Asthma

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Abstract

The objective of this article is to discuss some facts about modern immunomodulators that may be useful for asthma treatment. Another important objective is to dissipate myths that may cause negative impact in the doctor using these drugs. The initial focus is in stimulating immunomodulators that are able to induce the accentuation of normal response in immune-competent cells. Asthma is a chronic inflammatory disease that represents a public health problem with high number of deaths and elevated socio-economical impact. The pathology is characterized by the immediate stage, mediated by the acute response of inflammatory cells, and the late stage, which is responsible for the response involving specific cells of the immune system. Currently, the main kind of drugs used in asthma treatment is bronchodilators and anti-inflammatory agents, which relieve the bronchospasm and diminish the airway inflammation. However, therapies that use these drugs are not completely efficient and cause side effects. The shortage of safe drugs and the difficult access of underprivileged people to the treatments available stimulate the search for new substances that may be potentially useful in asthma treatment. Homeopathic products such as the Immunomodulator Medicine Canova, object of this work, represent a great pharmacological potency against asthma, since they may furnish several molecules with specific mechanisms for the pathology treatment and control. The search for more efficient and specific therapies for the asthmatic process has an important role in the discovery of new therapies against asthma.

Keywords: Asthma, chronic inflammation, immunomodulators, homeopathic medicament, Canova.

Introduction

Asthma is a chronic inflammatory disease characterized by hyper responsiveness (HR) of the lower airways and variable limitation of airflow, spontaneously reversible or with treatment, manifested clinically by recurrent episodes of wheezing, breathlessness, chest tightness and coughing, particularly at night and in the morning, awakening. It results from an interaction between genetics, environmental exposure and other specific factors that lead to the development and maintenance of symptoms (Busse e Lemanske, 2001; Cookson,1999; Kumar, 2001).

Prevalence

According to the Global Initiative for Asthma (Gina) there are over 300 million asthmatics in the world. This Group estimates that by 2025 the urban population will increase from 45 to 59%. So, 100 million asthmatics will be added to the world population. The highest incidence occurs in most industrialized countries.

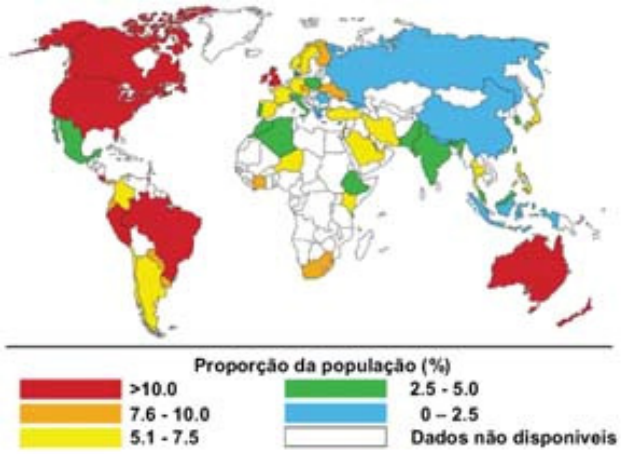

Figura 1. Perfil da prevalência de asma clínica no mundo (adaptado de Bousquet et al., 2005).

Asthma Pathology

The development of asthma may be defined by two characteristic phases: the immediate phase (or acute) and late stage, where the adaptive immune response is in evidence (Rang et al., 2004).

Immediate Phase

The immediate phase is the initial response to irritating stimuli that act on the receptors of sensory fibers (cholinergic) present in the smooth muscle of the airways, mucus-producing glands and bronchi. The stimuli that cause coughing, bronchial constriction and increased mucus production, are related to respiratory infections and exogenous agents, such as pollutants, cigarette smoke, allergens and cold air (Howarth, 1997; Rang et al., 2004).

The interaction of allergen with the body leads to the recognition of antigen by antigen presenting cells (APC), such as tissue macrophages (MØ) and dendritic cells (DC). When the antigen is a microorganism, it has components retained in its structure called *molecular patterns associated with the pathogen* (MPAP) that are essential in the process of recognition (Wagner & Roth, 1999; Bochner & Busse, 2004; Rang et al., 2004).

