CANADIAN ALLERGY & IMMUNOLOGY TODAY

SPECIAL SUPPLEMENT

NOVEL TOPICAL INTRANASAL THERAPIES IN THE MANAGEMENT OF ALLERGIC RHINITIS

Arif Janjua, MD, FRCPC
Saleh Okhovat, FRCS, ORL-HNS (Eng)

ABOUT THE AUTHORS

Arif Janjua, MD, FRCSC

Dr. Janjua is a full-time faculty member and Clinical Associate Professor in the Division of Otolaryngology – Head & Neck Surgery at the University of British Columbia (UBC). He completed his ENT residency training at the University of Toronto. He undertook further advanced fellowship training in Rhinology, Endoscopic Sinus Surgery and Endoscopic Skull Base Surgery at St. Joseph's Hospital and the University Health Network in Toronto.

Saleh Okhovat, FRCS, ORL-HNS

Dr. Okhovat is a clinical fellow in Rhinology & Endoscopic Skull Base Surgery at the University of British Columbia (UBC) under the supervision of Dr. Arif Janjua.

He graduated from Imperial College School of Medicine with distinction and completed his residency program in Otolaryngology and Head & Neck Surgery in Scotland, United Kingdom.

Canadian Allergy & Immunology Today is published 3 times per year in English and French.

This supplement contains approved educational content affiliated with *Canadian Allergy & Immunology Today* and qualifies for Section 2 (self-learning) credits towards the maintenance of certification.

For information on how this activity fits in the Royal College Maintenance of Certification (MOC) Program, please visit the Royal College's website (royalcollege.ca/moc). For more personalized support, please contact the Royal College Services Centre (1-800-461-9598) or your local CPD Educator.

If you would like to contribute to a future issue of *Canadian Allergy & Immunology Today* please email us at info@catalytichealth.com

This supplement was made possible through an educational grant from Viatris.

NOVEL TOPICAL INTRANASAL THERAPIES IN THE MANAGEMENT OF ALLERGIC RHINITIS

INTRODUCTION

Allergic rhinitis (AR) is one the most common immunologic conditions affecting adults. Its prevalence has increased over the last few decades and varies between 10-40% depending on geographical location, with up to 25% of Canadians being affected.[1]

It is defined as an IgE-mediated inflammatory process affecting the nasal mucosa in a previously sensitised individual.[2] When an atopic patient is exposed to an allergen, the patient develops specific IgE antibodies which become bound to mast cells. Re-exposure to this allergen results in two distinct phases of inflammation: an early phase occurring within minutes, due to mast cell degranulation which causes nasal itching, congestion and discharge; and a late phase occurring after several hours, due to eosinophil activation resulting in increased mucous production, nasal blockage and hyposmia.

The Allergic Rhinitis and its Impact on Asthma (ARIA) guidelines classifies AR based on duration, as well as severity of symptoms.[2] **(Table 1)**

There is a strong association between AR and asthma, frequently co-existing in up to 38% of patients, with 74%-89% of asthmatic patients reporting some rhinitis symptoms.[3]

Type II inflammatory cytokines are prevalent in both AR and chronic rhinosinusitis (CRS) resulting in a multifactorial aetiologic linkage between these two conditions. Mucosal oedema and inflammation result in damage to nasal cilia and disruption of the mucocilliary clearance and subsequent release of inflammatory cytokines, with propagation of mucosal inflammation resulting in CRS. Specific phenotypic subsets of CRS, most notably central compartment atopic disease (CCAD) and allergic fungal sinusitis appear to have a strong association with allergies and AR. This association underscores the importance of adequate treatment of rhinitis in

SYMPTOM DURATION	
Intermittent	Symptoms are present **less** than **4 days** a week or for **less** than **4 weeks**.
Persistent	Symptoms are present **at least 4 days** a week and for **at least 4 weeks**.
SYMPTOM SEVERITY	
Mild	None of the following is present.
Moderate to severe	At least **one** of the following is present: • Impairment of daily activities, leisure and/or sport • Impairment of school or work • Troublesome symptoms • Sleep disturbance

Table 1: The ARIA guidelines definitions of allergic rhinitis based on duration and severity of symptoms.

improving long-term outcomes of endoscopic sinus surgery in treating CRS with concomitant AR.[4]

Diagnosing AR requires a comprehensive history and examination. The type, duration and severity of symptoms, the presence of concomitant asthma or atopic disease, as well as family history should be explored. Anterior rhinoscopy and nasal endoscopy further aid in identifying signs of AR such as pale, inflamed nasal mucosa, inferior turbinate hypertrophy and/or the presence of nasal discharge.

