CLINICAL

O. Righi

NEW MANAGEMENT OF CHILDHOOD ASTHMA IN GENERAL PRACTICE

SUMMARY

The enrolled patients were affected by mild intermittent/persistent bronchial asthma and moderate asthma (mild and moderate degrees). Most patients (22/28) tested positive for dust mites, Parietaria, Gramineae and mould. The remaining patients did not have any allergy.
All the children were treated with GUNA-IL 12 4CH + GUNA INF GAMMA 4CH + GUNA-MATRIX + CITOMIX®.
GUNA-ALLERGY-PREV has been added specifically to the allergic patients.
The whole group was recommended a naturally basic diet and to rebalance the gut flora.
The patients have been clinically evaluated at the end of 1-2-3 months of therapy, according to specific trend. They were given a clinical diary to fill out at home, which covered different related symptoms and treatments.
In the children who followed preventive conventional treatments the established therapy has been maintained for 1 or 2 months, in relation to the clinical evolution and the number of drugs administered. Once the symptoms were stabilized, the conventional drugs were gradually suspended. Conventional treatment was maintained in case of need.
The patients have been evaluated for a period ranging between 12 and 24 months, testing the clinical trend before and after the beginning of the low dose treatment for equal periods of time.
The results are the following:
after 1 month of low dose treatment, the use of conventional drugs has been reduced or suspended. After 2-3 months, basically no patient was administered conventional treatment; conventional treatment was used only for brief periods due to bronchial asthmatic episodes.
All patients had an important improvement of the symptoms and their frequency.
This therapy has proved to be without negative side effects and it seems to be an excellent and advantageous therapeutic method for the balancing of the Th1-Th2 cells ratio.

PAROLE CHIAVE **BRONCHIAL ASTHMA, CITOMIX®, GUNA-ALLERGY-PREV, GUNA-MATRIX, GUNA-IL-12 4CH, GUNA-INF GAMMA 4CH, PHYSIOLOGICAL REGULATING MEDICINE, CYTOKINES**

INTRODUCTION

Bronchial asthma, the most frequent pathological chronic condition of childhood, is among the main chronic diseases responsible for child hospitalization and school absence, which results to be **3 times greater** than that of unaffected children.

40% of asthmatic children have sleep disorders (one to two nights per week) that can cause a decrease in the learning performance.

– Asthma is a frequent and important disease for the pediatrician; according to several statistics, on average **1** in **10** school-age children is affected.

The asthmatic condition greatly affects both the child and the family, since this disease strongly conditions the quality of life of the whole family.
– Asthmatic children are not only subject to a considerable number of scholastic absences, but they often result unable to perform sports activities regularly and are limited in their daily routine because of the excessive protection of their family. Moreover, parents miss many working days to assist children in the clinical activity of the disease and for the controls that it involves.

The implications on the whole community are very important, both in terms of quality of life and health care costs.
The WHO regards asthma as one of the main public health problems in the world.

– Despite the important progresses in the knowledge of the inflammation pathophysiology and of the immune mechanisms of the tissue, leading to the realization of new drugs, the incidence of asthma in children is still increasing.

CHILDHOOD ASTHMA – NATURAL HISTORY

Asthma is a chronic inflammatory disease in which the inflammation of the Respiratory Tract determines and is determined by bronchial hyperreactivity to a great number of triggers.

– In turn, this reaction generates an obstruction of the Respiratory Tract (that in normal conditions is completely reversible) and which causes the typical symptoms of asthma: cough, breathlessness, and dyspnoea.
Although the symptoms are easily recognizable, these do not represent the fundamental aspects of the disease.

The basis of this pathology is given by **inflammation of the Respiratory Tract**, responsible of the hyperreactivity of the disease.

The obstruction to the air passage is caused by bronchoconstriction, bronchial edema, hypersecretion of mucus and inflammatory cell response, including eosinophils, *key* cells of the disease.
The symptoms represent just the tip of the iceberg of the inflammatory process.

Despite inflammation is the pathogenetic agent of asthma, in children the ongoing changes and the different stages of maturation of the organs, of the lungs and of the Immune System in particular should be considered.

A child's lung is not the lung of a *small* adult.

There are physiological aspects that expose children to greater risks, in particular the reduced diameter of the organs of the respiratory tract that may be more easily obstructed by inflammatory exudates.

There are other physiological aspects to consider, including a reduced rib cage and less elasticity of the Respiratory Tract.

Lung growth during childhood is of paramount importance in the expression of asthma in children.
– The forced expiratory volume in a second (FEV-1) varies with age.

Lung function increases in the early childhood, until reaching the maximum level at the beginning of adulthood.

This causes the respiratory symptoms to decrease in late childhood as a result of the lung tissue growth.

– During growth, the tendency in asthmatic children to "recover" one's condition could be the result of the increase of the pulmonary function, not necessarily the result of a change in the allergic response of the Respiratory Tract.

However, the fact that asthma in children reduces lung development can have important consequences in the course of life; the decline expected during elderly life "begins" from a lower FEV-1 level.

In the patient suffering from asthma, the Respiratory Tract is characterized by an accentuated reactivity (bronchial hyperreactivity) which leads, by the action of triggering factors (allergens, exertion, sudden variations in temperature of the inspired air) to a rapid and sudden deterioration of the respiratory capacity (asthma attack).

– During the asthma attack it is produced an edema of the mucosa and the smooth muscle in the airways gets contracted (bronchoconstriction) resulting in a decrease in the flow of air into the lungs ("air hunger").

The state of inflammation of the airways which characterizes asthma leads to a tissue remodelling that is established slowly but irreversibly, causing smooth muscle thickening **(muscle hyperplasia)**, swollen glands that produce mucus **(glandular hyperplasia)**, formation of new blood vessels **(neoangiogenesis)**, **collagen deposition**, **thickening** of the epithelial basement membrane and **reduction** of the **elasticity** of the Respiratory Tract wall, which results in a weaker and weaker response to therapy.

– If not treated properly, asthma leads to irreversible obstruction of the airways.
Considered these issues, it is evident the importance of early diagnosis and therapy of asthma.

RISK FACTORS

The risk factors of asthma can be divided in individual factors and environmental factors.

