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RESEARCH ARTICLE

Clinical and Pharmacological Approaches to Optimize Outpatient Treatment of Bronchial Asthma

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Abstract

Asthma is a common chronic disease. There is no age-related predisposition to the disease, occurring in both adults and children. The study presents clinical trial of ANAFERON FOR CHILDREN® effect on URTI remission process in combination with mild and moderate bronchial asthma in children. The studies were based on a sample of 150 children (age 3-6 years, average age 4.1 ± 0.1), conducted during 2017-2019 in Moscow, the Russian Federation. The first group included 89 children taking ANAFERON once a day for 3 months; the second (control) group included the remaining 61 who took a placebo-treatment during the same time period. The presence of an autoimmune disease was an exclusion criterion. Significant difference of 2.5 times less occurring of the disease ($p = 0.0002$) was found between the average number for the experimental group compering to the control. Children from the experimental group were 2.2 times less likely to have exacerbations of bronchial asthma ($p = 0.013$). 3 days is the duration and maintenance period of symptoms for the experimental group, that's 3 times lower comparing to the control group-9 days ($p = 0.041$). The Mean Neutrophil Volume (MNV) was significantly reduced ($p = 0.001$), in a month, Squamous Epithelium Index (SEI) ($p = 0.009$) in the experimental group. The experimental group maintained significantly low values of MNV and DRE at the end of ANAFERON therapy ($p = 0.001$). Current management of bronchial asthma includes a Treatment Effectiveness Assessment (TEA) and Patient Safety with medications prescribed, as well as improving of therapeutic cooperation and the patients' quality of life. The use of ANAFERON reduces the frequency of URTI by 2.4 times in the 3-6-year-old children with bronchial asthma. Additionally, ANAFERON is well tolerated for children. The use of ANAFERON (as a preventive drug) reduces 1) occurring of mild and moderate bronchial asthma by 1.5 times; 2) the number of cases of bronchial asthma exacerbation by 2.2 times; 3) the duration of asthmatic attacks by 3 times. This is associated with cytoprotective effect of the drug on the olfactory epithelium, as well as its influence on reducing the number of children with low IFNλ (by 3.4 times in 3 months of therapy).

Keywords: *Bronchial asthma, Prevention, ANAFERON, Placebo, Cytological indicators.*

Introduction

Bronchial asthma is one of the most common chronic diseases [1]. There is no age-related predisposition to the disease, occurring in both adults and children [2]. With prolonged and progressive course of bronchial asthma, not only a decrease in the quality of life, but also subsequent disability of a person is possible [3]. Thus, bronchial asthma can influence economics due to its prevalence among young population. Bronchial asthma can lead to the most severe outcomes, up to the lethal, in the case of an inappropriate treatment or late diagnosis of the disease [4]. The onset of bronchial asthma is usually associated with the occurrence of chronic allergic inflammation of the bronchi, which is accompanied by mucus hypersecretion, presence of edema, and bronchial obstruction [5]. The consequence is an onset of asthma attacks, or labored breathing, depending on the severity of the disease [6]. The inflammatory processes are common for patients with moderate, severe as well as mild bronchial asthma, where the only differences are in the degree of inflammation and morphological changes of bronchial walls [7]. Even in patients with a mild asthma, over time, the disease can progress to a severe that occurs in up to one third of all incidences of hospitalization [8]. Thus, a constant control over disease can be an effective strategy for preventing asthma

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progression. Bronchial asthma of mild degree was observed in 80% of all patients, and mainly this group patient usually intent to self-medicating exacerbations of disease [9]. Children of this group dominate in the number of cases [10].Bronchial asthma is the most common of chronic diseases among children, the frequency of cases all over the world can vary from 5 to 12% [11].Moreover, bronchial asthma occurs twice more often among boys comparing to girls. A gender-related dependence disappears in adolescents, and the frequency balances between the sexes [12].However, differences remain between population groups and in groups of adults. Thus, bronchial asthma is more common for urban than rural people -7% and 5%. Material well-being also matters as bronchial asthma occurs twice more often among children of needy families - 12% and 5.5% accordingly [13, 14].Thus, bronchial asthma can occur and develop as a result of a combination of many factors - age, gender, social, etc. The Global Initiative for Asthma (GNIA) is prevalent among modern approaches to the treatment of bronchial asthma.

