



## A cost minimization analysis of Azelastine/Fluticasone combination nasal spray versus Azelastine and Fluticasone nasal sprays monotherapy in moderate to severe allergic rhinitis in Iran

Nayyereh Ayati<sup>1</sup>, Delara Babaie<sup>2</sup>, Shekoufeh Nikfar<sup>1</sup>, Erfan Rohani<sup>1</sup>, Marzieh Nosrati<sup>1</sup>, Pardis Zaboli<sup>3\*</sup>

<sup>1</sup> Department of Pharmacoeconomics and Pharmaceutical Administration, Faculty of Pharmacy, Pharmaceutical Management and Economics Research Centre, Tehran University of Medical Sciences, Tehran, Iran

<sup>2</sup> Department of Allergy and Clinical Immunology, Mofid Children's Hospital, Shahid Beheshti University of Medical Sciences, Tehran, Iran

<sup>3</sup> Iran Drug Selection Department, Iran Food and Drug Administration (IFDA), Tehran, Iran

### ABSTRACT

**Background:** Allergic Rhinitis (AR) is a symptomatic disorder which is due to allergen exposure and IgE inflammatory pathway activation in respiratory tract. The present study's purpose was to assess Azelastine/Fluticasone combination nasal spray cost-effectiveness in comparison with Azelastine and Fluticasone nasal sprays monotherapy, in mild to moderate AR patients in Islamic Republic of Iran (I.R.I.) health care system.

**Methods:** A literature review was performed in order to compare the effectiveness of Fluticasone/Azelastine (50µg/125µg) with Fluticasone (50µg) and Azelastine (125µg). The search was conducted in PubMed, ISI, Scopus, Cochrane, CRD York and Google Scholar based on a predefined PICO of the study. According to confirmed equal clinical effectiveness of two arms, a cost minimization analysis was done. As micro costing, direct medical costs (drugs' costs, GP office visits, office visit and allergy-related tests), based on official tariffs in Iran were calculated in a 14-day time horizon. Because of model's time horizon, which was less than 1 year, discount rate was not applied.

**Results:** The result of literature search were two RCTs in which the combination form had been compared with each of the spray of Azelastine and Fluticasone. Azelastine/Fluticasone would save 2.05\$ per patient for each course of treatment; and therefore recognized as cost-effective.

**Conclusions:** This study showed that Azelastine/Fluticasone combination was the cost saving alternative.

**Keywords:** Azelastine Fluticasone; Nasal spray; Allergic Rhinitis

**Citation:** Ayati A, Babaie D, Nikfar S, Rohani E, Nosrati M, Zaboli P. A cost minimization analysis of Azelastine/Fluticasone combination nasal spray versus Azelastine and Fluticasone nasal sprays monotherapy in moderate to severe allergic rhinitis in Iran. J Pharmacoeconomics & Pharm Manage 2017;3(1-2):21-23.

### 1. Introduction

Allergic Rhinitis (AR), as a global health problem, is a symptomatic disorder of nasal mucosal membrane. This is induced by an IgE-related membrane inflammation followed by an allergen exposure [1]. AR's characteristics are nasal itching, nasal obstruction, watery rhinorrhea and sneezing. In addition, conjunctive symptoms, headache and impaired smell may be occurred. AR was previously divided into perennial, seasonal and occupational disease. Seasonal AR (SAR) is caused by a wide variety of pollen allergens [2]. It is now graded upon symptoms' type, symptoms' duration and disease impact on patients' health related quality of life. Therefore, it is categorized to mild, moderate and severe AR[3].

AR diagnosis is generally based on patient's history and clinical examination of rhinitis and conjunctivitis symptoms [4]. Management of this condition consists of allergen avoidance, medical therapy and immune therapy.

Medical therapy includes oral and intranasal antihistamines and intranasal corticosteroids. Intranasal corticosteroids are first-line treatment in moderate to severe AR [2,5]. If monotherapy is not sufficient in controlling the symptoms of AR, especially in mild to moderate AR, combination therapy which is consisted of antihistamines and corticosteroids is recommended [6-8]. Two mostly used drugs in the management of AR are Fluticasone Propionate, a potent and locally active glucocorticoid and Azelastine Hydrochloride that is a second-generation antihistamine and an inflammatory mediator's inhabitant [9-12].

