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

Min-Hee Kim,1,2 Youme Ko,3 Jin-Hyang Ahn,1,2 Younghee Yun,1 Mi-Na Yun,2 Seong-Gyu Ko,3 Inhwa Choi1

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-DH-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.

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, rhinorrhea, 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. In animal studies, SCRT has suppressed the progression of AR and allergic asthma. A single randomised controlled clinical study was performed in Japan. 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.

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. 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. 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:

\[
n = \left( \frac{Z_{1-\alpha/2} + Z_{1-\beta}}{\sigma^2} \right)^2 \frac{r + 1}{\mu_1 - \mu_2}^2
\]
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 (rhinorhoea, 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 weeks; 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 UI/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, antileukotrienes 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’ 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), 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 (Socheon-gryongtang 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, Paonia 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

Kim M-H, et al. BMJ Open 2017;7:e016556. doi:10.1136/bmjopen-2017-016556
Table 1 Study schedule (12 weeks)

| Stage             | Screening (−1) | 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.

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

Rhinocconjunctivitis Quality of Life Questionnaire score

Rhinocconjunctivitis 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). 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. 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 intrainar reliability study was conducted. 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

Open Access
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. However, that questionnaire had many problems in application to clinical practice and has since been revised based on several studies and discussions. Consequently, the PI questionnaire for AR V.3.0 has been developed. This questionnaire classifies patients with AR as possessing lung-heat, lung-cold and 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 χ² 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 | 2 | 3 | 4 | 5 |
|----------|---|---|---|---|---|
| Question 1. Aversion to cold or heat | □ | □ | □ | □ | □ |
| | I have had considerable aversion to cold |
| | I have had slight aversion to cold |
| | Normal |
| | I have had slight aversion to heat |
| | I have had considerable aversion to heat |

| Question 2. Preference for warm or cold water | 1 | 2 | 3 | 4 | 5 |
|---------------------------------------------|---|---|---|---|---|
| | □ | □ | □ | □ | □ |
| | I have had considerable preference for warm water |
| | I have had slight preference for warm water a little |
| | Normal |
| | I have had slight preference for cold water |
| | I have had considerable preference for cold water |

| Question 3. Colour of face | 1 | 2 | 3 | 4 | 5 |
|--------------------------|---|---|---|---|---|
| | □ | □ | □ | □ | □ |
| | My face has been very pale |
| | My face has been a little pale |
| | Normal |
| | My face has been flushed a little |
| | My face has been flushed very much |

| Question 4. Shape and consistency of stool | 1 | 2 | 3 | 4 | 5 |
|------------------------------------------|---|---|---|---|---|
| | □ | □ | □ | □ | □ |
| | Liquid consistency with no solid pieces |
| | Soft blobs with clear-cut edges |
| | Smooth, soft, and sausage-like |
| | Lumpy sausage shaped or sausage-like with cracks in the surface |
| | Separate hard lumps |

| Question 5. Colour of urine | 1 | 2 | 3 | 4 | 5 |
|-----------------------------|---|---|---|---|---|
| | □ | □ | □ | □ | □ |
| | Completely transparent with no yellow colour |
| | Almost transparent with little yellow colour |
| | Light yellow |
| | Yellow |
| | 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 identification:
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 neutrophin 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.

Acknowledgements
We wish to acknowledge Hanpoong Phar. & Foods Co. Ltd. for providing investigational product support.

Contributors
MHK has written the initial manuscript for this trial. HYY, MNY and SGK have edited the first manuscript. JHA and MKH 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.

Funding
This trial has been registered with the ClinicalTrials.gov Identifier (NCT03099136). This study was funded by a grant from the Traditional Korean Medicine R&D Project, Ministry of Health & Welfare, Republic of Korea (HI12C1889 and HI13C0530).

Competing interests
None declared.

Patient consent
Obtained.

Ethics approval
Institutional Review Board at each research center (name of each centre and approval number): Kyung Hee University Hospital at Gangdong (KHHMC-OH-IRB 2015-04-009), Kyung Hee University Medical Center (KOMCRB-160321-HRBR-011), Pusan National University Hospital (2016-004) Dongguk University Medical Center (2016-03) and Semyung University Hospital (2016-01). Provenance and peer review
Not commissioned; externally peer reviewed.

