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ORIGINAL ARTICLE

The efficacy and tolerability of pollen extract in combination with hyaluronic acid and vitamins in the management of patients affected by chronic prostatitis/chronic pelvic pain syndrome: a 26 weeks, randomized, controlled, single-blinded, phase III study

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ABSTRACT

BACKGROUND: Chronic prostatitis/chronic pelvic pain syndrome (CP/CPPS) remains a challenging clinical condition to manage. Here, we evaluate the efficacy and tolerability of a new treatment option (suppositories) containing pollen extract in combination with hyaluronic acid and vitamins in the management of patients with CP/CPPS.
METHODS: In this prospective, randomized, controlled, single-blinded, phase-III study we enrolled CP/CPPS patients between March and December 2019. Participants were randomized (1:1) to the following treatment groups: 1) pollen extract suppositories 1 daily for 10 days; or 2) ibuprofen 600 mg 1 tablet in the morning for 10 days. At the enrolment time and at the follow-up evaluations (3, 6 months), all patients completed baseline questionnaires ([National Institutes of Health Chronic Prostatitis Symptom Index [NIH-CPSI] and Quality of Well-Being [QoL]) and underwent urological examination and microbiological evaluation. The primary endpoint was the quality-of-life assessment with Patients' Reported Outcomes (PROs).
RESULTS: One hundred and eighty-seven patients were screened. Finally, one hundred and twenty-four patients (mean age 34.6±3.9 years) were randomly allocated to the new pollen extract treatment (N.=63) or ibuprofen (N.=61) groups. At the end of follow-up examinations 56/63 group 1 patients (88.8%) showed a significant reduction of the NIH-CPSI total score, compared with 17/61 (27.8%) in group 2 ($P<0.0001$). Group 1 patients also reported a higher improvement in terms of PROs, when compared with the control group and group 1 patients reported a significant reduction of leucocyte count at the Meares-Stamey Test (-12; -4; $P<0.001$). Only mild adverse events were reported in the two groups and adverse events were less frequent in the pollen extract suppositories group.
CONCLUSIONS: The combination of pollen extract with hyaluronic acid and vitamins is more effective than ibuprofen in improving symptoms and Quality of Life in patients affected with CP/CPPS and has less side effects.

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KEY WORDS: Prostatitis; Urology; Symptom assessment.

Chronic prostatitis is one of the most common illnesses in men aged <50 years and has various clinical presentation forms.[1, 2] According to the classification of the National Institute of Health (NIH), category III chronic prostatitis/chronic pelvic pain syndrome (CP/CPPS) is most frequent.[3] Symptoms such as pelvic pain, painful voiding and ejaculation, and sexual dysfunctions are common, often having a significant impact on Quality of Life.[4] Treatment options for CP/CPPS not regarded as very effective and a number of aspects of the disease need exploration in more depth.[5] Antibiotics, anti-inflammatory medications, and alpha blockers are the traditional treatment options for CP/CPPS, although recent versions of international guidelines focus on an antibiotic-sparing approach in order to reduce the antibiotic usage and improve antibiotic stewardship.[5] On this background, there has been increased interest in the use of flower pollen extract for the management of CP/CPPS over the last years.[6] Several studies have shown that flower pollen extract preparations may contribute to a marked and lasting symptom reduction in young men with CP/CPPS as assessed by the National Institutes of Health-Chronic Prostatitis Symptom Index (NIH-CPSI) score.[7-9] A recent review article underlines that the use of flower pollen extract for the management of CP/CPPS patients is beneficial and significantly improves patients' Quality of Life, but the paper also indicates important aspects that warrants closer exploration in further studies.[10] Firstly, the suppository formulation seems to offer an improvement in therapy-related adverse effects by avoiding gastrointestinal absorption and the first pass metabolism. Moreover, a direct action on the rectum and the hypothesized effect of hyaluronic acid on perineal tenderness might facilitate an earlier therapeutic effect. Based on these considerations, the aim of the present study was to evaluate the efficacy and tolerability of a novel formulation (suppositories) containing pollen extract with hyaluronic acid and vitamins in the treatment of patients suffering from CP/CPPS.

