

The Frequency of Influenza-Like Illness in Patients with Allergic Asthma on Immunotherapy

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Abstract

Viral infections augment immediate and late allergic responses in the lungs of patients with allergic asthma. Certain viruses that typically exacerbate asthma have been noted to induce release of the cytokine interleukin-11 (IL-11) which is associated with airway hyperreactivity (AHR).

The aim of study: To determine the frequency of influenza-like illness in patients with allergic asthma on immunotherapy compared to the patients with allergic asthma receiving only antiasthmatic pharmacotherapy during the period of 1-year follow up.

Methods: In our study, we included 60 patients with allergic asthma, both genders who were subsequently divided into two treatment groups. Study group included 30 patients who received immunotherapy (immunotherapy group) and control group included 30 patients treated with standard pharmacotherapy, but not with immunotherapy (GINA proposal).

Results: There was a significant difference in influenza-like illness (ILI) between immunotherapy and control group of patients. A significantly higher percentages of patients in control group experienced cold and/or flu syndrome compared to immunotherapy group, which was observed at the 2nd, 3rd and 4th trimester ($X^2= 20.480$ $p=0.0001$). During the first trimester there was no difference in the number of patients with the cold/flu symptoms between the immunotherapy and control group. During the 2nd trimester, there was a significant decrease in the number of patients with cold/flu symptoms 3/30 (10%) in the immunotherapy group, while in the control group there was significantly higher number of patients with the cold/flu symptoms (11/30 (36 %)). In the 3rd and 4th trimester the frequency of patients with cold/flu symptoms was unchanged compared to the 2nd trimester in the immunotherapy group, while in the control group the frequency of patients with cold/flu symptoms increased from 20/30 (66%) at the 3rd to 27/30 (90%) in the 4th trimester. The number of patients reported to the physician due to bronchial hyperreactivity was dependent on the immunotherapy treatment ($p=0.0001$).

Conclusions: The frequency of influenza-like illness occurrence was significantly lower in patients treated with immunotherapy during one year of follow-up compared to the patients treated with antiasthmatic pharmacotherapy. The percentage of patients with influenza-like illness was 10% in the patients treated with immunotherapy at third and fourth trimester of the follow-up, whilst in patients on antiasthmatic pharmacotherapy, the percentage of patients with influenza-like illness increased from 66% in the third to 90% in the fourth trimester.

Abbreviations: IgE: Immunoglobulin E; AHR: Airway Hyperreactivity; IL: Interleukin; RSV: Respiratory Syncytial Virus; GINA: Global Initiative for Asthma; SCIT: Subcutaneous Immunotherapy; FEV: Forced Expiratory Volume; ILI: Influenza-like Illness

Introduction

Viral infections are a common trigger for asthma, particularly in the young and the elderly, and may initiate the development of asthma. Some children with asthma show evidence of typical asthmatic inflammation following viral infections in infancy, and they develop antiviral IgE during these infections. Children hospitalized with bronchiolitis have a higher incidence of asthma later in childhood; this association probably reflects a genetic predisposition to asthma. Viral infections augment immediate and late allergic responses in the lungs of patients with allergic asthma. Certain viruses that typically exacerbate asthma have been noted to induce release of the cytokine interleukin-11 (IL-11) which is associated with airway hyperreactivity (AHR) (Figure 1).

During infancy, a number of viruses have been associated with the inception of the asthmatic phenotype. Respiratory syncytial

virus (RSV) and Para influenza virus produce a pattern of symptoms including bronchiolitis that parallel many features of childhood asthma [1,2]. A number of long-term prospective studies of children admitted to the hospital with documented RSV have shown that approximately 40% of the patients will continue to wheeze or have asthma into later childhood [2].

On the other hand, evidence also indicates that certain respiratory infections early in life, including measles and sometimes even RSV, may protect against the development of asthma [3]. The data do not

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allow for specific conclusions to be drawn. Parasite infections do not in general protect against asthma, but infection with hookworm may reduce the risk.

The “hygiene hypothesis” of asthma suggests that exposure to infections early in life influences the development of a child immune system along a “nonallergic” pathway, leading to a reduced risk of asthma and other allergic diseases. Although the hygiene hypothesis continues to be investigated, this mechanism may explain observed associations between family size, birth order, day-care attendance, and the risk of asthma. For example, young children with older siblings and those who attend day care at increased risk of infections enjoy protection against the development of allergic diseases, including asthma later in life [2].

The interaction between atopy and viral infections appears to be a complex relationship in which the atopic state can influence the lower airway response to viral infection. Viral infections can then influence the development of allergic sensitization, and their interactions can occur when individuals are exposed simultaneously to both allergens and viruses. A number of mechanisms have been identified to explain how viral respiratory infections enhance airway responsiveness and provoke an attack of asthma. Firstly, all respiratory tract viruses enter and replicate within airway epithelial cells and can damage both ciliated and non-ciliated respiratory epithelial cells, leading to necrosis of the airway epithelium, ciliostasis, loss of cilia and impairment of mucociliary clearance [4]. However, it is likely that the clinical manifestations might be secondary to the release of proinflammatory mediators by damaged bronchial epithelial cells (BECs), as well as a direct cytotoxic effect of the virus. Secondly, mucociliary clearance is a critical innate defence system, and mucus overproduction is one of the major symptoms of asthma exacerbations, significantly contributing to the morbidity and mortality of asthmatic subjects.

