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Efficacy and safety of So-Cheong-Ryong-Tang in treatment of perennial allergic rhinitis: study protocol for a double-blind, randomised, parallel-group, multicentre trial

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ABSTRACT

Introduction So-Cheong-Ryong-Tang (SCRT) is a herbal medicine widely used in traditional medicine for treating allergic rhinitis (AR). In animal studies, SCRT has suppressed the progression of AR. The main purpose of this study is to assess the efficacy and safety of the SCRT for the treatment of perennial allergic rhinitis (PAR) and discover the underlying mechanisms resulting in anti-inflammatory effects in humans.

Methods and analysis We will conduct a double-blind, randomised, placebo-controlled, parallel-group, multicentre trial of Korean adults with PAR. For the study, 156 subjects with PAR will be recruited. The trial will consist of a 4-week oral administration of SCRT or placebo with two visits at 2-week intervals and an 8-week follow-up period with two visits at 4-week intervals. The primary outcome is a change in the total nasal symptoms score. The secondary outcomes include changes in the Rhinoconjunctivitis Quality of Life Questionnaire score, total serum IgE and cytokines levels.

Ethics and dissemination This study was approved by the Institutional Review Board at each research centre (name of each centres and approval numbers): Kyung Hee University Hospital at Gangdong (KHNMC-OH-IRB 2015-04-009), Kyung Hee University Medical Centre (KOMCIRB-160321-HRBR-011), Pusan National University Hospital (2016–004), Dongguk University Medical Centre (2016–03) and Semyung University hospital (2016–01). This result will be published in a peer-reviewed journal.

Trial registration number NCT03009136; Pre-results.

Strengths and limitations of this study

- This is the first double-blind, randomised, multicentre study that will be conducted to investigate the efficacy of So-Cheong-Ryong-Tang in treating perennial allergic rhinitis.
- Nasal endoscopy index for pattern identification will be used to examine efficacy of the drug based on pattern identification.
- Cytokine examination will be performed to discover the mechanisms underlying antiallergic activity in humans.
- The pattern identification questionnaire currently available is not validated. We plan to conduct a validation and reliability study and revise the questionnaire based on the results.

INTRODUCTION

Allergic rhinitis (AR) is an inflammatory disease of the nasal membranes resulted from an IgE-mediated allergic reaction.[1] The prevalence of AR is 10%–40% in worldwide and 16.2%±1.0% in South Korea.[2 3] AR can be classified as seasonal AR (SAR) (occurring during specific seasons) or perennial AR (PAR) (occurring year round). The major symptoms of AR are nasal congestion, rhinorrhoea, nasal itching and sneezing. AR is not a life-threatening disease, however, it has a significant impact on quality of life and causes social and economic burden.[4] Furthermore, untreated AR is a risk factor of asthma, rhinosinusitis, nasal polyps, otitis media and allergic conjunctivitis.[5]

In Korea, several herbal medicines have been used to treat AR. So-Cheong-Ryong-Tang (SCRT), also known as Sho-seiryo-to or Xiao-Qing-Long-Tang, is a mixed herbal formula that has been used for hundreds of years in Asian countries. Pattern identification (PI) is a tool that results in a diagnostic conclusion based on a cluster of concurrent symptoms and signs.[6] SCRT has been used to treat patients with lung–cold pattern and with AR, bronchitis, allergic asthma and common cold. When diagnosing AR, many traditional medicine clinicians use nasal endoscopy not only for observing disease severity but also for PI. For this reason, a nasal endoscopy index for PI of AR was developed, and inter-rater and intrarater reliability studies were conducted in the same year.[7 8]

In an exploratory study, specialists in the Department of Otorhinolaryngology of Traditional Korean Medicine (TKM) selected SCRT as the most preferred medicine in treating AR.[9] In animal studies, SCRT has suppressed the progression of AR and allergic asthma.[10–12] A single randomised controlled clinical study was performed in Japan.[13] However, the treatment period for the study was only 2 weeks and there was no follow-up period after the treatment. Furthermore, outcome measurement for evaluation the mechanisms underlying antiallergic and anti-inflammatory effects was not conducted and statistical analysis method used for primary outcome measurement was inappropriate.