Previous studies have shown that using Azelastine Hydrochloride nasal spray and Fluticasone Propionate nasal spray, in combination may provide a considerable therapeutic benefit for seasonal allergic rhinitis patients in comparison with monotherapy with either agents [13, 14]. Allergic rhinitis has a well-recognized impact on economics, society and also patients' quality of life and productivity, due to its effect on daily activities and social relationships [3, 15]. As a result, AR is associated with high costs and a considerable economic burden. A part of this is due to direct medical costs and the pharmaceuticals' costs [15]. The present study aims to assess Azelastine/Fluticasone combination nasal spray's cost-effectiveness in comparison with Azelastine and Fluticasone nasal sprays monotherapy in mild to moderate AR patients in Islamic Republic of Iran health care system.

### 2. Methods

A literature review was performed in order to compare the effectiveness of Fluticasone/Azelastine (50µg/125µg) combination therapy with Fluticasone (50µg) and Azelastine (125µg) monotherapy. The search was conducted in PubMed, ISI, Scopus, Cochrane, CRD York and Google Scholar databases for the published articles before 2017. Search key words included: "Azelastine and Fluticasone effectiveness", "Azelastine effectiveness", "Fluticasone effectiveness", "Azelastine and Fluticasone RCT", "Azelastine RCT" and "Fluticasone RCT". The inclusion criteria of the studies were AR patients as population; Azelastine and Fluticasone combination nasal spray as intervention; Azelastine nasal spray and Fluticasone nasal spray monotherapy as comparators; and

\* Corresponding author. Tel: (98) 21 61927451, E-mail: [pardis\\_zaboli@yahoo.com](mailto:pardis_zaboli@yahoo.com)

Article information: Received date:08/10/2016, Accepted date:13/04/2017, Available online:05/06/2017

**Table 1.** Dosage of comparative arms

Drug	Daily Usage	2 Weeks Usage	No of spray per device	Totally used devices in 2 weeks
Fluticasone 50µg	2 spray/ Nostril/ 1 daily = 4 spray/Day	56 spray	100 MD	0.56 device
Azelastine 125µg (10 ml)	2 spray/ Nostril/ 2 daily = 8 spray/Day	112 spray	70 MD	1.6 device
Azelastine/Fluticasone 125µg + 50µg (10 ml)	1 spray/ Nostril/ 2 daily = 4 spray/Day	56 spray	70 MD	0.8 device

**Table 2.** Price of comparative arms (acquisition cost)

Drug	Dosage Form	Unit Drug Price (IRR)	Unit Drug Price (\$)
Fluticasone 50µg	Nasal Spray	300,000	9.25
Azelastine 125µg (10 ml)	Nasal Spray	122,620	3.78
Total Weighted Mean Price:		420,000	12.94
Azelastine/Fluticasone 125µg + 50µg (10 ml)	Nasal Spray	372,200	11.46

**Table 3.** Non-acquisition cost components, in 14 days' time-horizon

Type	Sequence/ 14 days	Cost (USD)	Note
General Physician Visit	1	4.16	Equal in both comparative arms
Office visits to specialists (Allergist, ENT, Pulmonologist)	1	6.92	Equal in both comparative arms
Allergy-related tests	0.5	5.15	Equal in both comparative arms

**Table 4.** Final cost comparison of comparative arms of the study

Drug	Device used in 2 weeks	Drug Cost Used in 2 weeks (IRR)	Drug Cost Used in 2 weeks (\$)
Fluticasone 50µg	0.56	168,000	5.18
Azelastine 125µg (10 ml)	1.6	196,192	6.05
Azelastine/Fluticasone 125µg + 50µg (10 ml)	0.8	Total Cost: 364,192 297,760	11.22 9.18

finally the Total Nasal Symptom Score (TNSS) and Total Ocular Symptom Score (TOSS) as outcome of interest.

According to confirmed equal clinical effectiveness of two comparative arms in the aforementioned performed SR [13,16], a cost minimization analysis (CMA) from payer perspective was conducted. Due to equality of indirect medical costs for both comparative arms, this was not calculated. As micro costing, direct medical costs (the drugs' costs, general physician's office visits, specialist office visit and allergy-related tests), based on official tariffs in both public and private sectors (calculated by 80% and 20%, respectively) in Iran, were calculated. Study's time horizon was 14 days, due to selected time horizon of included RCTs. Weighted mean of prices of available brands of comparator in Iran's pharmaceutical market was used in order to calculate the drug costs. According to Iran's central bank statistics, dollar currency rate was considered 32447.29 Iranian Rial (IRR)/1 US dollar (\$)¹. Because of model's time horizon, which was less than 1 year, discount rate was not applied for calculated costs. Sensitivity analysis was not performed due to lack of model design and therefore absence of necessity in checking the model robustness.

