

**UNIVERSITY OF MEDICINE AND PHARMACY OF
CRAIOVA**

DOCTORAL SCHOOL



**CLINICAL AND BIOLOGICAL STUDY ON THE
EFFICIENCY OF ANTIINFLAMMATORY TREATMENT
IN ALLERGIC RHINITIS**

PhD Thesis Summary

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Cuprins

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Keywords: allergic rhinitis, markers of inflammation, allergic conjunctivitis, skin prick test, *Ambrosia elatior* pollen, anti-inflammatory treatment, mometasone furoate, desloratadine, montelukast, quality of life

Abbreviations

ARIA - Allergic Rhinitis and its Impact on Asthma

IL - interleukin

IgE – immunoglobulin E

NO - nitrogen oxides

ORL - otorhinolaryngology

SPIREs - synthetic peptide immunoregulatory epitopes

WHO - World Health Organization

GA²LEN - Global Allergy and Asthma European Network

GLORIA - Global Resources in Allergy

WAO – World Allergy Organization

HDL - high density lipoprotein

AAC - acuteallergic conjunctivitis

SAC - seasonale allergic conjunctivitis

PAC - perennialallergic conjunctivitis

Apo A1 – apolipoprotein A1

MF – mometasone furoate

DL - desloratadine

MTL - montelukast

1. KNOWLEDGE LEVEL IN ALLERGIC RHINITIS

1.1. Allergic rhinitis is a general health problem affecting 10-20% of the world population [1], underestimated and under diagnosed, with consequences on patient's quality of life having also an undervalued economic impact.

According to the definition provided by ARIA in 2008 allergic rhinitis is classified in intermittent and persistent in terms of duration, and mild or moderate/severe depending on the severity of the symptoms. In the pathogenesis of the disease in addition to the influence of various inflammatory and immunomodulatory cells such as mast cells, Th2 cells, B lymphocytes and eosinophils infiltrating the nasal mucosa as a result of exposure to airborne allergens, released cytokines such as IL-3, IL-4, IL-5, IL-13 [2], nasal epithelial cells have an important immunomodulatory effect releasing eicosanoids, cytokines, chemokines, endopeptidase [3,4]. This disease also causes a systemic inflammation which explains the relation between allergic rhinitis and asthma. Together with genetic factors there are also other incriminated risk factors: environmental factors, lifestyle, vitamin D deficiency [5,6,7]. Within aeroallergens, there can also appear house dust mites, allergens from plants (especially pollens of grasses and weeds), animal allergens. *Ambrosia elatior* weed pollen is a major cause of triggering allergic rhinitis for a large part of population. For the diagnosis of allergic rhinitis, there are significant elements such as medical history of the disease, objective and otorhinolaryngology examination, allergy testing, determining specific IgE, molecular diagnosis, specific nose tests as nasal IgE determining, cytological examination of nasal secretion, activation basophils test, measurement of NO in nasal exhaled air. In the management of allergic rhinitis a role is played by the patient's training in avoiding aeroallergens as a prophylactic measure and curatively speaking there is the anti-inflammatory treatment with intranasal corticosteroids, second generation H1-antihistamines, antileukotrienes. We must not forget about the treatment by specific allergen immunotherapy to which new vaccines were added as: recombinant allergen, epitopes of B cells combined with B preS hepatitis antigen, SPIREs - synthetic peptides immunoregulatory epitopes and biological treatments with monoclonal antibodies as omalizumab.

1.2. Therapeutic strategy in allergic rhinitis is based on international recommendations of ARIA guidelines (Allergic Rhinitis and its Impact on Asthma) in collaboration with WHO, GA²LEN (Global Allergy and Asthma European Network) as well as GLORIA (Global Resources in Allergy: Allergic rhinitis and allergic conjunctivitis, WAO 2001) providing an individualized treatment plan for patients with allergic rhinitis based on evidence.

