Clinical efficacy of implementing Bio Immune(G)ene MEDicine in the treatment of chronic asthma with the objective of reducing or removing effectively corticosteroid therapy: A novel approach and promising results

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Abstract. Asthma is one of the diseases that demonstrates a wide range of variation in its clinical expression, in addition to an important heterogeneity in the pathophysiological mechanisms present in each case. The ever-increasing knowledge of the molecular signalling routes and the development of the Bio Immune(G)ene Medicine [BI(G)MED] therapy in line with this knowledge has revealed a whole novel potential set of self-regulation biological molecules, that may be used to promote the physiological immunogenic self-regulation mechanisms and re-establish the homeostatic balance at a genomic, proteomic and cellular level. The aim of the present study is to demonstrate that the sublingual use of a therapeutic protocol based on BI(G)MED regulatory BIMUREGs in the treatment of chronic asthma may reduce or suppress corticosteroid therapy and avoid its harmful side effects which some patients suffer when using this treatment on a long-term basis. The clinical efficacy of BI(G)MED for chronic asthma was evaluated through a multi-centre study carried out in 2016 implementing a 6-month BI(G)MED treatment protocol for Bronchial Asthma. A total of 61 patients from private medical centres and of European countries including Germany, Austria, France, Belgium and Spain participated. The manuscript describes in detail the clinical efficacy of Bio Immune(G)ene regulatory BI(G)MED treatment protocol that allows the reduction or total removal of the corticosteroid dose in patients with chronic asthma. No adverse reactions were observed. The BI(G)MED regulatory therapy brings novel therapeutic possibilities as an effective and safe treatment of chronic asthma. BI(G)MED was demonstrated to significantly reduce asthma severity when parameter compositions were all analysed by categorical outcomes. Therefore, it is considered a good therapeutic alternative for patients who respond poorly to steroids.

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Abbreviations: BI(G)MED, Bio Immune(G)ene Medicine; EBMA, European Bio Immune(G)ene Medecine Association

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Introduction

Asthma is an inflammatory lung condition characterized by an exaggerated response of the airways, which remodelling is one of the most common medical pathologies of long duration. Allergic asthma is an inflammatory lung disease characterized by an abnormal response of lymphocytes T-helper 2 (TH2) after the inhalation of antigens (1,2).

It is well-established that a strong correlation exists between the presence of eosinophils and the presence of Th2 cells in the asthmatic airways and that classical Th2 cell-derived cytokines, namely interleukin (IL)-4, IL-5, IL-9 and IL-13, play critical roles in orchestrating and amplifying allergic inflammation in asthma (3).

More recently, roles for basophils, iNKT cells, Th17 cells, and a number of soluble mediators, including TSLP, IL-25, and IL-33, have also been proposed (4,5).

MicroRNAs (miRNAs) are small non-coding RNAs that regulate the function of the innate immune cells by controlling the stability and translation of mRNA in health and disease (6). The emerging role of miRNAs as biological agents in regulating immune and inflammatory responses in the lung has been recently reviewed (7,8). The main results indicate that these lung disorders can be attributed to abnormal immune responses to environmental stimuli and infections (9). Therefore, understanding the host natural systems of innate defences and regulating systems is essential for the development of new therapeutic approaches. In this regard, there is growing interest in the role of miRNAs in the regulation of host natural innate immune defence responses and in the inflammatory sequels of the respiratory disease.

The use of these miRNAs is opening a promising novel biological approach to improve asthma processes (10). In fact, a subset of miRNAs has been identified as potential therapeutic targets in asthma patients (1,11,12). Their role in regulating the

response to corticosteroids and airway hyper-responsiveness has also recently been verified. For example, the microRNA miR-9 regulates the glucocorticoid receptor signalling and the hyper-responsiveness of the airway resistant to steroids. Very recently, it has also been proposed that modulating the function of miR-9 could be a novel approach to the treatment of asthma, even for the patients who are resistant to steroid therapy (13).