Following infection a wide range of mediators are secreted including pro-inflammatory cytokines, chemokines, interferons, and growth factors. This leads to eosinophilic, neutrophilic, and lymphocytic inflammation, as well as mucus hyper secretion and likely airway remodelling. CCL, CC chemokine ligand; CCL5, RANTES (Regulated on Activation Normal T-cell Expressed and Secreted); CCL11, eotaxin; CCL24, eotaxin-2; CXCL, CXC chemokine ligand; CXCL 1, GRO-a (growth-related oncogene a); CXCL-5, ENA-78 (epithelial neutrophil activating protein-78); CXCL10, IP-10 (IFN- γ -inducible protein 10); DC, dendritic cell; FGF-2, fibroblast growth factor-2; GM-CSF, granulocyte macrophage-colony stimulating factor; ICAM-1, intercellular adhesion molecule-1; IFN, interferon; IL, interleukin; LDLR, low-density lipoprotein receptor; RV, rhinovirus; T1, cytotoxicCD81T lymphocyte type 1; TH1, T-helper1 CD41 T lymphocyte; TNF-a, tumour necrosis factor-a; VEGF, vascular endothelial growth factor [4].

The mucus that occludes the lumen in an asthma exacerbation is quite a complex biological material comprising a mixture of mucins MUC 5AC and MUC 5B, plasma proteins, and products of cell death. Also, a variety of proinflammatory cytokines, chemokines and proallergic cytokines are upregulated during the acute exacerbation of asthma. Macrophages produce inflammatory cytokines to recruit cells of the adaptive immune system, express a number of innate pattern-recognition receptors (PRRs) and play a key role in phagocytosis of bacterial organisms. Increased neutrophil counts and levels of IL-8, a potent chemoattractant for neutrophils, are found in the nasal secretions, sputum, and BAL fluid of allergic subjects undergoing experimental rhinovirus infection. Products of neutrophil activation could also cause airway obstruction through the production of elastase

which upregulates goblet cell mucus secretion [5]. Viral infection can also trigger increased recruitment and activation of eosinophils in the airway. Eosinophilic infiltrate is more prolonged and still present 6-8 weeks after infection [4].

Inhaled corticosteroids should give in combination with long acting β agonists (salmeterol and fluticasone) or (budesonide and formoterol). Macrolides have also immunomodulatory effects by reducing the expression of ICAM-1, IL6, and IL8. Azithromycin reduced rhinovirus replication, and in infants with RSV-induced bronchiolitis, clarithromycin reduced systemic inflammation acutely, which led to fewer wheezing episodes in the following 6 months [1,2,4].

The aim of the present study is to determine the frequency of influenza-like illness in patients with allergic asthma on immunotherapy compared to the patients with allergic asthma receiving only antiasthmatic pharmacotherapy during the period of 1-year follow up.

Materials and Methods

Our study was a comparative clinical study performed at the University Clinical Hospital in Prishtina in cooperation with the specialized Allergology Center Ylli in Pristina (Kosovo). We included 60 patients with allergic asthma, both genders who were subsequently divided into two treatment groups. Study group included 30 patients who received immunotherapy (immunotherapy group) and control group included 30 patients treated with standard pharmacotherapy, but not with immunotherapy (GINA proposal). Each patient in the immunotherapy group was treated with subcutaneous specific immunotherapy (SCIT) Novo Helisen Depot, Allergopharma Joachim Ganzer, Germany.

The criteria for the inclusion of the patients were: clinical diagnosis of allergic asthma, age between 15 and 30 years, both sexes. The criteria for the exclusion of the patients were the presence of other acute and chronic diseases of respiratory airways, presence of other allergic diseases (skin allergies, nutritive allergies etc.), and presence of acute and chronic diseases of other organic systems.

Diagnosis of bronchial asthma was established based on clinical history of recurrent wheezing, breathlessness, or cough (GINA) associated with significant reversibility of FEV1 (>15% from baseline) after inhalation of 400 μ g salbutamol when baseline was <80% predicted in addition to positive skin tests and increased serum level of IgE. Diagnosis of influenza-like illness was established based on the following clinical criteria: fever up to 102 degrees Fahrenheit, runny or stuffy nose, sore throat, cough, sneezing, fatigue, muscle aches, headache and watery eyes. Considerations for initiating immunotherapy included the presence of IgE mediated disease proven to benefit from immunotherapy, stable allergic asthma, documentation of sensitivity to allergens associated with symptoms, and symptoms of sufficient duration and severity:

- a. Two seasons of seasonal symptoms despite avoidance measures and pharmacologic therapy
- b. Perennial symptoms failing trials of avoidance measures and chronic pharmacologic therapy

Relative contraindications to Immunotherapy were beta 2 blocker treatment, pregnancy, hypersensitivity conditions not exclusively depended on IgE mechanisms, immune complex and autoimmune disease, immunodeficiency, unstable asthma.

Sensitivity to certain allergens was determined by skin prick tests

(SPTs). By “Practical guide to skin prick tests in allergy to aeroallergens: the wheal and erythema have been used to assess the positivity of the skin test. However, only the wheal is needed. The largest size of the wheal is considered to be sufficient. Wheal diameters ≥ 3 mm are considered positive in SPTs. It is considered that small wheals fewer than 3 mm of diameters are not significant in clinical studies whereas they are considered to be positive in epidemiologic studies [6]. In our study, we used Test Kit G, Allergopharma Joachim Ganzer, and Germany.

Statistical design

In order to perform a statistical analysis on the results of our study, we used a SPSS for Windows statistical program (version 19.0, SPSS Inc, Chicago, Illinois, USA) and Microsoft Excel (version 11, Microsoft Corporation, Redmond, WA, USA). For the analysis of nominal and ordinal variables, we used χ^2 test. In the case the expected frequencies were absent, we used Fisher’s exact test (for tables of contingency). We used a Shapiro Wilk test to analyze the symmetry of the distribution of continuous variables. When the distribution of the continuous variables was asymmetric in order to show their mean values and to measure the dispersion, we used a median and interquartile range; for comparison, we used non parametric tests (Mann-Whitney U test, Wilcoxon Test). For analysing connections and directions of the connections between variables, we used correlation tests, depending on the type of variables (Spearman, Pearson). The McNemar test was used in repeated analysis of the variables with two different outcomes (binary variables).

