Trend Analysis of Anti-Allergic Medicines During the 11-Year Period in Iran (2006-2017)

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Abstract- Up to 40% of the global and 7.4-41.3% of the Middle East population are affected by Allergic Rhinitis (AR). Patients with AR versus control group experience approximately twofold pharmaceutical expenditures and 1.8-fold number of visits. Since drug utilization can show various times of developing a disease in a country, it is used as an alternative for prevalence. In this study, we try to examine and explain the consumption of anti-allergic medicines during the past 11 years to have a perspective view of these kinds of medicines. In this descriptive and cross-sectional study that investigates anti-allergic medicines over a 11-year period (2006-2017), we used the Iranian pharmaceutical statistical datasheet published by the Iranian Ministry of Health. According to treatment guidelines of AR and WHO ATC code, we categorized anti-allergic medicines into five groups (antihistamines, Beta 2 agonists, Corticosteroids, Fixed-dose, and others), Then DIDs for these groups were calculated and analyzed. Based on our findings in this study, cetirizine, Loratadine, and Inhaled Salbutamol got the highest DID among all five groups, with 99.2, 65.4, and 57.6 retrospectively. Generally based on the third level of ATC code (second-generation anti-histamines, respiratory system drugs for obstructive airway disease, respiratory system nasal preparation, and corticosteroid for systemic use) are faced with ascending market sales. Generally, with the upward trend of anti-allergic medicines, we can conclude that the incidence of AR in Iran during the past 11 years has increased, and policymakers should follow this trend concerning a better supply chain.

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Keywords: Drug utilization; Trend analysis; Allergic rhinitis; Defined daily dose (DDD), The anatomical therapeutic chemical code (ATC code)

Introduction

Allergic Rhinitis or Hay fever is a nasal mucosal inflammatory disorder that is emerged in individuals by allergic immune responses related to immunoglobulin E (IgE) to allergens (1,2). Allergic Rhinitis (AR) is a heterogeneous disease that isn't diagnosed despite its high prevalence (3). This disease involves up to 40 % of people in the world, 23-30% in Europe, 12-30% in the US, and in other parts of the world, it varies from 2.9% to 54.1%. This amount in the Middle East and countries which are located in this region is 7.4-41.3% (1). A published meta-analysis in 2013 in Iran showed that the prevalence of AR in children aged 7-6 and 13-14 was 11.9% and 21.2%, respectively (4).

Those patients who got involved with AR vs. the control group experienced a twofold increase in medical expenditure and a 1.8-fold increase in the number of visits. Lack of treatment, low treatment, and lack of compliance with treatment leads to an increase in medicine expenditure (5).

Environmental control, medicine therapy, and allergen immunotherapy is used in the treatment of AR. In medicine therapy, antihistamines (oral and nasal), decongestants (oral and nasal), corticosteroids (oral and nasal), nasal cromolyns, nasal anticholinergics, and Locoterian receptor antagonist (LRA) are prescribed (6). In recent years, with the development of monoclonal

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antibodies like Omalizumab, a new way of treatment for AR has been opened, and physicians prescribe them for resistant AR or those which hasn't responded to other treatments (7,8).

Since studies showed that 38% of patients with AR have asthma, and up to 78% of asthmatic patients have AR (9), in this study, Beta2-agonists are also included.

Anti-histamines are the most consumed medicines for the prevention and treatment of allergic disorders with more than 70 years of history (9). In the first-generation group with high penetration in the brain, drowsiness, fatigue, and concentration and memory impairment, we have Chlorpheniramine, Clemastine, Cyproheptadine, Dimenhydrinate, and Hydroxyzine and in the second generation with the goal of reduction and elimination of drowsiness and anticholinergic side effects, we have Azelastine, Cetirizine, Fexofenadine, Ketotifen, and Loratadine in Iran (10).

Drug utilization studies are powerful instruments for identifying problematic areas in medicine consumption (11). Medicine consumption analysis can imply various incidence times of diseases in a country and can be used as an alternative for the prevalence of a disease (12).