Sublingual immunotherapy (SLIT) has been also reported to be effective and safe in the treatment of allergic rhinitis, in a systematic review type meta-analysis on the treatment of asthma, although the magnitude of effect reported was not very large (14). At the moment, there is an increasingly broad consensus to promote SLIT, and to consider SLIT as a safe alternative to subcutaneous therapy route (15).

Materials and methods

The Bio Immune(G)ene Medicine [BI(G)MED] as diagnostic method. As part of BI(G)MED therapeutic protocols, two specific biological laboratory tests are essentially used and systematically performed, regardless of diagnosis.

First a protein profile, as the blood protein profile provides a good overview of the humoral immune status. Second, a lymphocyte typing, as the characterization of lymphocytes allows to evaluate the cellular immune status.

This modality helps the healthcare provider to look at the overall response of the immune system of the patient and thereby act upon biological evidence-based to perform subsequent follow-up monitoring.

The two tests mentioned above are complemented by studies to analyse the existence of pathogenic microorganisms (bacterial, viral, fungal and parasitic). The existence of a reactivation of microbial agents must be identified by serological tests as a priority in all asthmatic process. Amongst the microbial agents, two of them have to be considered as a priority: *Respiratory Syncytial Virus* (RSV) and *Rhinoviruses* (16) as well as *Chlamydia pneumoniae* and *Mycoplasma pneumoniae* (17). It has to be taken into account that most pathogens have the potential to trigger or worsen into more or less a clinically latent asthmatic condition. In this context, we think that the presence and reactivation of *Epstein Barr Virus* (EBV) must always be explored.

Furthermore, in the case of bronchial asthma, it is essential to assess the levels of immunoglobulin E (IgE). The measure of IgE total and/or specific IgE allows to identify the potential of allergens involved in triggering the asthmatic process; nevertheless, the bacterial and viral serology tests are the main tests that can help to clarify the pathogenesis of the bronchial asthmatic process (18).

Only once a careful clinical and biological diagnosis has been carried out, is it possible to identify which BI(G)MED therapeutic protocol is best suited for modulating and improving the cell imbalances found in the asthmatic patient, in terms of: Th_2 predominant polarity, Th_{17}/Tregs disbalance and/or regulation of the intestinal barrier.

The BI(G)MED targets are several types of cells belonging to the innate immune system (i.e., eosinophils, basophils, CDs and macrophages), as well as the pathogens found in serological tests, either bacteria and/or viruses (19).

The BI(G)MED as a nanobiotherapy method. Nanotechnology is a growing sector. It uses nanovectors capable to transport an active substance where it should act in the organism, in order to increase its effectiveness while minimizing side effects. The BI(G)MED-nanovectors are so-called xylitol globules produced and analysed by Remedy Bank (Hoboken, Belgium), that will be given on a sublingual way to reach immediately the pharyngeal immune structures.

The BI(G)MED is included in this scientific field and relies on different methods and concepts. There are five fundamental pillars of BI(G)MED.

Nanomedicine refers to biomedical and pharmaceutical applications of nanosized cargos of drugs/vaccine/DNA therapeutics including nanoparticles, nanoclusters, and nanospheres. Such particles have unique characteristics related to their size, surface, drug loading, and targeting potential. This therapeutic approach is already well known in oncology (20,21).

Synthetic Biology is a high biotechnology field situated between molecular biology, organic chemistry, scientific engineering, nanobiotechnology and information technology. The aim of synthetic biology is to design and produce new biological parts, devices and systems as well as to re-shape what already exists in natural biological systems that have a proposed utility. By genetically manipulating the biosynthetic machinery involved in the assembly of natural products and exploiting Nature's strategies for synthesizing structurally diverse metabolites, compounds with enhanced biological features can be produced that were otherwise inaccessible using traditional synthetic methods (22).

The concept of hormesis belongs to classical pharmacology and helped to explain why the majority of substances have a reserved effect when they are diluted; 'Hormesis is now generally accepted as a real and reproducible biological phenomenon, being highly generalized and independent of biological model, endpoint measured and chemical class/physical stressor. The quantitative features of the hormetic dose response are generally highly consistent, regardless of the model and mechanism, and represent a quantitative index of biological plasticity at multiple levels of biological organization' (23,24).