For the statistical significance of the results, we used a value of $\alpha=0.05$. The p value of the statistical test is used for accepting or rejection of the hypothesis ($p \geq \alpha$: hypothesis is accepted; $p < \alpha$: hypothesis is rejected). All results would be elaborated, documented and presented in absolute and relative numbers and with statistical results by using statistical markers.

Results

In the experimental (immunotherapy) group, there were 11 (36.7%) females and 19 (63.3%) males, while in the control group 17 (56.7%) were females and 13 (63.3%) were males (Graph 1).

There was no significant difference in the gender distribution between the study and control group of patients ($\chi^2=2.41$, $p=0.121$) (Graph 1)

In the immunotherapy group there were 25(83.5%) patients from urban areas and only 5 (16.7%) patients from rural areas. In the control group, patients coming from rural and urban areas were represented equally (15(50%)) (Graph 2).

There was a significant difference in the distribution of the patients according to the living areas ($\chi^2=7.5$ $p=0.006$). We observed a significantly higher prevalence of patients from urban areas in the total study sample.

In the experimental (immunotherapy) group, there were 8 (26.7%) patients with elementary, 12 (40%) patients with secondary and 10 (33.3%) patients with higher education. In the control group 15 (50%) had elementary, 10 (33.3%) patients had secondary and 5 (16.7%) patients had higher education (Graph 3).

The level of education was weakly associated with a commitment to immunotherapy as a choice for the allergy treatment ($\rho=0.255$ $p=0.049$).

In the immunotherapy group, 18 (60%) patients reported intermediate and 12 (40%) patients reported high socioeconomic status. In the control group all three levels of socioeconomic status were reported; 12(40%) reported low, 11(36.7%) intermediate and 7 (23.3%) reported high socioeconomic status (Graph 4 and 5).