The current study examines 11-year medicine consumption in Allergic Rhinitis and its effective reasons, to have a picture of the prospective trend in Anti-Rhinitis drugs and also allocating resources and budget to this area.

Materials and Methods

In this descriptive cross-sectional and retrospective study, which is done with the goal of scrutiny of medicine consumption trends in Allergic Rhinitis, statistical time-series data for 11 years from 2006 to 2017 are examined. Medicines for Allergic Rhinitis are selected based on the UpToDate 2018 treatment guideline (13) and ATC categorization according to the suggested method of WHO has been applied (14). Defined Daily Dose (DDD) for all selected medicines based on ATC which had been published in 2018 were extracted. In the next level, the annual consumption of these medicines from the Iranian pharmaceutical database from 2006 to 2017 were examined. This database is published every year by the Iranian Food and Drug Administration in the form of a sales report of distributor companies to pharmacies (15).

39 pharmaceutical molecules based on ATC code and 137 dosage forms were examined in this article and those that after calculation got DID equal zero, were deleted. In the next stage, according to the DID formula (DDD/1000 inhabitant/day) or amount of medicine per 1000 people per day (16,17), the number of consumption for each medicine related to patients were obtained and ultimately shown on the diagram. All statistical calculations were applied by Microsoft Excell 2016.

$$\text{DDD/1000 population/day} = \frac{\text{Amount used in 1 year (mg)}*1000}{\text{DDD(mg) x population x 365(days)}}$$

In this study, medicines which were prescribed in Allergic Rhinitis based on guideline were included, that's why the calculation of UD90% was not possible.

Results

Followed by what was undertaken in this 11-year study on Anti-Rhinitis medicines, we categorized them into five groups: Anti-histamines, Beta2-Agonists, Corticosteroids, Fixed-dose, and others. The highest number in the Anti-histamines group are related to Cetirizine 99.17, Loratadine 65.43 and Cyproheptadine 33.53, in Beta2-agonists, are related to inhaled Salbutamol Sulfate 57.55, Salmeterol 10.86 and Oral Salbutamol Sulfate 6.73, in Corticosteroids, are related to Nasal Fluticasone 25.01, Hydrocortisone 17.18 and nasal Beclomethasone 8.02, in Fixed-dose are related to Salmeterol/Fluticasone 25.75, Budesonide/Formetorol 4.63 and Ipratropium/Fenoterole 0.29 and in Others group are related to Montelukast 12.75, Ipratropium 8.81. In general, Cetirizine, Loratadine, and Inhalated Salbutamole Sulfate had the highest number in DID.

Among first-generation Anti-histamines in this study, Cyproheptadine, Diphenhydramine, Oxymetazoline had an upward trend, and other medicines in this category had a downward trend. On the other hand, in second-generation Anti-histamines, all medicines had an ascending trend. In the latter group, two medicines, Cetirizine/Pseudoephedrine from 2011 to 2014 and Levocetirizine from 2009 to 2014, were temporarily available in the market.

Among Beta2-Agonist, inhaled Salbutamol and inhaled formoterol had an upward trend, and oral Salbutamol and inhaled Salmeterol experienced a descending trend.

In the Corticosteroids group, all of them except inhaled Beclomethasone showed ascending growth in consumption.

Within all five medicines in the Fixed-dose group, which were considered, an increasing trend has been observed, and only Salbutamol/Beclomethasone presented in the market permanently between 2008 to 2013.

In a group named "others," 2 types of medicines were considered: Anticholinergic (Ipratropium and

Tiotropium) and Montelukast, that all of them had an upward trend.

As it was shown in Diagram 1, among those medicines which are administered in Allergic Rhinitis in third level ATC, Respiratory system antihistamine for systemic use, Respiratory system drugs for obstructive airway disease, and Respiratory system nasal preparation have the highest Overall DID during 11 years.

Diagram 2 implies that as of 1st generation of Anti-histamines experience a descending trend, the 2nd generation has overtaken the market.

