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Evaluation of allergen immunotherapy in chronic rhinosinusitis. Proof-of-concept trial.

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Abstract

Due to the low control rate observed in some cross-sectional studies with conventional treatment and the high cost of biological therapies, there is a need to use complementary therapies that allow a balance between clinical control and the feasibility of their chronic use, especially in low- and middle-income health systems. Chronic inflammation of the nasosinusal mucosa is caused by diverse mechanisms, which are still not fully understood; it is known that the inflammatory process can begin years before the appearance of clinical symptoms, perhaps due to a genetic predisposition that favors the development of a mainly type 2 inflammatory response or due to epithelial damage caused by environmental factors. The understanding of the underlying mechanisms in chronic rhinosinusitis has undergone a conceptual evolution over time, leading to the realization that there are multiple underlying factors and therefore multiple causes; Obstruction of drainage complexes, fungal effects, nasal microbiome dysbiosis, among others. Type 2 inflammation is associated with the onset of the disease and also with complications of CRS such as the presence of polyps, lack of response to drug treatment, the need for recurrent surgeries, and loss of smell. This type of inflammation is present in 60 to 80% of patients with CRS. In patients with rhinitis where type 2 inflammation is present, allergen immunotherapy (ITA) for mites of the genus Dermatophagoides has proven to be an effective, safe and cost-effective tool. One of the commonalities between rhinitis and CRS is the predominance of IgE-mediated type 2 inflammation, which is key to an effective response with ITA. Some studies suggest that ITA could be an effective therapy in CRS. However, the available information is scarce and has methodological limitations, for example the absence of a control group, so it is not sufficient to recommend its use in clinical practice for CRS. In this project, we intend to conduct a proof-of-concept (POC) trial to test a hypothesis summarized in the following research question: Do patients with CRS over 18 years of age who receive ITA for Dermatophagoides for 12 months versus patients who do not receive ITA achieve greater clinical control according to the nasal provocation test? The results of the project may be the first step towards developing new therapeutic alternatives for CRS and better understanding the mechanisms that determine the behavior of the disease.

Guidelines

Pharmacotherapy: The standard pharmacotherapy for all patients is the use of triamcinolone nasal spray at 55 mcg/puff in each nostril every 12 hours. After the sixth month, for patients with clinical control according to the SNOT22-50% score, the spray frequency will be reduced to every 24 hours. During annual follow-up, if control persists, the spray will be discontinued, with subsequent escalation based on clinical control. If control is not achieved, antileukotrienes (montelukast 10 mg/day) and systemic steroid cycles (prednisolone 50 mg for 3 days, tapered every three days to 25 mg, 10 mg, 5 mg, and then discontinued) may be added to the treatment at the physician's discretion in cases of exacerbations. Frequency of adverse effects: The frequency of any adverse event, whether or not related to the therapies, will be collected and assessed according to the treating physician's judgment as "probable" or "improbable" in relation to the intervention. Polyps and/or surgery: Data will be recorded for patients who require surgery during follow-up or who develop polyps. Allergen immunotherapy: Allergen immunotherapy is the intervention in this study. It will be performed by administering a Derf/Derp (50/50%) allergen concentrate from Inmunotek Laboratories with an antigenic potency of 10,000 TU/ml. Administration will follow the standard rapid regimen: the initial dose will be administered subcutaneously in two divided doses (0.2 ml and 0.3 ml, 30 minutes apart) with a 30-minute interval between doses. Subsequent doses will be administered as a single dose (0.5 ml) with 30 minutes of follow-up monitoring. All patients will be instructed on warning signs and the need to avoid strenuous activity for 24 hours. The medication will be supplied according to the institution's protocol and provided by the healthcare system. Patients will be contacted one week and 48 hours prior to the immunotherapy administration to ensure it is administered on the scheduled date and to avoid any delays. In the event that the patient loses their social security coverage, the intervention and its costs will be covered by the study group, at no cost to the patient. The maximum interval between applications is considered to be 8 weeks (53), a period longer than this will be considered a deviation and will be reported for further analysis of its impact on the results obtained. Randomization: Before being assigned to the randomized group, patients must discontinue all therapies that Randomization may influence the clinical control of CRS four weeks prior to randomization (washout period). Randomization between the active and control groups will be performed using the Jamovi program with R modules, and the allocation will be done using a 1:1 scheme. Blinding of the intervention: The extracts will be supplied by Inmunotek; each vial will be blinded at a central pharmacy before being given to the administering personnel. The individuals administering the medication will be different from those preparing it at the central pharmacy and will not have access to the patients' clinical or demographic information. Throughout the study, patients in both groups will receive a monthly injection of the active substance and/or solvent. Bias control: Control of selection bias: Patients diagnosed with chronic respiratory syndrome (CRS) will be recruited based on diagnostic criteria that include objective tests (e.g., CT scan, nasofibrolaryngoscopy, provocation test, etc.). Recruitment staff will standardize their criteria through joint training and evaluation via pilot studies. The study population is representative of the most common CRS in the general population (38), which reduces the risk of prevalent cases, non-response bias, and other biases (56). Because the procedures performed in this project are part of routine clinical practice and are useful for the medical management of patients, they do not create an additional burden that would motivate patients to selectively drop out of the study. Furthermore, given that several procedures offered in the project are part of the study of their disease and will be offered free of charge within the research, adherence to the project may be better than with regular medical care. Additionally, the randomization of participants into the two groups reduces the likelihood of selection bias and helps to avoid a heterogeneous distribution of factors that could affect the outcome. Control of information bias (measurement bias): The variables to be measured are clinical and

