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ELABORATION OF A PATIENT-FRIENDLY TREATMENT STRATEGY WITH CAPSAICIN NASAL SPRAY IN PATIENTS WITH IDIOPATHIC RHINITIS

ACADEMIC MONOCENTER CLINICAL STUDY

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Introduction

A. Chronic rhinitis

Chronic rhinitis is affecting more than 200 million people worldwide. Its prevalence is estimated to be as high as 30% of the Western population. Rhinitis is defined as symptomatic inflammation of the inner lining of the nose and is characterized by the following symptoms: rhinorrhea, nasal blockage, nasal itching and/or sneezing. The cut-off point for defining rhinitis as chronic rhinitis is considered to be persisting symptoms for over more than twelve weeks (1) (2) (3).
Beside the classical symptoms, patients often suffer from nasal hyper reactivity (NHR) i.e. the induction of nasal symptoms by non-specific physical and chemical triggers such as temperature changes, smoke/scents, physical activity, emotional stress and changes in humidity (4) (5).

Chronic rhinitis can be divided into three major subgroups (Figure 1); based on the knowledge of the major etiological factor: infectious rhinitis, allergic rhinitis and non-allergic, non-infectious rhinitis or NANIR, in literature also referred to as NAR.

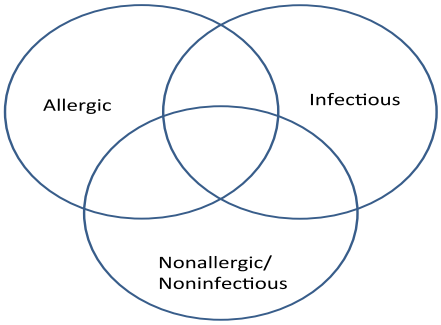

Figure 1: Visualization of the tree major subgroups within chronic rhinitis

B. Non-allergic rhinitis (NAR)

As we lack a uniform definition of NAR, epidemiology of NAR is difficult to accomplish. It is estimated that more than 50 million people in Europe suffer from NAR (2).
The diagnosis of NAR is based on exclusion of clinical signs of infection as well as exclusion of sensitization to airborne allergens.
As there are different phenotypes of NAR, good clinical history is the key to the right diagnosis.

Subgroups of NAR are occupational rhinitis, elderly or senile rhinitis, gustatory rhinitis, hormonal rhinitis and drug-induced rhinitis (as a cause of adverse effects of systemic treatment or because of abuse of decongestive nasal therapy) (6).
Up to 50% of the patients with NAR, are suffering from idiopathic rhinitis or IR (1), rhinitis of an unknown etiology.

C. Idiopathic rhinitis (IR)

Up to 20% of the adult population in Flanders suffer from IR. It is affecting a very heterogeneous group of patients. The diagnosis of IR is a diagnosis by exclusion. Allergy, infection, hormonally or drug induced rhinitis and other rare forms of rhinitis, such as elderly, gustatory, occupational or local allergic rhinitis have to be eliminated.

Often IR patients suffer from NHR (4) which implies that one or more nasal symptoms are induced upon encounter of environmental stimuli, such as humidity changes, temperature changes, smoke, other scents, irritants or strong odors. Although the problem of NHR in clinical practice is significant and IR represents a nasal condition with major impact on the quality of life, it still is largely neglected. Maybe because the mechanisms underlying NHR are not well understood. Several studies point towards the involvement of a neural mechanism such as neurogenic inflammation (7) (8).

In AR patients, NHR is associated with hyper innervation of the nasal mucosa with increased expression of calcitonin gene related peptide and Substance P in the nerve fibers, which is considered a sign of neuronal hyper reactivity. AR and IR patients show the same level of mucosal hyper innervation, suggesting a neuro-inflammatory involvement in both (8).

D. Capsaicin

In 1991, the Swiss research group of Lacroix et al., described for the first time that IR patients benefit from intranasal capsaicin spray (9). Their findings were confirmed by other researchers e.g. Riechelman et al. (10), Blom et al. (11) (12). In 1997, Blom et al. published the first placebo-controlled trial showing therapeutic efficacy (11).
Van Rijswijk et al. demonstrated in 2003 that five nasal applications on one day is as effective as five applications spread over two weeks (13), what makes the new treatment protocol more attractive both for patient and medical staff.