### 3. Results

The number of the articles which were in consistency with the inclusion criteria of the present study was two. The first study was a multicenter, randomized, double-blind study which was performed in 610 patients with moderate-to-severe nasal symptoms related to allergic rhinitis. These patients were randomized in to 4 groups and each group was treated with either one of the following nasal sprays; Azelastine, Fluticasone, Azelastine and Fluticasone and Placebo. The primary efficacy variable was the change in TNSS. The combination Azelastine/Fluticasone nasal spray caused a statistically significant improvement in the TNSS in comparison with either agent alone in patient population [14].

The second study was a double-blind randomized multicenter trial which was conducted in a two-week period in 151 AR patients with moderate to severe symptoms, in order to determine the effectiveness of concurrent use of intranasal Azelastine and intranasal Fluticasone propionate and the use of each drug alone. It was demonstrated that a substantial therapeutic benefit could be resulted from using Azelastine and fluticasone nasal spray in combination, in SAR patients [13]. The cumulative results of these two studies demonstrated that the effectiveness of Azelastine/ Fluticasone Combination nasal spray in eliminating the effects of allergic rhinitis was statistically superior to Azelastine nasal spray and Fluticasone nasal spray monotherapy.

¹ Access date to Iran's Central Bank Statistics: 16.07.2016

## Azelastine/Fluticasone combination nasal spray cost-effectiveness

Daily dosage of comparative arms is shown in table 1. Total usage of each drug in the 14- day time horizon for Fluticasone, Azelastine and Azelastine/Fluticasone is 0.56, 1.6 and 0.8 devices, respectively.

As it is shown in table 2, the total weighted mean price for Fluticasone (50µg) and Azelastine (125µg -10 ml) nasal sprays was 420,000 IRR (12.94 \$) and the price for Azelastine/Fluticasone (125µg + 50µg -10 ml) combination nasal spray was 372,000 IRR (11.46 \$). Other cost components are presented in Table 3; although, they are equal in both comparator arms.

If clinical effectiveness of Azelastine/Fluticasone combination nasal spray is considered equal to Fluticasone and Azelastine nasal sprays monotherapy, it would save 2.05\$ per patient for each course of treatment (Table 4). Therefore, this drug would be the dominant and cost-effective alternative.

### 4. Discussion

This 14-day economic evaluation in the payer perspective claims that Azelastine/ Fluticasone combination nasal spray is the dominant alternative in comparison with therapy with either of the drugs' monotherapy, when it is used in moderate to severe AR patients. The results of present study indicated that Azelastine/Fluticasone combination nasal spray was a more cost-effective alternative in comparison with either of the drugs alone.

This result is inconsistency with the following studies [13,17,18]. In Ratner et al study, it was demonstrated that combination therapy can benefit patients with moderate to severe or persistent seasonal allergy by improving TNSS symptoms and patient's compliance and also by lowering the costs of the therapy [13]. In a comprehensive medical-economic perspective study in 2014, it was showed that this combination therapy was a dominant alternative relative to its medical outcome and cost-effectiveness [17]. Another study by Harrow B. et al. in 2016, which studied resource utilization and costs of Azelastine/ Fluticasone nasal spray concurrent therapy in comparison with treatment with either of the drugs alone in AR patients, showed that concurrent therapy had better economic outcomes [18]. To the best of our knowledge, it was the first study which conducted cost-effectiveness analysis for the mentioned drug and patient population.

### 5. Conclusion

The results of this study showed that Azelastine/Fluticasone combination nasal spray was a cost saving alternative in comparison with Azelastine nasal spray and Fluticasone nasal spray in allergic rhinitis management in the Islamic Republic of Iran 's population.