The aims of this study were as follows: first, to investigate the short and long-term efficacy and safety of SCRT treatment in PAR patients; second, to investigate the efficacy of SCRT based on PI; third, to discover the underlying mechanisms resulting in anti-inflammatory effects of SCRT in patients with PAR and fourth, to develop a validated PI questionnaire for AR. We hypothesised as follows: (1) 4 weeks of SCRT administration would improve nasal symptoms in patients with PAR and these effects would last for 8 weeks following the end of the treatment period; (2) SCRT will be more effective in patients who show cold pattern in the nasal endoscopy index for PI or who are diagnosed with lung–cold pattern by clinicians; (3) total serum IgE, eosinophil count and cytokines levels would be altered following SCRT administration. We will conduct a double-blind, randomised, placebo-controlled, parallel-group, multicentre trial of Korean adults with PAR.

METHODS

Study design

This double-blind, randomised, placebo-controlled, parallel-group, five-centre trial will be conducted at the Department of Otorhinolaryngology of TKM in Kyung Hee University Hospital at Gangdong (Seoul, Korea), Kyung Hee University Medical Centre (Seoul, Korea), Pusan National University Hospital (Pusan, Korea), Dongguk University Medical Centre (Ilsan, Korea) and Semyung University hospital (Jecheon, Korea).

The trial will consist of a 4-week oral administration of SCRT with two visits at 2-week intervals and an 8 week follow-up period with two visits at 4-week intervals. Before enrolment, all subjects will undergo a 7-day run-in period. The enrolled subjects will be randomly allocated to two parallel groups: the SCRT group and the placebo group. The study design flow chart is shown in figure 1.