The research group of Prof. Dr. P.W. Hellings of the Department of Oto-rino-laryngology of the University Hospitals Leuven has more then six years of clinical experience with capsaicin (Figure 2), in treatment of patients with IR who do not respond well to the available treatment (i.e. intranasal corticosteroids).

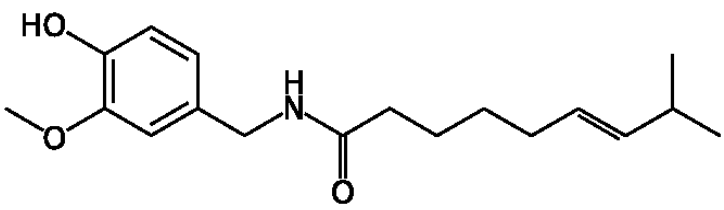

Figure 2: Structural formula of capsaicin

In a very recent academic proof-of-concept study, major therapeutic effects have been shown on nasal symptoms and reduction of NHR in 14 patients with IR. That fact that confirms the work of several former investigators and a numerous amount of studies in which the therapeutic effect of capsaicin was already proven (9) (10) (11) (12) (13).

E. TRP channels

Since decades capsaicin (8-methyl-N-vanillyl-6-nonenamide), the natural extract of red, hot chili pepper, is used as an analgesic in topical preparations (14) (15).
Prolonged exposure to capsaicin makes the afferent nerves insensitive not only to the pungent substance but also to other noxious stimuli. The process of defunctionalization of nociceptor fibers is the mechanism behind its analgesic properties (14) and its therapeutic properties are due to the effect of capsaicin on the transient receptor potential V1 (TRPV1) on the sensory C-fibers in the nasal mucosa (16).

Activation of these peripheral sensory nerve endings can trigger the TRP channel family - a family of chemoreceptors present in the airway lining.
Currently, a lot of research is devoted to these channels because there is a strong conviction that disturbances in afferent sensory mechanisms are very important in the pathogenesis of functional problems (17).

Members of the mammalian TRP family that are of specific importance for our research are TRPA1 (Ankyrin 1), TRPM8 (Melastatin 8) and TRPV1 (Vanilloid 1).
TRPA1 is very commonly expressed in the nasal mucosa and is functioning as a major irritant detector. Therefore it is believed to play a crucial role in occupational rhinitis.
The TRPM8 channel itself is activated by cold temperatures (as well as TRPA1) and TRPM8 activation leads to a cold sensation. Its function is not yet completely understood.
Interestingly, approximately nine months after capsaicin treatment, symptoms tend to recur. The underlying mechanism is still uncertain, but is currently being investigated by the fundamental research team of Prof. Dr. K. Talavera.

Objectives

A. Aims

Our primary aim is:

- To evaluate if two novel treatment modalities (explained more briefly on page 9 in paragraph 'Study Onset' of chapter 'Methodology') show non-inferiority on subjective evaluations (symptom score on a Visual Analogue Scale (VAS), Therapeutic Response Evaluation (TRE) and Rhinitis Quality of Life Questionnaire (RQLQ)) compared to the current treatment modality of capsaicin nasal treatment in patients with IR. The gathered data of this single center trial can be used to guide the decision on the set-up and the design of a larger multi-center trial being powered to prove non-inferiority.

Our secondary aims are:

- To evaluate if the two novel treatment modalities show non-inferiority compared to the current treatment modality of capsaicin nasal treatment in patients with IR on objective evaluations (Peak Nasal Inspiratory Flow (PNIF) measurements before and after CDA challenge).
- To evaluate the occurrence of adverse events at week 4, week 12 and week 26 and recurrence of symptoms and NHR at week 26 in the different treatment groups.

B. Hypothesis

Non-inferiority in efficacy of the two novel treatment regimes i.e. capsaicin nasal spray 0,01mM (2puffs/nostril/day) during 4 weeks and capsaicin nasal spray 0,001mM (2puffs/nostril/day) during 4 weeks compared to the current treatment of capsaicin nasal spray 0,1mM (5/day administered on a single day) with regard to the scores on week 4 (taking into account the baseline level).

C. Outcome

- VAS for major nasal symptom at week 4, week 12 and week 26. The region of equivalence is defined as a difference in VAS of less than 1.
- VAS for total and individual nasal symptoms at week 4, week 12 and week 26. The region of equivalence is defined as a difference in VAS of less than 1.
- TRE (based on a scale from 1 to 5) at week 4, week 12 and week 26. The region of equivalence is defined as a difference in percentage for patients of less than 10% in all different TRE scoring groups.

