REVIEW

Department of Pharmacology and Toxicology, Friedrich-Alexander University of Erlangen, Germany

Allergic rhinitis: meaningful and less meaningful combination treatments including reminiscences

I. Szelenyi

Received November 4, 2013, accepted November 29, 2013

Prof. Dr. I. Szelenyi, Department of Pharmacology and Toxicology, Friedrich-Alexander University of Erlangen, Fahrstrasse 17, 91054 Erlangen, Germany
istvan.szelenyi@fau.de

Pharmazie 69: 414–416 (2014) *doi: 10.1691/ph.2014.3913R*

Allergic rhinitis (AR) results from a complex allergen-driven mucosal inflammation in the nasal cavity. Current guideline-based therapy for allergic rhinitis include oral and nasal antihistamines, topical and systemic glucocorticoids, decongestants, antimuscarinic agents, mast cell stabilizing drugs, leukotriene-receptor antagonists, and others. In spite of guideline recommendations, most patients are using multiple therapies in an attempt to achieve symptom control. Therefore, more effective therapies for the management of AR are clearly required. Recently, a novel fixed dose combination containing azelastine and fluticasone propionate has successfully been introduced. At present, it represents the only meaningful topical drug combination. Perhaps, it will be followed by others.

1. Introduction

Allergic rhinitis (AR) is found in approximately 10% to 20% of the general population, with an even greater prevalence in children. Overall, AR affects several million subjects worldwide and its prevalence continues to increase. Therefore, it is a global health problem with consequences on quality of life, school and work performance. Additionally, it is an "expensive" disease because it causes high direct (medical) and indirect (loss of production) costs.

Rhinitis describes an inflammatory condition of the nasal mucosa that is characterized by the symptoms of itching, sneezing, rhinorrhoea and nasal blockage. Non-nasal symptoms commonly associated with AR include tearing, eye itching and redness (allergic rhinoconjunctivitis).

AR is a challenge to treat because many patients do not respond sufficiently to treatment. Furthermore, the disease severity is often underestimated and, consequently, inadequately treated (Stewart 2007). Many patients with AR do not achieve optimal symptom relief with single-agent therapy. An inadequate symptom relief is often the reason for changing medications. Several drugs such as glucocorticoids (GCs), antihistamines (AHs) are recommended for the treatment of rhinitis by the guidelines of AR and its impact on asthma (ARIA) (Brozek et al. 2010; Bousquet et al. 2012).

2. Antihistamines

Oral AHs have been used since the 1930 s in the treatment of AR. However, their undesired effects (mainly drowsiness, sedation, fatigue, seizures, cardiac toxicity) considerably have limited their use. The second generation AHs have been developed to reduce or eliminate the adverse effects that occur with older H_1-receptor antagonists. At present, several oral AHs such as cetirizine, ebastine, fexofenadine, loratadine, desloratadine, mizolastine, olopatadine, etc., are available for AR therapy. In addition to their primary mechanism of antagonising histamine at the H_1-receptor, these agents may act on other mediators of the allergic reaction. For AR, all modern AHs are effective and the choice should be based on other factors.

Interestingly and in contrast to the tradition (inhaled [topical] therapies of the lower respiratory tract, successful intranasal therapeutic use of disodium cromoglycate in AR), it is only recently that intranasal AHs have begun to be more widely used as a treatment for AR. Levocabastine was discovered at Janssen Pharmaceutica in 1979. In Europe, nasal azelastine was first marketed in 1991 in the United Kingdom for the treatment of AR and is currently marketed in approximately 90 countries under various proprietary names. Olopatadine (initially marketing in Japan in 2001) has been approved in the USA and Europe in 2008. All together, the popularity of nasal (topical) AHs is steadily growing.

Nasal AHs are considered to be at least as effective as oral AHs (Yáñez and Rodrigo 2002; Bousquet et al. 2012) or even more effective in suppression of total nasal symptoms (and rhinorrhoea, specifically) (Corren et al. 2005).