Materials and methods

Study design and schedule

This was a prospective, randomized, controlled, single-blinded, phase III clinical trial to evaluate the efficacy and safety of a novel suppository formulation containing a combination of pollen extract, hyaluronic acid and vitamins (Class IIa medical device; AIFA – Italian Government bylaw – flower pollen extract 7% paste, sodium hyaluronate, vitamin E, vitamin A, liposoluble extracts of malva, calendula and aloe vera) in comparison with a standard therapy (ibuprofen) in patients affected with CP/CPPS.

All consecutive CP/CPSS patients attending two tertiaries centers (Santa Chiara Hospital, Trento, Italy; and Mater Domini Hospital, Catanzaro, Italy) between March and December 2019 were screened for this study. Patients who accepted and signed the informed consent were included in the study and randomized (1:1), in two groups of treatment: group 1 (pollen extract suppositories once daily for 10 days); and group 2 (ibuprofen 600 mg 1 oral tablet in the morning for 10 days).

After inclusion, patients were scheduled for the enrollment visit that provided compilation of study questionnaires, and clinical urological examination including the Meares-Stamey Test, in line with our standard practice.[6, 8, 9, 11] The randomization was performed by means of a computer-generated sequence of treatment allocations by block randomization with a random number generator, as previously described.[12] Investigators were blinded to the block size to avoid selection bias. All patients were identified with a numeric code to ensure a blinded statistical analysis. During the study, the results were collected for each treatment group by the data analyzers using the identification code and the analyses were performed in blind. Therefore, we considered the study as a single-blinded study. The study schedule was based on the previous our paper and the manufacturer's instructions for the pollen extract (suppositories) group[8, 10] and on clinical practice for the ibuprofen group. We decided to use anti-inflammatory drug as comparator, because the reported management of CP/CPPS includes oral antibiotics, anti-inflammatory agents, a-blockers and analgesics. No evidence up to the moment are available regarding topical treatment. Ibuprofen was selected in accordance with the results obtained by Lee *et al.*[13] All patients were contacted by telephone on day 14 of the therapy to ensure that they were administering the drug correctly, to check for uniform treatment intervals and dosage, to obtain a good adherence and to evaluate possible adverse effects. The follow-up visits were scheduled at 3, 6 months after the initiation of treatment, with a urological and laboratory assessment including questionnaire collection and microbiological examination (Figure 1). At 1 month after the beginning of treatment all patients were contacted by phone in order to evaluate the adherence to therapy and possible adverse effects.

Inclusion and exclusion criteria

Inclusion criteria were the presence of pelvic pain symptoms for at least three months during the last six months before study entry in accordance with the European Association of Urology (EAU) guidelines: a score in the pain domain of the NIH-CPSI of >4; a microbiologically negative result in the Meares-Stamey four-glass test.[6-9] Patients with the following characteristics were excluded: subjects <18 and >50 years of age; patients affected by major concomitant diseases with known anatomical abnormalities of the urinary tract or with evidence of other urological diseases; patients with residual urine volume >50 mL resulting from bladder outlet obstruction; subjects with a reported allergy to pollen extract; patients who had recently (<4 weeks) undergone oral or parenteral treatment, or who were currently using prophylactic antibiotic drugs; all patients positive to tests for *Chlamydia trachomatis*, *Ureaplasma urealyticum*, *Neisseria gonorrhoeae*, Herpes Viruses (HSV 1/2) and *Human papillomavirus* (HPV).

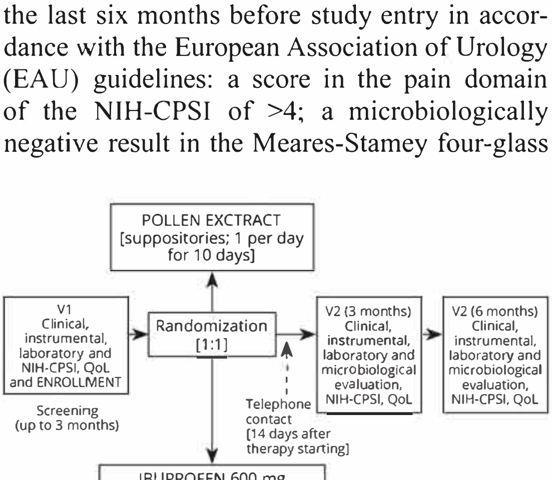

Figure 1.Study schedule.