Ab initio molecular dynamics simulation, improved to its current stage where the analysis of existing processes and the prediction of further chemical features and real-world processes are feasible (25), explains the dilution revitalization (dynamisation) process through molecular acceleration which is the interaction source with the aqueous substrate (26).

RNA interference is one of the most important epigenetic processes, preserved during evolution and responsible, through its post-transcriptional repression route, for the suppression of gene expression (27). The most important feature today of BI(G)MED is given by the therapeutic use of miRNAs.

The BI(G)MED scientific study described in this manuscript applies all these basic concepts to allergy and bronchial asthma at a diagnostic and therapeutic level. It works on well-known key cellular events and signalling pathways.

Characteristics of patients who participated in the study. We performed a multicentre study which involved 61 patients from private medical offices in several European countries, including Germany, Austria, Belgium, France and Spain. The sample included male and female patients of all ages in the

same proportion. That had a process of persistent bronchial asthma or allergic asthma, whose evolution had started at least two years ago. Patients who had asthma due to exercise have been specifically excluded from this study.

In the selection of patients it has been taken into consideration that they were not polymedicated by other diseases and in particular, that they had not ruled on a routine basis in the conventional treatment with β-mimetic agents but ruled only in case of acute asthma attacks.

Inclusion criteria were as follows: Any age and gender, regular asthma since at least 2 years prior to starting the study, treatment with corticosteroids (oral or inhaled) for at least two years.

Exclusion criteria, on the other hand, were as follows: Other conventional treatments for asthma (i.e., treatment with theophylline), coexistence of other illnesses of the immune system or chronic infections, patients undergoing chronic treatment with psychotropic drugs, patients unable to follow the study for whatever reason both physical or mental (in order to make sure there will be a good adhesion to the treatment).

Duration of the study. The study took place in 2016 over a 6-month period. During this time patients included in the study followed a BI(G)MED protocol treatment described later in detail. Four medical controls were carried out during the study, one at study entry and then follow-up checks were performed every 2 months.

BI(G)MED protocol and BIMUREGs used in this study. There were five Bio Immune(G)ene Regulators (BIMUREGs) used to improve the asthma process in this study. All these BIMUREGs were prepared strongly according to the nano-biologic method of dilution-dynamisation and all were certificated GPP. Their composition is as described in Table I. The therapeutic protocol followed for all patients of this study was as described in Table II.

All participants were instructed with recommendations for dosage, time and way of intake of the drugs. Opening the capsule that contains the BI(G)MED-formulas, then pouring its contents under the tongue till it's fully absorbed by the oral mucosa. Not to combine two BI(G)MED products at a time. To wait at least for half an hour in between the two doses. To always take BI(G)MED medication between meals, at least half an hour before eating.

In case of acute asthma episode, the following BI(G)MED-formulas were also used in combination: BIMUREG 4 + BIMUREG 5, two or three times daily alternately. The parallel use, or not, of Homeopathy and/or Phytotherapy, among other complementary therapies, was assessed. And the eventual use of β-mimetics and exceptionally corticosteroid, was also valued.

Monitoring and control parameters used to assess clinical symptoms. The following clinical and biological parameters were controlled regularly, i.e., at the beginning of the study, at months 2 and 4 and at the end of the study (i.e., after 6 months of treatment with BI(G)MED-formulas).

The clinical course was assessed by a BI(G)MED standardized questionnaire for asthma (Table III) with evaluation of wheezing (sibilances), cough, expectoration (cough-up), acute asthma crisis, dyspnea (breathless), as well as value of total IgE and percentage of eosinophils in peripheral blood.

Table I. BIMUREGs used in the study and their composition.