– Among the **individual factors** there is genetic predisposition: the probability of developing allergic asthma for those who do not have allergic parents is 5-10%; for those who have an allergic parent the probability is 25-50%; it rises to 75% when both parents are allergic.
Among the risk factors there is also atopy, the predisposition to a higher **IgE** synthesis.

Hyper-responsiveness of the airways also plays an important role.

– Among the **environmental factors** there is the massive presence of allergens and air pollution (both direct action, irritating for mucous membranes and as co-allergic factor, as a complex allergen is formed).
Respiratory infections play an important role; the lack of sufficient contacts with viruses and bacteria in the early years of life causes **reduction** of **Th1** lymphocytes and consequent **increase** in **Th2** lymphocytes.

Th1-Th2 BALANCE

The conclusions presented by recent studies on the changes in the development of immune functions during the first and second childhood help in the diagnosis and provide the explanation of the increased incidence of bronchial asthma in these periods.

– In the fetus and in the newborn the Immune System favours a Th2 response (increase in IgE and eosinophilic activation).
Contact with viruses and bacteria in the early years of life stimulates the Th1 response (delayed reactions of hypersensitivity) to the detriment of the Th2 response, shifting the Th1-Th2 balance towards a greater importance of Th1 (inhibition of atopic reactions) (FIG. 1).

With the maturation and exposure to microbial pathogens (in particular bacterial), the stimulation of Th1 lymphocytes occurs, restoring the Th1-Th2 balance.

– Recent research on asthma and on the causes of allergies, considered environmental exposure in early childhood.
It is interesting to focus that some environmental exposure, which once were considered a cause and an aggravating factor, could be "protective" if considered by the perspective of atopy and asthma.

In fact, although clearly beneficial, the reduction to daily exposures to pathogenic, bacterial and parasitic agents during childhood can reduce the "protective" effect of such infections against atopy and asthma.

Excessive hygiene produces the same result; moreover, the greater the number of children in the same family, the lower the probability that the younger children are affected by allergic bronchial asthma.
– Special eating habits can induce greater predisposition to asthma; excessive use of drugs (e.g. antibiotics), the presence or absence of parasitic infestations and tobacco smoke can increase the incidence of this pathology.

Following to the exposure to various infectious antigens during early childhood and with the maturation of the Immune System, the latter moves towards the Th1 cytokine profile, in most cases.
Th1 cytokines facilitate normal "non-allergic" reactions to the common environmental exposures.
In the last decades the successes obtained in the field of hygiene and public health have led to complete prevention of many childhood infections.

It is theorized that the relative absence of infectious antigenic exposures shifts the Th1-Th2 balance towards the **Th2** cytokine profile.

ASTHMA AND THE IMMUNE SYSTEM

Asthma is a chronic disease characterized by 3 main events that occur in the respiratory tract: **1)** partially reversible obstruction of the lower Respiratory Tract; **2)** increase of bronchial reactivity to different stimuli; **3)** inflammation.

– It is supposed that bronchial reactivity has a genetic basis.

Initially transitory, bronchial hyperreactivity is supported by a continuous stimulation (constant presence of triggering factors such as allergens, pollutants, infections) that evolves into a permanent state of hyperreactivity.

While bronchial reactivity has always been considered the clinical characteristic of asthma, inflammation of the Respiratory Tract represents the *key marker* of this disease.

Since the early studies, evidence that inflammation is one fundamental component of asthma has been given by autoptic findings.

Histopathological findings demonstrate bronchial infiltration by eosinophils, mast cells and lymphocytes.
Mast cells and eosinophils secrete a wide range of mediators that lead to tissue inflammation.
Other cytotypes such as lymphocytes, macrophages and epithelial cells produce other soluble factors (cytokines) that mediate inflammation in asthma.

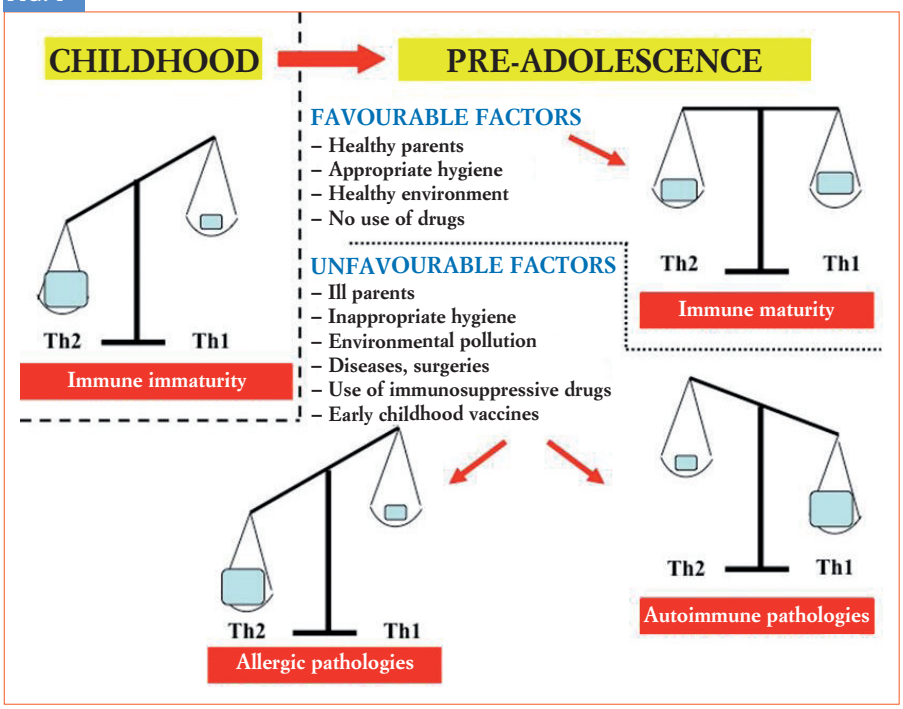
– The Respiratory Tract is infiltrated by neutrophils and eosinophils, degranulated mast cells resulting in the thickening of the epithelial basement membrane and in the occlusion of the bronchial lumen by the mucus.

The bronchial smooth muscles produce hyperplasia and hypertrophy, as well as hypertrophy of the calciform cells.
These findings are also characteristic of mild forms of asthma, though varying according to clinical severity.