Finally, with overall consideration of trend analysis of Anti Allergic medicine consumption based on third level ATC code and diagram 3, Respiratory system antihistamine for systemic use, Respiratory system drugs for obstructive airway disease, Respiratory system nasal preparation and corticosteroid for systemic use, all have ascending trends.

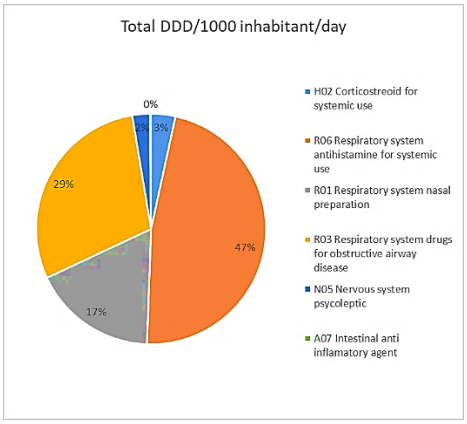

Diagram 1. Overall DID (DDD/1000 inhabitants/day) for Anti-allergic medicines based on ATC group 2006-2017

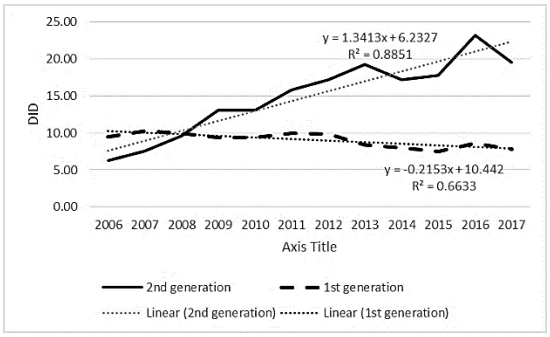

Diagram 2. The comparable trend for 1st and 2nd generation Anti-histamine 2006-2017

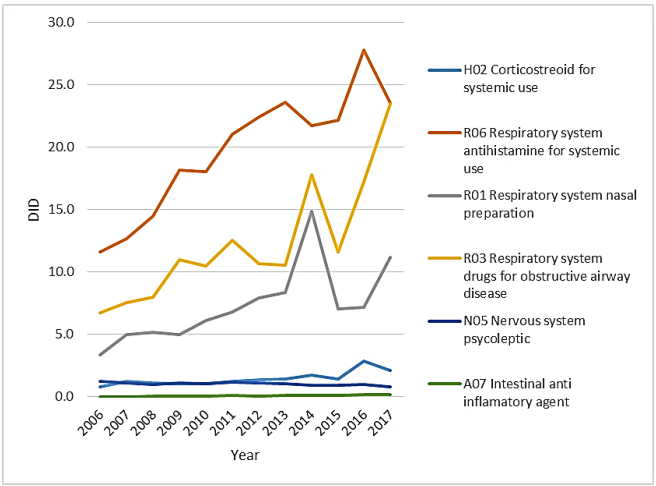

Diagram 3. the trend of anti-allergic medicine consumption based on ATC group, 2006-2017

Discussion

In the following study, the highest overall DID during 11 years belongs to systemic Anti-histamines, Beta2-Agonists, and systemic Corticosteroids. A probable reason for this event is related to treatment guideline priorities, which prefer to use local products and systemic Anti-histamines and prescribe systemic Corticosteroids for the second line (6). What is implied from the three highest DID, is that in a hypothetic population consists of 1000 people, 9.9%, 6.5%, and 5.7% use Cetirizine, Loratadine, and inhaled Salbutamol respectively per day in a year (14,18).

Many studies proved that Anti-histamines are mostly used in the treatment of AR, and amid them, the new generation, due to more safety and efficacy and lower interaction with other medicines, has gradually overtaken the first generation (19-23). The increasing trend of second-generation Anti-histamine coincides with the decreasing trend of first-generation Anti-histamine, which is shown in diagram 2 with a comparable view of these medicines for AR treatment from 2006 to 2017. Among these medicines, Cetirizine and Loratadine have the highest number of consumption rather than others. Some considerations such as lower price (24), long time presence in the market, being in the new generation Anti-histamines category with more efficacy and lower side effects ad drug interaction can be notable reasons for this ascending growth in consumption. It also can be said that these medicines are prescribed in other diseases besides AR (25) which should be deemed as an extra reason.