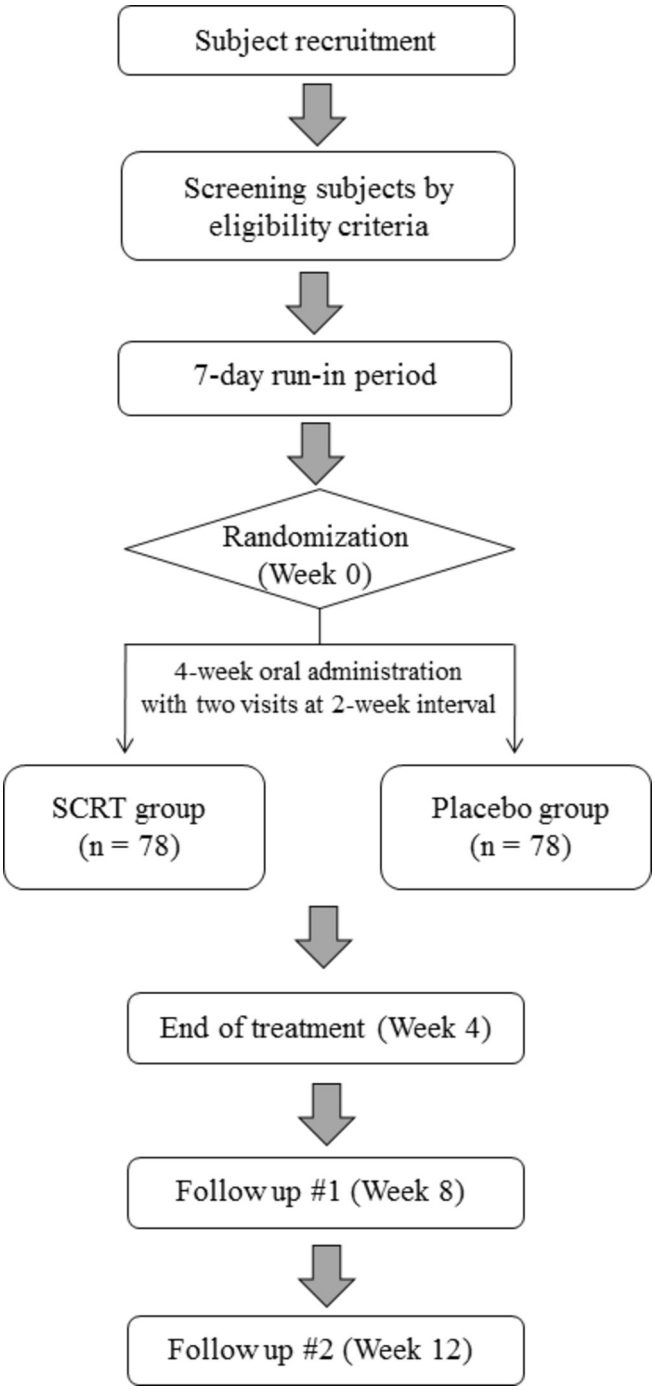

Figure 1 Study design flowchart. SCRT, So-Cheong-Ryong-Tang.

Sample size

Sample size calculations were performed to determine the number of subjects to be enrolled. The study aims to detect a difference between the two study groups in total nasal symptom score (TNSS) change prior to (visit 1) and following (visit 3) medication. To our knowledge, there exists one randomised clinical trial for SCRT use in patients with AR.[10] However, primary outcome measurement conducted in that study was not suitable to estimate sample size. We applied effect size and SD values obtained from other trials that used herbal medicines in patients with AR.[14–16] We thereby assumed that SCRT administration would improve TNSS score by 2.68 points, while placebo will improve it by 1.25 points and that the SD will be 2.809. The following formula was used to estimate the sample size:

$$n = \left(Z_{1-\frac{\alpha}{2}} + Z_{1-\beta} \right)^2 \sigma^2 (r+1) / r (\mu_1 - \mu_2)^2$$

In the present study, the ratio (r) of number of subjects in the SCRT group to the number in the placebo group will be 1:1. With a power of 80% (1–β) and a significance level of 5% (α), the required sample size is approximately 61 for each group. Considering an assumed dropout rate of 20%, 154 subjects will be required.

Recruitment

Subjects will be recruited using two strategies. One is to display recruitment posters outside the clinics of each centre. The posters will contain brief descriptions of inclusion and exclusion criteria, purpose of the study and intervention. The other is to place advertisements on the homepage of the hospitals and online communities of groups with geographical proximity to the hospital area.

Inclusion and exclusion criteria

The inclusion criteria are as follows: (1) age 18–60 years; (2) presence of two or more nasal symptoms (rhinorrhoea, nasal congestion, nasal itching and sneezing) with severity score ≥2 (0=no symptoms, 1=mild symptoms, 2=moderate symptoms, and 3=severe symptoms); (3) presence of nasal symptoms for over two consecutive years; and (4) positive reaction to one or more perennial allergens as evaluated in the skin prick test.

The exclusion criteria are as follows: (1) treatment with nasal/oral corticosteroids within the past month; nasal cromolyn or tricyclic antidepressants within the past 2 weeks or with nasal/oral decongestants, nasal/oral antihistamines or antileukotrienes within the past week; (2) presence of rhinosinusitis (paranasal sinus X-ray demonstrating mucosal thickening or partial or complete opacification of the paranasal sinuses); (3) presence of hypertension (systolic ≥180 mm Hg or diastolic ≥100 mm Hg); (4) presence of abnormal liver function (aspartate transaminase (AST) or alanine transaminase (ALT) ≥100 IU/L) or abnormal renal function (blood urea nitrogen (BUN) ≥30 mg/dL or creatinine ≥1.8 mg/dL (male), 1.5 mg/dL (female)); (5) presence of neoplasm, severe systemic inflammation or any other systemic disease that affects AR; (6) history of drug allergy; (7) history of anaphylaxis in response to allergic tests; (8) pregnancy or lactation or (9) participation in another clinical study within the past 3 months.