End-points

The primary end-point (efficacy) was improvement in Quality of Life, defined as improvement in the NIH-CPSI score (reduction of the NIH-CPSI total score by ≥25%) and the patient-reported outcomes (PRO).

Secondary endpoints were the rate of treatment-emergent adverse events (TEAEs) and serious adverse events, during the treatment and follow-up periods and alteration of the inflammatory index as deducted from the leucocyte count at the Meares-Stamey Test.

Questionnaires and microbiological considerations

The validated Italian versions of the NIH-CPSI[14] and the Italian version of the Quality of Well-Being (QoL), a validated, multi-attribute health scale were self-administered by all patients.[15] Higher scores on the QoL scale reflect a higher Quality of Life.[15] In line with our previous studies, the biological samples collected during the urological examination and during the Meares-Stamey Test were immediately taken to the laboratory, under refrigerated conditions, and analyzed for cultures and leucocytes count.[8, 9, 13] Microbiological culture tests were carried out in accordance with the methods described by Mazzoli.[16]

Safety and adverse effects evaluation

The safety of the compound and drug was assessed according to the nature and frequency of adverse drug reactions (ADRs). The association between ADRs and drug treatment was evaluated as in our previous studies by means of the Naranjo Adverse Probability Scale. Positive records for ADRs were blinded before analysis by clinicians, who simply retrieved reported ADRs in clinical record forms and completed the Naranjo probability scale analysis.[17]

Composition and characterization of the extracts used

Each administration contained flower pollen extract 7% paste, sodium hyaluronate, vitamin E, vitamin A, liposoluble extracts of malva, calendula and aloe vera, as described in the manufacturer's declaration (IDIPharma – Integratori Dietetici Italiani S.r.l, Aci Bonaccorsi, Catania, Italy).

This study was approved by the University of Catanzaro Institutional Review Board (number 48 of 22th February 2019). The study was conducted in line with Good Clinical Practice guidelines, in compliance with the ethical principles published in the latest version of the Declaration of Helsinki. Written informed consents were obtained from all patients prior to treatment. Furthermore, this study was conducted in line with the Consolidated Standards of Reporting Trials statement (The Ottawa Hospital Research Institute, Ottawa, ON, Canada).

Statistical analysis

The homogeneity of the groups at baseline was assessed by using the Student's *t*-test and Mann-Whitney U-Test for continuous variables and by the χ^2 test for categorical variables. General characteristics of the study participants were expressed with descriptive statistics (means, standard deviations or ranges). Analysis of variance (ANOVA) was used for comparing the means. The Bonferroni adjustment test was also used at the second stage of the ANOVA. We performed a per protocol analysis, including only those participants who completed the treatment schedule and follow-up visits. The calculation of the sample size needed for enrollment was based on the expected questionnaire results (improvement of Quality of Life) in line with published results from other studies.[7-9] The required sample size was calculated under the following conditions: difference between the groups, 35% of patients who reach a reduction in 25% of the NIH-CPSI total score; α error level, 0.05 two-sided; statistical power, 80%; and anticipated effect size, Cohen's d=0.5. Our calculation yielded 61 individuals per group. Statistical significance was achieved when P<0.05. All reported P values were two-sided. Statistical analyses were performed using SPSS software, version 11.0 (SPSS, Inc., Chicago, IL, USA) for Apple-Macintosh.

Results

From a group of 187 patients attending our centers during the enrolment period, 141 met the inclusion criteria and were randomly allocated as follows: 70 to group 1 and 71 to group 2 (Intention to treat group). Overall, 17 patients (12%) were lost during follow-up and were excluded from the final analysis that included 63 patients in group 1 and 61 patients in group 2 (Per protocol group) (Figure 2). No statistically significant differences in terms of group composition were identified at the enrollment time. All clinical and laboratory baseline data are displayed in Table I.