Diagnostic tests such as skin prick testing (SPT) (80% sensitivity and specificity; 15% with a positive SPT will not develop symptoms on exposure to allergens) and serum IgE levels could be considered when the diagnosis is uncertain or specific allergen identification is indicated.[5]

MANAGEMENT

Clinicians may consider adopting a multi-faceted approach to the management of AR utilising a broad range of topical therapeutics. **(Figure 1)** Further, the importance of patient education should not be overlooked as it is central to ensuring patient engagement and compliance with their treatment regimen and, ultimately, with optimal clinical outcomes. Using a patient-centric approach that is highlighted by shared decision-making of therapeutic agents allows patients to identify therapies that have provided them with the most sustainable symptomatic improvement. This approach allows patients to incorporate and titrate medications that work for them, according to fluctuations in their symptoms.

Topical drug delivery to the nasal mucosa remains the most effective method of controlling nasal inflammation and reducing symptoms, by allowing delivery of high dose medications directly to local inflammatory receptors, thereby increasing treatment success, while minimizing systemic side effects. Intranasal corticosteroid steroids (INCS) and intranasal antihistamines (INAH) are the most widely-advocated treatment modalities employed in the management of AR, with novel combination preparations of these two classes of drug demonstrating substantial improvement in symptom control when compared to INCS and INAH alone.

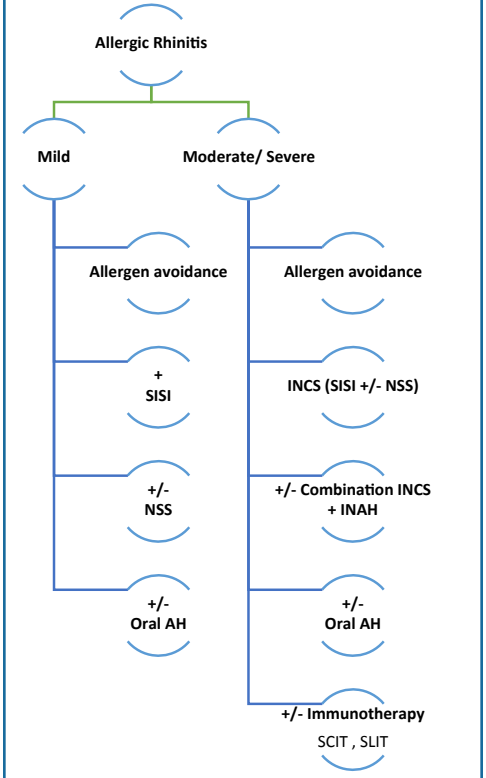

Fig 1. Proposed working algorithm for the management of AR.

SISI: Steroid-impregnated saline irrigation
NSS: Nasal steroid spay
INCS: Intranasal Corticosteroids
INAH: Intranasal Anti-histamines
SCIT: Subcutaneous immunotherapy
SLIT: Sublingual immunotherapy

INTRANASAL SALINE:

Intranasal saline has been widely utilized in the management of AR as both a standalone treatment, as well as an adjunctive option with a growing body of evidence supporting its use and efficacy.[6,7] In a systematic review of more than 50 relevant trials between 1994 and 2010 examining the use of intranasal saline in the treatment of AR, reviewers selected 10 relevant studies that satisfied the inclusion criteria (> 400 participants total) and found that when used in patients with AR, intranasal saline produced a 27% improvement in nasal symptoms, a 62% reduction in medication consumption, a 31% acceleration of mucociliary clearance (MCC) time and a 27% improvement in quality of life.[6]

Nasal irrigation has been used in varying concentrations and regimens with isotonic preparations shown to be most effective at improving MCC in AR and acute sinusitis patients.[7] Overall, intranasal saline has a significant benefit when used in any patient with AR. It is inexpensive, readily available, and well-tolerated with minimal side effects, making it suitable for long-term use.

