Research article

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Clinical and immunological effects of a treatment with desentizating low-dose multicomponents in IgE mediated and non IgE mediated food allergies: observational retrospective pilot study

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Abstract

Background. Alimentary allergy has high impact on the quality of life (Qol) of patients and their families: it represents an economic burden for individuals and National Health System. The disease, particularly frequent in pediatric age, recognizes different pathogenetic mechanisms and expresses itself through the production of IgE (IgE mediated form) antibodies or through cell-mediated immunune responses (non IgE mediated forms). The aim of this clinical observational retrospective study is to evaluate the effect of a long-term treatment with Low Dose Medicine (LDM) drugs in pediatric patients affected by IgE and non IgE mediated food allergy.

Objective. The purpose of the study is to determine the efficacy of the treatment with Allergy Plex (Guna Laboratory, Milan, Italy) to induce clinical and/or immunological tolerance both to IgE mediated and non IgE mediated food allergy; the secondary endpoint is to investigate the treatment tolerability, the reduction of positivity to Skin Prick test and Patch test to food allergens and the decrease on the peripheral blood of the specific IgE to food allergens. The treatment efficacy was measured through a clinical score.

Methods. In this study the immunomodulant activity of Allergy Plex 13, Allergy Plex 7 and Allergy Plex 10 (Guna S.p.A., Milano, Italy) was evaluated. In every patient the state of allergical clinical responses and the immuno-allergological state were evaluated by means of specific parameters letting know the regulatory response to the allergical Th fenotype.

Results. Data about Clinical tolerance to food, Symptomatological clinical score, ECP, ACTH, Cortisol; IL-4, IL-10 was collected. There was evidence of improvement of clinical score, reduction of the diameter of cutaneous pomphus obtained through the Prick test and a decrease of IgE specifics values.

Conclusion. The data issued from this study seem to confirm the efficacy of treatment with Allergy Plex in allowing the restoration of immune tolerance and the definite reduction of the clinical score. ***Clin Ter 2019; 170(1):e10-15. doi: 10.7417/CT.2019.2102***

Key words: *Food allergies, oral desensitazing, low dose medicine, multicomponent desensitazing, IL-4, IL-10, Th2, TReg*

Introduction

Food allergy (FA), an immunological reaction to food, is a disease strongly impacting the quality of life of affected subjects and their families, implying considerable health costs for both individuals and the National Health System.

In Europe the data concerning allergic conditions vary from 22% and 35% (1) and seem to affect mostly the range between 18-49 years (2). All over Western Europe allergic deseases are increasing in childhood (3) and food allergies are particularly present in pediatric age. In spite of the difficulties, FA is approximately evaluated around 3% of the total population (4). FA occurs mostly in the first years of life; 6-8% in the first 2 years, while it tends to diminish with age. A study published in 2009 by AAITO (Italian Territorial Hospital Allergist Association) about the causes of raise of FA in Italy, points out that allergies to food are 8% of total allergies. Vegetables 72% (fruit, legumes, tomato and so on), shellfish and seafood 13%, fish 4%, eggs 3%, milk 3%, cereals 2%, meat 1% are the causes of primary allergy (5). The most frequent cause of allergies to vegetables is represented by LTP, Lipid Transfer Proteins, that are contained mainly in peaches, apples, apricots, cherries, hazelnuts, peanuts and nuts. In pediatric age, cow's milk, eggs, soja, wheat and peanuts are responsible for about 90% of allergic reactions to food (6-8).

FA shows itself with different clinical status and the most commonly used diagnostic tests (cutaneous and /or serological) are not so sensible and specific to confirm or exclude definitevely a diagnosis (3,9,10).

At the current state of knowledge FA is originated by a disfunction of TRegulatory cells (TReg) (11), including TR1 and Th3 cells (12), which release IL-10 and TGF-β, CD4+ CD25+ and NKT cells (13-15).