1.3. In the chapter "Markers of inflammation in allergic rhinitis" we have shown that proteomic and lipidomic patterns seem to find new biomarkers of inflammation in allergic rhinitis. The first proteomic study in nasal mucus for healthy individuals identified 111 different proteins [8]. Apolipoprotein A1 which has anti-

inflammatory, antioxidant, antithrombotic and anti-fibrotic effect is a major component of high density lipoproteins (HDL) which mediate the transport of cholesterol from cells. It is expected to be a biomarker of inflammation severity and to highlight the effectiveness of treatment [9]. While eosinophils in nasal secretion are seen as a local marker of allergic disease, the level of eosinophils in serum is seen as a systemic marker of this disease [10,11].

1.4. Allergic conjunctivitis is the most common comorbidity of allergic rhinitis affecting between 10% and 25% of the global population [12,13]. GLORIA international guidelines classifies allergic conjunctivitis as follows: acute allergic conjunctivitis (AAC), seasonal allergic conjunctivitis (SAC), perennial allergic conjunctivitis (PAC) [14]. Finding a single treatment regimen that would be effective for the two diseases would further increase the adherence to the treatment.

2. PERSONAL RESEARCH

Personal research of this thesis began in 2011 at the beginning of my career as a specialist doctor in Clinical Allergy and Immunology in the Allergy Clinic of "Filantropia" Municipal Hospital in Craiova.

2.1. Research objectives. This thesis has six objectives that will be further developed:

2.1.1. Data on the prevalence of allergic rhinitis and sensitization to *Ambrosia elatior* pollen in Oltenia area.

2.1.2. The analysis of clinical efficacy of treatment with mometasone furoate (MF) alone or in combination with desloratadine (DL) / montelukast (MTL) based on individual and total symptoms score of allergic rhinitis for the patients with sensitization to *Ambrosia elatior* pollen .

2.1.3 and 2.1.4. Evaluating the treatment with MF as compared to DL/MTL for the patients with allergic rhinitis and sensitization to *Ambrosia elatior* pollen by the number of eosinophils in blood and nasal lavage and apolipoprotein A1 in serum.

2.1.5. Determination of the clinical efficacy of treatment with MF alone or in combination with DL/MTL on the allergic conjunctivitis as pathology associated to the patients with allergic rhinitis and sensitization to *Ambrosia elatior*.

2.1.6. Assessing life quality of the patients with symptoms of allergic rhinoconjunctivitis and sensitization to *Ambrosia elatior* pollen and the way they improved after treatment with MF alone or in combination with DL/MTL.

2.2. Material and method

The study group of 1004 patients diagnosed with allergic rhinitis out of which 490 patients with allergic rhinitis, with symptoms for at least two years before during the season of pollen and positive skin tests to *Ambrosia elatior* were monitored for a period of four years in the Clinic of Filantropia Hospital in Craiova, patients from all over Oltenia area but also few of the neighbouring counties.

For the 2nd objective, I have selected from the first group a total of 490 patients with allergic rhinitis, with symptoms for at least two years before during the pollen season and positive skin tests to *Ambrosia elatior* pollen.

For the third goal I have chosen a total of 450 patients excluding the patients with parasites and under treatment which could have influenced test results.

For the fourth objective I have included 52 patients in the study monitoring them clinically and through the determination of apolipoprotein A1 during *Ambrosia elatior* pollen season in 2015 for 4 weeks.

The fifth objective included 341 patients with rhino-conjunctivitis and sensitization to *Ambrosia elatior* pollen, monitoring treatment effectiveness for 4 weeks.

For the 6th goal I have applied a standard questionnaire in order to determine life quality when the disease shows initial signs and after 4 weeks of treatment for a group of 74 patients.

As working methods I have used: allergy anamnesis, allergy skin tests, clinical allergic rhinitis and conjunctivitis symptoms range, determination of the number of eosinophils in blood and nasal lavage, determination of the level of apolipoprotein A1 in serum, spirometry to confirm asthma as an associated disease. Symptoms intensity of the patients with rhinoconjunctivitis was evaluated according to the total and individual score of nasal and ocular symptoms using 4 points visual analogue scale. The patients in each study group were randomly assigned to three treatment groups: MF mono-therapy and MF+DL and MF+ MTL combinations, establishing treatment efficiency after data processing.