Compounds	Concentration (Mol)
BIMUREG 1	
IL-4	$1x10^{-10}$
IL-5	"
IL-9	"
IL-13	"
EGF	"
PGD2	"
GM-CSF	"
TNF-α	"
DNA (ADAM 33)	"
RNA (miR-9, -19a, -155)	"
BIMUREG 2	
IL-4	$1x10^{-10}$
IL-5	"
IL-10	"
IL-25	"
TGF-β	$1x10^{-8}$
Notch gene	"
CTLA-4	"
DNA (CTLA-4, Notch)	"
RNA (miR-21, -106a, -126)	"
BIMUREG 3	
IL-3	$1x10^{-10}$
IL-5	"
IL-9	"
IL-6	$1x10^{-8}$
IFN-γ	"
TGF-β	"
miR-126	"
DNA (IL-5)	"
RNA (let-7, miR-145, -223)	"
BIMUREG 4	
IL-4Rα	$1x10^{-10}$
IL-5	"
IFN-γ	"
LTC4	"
PGD2	"
HISTAMINE	"
miR-223	"
DNA (GATA-1)	"
RNA (miR-132, miR-221, -222)	"
BIMUREG 5	
IL-4	$1x10^{-10}$
IL-10	"
TNF-α	"
TGF-β	$1x10^{-8}$
IL-1RA	"
RNA (miR-146a)	"

Table II. Therapeutic protocol.

Time of day	Monday	Tuesday	Wednesday	Thursday	Friday	Saturday
Morning	BIMUREG 2		BIMUREG 2		BIMUREG 2	
Afternoon		BIMUREG 3		BIMUREG 3		BIMUREG 3
Evening	BIMUREG 1	BIMUREG 1	BIMUREG 1	BIMUREG 1	BIMUREG 1	BIMUREG 1

To evaluate the progress of the clinical symptoms, the standardised BI(G)MED questionnaire (Table III) was designed and translated into different EU languages. Patient's consent for participating in this study and for publication of material related was obtained from all study participants. Patients names were not included, only initials, age, sex and a number of questions for statistical analysis purposes. Only a minimum set of key clinical tests was included to facilitate the follow up in all cases.

It is important to specify here that all study participants were informed according to the principles of the Declaration of Helsinki, and that all doctors involved in this study officially declare having obtained oral consent from all patients.

Besides, due to the type of nanopreparations used as treatment throughout the study, no harmful side effects were to be expected, which was specified upfront to all the patients.

Finally, in the context of a study based on patients coming from private practices only, no ethical committee (involved in monitoring studies taking place in hospitals) could be solicited.

Results

The statistical analysis has been carried out on the XIstat programme, version 2015.2. The variables that have been valued in this study are: Wheezing (sibilances), cough, expectoration (cough-up), acute asthma crisis, dyspnea (breathless), total IgE, percentage of eosinophils and inhaled use of corticosteroids.

The data has been taken from 61 patients over 6 months. The variables described before have been valued specifically at the start of the study (time 0), at 2 months (time 2), at 4 months (time 4), and at 6 months (time 6). Depending on the nature of the variable, two types of analysis have been carried out.

For the variables of the dichotomous type Yes/No (i.e., wheezing, cough, expectoration, acute crisis) an analysis was done to compare the percentage of YES recorded at each stage of the study and the difference between these percentages have been compared to evaluate when they are significantly different and when they are not.

For the numeric type variables (i.e., dyspnea, total IgE, eosinophils % and inhaled corticosteroids) a mixed model analysis with repeated measurements has been carried out because the data was obtained from the same patients at different times. In this case, what has been evaluated is if the results obtained in these variables were statistically different overtime, and in particular, at what specific moments they were significantly different.

The main difference between one analysis and another is that in the first one percentages are compared while averages are compared in the second one. No analysis has been carried out for the variable oral corticosteroid because the great majority of data is 0 and it doesn't make sense to analyse them by statistical inference. In any case, we discuss the results obtained in the few cases that patients do not have values 0. For all the comparisons carried out a 5% level of error has been applied.