Subject withdrawal criteria

The subject withdrawal criteria are as follows: (1) use of medication that can affect nasal symptoms (nasal/oral corticosteroids, nasal cromolyn, tricyclic antidepressants, nasal/oral decongestants, nasal/oral antihistamines, antileukotriens and herbal medicines); (2) onset of rhinosinusitis (diagnosis with paranasal sinus X-ray); (3) onset or diagnosis of neoplasm, severe systemic inflammation or any other systemic disease that affects AR; (4) pregnancy; (5) medication compliance <80% at visits 2 and 3; (6) occurrence of a serious adverse event; (7) subjects's withdrawal of consent and (8) detection of eligibility violations, occurrence of other significant protocol violations during the study.

Skin prick test

The skin prick test will be performed to screen patients with AR, in accordance with routine procedures. For this test, seven common aeroallergens (*Dermatophagoides farinae*, *Dermatophagoides pteronyssinus*, dog fur, cat fur, *Alternaria tenuis*, *Aspergillus fumigatus* and cockroach),[17] negative controls (50% glycerine saline) and positive controls (0.1% histamine phosphate) will be used (Allergopharma GmbH & Co KG, Reinbek, Germany). The subjects who show a positive reaction to the skin prick test will be judged to have passed the screening phase.

Randomisation and blinding

Institute of Safety, Efficacy and Effectiveness Evaluation for Korean Medicine (ISEE), the contract research organisation (CRO) of this trial will enforce randomisation using an ISEE-developed web-based central randomisation programme. The randomised allocation sequence will be generated by researchers from ISEE using Microsoft Excel with block sizes of 2 and 4, and an allocation ratio of 1:1. Institution and age group stratifications are also performed. Following study drug manufacture by the pharmaceutical company (Hanpoong Pharm & Foods Co), drugs sealed in an opaque aluminium package will be labelled by number together alongside placebo drugs and allocated based on the randomisation number. Accordingly, SCRT and placebo packages will be provided to each centre. Following the screening phase, the screening number of each subject and the centre code are entered in the randomisation website. The subjects will be assigned a randomisation number and will receive the corresponding package, containing either SCRT or the placebo drug. All researchers and all subjects, excluding the statistician of ISEE, will be blinded for the assignments process until the trial is completed.

Intervention

Hanpoong Pharm & Foods Co manufactures the SCRT and placebo in compliance with Korea Good Manufacturing Practice standards. SCRT used in this study (Socheongryongtang extract granule Hangpoong) is comprised of dried, bitter, brown granules extracted with water. The extract is permitted and regulated by the Korean Food & Drug Administration and is composed of eight herbs: *Glycyrrhiza uralensis* Fischer 1 g *Zingiber officinale* Roscoe 0.5 g *Cinnamomum cassia* Blume 0.2 g, *Ephedra sinica* Stapf 0.5 g, *Pinellia ternata* Breitenbach 2.67 g, *Paeonia lactiflora* PALL 1 g, *Asiasarum sieboldi* F. Maekawa 0.5 g, *Schisandra chinensis* 2.67 g (per 9 g of granules). The placebo is made of lactose, corn starch and caramel colouring and has the appearance, shape, weight, taste and colour of the SCRT being administered. SCRT and placebo granules are sealed in opaque aluminium bags and administered to subjects in doses of 3 g. The pharmacists will instruct the subjects to dissolve SCRT or placebo from each package in

Table 1 Study schedule (12 weeks)

Stage	Screening	Active treatment (4 weeks)			Follow-up (8 weeks)	
Visit	−1	1	2	3	4	5
Weeks	−1	0	2	4	8	12
Informed consent and eligibility screening	○					
Demographic characteristics	○					
Medical/drug use history	○					
Skin prick test	○					
Allocation		○				
TNSS and RQLQ		○	○	○	○	○
Total IgE, eosinophil count		○		○		
Cytokines*		○		○		
Nasal endoscopy index for pattern identification		○		○		
Pattern identification by clinician		○				
Pattern identification questionnaire for allergic rhinitis		○				
Vital signs†	○	○	○	○	○	○
Laboratory tests for safety assessment‡	○			○		
Adverse events			○	○	○	○