3. Glucocorticoids

Intranasal Glucocorticoids (GCs) have proved to be an effective and safe form of AR therapy. However, as the number of new GCs has increased over the past decades, it has become important to consider whether significant differences exist between these agents. Pharmacologically, newer drugs such as mometasone furoate (MF), fluticasone propionate (FP) and fluticasone furoate (FF) appear to have substantially higher topical potencies and lower systemic bioavailabilities than older compounds. In clinical use, however, all the available drugs appear to be equally effective in controlling symptoms of AR. With regard to undesired effects, data suggest that novel GCs such as MF, FP and FF may have less potential for systemic effects during

prolonged use, particularly in children. Thus, novel GCs may be favoured in their use in some groups of patients with AR.
Nasal GCs are the most effective medications for treating AR. However, the onset of action was found to occur usually first some hours after application with a maximum effect after a few days. By contrast, oral and, first of all, topical AHs have a more rapid onset of action.
Symptoms, including nasal congestion, are better relieved by nasal GCs than by placebo. A meta-analysis has compared the effects of nasal AHs and nasal GCs with respect to symptoms of AR. Nasal GCs produced greater reduction of nasal symptoms than nasal AHs. There was a significant benefit to nasal GCs over AHs for nasal congestion. In contrast, there was no significant difference between nasal GCs and AHs in relieving ocular symptoms (Yáñez and Rodrigo 2002).
Nasal GCs have relatively few adverse effects which rarely require discontinuation of the drug. A delay in the attainment of normal height has been reported in children using intranasal beclomethasone but not other nasal GCs (Juniper et al. 2005); increased intraocular pressure and posterior subcapsular cataracts have been reported in adults (Lipworth 1999; Garbe et al. 1999). More recent data contradict these earlier observations (Gonzales et al. 2010).

4. Drug combinations

Most patients have moderate-to-severe disease frequently experience severe symptoms while receiving therapy and are dissatisfied with the therapy (Canonica et al. 2007; Valovirta et al. 2008) and consequently most patients are seeking a new medication or an additional self-medication (Demoly et al. 2001). Therefore, most physicians treat patients using multiple therapies to achieve quicker and more profound symptom relief (Bousquet et al. 2003).

4.1. Antihistamines combined with nasal glucocorticoids

Because antihistamines and nasal corticosteroids influence different pathogenetic mechanisms, patients with moderate or severe symptoms are commonly treated with both.
The fixed dose combination (FDC) of intranasal azelastine (125 μg) and FP (50 μg) administered as one dose per nostril b.i.d. has been shown to be significantly more efficacious in reducing baseline total nasal symptom score as compared to azelastine, FP and placebo. Ocular symptoms have also been improved (Hampel et al. 2010; Carr et al. 2012; Meltzer et al. 2013). In fact, the FDC has provided faster and more complete symptom control than first-line therapies may be considered the drug of choice for moderate-to-severe AR (Settipane and Schwindt 2013). Pharmacokinetic studies have revealed no drug-drug interactions (Derendorf et al. 2012).

4.2. Antihistamines combined with soft steroids?

Ten years ago, two promising candidates of soft GCs, loteprednol and etiprednol were suggested for therapeutic use. They would have been the ideal combination partner of AHs in the combination therapy of rhinitis. Indeed, loteprednol has proven to be effective not only in animals (Szelenyi et al. 2000) but also in humans suffering from AR (Krug et al. 2005). Additionally, loteprednol has demonstrated similar efficacy to other GCs in the treatment of allergic conjunctivitis with a greatly improved safety profile as loteprednol is less likely to elevate intraocular pressure (Bielory et al. 2012). It is generally accepted and therapeutically proven that drugs effectively treating allergic conjunctivitis are also able to suppress symptoms of AR. Correspondingly, there are nasal and ocular formulations for azelastine, olopatadine, disodium cromoglycate, several GCs to treat both allergic conjunctivitis and AR. Hopefully, a prince might be found who could reawaken Snow White loteprednol from eternal sleep. Indeed, it would be worth considering to revitalize loteprednol, at least, as partner of an AH in a novel FDC.

4.3. Combinations with decongestants

Oral decongestants are often combined with different classes of anti-rhinitis agents. Topical administration of such combinations is not recommended due to the timely limited use of topical decongestants.