2.3. Statistical data analysis

In order to assess the results of the research we used Microsoft Excel together with XLSTAT for MS Excel and IBM SPSS Statistics 20.0 software. I have described every analysis and study stage very accurately, taking into account every factor that could influence the results.

2.4. Results

2.4.1. In the first study I have identified a total of 1004 patients with allergic rhinitis in Oltenia area, with a proportion of men and women similar to the population of the researched area. Of all forms of diagnosed allergies net allergic rhinitis is definitely the main one (65.64%). The genetic factor (20.82%) cannot explain the high number of allergic patients in the area. 41.83% showed sensitivity to dust mites, 8.67% to moulds, 7.89% to animal epithelia, 77.09% sensitization to pollens. In Oltenia area, the number of patients with allergic rhinitis and sensitization to *Ambrosia elatior* pollen is greater than those with sensitization to mites and grass pollen. Persistent rhinitis accounted for 97.76% of the cases of allergic rhinitis, of which 88.13% as moderately severe form of gravity. Those with intermittent rhinitis represented 63.77% with moderately severe form. Out of the total patients with allergic rhinitis 47.11% had also allergic conjunctivitis and 35.66% had also associated asthma. Out of those with allergic rhinitis and sensitization to *Ambrosia elatior* pollen 73.06% had also associated allergic conjunctivitis and 22.65% had asthma. 46.33% were also polysensitized to *Artemisia vulgaris*. The incidence of allergic rhinitis caused by *Ambrosia elatior* increased significantly high in a period of 2 years.

Ambrosia elatior is a quarantine weed which was included in the official list of quarantine weeds in many countries. The number of people suffering from allergy to *Ambrosia* ranges from 2.5% in Finland to 60% in Hungary [15]. *Ambrosia* allergy epidemic can become an enormous burden in terms of health care costs worldwide Europe [16].

2.4.2. For the 2nd goal I have selected 490 patients with allergic rhinitis and positive skin tests to *Ambrosia elatior* pollen randomly divided into three treatment groups: monotherapy with MF 200mcg/day (2 sprays in each nostril once / day) and MF combinations 200mcg / day (2 sprays in each nostril once / day) + DL 5mg / day or MF 200µg/day (2 sprays in each nostril once/day)+ MTL 10 mg/day). Treatment efficiency was assessed once in 2 and 4 weeks, using a 4 points visual analogue scale (0 - no symptoms, 3 - very troublesome symptoms) with the calculation of individual and total nasal symptoms score (itching, sneezing, rhinorrhoea, congestion, the overall condition of the nose).