Most of the cells of the Respiratory Tract are activated and release preformed or recently synthesized chemical mediators, substances that play a direct role in the disease.

In the bronchoalveolar washing fluid

FIG. 1



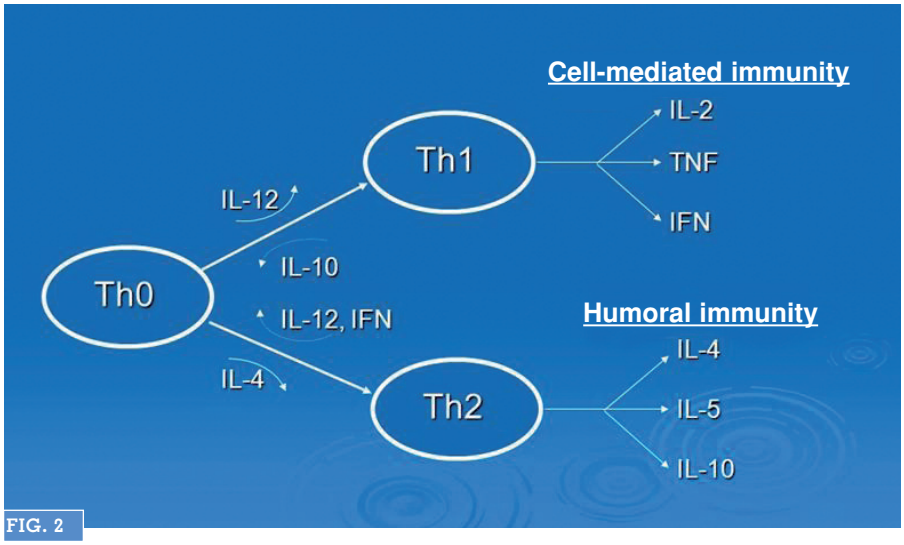


FIG. 2

and in the bronchial secretions there is an abundance of chemotactic chemokines as well as of cytokines that mediate inflammation.

From a purely inflammatory point of view, T helper 2 **(Th2)** lymphocytes play a fundamental role in the development of asthma because they stimulate the presence of **eosinophils** and the production of immunoglobulin E **(IgE)** by the B lymphocytes.

T lymphocytes are responsible for the reactions of cell-mediated immunity (activation of macrophages, Natural Killer cells, cytokines), while B lymphocytes are responsible for humoral immunity reactions through the production of antibodies (immunoglobulins).

Both eosinophils and IgE are fundamental elements in the process of inflammation given by allergy.

Insufficient contact with viruses and bacteria in early childhood, a condition that could occur when children live in a too much protected environment from a hygienic point of view, would prevent the establishment of a correct balance between Th1 and Th2 lymphocytes (hygienist hypothesis).

Th cells are divided into two subsets distinguished according to the cytokines produced:

– **Th1 → IL-2**, **IL-12**, **IFN-gamma**, and **TNF-beta**;
– **Th2 → IL-4**, **IL-5**, **IL-6**, **IL-10**, and **IL-13** (FIG. 2).

It is not clear if, and to what extent, the antigen nature can affect the quality of the response to produce an imbalance of the Th1 or Th2 phenotype.

– Th1 cells induce responses of delayed hypersensitivity and promote the activation of specific cytotoxic lymphocytes (CD8 + T cells and Natural Killers) for the secretion of IL-12 and IFN-gamma.

– Th2 cells are necessary for the differentiation and proliferation of the B cells, Their production of IL-4, IL-5, IL-6, IL-10, and IL-13 induces the differentiation of B lymphocytes in plasma cells; the production of IL-4 activates mainly the IgG-IgE switch (FIG. 3).

In contrast to the pro-asthma effects of Th2 cytokines, treatment with Th1 cytokines such as IFN-gamma decreases the recruitment of eosinophils during the allergic inflammation.

The molecules that can decrease IgE levels (lowering the production of Th2 cytokines and increasing the production of Th1 cytokines) can modulate allergic reactions.

Based on this assumption several studies, *in vitro* and *in vivo*, have tested the capacity of IL-12 to decrease the synthesis of Th2 cytokines.
In all experiments, it has been demonstrated that IL-12 influences allergic inflammation and bronchial hyperreactivity.

– Recently some studies have shown that treatment with IL-12 decreases IgE production *in vivo* and *in vitro* and that it has strong immunomodulatory effects on pulmonary inflammation.

These observations provide additional evidence in favour of the importance of the Th2-polarized cells and the relevance of associated cytokines in the induction and maintenance of the inflammatory events of the Respiratory Tract in the asthmatic patient.

To date, the control of mediators released by mast cells and eosinophils has been considered the main way to inhibit allergic reactions.
The data here presented suggest that the ability to control the T cell activation after stimulation by the allergen can lead to a therapeutic approach that can control asthma.

– These evidences indicate a new way to clarify the pathophysiology of asthma suggesting also an innovative therapeutic approach through the rebalancing of the cytokines responsible of allergic-inflammatory reactions of the Respiratory System.

CYTOKINES, INFORMATION AND LOW DOSE

The Immune System is composed of cells whose functioning depends on their communication that takes place either by direct contact or through cytokines and chemokines, a true **network** for the organism.

These molecules are active within a complex communication network and reflect and support different immune responses.

The chemical and biological characteristics of the antigen, and the circumstances in which it meets the host, influences the type of System response through the activation of specific subgroups of T helper lymphocytes (Th).
In turn, Th lymphocytes organize the immune response producing specifics cytokines.
Furthermore, certain types of diseases are characterized by the involvement of specific cytokines.

– In response to viruses, bacteria, tumors and transplants, the subgroup **Th1** is activated.
This subgroup, which can be identified for the production of IL-12 and INF-gamma, enhances the cellular defence (cytotoxic lymphocytes, macrophages), stimulating the synthesis of proinflammatory cytokines **(IL-1**, **TNF-α**, **IL-6)**.
Otherwise, soluble antigens and parasites determine a **Th2** lymphocyte response, which can be identified for the production of **IL-4**, **IL-5** and **IL-10**, reinforce the humoral defence and induce the activation of eosinophils and of basophils.