Oral challenge test is the Gold Standard for the clinical diagnosis of the food allergy both in the IgE mediated and non IgE mediated form (16).

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Many departments of pediatric allergology and not, have carried out for many years the oral desensitization for food (DO) in the most resistant food allergy forms (milk, egg) which don't develop tolerance in the growth age (17). The use of very low concentrations of specific food, orally administrated, represents a further therapeutic approach of immunomodulation which might allow a physiological tolerance to food in subjects with immunological response to food (18).

Materials and methods

Study design

This is a clinical observational retrospective study aimed to evaluate the effect of a long-term treatment with desensitizing multicomponent drugs named Allergy Plex (GUNA Laboratory, Milan, Italy) in pediatric patients affected by IgE mediated and non IgE mediated food allergy to Solanaceae, cereals or fruit, with gastrointestinal symptoms or atopic dermatitis. Allergy Plex induces desentization to specific food by the immune system modulation (19,20). In this study immunomodulant activity of Allergy Plex 13, Allergy Plex 7 and Allergy Plex 10 was evaluated. The drugs were assumed on an empty stomach and between meals (30 minutes before or 1 hour after), in a dose of 10 sublingual drops three times daily.

The study was based on the data collected during a period from September 2012 and September 2013 regarding 30 individuals (19 boys and 11 girls aged 4-12) treated with Allergy Plex or DO. All the patients were monitored in a variable observational period of 5-7 months, with an average duration of 6 months. Two groups of patients were considered and compared. All of them were treated in the Department of Pediatric Allergology, Nuovo Regina Margherita Hospital, Asl Rome A, Rome; all were screened because they showed a comparable clinical status and were affected by the same food allergies.

The first group, composed by 20 patients, had assumed a treatment with Allergy Plex for food (Allergy Plex group) during three consecutive months. A second group, composed by 10 patients, had been treated with DO (DO group) for the same period of time (control group). Both groups had then been followed for three months from the end of the treatment (Follow-up, FU).

Every patient had been clinically and immunologically evaluated at the beginning of the therapy (T0), after 3 months of treatment (T1) and after 3 months from the end of the treatment (T2FU), in accordance with the current clinical procedure carried out in the Department. None of the considered patients received administration of antihistamines and /or corticosteroids during the testing period.

The aim of this study was to evaluate, by means of the collected data, whether the Allergy Plex treatment might induce clinical and/or immunological tolerance both to IgE mediated and non IgE mediated food allergy.

Inclusion criteria

All patients were aged between 4 and 12 years, all affected by IgE mediated and non IgE mediated food allergy with gastrointestinal disorders or atopic dermatitis, having been previously subjected to Prick or Patch tests for a food class (solanaceae, cereals, or fruit and so on).

Patients who had previously been affected by anaphylactic shock, or severe allergic reaction to specific food, like milk or egg (shock, edema of glottis, generalised angioedema, severe asthma), allergic to fish, shellfish, nuts, hazelnuts, peanuts, or subjects under topic or systemic therapy with antistaminic or cortisone, or with calcineurin inhibitors (Tacrolimus, Pimecrolimus), were excluded from the evaluation.

Outcomes

The primary Endpoint of the research was established in the clinical tolerance to specific food (challenge) in a 3 an 6 months period (T1-T2FU).

The secondary Endpoints were tolerability and compliance to the treatment; the reduction of positivity to Skin Prick Test, Prick by Prick and Patch test to food allergens; the reduction of specific serum standard and molecular IgE to food allergens; cytokines movement associated with tolerance mechanism (IL-10, IL-4).

The treatment efficacy was evaluated by means of a clinical symptomatological score obtained by adding points (0-4) for everyone of the following symptoms: itching, eritemato-eczematous lesions, abdomen pains, diarrhea, meteorism and costiveness.

Immunological evaluation *in vivo* (Skin Prick Test for food allergens; Prick by Prick; Patch test observed after 48-72 hours) and *in vitro* (total and specific IgE; cationic protein of eosynophils (ECP) was carried out; also, a study of serum cytokines associated to the tolerance mechanism (IL-10, IL4), a study of stress mediators (ACTH, cortysol, PRL) and a challenge test were performed.