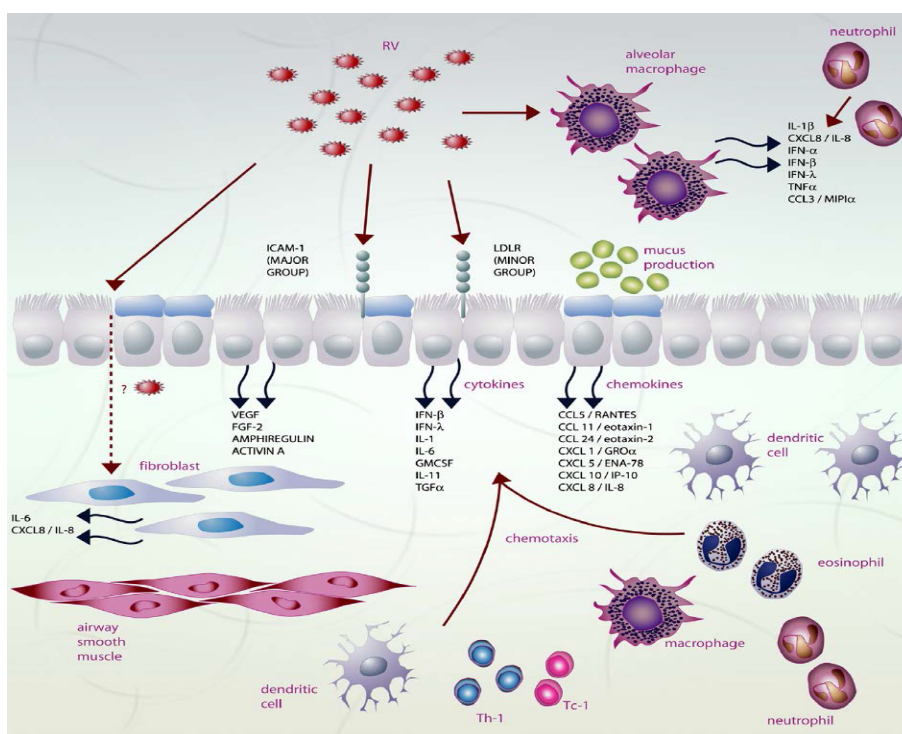
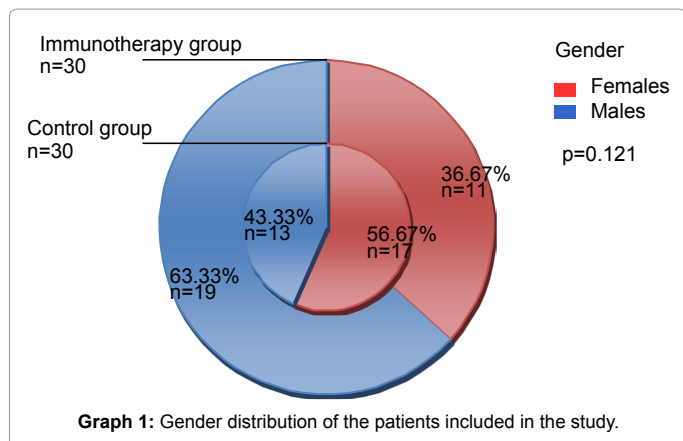
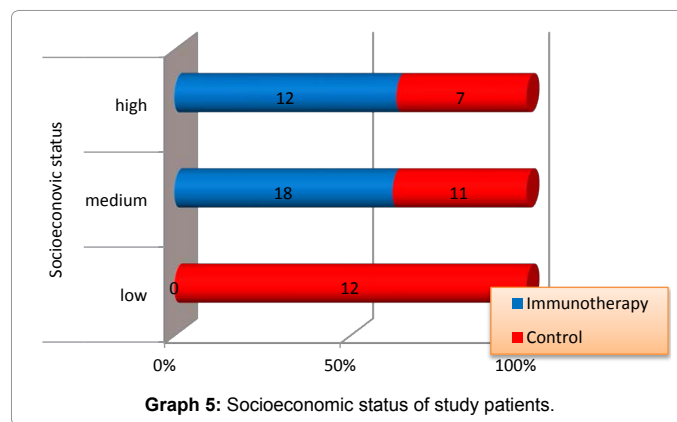
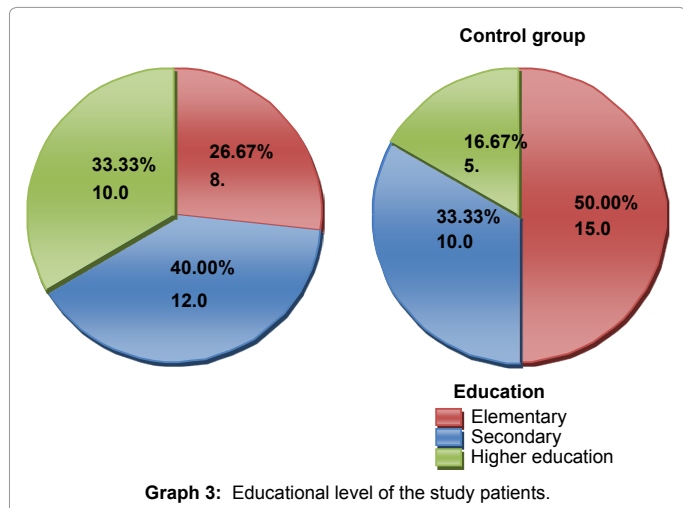
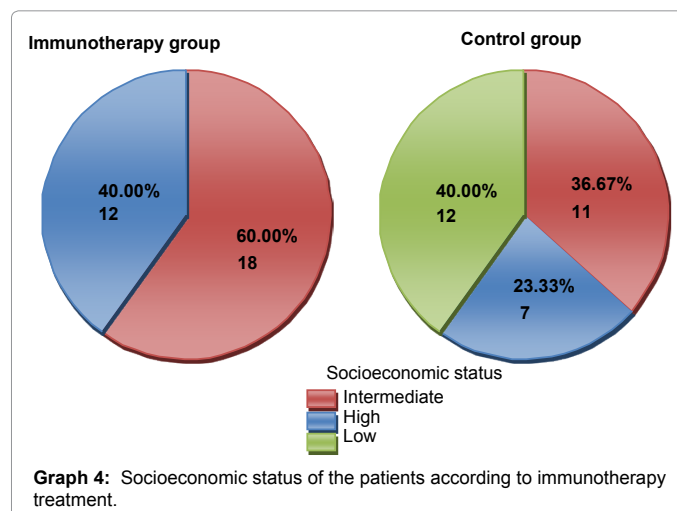
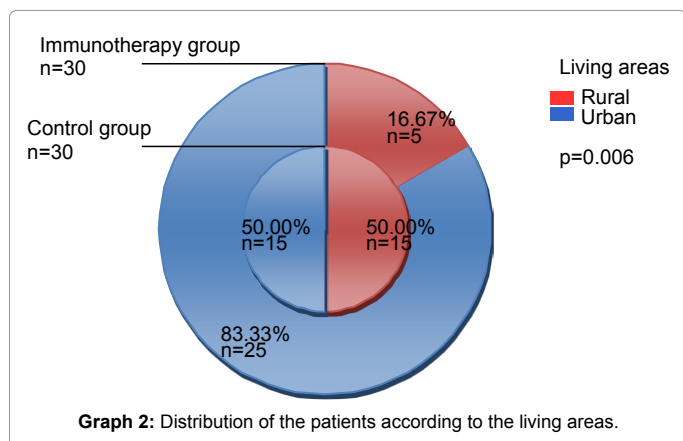


Figure 1: Epithelial and immune cell responses to rhinovirus infection. Taken from: The role of viruses in acute exacerbation of asthma [4].



The mono- or polysensitization was weakly associated with the immunotherapy as a choice for the allergy treatment ($\rho=0.408$, $p=0.001$).

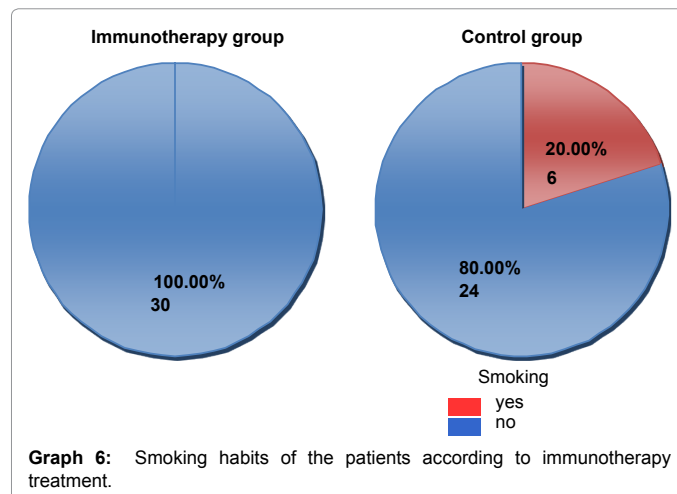
The median age of the patients in control group was 32.0 (27.0-46.2) years. The youngest patient was 17 and oldest 52 years. The median age of the patients in immunotherapy group was 31.5 (25.0-41.5) years. The youngest was 15 and oldest was 53 years old (Table 1).