There are other subgroups of T lymphocytes with complex regulatory functions, which can be recognized for the production of typical cytokines.

– **Th1** cytokines are produced by lymphocytes themselves, but mostly by activated macrophages. They are **pro-inflammatory** because they promote the recruitment of immune and inflammatory cells on the site of the lesion.
Th2 cytokines are **anti-inflammatory** because they can fight the action of the pro-inflammatory ones.

Th3 type cytokines are regulatory.

The secretion of cytokines is a self-limited phenomenon that contributes to the defence organization and that finishes with the accomplishment of an effective immune response.

In some conditions, some cytokines are over-expressed in **quantity** (as in sepsis for macrophage cytokines and in anaphylaxis for Th2 cytokines) or in **duration** (as in chronic inflammatory diseases and granulomatous diseases).

In such cases the toxic effects of these molecules exceed their usefulness in the organization of the immune response.
The use of cytokines at pharmacological doses has caused serious side effects, including heart arrhythmia and death.

Therefore, the use of low dose, appropriately activated, cytokines has been devoted great attention in order to avoid the side effects typical of pharmacologically-active high doses.

The attention of Physiological Regulating Medicine (PRM) has focused on the role of messenger molecules who act as medicines; they help an ill organism to return to the original physiological conditions thanks to the **oral administration of low and physiological doses of activated messenger molecules**.

In this way PRM is essential in the care of children. Through the use of low-concentration cytokines, the normal physiological functions of the organs defending the organism can be restored, without attacking them, as conventional drugs, but stimulating them to greater reactivity.

In a disturbed biological balance, such low-dose SKA (Sequential Kinetic Activation) medicines convey information to rebalance the cell activity.

The most critical point of conventional therapies which are currently being used lies in their inability to act on the aetiology which unites all allergic atopic diseases, which is the imbalance of the Th1-Th2 response.

The use of a therapy based on cytokines produced by the Th1 lymphocyte subpopulation (such as IL-12 and IFN-gamma), designed to counteract the over-expression of Th2 cytokines, represents the most advanced pharmacological approach in the field of clinical application of the principles of immune therapy.

– Starting from these considerations, some trials have been recently launched

FIG. 3

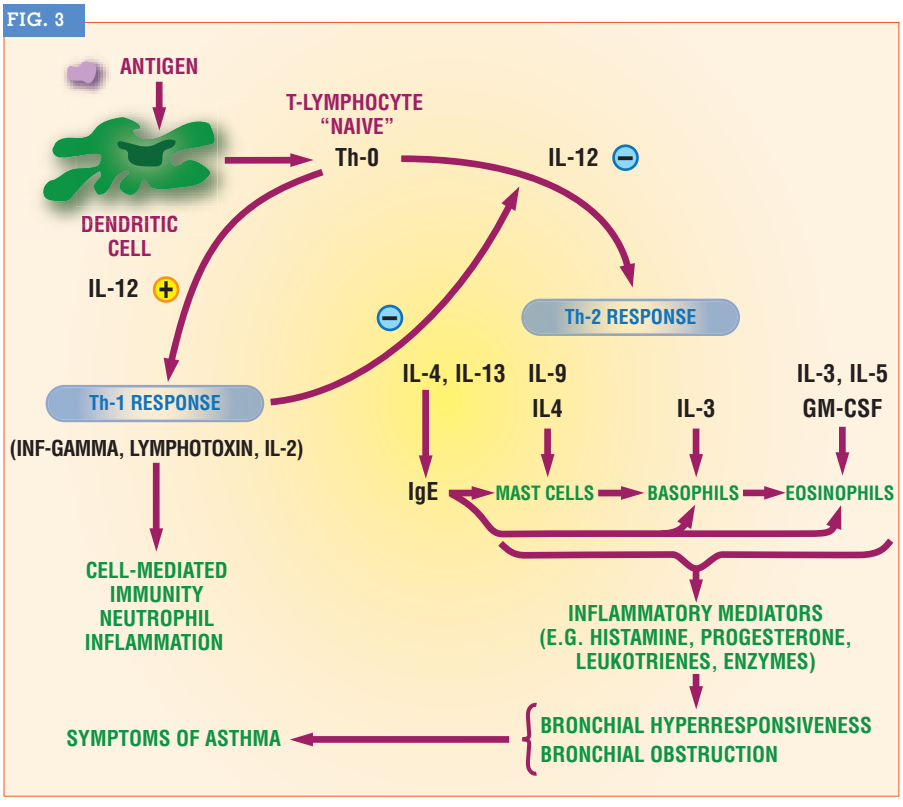
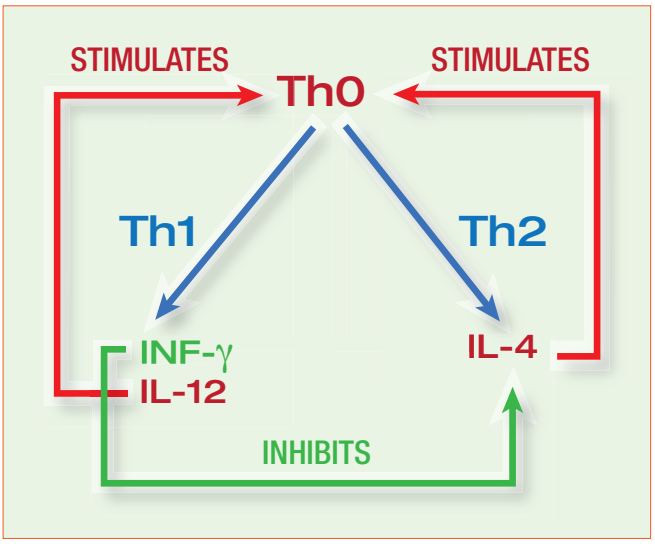


FIG. 4



and concluded in order to investigate the feasibility and effectiveness of a therapeutic intervention based on Low Dose Medicine for allergic diseases, above all pediatric ones.

– *In vitro* it has been shown that some Th1 SKA-activated low dose cytokines (in particular **IL-12** and **IFN-gamma**), modulate the expression of the Th2 overexpressed cytokines in order to re-balance the response Th1-Th2.