### 8. References

- (1) Khaltaev N, Bousquet J. Allergic Rhinitis and its Impact on Asthma Update (ARIA 2008) the Perspective from Spain. *J Investig Allergol Clin Immunol.* 2008; 18(5):327-34.
- (2) Van Cauwenberge P, Bachert C, Passalacqua G, Bousquet J, Canonica G, Durham S, et al. Consensus statement on the treatment of allergic rhinitis. *Allergy.* 2000; 55(2):116-34.
- (3) Fairchild CJ, Durden E, Cao Z, Smale P. Outcomes and cost comparison of three therapeutic approaches to allergic rhinitis. *Am j Rhino Allergy.* 2011; 25(4):257-62.
- (4) Skoner DP. Allergic rhinitis: definition, epidemiology, pathophysiology, detection, and diagnosis. *J Allergy Clin Immunol.* 2001; 108(1):S2-S8.
- (5) Sur DK, Plesa ML. Treatment of Allergic Rhinitis. *Am Family Physician.* 2015; 92(11).
- (6) Dykewicz MS, Fineman S, Skoner DP, Nicklas R, Lee R, Blessing-Moore J, et al. Diagnosis and management of rhinitis: complete guidelines of the Joint Task Force on Practice Parameters in Allergy, Asthma and Immunology. *Ann Allergy Asthma Immunol.* 1998; 81(5):478-518.
- (7) Casale TB, Blaiss MS, Gelfand E, Gilmore T, Harvey PD, Hindmarch I, et al. First do no harm: managing antihistamine impairment in patients with allergic rhinitis. *J Allergy Clin Immunol.* 2003; 111(5):S835-S42.
- (8) Kay GG, Plotkin KE, Quig MB, Starbuck VN, Yasuda S. Sedating effects of AM/PM antihistamine dosing with evening chlorpheniramine and morning terfenadine. *Am J Managed Care.* 1997; 3:1843-8.
- (9) Harding SM. The human pharmacology of fluticasone propionate. *Respir Med.* 1990; 84:25-9.
- (10) Nathan RA, Bronsky E, Fireman P, Grossman J, LaForce C, Lemanske Jr R, et al. Once daily fluticasone propionate aqueous nasal spray is an effective treatment for seasonal allergic rhinitis. *Ann Allergy.* 1991; 67(3):332-8.
- (11) Meltzer EO, Weiler JM, Dockhorn RJ, Widlitz MD, Freitag JJ. Azelastine nasal spray in the management of seasonal allergic rhinitis. *Ann Allergy.* 1994; 72(4):354-9.
- (12) Bernstein JA. Azelastine hydrochloride: a review of pharmacology, pharmacokinetics, clinical efficacy and tolerability. *Curr Med Res Opin.* 2007; 23(10):2441-52.
- (13) Ratner PH, Hampel F, Van Bavel J, Amar NJ, Daftary P, Wheeler W, et al. Combination therapy with azelastine hydrochloride nasal spray and fluticasone propionate nasal spray in the treatment of patients with seasonal allergic rhinitis. *Ann Allergy Asthma Immunol.* 2008; 100(1):74-81.
- (14) Hampel FC, Ratner PH, Van Bavel J, Amar NJ, Daftary P, Wheeler W, et al. Double-blind, placebo-controlled study of azelastine and fluticasone in a single nasal spray delivery device. *Ann Allergy Asthma Immunol.* 2010; 105(2):168-73.
- (15) Cardell L-O, Olsson P, Andersson M, Welin K-O, Svensson J, Tennvall GR, et al. TOTALL: high cost of allergic rhinitis—a national Swedish population-based questionnaire study. *NPJ Prim Care Respir Med.* 2016; 26:15082.
- (16) Hampel FC, Ratner PH, Van Bavel J, Amar N, Daftary P, Wheeler W, et al. Double-blind, placebo-controlled study of azelastine and fluticasone in a single nasal spray delivery device. *Ann Allergy Asthma Immunol.* 2010; 105(2):168-73.
- (17) May U. [Socio-economic impact of allergic rhinitis and perspectives of appropriate therapy]. *MMW Fortschritte der Medizin.* 2014; 156 Suppl 2:39-47.
- (18) Harrow B, Sedaghat AR, Caldwell-Tarr A, Dufour R. A Comparison of Health Care Resource Utilization and Costs for Patients with Allergic Rhinitis on Single-Product or Free-Combination Therapy of Intranasal Steroids and Intranasal Antihistamines. *J Managed Care Special Pharm.* 2016; 22(12):1426-36.