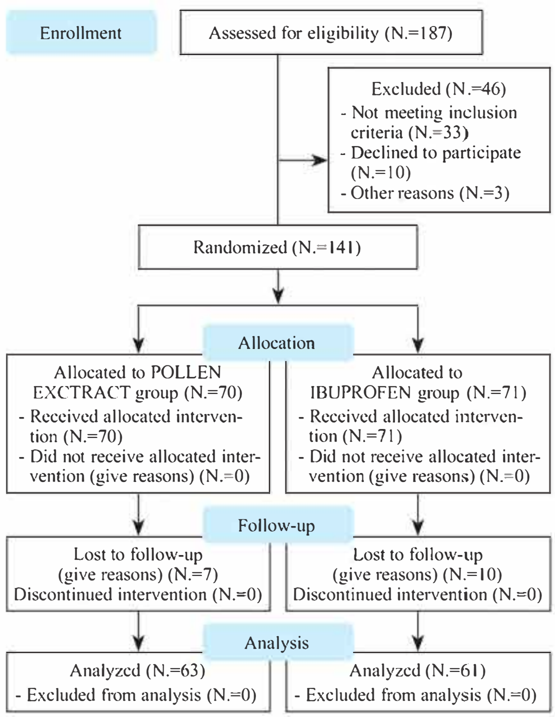

Figure 2.—Flowchart of the study.

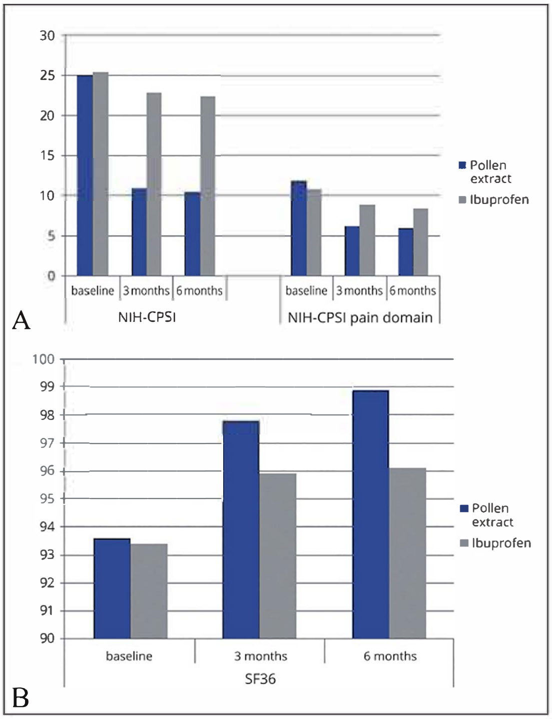

Figure 3.~~A,~~ B) Results at 3 and 6 months of follow-up evaluations.

Clinical results at follow-up evaluation

All questionnaire results at follow-up examinations are listed in Table II. At the end of the treatment period, 56/63 patients (88.8%) in group 1 reported a significant reduction in the NIH-CPSI total score (more than 25% from baseline), compared with 17/61 (27.8%) in group 2 (P<0.0001) (Figure 3). The reductions in the NIH-CPSI t score was confirmed by the results of the SF-36 questionnaires (mean SF-36 value in group 1: 98.9±2.1; mean SF-36 value in group 2: 96.1±5.1 [P<0.001]) (Figure 3). Moreover, patients treated in group 1 reported a higher improvement in terms of PROMS, when compared with patients in group 2.

Subanalysis of the NIH-IIIa category

Thirty-two patients met the criteria for inflammatory CP/CPPS category. Eleven patients in group 1 showed a reduced leukocyte count as per Meares-Stamey Test at the follow-up evaluation, when compared with the patients in group 2 (-12; -4; P<0.001) (Table III).

Safety and tolerability profile

All patients reported a good compliance with the novel compound, as no patients required interruption of the treatment. At the follow-up examinations, no TEAEs or severe adverse effects were reported in any of the two groups. Overall, adverse events were less frequent in group 1, in which 1 patient out of 63 (1.5%) reported anal pain that, however, did not require treatment interruption. Four patients in group 2 (6.5%) reported mild adverse effects (nausea). The Table IV shows all adverse drug reactions (ADRs) reported by the patients in the two groups.

Discussion

Major findings

Herein, we demonstrated that clinical efficacy of a novel medical compound containing a mixture of pollen extract, hyaluronic acid and vitamins for the management of patients suffering from CP/CPPS was superior to that of a standard regimen of ibuprofen and had a more favorable safety and tolerability.