MATERIALS AND METHODS

Following what above presented, it has been proposed for 28 pediatric patients suffering from bronchial asthma a treatment with low dose SKA cytokines and *low dose* medicines.

– The medicines used in the study are biological (physiologically present in the body) low dose molecules, draining medicines that act on the Immune System, promoting the specific and non-specific desensitization to the most common allergens causing respiratory diseases.

– GUNA-IL-12 and GUNA-INF GAMMA

– The use of GUNA-IL-12 and of GUNA-INF GAMMA in physiological concentration 4CH [corresponding to the same concentration in which they are present in transmembrane receptors and in the extra-cellular matrix (ECM)], favours the Th1 response and restores the balance Th1-Th2.
Because different cytokines can have different effects on the same cell, that is a cytokine can antagonize the effect of another (e.g. IL-4/INF-GAMMA), in Physiological Regulating Medicine are used the **antagonistic cytokines** to contain the biological effect, not different dilutions of the same cytokine.
– In pathological conditions it is observed an imbalance; for example, in acute inflammatory diseases the Th1 "part" is preeminent. In such cases the therapy consists in "increasing" the Th2 part (IL-4, IL-10, TGF-BETA) to rebalance the immune balance.

• In allergic diseases the Th2 part is preeminent; in these cases the therapy consists in increasing the Th1 part (IL-12, INF-GAMMA).

To sum up, the use of GUNA-IL-12 and GUNA-INF GAMMA in physiological dilution 4CH, is able to produce the Th2-Th1 rebalance.
At the same time, Th1 interleukins are able to inhibit the secretion of Th2 interleukins (FIG. 4).

– GUNA-MATRIX

The use of this medicine finds a precise rationale because the ECM plays a key role in all inflammatory processes: the storage of allergens in the ECM determines a high level of reactive hypersensitivity in the target tissue.
The detoxification of the ECM represents, therefore, the keystone for maintaining or restoring health.
The delicate systems that regulate the balance health-disease are in the ECM: it is here that, through the cytokines and the neural and endocrine components, PNEI information is carried in order to coordinate and control functions.
The modifications of the ECM influence the cellular dynamics: here a great amount of information can be stored and transmitted to the cells as instructions for their physiological functioning.
– Transferring messages from a system to another may be hampered, inhibited or modified, with consequent alteration of the System itself.

– GUNA-MATRIX acts on the ECM (mesenchymal draining).

– CITOMIX®

– The action of CITOMIX® can depend on non-specific effect in controlling inflammation of the Respiratory System and can be connected to the ability to influence the release of radical superoxides (reducing it) in the granulocytes of the peripheral blood.
50-80% of all the affected cells by an inflammatory reaction are granulocytes; with the migration to the inflammatory outbreak, these release elastase, collagenase, phosphatase, lipase, etc.
The released enzymes damage the surrounding tissue and increase the inflammatory process.
The same enzymes exert stimulation on fibroblasts and promote repair of the damaged tissue, which leads to a fibrotic modification of the lungs.

– GUNA-ALLERGY-PREV

GUNA-ALLERGY-PREV is a PRM medicine designed for effective specific and non-specific desensitization for the

most common and widespread airborne allergens and for a prompt modulation of the inflammatory symptomatology (conjunctival burning, hyperlacrimation, photophobia, itching and nasal obstruction, serous rhinorrhoea, headache, cough, asthmatic crises).

In PRM therapy of childhood asthma, there are four basic pillars:

• Draining of the ECM.

At this stage it is important to use GUNA-MATRIX and CITOMIX®.

• Induction of the immune tolerance, through the administration of low dose allergens (GUNA-ALLERGY-PREV).

• Production of the Th2 → Th1 switch, in order to restore the immune balance; in this way we act at the origin of the clinical manifestation.

Th1 interleukins inhibit the secretion of interleukins Th2 (GUNA-IL-12 and GUNA-INF GAMMA in physiological dilution 4CH).

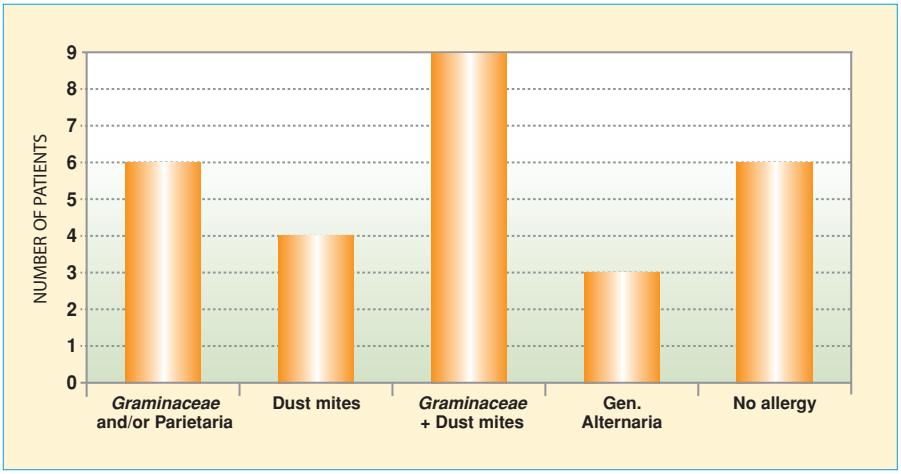
• Basic therapy with CITOMIX® that determines non-specific stimulation of the Immune System.

▶ This clinical trial included **28 patients**, aged between **4 years and 2 months** and **13 years**.

Patients were affected of allergic and non-allergic bronchial asthma, or presented recurrent bronchial obstruction.

15 children, patients in specialized centres, had been tested for functionality of the Respiratory System according to age; all patients had performed cutaneous allergy tests (skin prick test) for the most common airborne allergens.

The analysed children were: allergic to *Graminaceae* and/or to Parietaria *(Parietaria officinalis)* **(6)**; allergic to mites **(4)**; positive to skin prick tests for *Graminaceae* and mites **(9)**; positive for Gen. Alternaria **(3)**; negative to skin prick tests **(6)** (of these 3 presented documented stress-induced asthma) (TAB. 1).