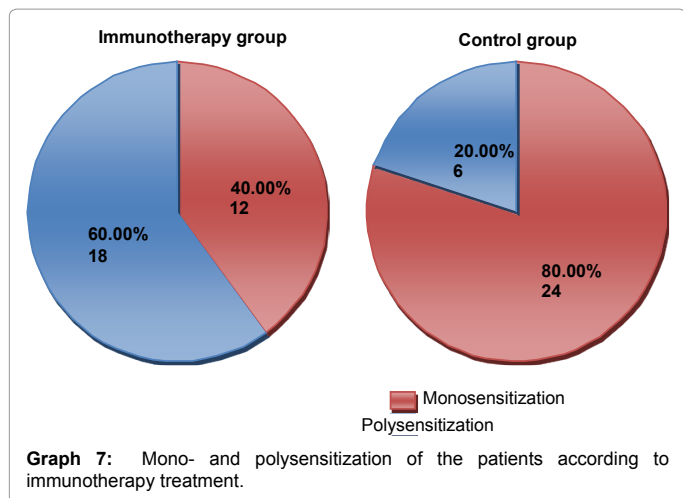


Socioeconomic status was weakly associated with the immunotherapy as a choice for the allergy treatment in our study ($\rho=0.370$, $p=0.004$).

In immunotherapy group there were no patients with smoking habits, while in the control group 6 (20%) patients were smoking (Graph 6).

In experimental (immunotherapy) group, 18 (60%) patients were poly-sensitized and 12(40%) were mono-sensitized patients. In control group 24 (80%) of patients were mono-sensitized and 6 (20%) were poly-sensitized patients (Graph 7).

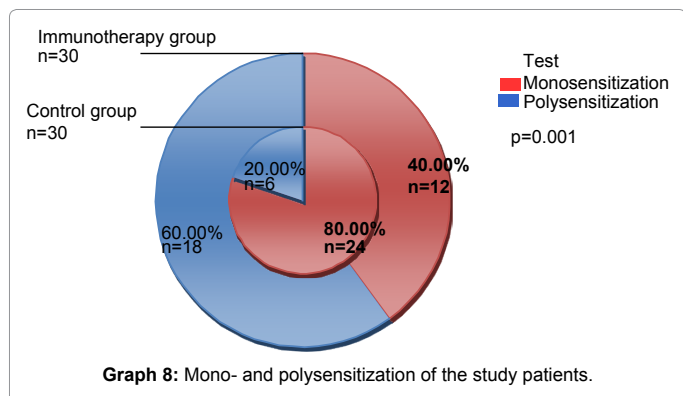




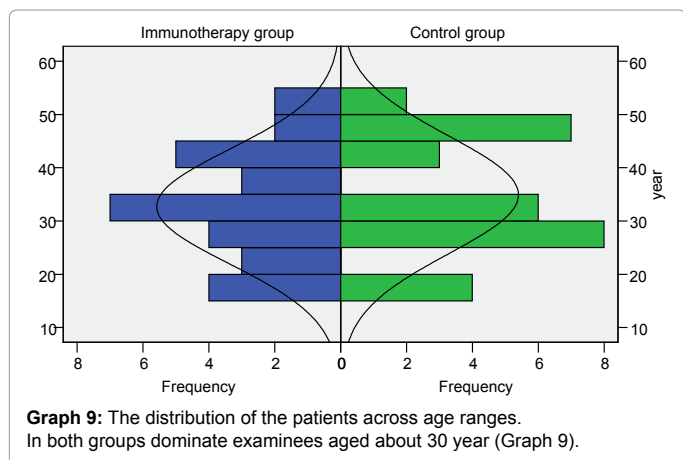
Graph 7: Mono- and polysensitization of the patients according to immunotherapy treatment.

	N	Percentiles				
		Minimum	Maximum	25 th	50 th (Median)	75 th
Control group	30	17.00	52.00	27.00	32.00	46.25
Immunotherapy group	30	15.00	53.00	25.00	31.50	41.50

Table 1: Age of the patients in immunotherapy and control group.



Graph 8: Mono- and polysensitization of the study patients.



Graph 9: The distribution of the patients across age ranges. In both groups dominate examinees aged about 30 year (Graph 9).

In both groups dominate examinees aged about 30 year (Graph 8 and 9).

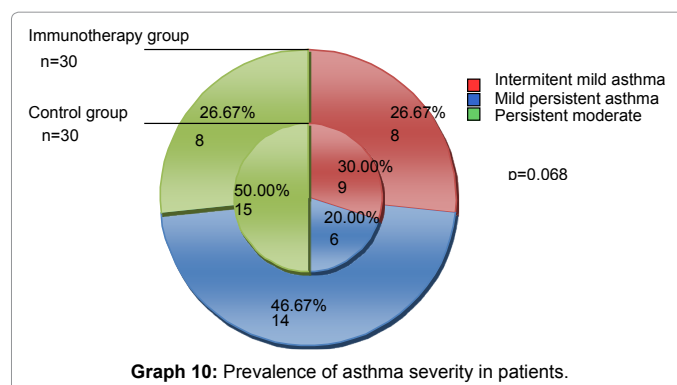
The prevalence of intermittent mild asthma, mild persistent asthma and persistent moderate asthma was not significantly different in the

immunotherapy group of patients compared to control group ($\chi^2=5.515$ $p=0.068$) (Graph 10).