- NHR (objectively measured by PNIF before and after CDA challenge) in all treatment modalities at week 4, week 12 and week 26. The region of equivalence is defined as a drop in PNIF of less than 10%.
- Appearance of adverse events at week 4, week 12 and week 26.
- Recurrence of symptoms (based on a scale of 1 to 5) at week 26.

Study design

A. Type of study

This academic, mono center, randomized, double blind, double dummy, placebo controlled, parallel-group study will be carried out in the Department of Oto-rino-laryngology of the University Hospitals Leuven in 2014, and be running until March 2018.

The following milestones will be outlined:

- August 2014: Preparation of the logistics of the clinical trial.
- September 2014: EudraCT number application and submission at CTC and MEC of the University Hospitals Leuven, without major expected problems in the light of the previous proof-of-concept study and reputation of the research team of Prof. Dr. Peter Hellings.
- January 2015: First IR patient included in this trial.
- July 2015: Last visit of first included patient.
- October 2017: Last IR patient included in this trial.
- April 2018: Last visit of last included patient, all ELISAs performed, and start of data analysis.

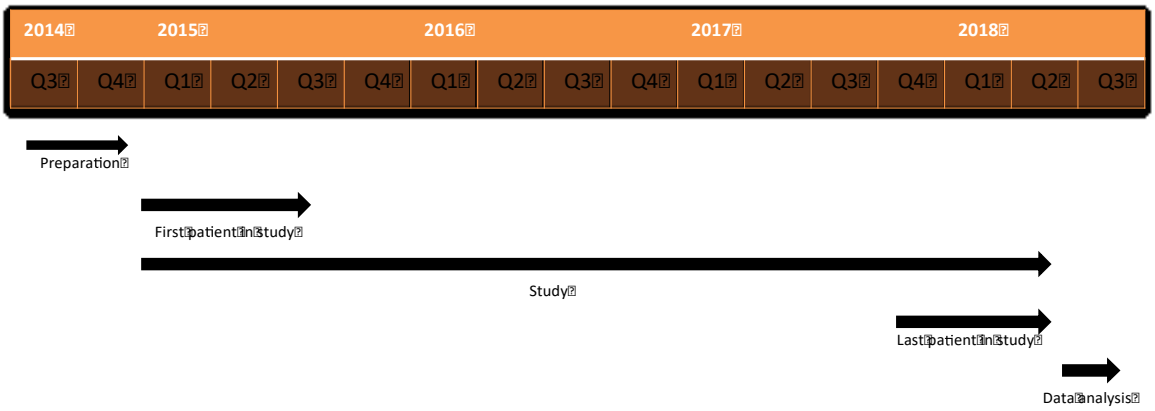

Table 1: Visualization of the time management of the study

Involved investigators:

- Apr. Sofie Mees, PhD fellow (screening and clinical follow-up) (telephone number: +32 16 33 24 03)
- CTA Emily Dekimpe
- Brecht Steelant, PhD fellow
- Inge Kortekaas Krohn, PhD fellow
- CTA Ina Callebaut, PhD
- Dr. Laura Van Gerven MD, PhD (recruitment, screening and clinical follow-up)
- Prof. Dr. Peter Hellings (recruitment and screening and principal investigator)

B. Inclusion criteria

The following criteria will be administered for the screening of a patient in order to obtain inclusion of the patient in our study:

- IR patients with at least 2 persistent (> 12w) rhinological symptoms (nasal discharge, sneezing, nasal congestion) for an average of at least 1 h per day,
- IR patients with a total nasal symptoms score (TNS) of 5 or more on a visual analogue scale (VAS).
- Age > 18 and < 60 years.
- Written informed consent.
- Willingness to adhere to visit schedules.
- Adequate contraceptive precautions in female patients with childbearing potential. **

C. Exclusion criteria

Patients meeting the following criteria will be excluded out of the study:

- Patients with concomitant allergic rhinitis, demonstrated by positive skin prick test (Hal reagents) and/or IgE in blood. *
- Patients with structural abnormalities: nasal polyps, severe septal deviation (septum reaching concha inferior or lateral nasal wall), septal perforation, hypertrophy of the inferior turbinates.
- Patients with local allergic rhinitis (LAR) or entopy.
- Systemic steroid treatment less than 4 weeks before the inclusion in the study, nasal steroid spray less than 4 weeks before the inclusion, oral leukotriene antagonists or long-acting antihistamines less than 2 weeks before the inclusion.
- Inability of the patient to stop taking medication affecting nasal function like ß-blockers.
- History of prolonged use or abuse of decongestant nasal spray like xylometazoline spray and/or use or abuse of decongestive oral medication.
- Evidence of infectious rhinitis/rhinosinusitis or common cold within 4 weeks prior to inclusion.