4.4. Anticholinergics

Parasympathetic stimulation in the nasal cavity causes vasodilation resulting in watery secretion. Muscarinic receptor blockade through anticholinergic drugs such as ipratropium inhibits mucous secretion, rhinorrhoea, reduces congestion and sneezing. Ipratropium, the prototype nasal antimuscarinic drug is mainly used in the treatment of vasomotor rhinitis (Tran et al. 2011). Correspondingly, the ARIA guidelines suggest its use only in rhinorrhoea, without benefit for other symptoms of AR (Brozek et al. 2010).

4.5. Antihistamines combined with anticholinergics or glucocorticoids

From the pharmacotherapeutic point of view, such combinations do not make any sense and consequently they are not required.

4.6. Herbal combinations

The use of complementary and alternative medicine (CAM) has gained worldwide popularity in the last few decades (Nahin et al. 2009; Newton et al. 2009; Gottschling et al. 2013). Traditional remedies like herbal medicines are more popular than even before. Asian countries such as China, Korea, India and Japan are well-known all over the world for medicinal plants which possess a wide range of pharmacological properties. There are several herbal mixtures suitable to treat AR. Interestingly, there is only one herb which is common in all herbal mixtures used in Asian countries mentioned, namely, liquorice (*Glycyrrhiza uralensis*), a flavouring plant native to Asia with its main active ingredient, glycyrrhizin. In Europe, there is no such variety as in Asia. Two plants, both native to Europa, dominate the market: ivy (*Hedera helix*) and thyme (*Thymus vulgaris*).
Based on our long-lasting experience with medical plants, novel herbal formulas should and could be developed but the developmental hurdles are incomparably high. It should be kept in mind that the development of a novel herbal mixture is not much different from that of a new chemical entity (NCE). Unfortunately and in contrast to the NCE, the herbal formula does not receive a corresponding patent protection. Consequently, political and regulatory changes are necessary to make the development of novel herbal mixtures more profitable.

5. Outlook

There are some FDCs available for the treatment of AR. The most promising combinations consist of an AH and a GC. One such a FDC, Dymista® containing azelastine and FP is already on the market and may represent a new standard for assessing

relevance of the drug therapy in AR. Probably, others will follow. One interesting candidate for a FDC is loteprednol being effective in allergic conjunctivitis, but forgotten for AR.

This research paper was presented during the 9th Conference on Retrometabolism Based Drug Design and Targeting, May, 12–15, 2013, Orlando, FL, USA.

References

Bielory BP, O'Brien TP, Bielory L (2012) Management of seasonal allergic conjunctivitis: guide to therapy. Acta Ophthalmol 90:399–407.

Bousquet J, Lund VJ, van Cauwenberge P, Bremard-Oury C, Mounedji N, Stevens MT, El-Akkad T (2003) Implementation of guidelines for seasonal allergic rhinitis: a randomized controlled trial. Allergy 58:733–41.