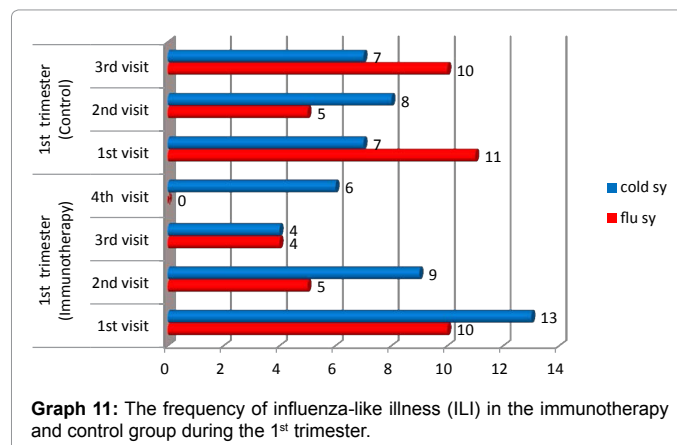
The frequency of influenza-like illness during the 1st trimester was not significantly different in patients on immunotherapy compared to control group of patients during 1st trimester ($p=0.4$) (Graph 11).

During the second trimester there were no patients on immunotherapy with symptoms of cold. The differences in the frequency of cold and/or flu during 2nd trimester were not significantly different in the group of patients on immunotherapy compared to control group of patients ($p=0.22$) (Graph 12).

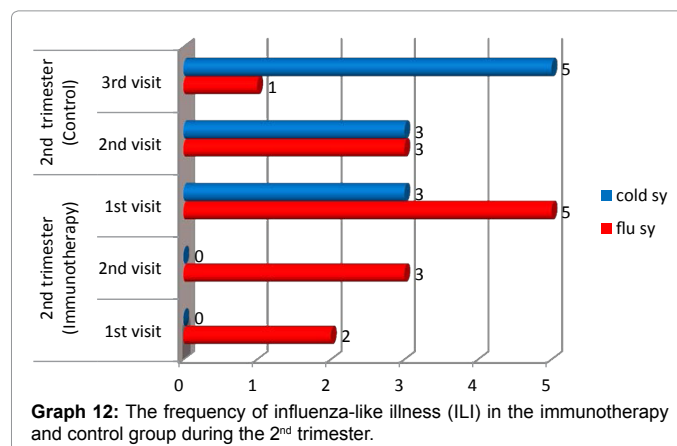
In the group of patients on immunotherapy the occurrence of cold and/or flu syndrome was low; 3 or less case at each visit during



Graph 10: Prevalence of asthma severity in patients.



Graph 11: The frequency of influenza-like illness (ILI) in the immunotherapy and control group during the 1st trimester.



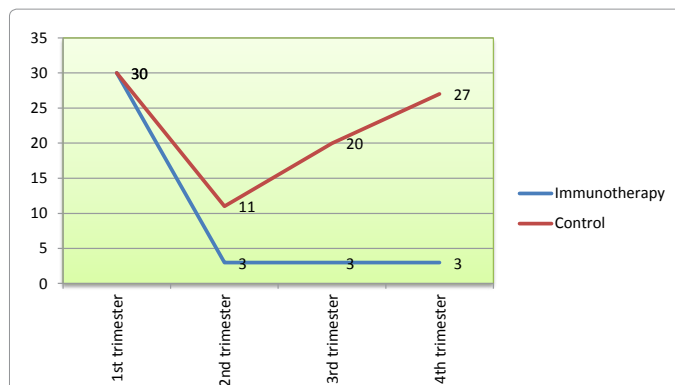
Graph 12: The frequency of influenza-like illness (ILI) in the immunotherapy and control group during the 2nd trimester.

the 3rd trimester. There was one patient with cold symptoms. The differences in the cold and/or flu occurrence during 3rd trimester were not significantly different in the group of patients on immunotherapy compared to control group of patients (p=0.09) (Graph 13).

In the group of patients on immunotherapy the frequency of cold and/or flu syndrome was low; 2 or less case at each visit during the 4th trimester. There was one patient with cold symptoms. The differences in the cold and/or flu syndrome frequencies during 4th trimester were not significantly different in the group of patients on immunotherapy compared to control group of patients (p=0.74) (Graph 14).

There was a significant difference in influenza-like illness (ILI) between immunotherapy and control group of patients. A significantly higher percentages of patients in control group experienced cold and/or flu syndrome compared to immunotherapy group, which was observed at the 2nd, 3rd and 4th trimester ($X^2 = 20.480$ p=0.0001).

During the first trimester there was no difference in the number of patients with the cold/flu symptoms between the immunotherapy and control group. During the 2nd trimester, there was a significant decrease in the number of patients with cold/flu symptoms 3/30 (10%) in the immunotherapy group, while in the control group there was significantly higher number of patients with the cold/flu symptoms (11/30 (36 %)). In the 3rd and 4th trimester the frequency of patients with cold/flu symptoms was unchanged compared to the 2nd trimester in the immunotherapy group, while in the control group the frequency of patients with cold/flu symptoms increased from 20/30 (66%) at the 3rd to 27/30 (90%) in the 4th trimester. The number of patients reported



Graph 15: The frequencies of influenza-like illness (ILI) during 1-year follow-up in immunotherapy and control group of patients.

to the physician due to bronchial hyperreactivity was dependent on the immunotherapy treatment (p=0.0001) (Graph 15).