*Only for 32 subjects recruited in Kyung Hee University Hospital at Gangdong (interferon gamma, IL-4, IL-5, IL-8, IL-10, IL-13 and tumour necrosis factor alpha).
†Blood pressure, pulse (heart rate), body temperature.
‡Complete blood cell counts, levels of aspartate transaminase, alanine transaminase, blood urea nitrogen and creatinine
IL, interleukin; RQLQ, Rhinoconjunctivitis Quality of Life Questionnaire; TNSS, Total Nasal Symptoms Score.

water and take the solutions 30 min after each meal three times per day for 4 weeks. All subjects will be required to return remains of drugs for calculating compliance.

Outcome measurement

Primary outcome

Primary outcome in the present study is the difference between the two study groups in TNSS change observed prior to (visit 1) and subsequent to (visit 3) medication. The TNSS evaluates symptoms of rhinorrhoea, nasal congestion, nasal itching and sneezing on a four-point scale. The total score range is from 0 to 12, where 0=no symptoms, 1=mild symptom(s) (present but bearable), 2=moderate symptom(s) (present and uncomfortable) and 3=severe symptom(s) (unbearable). TNSS will be measured during visits 1, 2, 3, 4 and 5. The study schedule is detailed in table 1.

Secondary outcomes

Rhinoconjunctivitis Quality of Life Questionnaire score

Rhinoconjunctivitis Quality of Life Questionnaire (RQLQ) is self-report questionnaire used to assess the quality of life in patients with AR. The questionnaire has seven domains: activity limitations, sleep disturbances, non-hay fever symptoms, practical problems, nasal symptoms, ocular symptoms and emotional problems. Subjects will be asked to recall their experiences during the previous week and to rate each question on a ranging from 0 (no impairment) to 6 (severe impairment).[18 19] RQLQ baseline value will be measured just prior to the start of the experiment and then again during visits 1, 2, 3, 4 and 5.

Total serum IgE, eosinophil count and cytokines levels

Cytokines will not be measured for all participants and cytokines level will be measured only in one centre (32 subjects), Kyung Hee University Hospital at Gangdong, as a pilot study. Total serum IgE, eosinophil count and cytokine levels (interferon gamma, interleukin (IL)-4, IL-5, IL-8, IL-10, IL-13 and tumour necrosis factor alpha) will be measured during visits 1 and 3. SCRT has been observed to regulate cytokines in animal studies.[10–12] However, no clinical study has observed the effect of SCRT on cytokine regulation.

Nasal endoscopy index for pattern identification

For PI of AR, nasal endoscopy index was developed in 2013 (figure 2) and inter-rater and intrarater reliability study was conducted.[7 8] In this study, one specialist in the department of Otolaryngology of Korean Medicine at each centre will evaluate the nasal endoscopy index during visits 1 and 3.

Scoring method is as follows: the doctor checks the score following observation of the nasal membrane and inferior turbinate of the patient via nasal endoscopy. In evaluating the nasal membrane colour, either the pale score or hyperaemia score must be 0 (for example, when pale score is 2, hyperaemia score should be 0; if the