This guide was established by a group of leading international researcher [15].Russian specialists also created a guide on diseases associated with respiratory system, as well as federal guidelines for the treatment and preventive measures of bronchial asthma. Nowadays, the main aspect in treatment of bronchial asthma is the principle of minimal necessity [16].The main responsibility of medical doctor is to determine the disease severity, in order to prescribe subsequent therapy, as well as evaluation of asthma control by the patient [17].The primary and secondary prevention strategies of bronchial asthma are distinguished. Primary prevention interventions are avoidance measures, aimed at preventing occurrence of bronchial asthma in people at risk. This is the presence of breastfeeding (in the case of infancy) or quitting smoking that is known to provoke bronchial asthma. Secondary prevention should be applied for children who have no symptoms of bronchial asthma yet [18].

The risk of bronchial asthma occurrence increases by half for a child that s/he has history of allergy or if a family member has bronchial asthma. Meanwhile, in case of atopic dermatitis (eczema) or rhinitis, the probability is less significant, up to 20% [19].Recently, pharmacotherapy has been used quite widely in combination with preventive measures [20].

Asthma attacks and bronchial obstruction can increase with the disease dynamics, lasting for 6-8 hours, and may leads to dysfunction of lymphatic drainage system of the lungs. Coughing attacks are common during milt asthma. Adrenal gland disorders can occur along with the development of severe bronchial asthma, especially in children [21].Recently, the majority of bronchial asthma cases occur among a teenager that's due to absence or inadequate treatment regimen [22].The third part of all bronchial asthma cases refers to an atopic phenotype [23].Bacterial and viral infections are common precipitants of bronchial asthma. URTI is the most frequently spread respiratory tract infection (RTI) among children. There is a direct relationship between the development of bronchial asthma and the presence of URTI. Thus, the prevention of URTI is a primary measure of secondary prevention strategy [24].

Drugs inducing non-specific resistance to infection should get the primally attention among all medication for URTI. Meanwhile, the choice of the drug should consider any negative consequences, in particular, drug allergy. The study focuses on bronchial asthma cases among children as the most susceptible age group. ANAFERON FOR CHILDREN® is considered as the most promising drug. ANAFERON (state registration No. 000372/01-2001, Materia Medica Holding) contains antibodies to human IFN-gamma (the main active ingredient, per 1g of tablet there is 0.003g of antibody purified by affinity). ANAFERON belongs to antiviral drug with immunomodulatory activity, according the mechanism of action. ANAFERON is not a drug used exactly for asthma treatment, but due to its antiviral and immunostimulating effects, it can be effective in treating mild to moderate bronchial asthma. The goal of study is to present clinical trial of ANAFERON FOR CHILDREN® effect on URTI remission process in combination with mild and moderate bronchial asthma in children.

Material and Methods

Material

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The studies were based on a sample of 150 children attending kindergarten No. 15, conducted during 2017-2019 in Moscow, the Russian Federation. Generally, there were no cases of hospitalization for mild and moderate bronchial asthma as well as URTI registered that influenced on the choice of location. The age range of children in the sample is from 3 to 6 years. Inclusion criteria are 1) presence of mild to moderate bronchial asthma of atopic phenotype; 2) stable or unstable remissions of the disease; 3) monovalent or polyvalent sensitization; 4) age range of 3-6 years. Likewise, informed consent from parents must be available. The essence of informed consent is to provide information sharing of the therapy features. The presence of an autoimmune disease was an exclusion criterion. Individually, children were selected in the study sample referring to their anamnesis that indicated the relationship of bronchial asthma with URTI. The children were divided into two groups with the help of random sampling method. The first group included 89 children, the second (control) group - the remaining 61 (Table 1).

Table 1: Clinical parameters of children from the studied groups

Primary Diagnosis	Concomitant Diagnosis	Experimental Group (ANAFERON FOR CHILDREN®), ppl	Control Group (Placebo-treatment), ppl
Mild Intermittent Asthma		59	50
Mild Persistent Asthma		12	5
Moderate Asthma		10	6
	Cold Complications	51	33
	Atopic Dermatitis	48	22
	Allergic Rhinitis	39	25
	Chronic Allergic Rhinitis	6	3
	Chronic Tonsillitis	22	17
	Adenoid Vegetation, Grade I and II	17	19
	Dental Caries	4	3

Children from experimental group took ANAFERON once a day for 3 months, while the control group received a placebo-treatment (1 tablet daily) during the same time period

Children diagnosed with URTI were receiving URTI treatment (antipyretic drugs, as well as decongestants and other key element in symptomatic therapy) along with the studied drug according to the standard therapy regimen. Basic treatment was carried out according to the protocol "Bronchial asthma in children: diagnosis, treatment and prevention" [25].