Statistical Analysis

After submission to descriptive analysis of all data, the primary endpoint was evaluated by the McNemar exact test for both groups at T1 *vs* T0; since it was a composite endpoint, its significance had to be set at $p < 0.025$. The exact McNemar test was also used for the other within group comparisons T0 *vs* T2FU and T1 *vs* T2FU.

The Fisher's exact test was used for between group comparison of challenge positivity at T1 and T2FU.

Score as well as other continuous varables were compared by the Friedman test, followed by post-hoc test according to Conover, or by repeated measures ANOVA (between and within), followed by post-hoc according to Bonferroni.

Results

Of the 30 patients included in the trial, 20 were assigned to the Allergy Plex group, and 10 to the DO group (Table 1).

The observed sample was equally distributed in the two groups according to a gender criterion (19 boys, 11 girls) (Pearson test: $p= 0.8934$) and age (Welch test: $p= 0.7510$).

Table 1. Lists, for the Allergy Plex group and the DO group, the number of observed subjects, the population characteristics, the symptomatology and the treatment they received.

	Allergy Plex group	DO group
Subjects n°	20	10
Boys	8	4
Girls	12	6
Age(Mean)	7.5	7.8
Gastrointestinal disorders (GI)	11 (55%)	7 (70%)
Atopic Dermatitis (AD)	4 (20%)	3 (30%)
GI + AD	5 (25%)	0 (0%)n
Allergy Plex 13 for solanaceae	9 (45%)	-
Allergy Plex 7 for cereals	8 (40%)	-
Allergy Plex 10 for fruit	3 (15%)	-
D.O. for solanaceae	-	5 (50%)
D.O. for cereals	-	4 (40%)
D.O. for fruit	-	1 (10%)

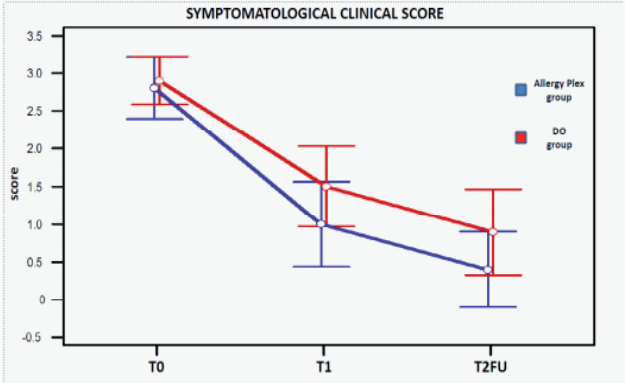

Fig. 1. The figure shows significant reduction of the Symtomatological Clinical Score in the Allergy Plex group at T0-T1, T0-T2FU and T1-T2FU. Also, the score is considerably reduced at T0-T1, T0-T2FU and T1-T2FU. The reduction shown in the Allergy Plex group is significantly higher.

As shown in the description of the analisis, the principal endpoint (challenge evolution in the two groups) is not normally distributed (which is to be expected, being binary categorical variable); among the secondary endpoints the score is not normally distributed as well. The others quantitative variables have generally a normal trend.

Primary Endpoint

Clinical tolerance to food

The challenge evolution in the Allergy Plex group implies a significant improvement of the patient response. At T0, negativity at baseline is 0%, becoming 45% at T1 (exact McNemar test: p= 0.0039) whereas at T2FU, it is 75% (exact McNemar test: p= 0.0001 compared to the baseline and p= 0.0313 compared with T1).

The challenge evolution in the DO group shows a significant improvement of the patient response. At T0 negativity at baseline is 0%, at T1 it is 80% (exact McNemar test: p= 0.0078), while at T2FU it is 100% (p not calculable with baseline, and p = 0.5000 compared with T1).

