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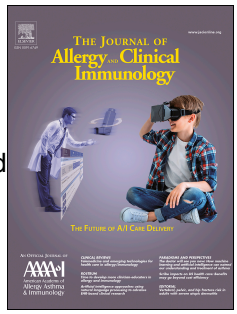

Low-dose capsaicin (0.01 mM) nasal spray is equally effective as the current standard treatment for idiopathic rhinitis: a randomized, double-blind, placebo-controlled trial

Laura Van Gerven, MD, PhD, Brecht Steelant, PhD, Leen Cools, MSc, Ina Callebaut, PhD, Wout Backaert, MD, Jan de Hoon, MD, PhD, Els Ampe, PhD, Karel Talavera, PhD, Peter W. Hellings, MD, PhD

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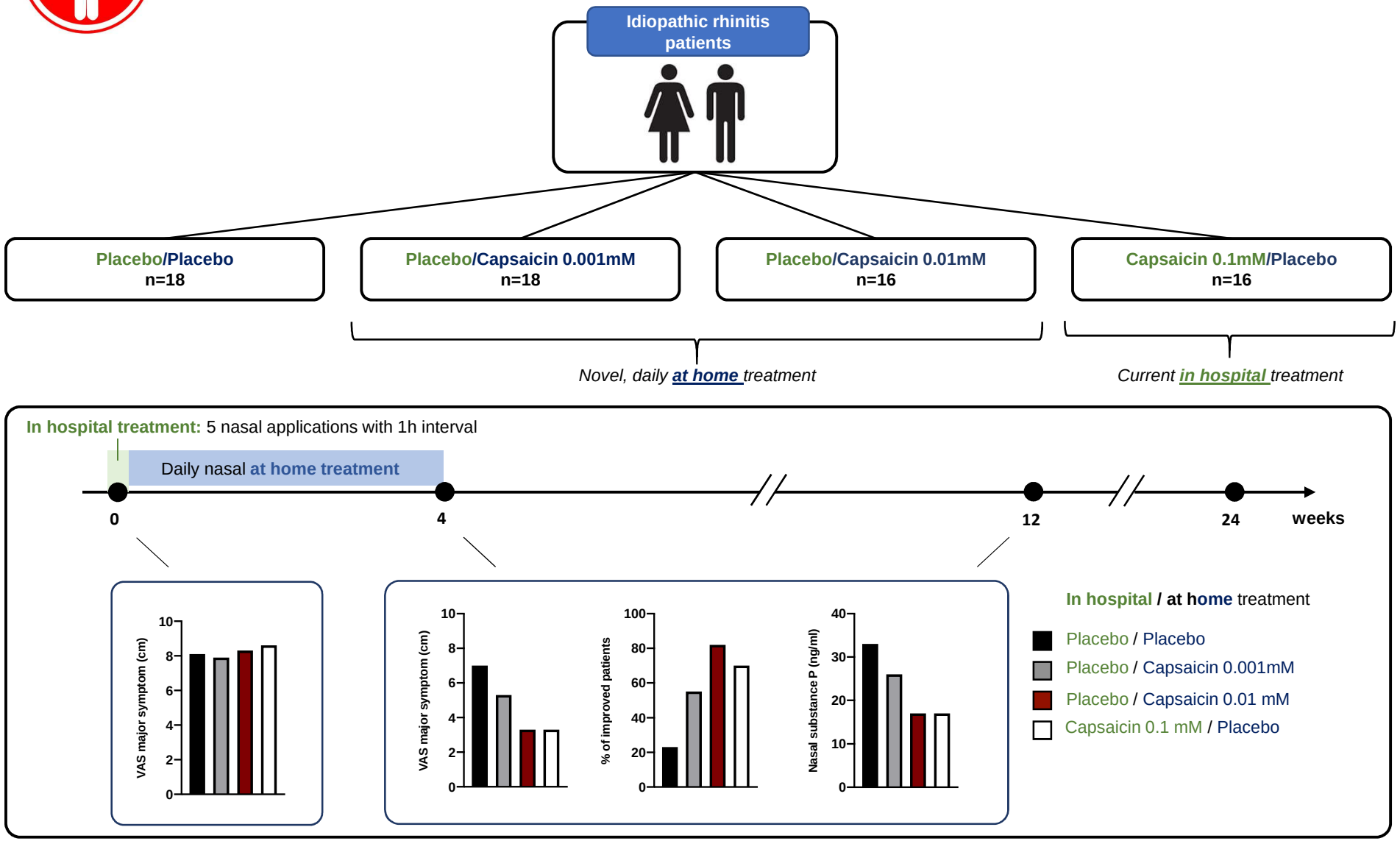