laboratory-based. The clinical variables of interest in the study can be compared using objective instruments, as can laboratory tests such as nasal provocation tests and immunoglobulin measurement tests, thus reducing the risk of measurement bias. The operators performing these procedures will not have access to the patients' clinical or demographic information, so blinding prevents potential bias in the interpretation of the tests between groups. Sampling process and sample size calculation: We will use convenience sampling. Hypothesis testing is commonly used in confirmatory studies, where a Type I error rate of 5% and a Type II error rate of 20% are typically used when evaluating interventions. For a point-of-care (POC) study, which is exploratory in nature, a sample size is required that allows for a high probability of reproducing the results later. If the result is positive for the intervention but is not replicated in a confirmatory study, it implies a loss of memory for those conducting the study. However, a sample size for an exploratory study that meets the requirements of a confirmatory study is also costly, which contradicts the objective of POC studies, which is precisely to save resources. Therefore, in POC studies, the interest in calculating the sample size is not to achieve the sampling power of a confirmatory study, but rather to define the probability of achieving a reproducible significant difference in a subsequent confirmatory study.

Materials

Conventional therapy: triamcinolone nasal spray (55mcg puff every 12 hours), fexofenadine (120mg/day). Immunotherapy: Derf/Derp extract (0.5ml monthly, 10,000 TU/ml) administered in an "ultra-rush" regimen. Blomia allergen extract (Inmunotek laboratory) at a concentration of 15 µg/ml (stock concentration 1:1) in each nostril. Application: a) Puff with a 0.01 dilution (1:100) of the initial concentration, b) Puff with a 0.1 dilution (1:10) of the initial concentration, c) Puff with the stock concentration (1:1).

Safety warnings

All patients will be instructed on warning signs and the need to avoid strenuous activity for 24 hours after administration of the allergen immunotherapy.

Ethics statement

Patients who agree to participate must sign an informed consent form.

Before start

Before starting the administration of the Blomia allergen extract, nonspecific nasal hyperreactivity will be assessed with 500 mcg of saline solution (47).

protocol

1 **METHODOLOGY**

Studio

design

A
proof-of-concept trial study with a marketed molecule, applied to a population with RSC who will be randomized into an active group (receiving immunotherapy plus conventional therapy) and a comparator group (conventional therapy only) with follow-up for at least 12 months.
Conventional therapy will consist of triamcinolone nasal spray, one 55mcg puff every 12 hours, and the antihistamine fexofenadine 120mg/day. Immunotherapy (Derf/Derp extract 0.5ml monthly, 10,000 TU/ml) will be administered in an "ultra-rush" regimen with an initial dose divided into 0.2ml and 0.3ml, administered 30 minutes apart, while the maintenance dose will be a monthly administration of 0.5ml for at least 12 months. To evaluate the response to immunotherapy, the primary outcome will be the Dermatophagoides nasal challenge test (NRT), and the secondary outcome will be improvement in quality of life.

