-term use of oxy- and xylometazoline nasal sprays induces rebound swelling, tolerance, and nasal hyperreactivity. Rhinology 34:9–13, 1996.
39. Mortuaire G, de Gabory L, Francois M, et al. Rebound congestion and rhinitis medicamentosa: Nasal decongestants in clinical practice. Critical review of the literature by a medical panel. Eur Ann Otorhinolaryngol Head Neck Dis 130:137–144, 2013.
40. Ramey JT, Bailen E, Lockey RF. Rhinitis medicamentosa. J Investig Allergol Clin Immunol 16:148–155, 2006.
41. Bousquet PJ, Combescure C, Neukirch F, et al. Visual analog scales can assess the severity of rhinitis graded according to ARIA guidelines. Allergy 62:367–372, 2007.
42. Demoly P, Bousquet PJ, Mesbah K, et al. Visual analogue scale in patients treated for allergic rhinitis: An observational prospective study in primary care: Asthma and rhinitis. Clin Exp Allergy 43:881–888, 2013. □