Methods

The duration of the clinical observation was six months. The studied parameters included the frequency and duration of URTI, as well as bronchial asthma exacerbation. Exacerbation was analyzed based on parents' diary entries. Drug tolerance was assessed based on the incidence of complications and the severity of side effects. Epidemic Performance Ratio and Index were assessed on the data obtained (hereinafter - EPR and EPI, respectively, Bronchial asthma, 2004). A smear was taken from the surface of the nasal mucous membrane before the experiment, as well as 30 and 90 days after. Afterwards, the average indicator of the following parameters was calculated: a) Destruction or Removal Efficiency (DRE) b) Mean Neutrophil Volume (MNV); c) Squamous Epithelium Index (SEI) d) Columnar Epithelium Index (CEI). The enzyme-linked immunosorbent assay (ELISA) was used to evaluate human IFN-gamma (IFNλ) level. The assay uses for quantifying substances such as proteins using antibodies directed against the protein to be measured. Identified substances include viral proteins, as well as microbial residues.

Statistical Analysis

STATISTICA v.6.0 (Stat Soft, Inc.) software was used for all statistical calculations. Statistical analysis of the results was carried out using Descriptive Statistics, namely Median (M) and Quartiles 1-3 (Q1; Q2; Q3 ;). A statistical significance test was performed using Contingency Tables to determine the probability value for a Chi Square, as well as Fisher's exact test (P-value). Two independent samples were compared using the Mann-Whitney U test; for a larger number of independent samples was used the Kruskal-Wallis test. The Kruskal-Wallis Z-test was used to establish the significance of differences between groups by pairwise comparison of values with adjustments for

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multiple comparisons. Dependent samples were evaluated by the Wilcoxon Signed Rank test (for two samples) and the Friedman test (for multiple samples).

Results

A general tendency towards a decrease of URTI incidents among children diagnosed with bronchial asthma was revealed (Table 2).

Table 2: The incidence and frequency of bronchial asthma exacerbation in the experimental (1) and control (2) groups over a period of 3 months (90 days)

Clinical Indicators	Frequency of Exacerbations, throughout the period	Group 1, number of cases	Group 2, number of cases
Frequency of URTI	0	39	15
	1	41	17
	2	9	29
	M±m	0.59±0.01*	1.39±0.02
Frequency of Bronchial Asthma Exacerbation	0	53	22
	1	32	27
	2	4	12
	M±m	0.39±0.07*	0.86±0.014

M ± m - mean value and mean errors, * - significant difference between groups

Significant difference of 2.5 times less occurring of the disease (p = 0.0002) was found between the average number for the experimental group compering to the control. No significant differences between groups were found (p = 0.05) in frequency of URTI cases throughout 3-6 months period. Therefore, the use of ANAFERON reduces the frequency of URTI and exacerbations of bronchial asthma by more than 2 times. Approximately one third of children did not suffer URTI and did not experience asthma attacks for the first three months. (Table 2).After six months of the experiment (3 months of treatment and 3 months of observation), this amount slightly decreased to 25%, but the morbidity of children from the control group was 1.5 times higher (EPI = 1.50). ANAFERON had a positive effect on the health of children suffering from bronchial asthma, in the first three months. More than a half of children had no sign of exacerbation which is half higher than that for control group. Meanwhile, children from the experimental group were 2.2 times less likely to have exacerbations of bronchial asthma (p = 0.013). 3 days is the duration and maintenance period of symptoms for the experimental group, that's 3 times lower comparing to the control group-9 days (p = 0.041). The frequency of occurrence and duration of symptoms in the period after 3 up to 6 months shows no significant differences (p = 0.662, p = 0.12, respectively).There was not a single case of any complications and side effects while using ANAFERON, which indicates drug' positive tolerance. A significant difference in the level of IFNλ was found between the number of children before and after treatment (Table 3).

Table 3: The experimental group, the frequency of IFNλ cases of different levels before and after treatment

Observation Period	Number of Children	IFNλ Level		
		low	high	moderate
Before Treatment	89	48	29	12
in 3 Months	89	14	51	24

It was revealed that after taking ANAFERON, the number of children with low IFNλ (p = 0.035) decreased by 3.4 times, and vice a versa the number of children with high IFNλ increased by 1.7 times (p = 0.042). From a histological view point, the condition of the nasal mucosa in children with bronchial asthma improved after taking ANAFERON. That is clearly shown by normalization of the following measure in a month of therapy: MNV (p = 0.001), SEI (p = 0.002), CEI (p = 0.001), DRE (p = 0.001) comparing to the control group. There were no statistically significant differences in the above measure before the experiment. The significant differences between the experimental and control groups remained for most cytological parameters until the end of 3 months, namely: DRE, MNV, SEI (p = 0.020, p = 0.025, p = 0.040, respectively). No significant differences between groups were found for cytological parameters at the end of therapy (3 months). The following dynamics was observed within the groups The MNV was significantly reduced (p = 0.001), in a month, SEI (p = 0.009) in the experimental group. The experimental group maintained significantly low values of MNV and DRE at the end of ANAFERON therapy (p = 0.001). Meanwhile, there were no statistically

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significant changes in SEI and CEI during all three months of observation. No significant differences were found in the above cytological indices for the control group.