INTRANASAL CORTICOSTEROID THERAPY

INCSs are the mainstay of treatment for moderate-to-severe AR. Their potent anti-inflammatory properties enable suppression of early and late phase allergic response by inhibiting pro-inflammatory type II cytokine (IL-5 and IL-13) release, reducing inflammatory cell proliferation and reducing their subsequent presence in nasal secretions.[8,9]

INCSs have a significantly greater efficacy of symptom reduction compared to placebo, anti-histamines (oral or topical) and leukotriene receptor antagonists.[10,11] When compared to the INAH azelastine, INCS are significantly superior at alleviating rhinorrhea, with comparable reduction in nasal symptom scores.[12] A recent systematic review and meta-analysis including five randomized controlled trials with a total of 990 patients found INCS to be superior to oral anti-histamines (OAH) in improving nasal symptoms and quality of life, relieving nasal obstruction and rhinorrhea.[13] INCS reduce nasal symptoms, in particular nasal congestion, within the first 12-hour interval for evaluation of symptoms .[14] A recent double-blind, placebo-controlled, randomized, parallel-group study of the as-needed usage of fluticasone propionate nasal spray in the management of seasonal allergic rhinitis was performed in which twenty-six subjects in each group completed the 4-week study. The results demonstrated that INCS is more effective when used in daily dosing strategies, whilst the as-needed INCS use is found to be as effective as placebo in management of AR, emphasising the importance of prolonged daily use to achieve maximal effect.[15]

No significant difference in efficacy has been demonstrated between different agents.[16] Therefore, tolerability and compliance with therapy is largely dependent on such factors as taste, smell and pharyngeal irritation, which should be considered when choosing between INCSs.

Common side effects include anterior septal dryness, local irritation, nasal pain and burning. Epistaxis in particular may be observed in as much as 20% of patients, which can usually be overcome by corrected use of the intranasal delivery device or simple nasal lubrication measures overnight.[17] Systemic absorption is minimal with very low risk of suppression of hypothalamic-pituitary axis.[18]

COMBINATION THERAPY: STEROID-IMPREGNATED SALINE IRRIGATION (SISI)

Clinicians may consider the utilisation of twice-daily steroid impregnated saline irrigation (SISI) as a first-line topical therapy for patients with AR and CRS. This allows for the combined and additive therapeutic benefits of saline irrigation with INCS, most notably the improved MCC and nasal congestion symptom improvement. This approach also facilitates topical drug delivery throughout the entire nasal cavity (anteriorly and posteriorly), thereby allowing better control of global mucosal congestion. Finally, it avoids the common side effects of nasal steroid spray use, such as anterior septal dryness and epistaxis. This modality of topical drug delivery has been shown to provide a meaningful improvement in symptoms and endoscopy scores in patients with CRS.[19]

Clinicians may find that adding spray preparations, of either INCS alone or combination INCS and INAH to this rinsing regime offers the added benefit of targeting mucosal inflammation anteriorly, with INCS and INAH notably targeting the anterior heads of inferior turbinates, while the SISI work better posteriorly within the nasal cavity. This 'combined' mucosal inflammatory control regime seems to offer enhanced global oedema reduction and improve overall airflow thereby significantly reducing overall nasal congestion.

INTRANASAL ANTI-HISTAMINES

Histamine-mediated cytokine release is an important component of the early and late phase allergic reaction in AR. INAHs are novel therapeutics enabling delivery of high concentrations of H2-receptor antagonists directly onto the nasal mucosa, enhancing local anti-inflammatory effect whilst avoiding systemic side effects.[20]

These agents have a faster onset of action compared to OAHs (< 15 minutes) and are effective at alleviating nasal symptoms when compared with placebo.[21] INAHs provide not only an effective rescue therapy solution but also demonstrate higher efficacy when used continuously.[22] They are more effective for nasal symptom control than OAHs alone and combination treatment with both OAHs and INAHs confer no additive benefit in alleviating nasal symptoms.[23] When compared with INCSs, INAHs used as monotherapy are less effective in controlling nasal congestion but show superiority in relieving ocular symptoms.[24] INAHs are safe with very few side effects, the most notable of which is a bitter taste which can impact tolerability and compliance.