A prime example of MPAP is bacterial lipopolysaccharide (LPS) that is closely linked to the outbreak of the initial response of asthma attack (Wagner & Roth, 1999; Bochner & Busse, 2004; Singh & Schwartz, 2005). The LPS, a bacterial endotoxin, is a constituent of the outer membrane of Gram-negative bacteria and has a powerful ability to stimulate the immune response (Liu, 2002).

When the interaction of antigen with the glycoproteins present in the receptors expressed on the APC takes place, a series of responses is initiated by activating the main immediate pro-inflammatory cytokines, such as tumor necrosis factor (TNF-α), interleukin 1 (IL-1). These cytokines increase vascular permeability, allowing the exudation of fluid containing other inflammatory mediators, chemotaxins, expression of

adhesion molecules (selectins and integrins), bradykinin formation and pro-inflammatory transcription factors (NF-κB and AP-1) (Wagner & Roth, 1999; Rang et al., 2004; Leath et al., 2005).

The first cells to reach the affected site are neutrophils, and its engagement is the first sign of early inflammatory response. These cells release leukotriene LTB4 type (chemotactic agent), induce cyclooxygenase type 2 (COX-2) and type 5 lipoxygenase (LOX-5) - enzymes involved in the production of eicosanoids and leukotrienes - increase expression of C3b opsonin and are capable of producing reactive oxygen species (ROS) involved in tissue injury (Wagner & Roth, 1999, Rang et al., 2004; Lazaar & Panettieri, 2004). Next, mast cells, endothelial cells and platelets are activated. The interaction of allergen with IgE (antibody involved in allergic response) is able to promote degranulation of mast cells and, consequently, the release of histamine, PGD2 and cysteinyl-leukotrienes LTC4 and LTD4, all powerful spasmogenics. At the same time, the interaction of allergen with platelets can promote the production of thromboxane A2 (TXA2) and platelet activating factor (PAF). Like histamine, PAF and TXA2 also have spasmogenic action on the bronchial muscle. Endothelial cells increase the secretion of nitric oxide (NO) that relaxes smooth muscle behind, further increasing vascular permeability and causing cytotoxic effects (Wagner & Roth, 1999; Rang et al., 2004; Lazaar & Panettieri, 2004; Redington, 2006).

The prior sensitization of the individual, genetic predisposition and other factors, create an allergic state in the body which favors the interaction of circulating IgE with its receptors present on B cells (memory cells), MØ, mast cells, monocytes, eosinophils and APC (Wong & Koh, 2000). This interaction amplifies the release of spasmogenics and other mediators capable of activating the helper T cell type 2 (Th2) and promoting the differentiation of B cells. In parallel, there is the induction of eosinophilia (increased number of eosinophils), production of fibroblasts and tissue remodeling with increased recruitment of neutrophils and hyperresponsiveness.

Various cytokines and chemotaxins released in response to the first stimulus attract leukocytes, particularly eosinophils and T cells to the inflammatory area. The excessive presence of eosinophils and lymphocytes promote the late phase of asthma, where cells of specific immune response are involved.

Late Stage

This step consists of a progressive inflammatory reaction, with special features such as the presence of Th2 lymphocytes, B cells and eosinophils in larger numbers. The imbalance of Th2/Th1 type cytokines promotes the occurrence of this phase. Th2 cells produce cytokines (eg IL-5) that are capable of amplifying its own proliferation, of B cells and eosinophils, once more beginning the activation cycle.

In the late phase there is the deposition of extracellular matrix, increased cell mass of bronchial smooth muscle, hyperplasia of the glands that produce mucus and tissue remodeling. The matrix deposition leads to pulmonary edema, increased mucus secretion and thickening of the airways contributing to tissue injury with loss of epithelium and changes in mechanical properties of the airways (Lazaar & Panettieri, 2004; Luster & Tager, 2004; Epstein, 2006).