Low-dose capsaicin (0.01 mM) nasal spray is equally effective as the current standard treatment for idiopathic rhinitis: a randomized, double-blind, placebo-controlled trial

Authors

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Capsule summary: High dose intranasal capsaicin (0.1 mM) is the only specific treatment for idiopathic rhinitis but patient- and physician-unfriendly. We show that nasal administration of a 0.01 mM low dose capsaicin improves nasal symptoms and might replace the current therapeutic approach.

Key words: Capsaicin, idiopathic rhinitis, non-allergic rhinitis, substance P

Abbreviations: SP: substance P; TRE: therapeutic response evaluation; VAS: visual analogue scale

Conflict of interest: The authors declare no conflicts of interest.

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To the Editor:

A significant proportion (25-30%) of patients suffering from persistent rhinitis have nasal symptoms without clinical evidence of endonasal infection or systemic signs of sensitization to aeroallergens, a condition often referred to as non-allergic rhinitis(1). Up to 50% of non-allergic rhinitis patients are classified as idiopathic rhinitis (IR) after exclusion of occupational, elderly, gustatory, hormonal and drug-induced rhinitis(1). IR remains a therapeutic challenge due to the inefficacy of intranasal corticosteroids(2). Intranasal administration of capsaicin at high dose (0.1 mM) is currently the best therapeutic option for IR(3). However, this treatment has limitations since it is uncomfortable for patients due to the need of prior local anesthesia, it is time-consuming (5 consecutive applications with 1h intervals) and because it is incompletely understood in terms of working mechanism(4). Thus, research for better capsaicin treatment formulations and protocols is warranted.

To this aim, we conducted a randomized, double-blind, placebo-controlled trial, in which we compared the effect of two lower dose capsaicin nasal sprays (0.01 mM and 0.001 mM) that could be self-administered, with the current capsaicin treatment (0.1 mM) in suppressing nasal symptoms. Additionally, because of the implication of substance P (SP) in IR(5)(6)(7), we evaluated how its nasal levels are affected by capsaicin treatment to better understand the underlying working mechanism. The study was approved by the Medical Ethical Committee of the University Hospitals of Leuven and was registered at ClinicalTrials.gov (NCT02288156). Sixty-eight well-characterized IR patients **(Table E1)** were randomized in 4 treatment arms: i.e. Placebo/Placebo; Placebo/Capsaicin 0.001 mM; Placebo/Capsaicin 0.01 mM and Capsaicin 0.1 mM/Placebo. Patients received 5 intranasal applications (2 puffs/nostril, 0.4 ml/puff) of either placebo or capsaicin 0.1 mM on a single day with 1h intervals. After the treatment visit, patients who had received the current capsaicin treatment (capsaicin 0.1 mM) were send home with a nasal spray containing placebo for daily use (Cap 0.1/Placebo). Patients who were treated with

placebo at the treatment visit either received a nasal spray containing placebo (Placebo/Placebo), capsaicin 0.001 mM (Placebo/Cap 0.001) or capsaicin 0.01 mM (Placebo/Cap 0.01) **(Figure 1** and **Supplementary Figure E1).** All patients were asked to stop their treatment after 4 weeks, and to score their major and individual nasal symptoms on a visual analogue scale (VAS) at screening, follow-up (FU) 1, FU2 and FU3. The therapeutic response evaluation (TRE) was assessed at FU1, FU2 and FU3. SP levels were determined in nasal secretions, collected at screening, FU1 and FU2. More details on patient selection and methodology is provided in the online repository.