Discussion

Bronchial asthma severity can be divided into several groups intermittent, persistent-mild, persistent-moderate, and persistent-severe [26].Mild (intermittent) asthma symptoms occur rarely (no more than once in 7 days), exacerbations are also short-term, nighttime flare-ups occur twice a month at most. With persistent-mild asthma, attacks are more frequent, but less than once a day and nighttime flare-ups occur more often. Generally, with a persistent asthma, flare-up may affect patient's health and activity. Persistent-moderate asthma is characterized by more often nighttime flare-ups (more than once a week), symptoms occur daily, patient's condition worsens noticeably. Mostly, patients with persistent-moderate asthma are prescribed short-acting beta-2 agonists (SABAs) daily.

Finally, with persistent-severe asthma, symptoms occur daily with frequent exacerbations and a significantly limit normal activities. Thus, severe exacerbations can be observed with a mild level of disease, which determines the course of treatment, same as for moderate level. This issue is very important when choosing a patient treatment strategy [27].Current management of bronchial asthma includes a Treatment Effectiveness Assessment (TEA) and Patient Safety with medications prescribed, as well as improving of therapeutic cooperation and the patients' quality of life. Particularly, the combination therapy of ICS (inhaled corticosteroids) and long-acting beta-2 agonists is widely used [28].Results of several studies indicate that 71% asthma control can be achieved with such combination of drugs compared to 45% with only one of them used (Fluticasone in this case) [29].

One of the most effective combinations of drugs was revealed, namely Fluticasone and Salmeterol, 2 times a day, standard dosage (SERETIDE®). Important that only cases of mild and moderate bronchial asthma was considered. Severe asthma requires immediate hospitalization. Another combination of drugs, ICS and Formoterol, is also quite used [30].It is used for inhalation in combination with budesonide. Meantime, the control therapy is used when the patients adjust the dosage and frequency of use in accordance with their own well-being. There are combinations of both drugs in one (FORADIL COMBI®), and separate. Meanwhile, there were no statistically significant differences observed between combined and separate drug use (single tablet regimen) [31].The use of this combination allowed not only to increase bronchial asthma control, but also to avoid intake of short-acting bronchodilators. The use of Tiotropium Bromide (SPIRIVA®, HANDHEILER dry powder inhaler) has been separately developed [32].This drug combines bronchodilator, anti-inflammatory and bronchoprotective properties. Important is the role of psychophysiological stress in patients with asthma. Psychophysiological stress can induce symptoms of asthma as it modifies the inflammatory response of the respiratory tract caused by irritants, allergens and infections. Thus, stress management should be included to the treatment regimen [33, 34].The study demonstrated the positive effect of ANAFERON FOR CHILDREN® on the cytological aspects of the nasal mucosa.

The obtained results confirmed the high-reliability properties. Apparently, the effect of the drug was influenced by endogenous IFN effect on the processes in the body associated with metabolic activity and localization on the mucosa of nasal cavity. Eventually, the elasticity of cell membrane, and the colloidal state of cytoplasm improve. The microbial dissolution occurs, that leads to decreased phagocytic function in neutrophils. Consequently, the structure of a neutrophil is preserved. The restoration of epithelium of the nasal mucosa was observed and it positively influenced on barrier function. As a result, frequency of URTI and partially the frequency of asthma attacks reduced.

Conclusions

The use of ANAFERON reduces the frequency of URTI by 2.4 times in the 3-6-year-old children with bronchial asthma. Additionally, ANAFERON is well tolerated for children. The use of ANAFERON (as a preventive drug) reduces 1) occurring of mild and moderate bronchial asthma by 1.5 times; 2) the number of cases of bronchial asthma exacerbation by 2.2 times; 3) the duration of asthmatic attacks by 3 times. This is

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associated with cytoprotective effect of the drug on the olfactory epithelium, as well as its influence on reducing the number of children with low IFNλ (by 3.4 times in 3 months of therapy).

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