Morbidity

Asthma is a major cause of morbidity in patients of all ages. The magnitude of the disease in a community can be measured by indicators that reflect the impact on the patients' quality of life, such as hospital admissions, outpatient visits, absence from school or work, among others.

Hospital Morbidity

Asthma has a major impact on the lives of children and family. A high number of asthmatic children seek emergency services and frequently need hospitalization. Chatkin et. al. (2000), analyzing emergency services in southern Brazil showed that 31% of asthmatic children were seen in emergency rooms in the last year, 57% had consulted a doctor and 26% were hospitalized.
Asthma has recognized seasonal periodicity, a phenomenon that is reflected in morbidity and mortality. There is a clear reflection of hospital admissions for asthma in all ages in the period between the months from May to September / October.

Outpatient Morbidity

Ratings on the proportion of primary care visits, another parameter to study the impact of asthma in a community, the demand for health services, are difficult to implement. Camargos and Profeta (2003) studied 560 children between 4 and 14 years old in a pulmonology clinic in central Minas Gerais, served from April 1996 to December 2000. They found that 42.7% of these children had been hospitalized in the last 12 months and 92.7% had sought care in emergency services.
Thus, we can say that asthma is responsible for much of the demand for health services, occupying the attention of the health worker, both in hospitals and ambulatory services.

Functional diagnosis

Spirometry
Are indicative of asthma (Busse e Lemanske, 2001; Rees, 2005; Isaac, 1998 (A) e 1998 (B)):

- Obstruction of the airways characterized by reduction in FEV1 * (less than 80% of predicted) and the ratio FEV1 / FVC ** (less than 75% in adults and 86% in children);
- Airflow obstruction that disappears or improves significantly after bronchodilator use (FEV1 increase of 7% over the predicted and 200 ml in absolute value, after inhaled beta-2 short-term); airflow limitation unresponsive bronchodilator in test alone should not be interpreted as irreversible obstruction of airways;
- Spontaneous increases of FEV1 by 20% over time or after the use of corticosteroids (30 to 40 mg once a day *** for 2 weeks) exceeding 250 ml.

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* FEV1: volume of air forcibly exhaled in one second
** FVC: forced vital capacity
*** VO: oral

Peak expiratory flow (PEF)

PEF is important for the diagnosis and control of asthma. The diurnal variation of PEF can be used to document the obstruction of airflow. Are indicative of asthma: (Cookson,1999; Vollmer, Osborne e Buist, 1998)

- Increase of at least 15% of PEF after inhalation of a bronchodilator or a course of oral corticosteroids (Vollmer, Osborne e Buist, 1998);
- Diurnal variability in PEF greater than 20% (difference between the highest and lowest extent of the period) considering measurements made in the morning and afternoon, over a period of 2 to 3 weeks (Fleming e Crombie, 1987).

Immunomodulators

Concept

In recent years, immunology, the science that studies the body's defense, has been more studied and known, contributing significantly to elucidate the mechanism of various diseases and therefore how to treat them.

The molecular biology that looks at how molecules work and medical genetics that today is finding the human genome elucidating how each gene works, also have been advancing quickly, and being able to bring to light hitherto unknown diseases. Any disease causes reactions of your defense system (immunology) in the body. This system, therefore, is linked to the resistance of the person, acting in a more appropriate way when there is balance and health. In asthma, for example, the irritant stimuli responsible for the infection directly attack the weakened immune system, making natural defenses more difficult.

All viral, bacterial, fungal and inflammatory diseases awaken in the body of the person a reaction of your immune system. This is done mainly by lymphocytes that are inflammatory cells and carry messages to the whole body. These messages are responsible for the whole inflammation process that indicates that our body is defending itself. That is why there is the redness, warmth, swelling, formation of secretion and also fever. It is also why in internal diseases tests are altered showing signs of infection and / or inflammation.

It is impossible to survive without the immune system, but paradoxically it is responsible for most of the signs and symptoms of the disease.

In allergic processes, for example, a person rejects a particular substance and the immune system causes the hives, itching, peeling and so on.

In this new era of medicine, we can count on the immunomodulatory drugs that are active drugs in the chain of immune system. So they will act properly by helping the body have a better defense, avoiding the side effects that occur because of inflammation and bronchospasm.