- Pregnancy or lactation. **
- Any disorder of which might compromise the ability of a patient to give truly informed consent for participation in this study.
- Enrollment in other investigational drug trial(s) or receiving other investigational agent(s) for any other medical condition.
- Contra-indications for the use of local anesthesia (cocaine 5%).
- Smoking or occupational exposure to irritants (like hypochlorite, persulfates, isocyanates).
- Nasal malignancies or severe comorbidity like granulomatosis or vasculitis.

*Note *:*
Patients with underlying allergic disease are defined by positive skin prick test for the 18 most prevalent inhalant allergens (house dust mite, timothy grass, smooth meadow grass, orchard grass, nettle, plantago, oxeye daisy, mugwort, alder, birch, hazel, horse, cat, dog, rabbit, Alternaria, Aspergillus and Cladosporium - HAL Allergy, Leiden, The Netherlands) and/or positive IgE analysis in the blood.
*Note **:*
Female patients with childbearing potential will be offered a pregnancy test at the screening.

D. Possible hurdles

Based on the former studies in which the therapeutic effect of capsaicin is proven (9) (10) (11) (12) (13) (18) and given the fact that capsaicin is well tolerated and side effects are minimal, it is very unlikely to be subject of foreseen or unforeseen obstacles in the elaboration of this study protocol. Beside minor inconveniences such as rhinorrhea, sneezing and watery eyes, there are no other known side effects.

With regard to the safety of all individuals, the study will immediately be abrogated and the treatment protocol we will un-blinded at once, in case of any allergic reaction or any other adverse event.

Methodology

A. Study onset

This study will include 4 parallel arms of equal sample size.
120 IR patients will be included in this four-arm study (n=30 patients per treatment arm).
Group I Caps/Plac will receive capsaicin nasal spray at similar dose (0,1mM) as in the previous studies, followed by daily application of 2 puffs of placebo spray in each nasal cavity (n=30).
Group II Plac/Caps high will receive placebo at visit 3, followed by capsaicin nasal spray at 0,01mM (2 puffs in each nostril) per day for 4 weeks (n=30).
Group III Plac/Caps low will receive placebo at visit 3, followed by capsaicin nasal spray at 0,001mM (2 puffs in each nostril) per day for 4 weeks (n=30).
Group IV Plac/Plac will receive placebo nasal spray at visit 3, followed by placebo nasal spray (2 puffs in each nostril) per day for 4 weeks (n=30).

The study protocol is illustrated in the picture below.

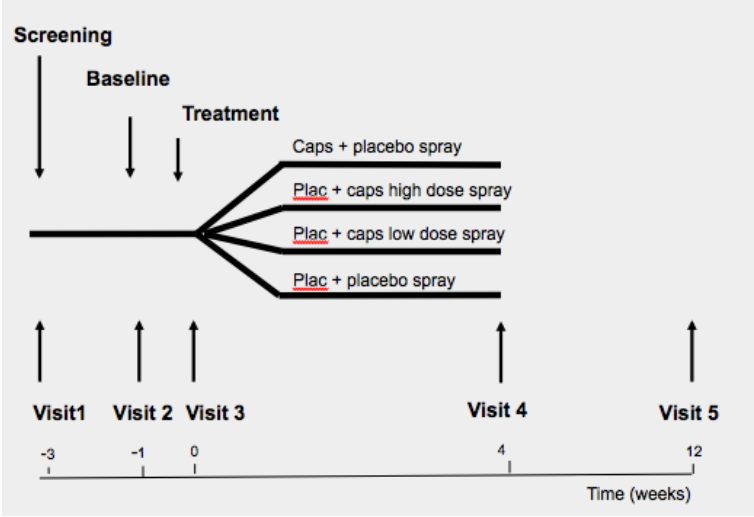

Figure 3: Visualization of the study protocol with four treatment arms

B. Product preparation

Mrs. Apr. Els Ampe of the Laboratory of Clinical Pharmacology and Pharmacotherapy at the Department of Pharmaceutical and Pharmacological Sciences of the Catholic University of Leuven will prepare all nasal solutions.