At FU1 and FU2, VAS major symptom was significantly reduced in the Cap 0.1/Placebo and the Placebo/Cap 0.01 group compared to the Placebo/Placebo group **(Figure 2A).** Similarly, VAS nasal obstruction was significantly decreased for both groups at FU2 **(Figure 2B)**. Nasal symptoms were not altered in Placebo/Cap 0.001 versus the Placebo/Placebo group. At FU1, TRE showed an 82% improvement in the Placebo/Cap 0.01 group, which was higher than the TRE of Cap 0.1/Placebo group (71%) **(Figure 2C)**. At FU2, a TRE of 73% was still observed for the Placebo/Cap 0.01 group versus Placebo/Placebo **(Figure 2D)**. At FU3, no significant improvement could be observed in any of the arms (data not shown).

Previously, we reported increased SP concentrations in nasal secretions of IR patients compared to healthy controls(7). Here, we found that nasal SP levels of patients in the Placebo/Cap 0.01 and Cap 0.1/Placebo group were significantly decreased compared to patients in the Placebo/Placebo at FU2 (**Figure 2E**). No significant difference in nasal SP levels between the Placebo/Cap 0.001 and Placebo/Placebo group was observed. Interestingly, SP positively correlated with VAS major symptom ($r = 0.34$; $P < 0.05$) (**Figure 2F**) and VAS nasal obstruction (**Supplementary Figure E2**). No correlation between SP and other VAS scores were found at FU1 and FU2 in any of the arms (data not shown). Given that only 70-80% of IR patients will benefit from capsaicin treatment, we studied whether SP could serve as a biomarker to predict

97 therapeutic response. Patients reporting therapeutic improvement at FU1 had a clear reduction in
98 nasal SP levels, which was not observed in patients without therapeutic improvement (**Figure 2G**).
99 A decline in nasal SP of more than 7.08 ng/ml had a sensitivity of 72% and specificity of 75% to
100 predict therapeutic continuation (**Figure 2H**).

101 Until now, capsaicin is not routinely used in clinical practice, although symptom reduction
102 is observed in 70-80% of IR patients(3,4,6–8). Therefore, the present study was designed to
103 compare novel low dose capsaicin treatment with the current therapy in improving nasal
104 symptoms and to evaluate the role of SP in the pathology of IR. Daily nasal administration of low
105 dose capsaicin was well-tolerated and similarly reduced nasal symptoms as the current capsaicin
106 treatment at FU1 and FU2, which adds novel information to a recent Cochrane review on the use
107 of capsaicin in the management of non-allergic rhinitis(3). Furthermore, capsaicin 0.01mM
108 improved therapeutic response at FU1 and FU2. Interestingly, 23% of patients on placebo
109 treatment reported therapeutic improvement, which might be due to daily nasal rinsing.
110 Secondly, we further explored the role of SP in the pathophysiology of IR. Self-administration of
111 capsaicin 0.01 mM reduced SP levels at FU2. Additionally, we found a positive correlation
112 between SP and nasal obstruction, suggesting that IR symptoms result from abnormally increased
113 SP levels. As SP increases mucus secretion, suppressing SP might represent a novel therapeutic
114 approach, at least in IR(5). Lastly, we investigated whether SP might serve as a biomarker to
115 predict the therapeutic response to capsaicin. A decrease in SP of 7.08 ng/ml at FU1 had a
116 sensitivity of 72% and a specificity of 75% to predict response to therapy. The strength of this
117 study lies within the meticulous patient selection and characterization, the well-conducted study
118 design with 4 groups including a placebo and a current standard treatment group. In the past, the
119 recruitment of ill-defined non-allergic rhinitis patients resulted in confusing and contradictory
120 data, such as the effect of corticosteroids in non-allergic rhinitis(2,9). The major limitation of our
121 clinical trial, however, is the relatively low number of patients, which resulted from the strict
122 inclusion and exclusion criteria. Furthermore, no objective parameter to evaluate therapeutic

response was utilized and no specific question on adverse effects was being considered, which is warranted for follow-up studies.

In conclusion, capsaicin 0.01 mM is equally effective in suppressing nasal symptoms compared to the current capsaicin treatment, and therefore might be a good, novel therapeutic option for IR patients.