Secondary endpoints

Symptomatological Clinical Score

The score is significantly reduced in the Allergy Plex group (Friedman test: p= <0.00001): reduction is particularly significant (according to Conover test: p = <0.05) between T0 and T1, T0 and T2FU, and between T1 and T2FU (Fig. 1).

Repeated measures ANOVA show a difference between the groups (p= 0.015), the reduction observed in the Allergy Plex group resulting significantly higher, as it is also confirmed by the U Mann Whitney test at T0 (p= 0.5280), at T1 (p= 0.0333) and at T2FU (p= 0323).

Eosynophils Cationic Protein (ECP), Prolactin (PRL), ACTH, Cortisol

Repeated measures ANOVA show that ECP is significantly reduced in the Allergy Plex group (test F: p < 0.001); in particular reduction is considerable between T0 and T1 (Bonferroni's corrected test: p < 0.0001) and between T1 and T2FU (p= 0.0001). In the DO group ECP is not significantly reduced (test F: p= 0.162). The group x factor interaction analysis (p< 0.001) shows that the difference in measuring depends on the group to which subjects were assigned.

Repeated measures ANOVA show significant reduction of PRL in the Allergy Plex group (test F: p< 0.001). In particular, reduction is considerable between T0 and T1 (Bonferroni's corrected test: p= 0.0064), between T0 and T2FU (p= 0.0001) and between T1 and T2FU (p= 0.0001). In the DO group, reduction is still significant in toto (test F: p< 0.001), between T0 and T1 (Bonferroni's corrected test: p= 0.0083), between T1 and T2FU (p= 0.0118), but not between T1 and T2FU (p= 0.0507) (Fig. 2). The group x factor interaction (p< 0.001) difference between measures depends on which group subjects had been assigned to.

The figure shows PRL significant reduction in the Allergy Plex group at T0-T1; T0-T2FU; T1-T2FU. In the DO group reduction is significant between T0 and T1, between T0 and T2FU, but not between T1 and T2FU.

ACTH remains stable without significant variations in the Allergy Plex group (test F: p= 0.060) and in the DO group (testF: p= 0.098). Being either in a group or another had no effects on the results (p= 0.531).

Cortisol is significantly reduced in the Allergy Plex group (test F: p= 0.001). Reduction is significant between T0 and T2FU (Bonferroni's corrected test: p= 0.0120) and between

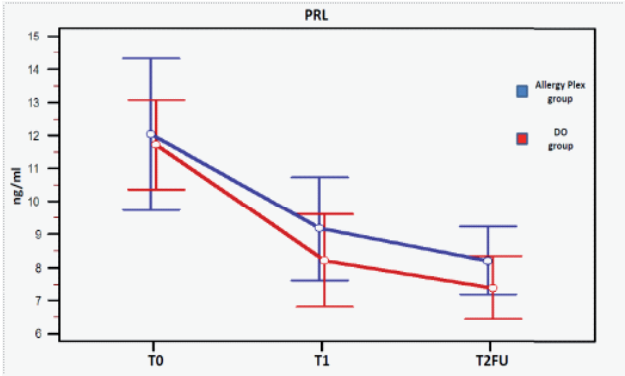

Fig. 2. The figure shows PRL significant reduction in the Allergy Plex group at T0-T1; T0-T2FU; T1-T2FU. In the DO group reduction is significant between T0 and T1, between T0 and T2FU, but not between T1 and T2FU

T1 and T2FU (p= 0.0341), but not between T0 and T1 (p= 0.0605). In the DO group cortisol doesn't vary significantly (test F: p= 0.175). Being either in a group or another didn't produce significant differences (test F: p= 0.061), (Fig. 3).