INAH preparations are readily available in Europe and other parts of the world. Currently in Canada, there are no stand alone INAH preparations that are commercially available. At present, INAH can only be prescribed in combination with INCS (as a single spray formulation).

COMBINATION INCS AND INAH THERAPIES

The combination fluticasone propionate (FP) and azelastine hydrochloride (AZE) spray is a novel preparation allowing for concomitant delivery of INCS and INAH in a single device. It has

been shown to be more effective at reducing nasal symptoms in moderate-to-severe AR, when compared with either placebo, FP or AZE alone.[25,26] In particular, it has a rapid onset of action of 5-10 minutes (5 minutes for TNSS and 10 minutes for other assessments (TOSS, T7SS, and VAS).[27] Furthermore, it alleviates nasal symptoms days earlier than other monotherapies (FP, AZE).

The main advantages of using a combination topical therapy includes: 1) its rapid onset of action, which can aid significantly with patient compliance, 2) the concurrent reduction of ocular symptoms, 3) its ease of use and convenience as a single spray device, and 4) its homogenous distribution of medication with increased retention resulting in reduced run off.

It is for these reasons that several guidelines have recommended its use for moderate to severe AR and as first-line therapy in seasonal allergic rhinitis.[2,21]

Moreover, there is emerging evidence to support a potential role of the combination fluticasone propionate (FP) and azelastine hydrochloride (AZE) spray in the management of non-allergic rhinitis (NAR), with studies demonstrating sustained symptomatic improvement in this group of patients.[28] It is thought that azelastine's direct inhibitory actions on the activity of transient receptor potential vanilloid 1 (TRPV1) which is over expressed in patients with NAR, accounts for its anti-inflammatory effects.[29]

Incorporating this combination treatment early into the algorithm for patients with moderate-to-severe AR, and often in combination with SISI may yield positive benefit and may provide an effective approach to targeting nasal mucosal inflammation anteriorly and posteriorly within the nasal cavities.

CONCLUSION

Advances in novel intranasal topical therapeutics have enabled different methods for delivery of high potency medication directly to the nasal mucosa. This improves control of local mucosal inflammation and reduces systemic side effects from medications.

INCS remain the first-line treatment modality of choice and are safe and effective. These agents can be delivered either in spray form, which seems to preferentially target the anterior nasal cavity, or used in combination with SISI that additionally improves MCC and has a greater effect on global congestion (anteriorly and posteriorly in the nose).

Combination INCS and INAH are substantially more effective at controlling nasal inflammation and improving symptoms than monotherapy alone. Delivered as a single-spray formulation enhances patient compliance with INCS treatment and this modality also has the added benefit of a rapid onset of action as well as significantly reducing ocular symptoms. The main disadvantage of this treatment is the cost of the medication.

Patient education that empowers patient-centric decision making regarding topical nasal therapies will improve compliance with treatment and enable the patient to tailor their treatment according to fluctuations in their symptoms.

References

1.Keith PK, Desrosiers M, Laister T, Schellenberg RR, Waserman S. The burden of allergic rhinitis (AR) in Canada: perspectives of physicians and patients. Allergy Asthma Clin Immunol. 2012.

2.Bousquet J, Khaltaev N, Cruz AA, et al. Allergic rhinitis and its impact on asthma (ARIA) 2008 update (in collaboration with the World Health Organization, GA(2)LEN and AllerGen). Allergy 2008; 63 (Suppl 86): 8–160.

3. Leynaert B, Neukirch C, Kony S, et al. Association between asthma and rhinitis according to atopic sensitization in a population-based study. J Allergy Clin Immunol. 2004;113:86-93.

4. Marcus S, Roland LT, DelGaudio JM, Wise SK. The relationship between allergy and chronic rhinosinusitis. Laryngoscope Investig Otolaryngol. 2018 Dec 20;4(1):13-17. doi: 10.1002/lio2.236. PMID: 30828613; PMCID: PMC6383312.

