Journal of Applied Pharmaceutical Science

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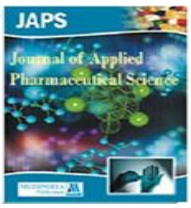


ISSN: 2231-3354
Received: 04-07-2011
Revised on: 07-07-2011
Accepted: 09-07-2011

# Cost effectiveness analysis of five different treatment alternatives in seasonal allergic conjunctivitis

**Guvenc Kockaya and Albert Wertheimer**

**Guvenc Kockaya**
*General Directorate of Pharmaceuticals and Pharmacy, Pharmacoeconomy Department, Turky.*

**Albert Wertheimer**
*Temple University, School of Pharmacy, Center for Pharmaceutical Health Services Research*

***For Correspondence**:
**Guvenc Kockaya**
*Sogutozu M. 2176. Sok. N:5 K:9 Cankaya-Ankara Turkey*
*Phone : + 90 544 795 0880*

**ABSTRACT**

Seasonal allergic conjunctivitis is an illness which decreases quality of life and is common in society. Pharmacoeconomic evaluation about seasonal alergic conjunctivitis has not been measured in Turkey. The aim of our study is to understand the cost-effective medicines which are used for seasonal allergic conjunctivitis with Turkish data. In our study, effectiveness data from randomized controlled trials done with fluorometholon, epinastin, olopatadin, emedastin and ketotifen were used. Different effectiveness data reported in the trials were reduced to one single dataset. For cost data, direct costs like drug cost and physician meetings were counted in the calculation. Incremental cost effectiveness analysis (ICER) was performed with effectiveness and cost data which were obtained. In cost analysis lowest treatment cost was established by fluorometholon (US$ 38.94) and followed by ketotifen (US$ 43.41),epinastine (US$ 43.60), olopatadine (US$ 44.05) and emedastine (US$ 44.92), respectively. When the drugs compared for incremental cost-effectiveness, emedastine was dominated by ketotifen and emedastine dominated by olopatadine; ketofien could be compared with fluorometholon and olopatadine. Turkish data obtained and analyzed were similar with the literature. Reimburstment foundations can feature preparations which contain olopatadin and epinastin in treatment protocols, in the light of obtained data.

***Key words***: Pharmacoeconomics , cost-effectiveness, allergic conjunctivitis, olopatadine, ketotifen.

## INTRODUCTION

About 15-20% of the population worldwide are effected by seasonal allergic rhinitis (SAC) which occurs from type 1 allergic reactions. (Weeke 1987, Abelson et al 1993) Most of patients are allergic to agents including pollen and animals (Abelson et al 1993b).The most common symptom of SAC is ocular itching. In addition, conjunctival redness, tearing, mucus discharge, chemosis and lid edema are other common symptoms of SAC. Mast cells play an important role in the pathogenesis of SAC (Irani et al., 1990). The basic principle of treatment is keeping a patient away from allergic agents. However this treatment approach does not often work because most allergic agents are in the air (Verin et al., 2001). H-1 receptor blockage, mast cell stabilization, and the blocking of cytokine production and prostoglandin formation are prefered in drug treatment of SAC (Bielory, 2002). SAC causes increases in health costs, decreasing of quality of life, increasing disability days from work and school. However SAC`s cost was established at nearly US$13,51 billion in 2009, but there is not enough pharmacoeconomic analysis about treatment of SAC (Lafuma et al., 2002). When a computer search was done using PubMed with “allergic conjunctivitis and cost effectiveness” and “cost of seasonal conjunctivitis”, 11 and 27 article could be reached, respectively. Pharmacoeconomic evaluation was done only in 5 of these 38 articles. However these articles are for European countries, and there was not any imformation

**Table 1:** Total sales of SAC treatment options.

| | Year 2008 | Year 2009 | Year 2010 |
|---|---|---|---|
| Olopatadine | US $ 6.405.895 | US $ 6.086.228 | US $ 5.302.353 |
| Ketotifen | US $ 4.701.416 | US $ 5.375.028 | US $ 4.488.300 |
| Emedastine | US $ 2.920.745 | US $ 2.922.755 | US $ 3.329.461 |
| Epinastine | US $ 3.509.633 | US $ 3.110.419 | US $ 2.746.495 |
| Fluorometholon | US $ 201.246 | US $ 130.572 | US $ 48.077 |
| Total | US $ 17.738.935 | US $ 17.625.002 | US $ 15.914.686 |

*SAC: Seasonal Allergic Conjunctivitis.