The solution of the first treatment arm (Group I Caps/Plac) containing capsaicin 0,1mM is prepared using the formula previously reported by Van Rijswijk et al. (13). In brief, the solution contained capsaicin at 0,1mM with 30,3mg pelargonic acid

vanillylamide (= synthetic capsaicin powder) dissolved in 3,3mL Ethanol 96° and diluted in a buffered 1L NaCl solution 0,9% with benzalkonium as preservative.

The solution of the second treatment arm (Group II Plac/Caps high) with capsaicin 0,01mM is a ten-time dilution of the first solution.

The solution of the third treatment arm (Group III Plac/Caps low) with Capsaicin 0,001mM is a hundred-time dilution of the original solution.

The placebo solution contained the same buffer, but no pelargonic acid vanillylamide (= synthetic capsaicin powder).

C. Sample size and setting

The current study is not designed to prove non-inferiority, but serves as a pilot study to evaluate if non-inferiority is observed for the two novel treatment regimes compared to the current treatment regime. As many as possible IR patients matching the inclusion criteria (see above) will be recruited during the recruitment period. Based on previous experience in the center, the expected total number of IR patients equals 120 taking into account a recruitment period of three years. If it is possible to include 120 patients before the time frame of three years has finished, recruitment will be stopped earlier. If by any unforeseen circumstances, after three years still not enough patients are included in the study, recruitment will be running until a total number of 120 patients will be obtained.

Note:
A drop out rate of 10% due to concomitant infection, loss of follow-up or non-related adverse events is possible during the setting.

D. Statistics

A linear model for longitudinal measures (More specifically, a direct likelihood approach is adopted using an unstructured covariance matrix (Molenberghs and Kenward, 2007, Section 14.4)[1].) will be used to compare the evolution of VAS, RQLQ and drop in PNIF between the four groups, with the baseline value as a covariate. A transformation of the outcome will be considered when needed to handle skewness in the distribution of the model residuals. Differences between the groups will be compared with the a- priori defined regions of equivalence (see section Outcomes). 95% confidence intervals for differences at specific time points will be reported. Note again that the aim of this pilot study is to describe the pattern of the differences, and not to prove non-inferiority based on these confidence intervals. For the evaluation of the TRE, a

[1] G. Molenberghs and M.G. Kenward. Missing Data in Clinical Studies. Hoboken, NJ : John Wiley & Sons, 2007.

logistic regression model using generalized estimating equations (GEE)[2] will be used to compare the evolution in proportion patients free of complaints (TRE score 5), with the baseline TRE score as covariate.

E. Patient recruitment

Patients will be enrolled by four different strategies:

- Patients with a new diagnosis of IR who visit the ENT department at the University Hospital of Leuven will be offered the possibility to take part in this study and will be screened for in- and exclusion criteria.
- An announcement at the University website will be placed, explaining the aims and a short study protocol.
- An announcement 'ad valvas' in the University Hospitals of Leuven will be placed, explaining the aims and a short study protocol.
- ENT doctors will be contacted in order to provide them the possibility to offer their IR patients without AR with at least one nasal symptoms (rhinorrhea, nasal blockage, nasal itching and/or sneezing (1)) and/or NHR symptoms induced upon encounter of certain stimuli (humidity changes, temperature changes, smoke other scents, physical activity and emotional stress (5)) with capsaicin nasal spray.
- An advertisement will be placed in local newspapers such as Metro, Randkrant, …

Prior to any study-related measure, patients will be informed both verbally and in writing about the aim and nature of the study, the anticipated benefits and risks, the discomfort to which they may be exposed, and also about their right to withdraw from participation in the study at any time after their own free will. After given informed consent, patients will be offered a screening visit with Prof. Dr. Peter Hellings, Dr. Laura Van Gerven at week -3. CTA Emily Dekimpe and Apr. Sofie Mees will plan all visits.
All eligible patients will be invited to return after three weeks for randomization and start of the study.

Patients will receive a financial compensation for transportation and participation in agreement with the current standards of the local Medical Ethical Committee of the University Hospitals of Leuven (see Informed Consent Form).

