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Intravenous gold-induced autologous serum injection therapy (Go ACT®) as a new treatment for seasonal pollen-based allergies

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Abstract. – OBJECTIVE: This prospective case study investigated the new therapeutic paradigm of autologous gold-induced immunotherapy (Go ACT®) in the treatment of pollen-based allergies. The safety and clinical efficacy of Go ACT® was investigated by assessing patients in the first pollen season following treatment with Go ACT®.

PATIENTS AND METHODS: In this prospective case study, patients were enrolled who had a proven pollen allergy and had been previously unsuccessfully treated with standard medication. Clinical improvement following Go ACT® treatment was analyzed using symptom scores, ARIA classification and symptom control. The data generated in the case study were compared to the data from the previous pre-treatment pollen season.

RESULTS: 16 patients were included in this study. The treatment was well tolerated by all patients. On completion of the study all of the patients rated the tolerability of the treatment as either good or very good. Local reactions to the treatment were not seen. No Serious Adverse Events (SAEs) occurred. The symptom scores decreased significantly from the 2016 pollen season to the 2017 pollen season in patients who received Go ACT® treatment. Analysis of the ARIA classification showed that 81.0% of patients had persistent, moderate-to-severe rhinitis before treatment. Following treatment 7.1% of patients had persistent, moderate-to-severe rhinitis. A total of 62.4% of patients in the study achieved symptom control. A total of 38.8% of patients required no symptomatic medication after Go ACT® treatment. The rhino-conjunctivitis score was significantly lower after the treatment.

CONCLUSIONS: This study has shown that Go ACT® treatment is safe, effective, well- tolerated and accepted by patients suffering from pollen allergy. The results of the symptom scores, RCAT, ARIA classification show that Go ACT® treatment elicits immediate beneficial effects during the pollen season under treatment and for the season following treatment.

Key Words:
Go ACT®, Gold induced serum, Pollen, Seasonal allergy.

Introduction

Allergy is an immunoglobulin E (IgE) mediated hypersensitivity disease with food allergy affecting up to 10% of the population[1]. Allergic patients suffer a wide variety of symptoms, including rhinoconjunctivitis[2], asthma[3], dermatitis[4], gastritis[5] and occasionally life-threatening systemic anaphylaxis[6]. Patients suffering from allergy are usually treated by using symptomatic medication, such as oral antihistamines[7], intranasal corticosteroids[8], inhaled corticosteroids[9] and β2-adrenergic receptor antagonists[10].

Allergen-specific immunotherapy (SIT) is an alternative approach which aims to modify the underlying pathological immune response[11] and it involves the therapeutic vaccination with the disease-causing allergens. Some workers[12,13] support the concept that the induction of allergen-specific blocking IgG antibodies is a key mechanism of action of SIT, but also cellular mechanisms have been proposed. Nevertheless, it has been recognized that the use of natural allergen extracts for the preparation of the vaccines is a potential bottleneck to future development towards a widely used treatment[14]. At present SIT is only offered by specially trained physicians[15]. It requires multiple increasing allergen doses to reach the therapeutically effective maintenance dose. At present relatively few patients suffering from allergy benefit from SIT[16].

Molecular cloning techniques have enabled the isolation of allergen-encoding cDNAs from various allergen sources and the subsequent production of allergens in recombinant form[17]. Diagnostic tests

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have been developed based on recombinant allergens[18] along with IgE epitope mapping[19] which allow for a more precise diagnosis of allergy and monitoring of immune responses during treatment.

An innovative technique has been developed to produce an *in vitro* conditioned serum rich in cytokines (GOLDIC®) by utilizing specialized gold particles. The first *in vitro* and *in vivo* studies showed that this gold activated serum has impressive anti-inflammatory effects[20,21]. The GOLDIC® procedure has been demonstrated to upregulate plasma gelsolin (pGSN) levels and pGGSN has been shown to have an important role in inflammation and tissue regeneration[22]. This study evaluated the novel Go ACT® treatment using intravenous infusion of autologous gold-activated patient serum. The process has been called autologous gold-induced immunotherapy (Go ACT®). The aim of the study was to analyze the efficacy, tolerability and safety of the Go ACT® treatment.