On the one hand, Inhalated Salbutamol is known as the cheapest Beta2-agonist against others and on the other hand it is used in the treatment of many respiratory diseases (25), so as a result, inhalated Salbutamol has become the third most utilized medicine in this study. There is evidence for more efficacy of Fixed-dose preparations rather than Beta2-agonists that hasn't seen in this work (26,27).

Leukotriene Receptor Antagonist medicines regarding efficacy and safety in Allergic Rhinitis treatment act like Histamine antagonists, the difference is that selective histamine antagonists are appropriate for daily nasal symptoms like congestion, nose running, itching and sneeze and Leukotriene receptor antagonist are good for nightly symptoms like difficulty in falling asleep, night awakening, nasal congestion in awakening time. This issue besides the low price of this medicine (24) proves the ration of the ascending trend of Montelukast consumption which is like other new generation anti-histamines (28-30). Montelukast is the representative of Leukotriene Receptor Antagonists in this study, can be utilized as the first line in Allergic Rhinitis with extended improvement effect in nasal and ophthalmic symptoms and also cause the high quality of life in patients. A combination of Montelukast and Loratadine significantly improves daily and nightly symptoms of patients rather than Montelukast alone (31). In this study, the consumption amount of Montelukast for 11 years has been almost threefold, which approves the result of another independent study (30).

Although fexofenadine is effective in Allergic Rhinitis (32), this medicine hasn't been successful considering the high consumption of Anti-histamines yet. One of the possible reasons can be its late attendance at the market in 2008 and also higher prices in comparison with other medicines in this category (24).

In a cohort of 12367 patients, it was showed that the most indication of levocetirizine is for Allergic Rhinitis, and it is well tolerated by patients (22,33). But it seems that this medicine was not successful in finding a good position in the Iranian market, which experienced a peak immediately after its entrance to the market and left the market early. It is thought that its higher price (24), lower efficacy (34), similar adverse effect to other second-generation Anti-histamines (35), and weak marketing are obstacles for the maintenance and presence of this medicine.

Most studies have shown that 99% of British specialists prescribe nasal steroids for treatment of Allergic Rhinitis and their efficacy and cost-effectiveness as the first line is higher than first-generation Anti-histamines and Leukotriene Receptor Antagonists (11, 30,36-39); the same result has been shown in this work because nasal Fluticasone has the highest amount of consumption among corticosteroids.

Since it is implied from diagram 3, based on ATC in the third level, systemic corticosteroids, systemic Anti-histamines, nasal preparations, and Obstructive airway disease medicines all have ascending trend, and this issue claim growth of Anti Allergic medicines regarding the number of patients, prevalence and production upward.

We should say that in 2014 and 2016, the market experienced peaks which can be explained by fluctuated supply as the main reason and some other factors like currency rate, sanction, domestic production and import that could be complied with this matter because, despite this peak, the market finally continue its trend with decreasing its consumption in the next year and using inventory stock.

Noticing the point that drug utilization studies are a strong instrument for determining the problematic points in medicine consumption (11) and the aim of ATC/DDD system is introducing an instrument to examine drug utilization and researches to increasing quality of medicine consumption (14), it can be said that drug utilization analysis implies different times of incidence of a disease in a country and is used as an alternative for prevalence (12). Ultimately information presented by drug utilization gives us an estimated consumption, and it should be deemed that DDD supplies fixed unit measurement besides price, currency, packaging size, and strength, and it gives the researcher the possibility of assessing the trend of medicine consumption for comparison between population (16).

This article has some limitations like sales number to pharmacies, statistical errors of companies in reporting which didn't have a significant effect on the result of this work.

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