If we take into account the dichotomous variables such as wheezing, cough and expectoration it has been observed that the percentage of YES diminishes over time. However, we have to analyse if this reduction is statistically significant.

The results are obtained from carrying out a hypothesis testing to compare the four YES percentages obtained at each stage. As the P-value for wheezing and cough is less than 0.0001 and, for the expectoration variable is less than 0,05 with the chi-square test as well as with the Montecarlo method, the conclusion is that these percentages are not statistically equal, that is to say, they are statistically significant. The Marascuilo procedure has been used to analyse between what stages we find the significant differences and at what other stages we don't. In these cases, we find that the YES percentage at the initial stage (0) is significantly different to the YES percentages obtained at 2 months (time 2), 4 months (time 4) and 6 months (time 6) while no significant differences are observed between the percentages obtained at 2 months, 4 months and 6 months (Figs. 1-3).

With respect to the contrast in the acute asthma crisis (with a P-value slightly above 0.05) the conclusion is that these percentages are statistically different between initial stage and after 6 months of treatment (Fig. 4).

On the other hand, if we take into account the quantitative variables such as dyspnea, total IgE, percentage of eosinophils and the corticosteroids dose we obtain results from carrying out a hypothesis testing to compare the four mean averages of each of these variables obtained at each stage. As the P-value (in the case of dyspnea and the corticosteroids dose) is less than 0.0001 and (in the case of the total IgE and the percentage of eosinophils) is less than 0.05, the conclusion is that these averages are not statistically the same. The Tukey post-hoc contrast has been used to analyse at what stages we find the significant differences and at what stages we don't.

In the case of dyspnea we find that the mean average of this variable is significantly different at the initial stage from the measures obtained at 2 months, 4 months and 6 months. The means obtained after 2 months and 6 months are also significantly different, whilst no significant differences are observed between the 2 months and 4 months measures or between the 4 months and 6 months measures. We could say that we go

Table III. BI(G)MED standardised questionnaire for asthma multicentre study in reduced format.

Age of patient: Gender: F/M Country:	Initial Control	2nd month	4th month	6th month
How many years of evolution have your asthma process?				
What kind of treatment are you taking at study entry?				
How many doses of corticosteroids either oral or inhaled are currently needed?				
How many times have you been treated in A&E during the last months?	Last 6 months before the study?			
Have you been hospitalized? If yes, was it for longer than 24 hours? How many times?	Yes/No			
Or were you just treated for a few hours and then sent home? If yes, how many times?	Yes/No			
Do you suffer from breathlessness (dyspnea)? 1. Due to physical effort? 2. During normal activity? 3. Even with minimum effort and below normal activity?	Yes/No Yes/No Yes/No Yes/No			
Did you have any cough/s?	Yes/No			
Maintenance dose of corticosteroids: • Oral corticosteroids: How many mg/day? • Inhaled corticosteroids: How many mcg/day?				
Biological evolution: • Total IgE • Eosinophils in %				
Two additional considerations: to assess implementation and enforcement of the BI(G)MED protocol by the patient				
Have you taken the BI(G)MED formulas regularly as indicated?	Yes/No			
What corticosteroids dose are you taking at the moment?				

from dyspnea occurring with a normal lifestyle (phase 2 of dyspnea) to dyspnea when doing exercise (phase 1), that is to say, one degree less of dyspnea than before the treatment was started (Fig. 5).

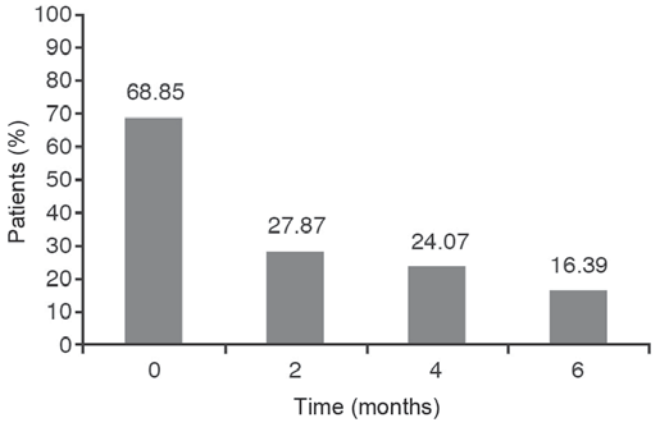

Figure 1. Patients with sibilances. The percentage of patients with sibilances at the initial stage (0) is significantly different from the percentages obtained at 2 months (2), 4 months (4) and 6 months (6), while no significant differences are observed between the percentages obtained at 2 months (2), 4-months (4) and 6 months (6).