Discussion

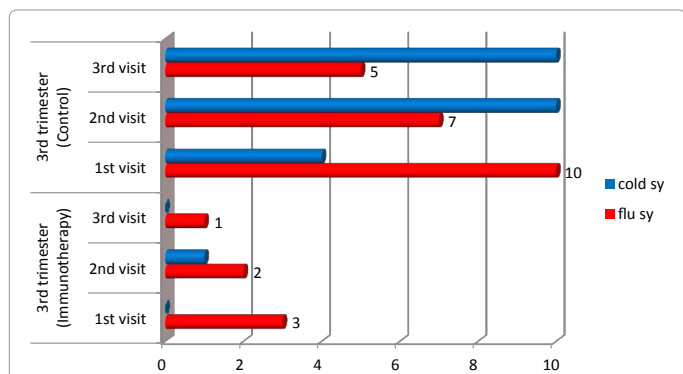
According to the data from “Global Atlas of Asthma” (2014, EAACI) [7], the prevalence of asthma varies across different countries and depends on research methodology. According to the ECHRS (European Community Respiratory Health Survey) wheezing is defined as: “Have you had wheezing or whistling in your chest at any time in the last 12 months?” The diagnosis of asthma is defined as “Age and sex standardized prevalence of positive response to at least one the following: 1) an asthma attack in the last 12 months; 2) currently taking medication for the treatment of asthma”.

The prevalence of asthma varies from 2.0 (Estonia), 4.1 (Bombay, India), 11.9 (Australia) to 32.0 (Dublin, Ireland) in 20-44 years old adults. GALEN (Global Allergy and Asthma Network of Excellence), a study which included 15 European countries with the age range of the participants 15-74 years (2008-2009), has reported asthma prevalence from 5.1 (Macedonia) to 16.8 (Portugal).

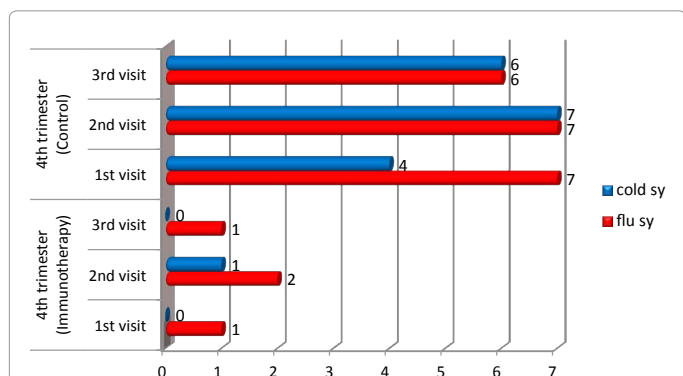
We included 60 adults with asthma in our study; 30 patients were treated with specific immunotherapy (Novo Helisen Depot, Allergopharma, Germany) (Immunotherapy group), while 30 patients were administered solely antiasthmatic pharmacotherapy according to the GINA guidelines but not immunotherapy (Control group). The mean age of the control group of patients was 32 years. The youngest patient was 17 and oldest was 52 years of age. In the immunotherapy group mean age of the patients was 31.5 years; youngest was 15 and oldest was 53 years old (Table 1). The age range of the patients included in our study was similar to the age of the patients included in a study by Corrigan et al. (18-58, and 18-59 years) [8].

A study by Reinhold et al. [9] included patients treated with subcutaneous immunotherapy (SIC) who were far younger compared to patients included in our study, with the mean age of 10.0 ± 3.1 years, while in a study by Jacobsen L et al [10], patients were from 16 to 25 years old. Currently, generally the accepted standpoint is that the administration of subcutaneous immunotherapy is recommended for any patient older than 5 years. This study included 11 (36.7%) females and 19 (63.3%) males. In the control group 17 (56.7%) were females and 13 (43.3%) were males. There was no significant difference in gender distribution of the patients between immunotherapy and control group ($\chi^2 = 2.41$ p=0.121) (Graph 1).

Majority of the patients in the immunotherapy group were from



Graph 13: The frequency of influenza-like illness (ILI) in the immunotherapy and control group during the 3rd trimester.



Graph 14: The frequency of influenza-like illness (ILI) in the immunotherapy and control group during the 4th trimester.

urban areas (25 (83.3%)), while in the control group equal proportion of the patients were from urban and rural areas (15 (50%)). There was a significant difference in the distribution of the patients according to the living areas ($\chi^2=7.5$ $p=0.006$) (Graph 2).

The higher prevalence of urban population in the immunotherapy group can be explained by the fact that administration of SCI requires adherence to the specific scheme schedule, which probably is not convenient for the rural population (Novo Helisen Depot, Allergopharma Joachim Ganzer). Educational level of the patients in the immunotherapy group was significantly higher in the immunotherapy group (33.3% with higher education, 40% with secondary and 26.7% with elementary education) compared to the control group (Graph 3). Educational level of the patients directly contributes to the understanding of SCIs mechanism of action and therefore contributes to better cooperation and adherence to the SCI treatment. Patient's awareness of the SCI treatment importance is not a problem only in our country, but has been reported in other far more developed countries. It has been reported that only 16.5% of the patients in Germany is currently taking appropriate allergen immunotherapy[11].

In the immunotherapy group, the socioeconomic status of the patients was reported as intermediate and high by 60% and 40% of the patients respectively, while in the control group all three degrees of socioeconomic status were reported 40% low, 36.7% intermediate and 23.3% high socioeconomic status (Graph 4). Our study results show that socioeconomic status of the patients was not associated with immunotherapy preference choice for the asthma treatment. This can be explained by the fact that medical institutions on Kosovo and the Health Ministry of Kosovo have not, in their programs, introduced patient's education of the specific immunotherapy and its benefits for the patient.