The immunomodulator will make the lymphocyte response more efficient, contributing to the formation of a larger amount of cytokines that are the principal agents of defense. The modern anti-asthma therapy still includes studies that aim to decrease the inflammatory process, such as inhibitors of TNF-α, prostaglandin inhibitors, modulators of cytokines and monoclonal anti-IgE.

It is interesting to emphasize that the development of these drugs was only possible because the current technology has brought greater awareness to the area in question deciphering all the steps used in the immune response to several types of diseases.

They will also be effective for treating all immunodeficiencies, genetic or not, and autoimmune diseases such as vitiligo and systemic lupus erythematosus among others. So we're walking into the 3rd millennium to use smart drugs that attack less and are more effective in curing the disease as they enhance and recover the natural defenses of the human body.

Immunotherapy Agents in Clinical Practice

Stimulating Immunomodulators

The immune response is a complex and highly regulated sequence of events involving various cell types and soluble substances. It is triggered when an antigen enters the body, or when there is cell transformation. Antigen makes contact with a specialized class of cells called antigen presenting cells (APC). The answers to most of the antigens of a protein can only begin after capture, processing and presentation of antigen by an APC. The reason is that T cells (T lymphocytes) only recognize antigens that are linked to proteins of the major histocompatibility complex (MHC) on the surfaces of cells. There are two different classes of MHC proteins, each recognized by one of two main subpopulations of T lymphocytes. The proteins of class I MHC are expressed by virtually all types of somatic cells and used to present substances to CD8 T cells, most of which is cytotoxic. Therefore, virtually any cell type can present antigens to cytotoxic T cells and thus act as a target of a cytotoxic response. Furthermore, the proteins of class II MHC are only expressed by macrophages and some other cell types and are necessary for antigen presentation to CD4 T cells - the subpopulation of lymphocytes that includes most of the helper cells. As the activation of helper cells is required for practically all immune responses, the APC displaying the class II proteins play a key role in controlling these responses. Thus, the main APC are macrophages - voracious phagocytes that can easily capture particulate antigens and present simultaneously, several different antigens, one in each of its numerous surface MHC proteins. In addition to showing antigens, activated macrophages also secrete cytokines such as TNF-α and IL-1, which control the proliferation, differentiation and effector function of lymphocytes.

Macrophages are located in the tissues (histiocytes) and derive from a circulating blood leukocyte, called monocyte. The survival time of a tissue macrophage is approximately two to four months. During this period of time, some macrophages remain immobile, while others wander incessantly by amoeboid movement. In both cases, the cell performs a continuous collection in its circulating mean through the process of pinocytosis. Whenever facing stimuli, the cell undergoes a process called macrophage activation, characterized by a rapid increase in metabolism, motility and

phagocytic activity. The activated macrophages are slightly larger and more effective in destroying bacteria and other pathogens. Many new proteins are synthesized with the activation process, including nitric oxide synthase, whose product (NO) plays an important role in the bactericidal function of macrophages.

The activated macrophages are avid phagocytes that engulf any foreign particles or cell debris with which they come into contact and specifically secrete a variety of biologically active substances circulating in the tissues. So far more than 100 products secreted by macrophages have been identified. Some products such as lysozyme, complement components and hydrogen peroxide, exhibit antimicrobial activity. Others, such as elastases and collagenases, act to liquefy and remodel the extracellular matrix, this action facilitates cell migration and aid the healing process.

Macrophages also secrete numerous cytokines that influence the growth and activity of other cell types. Therefore, using two types of regulatory interactions: antigen presentation and signaling cytokines with lymphocytes, macrophages play a crucial role in the initiation and coordination of almost every type of acquired immune response, and is the main cellular component of innate immunity (or natural).