TAB. 1

– In most of the patients, the persistence of symptoms and the clinical characteristics of the disease had made it necessary an ongoing therapy with inhaled corticosteroid, corticosteroid associated with long-acting bronchodilator and/or with Montelukast. Only 3 patients had been firstly suggested a therapy with low dose interleukins.

19 patients presented symptoms typical of persistent-mild asthma and the remaining 9 patients presented symptoms typical of persistent-moderate asthma (classification by GINA) (FIG. 5, TAB. 2).

Patients have been monitored for periods ranging between 12 and 24 months.

The observation period has been divided in two overlapping periods for duration; for each of these it was calculated the number of bronchial obstruction episodes.

The first period covers the one prior to the treatment with interleukins, in which the patient was treated with conventional drugs or no preventive therapy.

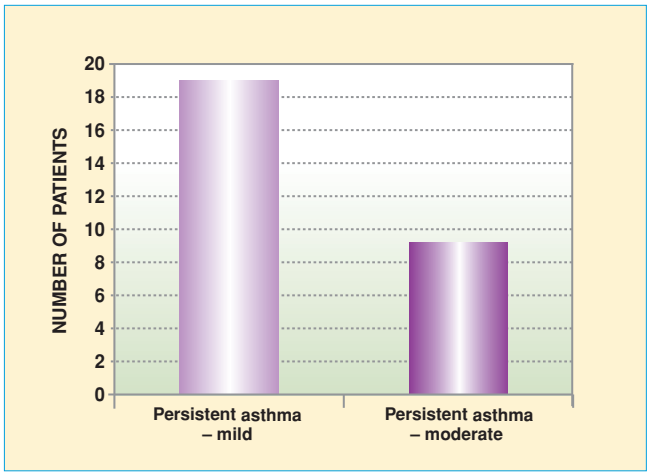
In the second period, conventional drugs were initially associated with Interleukin and the low dose therapy.

Considering all patients (28): **10** were in continuous treatment with inhaled corticosteroids; **4** associated Montelukast with the therapy with inhaled corticosteroids; **6** were treated exclusively with Montelukast; **5** were treated with inhaled corticosteroids associated with long-acting bronchodilator; **3** were not following any therapy at enrolment (TAB. 3).

FIG. 5

	Symptoms	Night symptoms	FEV1 or PEF
STEP 4 Severe Persistent	Continuous Limited physical activity	Frequent	FEV1 ≤ 60% expected PEF variability > 30%
STEP 3 Moderate Persistent	Daily attacks limiting the activity	1/week	FEV1 ≤ 60-80% expected PEF variability > 30%
STEP 2 Mild Intermittent	> 1/week but < 1/day	> 2/month	FEV1 ≥ 80% expected PEF variability 20-30%
STEP 1 Intermittent	< 1/day	≤ 2/month	FEV1 ≥ 80% expected PEF variability < 20%

TAB. 2



The change of therapy was determined by the fact that the clinical situation was not stabilized (50%); the other 50% decided to change therapy for poor confidence in the conventional medical therapy and fear of side effects.

– The clinical course was evaluated on the basis of the data entered in a monthly clinical diary regarding symptoms and therapies (TAB. 4).
Patients were administered the Interleukins; for the first period (1-2 months) the ongoing conventional therapy has been maintained; when the clinical condition resulted stable, anyway never before the completion of the first month of therapy, the conventional therapy was suspended.
For the patients who took two drugs, the suspension took place gradually, interrupting a drug first and, after about another month – along with the stabilization of the symptoms – the second one was also suspended.

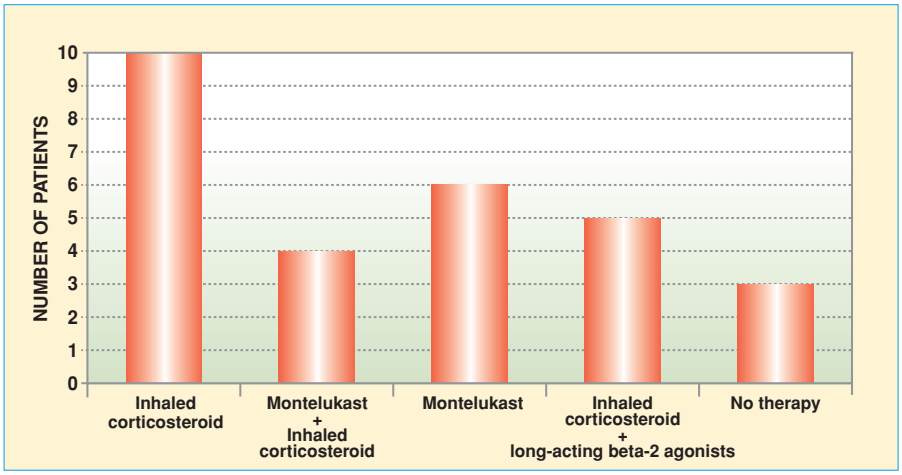
For all the enrolled patients the therapy consisted in: **GUNA-IL-12 4CH**, **GUNA-INF GAMMA 4CH**, **CITOMIX®** and **GUNA-MATRIX**.
This therapy was integrated with **GUNA-ALLERGY-PREV** if the asthma was due to an allergic pathology (22 patients).
– The therapy was implemented in cycles of 3-6 months and resumed during the expected critical periods.

RESULTS

After 2 months of therapy the number of bronchial obstruction episodes decreased in all the patients, with a radical reduction in the use of bronchodilators, antihistamines and cortisone taken orally.
– The decrease in the use of bronchodilators was significant.
Patients on average used bronchodilators **11** days/month; in the first 45-50 days this number dropped to **6** days/month, and was reduced to **3** days/month after 3 months of therapy (TAB. 5).

In 2 patients the interruption of the cytokine-based therapy caused, after 3-5 months, new bronchial obstruction episodes (their parents then decided to resume the low dose treatment).
No patient stopped spontaneously the therapy.
Generally, the average number of bronchial obstruction episodes in the months before the beginning of the low dose therapy was **6.7**; during the low dose treatment the number fell on average at **2.5** (TABs. 6, 7, 8).

TAB. 3



DISCUSSION

The results of this trial can be explained by the principles of Physiological Regulating Medicine.
The conclusive evaluations are given by the doctor's opinion and feedbacks from the patient and his/her family.
From a clinical point of view the final evaluation is positive: a clear reduction in symptoms was objectively recorded in all the analysed patients.