F. Randomization

Mrs. Ellen Dilissen will provide a randomization list.

- [2] G. Molenberghs and G. Verbeke (2005). Models for discrete longitudinal data, Springer-Verlag, New-York

For tracking purposes and for double-blinded randomization, all patients will be allocated a study number starting with Caps001 until Caps120.
Patients will be allocated on a one to one base to receive either capsaicin nasal spray or placebo.
For each patient, an envelope with the study code will be kept in a locker at the office of the CTA Emily Dekimpe (+32 16 3 40757) of the Outpatient clinic of the Department of Otorhinolaryngology, Kapucijnenvoer 33i, 3000 Leuven, in case of urgent need to un-blind the study in case of any adverse event.

As this study will include four parallel arms of equal sample size, the 120 included IR patients will be randomized in four equal groups of each 30 patients (n=30 patients per treatment arm). A block randomization with varying block sizes will be used.

G. Demographic and clinical information

Patient's demographic information as well as general medical history will be gathered from medical records and verified during the screening visit to the Outpatient clinic.
Demographic data of importance are: age, gender, smoking, occupation, exposure to agents during professional or recreational activity, concomitant bronchial disease (asthma, COPD), aspirin intolerance and current medication use.
The respective information is gathered in case report forms (CRFs) and will be analyzed by GraphPad Prism 6.

H. Time schedule and visit table

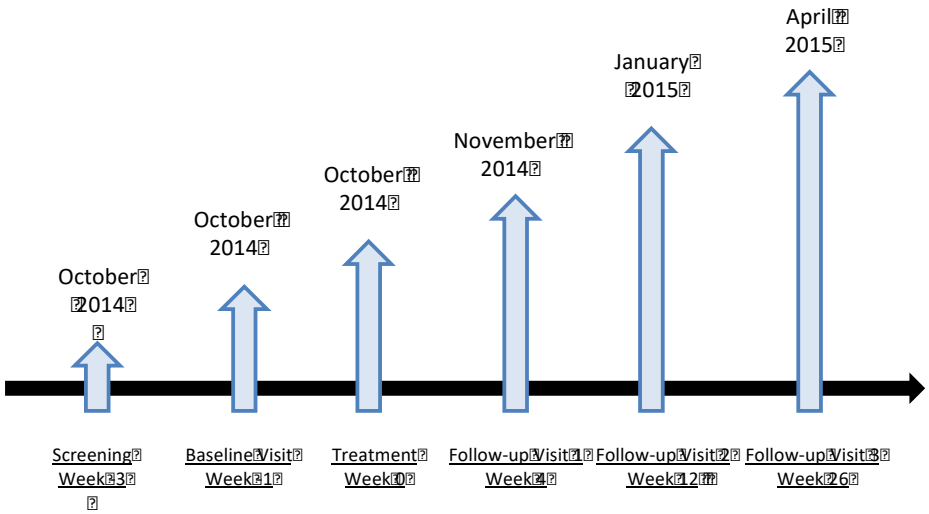

Table 2: Schematic visualization of the timeframe and visit table

As demonstrated in table 1, the included patients will visit the ENT Department of UZ Leuven at six occasions.

- Screening visit (week -3)

Explanation of study, study protocol and treatment.
Inclusion in study after signing the informed consent form.
Evaluation of inclusion and exclusion criteria.
Pregnancy test for women with childbearing potential.
Skin prick test for common aero-allergens if not yet performed.
Blood tests for total and/or specific IgE.
Nasal endoscopy for exclusion of anatomic deformities, rhinosinusitis or nasal polyps.
Symptom evaluation using VAS scores for individual and total nasal symptoms.
Quality of life evaluation using the rhinitis quality of life questionnaire (RQLQ).

- Baseline visit (week -1):

Re-evaluation of the inclusion and exclusion criteria.
Clinical nasal examination including nasal endoscopy.
NHR challenge (by CDA provocation and/or hyperosmolar discs).
Nasal fluid collection before and after NHR challenge.
Evaluation of nasal airflow by peak nasal inspiratory flow (PNIF) device before and after NHR provocation.
Symptom evaluation using VAS scores for individual and total nasal symptoms.
Quality of life evaluation using the rhinitis quality of life questionnaire (RQLQ).