5. Seidman MD, Gurgel RK, Lin SY, Schwartz SR, Baroody FM, Bonner JR, Dawson DE, Dykewicz MS, Hackell JM, Han JK, Ishman SL, Krouse HJ, Malekzadeh S, Mims JW, Omole FS, Reddy WD, Wallace DV, Walsh SA, Warren BE, Wilson MN, Nnacheta LC; Guideline Otolaryngology Development Group. AAO-HNSF. Clinical practice guideline: Allergic rhinitis. Otolaryngol Head Neck Surg. 2015 Feb;152(1 Suppl):S1-43. doi: 10.1177/0194599814561600. PMID: 25644617.

6. Hermelingmeier KE, Weber RK, Hellmich M, Heubach CP, Mosges R. Nasal irrigation as an adjunctive treatment in allergic rhinitis: a systematic review and meta-analysis. Am J Rhinol Allergy. 2012;26:e119–e125. [PubMed: 23168142]

7. Ural A, Oktemer TK, Kizil Y, Ileri F, Uslu S. Impact of isotonic and hypertonic saline solutions on mucociliary activity in various nasal pathologies: clinical study. J Laryngol Otol. 2009;123:517–521. [PubMed: 18957157]

8. Erin EM, Leaker BR, Zacharasiewicz AS, Higgins LA, Williams TJ, Boyce MJ, de Boer P, Durham SR, Barnes PJ, Hansel TT. Single dose topical corticosteroid inhibits IL-5 and IL-13 in nasal lavage following grass pollen challenge. Allergy. 2005 Dec;60(12):1524-9. doi: 10.1111/j.1398-9995.2005.00928.x. PMID: 16266385.

9. Holm A, Dijkstra M, Kleinjan A, et al. Fluticasone propionate aqueous nasal spray reduces inflammatory cells in unchallenged allergic nasal mucosa: effects of single allergen challenge. J Allergy Clin Immunol. 2001. https ://doi.org/10.1067/mai.2001.11352 0.

10. Weiner JM, Abramson MJ, Puy RM. Intranasal corticosteroids versus oral H1 receptor antagonists in allergic rhinitis: systematic review of randomised controlled trials. BMJ. 1998;317:1624-1629.

11. Wilson AM, O'Byrne PM, Parameswaran K. Leukotriene receptor antagonists for allergic rhinitis: a systematic review and meta-analysis. Am J Med. 2004a;116:338-344.

12. Carr WW, Ratner P, Munzel U, et al. Comparison of intranasal azelastine to intranasal fluticasone propionate for symptom control in moderateto- severe seasonal allergic rhinitis. Allergy Asthma Proc. 2012.

13. Juel-Berg N, Darling P, Bolvig J, et al. Intranasal corticosteroids compared with oral antihistamines in allergic rhinitis: a systematic review and metaanalysis. Am J Rhinol Allergy. 2017

14. Fokkens WJ, Cserhati E, dos Santos JM, et al. Budesonide aqueous nasal spray is an effective treatment in children with perennial allergic rhinitis, with an onset of action within 12 hours. Ann Allergy Asthma Immunol. 2002;89:279–284.

15. Jen A, Baroody F, de Tineo M, Haney L, Blair C, Naclerio R. As-needed use of fluticasone propionate nasal spray reduces symptoms of seasonal allergic rhinitis. J Allergy Clin Immunol. 2000;105:732–738. [PubMed: 10756223]

16. Meltzer EO. Formulation considerations of intranasal corticosteroids for the treatment of allergic rhinitis. Ann Allergy Asthma Immunol. 2007;98:12-21.

17. Rosenblut A, Bardin PG, Muller B, et al. Long-term safety of fluticasone furoate nasal spray in adults and adolescents with perennial allergic rhinitis. Allergy. 2007;62:1071–1077.

18. Ratner PH, Meltzer EO, Teper A. Mometasone furoate nasal spray is safe and effective for 1-year treatment of children with perennial allergic rhinitis. Int J Pediatr Otorhinolaryngol. 2009;73:651–657. [PubMed: 19233485]

19. Tait S, Kallogjeri D, Suko J, Kukuljan S, Schneider J, Piccirillo JF. Effect of Budesonide Added to Large-Volume, Low-pressure Saline Sinus Irrigation for Chronic Rhinosinusitis: A Randomized Clinical Trial. JAMA Otolaryngol Head Neck Surg. 2018;144(7):605–612.