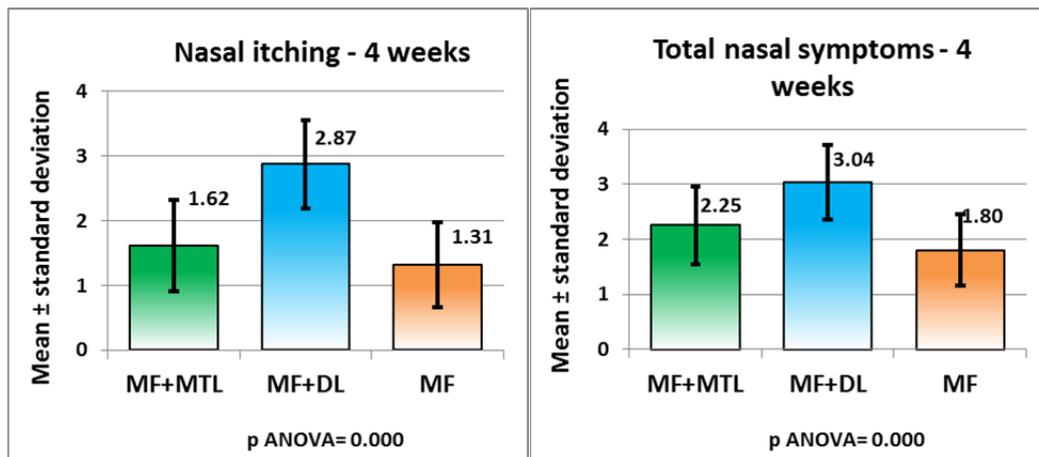


Figure No.1 Evolution of itching (left) and general state of the nose (right) every 4 weeks depending on treatment

All three treatment regimens improve nasal symptoms and overall condition [17], but the combination MF + DL is more effective than MF + MTL combination or MF alone administration both for itching and general condition (Figure no.1). For sneezing and rhinorrhoea MF+DL combination or MF+MTL is more effective than MF monotherapy. Between the two combined therapies there are no significant differences. For nasal congestion there are significant differences between MF+DL or MF+MTL combination as compared to MF monotherapy, but between MF+DL and MF+MTL combinations I have noticed differences in 2 weeks time, but in 4 weeks time there are no more such significant differences.

2.4.3. Within objective 3, when using the same regimen and monitoring, but checking the effectiveness by determining the number of total eosinophils in blood and nasal secretion, the group was restricted to 450 patients, excluding patients with parasites or who were under treatment, which would have influenced biological values. Before treatment the number of eosinophils was increased to 36% in blood and 87% in nasal secretions (Figure no.2), but it was not correlated to the severity of allergic rhinitis symptoms, Pearson correlation coefficient being very close to zero in both cases. All three treatment regimens have reduced the number of eosinophils both in blood and nasal secretion, but I did not notice any statistically significant differences between them, therefore, it cannot be used as a criterion for assessing the effectiveness of therapy by the type of medication.

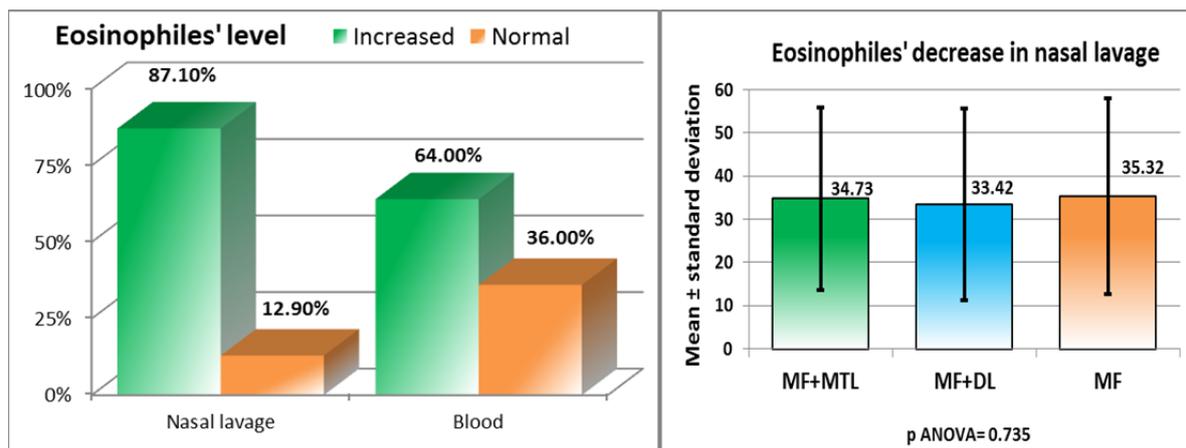


Figure No. 2 Distribution of eosinophils in nasal secretion and blood (left); decrease in the number of eosinophils after 4 weeks of treatment (right)

2.4.4.In the study investigating serum levels of apolipoprotein A1 (Apo A1) for the patients with allergic rhinitis and sensitization to *Ambrosia elatior* pollen have included 52 patients who followed inclusion and exclusion criteria. The same regimen was used on 3 homogeneous groups as average age, sex and form of allergic rhinitis and the patients were monitored for 4 weeks.