- Randomization and start of treatment (week 0):

Explanation treatment i.e. five applications of capsaicin/placebo nasal spray with a one-hour interval, followed by handing over the capsaicin nasal spray or placebo for the following four weeks.
Brief nasal examination.
Evaluation of adverse events.
Two weeks after treatment, patients will be contacted by telephone in order to evaluate adverse events, check adherence and evaluate therapeutic response.

- Follow-up visit 1 (week 4):

Nasal examination including nasal endoscopy.
NHR measurements by CDA and/or hyperosmolar discs.
Nasal fluid collection by Merocell (both nostrils) for measurement of neuromediators before and after NHR measurements.
Measurement of PNIF before and after NHR measurements.
Evaluation of the therapeutic response (TRE) on a scale from 1 (= no relief of symptoms) to 5 (= total relief of symptoms).
Symptom evaluation (VAS) for INS and TNS.
Quality of life evaluation using the RQLQ.

Evaluation of adverse events and check of adherence.

- Follow-up visit 2 (week 12):

Identical to FU 1

- Follow-up visit 3 (week 26):

Nasal examination including nasal endoscopy.
Evaluation of the therapeutic response (TRE) on a scale from 1 (= no relief of symptoms) to 5 (= total relief of symptoms).
Symptom evaluation (VAS) for INS and TNS.
Quality of life evaluation using the RQLQ.
Evaluation of adverse events and check of adherence.

	Screening week -3	Baseline week -1	Treatment week 0	FU visit 1 week 4	FU visit 2 week 12	FU visit 3 week 26
Explanation study and protocol	x					
Informed consent	x					
Evaluation in-and exclusion criteria	x	x				
Pregnancy test (If necessary)	x					
SPT (If necessary)	x					
Blood analysis	x					
ENT exam with nasal endoscopy	x	x	x	x	x	x
Nasal fluid collection		x/x*		x/x*	x/x*	
Explanation R/	x		x			
Start R/, handing over study medication and diary			x			
NHR measurements		x		x	x	
TRE				x	x	x
Symptom evaluation VAS	x	x		x	x	x
Symptom evaluation RQLQ	x	x		x	x	x
AEE and check adherence			x	x	x	x

ENT: ear, nose, throat
TRE: therapeutic Response Evaluation
AEE: Adverse Events Evaluation
*: x/x = before and after NHR measurements

Table 3: Overview of registrations and sample collections that were performed at each visit

I. Variables

- Clinical ENT exam:

Nasal endoscopy will be performed by an experienced MD.

- Skin Prick Test (SPT):

SPT for the 18 most prevalent inhalant allergens (e.g. house dust mite, grass, mugwort, alder, birch, hazel, pet animals, Alternaria, Aspergillus) provided by HAL Allergy, will be performed by investigators Apr. Sofie Mees or CTA Emily Dekimpe.

- Blood analysis:

Blood samples will be taken by an MD. Total IgE will be measured in the serum and if according to anamnestic details and/or lack of uniformity of the SPT specific IgE of necessary allergens will be determined.

- NHR challenge by Cold Dry Air (CDA) provocation (19):

Patients will be asked to acclimatize to room temperature for 20 minutes prior to exposure to CDA.
All provocations will be performed by Apr. Sofie Mees or CTA Emily Dekimpe.
Through a transparent anesthesia mask, placed over nose and mouth of the patient, compressed dry air for medical use will be delivered for 15 minutes (25L/minute). Patients will be instructed to breathe through the nose only. The temperature of the air reaching the nose will be approximately -10°C and the relative humidity less than 10-15%.

- Peak Nasal Inspiratory Flow (PNIF) measurement:

Nasal congestion will be evaluated by three consecutive measurements performed by Apr. Sofie Mees or CTA Emily Dekimpe using a PNIF device before and immediately after CDA provocation.
Hereby, an anesthesia mask will be placed over nose and mouth of the patient. After expiration by mouth, patients will be instructed to carefully close their mouth and forcefully inspire air through the nose.

- Collection of nasal secretions:

Nasal fluid will be collected by Apr. Sofie Mees by placing a small nasal sponge (Merocell 4 cm) between the middle and inferior turbinate for five minutes. This technique is a-traumatic and painless for the patient, and allows a rapid collection of nasal secretions without the need for local anesthesia. The fluid obtained before will be stored at -20°C until analysis.