**Table 2 :** Effectiveness Data

| | Itching | | Redness | | Tears | | Eye Flap Inflamation | | Konjonctivitis | | Cytology of konjunctiva | | Estimated Symtom Score (ESS) | | Absolte Decrease in ESS | Percantage decrease in ESS |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Bs. | End | Bs. | End | Bs. | End | Bs. | End | Bs. | End | Bs. | End | Bs. | End | | |
| Olopatadin | 2.60 | 0.60 | 2.60 | 0.80 | 1.55 | 0.45 | 1.00 | 0.25 | 1.15 | 0.20 | 2.44 | 1.27 | 1,89 | 0,59 | 1,29 | 68 |
| Ketotifen | 2.70 | 0.80 | 2.75 | 0.95 | 1.45 | 0.45 | 1.05 | 0.30 | 1.20 | 0.25 | 2.36 | 1.26 | 1,91 | 0,66 | 1,25 | 65 |
| Epinastin | 2.55 | 1.00 | 2.65 | 1.10 | 1.30 | 0.30 | 1.15 | 0.15 | 1.21 | 0.15 | 2.36 | 1.27 | 1,87 | 0,66 | 1,20 | 64 |
| Emedastin | 2.60 | 1.00 | 2.70 | 1.25 | 1.45 | 0.60 | 1.15 | 0.40 | 1.20 | 0.30 | 2.31 | 1.42 | 1,90 | 0,82 | 1,07 | 56 |
| Fluorometholon | 2.60 | 1.50 | 2.70 | 1.75 | 1.40 | 0.40 | 1.30 | 0.40 | 1.20 | 0.45 | 2.26 | 1.35 | 1,91 | 0,97 | 0,93 | 48 |

- Bs.: Baseline

about Turkey. Total sales of five major SAC treatment options were US $ 15.514 million according to the IMS data in 2010 (Table 1). In the light of this we studied a pharmacoeconomic evaluation of SAC treatment options in Turkey. Our study is unique in the light of the approach. It is unique also, in the literature because of itscomparison of 5 different medicines for SAC treatment.

## MATERIALS AND METHODS

Effectiveness data of randominized, prospective, double blind, placebo controlled trials of Brozan and colleagues which was done in Baskent University Hospital and published in 2009 was used (Borazan et al., 2009). Olopatadine HCI 0.1%, ketotifen fumarate 0.025%, epinastine HCI 0.05%, emedastine 0.05% and fluorometholone acetate 0.1% ophthalmic solutions were compared in SAC treatment in the Borazan trial. 100 patients who were treated at Baskent University Hospital for SAC were included in the trial. Patients were randominazid to 5 different groups. They were administered olopatadine, ketotifen fumarate, epinastine, emedastine or fluorometholone acetate with each eye instilled twice daily for 2 weeks. One eye of each patient was treated with the study drug and the other was treated with a placebo. Signs and symptoms of allergic conjunctivitis (itching, redness, tearing, chemosis and eyelid swelling) were scored on a 4-point scale. Each symptom was assessed at baseline and then again after 1 and 2 weeks of the treatment. Ocular surface variables were assessed by conjunctival impression cytology (Borazan et al., 2009).

Arithmetic means of effectiveness data (scores of signs and symptoms) were calculated for each medicine to include calculation of just one effectiveness datapoint for pharmacoeconomic analysis, named as an estimated symptom score (ESS). Absolute decreases of scores of signs and symptoms which were caused by medicines from the baselines were calculated after ESS calculation. In addition, the absolute decreases in percentage for ESS were calculated too.(Table 2).

The Price list published by the General Directorate of Pharmaceuticals and Pharmacy on 04.09.2009 was used. Each molecule has only one form in the Turkish medicine market without any generic forms. Therefore, the cost of each molecule`s only one form was included in the calculation. Cost of physician visits were added to the calculation too, first visit for iniating the treatment, second visit for controling the treatment. Cost of physician visits were taken from the Health Application Statement which was published by the Social Security Institution in 2010. 1.50 was used as the exchance rate of converting Turkish Liras to US dolars (Table 3).

**Table 3:** Cost Data

| | Cost |
|---|---|
| Physician Visit | US$ 17.42 (26.14 TL) |
| Olopatadine (Patanol %0,1 lik Opthalmic Solution) | US$ 9.2 (13,80 TL) |
| Ketotifen (Zaditen %0.025 Eye Drop) | US$ 8.56 (12,84 TL) |
| Epinastine (Relestat 0.5MG/ML Eye Derop) | US$ 8.74 (13,12 TL) |
| Emedastine (Emadine %0.05 5 ML Opthalmic Solution) | US$ 10.06 (15,10 TL) |
| Fluorometholon (Fluorospos Eye Drop 1 MG/ML 5 ML) | US$ 4.08 (6,13 TL) |

US$: United States Dollars TL: Turkish Liras

Incremental cost effectiveness analysis was performed in the light of effectiveness and cost data. (Table 4). In addition, a cost effectiveness analysis was performed in the light of mean absolute and percantage chance in symptom scores (Table 5). Also a sensitivity analysis was performed for different situations.