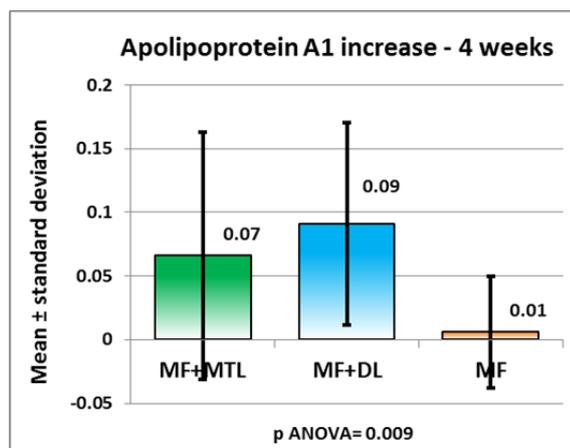


Figure No.3 The evolution of apolipoprotein A1 after 4 weeks according to the regimen.

Compared to standard values, the Apo A1 level was initially lowered and inversely correlated with the intensity of symptoms, meaning that the lower the level is, the higher the symptom severity is, but the result is not statistically significant.

After 4 weeks of treatment the Apo A1 level increased for the patients treated with MF+DL combination and MF+MTL compared to those treated with MF monotherapy (Figure no.3); between the 2 combined treatment regimens there are no statistically significant differences. However, the results are slightly better when associating glucocorticoid H1 antihistamine. My study highlights disease systemic

effect with a decrease in apolipoprotein A1 in the acute phase of the disease and its increase after a positive evolution under specific antiinflammatory treatment using glucocorticoid i.n. and antihistamine H1 or antagonists of cysteinyl-leukotrienes. It has been shown to have anti-inflammatory, antioxidant, antithrombotic and anti-fibrotic properties. Park et W-S study's conclusion in 2013 was that apolipoprotein A1 reduces inflammation in the airways and it could be a therapeutic strategy in chronic inflammatory diseases which are associated with epithelial barrier defects [18].

2.4.5. For the 5th goal I have studied the clinical effectiveness of treatment with MF compared to MF+DL and MF+MTL combinations on a group of 341de patients with symptoms of rhino-conjunctivitis for at least two years before and positive prick skin tests to *Ambrosia elatior* pollen. Three groups of patients with similar characteristics (number, gender, average age) and the 3 treatment regimens were also monitored, administrating the dosage above. The study showed that MF+DL treatment combination significantly improves ocular symptoms for the subjects with allergic rhinoconjunctivitis and sensitization to *Ambrosia elatior* pollen. During our study, ocular itching was the most bothersome symptom and thus adding desloratadine orally as H1 antihistamine to mometasone furoate intranasal we achieved better improvement in itching (Figure no.4) and overall condition as other studies have shown [19], as well as significant differences in terms of tearing and redness compared to the monotherapy with mometasone furoate.

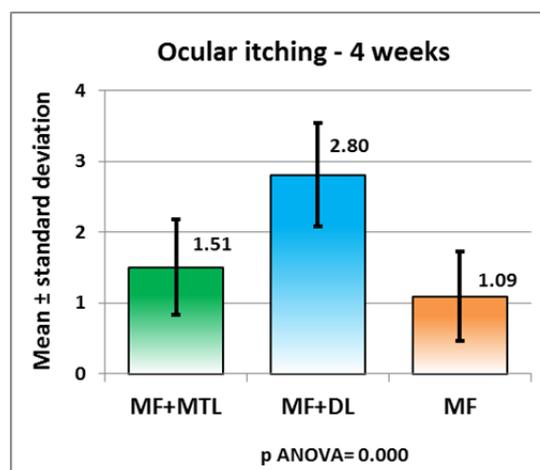


Figure No.4 The evolution of ocular itching after 4 weeks depending on treatment.