IL-4, IL-10

IL-4 is significantly reduced in the Allergy Plex group (test F: p< 0.001). The reduction is significant between T0 and T1 (Bonferroni's corrected test: p< 0.0001), between T0 and T2FU (p< 0.0001) and between T1 and T2FU (p = 0.0056). In the DO group too, IL-4 is significantly reduced (test F: p< 0.001). Reduction is significant between T0 and T1 (Bonferroni's corrected test: p< 0.0001) between T0 and T2FU (p< 0.0001) and between T1 and T2FU (p= 0.0050). Being either in a group or another doesn't produce significant variations.

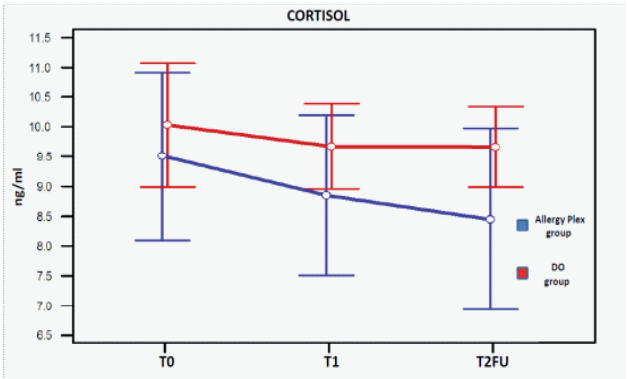

Fig. 3. The figure shows a significant Cortisol reduction in the Allergy Plex group. Reduction is significant between T0 and T2FU and between T1 and T2FU, but not between T0 and T1. In the DO group cortisol doesn't produce significant variations.

IL-10 increases significantly in the Allergy Plex group (test F: p< 0.001). Increase is significant between T0 and T1 (Bonferroni's corrected test: p< 0.0001), between T0 and T2FU (p< 0.0001) and between T1 and T2FU (p= 0.0001). Also in the DO group IL-10 increases significantly (test F: p< 0.001). Increase is significant between T0 and T1 (Bonferroni's corrected test: p= 0.0166), between T0 and T2FU (Bonferroni's corrected test: p= 0.0112) and between T1 and T2FU (p= 0.0283).

Being either in a group or another produces significant variability (test F: p< 0.001), because the increase of IL-10 in the Allergy Plex group is greater than in the DO group.

Other secondary end points

Given the short number of many quantitative measures concerning the Prick test and the serum specific IgE dosing, we were able to do statistical inference only for these variables: wheat Prick test, potato Prick test, tomato Prick test, wheat specific IgE, tomato specific IgE, for the Allergy Plex group only.

Wheat, Potato, Tomato Prick test Allergy Plex group

The Friedman test shows that In the Allergy Plex group the wheat Prick test is significantly reduced (p= 0.00802). Reduction is significant (p< 0.05) according to the Conover test between T0 and T1 and T0 and T2FU, but not between T1 and T2FU.

The Friedman test shows that in the Allergy Plex group the potato Prick test is significantly reduced (p= 0.00001). The reduction is considerable (p< 0.05), according to the Conover test, between T0 and T2FU and between T1 and T2FU, but not between T0 and T1.

The Friedman test shows that in the Allergy Plex group the tomato Prick test is significantly reduced (p= 0.0003). The reduction is considerable, (p< 0.05) according to the Conover test between T0 and T2FU and between T1 and T2FU, but not between T0 and T1.

Wheat and Tomato specific IgE Allergy Plex group

The Friedman test shows that in the Allergy Plex group specific IgE for wheat is significantly reduced (p= 0.01819). The reduction is considerable (p< 0.05) according to the Conover test, between T0 and T2FU only, not between T0 and T1, nor between T1 and T2FU.

The Friedman test shows that in the Allergy Plex group specific IgE for tomato is significantly reduced (p= 0.00229). Reduction is considerable (p= 0.05) according to the Conover test, between T0 and T2FU and between T1 and T2FU, but not between T0 and T1.