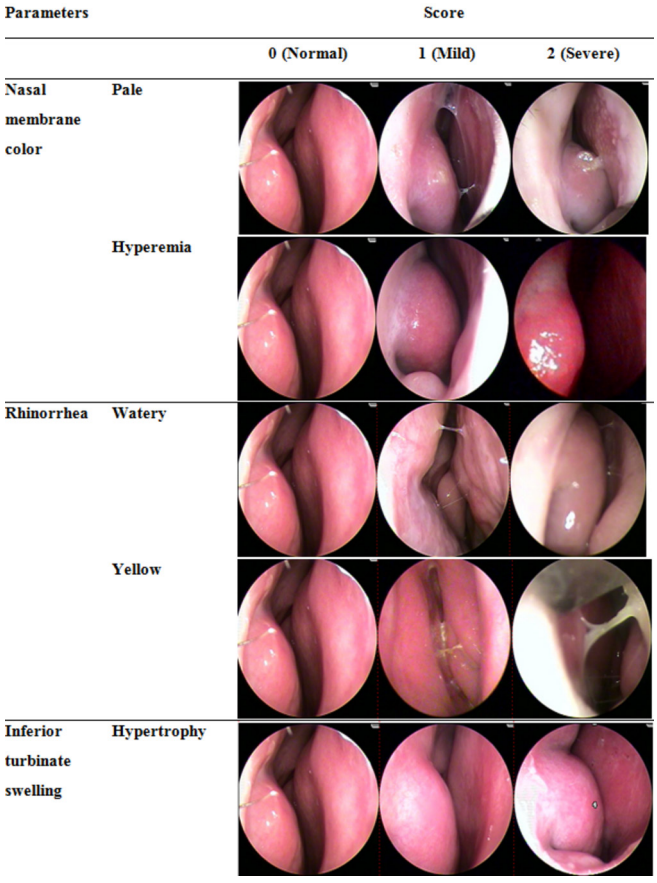

Figure 2 Nasal endoscopy index for pattern identification.

nasal membrane colour is normal, both pale and hyperaemia scores are 0). The same rule is applied in case of the rhinorrhoea score. If there is no rhinorrhoea, both the watery score and the yellow score are 0. Cold score is the sum of the pale score as measured while evaluating the nasal membrane parameter and the watery score as measured while evaluating the rhinorrhoea parameter. Heat score is the sum of the hyperaemia score as measured while evaluating the nasal membrane parameter, and the yellow score as measured while evaluating the rhinorrhoea parameter. Inferior turbinate swelling score is not used to evaluate cold or heat patterns but used to evaluate nasal obstruction.

Pattern identification by the clinician

Specialists in the department of Otolaryngology of TKM at each centre will select a pattern for each subject from among lung–heat, lung–cold and spleen qi deficiency through face-to-face diagnoses, based on body and nasal conditions. We will investigate the efficacy of SCRT based on PI.

Pattern identification questionnaire for allergic rhinitis

PI questionnaire for AR V.1.0 was developed in 2008 by specialists in the Department of Otolaryngology of TKM, based on systemic and nasal symptoms and signs.[20] However, that questionnaire had many problems in application to clinical practice and has since been revised based on several studies and discussions.[21–23] Consequently, the PI questionnaire for AR V.3.0 has been developed.[24] This questionnaire classifies patients with AR as possessing lung-heat, lung-cold or spleen qi deficiency and can be applied for both SAR and PAR. We plan to conduct a validation and reliability study and revise the questionnaire based on the results of this study (table 2).

Safety outcomes

The levels of AST/ALT, BUN/creatinine and complete blood counts including white blood cell, red blood cell, haemoglobin, haematocrit and platelet count will be measured at screening and during visit 3 and visit 5. The investigator will ask subjects questions regarding adverse events (AEs) during every visit and record details of AEs in case report forms. All AEs will be monitored by independent clinical research associate (CRA). When serious adverse events occur, the investigator will provide treatment immediately and report to the institutional review board (IRB) within 24 hours from the time of recognition.

Quality control

To protect the rights and welfare of the subjects and to maintain the quality of the study, monitoring will be performed. ISEE, the CRO of this study, will send a clinical research associate (CRA) to five centres at least four times (after the first subject is enrolled, after half of planned enrolment is complete, after planned enrolment is complete and after all visits of subjects have occurred) during the study and the CRA will visit each centre additionally on request. The CRA will check if the trials are proceeding according to the protocol by performing cross-checks of the informed consent form, CRF, original chart of subjects and drug management records.