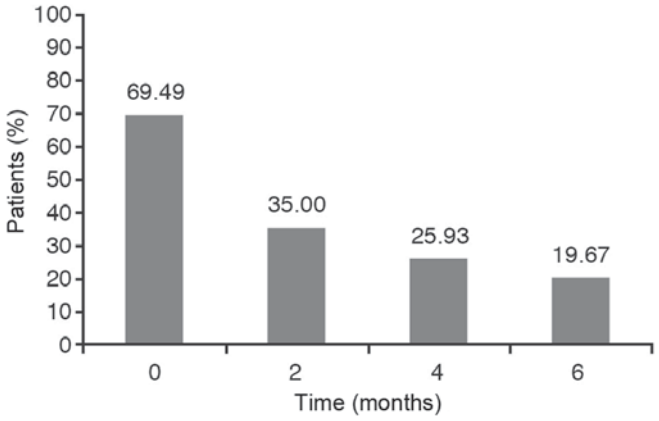

Figure 2. Patients with cough. The percentage of patients with cough at the initial stage (0) is significantly different from the percentages obtained at 2 months (2), 4 months (4) and 6 months (6), while no significant differences are observed between the percentages obtained at 2 months (2), 4 months (4) and 6 months (6).

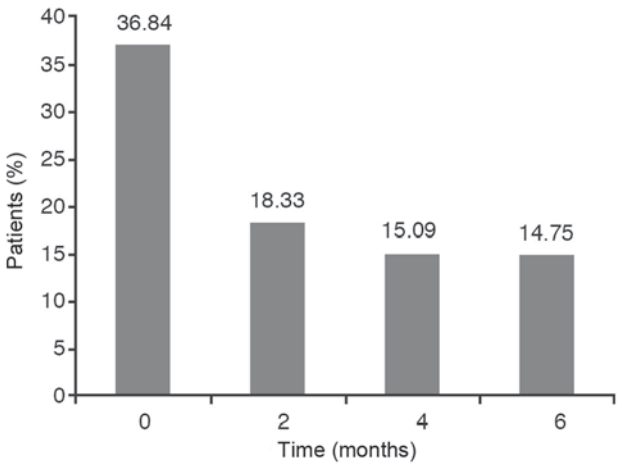

Figure 3. Patients with expectoration. The percentage of patients with expectoration at the initial stage (0) is significantly different from the percentages obtained at 2 months (2), 4 months (4) and 6 months (6), while no significant differences are observed between the percentages obtained at 2 months (2), 4 months (4) and 6 months (6).

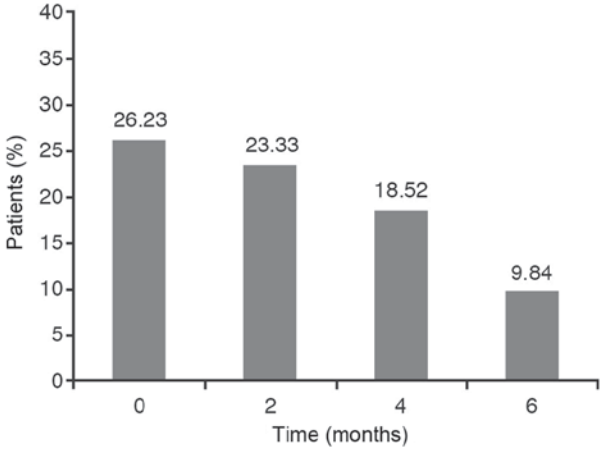

Figure 4. Patients with acute crisis. With respect to the contrast in the acute asthma crisis (with a P-value slightly above 0.05) the conclusion is that these percentages are statistically different between initial stage and after 6 months of treatment.