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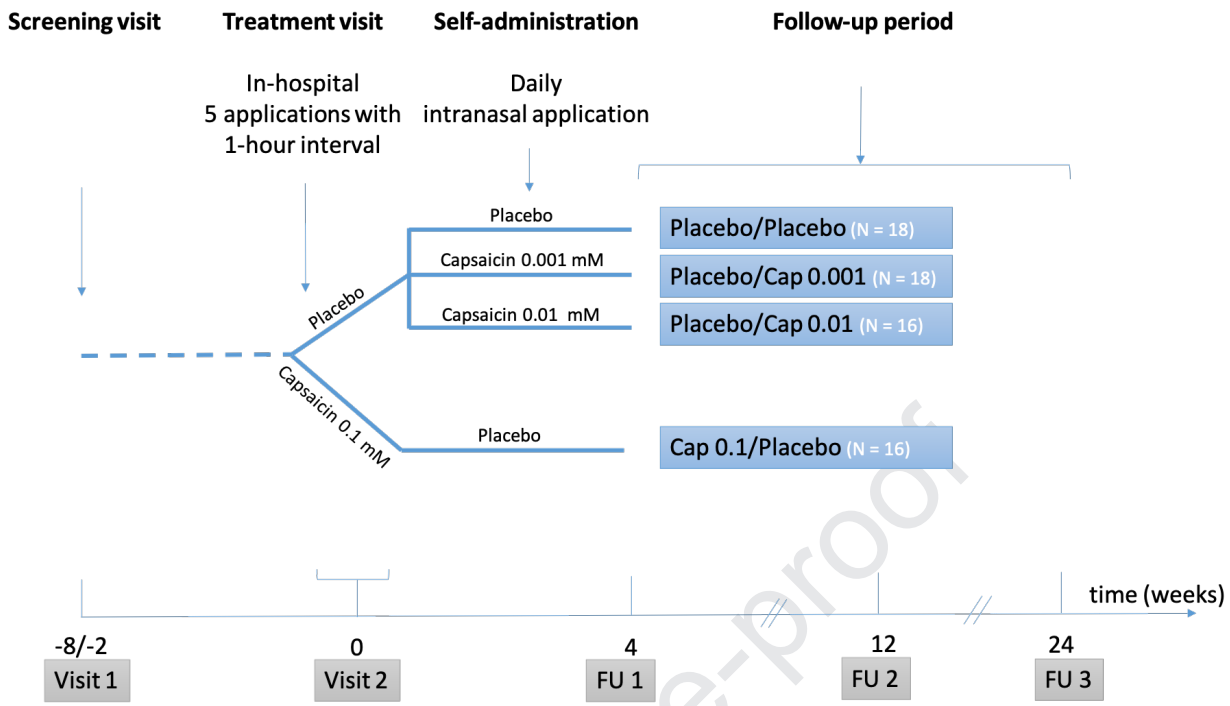