Homeopathic Immunomodulator

Immunomodulator Canova®

The results of asthma treatment depend on factors that relate to the individual and the environment surrounding. Concerning individual aspects, we must consider the compatibility of clinical and psychological condition of patients with the treatment, especially in small patients, and the effects of treatment on the development of life. Regarding environmental aspects, the characteristics of the modus vicendi and family history. The treatment of asthma usually includes the application of more than one of the therapeutic methods. The combination of these methods aims to obtain higher rates of positive results, with smaller anatomical losses and more preservation of pulmonary function and, mainly, lower toxicity.

The biggest failure of conventional treatment is due to drug resistance. This resistance occurs, among other things, because of the discontinuation of treatment due to severe side-effects, and more serious still is the phenomenon of multidrug resistance.

A atuação do medicamento imunomodulador Canova®, sobre esses pacientes, promove a adesão ao tratamento pela melhora persistente, tão importante ao tratamento pela continuidade de efeitos mais seguros e eficazes.

The role of immunomodulator Canova ® on these patients, is to promote the adherence to treatment because of persistent improvement, so important to the continuity of safer and more effective effects.

The immunomodulator Canova ®

Canova is a homeopathic formulation product which is characterized by streamlined dilutions of Aconitum napellus + associations, all described in the main International Homeopathic Pharmacopoeia, including the Brazilian, German and American. The Canova medicine is produced in accordance with a specific formulation, already patented by Canova of Brazil Ltda.

Its production technique is based on the principles dictated by Hanneman, founder of Homeopathy, which is widely used by European medicine for more than two hundred years and which currently accounts for 40% of the American market, just to mention the western world in which we live. They are homeopathic components added in a sequence synergistically, multiplying the therapeutic effect of this complex homeopathic medication in the homeopathic mold through a technique called succussion, followed by dilution to form a specific and innovative product.

Clinical indications for the homeopathic medicine Canova

The homeopathic medicine Canova is characterized as a stimulating immunomodulator, as clearly demonstrated in scientific studies conducted in several Brazilian Universities. It should be used in diseases where the immune system is compromised, or when a more effective action of this system is required. There are many medical situations in which the immune system is affected, like, just to name a few examples, in cases of parasitic, infectious and inflammatory and neoplastic frames. In clinical situations it is common for the body to increase the production of a substance called tumor necrosis factor (TNF-α), which has a toxic effect on the body, producing a dramatic medical state and end, usually fatally, in one called cachexia. One of the most potent actions of the medicine Canova® is precisely regulate the production of this substance, also known as TNF-alpha, among other factors.

Scientific studies explain the action of Canova ®

The medicine Canova ® began to receive scientific and systematic studies of Brazilian Universities from 1997. Two lines of research began then:
a) on one side studying how the drug had its action;
b) the other side is researching its safety.

Tasks were distributed in several research centers. It was demonstrated that Canova has no LD 50, no genotoxicity or mutagenicity. Thus satisfy the concern for safety. Also researches began to explain how the drug works and it was noticed that the main action takes place on a cell of the immune system, called macrophage. These cells are found throughout the human body (eg skin, viscera, blood vessels, lungs, tissues) and are defense cells. It was observed that the homeopathic medicine Canova acts on macrophages, inducing a change in the resting state in which they are to become activated cells. Metabolism becomes more intense, they become larger, also activating other cells of the immune system, or when replacing them when they are functionally absent.
It was also demonstrated the metabolic changes that take place on macrophages, confirming that with the use of Canova, the resting defense cell is activated, and then modulating the optimal response of the immune system, justifying the patients' improvement, even in those terminally ill or very toxic by disease, can react and get recovery with quality of life. It also explains why the medication should be of constant use, as macrophages, like most cells of the immune system, are short-lived.

Objective

The general aim of this study is to evaluate the effectiveness of immunomodulator Canova® and the paradigms of development of asthma episodes in patients bearing this disease in the ambulatory of the Clinica Médica in the city of Riachinho/ MG.

Study Format

We followed 57 children / adolescents with asthma, all male and between 7 and 16 years old for 90 days between the months of July to November 2006, thus classified:

Classification of the asthma state

Classification	N=57	%	Control	%	Canova	%
Persistent mild	15	26%	8	14%	7	12%
Persistent medium	18	32%	9	16%	9	16%
Persistent severe	24	42%	12	21%	12	21%

This study was discussed with the clinical board of the City Hospital of Riachinho / MG and approved by the Ethics Committee of this Hospital.