## RESULT AND DISCUSSION

The greatest decrease in absolute ESS was established by olopatadine and followed by ketotifene (1.25), epinastine (1.20), emedastine (1.07) and fluorometholon (0.93), respectively. The

**Table 4:** Incremental Cost Effectiveness Analysis.

| | Total Cost of Treatment (US$) | Incremental Cost (US$) | Absolute decrease in ESS | Incremental Absolute Decrease in ESS | Incremental Cost Effectiveness Ratio (US$/Absolute Decrease in ESS) |
|---|---|---|---|---|---|
| Fluorometholon | 38.94 | - | 0,93 | - | - |
| Ketotifen | 43.41 | 4.47 | 1.25 | 0.32 | 13.9 |
| Epinastine | 43.6 | Dominated | 1.20 | Dominated | Dominated |
| Olopatadine | 44.05 | 0.64 | 1.29 | 0.04 | 16 |
| Emedastine | 44.92 | Dominated | 1.07 | Dominated | Dominated |

ESS : Estimated Symptom Score

**Table 5 :** Cost-effectiveness analysis.

| | Total Cost of Treatment (US$) | Percentage Decrease in ESS | Absolute Decrease in ESS | Cost of Per 1% Decrease in ESS (US$) | Cost of Per One Point Decrease in ESS (US$) |
|---|---|---|---|---|---|
| Fluorometholon | **38.94** | 48 | 0,93 | 0.81 | 41.87 |
| Ketotifen | 43.41 | 65 | 1.25 | 0.66 | 34.72 |
| Epinastine | 43.60 | 64 | 1.20 | 0,68 | 36.33 |
| Olopatadine | 44.05 | **68** | **1.29** | **0.64** | **34.14** |
| Emedastine | 44.92 | 56 | 1.07 | 0.80 | 41.99 |

ESS : Estimated Symptom Score

greatest decrease in percentage of ESS was established by olopatadine(68%) and followed by ketotifen (65%), epinastine (64%), emedastine (56%) and fluorometholon (48%), respectively. (Table 2).

Lowest treatment cost was established by fluorometholon (US$ 38.94) and followed by ketotifen (US$ 43.41),epinastine (US$ 43.60), olopatadine (US$ 44.05) and emedastine (US$ 44.92), respectively.

When the drugs compared for incremental cost-effectiveness, emedastine was dominated by ketotifen and emedastine dominated by olopatadine; ketofien could be compared with fluorometholon and olopatadine. Incremental cost of ketotifen for per one point reduction in ESS was US$ 13.9 compared with fluorometholon. Incremental cost of olopatadine for per one point reduction in ESS was US$ 16 compared with ketotifen. Olopatadine dominated emedastine and ketotifen dominated epinastine (Table 4).

Lowest cost for per one point reduction in ESS was established by olopatadine (US$ 34.14) and followed by ketotifen (US$ 34.72) , epinastine (US$ 36.33 TL), fluorometholon (US$ 41.87) and emedastine (US$ 41.99), respectively. Lowest cost for per 1% reduction in ESS was established by olopatadine ( US$ 0.64) and followed by ketotifen (US$ 0.66), epinastine (US$ 0.68), emedastine (US$ 0.80) and fluorometholon (US$ 0.81), respectively. Results of the study are similar with the published studies which are about seasonal allergic conjonctivitis in other countries.

Alexander and colleagues performed a randomized, crossover study, about ophthalmic solutions of nedocromil sodium 2% and olopatadine hydrochloride 0.1% for comparing the effectiveness and acceptability in 28 patients with perennial allergic conjunctivitis and previous olopatadine experience in 2 weeks. It was reported that both drugs significantly ($P < .01$) and comparably decreased erythema, conjunctival injection, and overall conjunctival signs from baseline. Comparable improvement also occurred in quality-of-life scores. Both physicians and patients judged nedocromil and olopatadine to be similarly effective in preventing signs and symptoms. Nedocromil sodium 2% is an effective treatment for perennial allergic conjunctivitis. Patients receiving olopatadine can be switched to nedocromil with no loss in efficacy or satisfaction, but with a reduction in cost (Alexander et al., 2000).