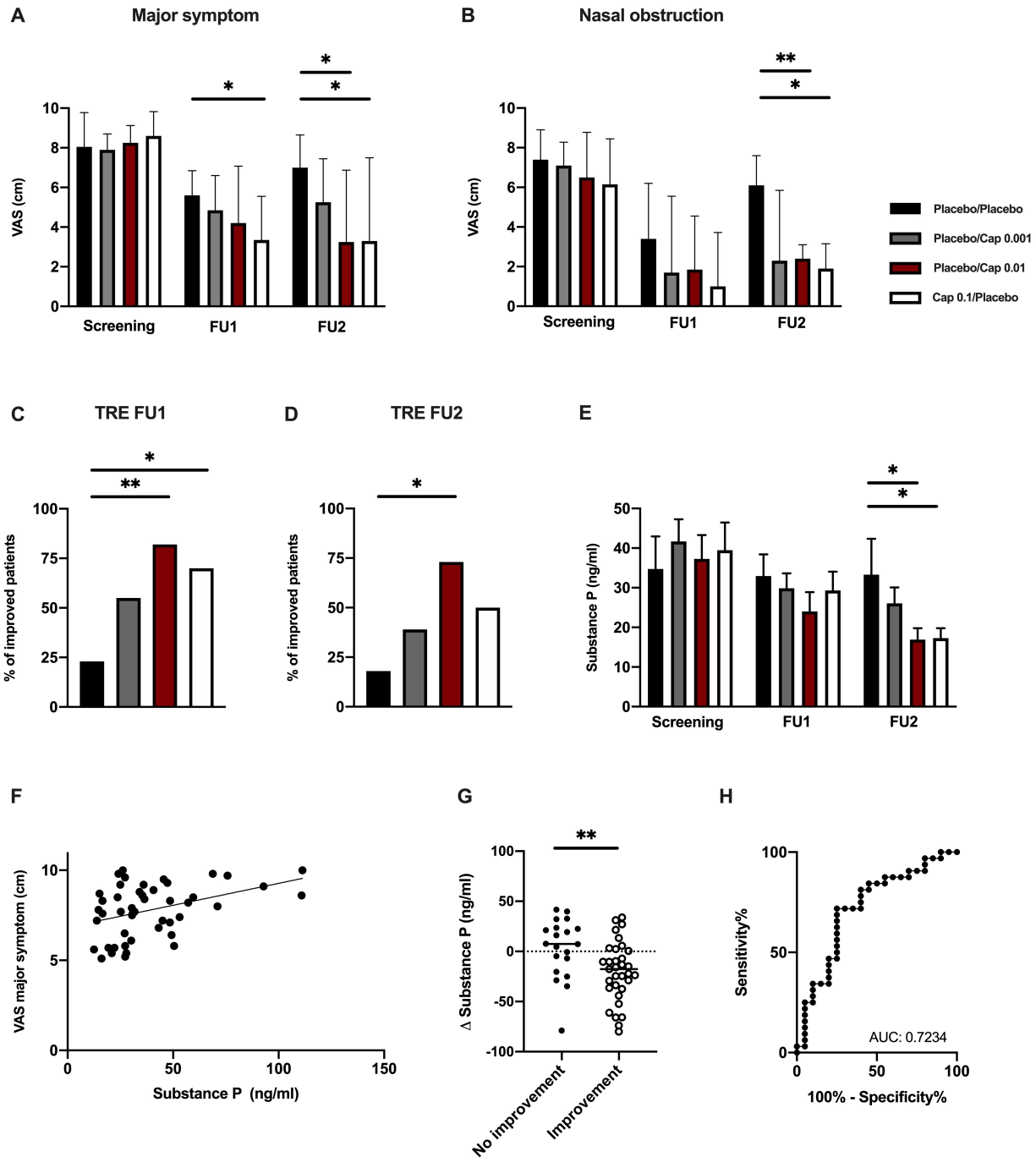
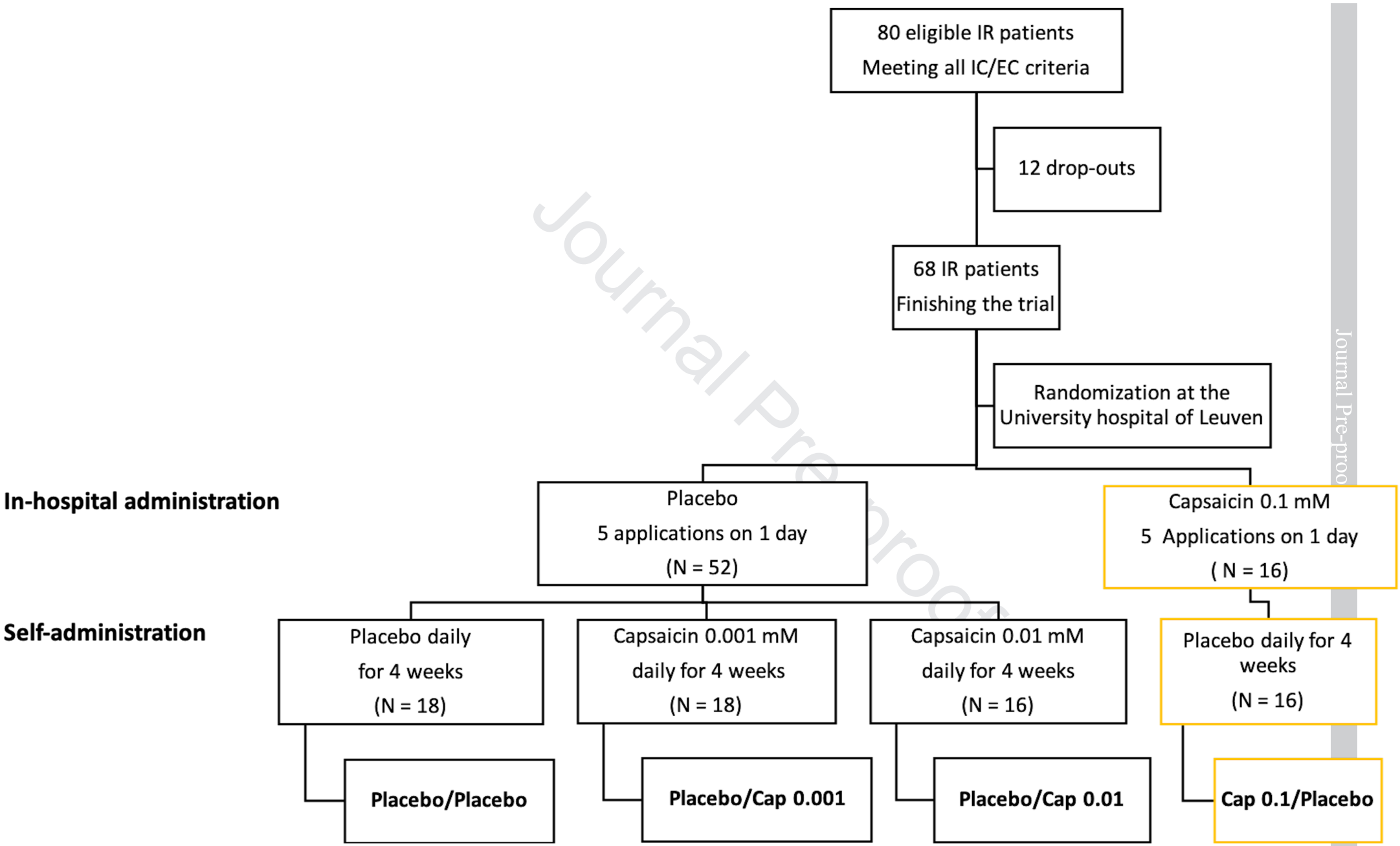
Figure Legends and tables