All those responsible (father and / or mother) for the patients involved signed an accession protocol to the study, after being informed of the terms of the study.

It was applied in all the characters the following test to define the classification of asthma:

Questionnaire applied:

1. Has or has had recurrent episodes of breathlessness (dyspnea)?
2. Has or has had seizures or recurrent episodes of wheezing (wheezing)?
3. Has a persistent cough, particularly at night or on awakening?
4. Wake because of cough or shortness of breath?
5. Do you cough, wheeze or have chest tightness after physical activity?
6. Displays cough, wheeze or chest tightness after exposure to allergens such as mold, dust and animals, or irritants such as cigarette smoke and perfume, or after colds or emotional disorders such as laughter or crying?
7. Use any medication when symptoms occur?
8. There is relief of symptoms after the medication?
9. Is there a family history of allergic diseases or asthma?
10. Has or has had symptoms of allergic diseases (especially rhinitis or dermatitis)?

We used the following criteria for the classification of asthma:

Classification of the asthma severity

Symptoms	Rare	Weekly	Daily	Daily or continuous
Awakening at night	Rare	Monthly	Weekly	Almost Daily
Need of beta-2 (for relief)	Rare	Eventual	Daily	Daily
Limitation of activity		Present in exacerbation	Present in exacerbation	Persistent
Exacerbation	Rare	Affect activity and sleep	Affect activity and sleep	Frequent
VEF 1 or PFE	> 80%	> 80%	60 a 80%	< 60%
Variation VEF1 or PFE	<20%	20 a 30%	> 30%	> 30%

FEV1: The volume of air forcibly exhaled in one second, PEF: Peak Flow expired.

Evaluations were made monthly for three months of lung function (FEV1 and PEF):

All the control group was treated with:

- Inhaled corticosteroids 250 mcg every 12 hours.
- Theophylline slow release of 12/12 hours
- Oral corticosteroids, prednisone, in doses of 10 mg / day.

The Canova group was treated only with the immunomodulator Canova in the following presentation and posology:

- **Inhalant**: 3 ml of non-diluted medicine in nebulizations of 4 minutes every 8 hours.
- **Drops**: 10 drops under tongue 4 times a day.

Classification of the control state of the asthmatic patient

	Controlled	**Partially controlled (at least 1 a week)**	**Not controlled**
Daytime Symptoms	None or minimum	2 or more a week	3 or more
Awakening at night	None	At least 1	
Need of rescue remedies	None	2 or more a week	
Limitation of activity	None	Present any moment	
PFE or VEF1	Normal or almost normal	<80% do predito	
Exacerbation	None	1 or more a year	

FEV1: The volume of air forcibly exhaled in one second, PEF: Peak Flow expired.

Results:

The treatment with Canova® significantly reduced the number of attacks: 53 percent seizure-free during the first month to 77 percent seizure-free in the third month, thus reducing the number of eosinophils in the blood.

The rate of worsening with hospital admittance was:

Hospitalization rates

Hospitalization	**Control group**	**Canova group**
Yes	40,5%	8,6%
No	59,5%	91,4%

Conclusion:

The probable mechanism of action of the immunomodulator Canova® is by blocking the production of cytokines IL-2 and IL-4 of activated T cells, which contribute to the inflammatory response, downregulation of allergen-specific IgE response, in addition to the immunomodulatory effect, improving body defenses. The action of Canova® in blocking IL-2 occurs after transcription, inhibiting protein synthesis without affecting gene expression of IL-2. Canova® reduces the levels of circulating IgE antibodies. When using appropriate doses of Canova®, the amount of anti-idiotype antibodies increases, bind to IgE, removing it from circulation. Another possible mechanism is related to downregulation of Fc receptor-GIIB in signaling of B lymphocyte.

In conclusion, the immunomodulator Canova® is effective in children and adolescents with persistent asthma, whether mild, moderate or severe.

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