Jennie Gane et al claim that controlled trials are necessary both in seasonal and perennial allergic conjunctivitis for children and adults in order to compare leukotriene antagonists to oral H1 antihistamines or intranasal corticosteroids [20].

From this point of view I believe that my study meets the requests formulated by various researchers such as Jennie Gane et al. and analyzes the influence of the effectiveness of local therapy with anti-inflammatory nasal corticosteroid and combination between MF and oral H1 antihistamine or oral cysteinyl-leukotriene antagonist for combined allergic conjunctivitis.

2.4.6. Life quality of the patients with rhinoconjunctivitis was assessed on a group of 74 patients selected from the group of the first objective who were checked during 2015 and who followed mentioned inclusion and exclusion criteria.

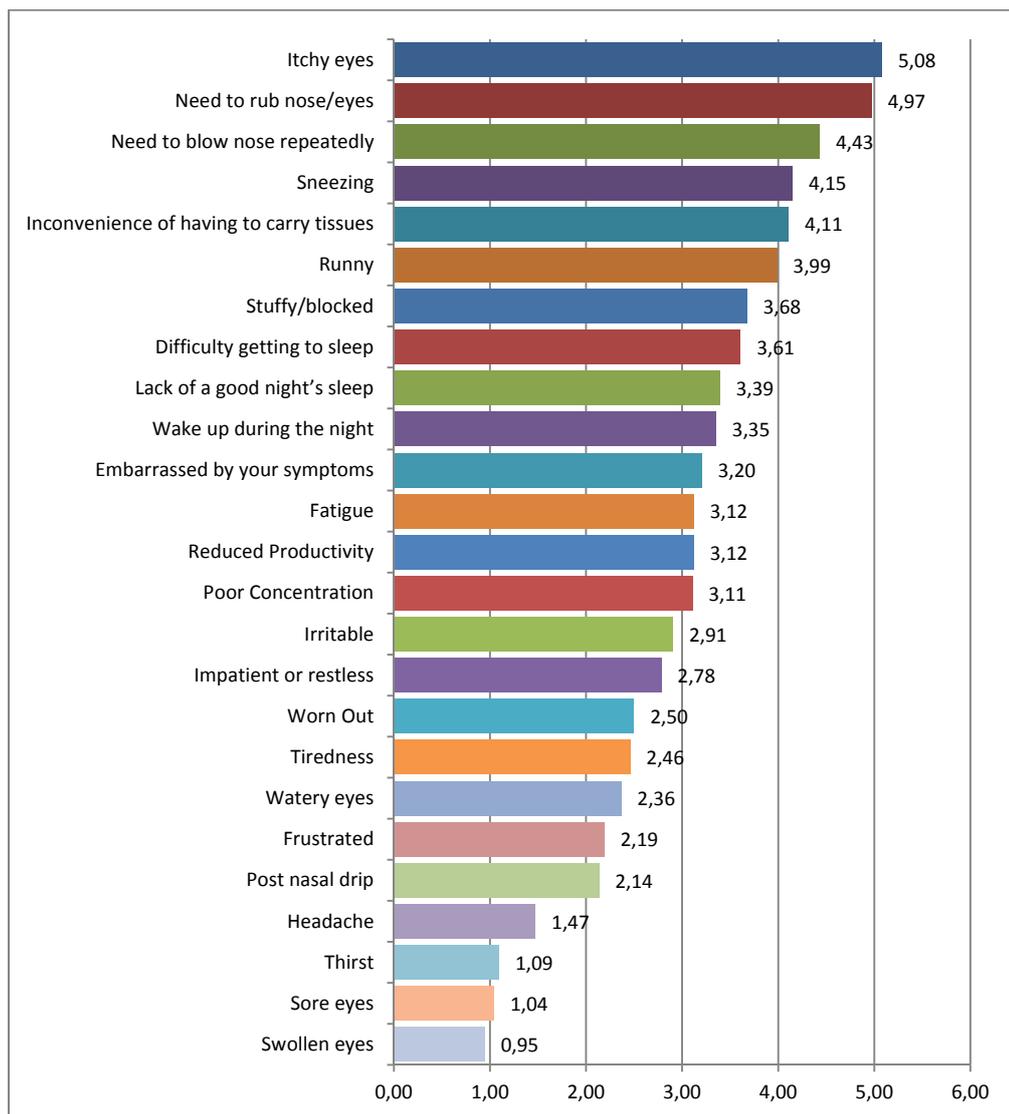


Figure No .5 Problems that lower the quality of life for the patients with symptoms of rhino-conjunctivitis with sensitization to *Ambrosia elatior* pollen depending on the degree of affection

All patients had to remember how they were affected by the symptoms of rhino-conjunctivitis in the previous week to the check up and answer on a scale from

0-7 points (0 - were not troubled, 6 - were extremely troubled). The overall score of the questionnaire is an average of those 28 questions and individual score on fields is an average of every field. After selecting the patients and having them filled in the form, they were randomly divided into three groups and received the same treatment regimen. Ocular and nasal itching are the problems which affected the quality of life for the patients with symptoms of rhinoconjunctivitis with sensitization to *Ambrosia elatior* pollen are (Figure no.5).

Generally speaking, the quality of life for the patients with acute allergic rhinoconjunctivitis and *Ambrosia elatior* pollen sensitization has significantly improved when associating MF i.n. and DL oral, enabling them to lead a normal life.

3. FINAL CONCLUSIONS

1. Mites and pollens are the main sources of allergens for the patients with allergic rhinitis.

2. Weeds and grass pollens are the most representative sources of allergenic pollens.

3. The study provides original data on the prevalence of allergic rhinitis and sensitization to *Ambrosia elatior* pollen in Oltenia area as well as its incidence in recent years, when the number of the sensitized people has significantly increased.