Bousquet J, Schünemann HJ, Samolinski B, Demoly P, Baena-Cagnani CE, Bachert C, Bonini S, Boulet LP, Bousquet PJ, Brozek JL, Canonica GW, Casale TB, Cruz AA, Fokkens WJ, Fonseca JA, van Wijk RG, Grouse L, Haahtela T, Khaltaev N, Kuna P, Lockey RF, Lodrup Carlsen KC, Mullol J, Naclerio R, O'Hehir RE, Ohta K, Palkonen S, Papadopoulos NG, Passalacqua G, Pawankar R, Price D, Ryan D, Simons FE, Togias A, Williams D, Yorgancioglu A, Yusuf OM, Aberer W, Adachi M, Agache I, Aït-Khaled N, Akdis CA, Andrianarisoa A, Annesi-Maesano I, Ansotegui IJ, Baiardini I, Bateman ED, Bedbrook A, Beghé B, Beji M, Bel EH, Ben Kheder A, Bennoor KS, Bergmann KC, Berrissoul F, Bieber T, Bindslev Jensen C, Blaiss MS, Boner AL, Bouchard J, Braido F, Brightling CE, Bush A, Caballero F, Calderon MA, Calvo MA, Camargos PA, Caraballo LR, Carlsen KH, Carr W, Cepeda AM, Cesario A, Chavannes NH, Chen YZ, Chiriac AM, Chivato Pérez T, Chkhartishvili E, Ciprandi G, Costa DJ, Cox L, Custovic A, Dahl R, Darsow U, De Blay F, Deleanu D, Denburg JA, Devillier P, Didi T, Dokic D, Dolen WK, Douagui H, Dubakiene R, Durham SR, Dykewicz MS, El-Gamal Y, El-Meziane A, Emuzyte R, Fiocchi A, Fletcher M, Fukuda T, Gamkrelidze A, Gereda JE, González Diaz S, Gotua M, Guzmán MA, Hellings PW, Hellquist-Dahl B, Horak F, Hourihane JO, Howarth P, Humbert M, Ivancevich JC, Jackson C, Just J, Kalayci O, Kaliner MA, Kalyoncu AF, Keil T, Keith PK, Khayat G, Kim YY, Koffi N'goran B, Koppelman GH, Kowalski ML, Kull I, Kvedariene V, Larenas-Linnemann D, Le LT, Lemière C, Li J, Lieberman P, Lipworth B, Mahboub B, Makela MJ, Martin F, Marshall GD, Martinez FD, Masjedi MR, Maurer M, Mavale-Manuel S, Mazon A, Melen E, Meltzer EO, Mendez NH, Merk H, Mihaltan F, Mohammad Y, Morais-Almeida M, Muraro A, Nafti S, Namazova-Baranova L, Nekam K, Neou A, Niggemann B, Nizankowska-Mogilnicka E, Nyembue TD, Okamoto Y, Okubo K, Orru MP, Ouedraogo S, Ozdemir C, Panzner P, Pali-Schöll I, Park HS, Pigearias B, Pohl W, Popov TA, Postma DS, Potter P, Rabe KF, Ratomaharo J, Reitamo S, Ring J, Roberts R, Rogala B, Romano A, Roman Rodriguez M, Rosado-Pinto J, Rosenwasser L, Rottem M, Sanchez-Borges M, Scadding GK, Schmid-Grendelmeier P, Sheikh A, Sisul JC, Solé D, Sooronbaev T, Spicak V, Spranger O, Stein RT, Stoloff SW, Sunyer J, Szczeklik A, Todo-Bom A, Toskala E, Tremblay Y, Valenta R, Valero AL, Valeyre D, Valiulis A, Valovirta E, Van Cauwenberge P, Vandenplas O, van Weel C, Vichyanond P, Viegi G, Wang DY, Wickman M, Wöhrl S, Wright J, Yawn BP, Yiallouros PK, Zar HJ, Zernotti ME, Zhong N, Zidarn M, Zuberbier T, Burney PG, Johnston SL, Warner JO (2012) Allergic rhinitis and its impact on asthma (ARIA): achievements in 10 years and future needs. J Allergy Clin Immunol 130: 1049–1062.

Brozek JL, Bousquet J, Baena-Cagnani CE, Bonini S, Canonica GW, Casale TB, van Wijk RG, Ohta K, Zuberbier T, Schünemann HJ (2010) Allergic rhinitis and its impact on asthma (ARIA) guidelines: 2010 revision. J Allergy Clin Immunol 126: 466–476.

Canonica GW, Bousquet J, Mullol J, Scadding GK, Virchow JC (2007) A survey of the burden of allergic rhinitis in Europe. Allergy 62 Suppl 85: 17–25.

Carr WW, Ratner P, Munzel U, Murray R, Price D, Canonica GW, Mullol J, Virchow JC, Lieberman P, Meltzer E, Bachert C (2012) Comparison of intranasal azelastine to intranasal fluticasone propionate for symptom control in moderate-to-severe seasonal allergic rhinitis. Allergy Asthma Proc 33: 450–458.

Corren J, Storms W, Bernstein J, Berger W, Nayak A, Sacks H (2005) Effectiveness of azelastine nasal spray compared with oral cetirizine in patients with seasonal allergic rhinitis. Clin Ther 27: 543–553.