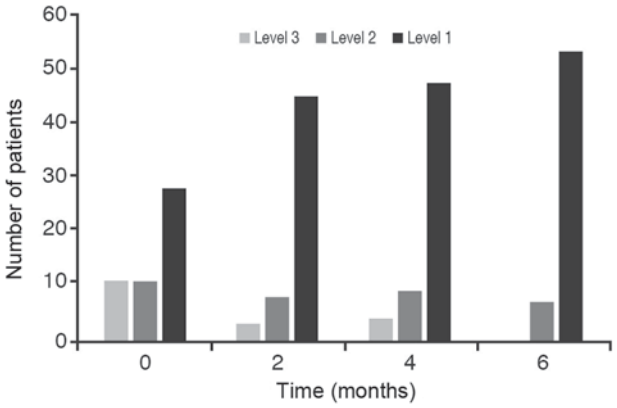

Figure 5. Dyspnea. The number of patients with level 3 of dyspnea (even with minimum effort and below normal activity) and level 2 of dyspnea (during normal activity) is significantly lower after 2 months, 4 months and 6 months. On the contrary, the number of patients with level 1 of dyspnea (due to physical effort) is significantly larger after 2 months and keeps on increasing at 4 and 6 months. As a conclusion, we mainly go from dyspnea occurring with a normal lifestyle (level 2 of dyspnea) to dyspnea when doing exercise (level 1), that is to say one degree less of dyspnea than before the treatment was started.

For the IgE total, the mean average at the initial stage is significantly different to the mean average obtained at 6 months. It is also quite pronounced (without being statistically significant at 5%) between the average at the initial stage and at 4 months. The remaining comparisons are not at all significant (Fig. 6).

For the eosinophils (Fig. 7) the same statistical result is obtained as in IgE (Fig. 6). In the graph showing the inhaled corticosteroids (Fig. 8) we observe that the average of this variable is significantly different at the initial stage from the averages obtained at 2 months, 4 months and 6 months. The difference is also quite pronounced (without being statistically significant) between 2 months and 6 months, whilst no significant differences are observed between the rest of comparisons.

When we interpret the results, we can conclude that there is a noticeable improvement of the variables in the study as a

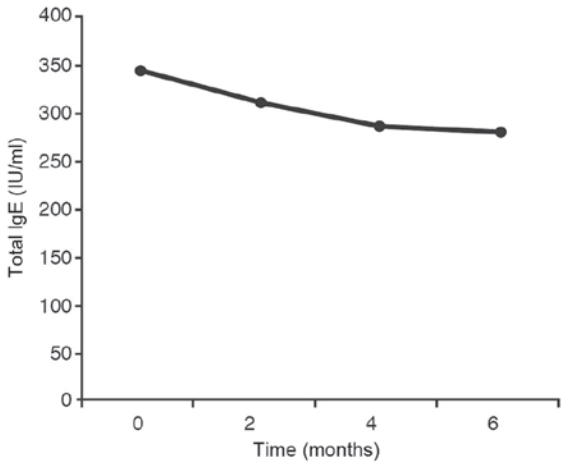

Figure 6. Total IgE. The mean average at the initial stage is significantly different to the mean average obtained at 6 months. It is also quite pronounced (without being statistically significant at 5%) between the average at the initial stage and at 4 months. The remaining comparisons are not significant.