This determined the reduction of the bronchial obstruction episodes in each patient, with a decrease in the number of children's school absences and their parents' work absences.
It was possible to reduce the administration of conventional antiasthmatic drugs and bronchodilators.
It has also to be mentioned that children referred a clear sensation of improved well-being, both physically and psychologically, which was confirmed by parents.

– Compliance was excellent because, apart from the proven clinical result, the

parents were reassured by the fact that the therapy was effective, well tolerated and without side effects.

CONSIDERATIONS AND CONCLUSIONS

Childhood bronchial asthma is one of the most common pathologies and represents one significant cause of human and social costs, with remarkable impact on daily activities and on the children's quality of life as well as that of their families.

Most of the patients included in the study started the PRM therapy because their parents were worried of the side effects given by the conventional drugs and/or because the ongoing conventional therapy was poor in controlling symptoms.

– What motivated to continue the proposed therapy was the significant reduction of bronchial obstruction episodes with evident clinical improvement.

The comparison with conventional therapy highlights:
1) minor use of the antihistamines;
2) lower use of cortisone inhalers;
3) lower use of beta2-agonist.

The PRM therapy resulted in a good disease control, a good quality of life, with very few school absences.

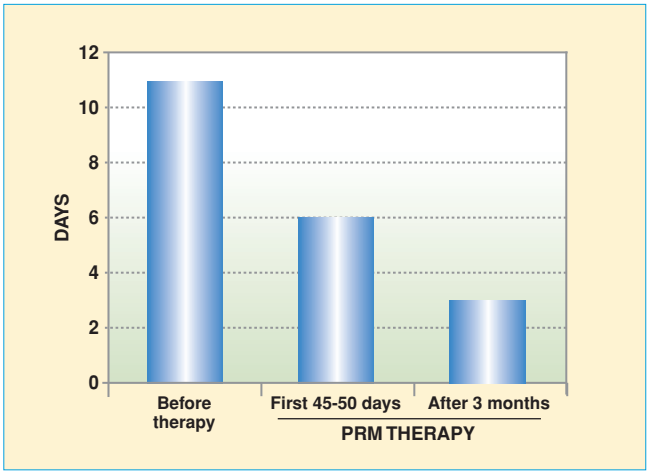
After the first month of PRM therapy the use of conventional drugs was greatly reduced until complete elimination. The asthmatic crises decreased significantly.

The results were very satisfactory, both for the reduction of the symptoms and for the total lack of collateral effects, as well as the excellent compliance.

It is believed that the use of IL-12 4CH and of INF-GAMMA 4CH SKA, together with the draining therapy, represents an interesting therapeutic novelty in the treatment of childhood bronchial asthma.

		1	2	3	4	5	6	7	8	9	10	ETC.			
COUGH	Day														
	Night														
HISS OUT OF BREATH	Day														
	Night														
BLOCKED NOSE															
FEVER															
SCHOOL ABSENCES															
Aerosol															
Bronchodilator															
Cortisone															
Antibiotics															

TAB. 4



TAB. 5
Days/month using bronchodilator.

– Physiological Regulation Medicine offers innovative therapeutic tools, and thanks to the physiological dilution (4CH) allergic diseases and asthma in children can be treated with higher serenity. ■

References

- Agarwal A., Singh M., Chatterjee B.P., Chauhan A., Chakraborti A. – Interplay of T Helper 17 Cells with CD4(+)CD25(high) FOXP3(+) Tregs in Regulation of Allergic Asthma in Pediatric Patients. Int J Pediatr. **2014**.
- Bachert C., van Kempen M., van Cauwenberge P. – Regulation of proinflammatory cytokines in seasonal allergic rhinitis. Int Arch Allergy Immunol. **1999** Feb-Apr.
- Benson M., Strannegård I.L., Wennergren G., Strannegård O. – Low levels of interferon-gamma in nasal fluid accompany raised levels of T-helper 2 cytokines in children with ongoing allergic rhinitis. Pediatr Allergy Immunol. **2000** Feb;11(1):20-8.

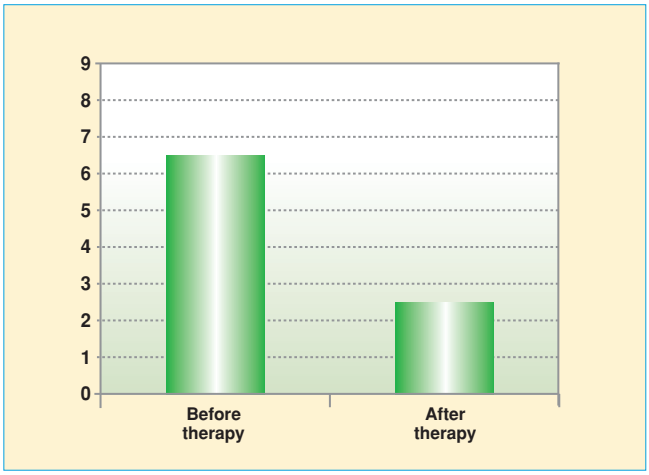
TAB. 6

Key
C inal = Inhaled corticosteroid.
B inal = Inhaled bronchodilator, long acting.
n.t. = No therapy.