Results in comparison with other studies

The efficacy of pollen extract in the treatment of patients affected by CP/CPPS has been assessed in several clinical studies which demonstrated significantly improved total symptoms, pain, and QoL in patients with inflammatory CP/CPPS without severe side-effects.[7-10, 18-22] In particular, Cai *et al.* in a review article and meta-analysis demonstrated that flower pollen extract could significantly improve patients' Quality of Life (OR=0.52 [0.34-.0.81]; P=0.02) without significant adverse events.[10] In the present study we evaluated a new administration form of pollen extract: the suppositories. In suppositories the soothing effect of pollen extract is probably improved by the presence of hyaluronic acid. Chronic prostatitis often presents with the pain due to perineal floor muscle spasm with consequent compression and inflammation of the pudendal nerves.[22] Perineal floor muscle spasm is often associated with rectal mucosa inflammation and hemorrhoids resulting in a self-

TABLE I.—*Demographic and clinical patient's data at the enrolment time.*

Variables	Pollen extract group	Ibuprofen group	P
	Total or mean (SD or %)	Total or mean (SD or %)	
Patients (N.)	63	61	
Age	34.3±5.1	33.9±5.3	0.66
Educational qualification			
Primary School	3 (4.7)	3 (4.9)	>0.99
High School	42 (66.6)	39 (63.9)	
University	18 (28.7)	19 (31.2)	
Smoking			
Yes	10 (15.9)	8 (13.1)	0.80
No	53 (84.1)	53 (86.9)	
Sexual behavior			
1 partner	59 (93.6)	58 (95.1)	>0.99
>1 partners	4 (6.4)	3 (4.9)	
Contraceptive use			
Condom	34 (55.7)	30 (49.1)	0.71
Coitus interruptus	29 (44.3)	31 (50.9)	
Start of CP/CPPS history (months)	21.3±6.4	20.9±6.1	0.72
Symptoms Score at baseline			
NIH-CPSI	25.0±3.3	25.3±3.1	0.60
SF-36	93.6±1.0	93.4±1.6	0.40
Clinical presentation			
Dysuria	30 (47.7)	32 (52.5)	0.71
Urgency	6 (9.5)	5 (8.2)	
Dysuria + frequency	5 (7.9)	4 (6.5)	
Burning	22 (34.9)	20 (32.8)	
Pain			
Perineal	30 (47.7)	31 (50.8)	0.85
Scrotal	3 (4.7)	3 (4.9)	
Suprapubic	10 (15.9)	5 (8.2)	
Lower abdominal	20 (31.7)	22 (36.1)	
Pain frequency			
Daily	58 (92.1)	54 (88.5)	0.55
Weekly	5 (7.9)	7 (11.5)	
Sexual symptoms			
Erectile dysfunction (ED)	12 (19.1)	10 (16.4)	>0.99
Premature ejaculation (PE)	19 (30.1)	21 (34.4)	
ED+EP	7 (11.1)	6 (9.8)	
No symptoms	25 (39.7)	24 (39.4)	

The table shows all baseline characteristics and clinical parameters the enrolment time.
SD: Standard deviation; N.: number; CP/CPPS: chronic prostatitis/chronic pelvic pain syndrome; NIH-CPSI: NIH Chronic Prostatitis Symptom Index; SF-36: Short Form-36.

maintaining inflammation cycle.[23, 24] We believe the moisturizing, emollient and soothing action of this new administration form contribute to a reduction of rectal mucosa inflammation by the filmogenic structure of hyaluronic acid and the pollen extract paste. Moreover, the liposoluble extracts are thought to maintain the hydration and elasticity of the rectal mucosa. Recently, Di Vico *et al.* investigated the role of suppository treatment containing pumpkin seeds, centella asiatica, boswellia, helichrysum, acetate vitamin E, melaleuca alternifolia and hyaluronic acid (named Proxelan®, Farma-Derma, Sala Bolognese, Bologna, Italy), in CP/CPPS.[25] They concluded that Proxelan® (Farma-Derma) monotherapy may represents a promising treatment in patients with CP/CPPS.[25] Moreover, new therapeutic modalities have been purposed in the last years for the management of CP/CPPS with interesting results. Low-intensity extracorporeal shock wave therapy and pelvic floor exercises have been evaluated in clinical trials in CP/CPSS patients with interesting results, showing that the treatment efficacy is improved by a multi-pathways therapy that is able to act at local level.[26-28]