Project hypothesis

The hypothesis of the study is that patients with CRS over 18 years of age who receive ITA for Dermatophagoides versus those who do not receive ITA achieve better clinical contro

Sources for patient

recruitment and selection

Recruitment sources will be allergy and otolaryngology centers located in Medellín. Among those invited are: Hospital Alma Mater de Antioquia, Unidad Alergológica, Clínica SOMER, Clínica Antioqueña de Otorrinolaringología-ORLANT, and IPS-NASAL.
Patient identification will be carried out through evaluation by physicians specializing in chronic rhinosinusitis (allergists and otolaryngologists). The medical records of participating centers will be searched for patients diagnosed with chronic rhinosinusitis or related diagnoses that could indicate chronic rhinosinusitis (J010 to J014, J018, J019, J320 to J324, J328, J329, J300 to J304, J310, J330, J331, J338, J339, J450, J451). With this data we will build a database of eligible patients who will be contacted and, if they meet the selection criteria, will be randomized and subsequently scheduled for data collection.

Previous
studies conducted with the institutions that will be invited to participate (38), this allows us to affirm that
the profile of patients with CRS treated by otolaryngology and allergology is
the same in 90% of cases since it comes from the same population.

Selection
criteria
Patients with primary CRS with clinically relevant IgE sensitization to
mites (Der f and Der p) will be included. CRS is defined according to the
clinical criteria proposed in the 2020 EPOS guidelines (European Consensus on Rhinosinusitis and Nasal Polyposis 2020) with confirmation by paranasal sinus CT and endoscopy; over 18 years of age without polyps, with IgE antibodies to Dermatophagoides spp, and a baseline SNOT22 score greater than 30 points after one month without conventional treatment.
Patients
with a known contraindication to conventional treatment or intra-abdominal therapy (ITA) will be excluded, as will those suffering from a condition that resembles symptoms of chronic rhinosinusitis (CRS) and that could affect the interpretation of assessment scales (e.g., congenital nasal cavity structural abnormalities, post-traumatic abnormalities, and peripheral neuropathies) or causes of secondary chronic rhinosinusitis such as ANCA-related vasculitis, primary ciliary atrophy, cystic fibrosis, selective immunodeficiencies, or rhinosinusitis secondary to tumors. Patients currently receiving medications that could affect the clinical evaluation or those whose disease severity indicates biological therapy or sinus surgery will also be excluded.

Measurement
instruments and clinical outcomes
IgE
sensitization assessment (atopy): Atopy is an inclusion
criterion and will initially be measured using skin and serum tests to enroll patients in the study. Among the selected patients, we will measure IgE levels in nasal mucus and perform provocation tests.
Sensitization to allergenic extracts of Dermatophagoides pteronyssinus, Dermatophagoides farinae, Blomia tropicalis, dog, cat, Aspergillus fumigatus, Alternaria alternata, Cladosporum herbarum, and Cynodon dactylon will be tested in skin, blood, and mucus. For skin testing, we will follow international recommendations (43) For
blood and mucus tests, rBlo t 5, rBlo t 13, and rBlo t 21 will be additionally tested using the ImmunoCAP and/or ELISA technique. (38), In addition, eosinophil counts and total IgE levels will be measured. Nasal mucus collection

will follow the method proposed by Naclerio (44, 45) with modifications (46).

Nasal challenge test (NCT): The clinical relevance of dust mite atopy is an inclusion criterion for the study, and its assessment using nasal provocation testing (NPT) will be the reference parameter for evaluating the primary outcome. This relevance will be assessed using validated and standardized protocols (38, 46, 47):

a) Nasal anatomy is evaluated using anterior rhinoscopy and acoustic rhinometry.

b) Blomia allergen extract (Inmunotek laboratory) is applied at a concentration of 15 µg/ml (stock concentration 1:1) in each nostril. The application will be done gradually based on previous studies:

a. Puff with a 0.01 dilution (1:100) of the initial concentration

b. Puff with a 0.1 dilution (1:10) of the initial concentration

c. Puff with the stock concentration (1:1) After the first two doses, the patient will be observed for 30 minutes; after the second and third doses, for one hour. Before starting the administration of the Blomia allergen extract, nonspecific nasal hyperreactivity will be assessed with 500 mcg of saline solution (47).