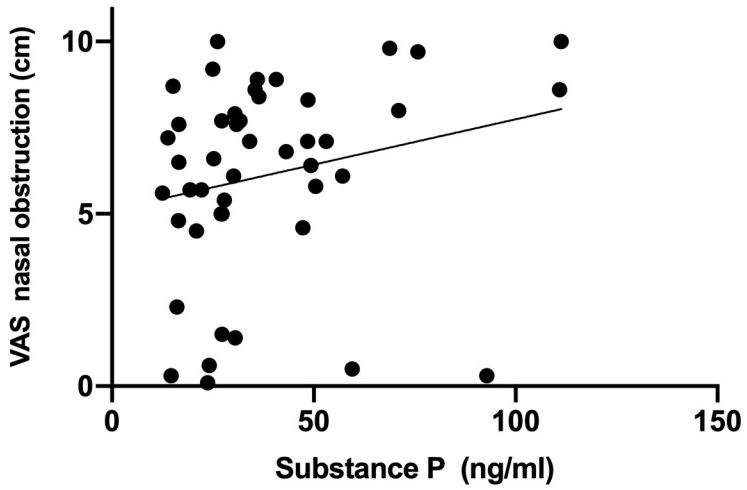
Figure 1: Schematic overview of the study design.

Figure 2: Effect of capsaicin treatment on nasal symptoms, therapeutic response and substance P. **A-B.** Effect of capsaicin treatment on VAS major symptom and nasal obstruction at screening, follow-up (FU) 1 and FU2. **C-D.** Therapeutic response evaluation (TRE) at FU1 and at FU2**. E.** Substance P levels in nasal secretions at screening, FU1 and FU2. **F.** Correlation between VAS major symptom and substance P levels in nasal secretions at screening in all patients. **G.** Difference in substance P between FU1 and screening. **H.** Receiver operating characteristic curve for delta substance P. * $P < 0.05$, ** $P < 0.01$.