It has been reported by "European Declaration on Immunotherapy" (2013) [12], that the total cost of asthma treatment in Europe is 17.7 billion; 0.5 billion inpatient care, 3.6 billion direct (medication cost), 9.8 billion productivity losses and 3.8 billion outpatient care. In support of benefits which SIT offers, the results of the study by Peterson et al. show that the direct cost per patient/year before SIT (equivalent to standard care) was DKK 2.580. The investment in SIT was DKK 27.545 (in present values) per patient over a 4-year period. After SIT, the cost was reduced to DKK 1.072 per patient/year. In the long term, prospective introduction of SIT incurred additional present-value direct costs of DKK 13.676 per patient treated and DKK 2.784 per patient/year of improved well-being. However, when indirect costs were included in the economic evaluation, SIT was shown to be net beneficial.

In the immunotherapy group, there were no active smokers while in the control group there were 6 (20%) smokers and 24 (80%) non-smokers (Graph 6). The reason for such findings is the fact that tobacco smoke contains several different harmful ingredients including hydroxylated polycyclic aromatic hydrocarbons, carbon monoxide, carbon dioxide, nitric oxide, nicotine, acrolein, etc. [13-15] which are internal irritants and highly prohibited to patients on SCI. Therefore, there were no active smokers in the immunotherapy group.

A WAO-ARIA-GALEN consensus document on molecular-based allergy diagnostics [16] describes mono-sensitization as sensitization to one allergen source (*Dermatophagoide pteronissinus*) or to a closely related taxonomical family or group of allergen sources (i.e. mites). Poly (or multi-) sensitization is sensitization to three or more allergen sources (e.g. mite, birch, grass pollen). In the immunotherapy group of patients, there were more patients with polysensitization 18 (60%)

compared to patients with monosensitization 12 (40%), while in the control group majority of the patients were mono-sensitized 24 (80%) (Graph 7).

According to the "Position paper: Immunotherapy" [17] one of the criteria for specific immunotherapy induction is stable allergic asthma with the FEV1 values >70%. In our immunotherapy group 8 (26.6%) patients had intermittent asthma, 14 (46.6%) had mild persistent asthma and 8 (26.6%) had moderate persistent asthma. In the control group of patients, 9 (30%) had intermittent asthma, 6 (20%) mild persistent asthma, and 15 (50%) had moderate persistent asthma, without significant difference in asthma severity degrees between the study groups ($\chi^2=5.515$ $p=0.068$) (Graph 10). Hoheisen et al. [18] included 2.931 patients in their study conducted from October 2001 to December 2005. Out of those patients, 1052 had asthma (49% had mild, 43% moderate and 8% had severe asthma). Trebucon et al. [19] included 735 paediatric patients in their study; 64.0% had asthma out of which 52.7% had mild to moderate asthma.

The frequency of influenza-like illness during 1-year of follow-up in the group of patients on immunotherapy significantly decreased during the study period, which was not observed in the control group of patients. In the control group of patients, a significant increase in the episodes of influenza-like illness was observed ($\chi^2=20.480$ $p=0.0001$). The number of patients who visited the physician for bronchial hyperreactivity (BHR) depended on whether they were treated with immunotherapy (Graph 15). During the first trimester, both immunotherapy and control group had an equal number of influenza-like illness episodes (Graph 11). In the second trimester, a decrease in the number of influenza-like illness episodes was observed in immunotherapy group of patients 3/30 (10%), whereas in the control group those episodes were significantly higher and were observed in 11/30 (36%) patients (Graph 12). During the third and fourth trimester, the frequency of influenza-like illness episodes did not change compared to the 2nd trimester and was 3/30 (10%) in the immunotherapy group, whilst in the control group there was an increase in ILI episodes from 20 (66%) to 27 (90%) episodes (Graph 13, Graph 14).

Several mechanisms have been identified to explain how acute respiratory infections increase airway responsiveness and provoke an attack of asthma. Firstly, all respiratory tract viruses enter and replicate within airway epithelial cells and can damage both ciliated and non-ciliated respiratory epithelial cells, leading to necrosis of the airway epithelium, ciliostasis, and loss of cilia and impairment of mucociliary clearance [20]. However, it is likely that the clinical manifestations might be secondary to the release of proinflammatory mediators by damaged bronchial epithelial cells (BECs), as well as a direct cytotoxic effect of the virus [4]. Secondly, mucociliary clearance is a critical innate defence system, and mucus overproduction is one of the major symptoms of asthma exacerbations, significantly contributing to the morbidity and mortality of asthmatic subjects [4].

T-cells, NK cells and mast cells are major sources of IL-3. The prominent source of IL-3 appears to be activated T cells although other cell types have also been reported to produce it [21]. IL-3 plays a role in allergic diseases by preventing the apoptosis of basophiles via PI3K in vitro but has little effect on basophiles survival in vivo. In eosinophils, IL-3 induces the expression of HLA-DR and the co-stimulatory molecule B7.2 (CD86) on their surface. Therefore, IL-3-treated eosinophils are able to present antigenic peptides and support antigen-specific T-cell proliferation in allergic and parasitic diseases.

In a mouse model of allergic airway inflammation, β -chain-deficient

mice showed reduced expansion and accumulation of eosinophils in the lung, inhibition of airway hyperresponsiveness, mucus hypersecretion, and IgE production. A natural occurring mutation in the IL-3 gene (Ser27Pro) was shown to have protective effects on the development of asthma [22,23].

Conclusions

The frequency of influenza-like illness occurrence was significantly lower in patients treated with immunotherapy during one year of follow-up compared to the patients treated with antiasthmatic pharmacotherapy. The percentage of patients with influenza-like illness was 10% in the patients treated with immunotherapy at third and fourth trimester of the follow-up, whilst in patients on antiasthmatic pharmacotherapy the percentage of patients with influenza-like illness increased from 66% in the third to 90% in the fourth trimester.

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