Statistical analysis

A statistician independent from researchers will use SPSS V.21 (IBM) to manage and analyse the data. An intent-to-treat (ITT) analysis is an analysis method employed for evaluating data collected from a subject who takes the study drug at least once. In ITT analysis, missing data are replaced via the last observation carried forward method. A per-protocol (PP) analysis is used to evaluate data collected from a subject who completes all steps of the experimental protocol. Efficacy measurement analysis will mainly use ITT analysis while PP analysis will be additionally carried out if statistically significant. Further, the analyses will be fully described. Safety evaluation will be conducted by ITT analysis.

Data will be displayed as the mean and SD for continuous variables and n (%) for categorical data. The baseline characteristics will be compared by an independent t-test for continuous values and χ^2 test or Fisher's exact test for categorical values. The differences of TNSS, RQLQ, IgE, eosinophil count and cytokines during visit 1 and visit 3 between the SCRT and placebo groups will be compared using an independent t-test. A repeated-measures analysis of variance (ANOVA) test with

Table 2 Pattern identification questionnaire for allergic rhinitis, V.3.0

First questionnaire					
We would like to know more about any problems you have experienced recently. Please answer all of the questions by marking the answer that most closely applies to you. Question 1–6: 0: disagree strongly, 1: disagree, 2: agree, 3: agree strongly					
Condition		**0**	**1**	**2**	**3**
1. My face is pale or yellowish					
2. I have a feeling of fullness in my stomach after eating					
3. I have indigestion					
4. My stool is loose					
5. I usually feel tired or languid					
6. I have a poor appetite and eat just a little food					
7. I have a thin body (According to BMI): 0:≥22, 1:≥20,<22, 2:≥18.5, <20.0, 3:≤18.5) *BMI=weight (kg)/(height (cm)×height (cm))					
- Scores≥11 → Do not need to complete second questionnaire. - Scores<10 → Complete second questionnaire.					
Second questionnaire					
Question 1-5: Please answer all of the questions by marking the answer that most closely describes your symptoms over the last 2 weeks.					
Question 1. Aversion to cold or heat	1 □ I have had considerable aversion to cold	2 □ I have had slight aversion to cold	3 □ Normal	4 □ I have had slight aversion to heat	5 □ I have had considerable aversion to heat
Question 2. Preference for warm or cold water	1 □ I have had considerable preference for warm water	2 □fidentiality of their persona I have had slight preference for warm water a little	3 □ Normal	4 □ I have had slight preference for cold water	5 □ I have had considerable preference for cold water
Question 3. Colour of face	1 □ My face has been very pale	2 □ My face has been a little pale	3 □ Normal	4 □ My face has been flushed a little	5 □ My face has been flushed very much
Question 4. Shape and consistency of stool	1 □ Liquid consistency with no solid pieces	2 □ Soft blobs with clear-cut edges	3 □ Smooth, soft, and sausage-like	4 □ Lumpy sausage shaped or sausage-like with cracks in the surface	5 □ Separate hard lumps
Question 5. Colour of urine	1 □ Completely transparent with no yellow colour	2 □ Almost transparent with little yellow colour	3 □ Light yellow	4 □ Yellow	5 □ Dark yellow or light orange colour
Question 6–7: Clinician's assessment questions					

Continued

Table 2 Continued

Question 6. Clinician checks the score after enquiring about the colour and viscosity of rhinorrhoea	1 □ Totally watery and transparent	2 □ Slightly watery and transparent	3 □ Slightly sticky and transparent	4 □ Slightly sticky and yellowish	5 □ Totally sticky and yellowish
Question 7. Clinician checks the score after observing the nasal membrane colour of the patient using nasal endoscopy and referring to the pictures.	1 □ Severe pale	2 □ Mild pale	3 □ Normal	4 □ Mild hyperaemia	5 □ Severe hyperaemia

Pattern identificaiton:
Lung–cold: first questionnaire scores<10, second questionnaire score ≥21.
Spleen qi deficiency: first questionnaire scores ≥11.
Lung-heat: first questionnaire scores<10, second questionnaire score ≥7,<20.