A
Major symptom
VAS (cm)
Screening
FU1
FU2
B
Nasal obstruction
VAS (cm)
Screening
FU1
FU2
Placebo/Placebo
Placebo/Cap 0.001
Placebo/Cap 0.01
Cap 0.1/Placebo
C
TRE FU1
% of improved patients
D
TRE FU2
% of improved patients
E
Substance P (ng/ml)
Screening
FU1
FU2
F
VAS major symptom (cm)
Substance P (ng/ml)
G
Δ Substance P (ng/ml)
No improvement
Improvement
H
Sensitivity%
AUC: 0.7234
100% - Specificity%




VAS nasal obstruction (cm)
10
5
0
0
50
100
150
Substance P (ng/ml)

Online Repository

Table E1: Patient characteristics at screening.

	Placebo/ Placebo	**Placebo/ Capsaicin (0.001 mM)**	**Placebo/ Capsaicin (0.01 mM)**	**Capsaicin (0.1mM)/ Placebo**
N	18	18	16	16
Age (mean ± SD)	45 ± 15	48 ± 14	45 ± 10	50 ± 14
Gender (male/female)	8/10	9/9	9/7	7/9
Nasal symptoms	56% Nasal obstruction	50% Nasal obstruction	44% Nasal obstruction	31% Nasal obstruction
	39% Rhinorrea	28% Rhinorrea	44% Rhinorrea	44% Rhinorrea
	5% Sneezing	11% Sneezing	0% Sneezing	25% Sneezing
	0% Itch	11% Itch	12% Itch	0% Itch
Allergy (SPTs)	0%	0%	0%	0%
Responders to INCS	0%	0%	0%	0%
Smokers	0%	0%	0%	0%

7

Online Repository

Low-dose capsaicin (0.01 mM) nasal spray is equally effective as the current standard treatment for idiopathic rhinitis: a randomized, double-blind, placebo-controlled trial

Methods

Patient selection

Eighty IR patients were recruited via the outpatient clinic of the Otorhinolaryngology Department of the University Hospitals of Leuven, Belgium between May 2015 and July 2017.

IR patients were defined as non-smoking patients suffering from at least 2 of the following complaints: nasal obstruction, rhinorrhea, sneezing and itch, for more than 1 hour a day and for more than 1 year. These patients had negative skin prick test (SPT) results, no clinical signs of infection (i.e. no discolored secretions) and no anatomical nasal abnormalities responsible for nasal symptoms. The inclusion criteria were the following: IR patients between 18 and 65 years old who signed the informed consent, with reported inefficacy of intranasal corticosteroid treatment at recommended dose (mometasone furoate 50 µg/spray: 2x2 daily or fluticasone furoate 50 µg/spray: 2x2 daily) for at least 4 weeks. In our experience, patients with local allergic rhinitis (LAR) do benefit from intranasal corticosteroids, since the underlying pathophysiology is mainly IgE-mediated and thus responsive to the classic anti-inflammatory treatment[13]. By including non-allergic rhinitis patient that are "non-responsive to intranasal corticosteroids", patients with local allergic rhinitis were effectively excluded.

Exclusion criteria were: a positive SPT for the 18 most frequent inhaled allergens in Belgium (house dust mite, pollen of timothy grass, smooth meadow grass, orchard grass, nettle, plantago, oxeye daisy, mugwort, alder, birch, hazel, horse, cat, dog, rabbit, spores of *Alternaria*, *Aspergillus* and *Cladosporium*; HAL Allergy, Leiden, The Netherlands), pregnancy or lactation, systemic disorders or malignancies, use of medication affecting nasal function, use of local and/or systemic corticosteroids 4 weeks prior to the study, history of prolonged use or abuse of decongestant nasal spray such as xylomethazoline. Patients with colored secretions and/or inflammation at the level of the osteomeatal complex were excluded after nasal endoscopy.

During the entire study duration nasal medication was prohibited.

Study design

The study was approved by the Medical Ethical Committee on Clinical Investigations of the University Hospitals of Leuven and was registered at ClinicalTrials.gov (NCT02288156). The IR patients were invited for an outpatient visit to the Department of Otorhinolaryngology of the University Hospitals of Leuven on 5 occasions **(Figure 1** and **Supplementary figure E1)**.