Quality of life assessment and other clinical assessments: To assess quality of life, the SNOT22 scale (“Sino-Nasal Outcome Test”) will be used.(28, 48). The SNOT22 questionnaire has translations and back-translations in Spanish and is recommended in clinical guidelines (2, 49). We will conduct a pilot study with the first 20 participants to evaluate some properties of reproducibility (inter- and intra-observer reliability), validity (content, appearance), sensitivity, and utility (50). The SNOT22 is a specific indicator of the impact on quality of life secondary to symptoms caused by nasosinusal inflammation; however, it is frequently used as a measure of disease control (28, 48). It consists of 22 questions that can be divided into four domains, which has allowed it to also be used to assess the impact of the disease according to its severity. This questionnaire has proven to be sensitive to change and useful for evaluating different interventions (51, 52) with a minimal clinically relevant difference (MCRD) with changes of 9 points. This scale will be evaluated in three ways: Frequency of patients with MCRD for the scale. Frequency of patients with SNOT22-50%, which refers to the number of patients who achieve a reduction of at least 50% in relation to the baseline

SNOT22. Frequency of patients with SNOT22-90%, which refers to the number of patients who achieve a reduction of at least 90% in relation to the baseline SNOT22.
The Visual
Analogue Scale (VAS) consists of the subjective evaluation of the intensity of symptoms as perceived by the patient (2). It
is also useful for assessing how the patient perceives the impact of the interventions and their results (53), in
addition, its results have been correlated with other scales (53, 54). The score provides a general but not specific overview, as it lacks defined assessment domains. It will be used to evaluate the patient's perceived overall control and olfactory perception (55).
We will perform a nasal assessment of the cardinal symptoms of rhinitis at each follow-up appointment and during each provocation using the TNSS (Total Nasal Symptom Score). This scale consists of four domains where the intensity of itching, sneezing, nasal congestion, and rhinorrhea over the past 12 hours is evaluated according to the patient's perception. The maximum severity score is 12 points (3 points for each area), and a score of 0 points indicates the absence of symptoms (54). We
will also assess the Lebel scale during the provocation, which has 4 domains with a maximum severity score of 11 points and a minimum of 0 points (55). The scale takes into account the physician's observation during the anterior rhinoscopy and also the patient's perception of the four cardinal symptoms (itching, sneezing, obstruction, and rhinorrhea). We will also evaluate the minimum transverse area (mean rhinometry) during the provocation (56). The interpretation of a positive provocation test result will be made in accordance with international recommendations (38). In
patients presenting with conjunctivitis as a comorbidity, we will evaluate the TOSS (Total Ocular Symptom Score) scale **(57)** and in patients with asthma, the ACT (Asthma Control Test) (58).
Pharmacotherapy: he standard pharmacotherapy for all patients is the use of triamcinolone nasal spray at 55 mcg/puff in each nostril every 12 hours. After the sixth month, for patients with clinical control according to the SNOT22-50% score, the spray frequency will be reduced to every 24 hours. During annual follow-up, if control persists, the spray will be discontinued, with subsequent escalation based on clinical control. If control is not achieved, antileukotrienes (montelukast 10 mg/day) and systemic steroid cycles (prednisolone 50 mg for 3 days, tapered every three days to 25 mg, 10 mg, 5 mg, and then discontinued) may be added to the treatment at the physician's discretion in cases of exacerbations.
Frequency of adverse effects: The frequency of any adverse event, whether or not related to the therapies, will be collected and assessed according to the

treating physician's judgment as "probable" or "improbable" in relation to the intervention.
Polyps and/or surgery: Data will be recorded for patients who require surgery during follow-up or who develop polyps.

Allergen immunotherapy
Allergen immunotherapy is the intervention in this study. It will be performed by administering a Derf/Derp (50/50%) allergen concentrate from Inmunotek Laboratories with an antigenic potency of 10,000 TU/ml. Administration will follow the standard rapid regimen: the initial dose will be administered subcutaneously in two divided doses (0.2 ml and 0.3 ml, 30 minutes apart) with a 30-minute interval between doses. Subsequent doses will be administered as a single dose (0.5 ml) with 30 minutes of follow-up monitoring. All patients will be instructed on warning signs and the need to avoid strenuous activity for 24 hours. The medication will be supplied according to the institution's protocol and provided by the healthcare system. Patients will be contacted one week and 48 hours prior to the immunotherapy administration to ensure it is administered on the scheduled date and to avoid any delays. In the event that the patient loses their social security coverage, the intervention and its costs will be covered by the study group, at no cost to the patient. The maximum interval between applications is considered to be 8 weeks (53), a period longer than this will be considered a deviation and will be reported for further analysis of its impact on the results obtained.
Randomization:
Before being assigned to the randomized group, patients must discontinue all therapies that Randomization:may influence the clinical control of CRS four weeks prior to randomization (washout period). Randomization between the active and control groups will be performed using the Jamovi program with R modules, and the allocation will be done using a 1:1 scheme.
Blinding of the intervention: The extracts will be supplied by Inmunotek; each vial will be blinded at a central pharmacy before being given to the administering personnel. The individuals administering the medication will be different from those preparing it at the central pharmacy and will not have access to the patients' clinical or demographic information. Throughout the study, patients in both groups will receive a monthly injection of the active substance and/or solvent.