20. Nickels AS, Dimov V, Wolf R. Pharmacokinetic evaluation of Oloptadine for the treatment of allergic rhinitis and conjunctivitis. Expert Opin Drug Metab Toxicol. 2011;7:1593-1599.

21. Wise SK, Lin SY, Toskala E, Orlandi RR, Akdis CA, Alt JA, Azar A, Baroody FM, Bachert C, Canonica GW, Chacko T, Cingi C, Ciprandi G, Corey J, Cox LS, Creticos PS, Custovic A, Damask C, DeConde A, DelGaudio JM, Ebert CS, Eloy JA, Flanagan CE, Fokkens WJ, Franzese C, Gosepath J, Halderman A, Hamilton RG, Hoffman HJ, Hohlfeld JM, Houser SM, Hwang PH, Incorvaia C, Jarvis D, Khalid AN, Kilpeläinen M, Kingdom TT, Krouse H, Larenas-Linnemann D, Laury AM, Lee SE, Levy JM, Luong AU, Marple BF, McCoul ED, McMains KC, Melén E, Mims JW, Moscato G, Mullol J, Nelson HS, Patadia M, Pawankar R, Pfaar O, Platt MP, Reisacher W, Rondón C, Rudmik L, Ryan M, Sastre J, Schlosser RJ, Settipane RA, Sharma HP, Sheikh A, Smith TL, Tantilipikorn P, Tversky JR, Veling MC, Wang Y, Westman M, Wickman M, Zacharek M. International Consensus Statement on Allergy and Rhinology: Allergic Rhinitis. Int Forum Allergy Rhinol. 2018 Feb;8(2):108-352. doi: 10.1002/alr.22073. PMID: 29438602; PMCID: PMC7286723.

22. Scadding GK, Durham SR, Mirakian R, Jones NS, Leech SC, Farooque S, Ryan D, Walker SM, Clark AT, Dixon TA, Jolles SR, Siddique N, Cullinan P, Howarth PH, Nasser SM; British Society for Allergy and Clinical Immunology. BSACI guidelines for the management of allergic and non-allergic rhinitis. Clin Exp Allergy. 2008 Jan;38(1):19-42. doi: 10.1111/j.1365-2222.2007.02888.x. PMID: 18081563; PMCID: PMC7162111.

23. LaForce CF, Corren J, Wheeler WJ, Berger WE. Efficacy of azelastine nasal spray in seasonal allergic rhinitis patients who remain symptomatic after treatment with fexofenadine. Ann Allergy Asthma Immunol. 2004;93:154-159.

24. Yanez A, 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. 2002;89:479-484.

25. Carr W, Bernstein J, Lieberman P, et al. A novel intranasal therapy of azelastine with fluticasone for the treatment of allergic rhinitis. J Allergy Clin Immunol. 2012a;129:1282-1289.

26. Debbaneh PM, Bareiss AK, Wise SK, McCoul ED. Intranasal Azelastine and Fluticasone as Combination Therapy for Allergic Rhinitis: Systematic Review and Meta-analysis. Otolaryngol Head Neck Surg. 2019 Sep;161(3):412-418. doi: 10.1177/0194599819841883. Epub 2019 Apr 9. PMID: 30961435.

27. Bousquet, Jean, et al. Onset of action of the fixed combination intranasal azelastine-fluticasone propionate in an allergen exposure chamber. The Journal of Allergy and Clinical Immunology: In Practice 6.5 (2018): 1726-1732.

28. Price D, Shah S, Bhatia S, et al. A new therapy (MP29-02) is effective for the long-term treatment of chronic rhinitis. J Investig Allergol Clin Immunol. 2013; 23(7): 495-503.

29. Cheng LH, Lee JC, Wu PC, Lin YY, Chu YH, Wang HW. Azelastine nasal spray inhibiting sympathetic function on human nasal mucosa in patients with allergy rhinitis. Rhinology. 2019 Aug 1;57(4):268-272. doi: 10.4193/Rhin18.274. PMID: 30887967.

CANADIAN ALLERGY & IMMUNOLOGY TODAY

SPECIAL SUPPLEMENT

TO REGISTER FOR AND RECEIVE FUTURE ISSUES, PLEASE VISIT CANADIANALLERGYANDIMMUNOLOGYTODAY.CA