Patients and Methods

Study Design

This prospective case study enrolled patients with a history of seasonal pollen allergy. All of the patients in the study had been unsuccessfully

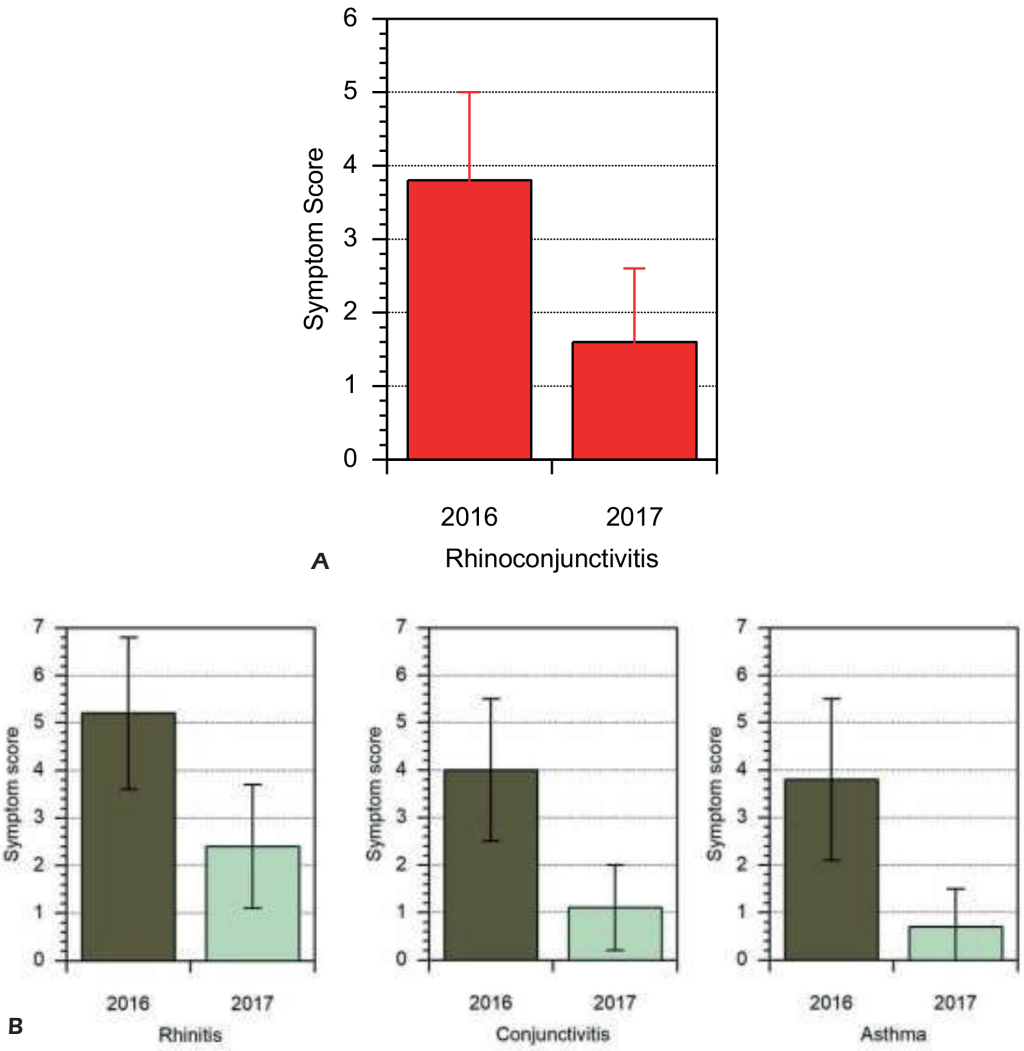

Figure 1. A, Changes in Rhino-conjunctivitis Symptom Scores (0-6 points). The difference between both seasons is shown as mean/SD. The p values between 2016 and 2017 were obtained using the Wilcoxon-Mann-Whitney test. All 2017 data showed significant improvements ($p < 0.001$). **B,** Changes in Rhinitis, Conjunctivitis and Symptom Scores. The difference between both seasons is shown as mean/SD. The p values between 2016 and 2017 were obtained using the Wilcoxon-Mann-Whitney test. All groups showed significant improvements in 2017 ($p < 0.001$).