TABLE II.—*Questionnaire results at the 3 and 6 months follow-up visits.*

Variables	Pollen extract group	Ibuprofen group	P
	Mean (SD)	Mean (SD)	
3 months			
NIH-CPSI			
Pretreatment	25.0±3.3	25.3±3.1	0.60
Post-treatment	10.9±4.2	22.8±4.1	<0.001
P	<0.001	0.0002	
(NIH-CPSI pain domain)			
Pretreatment	11.8±2.7	10.8±3.1	0.57
Post-treatment	6.2±2.1	8.8±1.9	<0.001
P	<0.001	<0.001	
Reduction of NIH-CPSI pain domain	-4.9±0.5	-1.9±0.5	<0.001
SF-36‡			
Pretreatment	93.6±1.0	93.4 ±1.6	0.40
Post-treatment	97.8±3.1	95.9±1.7	<0.001
P	<0.001	<0.001	
6 months			
NIH-CPSI			
Pretreatment	25.0±3.3	25.3 ±3.1	0.60
Post-treatment	10.4 ±3.0	22.3 ±3.0	<0.001
P	<0.001	<0.001	
(NIH-CPSI pain domain)			
Pretreatment	11.8±2.7	10.8±3.1	0.57
Post-treatment	6.0±2.0	8.4±2.1	<0.001
P	<0.001	<0.001	
Reduction of NIH-CPSI pain domain	-4.9±0.9	-2.0±0.4	<0.001
SF-36‡			
Pretreatment	93.6±1.0	93.4 ±1.6	0.40
Post-treatment	98.9±2.1	96.1±5.1	<0.001
P	<0.001	<0.001	

The table shows all questionnaire results at the follow-up visit.
SD: Standard deviation; NIH-CPSI: NIH Chronic Prostatitis Symptom Index; SF-36: Short Form-36.

TABLE III.—*Leukocyte evaluation at the enrolment time and at the results at the 3 and 6 months follow-up visit on 32 NIH-IIIa class patients.*

Variables	Pollen extract group	Ibuprofen group	P
	Mean (SD)	Mean (SD)	
Patients (N.)	18	14	
3 months			
Pretreatment	15±1	16±2	0.07
Post-treatment	5±1	11±3	<0.001
P	<0.001	0.06	
6 months			
Pretreatment	15±1	16±2	0.07
Post-treatment	3±1	9±3	<0.001
P	<0.001	<0.001	

The table shows the leukocyte evaluation at the enrolment time and at the results at the 3 and 6 months follow-up visits.
SD: Standard deviation.

TABLE IV.—*Safety and tolerability profile.*

Variables	Pollen extract group	Ibuprofen group	P
	N. (%)	N. (%)	
Adverse drug reactions (ADRs)			
Systemic			
Nausea	1 (1.5)	4 (6.5)	0.11
Epigastric pain	-	1 (1.6)	
Local irritation			
Anal pain	1 (1.5)	na	-
Pruritus ani	-	na	
Burning	-	na	
Treatment interruption	-	-	

The table shows all adverse drug reactions (ADRs) reported by the patients.
na: not applicable.

The present study provides important clinical results that are relevant for the management of CP/CPSS patients. This is the first study that assessed the efficacy and safety of a novel formulation of pollen extract.

Limitations of the study

Limitations that should be considered when interpreting our study results are the selected patient population and the non-double blinded design of the study. The lack of a placebo could be considered as a limitation of the study, but several authors stated that the use of placebos is often unethical, in CP/CPPS patients because several alternative treatments have been purposed and alternative study designs would produce similar results with less risk to individual research participants.[29]

Conclusions

A novel combination of pollen extract, hyaluronic acid and vitamins is safe and is able to improve Quality of Life in patients affected with CP/CPPS, in particular in the NIH category IIIa patients. We could show a superiority of pollen extract compared to a standard anti-inflammatory therapy with ibuprofen. Furthermore, the clinical efficacy of the compound in terms of symptoms reduction is underpinned by a significant reduction in the number of leukocytes, as demonstrated by the Meares-Stamey test results. The tolerability and side effect of pollen extract is also superior to a standard regimen of antiflogistics. Given the lack of proven efficacy of conventional therapies, alternative treatment options are urgently required, and the suppository of pollen extract used in the present study seems to be a noteworthy option for this difficult patient category.

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