This study was performed in a randomized, double-blind, placebo-controlled way. Patients were seen at a screening visit to check inclusion and exclusion criteria.

During the treatment visit, patients were randomized in 4 arms in a 1/4 ratio: i.e. Arm 1 = Placebo/Placebo; arm 2 = Placebo/Capsaicin 0.001 mM; arm 3 = Placebo/Capsaicin 0.01 mM and arm 4 = Capsaicin 0.1 mM/Placebo. In brief, patients received 5 intranasal applications (2 puffs in each nostril, 0.4 ml/puff, per application) of either placebo or capsaicin 0.1 mM on a single day with 1-hour intervals. The nasal mucosa was anaesthetized prior to the first 2 applications by applying cocaine 5% nasal spray (same volume/spray as mentioned above). To ensure effective local anesthesia, an interval of 15 min was maintained between the cocaine and blinded nasal spray application.

After the treatment visit, patients who had received the current standard treatment with capsaicin 0.1 mM were send home with a nasal spray for daily use that contained placebo (Cap 0.1/Placebo). The other patients who were treated with placebo during the treatment visit, received a nasal spray containing placebo (Placebo/Placebo), capsaicin 0.001 mM (Placebo/Cap 0.001) or capsaicin 0.01 mM (Placebo/Cap 0.01) **(Figure 1).** All patients were asked to stop their treatment after 4 weeks. All patients were invited for a follow-up visit after 4, 12 and 24 weeks.

Capsaicin and placebo solutions were prepared at the Center for Clinical Pharmacology at the University Hospitals of Leuven and the solutions were blinded. The placebo solution contained the same buffer but lacked pelargonic acid vanillylamide.

The sample size was calculated to have at least 80% power to detect a significant difference in change in VAS for major symptoms between baseline and week 12 (FU2). Previously, we showed a clear reduction in VAS major symptoms after capsaicin treatment compared to placebo at week 12[6, 7]. Assuming a 50% reduction in VAS major symptom at week 12, setting α at 0.0125 (application of Bonferroni correction for the 4 groups) and with an unequal group size (3/4 capsaicin, 1/4 placebo) and using a two-sample t-test, 16 patients were needed to detect a ratio of geometric means equal to 2 (i.e. VAS for major symptom being 2-fold higher in placebo group). Taking into account a drop-out rate of 20%, 76 patients in total were needed (19 patients per group).

Evaluation of nasal symptoms

All participants were asked to mark the typical nasal symptoms of IR, i.e. rhinorrhea, nasal obstruction, itch and sneezing on a visual analogue scale (VAS 0-10) at the screening visit (visit 1) and

at follow-up visit 1 (FU1) (at week 4), FU2 (at week 12) and FU3 (at week 24). Only if the VAS score was more than 2, the symptom was considered relevant. The major nasal symptom was selected based on the highest VAS score at screening. At FU1, FU2 and FU3, a therapeutic response evaluation (TRE) was performed. IR patients were asked to score the overall improvement of their symptoms compared to baseline, i.e., 0 = no reduction of symptoms, 1 = reduction of symptoms.

Collection of nasal fluid and Substance P measurement

At screening visit, FU1 and FU2, nasal secretions were collected before the CDA provocation as described earlier[6]. For the collection of nasal secretions, a nasal sponge (Ivalon Surgical products, San Diego, CA, USA) was weighed and inserted in each nostril for 5 minutes. Afterwards, the sponge was removed and weighed again. A volume of saline was added depending on the weight of the collected sponge (1/5 dilution). The sponge was then squeezed and centrifuged at 1500 g at 4°C for 5 minutes. Supernatant was stored at -20°C for further analysis. In nasal secretions, substance P was determined with ELISA according to the manufacturer's guidelines (Cayman chemicals, Ann Arbor, Michigan, USA).

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Tables and figure Legends

Table E1: Patient characteristics at screening.

Figure E1: Flow chart of eligible patients with idiopathic rhinitis and randomization in the different treatment arms. IR= idiopathic rhinitis, IC= inclusion criteria, EC= exclusion criteria, TRE= therapeutic response evaluation.

Figure E2: Correlation between substance P and nasal obstruction at follow-up 1. Spearman correlation r = 0.32; P<0.05.