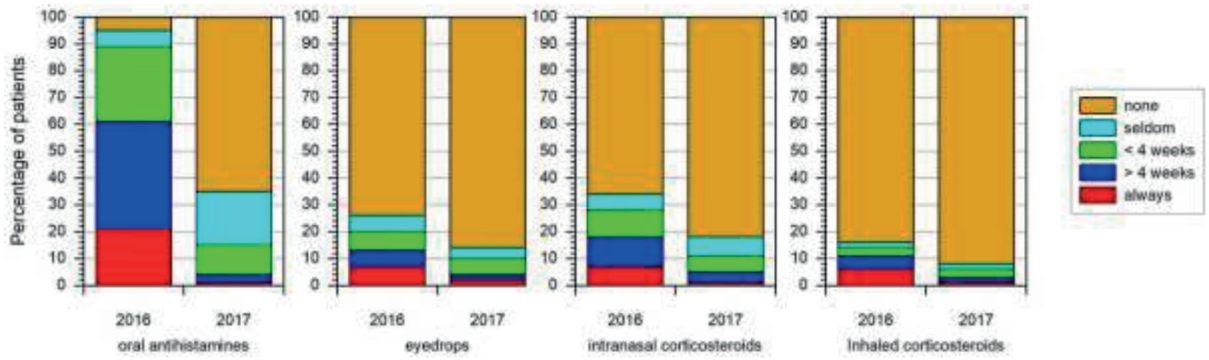

Figure 2. The Changes in Symptomatic Medication Use. The frequency of the use of different symptomatic medications was assessed retrospectively at V1 for the 2016 pollen season and after Go ACT® treatment at V4 for the 2017 pollen season.

pre-treated using standard allergy medication. All patients were informed in detail about the benefits and risks of the Go ACT® treatment and they all gave their written informed consent to participate in the study. The study was carried out according to the guidelines of Good Clinical Practice (GCP).

A total of 16 patients suffering from pollen allergy were treated with Go ACT® in the iRegMed Center for Regenerative Medicine in Tegernsee/Germany. All patients received 4 consecutive intravenous injections of Go ACT® which were carried out at intervals of 7 days. Each treatment was therefore spread over 1 month.

Target Criteria

The primary screening criterion in this study was the demonstration of the effectiveness of Go ACT® therapy in patients diagnosed with birch, alder, and/or hazel pollen–induced allergic rhinitis, rhino-conjunctivitis or asthma. The exclusion criteria for the study were no proven pollen allergy and patients aged under 18 years.

The study consisted of four Go ACT® treatments: 1) Treatment was initiated at the baseline visit (V1). 2) Treatment before the early spring pollen season (V2). 3) Treatment during the peak of the pollen season (V3). 4) Treatment after the pollen season (V4).

Study Endpoints

The primary endpoints were parameters of clinical improvement compared to the previous pollen season (assessed retrospectively from V1 to V4). This was assessed by the change in symptom scores and any changes in symptomatic standard medication use. Any changes in the Allergic Rhinitis and its Impact on Asthma (ARIA) classification were also noted.

The secondary endpoints included safety criteria as follows:

Physical examination, vital function and documentation of any Serious Adverse Events (SAEs). Safety monitoring took place during the entire study. The MedDRA version 12.1 documentation system was used to record all of the data.

Assessment of Improvement in Clinical Parameters

Symptom Scores

Nasal symptoms (sneezing, rhinorrhea, nasal pruritus and nasal congestion), ocular symptoms (ocular pruritus, redness, and watery eyes), and pulmonary symptoms (dyspnea and coughing) were assessed at V1 (previous pollen season of 2016) and V4 (after the 2017 pollen season). Symptom intensity was characterized as none, mild, moderate and severe. In addition, rhinitis, conjunctivitis, and asthma symptoms were assessed at V1 and at V4 (during the peak of the 2017 pollen season). Symptom evaluation of rhinitis, conjunctivitis, and asthma was based on the combination of the level of discomfort:

- no symptoms = 0
- mild symptoms = 1
- moderate symptoms = 2
- severe symptoms = 3

and the frequency of occurrence:

- rare = 1
- < 4 weeks = 2
- 4 weeks = 3
- always = 4

The rhino-conjunctivitis score was based on the level of discomfort of rhinitis and conjunctivitis symptoms and was rated on a scale from 0 to 6. Mild or no symptoms were scored as 0-2 points

and moderate to severe symptoms were scored as 3-6 points.