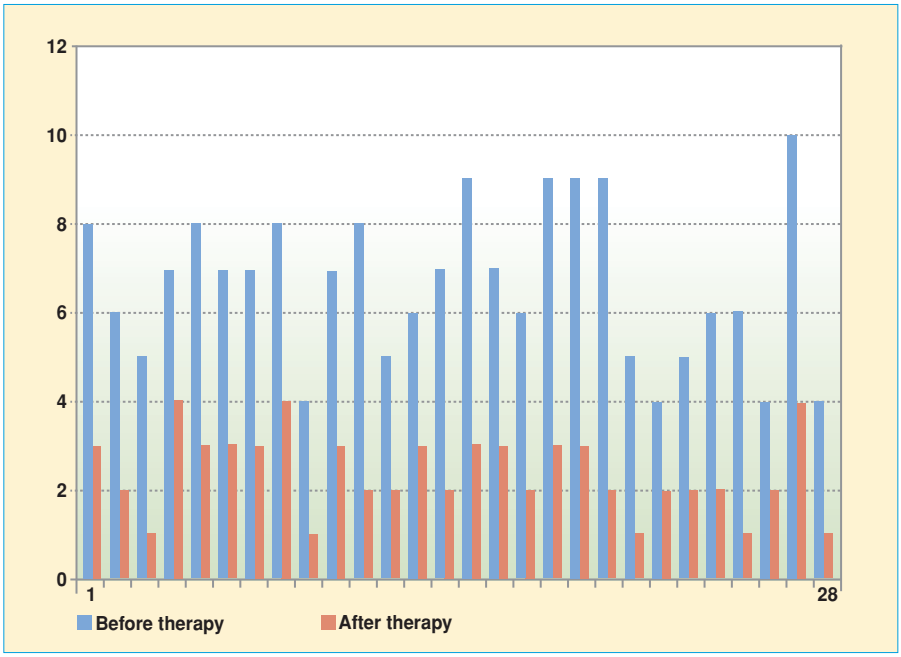
Observational period (months)	Previous therapy	Number of episodes before t.	Number of episodes after t.
12 + 12	C inal	8	3
12 + 12	C inal + B inal	6	2
10 + 10	Montelukast	5	1
12 + 12	C inal + B inal	7	4
12 + 12	C inal + Montelukast	8	3
12 + 12	C inal + Montelukast	7	3
12 + 12	C inal + B inal	7	3
12 + 12	C inal + B inal	8	4
8 + 8	Montelukast	4	1
10 + 10	C inal + Montelukast	7	3
10 + 10	Montelukast	8	2
12 + 12	C inal + Montelukast	5	2
10 + 12	Montelukast	6	3
8 + 8	Montelukast	7	2
10 + 10	Montelukast	9	3
12 + 12	C inal	7	3
12 + 12	C inal	6	2
12 + 12	C inal	9	3
10 + 10	n.t.	6	2
8 + 8	n.t.	6	1
12 + 12	C inal	9	3
8 + 8	C inal	5	2
7 + 7	C inal	5	1
6 + 6	n.t.	4	2
10 + 10	C inal	5	2
12 + 12	C inal	6	2
9 + 9	C inal	4	1
12 + 12	C inal + B inal	10	4

TAB. 7

Average number of bronchial obstruction episodes before and after PRM therapy.



- Bianchi I. – Citochine e interferoni: farmacologia e clinica. Nuova Ipsa, Palermo; **2007**.
- Delzoppo G.P. – Terapia della bronchite asmatica in età pediatrica: protocollo omeopatico vs. protocollo allopatico corrispondente di riferimento. La Med. Biol., **2004**/1; 3-7.
- GINA – Linee Guida Italiane. Workshop GINA. Modena, 11-13 marzo **2004**.
- Heine H. – Manuale di Medicina Biologica- Regolazione di base e matrice extracellulare. Guna Ed., Milano; **2009**.
- Huang J., Zhang M., Zhang X., Wang L. – Airway hyperresponsiveness and small airway function in children with well controlled asthma. Pediatr Res. **2015** Feb 26.doi:10.1038/pr. 2015.42.
- Hui Y., Xie J.J., Li L., Xiang H.X., Mu H.J., Yin Y., Zhang X.J. – Association between suppressors



TAB. 8

Number of bronchial obstruction episodes before and after PRM therapy.

of cytokine signaling mRNA expression and Th1/Th2 balance in children with asthma. Zhongguo Dang Dai Er Ke Za Zhi. **2012** Oct;14(10):755-8.

– Jirapongsananuruk O., Leung D.Y. – Clinical applications of cytokines: new directions in the therapy of atopic diseases. Ann Allergy Asthma Immunol. **1997** Jul;79(1):5-16.
– Klok T., Kaptein A.A., Brand P.L. – Non-adherence in children with asthma reviewed: the need for improvement of asthma care and medical education. Pediatr Allergy Immunol. **2015** Feb 23. doi: 10.1111/pai.12362.
– Koulouri M., Vrachnou E., Liatsis E., Konstantopoulos A., Kanariou M. – Evaluation of intracellular cytokines IL-2, IFN , IL-4 and IL-5 in children with atopic dermatitis and correlations with other immunological and epidemiological parameters. Clin Transl Allergy. **2014** Feb 28;4 (Suppl 1 3rd Pediatric Allergy and Asthma Meeting).
– Malzac J.L.R. – Materia Medica Omeopatica di Immunologia Clinica. Nuova Ipsa Editore; **2007**.
– Mazza C. – L'allergia. Strategia terapeutica secondo l'Omotossicologia e la Medicina Fisiologica di Regolazione. Nuova Ipsa Editore, Palermo; **2011**.
– Noutsios G.T, Floros J. – Childhood asthma: causes, risks, and protective factors; a role of innate immunity. Swiss Med Wkly. **2014** Dec 24;144:w14036 .
– Ren Y.F., Li H., Xing X.H., Guan H.S., Zhang B.A., Chen C.L., Zhang J.H. – Preliminary study on pathogenesis of bronchial asthma in children. Pediatr Res. **2015** Jan 13.
– Sarinho E.S., Azoubel-Antunes A., Rêgo M.J., Brayner-Cavalcanti M., Lins E., Lins T.U., Pitta I.D., Pitta M.G. – Evaluation of Th17-related cytokines and IFN production from blood mononuclear cells of moderate and severe asthmatic children reveals methylprednisolone does not decrease IL-22 levels. J Asthma. **2014** Sep 17:1-5.
– Sybilski A.J., Lusawa A., Lipiec A., Piekarska B., Raciborski F., Krzych-Falta E., Tomaszewska A., Samolioski B. – The effects of disease awareness on lifestyle changes and the use of preventive measures in asthma patients. - Allergy Asthma Proc. **2015** Mar;36(2):14-22. doi: 10.2500/aap.2015.36.3822.
– Vidal G.A. – Pediatric asthma control and quality of life questionnaires. Rev Chil Pediatr. **2014** Jun;85(3):359-66.

author

Dr. Ornella Righi, MD
– Specialist in Pediatrics
Via Marconi, 74
I – 29010 Pontenure (PC)