Pinto and colleagues perfomed a cost effectiveness study of emedastine versus levocabastine in the treatment of allergic conjunctivitis in 7 European countries. It was reported that in all European countries, the cost of failure was lower with emedastine. Emedastine was found to be economically dominant relative to levocabastine, i.e. more effective and less expensive, in Belgium, Germany, Portugal and Sweden; in France, The Netherlands and Norway the incremental cost was low (less than 1 euro per additional symptom-free day) (Pinto et al., 2001).

Lafuma and colleagues performed a systematic review about olopatadin. It was reported that olopatadin could save around 10 euros of relapse direct costs in a range of European settings. Pitt and colleagues administered an EQ-5D Health Questionnaire, the Rhinoconjunctivitis Quality of Life Questionnaire (RQLQ), the National Eye Institute (U.S.) Visual Functioning Questionnaire 25 (VFQ-25), and a specially developed Health Economic and Demographic Questionnaire in patients between 16 and 80 years of age. The inclusion criteria for cases were that participants: 1) experienced itchy, bloodshot and watering eyes at some time between February and August every year since 1999, and 2) considered it likely that this was in response to seasonal allergens. Controls were drawn from the same sources and were age- and sex-matched to cases. It was reported that the total of both the public health care and private out-of-pocket costs of SAC in the study population ranged on average between 64.61 British pounds for a pensioner to pound sterling 123.69 for a person with SAC in

paid employment. Medications that reduce this demand on health care systems and out-of-pocket expenses by patients could be of potential importance in reducing the overall economic and health burden of illness posed by SAC (Pitt et al., 2004).

Smith and colleagues performed an economic and quality of life impact study of seasonal allergic conjunctivitis in a Spanish setting. EQ-5D, VFQ-25, RQLQ and HEDQ instruments were used. It was reported that SAC causes a decrease in quality of life (Smith et al., 2005).

In the light of published data, it could be concluded that olopatadin was reported as a cost effective treatment in each of two different analyses when compared with other treatments, emedastin was cost effective in only one analysis. In addition, it was reported that SAC causes a decrease in quality of life in all published analysis.

There are some limitations of the analysis. ESS was calculated for each medicine because of calculating just one effectiveness datapoint for the pharmacoeconomical analysis. So if different pharmacoeconomic analysis could be performed with more specific symptom scores, more accurate results could be acquired. In our analysis, only the effectiveness of different treatments were compared in the incremental cost effectiveness analysis but quality of life was not included in the analysis. Because there are not any published quality of life data with SAC treatment for the Turkish population. If a quality life (QAL) analysis about SAC treatmnt would be published for the Turkish population, it is necessary for the analysis of the data of QAL to have more precise results.

In the sensivitiy analysis, if the price of olopatadine decreases 10%, olopatadin can dominate all other alternative treatments in an incremental cost effectiveness analysis in which fluoromethelon is not included. If the price of epinastine and emedastine decrease 10% and 15%, repectively, fluorometholon would be compared with epinastine, epinastine would be compared with emedastine, emedastine would be compared with ketotifen and ketotifen would be compared with olopatadine.

The cost-effectiveness analysis of SAC`s treatments had not been performed yet for Turkey as other cost of treatment in different diseases. In addition, only 2 or 3 different treatments were compared in most of published studies. So our study is unique for the literature because it compares 5 different treatments and is performed for Turkey. The incidence of SAC (5-22%) (Tomac 2004) lead to increase our study`s importance for the literature.

## CONCLUSION

According to the analysis, the lowest treatment cost was established by fluorometholon. Because included forms of fluorometholon`s price are approximately 55% lower than all SAC treatment alternatives. However fluoromethelon has the lowest treatment cost, cost of mean absolute decrease in symptom score of all alternatives except emedastine were lower than fluorometholon. If an incremental cost efectiveness analysis were performed without fluorometholon, ketotifen could be compared with olopatadine.

Our analysis is compatible with the published analyses. It was concluded that olopatadine has the highest mean absolute and percentage decrease in estimated symptom score. Because of these olopatadine has the lowest cost for one point or 1% decrease in estimated symptom score. Olopatadine was followed by ketotifen. This is similar in total sales too. Olopatadine had the highest total sales in last three years. It was followed by ketotifen also in sales. It could be said that Turkish physicians choose olopatadine according to other SAC treatment options. The analysis includes important results for the reimbursement agencies and organizations. The reimbursement includes foundation which in Turkey can promote olopatadine and ketotifen in the treatment of SAC in the light of these results. Further analysis is needed with new published effectiveness data or changes in costs or when newer products reach the market in the future.

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