Symptomatic Medication

At V1 and V4 patients were asked to retrospectively report the symptomatic medication they had used during the 2016 and 2017 pollen seasons. This included the use of oral antihistamines, intranasal corticosteroids, eye drops, inhaled cortisteroids and β2-adrenergic receptor antagonists. The frequency of use was also recorded (none, seldom, < 4 weeks, > 4 weeks and always).

ARIA Classification of Rhinitis

Rhinitis symptoms occurring during the pollen seasons of 2016 and 2017 were classified as persistent or intermittent and mild or moderate-severe based on the ARIA classification of rhinitis[23]. The term persistent rhinitis was used when symptoms lasted > 4 days/week or > 4 consecutive weeks and intermittent rhinitis when symptoms lasted < 4 days/week or < 4 consecutive weeks. The patients who suffered allergies to hazel, alder, and birch tree pollen were all considered to be suffering from persistent rhinitis. This was because the patients showed allergic symptoms from January until mid-April which is when those trees are in bloom in Germany.

Symptom Control

The German version of the validated Rhinitis Control Assessment Test (RCAT)[24] was used to determine whether patients' rhinitis symptoms were controlled in the peak of the 2017 pollen season. The RCAT is based on six items:

1. Nasal congestion.
2. Sneezing.
3. Watery eyes.
4. Sleep disruption.
5. Limitation of normal activities caused by symptoms.
6. Self-rating by patients of symptom control.

The frequency of occurrence of each item within a 1-week recall period was assessed on a five-point scale (never = 5, rarely = 4, sometimes = 3, often = 2 and extremely often = 1). A sum of six scores lower than 21 suggests that rhinitis symptoms are uncontrolled. A total score equal to or higher than 22 means that the patient has achieved symptom control.

Statistical Analysis

The target values regarding the endpoints of the study are mostly presented descriptively. Statistical analyses were performed using Sigmastat statistics program. The data showed normal distribution and the analysis was carried out using the paired *t*- test. Categorical data were presented as absolute and percentage frequencies. The differences between the 2016 and 2017 pollen seasons within a group were analyzed using the Wilcoxon-Mann-Whitney test. Categorical differences between groups were analyzed using the chi-square test; a p-value of < 0.05 was considered significant. Missing data were not included in any calculations.

Results

Study Population

16 patients were enrolled in this study. The 16 patients started with the Go ACT® therapy during the pollen season. The mean age of patients was 38.0 years (range from 20 to 62 years). There were more female than male patients in this study (10 female and 6 male). Further patient characteristics are presented in Table I.

Tolerability Assessed by Patients and Investigator

Almost all patients (96.1%) assessed their Go ACT® treatment tolerability as good or very good. The analysis of the patient assessments (after the pollen season at V4) showed excellent overall tolerability. In addition, patients documented any local (pharyngeal) and systemic (skin and respiratory) reactions in a diary on a daily basis.

Local Reactions (at the Injection Site)

No patients reported any local reactions in the patient diary.

Systemic (Skin, Respiratory, General) Reactions

Systemic reactions documented by the patients occurred rarely during the post-treatment phase. Twelve patients (75%) reported a systemic reaction 24 hours after the first or second injection similar to flu (shivering, sensation of heat) which resolved in time with no further treatment needed.

Serious Adverse Events

The Go ACT® treatment was well tolerated throughout the different treatment schedules. No reports of SAEs were documented.

Improvement of Clinical Parameters

The improvement of clinical parameters, after Go ACT® treatment, in the whole study popu-

Table I. Patient characteristics (n = number; SD = standard deviation).

Total number of Patients (n)	16	
Age (years),	38.0 (mean)	16.9 (SD)
Female (n)	10 (62%)	
Male (n)	6 (38%)	
Asthmatic patients (n)	5 (31%)	
Sensitisation to birch pollen (n)	13 (81%)	RAST class (mean/SD) 3.42/1.17
Sensitisation to hazel pollen (n)	14 (88%)	RAST class (mean/SD) 3.04/ 1.41
Sensitisation to alder pollen (n)	11(69%)	RAST class (mean/SD) 3.09/1.51

lation was determined by comparing the symptom scores, ARIA classification and the use of symptomatic medication between the 2016 pollen season before treatment (assessed at V1) and the 2017 pollen season after treatment (assessed at V4). The assessment was also based on the level of symptom control in the 2017 pollen season. Both of these parameters were assessed during the peak of the 2017 pollen season at V4.