4. In Oltenia, the number of patients with allergic rhinitis and sensitization to *Ambrosia elatior* pollen has exceeded that of the patients sensitized to dust mite and grass pollen.

5. The symptoms of the patients with allergic rhinitis and sensitization to *Ambrosia elatior* pollen are in terms of severity moderately severe.

6. Three-quarters of these patients have also symptoms of allergic conjunctivitis and the symptoms are comparable in terms of severity to those of allergic rhinitis.

7. The dominant symptom is nasal and ocular itching.

8. In practice, the use of a single treatment regimen improving both nasal and oral symptoms would increase patient's compliance to treatment.

9. The combination i.n. mometasone furoate + oral desloratadine proved more effective than the other treatment regimens by ameliorating nasal itching, ocular symptoms and general condition.

10. Serum apolipoprotein A1 level was correlated inversely with the severity score of allergic rhinitis although it was not significant statistically. The combination

MF +DL combination was more effective than MFmono-therapy, increasing more the level of serum apolipoprotein A1.

11. The study on serum level of apolipoprotein A1 as a response to treatment for the patients with allergic rhinitis and sensitization to *Ambrosia elatior* pollen is the first study carried out in Romania and it may open the way to new therapeutic strategies for the patients with allergic rhinitis.

12. The treatment with MF + DL proved more effective in terms of ocular itching, tearing, eye congestion, but also in terms of general condition for the patients with allergic rhinitis and sensitization to *Ambrosia elatior* pollen, having also associated symptoms of allergic conjunctivitis.

13. The quality of life for the patients with allergic rhino-conjunctivitis and sensitization to *Ambrosia elatior* pollen is affected by disease symptoms. Work tasks fulfilment, recreation or outdoor activities, and driving are only some of the elements of the quality of life that are extremely affected by these symptoms.

14. MF + DL combination brings additional benefit compared to mometasone furoate monotherapy in terms of these patients' quality of life.

15. This present study is meant to an alarm bell to local authorities, but also to a national level so that measures are to be taken in order to eradicate this weed.

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