- Processing of nasal secretions:

The following mediators will be evaluated: total and/or specific IgE, Substance P (SP), VIP, Neurokinin A, CGRP, IL 4, IL 5, …
Analysis will be made using ELISA and/or ImmunoCAP and/or CBA.
Additionally, the functionality of the TRPV1 will be investigated by calcium-imaging experiments.

Of note:
Because research concerning immunological features is rapidly evolving, it is possible that other neuromediators/proteins are analyzed or other scientific techniques are tried and tested on available samples of nasal fluid and/or biopsy.
In order to provide future patients better treatment options, excess of nasal secretions/biopsies will never be discarded.

- Product application:

On the day of the treatment, all IR patients will be treated by Prof. Dr. Peter Hellings, Dr. Laura Van Gerven, Apr. Sofie Mees or CTA Emily Dekimpe with a blinded nasal spray (capsaicin or placebo) five times with one-hour intervals as described by the treatment protocol of Van Rijswijk et al. (13). The nasal mucosa of all patients will be anaesthetized prior to the first three applications by 2 puffs of cocaine 5% nasal spray in each nostril. To ensure effective local anesthesia, an interval of 10 to 15 minutes was maintained.
To protect the eyes of the patients against potential irritating particles of capsaicin, all individuals will be suggested to close their eyes during the application of capsaicin nasal spray.
After finalizing the treatment protocol, the patient will be handed over a nasal spray containing capsaicin 0,01mM, capsaicin 0,001mM or placebo to take home and to use for the consecutive four weeks, labeled with his/her allocated study number (Caps001-Caps120) and the usage (2 puffs in each nasal cavity once daily).

- Evaluation of nasal symptoms by VAS scores:

All patients will be asked to mark the typical nasal symptoms on a visual analogue scale for individual (INS) and total nasal symptoms (TNS) before treatment and at week 4, 12 and 26. A visual analogue scale is a measurement of a patient's subjective evaluation of symptom severity by indicating a position on a line between two endpoints, which represent a well-validated and easy technique of the evaluation of symptom severity. Indeed, VAS scores for TNS have recently been validated and proposed as a means of evaluation of symptom control in rhinitis (20).

- Evaluation of quality of life by Rhinitis Quality of Life Questionnaire:

Functional problems that are most troublesome to adults with rhinitis will be measured by the RQLQ by 28 questions in 7 domains (activity limitation, sleep problems, nose symptoms, eye symptoms, non-nose/eye symptoms, practical problems and emotional function). There are three 'patient-specific' questions in the activity domain, which allow patients to select three activities in which they are most limited by their rhinitis. Patients recall how bothered they have been by their rhinitis during the previous week and to respond to each question on a 7-point scale (0 = not impaired at all and 6 = severely impaired). The overall RQLQ score is the mean of all 28 responses and the individual domain scores are the means of the items in those domains. The RQLQ has excellent measurement properties and has been used extensively throughout the world both in clinical practice and clinical trials. The validation studies have shown that these properties are very similar to

those found for the Asthma Quality of Life Questionnaire (21). Patients will be asked to score RQLQ before treatment and at week 4, 12 and 26.

- Adherence evaluation:

Patients will be asked to bring their nasal spray with them on follow up visit 2 at week 4. Weighing the residual fluid on day 28 will objectively check adherence.
All patients will be asked to write down their symptoms, adverse events and degree of sensitization/desensitization in a dairy (see addendum). The diary will be handed over to them at the day of the treatment.

- Therapeutic Response Evaluation (TRE):

TRE will be measured on a 1 to 5 scale.
5 klachten zijn volledig verdwenen = klachtenvrij
4 klachten zijn bijna volledig verdwenen
3 klachten zijn verminderd, doch nog aanwezig
2 klachten zijn licht verminderd, doch nog sterk aanwezig
1 klachten zijn onveranderd ten opzichte van vóór de behandeling
Patients will be asked to score their symptom relief on week 4, week 12 and week 26.

- Evaluation of recurrence of symptoms:

The recurrence of symptoms will be measured on a 1 to 5 scale.
5 klachten zijn volledig terug aanwezig
4 klachten zijn voor een aanzienlijk deel terug aanwezig
3 klachten zijn nog steeds duidelijk verminderd
2 klachten zijn licht verminderd, doch beginnen terug te keren
1 klachten zijn nog steeds volledig verdwenen
Patients will be asked to score their recurrence of symptoms at week 26.

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