Bonferroni post hoc test will be used to evaluate the changes in TNSS, RQLQ, IgE, eosinophil count, cytokines and safety assessment measurements throughout the experiment. Pearson correlation test will be used to analyse the relationship between cold and heat scores of nasal endoscopy index and TNSS changes. ANOVA will be used to analyse correlation between PI pattern (PI of clinician and PI questionnaire for AR) and TNSS changes. In all tests, a value of $p<0.05$ will be considered statistically significant.

Ethics and dissemination

This study was approved by the IRB of Kyung Hee University Hospital at Gangdong (KHNMC-OH-IRB 2015-04-009), Kyung Hee University Medical Centre (KOMCIRB-160321-HRBR-011), Pusan National University Hospital (2016–004), Dongguk University Medical Centre (2016–03) and Semyung University hospital (2016–01). This trial has been registered with ClinicalTrials.gov (NCT03009136) on January 2017. The trial will be performed in compliance with the Declaration of Helsinki and according to Good Clinical Practices as described by the Korea Food and Drug Administration.

Written informed consent will be obtained by the investigator from all subjects prior to enrolment. The investigator will explain the study in non-scientific language. All subjects will be given enough time to decide whether they wish to participate in the trial. The confidentiality of their personal information will be protected. Each subject will be assigned a study identification number at enrolment and will be represented in the data by that number. Throughout and subsequent to the trial, all documents and data will remain secure in a locked cabinet or as password-protected computer files.

DISCUSSION

In many cases of AR, symptoms are prolonged for years. Therefore, it is necessary to develop medicines that have no adverse effects when employed as long-term therapy and have long-lasting effects. The main medications currently used for AR are antihistamines, nasal steroids, nasal decongestants and leukotriene receptor antagonists. However, long-term use of many of these AR medications can result in adverse effects. Antihistamines have limited efficacy in treating nasal congestion and commonly induce adverse effects such as sedation and weight gain.[25 26] Nasal decongestants are useful against nasal obstruction, but their use for over a week is not recommended owing to the adverse effects induced and low drug tolerance.[27] For these reasons, traditional Chinese Medicine (TCM) composed of natural herbs has recently gained much attention as a potential source for therapeutic AR medicine.[28]

SCRT is an herbal medicine widely used in both TKM and TCM for treating AR. Previous studies reported that SCRT exhibits antiallergic effects by inhibiting Th2 cytokine release and decreasing infiltration of inflammatory cells onto nasal mucosa in an ovalbumin-induced AR model.[7 8] Another study reported that SCRT exerts a preventive effect against asthma via regulation of neutrotrophin in an allergy-based asthma disease model.[29]

In previous clinical studies, Bu-zhong-yi-qi-tang displayed anti-inflammatory activity, suppressing total serum IgE and the IL-4-stimulated production of prostaglandin E2 and leukotriene C4 by polymorphonuclear neutrophils in patients with PAR.[30] In another clinical study, Xin-yi-san was demonstrated to exert an antiallergic effect by enhancing IL-0 and IL-8 production.[31] Based on these studies, we hypothesised that SCRT may regulate cytokine levels in AR patients.

To our knowledge, this is the first study to investigate the efficacy of SCRT for Korean adult patients with PAR, as a multicentre study with a follow-up of 8 weeks. This study will provide evidence regarding the use of SCRT for the treatment of AR.

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Contributors MHK has written the initial manuscript for this trial. YHY, MNY and SGK have edited the first manuscript. JHA and MHK have revised the manuscript. YMK will monitor this trial. IHC has conducted all the procedures for this protocol. All authors have read and approved the final manuscript.

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Competing interests None declared.

Patient consent Obtained.

Ethics approval Institutional Review Board at each research center (name of each centre and approval numbers): Kyung Hee University Hospital at Gangdong (KHNMC-OH-IRB 2015-04-009), Kyung Hee University Medical Center (KOMCIRB-160321-HRBR-011), Pusan National University Hospital (2016-004) Dongguk University Medical Center (2016-03) and Semyung University Hospital (2016-01).

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