Reduction in Symptom Scores Compared to the Previous Season

Symptom scores were significantly lower after Go ACT® treatment (V4). The mean rhino-conjunctivitis score assessed at V4 for the 2017 season was 81.5% lower than that of the 2016 pollen season as assessed at V1 (Figure 1A). This corresponds with the mean rhinitis, conjunctivitis and asthma symptom scores which showed a reduction of 70.8%, 84.6%, and 91.8% respectively (Figure 1B).

Reduced Symptomatic Medication Use After Go ACT® Treatment Compared to the Previous Season

Almost all patients (94.2%) reported using symptomatic medications during the 2016 pollen season. The proportion of patients who no longer needed symptomatic medications during the pollen season increased from 8.8% in 2016 to 34.3% in 2017 (after Go ACT® treatment). The use of oral antihistamines decreased substantially (Figure 2).

Reduced Rhinitis Symptoms according to a Modified ARIA Classification of Rhinitis Compared to the Previous Season

According to the ARIA classification of rhinitis, most patients in this study (81.0%) suffered from persistent, moderate-to-severe rhinitis during the 2016 pollen season. Intermittent, moderate-to-severe rhinitis was observed in 7.1% of patients, whereas intermittent, mild rhinitis was found in 3.8% of patients. From the 2016 pollen season to the 2017 pollen season after Go ACT® treatment symptoms in the study cohort improved markedly, such that only 10.6% of the patients presented with persistent, moderate-to-severe rhinitis during the 2017 pollen season.

Discussion

The results of this study show that the Go ACT® treatment can lead to an effective reduction in seasonal allergic symptoms. Symptom scores decreased significantly from the 2016 pollen season to the 2017 pollen season. Prior to treatment, 81.0% of patients were classified as having persistent, moderate-to- severe rhinitis according to the ARIA classification, but only 7.1% were classified as such after treatment. In all, 62.4% of patients achieved symptom control, and 34.3% of patients required no symptomatic medication after treatment. No SAEs or anaphylaxis occurred.

The results of this study show that a reduction of seasonal allergic symptoms can be achieved when using Go ACT® treatment with a good tolerability of the treatment. This finding was further supported by the evaluations provided by patients. The patients in the study were asked to document all side-effects on a daily basis during the up-dosing phase and more than 75of patients did not record any side effects. All of the side effects which were reported were mild. General reactions were reported by 80% of the patients but once again mild reactions predominated, and they resolved without any further treatment. All

patients (100%) rated the tolerability of the treatment as good or very good.

Clinical Improvement

In this study almost 50% of patients experienced a reduction in their allergic symptoms from persistent to moderate in the pre-treatment 2016 pollen season to intermittent to mild in the first pollen season (2017) following Go ACT® treatment. The results of the RCAT also demonstrated that symptoms in patients receiving Go ACT® decreased from the 2016 pollen season to the 2017 pollen season.

An important criterion used to verify the effectiveness of an immunotherapy product is the proportion of treated patients who no longer need symptomatic medication. Overall, two out of every three patients (62.4%) in this study achieved symptom control and a third (34.3%) stopped using symptomatic medication completely during the 2017 pollen season.

One of the limitations of this investigation is that there was no control group and seasonal factors (e.g., low pollen counts) were not considered. The next step will be to carry out a double-blind, randomized, placebo-controlled trial (RCT) using the data in this study as the starting point. Nevertheless, this study shows promising results in the treatment of pollen induced allergy.

Conclusions

This is the first report of the use of Go ACT® technology in the treatment of seasonal allergic allergy. The primary outcome of this study was that Go ACT® treatment is safe, well tolerated and well accepted by patients. The results of Go ACT® treatment (including symptom scores, RCAT, ARIA classification and use of standard medication) show that treatment with Go ACT® has a beneficial effect in the first pollen season following treatment. The data in this manuscript will be the basis of a Randomized Control Trial (RCT) of Go ACT® technology in the treatment of seasonal allergy.

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Conflict of Interest

U. Schneider is CEO of Arthrogen GmbH the manufacturer of Go ACTP. Hollands has no conflicts of interest.

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