Bias control
Control of selection bias: Patients diagnosed with chronic respiratory syndrome (CRS) will be recruited based on diagnostic

criteria that include objective tests (e.g., CT scan, nasofibrolaryngoscopy, provocation test, etc.). Recruitment staff will standardize their criteria through joint training and evaluation via pilot studies. The study population is representative of the most common CRS in the general population (38), which reduces the risk of prevalent cases, non-response bias, and other biases (56). Because the procedures performed in this project are part of routine clinical practice and are useful for the medical management of patients, they do not create an additional burden that would motivate patients to selectively drop out of the study. Furthermore, given that several procedures offered in the project are part of the study of their disease and will be offered free of charge within the research, adherence to the project may be better than with regular medical care. Additionally, the randomization of participants into the two groups reduces the likelihood of selection bias and helps to avoid a heterogeneous distribution of factors that could affect the outcome.

Control of information bias (measurement bias): The variables to be measured are clinical and laboratory-based. The clinical variables of interest in the study can be compared using objective instruments, as can laboratory tests such as nasal provocation tests and immunoglobulin measurement tests, thus reducing the risk of measurement bias. The operators performing these procedures will not have access to the patients' clinical or demographic information, so blinding prevents potential bias in the interpretation of the tests between groups.

Sampling process and sample size calculation

We will use convenience sampling. Hypothesis testing is commonly used in confirmatory studies, where a Type I error rate of <5% and a Type II error rate of <20% are typically used when evaluating interventions. For a point-of-care (POC) study, which is exploratory in nature, a sample size is required that allows for a high probability of reproducing the results later. If the result is positive for the intervention but is not replicated in a confirmatory study, it implies a loss of memory for those conducting the study. However, a sample size for an exploratory study that meets the requirements of a confirmatory study is also costly, which contradicts the objective of POC studies, which is precisely to save resources. Therefore, in POC studies, the interest in calculating the sample size is not to achieve the sampling power of a confirmatory study, but rather to define the probability of achieving a reproducible significant difference in a subsequent confirmatory study.

The primary outcome has a dichotomous (positive and negative) result, based on previous studies with immunotherapy in rhinitis (37, 57), For potential

utility in real-world clinical practice, we define a difference of at least 30% in favor of the intervention as clinically relevant. Based on this assumption, a sample size with the following statistical factors—a Type I error (α) of 0.05, a Type II error (β) of 0.1, a statistical power of 90%, a two-tailed test, and an effect size of at least 0.2—requires at least 130 patients per group.

According to the formula proposed by Yin-Yin (58):

Where basically, the probability of reproducing the results in a future confirmatory study is calculated based on the statistical factors previously described, assuming a certain number of subjects to be included; With 35 patients per group there is a probability of at least 0.7 that the results of the POC study will be reproduced in a subsequent confirmatory study; with 99 patients per group, the probability is 0.8.

Data processing and análisis

Patients who agree to participate must sign an informed consent form (see appendix "informed consent"). For the analysis, once the information is collected, missing or atypical data will be checked to avoid inconsistencies, and a descriptive analysis of the characteristics of the enrolled patients will be performed. The mean, median, standard deviation, and range will be used as summary measures for quantitative variables, according to their distribution.

For qualitative variables, frequency distributions and percentages will be used.

The Shapiro-Wilk test will be used to assess whether the distribution of continuous variables is normal. A p-value ≤ 0.05 will be used to define whether there is a normal distribution; in this case, we reject the null hypothesis that the distribution is normal. We will compare continuous variables with an unpaired t-test if the data distribution is normal, or with the Mann-Whitney U test if it does not meet this criterion. Categorical variables will be analyzed using the chi-square test of independence if the expected frequencies are greater than 5 in all cases; otherwise, they will be analyzed using Fisher's exact test (a p-value <0.05 will be considered significant in both cases). We will perform multiple regression analysis according to the nature of the variables.

Protocol references

(5, 16, 17, 18, 19, 20, 21-28, 29, 30, 31-35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, 50, 51, 52, 53, 54, 55, 56, 57, 58)