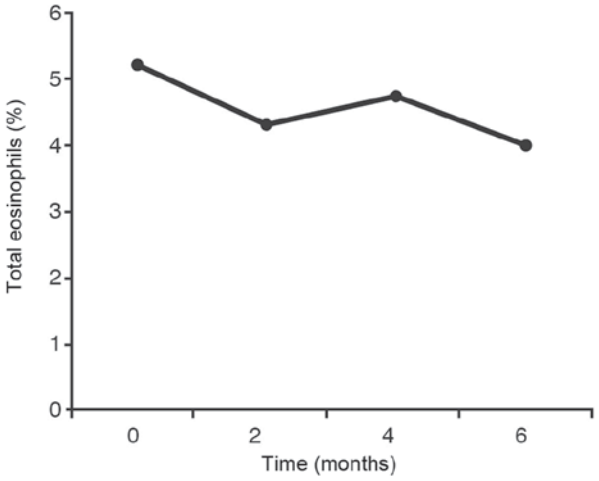

Figure 7. Eosinophils. The mean average at the initial stage is significantly different to the mean average obtained at 6 months.

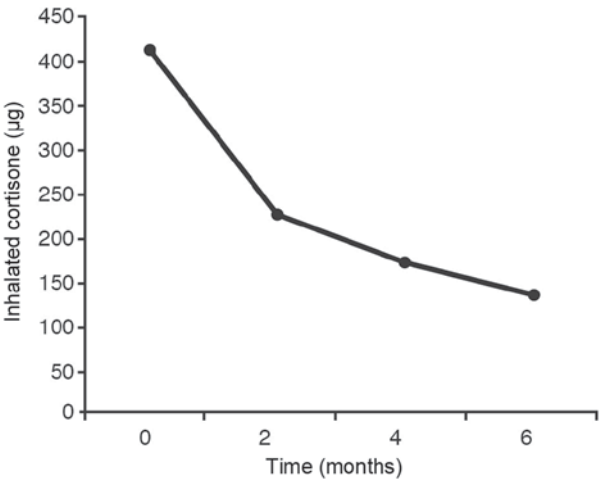

Figure 8. Inhaled corticosteroids. We observe that the average of this variable is significantly different at the initial stage from the averages obtained at 2 months, 4 months and 6 months. The difference is also quite pronounced (without being statistically significant) between 2 months and 6 months, whilst no significant differences are observed between the rest of comparisons.

whole. The use of the BI(G)MED protocol clearly improved the clinical symptoms and the biological parameters tested on one hand and on the other hand there is a significant reduction of the dose of inhaled corticosteroids in the long-term treatment of asthmatic patients that participated in this study. It is probably useful to specify here that no participant in the study followed oral corticosteroid therapy as a disease-modifying treatment of asthma, all used corticosteroids in inhaled form as basic treatment. In addition, only a few of them have exceptionally used oral corticosteroid therapy in the case of a particularly severe acute asthma crisis. For this reason, we have not introduced doses of oral corticosteroids as an evolutionary parameter in our study.

Discussion

The BI(G)MED can improve the evolution of chronic asthma and reduce the dose of corticosteroid treatment in asthmatic patients of long evolution. It even allows suppressing corticosteroids in some cases. Thus opening up new therapeutic possibilities, promoting self-regulation of immune-genetic mechanisms and restoring the homeostatic balance at genomic, proteomic and cellular levels. Furthermore, it becomes a new alternative for those patients who respond poorly to corticosteroid therapy, even at high doses.

The Bio Immune-regulatory 'BI(G)MED'-formulas, so-called 'BIMUREGs', used in this study have managed to stabilize first, and thereafter to slow down and to stop the development and evolution of bronchial chronic asthmatic processes. Additionally, it improves other allergic manifestations. With, the added value that it has been proven to be a safe, innocuous and lacking in side effects nanotherapy.

And thanks to the therapeutic effects in line with the laws from quantum physics, hormesis and nanobiotechnology, it becomes possible to prevent some patients from the damaging effects that the long-term corticosteroid treatment for chronic asthma causes, and thereby open up new possibilities for a predictive, preventive and personalised medicine.

In conclusion, we can state that the BI(G)MED is actually a bio-medical nanotherapy approach of the highest order in the sense that it mimics nature in its most intimate essence, and our study demonstrates its efficacy in a disabling illness such as chronic bronchial asthma.

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