Demoly P, Allaert FA, Lecasble M; PRAGMA (2002) ERASM, a pharmacoepidemiologic survey on management of intermittent allergic rhinitis in every day general medical practice in France. Allergy 57: 546–554.

Derendorf H, Munzel U, Petzold U, Maus J, Mascher H, Hermann R, Bousquet J (2012) Bioavailability and disposition of azelastine and fluticasone propionate when delivered by MP29–02, a novel aqueous nasal spray. Br J Clin Pharmacol 74: 125–133.

Garbe E, LeLorier J, Boivin JF, Suissa S (1997) Inhaled and nasal glucocorticoids and the risks of ocular hypertension or open-angle glaucoma. JAMA 277: 722–727.

Gonzalez AV, Li G, Suissa S, Ernst P (2010) Risk of glaucoma in elderly patients treated with inhaled corticosteroids for chronic airflow obstruction. Pulm Pharmacol Ther 23: 65–70.

Gottschling S, Gronwald B, Schmitt S, Schmitt C, Längler A, Leidig E, Meyer S, Baan A, Shamdeen MG, Berrang J, Graf N (2013) Use of complementary and alternative medicine in healthy children and children with chronic medical conditions in Germany. Complement Ther Med 21 Suppl 1: S61–9.

Hampel FC, Ratner PH, Van Bavel J, Amar JJ, Daftary P, Wheeler W, Sacks H (2010) Double-blind, placebo-controlled study of azelastine and fluticasone in a single nasal spray delivery device. Ann Allergy Asthma Immunol 105: 168–173.

Juniper EF, Ståhl E, Doty RL, Simons FE, Allen DB, Howarth PH (2005) Clinical outcomes and adverse effect monitoring in allergic rhinitis. J Allergy Clin Immunol 115 (3 Suppl 1): S390–413.

Krug N, Hohlfeld JM, Geldmacher H, Larbig M, Heermann R, Lavallee N, Nguyen DT, Petzold U, Hermann R (2005) Effect of loteprednol etabonate nasal spray suspension on seasonal allergic rhinitis assessed by allergen challenge in an environmental exposure unit. Allergy 60: 354–359.

Lipworth BJ (1999) Systemic adverse effects of inhaled corticosteroid therapy: A systematic review and meta-analysis. Arch Intern Med 159: 941–955.

Meltzer E, Ratner P, Bachert C, Carr W, Berger W, Canonica GW, Hadley J, Lieberman P, Hampel FC, Mullol J, Munzel U, Price D, Scadding G, Virchow JC, Wahn U, Murray R, Bousquet J (2013) Clinically relevant effect of a new intranasal therapy (MP29–02) in allergic rhinitis assessed by responder analysis. Int Arch Allergy Immunol 161: 369–377.

Nahin RL, Barnes PM, Stussman BJ, Bloom B (2009) Costs of complementary and alternative medicine (CAM) and frequency of visits to CAM practitioners: United States, 2007. Natl Health Stat Report 18: 1–14.

Newton JR, Santangeli L, Shakeel M, Ram B (2009) Use of complementary and alternative medicine by patients attending a rhinology outpatient clinic. Am J Rhinol Allergy 23: 59–63.

Settipane RA, Schwindt C (2013) Chapter 15: Allergic rhinitis. Am J Rhinol Allergy 27 Suppl 1: S52–5.

Stewart MG (2008) Identification and management of undiagnosed and undertreated allergic rhinitis in adults and children. Clin Exp Allergy 38: 751–760.

Szelenyi I, Hochhaus G, Heer S, Kusters S, Marx D, Poppe H, Engel J (2000) Loteprednol etabonate: a soft steroid for the treatment of allergic diseases of the airways. Drugs Today 36: 313–320.

Tran NP, Vickery J, Blaiss MS (2011) Management of rhinitis: allergic and non-allergic. Allergy Asthma Immunol Res 3:148–56.

Valovirta E, Myrseth SE, Palkonen S (2008) The voice of the patients: allergic rhinitis is not a trivial disease. Curr Opin Allergy Clin Immunol 8: 1–9.

Yáñez A, Rodrigo GJ (2002) 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.