Discussion

This observational retrospective study was aimed to assess whether desensitizing multicomponent low dose drugs (Allergy Plex, GUNA Laboratory, Milan, Italy), might exert a clinical and immunoendocrine modulatory activity. FA is particularly frequent in pediatric age and it's due to either IgE production like antibodies or cell-mediated mechanisms

(13). FA can negatively impact on patients and family life. Furthermore, economic burden is considerable, in terms of health costs and working days lost by the parents of young patients affected by this pathology, as well as in terms of admittance to hospital emergency or departments (4). It's a disease with peculiar characteristics affecting genetically predisposed individuals, whose transmission is not in line with the mendalian genetics laws, but due to genetic components causing a predisposition. This pathology is not induced by toxic substances or infectiuos agents, but by food components, usually harmless for most people, able yet to induce immediate or delayed allergies, even lethal in some cases (1).

In this study the clinical Allergy Plex therapy efficacy is proved by the improvement of the symptomatological clinical score, by reduction of the diameter of the cutaneous pomphus obtained by the Prick test with standardised allergenic extracts to tomato, potato or wheat, and by the decrease of specific IgE values for wheat and tomato.

The results support the hypothesys that the Allergy Plex treatment didn't induce immediate tolerance, as it was seen in DO; tolerance was instead reached in a longer time and was afterwards maintained for a long time. Allergy Plex induced tolerance is maintained also by a discontinuous assumption of the offending food, whereas in DO a daily assumption of the food responsible for the allergy is necessary (21). A significant increase of IL-10 levels, definitely higher in the Allergy Plex group than in the DO group, was observed.

That proves the important activation of the TReg lymphocytes clone, which, as it is known, exerts a regulatory function on pro-inflammatory lymphocyte clones, particularly on Th2 clone (12,20). As for IL-4, typical Th2 cytokine, Allergy Plex induced modulation showed the treatment efficay on Th2 lymphocytes involved in the allergic process (22,23). There is also evidence of the inflammation reduction in ECP and IL-4 values reduction in the patients treated with Allergy Plex (14,24).

The effect that the Allergy Plex therapy exerts on the endocrine system is varoius. ACHT doesn't vary in none of the groups as observed in previous studies (25), whereas PRL and cortisol are significantly and progressively reduced in the Allergy Plex Group. PRL is a strong inductor of the lymphocytes response and a well-known modulator of the TReg response. The decrease of PRL in a normal range, as seen in previous trials, confirms reduced Th2 activation, throughout neuro-endocrine mechanisms. A similar importance can be found in cortisol, powerful immunosuppressor whose reduction entails normal Th1 activity restoration, and consequently significant effect over the inflammation control.

Moreover, these last data provide information about the modulatory activity of the therapy on the hypothalamus-pituitarys-adrenal axis (25).

A limitation of this observational retrospective study is the reduced number of considered patients. On the other hand, we tried to screen comparable patients as much as possible. We know there is a need for others studies to confirm these data, and to assess the long-term capacity of the modulating immuno-endocrine activity of these preparations.

Conclusions

The indications this study provides, seem to confirm the Allergy Plex treatment efficacy in allowing immune tolerance restoration, with challenge negativity and reduction of symptomatological clinical score. This last finding suggests that Allergy Plex therapy may lead to stronger activation of TReg lymphocytes, thus allowing inflammation control and immune tolerance restoration. The data regarding Allergy Plex treatment safety and tolerability seem to confirm the data about LDM previously provided in other studies; during the treatment none of the subjects reported adverse effects, or lack of tolerability.

Acknowledgments

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List of abbreviations

AAITO	Italian territorial Hospital Allergist Association
ACTH	Adreno Cortico Tropic Hormone
AD	Atopic Dermatitis
ECP	Eosinophil cationic protein
FA	Food Allergy
FU	Follow Up
IgE	Immunoglobulin E
IL	Interleukin
LDM	Low Dose Medicine
LTP	Lipid Tranfer Protein
NKT	Natural Killer T
OD	Oral desensitization
PRL	Prolactin
TGFβ	Trasforming Growth factor β
Th	T helper
TReg	T Regulatory

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