Open Access
This is an Open Access article distributed in accordance with the Creative Commons Attribution Non Commercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited and the use is non-commercial. See: http://creativecommons.org/licenses/by-nc/4.0/

© Article author(s) (or their employer(s) unless otherwise stated in the text of the article) 2017. All rights reserved. No commercial use is permitted unless otherwise expressly granted.

REFERENCES
1. de Boer CM, Roeder E, Pols DH, et al. Sensitisation patterns and association with age, gender, and clinical symptoms in children with allergic rhinitis in primary care: a cross-sectional study. Prim Care Respir J 2013;22:155–60.
2. Bousquet J, Khaetaev N, Cruz AA, et al. Allergic Rhinitis and its Impact on Asthma (ARIA) 2008 update (in collaboration with the World Health Organization, GA2LEN and AllerGen). Allergy 2008;63:8–160.
3. Bousquet PJ, Leynaert B, Neukirch F, et al. Geographical distribution of atopic rhinitis in the European Community Respiratory Health Survey I. Allergy 2008;63:1301–9.
4. Apfelbacher CJ, Jones C, Hankins M, et al. Validity of two common asthma-specific quality of life questionnaires: Juniper mini asthma quality of life questionnaire and Sydney asthma quality of life questionnaire. Health Qual Life Outcomes 2012;10:97.
5. Schramm B, Ehiken B, Smala A, et al. Cost of illness of atopic asthma and seasonal allergic rhinitis in Germany: 1-yr retrospective study. Eur Respir J 2003;21:116–22.
6. World Health Organization. WHO International standard terminologies on traditional medicine in the Western Pacific Region. 80. Western Pacific Region: World Health Organization, 2007.
7. Yun YH, Park JS, Kim KS, et al. Study on the development of guideline for assessing anterior nasal cavity using nasal endoscopy on allergic rhinitis patients. Korean J Orent J Prev Med Soc 2013;17:199–207.
8. Kim K, Yun Y, Nam HJ, et al. Inter- and intra-rater reliability of a nasal endoscopy index for pattern identification in patients with allergic rhinitis. Orient Pharm Exp Med 2015;15:167–71.
9. Kim N-K, Lee D-H, Seo E-S, et al. Treatment packages of persistent allergic rhinitis for developing PRCT protocols: an expert survey. J Oriental Med Prev Med 2013;17:143–53.
10. Ku JM, Hong SH, Kim SR, et al. Anti-allergic effects of So-Cheong-Ryong-Tang in ovalbumin-induced allergic rhinitis model. Eur Arch Otorhinolaryngol 2016;273:123–31.
11. Mo JH, Lee SE, Wee JH, et al. Anti-allergic effects of So-Cheong-Ryong-Tang, a traditional Korean herbal medicine, in an allergic rhinitis mouse model. Eur Arch Otorhinolaryngol 2013;270:923–30.
12. Kim HW, Lim CY, Kim BY, et al. So-Cheong-Ryong-Tang, a herbal medicine, modulates inflammatory cell infiltration and prevents airway remodeling via regulation of interleukin-17 and GM-CSF in allergic asthma in mice. Pharmacogn Mag 2014;10:5506–11.
13. Baba S, et al. Double-blind clinical trial of Sho-seiryu-to(TJ-19) for perennial nasal allergy and allergic rhinitis. Phytomedicine 2015;22:389–405.
14. Kim MH, Son J, Nam HJ, et al. Hyeonggaeaengo-yang for treatment of allergic and nonallergic rhinitis: a prospective, non-randomized, pre-post study. Evid Based Complement Alternat Med 2016;2016:1–7.
15. Jung JW, Kang HR, Ji GE, Ge J, et al. Therapeutic effects of fermented red ginseng in allergic rhinitis: a randomized, double-blind, placebo-controlled study. Allergy Asthma Immunol Res 2011;3:103–10.
16. Yang SH, Yu CJ, Chen YL, et al. Traditional Chinese medicine, Xin-yi-san, reduces nasal symptoms of patients with perennial allergic rhinitis by its diverse immunomodulatory effects. Int Immunopharmacol 2010;10:951–8.
17. Min KU, Kim YY, Kang SY. Epidemiologic study on inhalant allergens in perennial allergic rhinitis. Allergy asthma & respiratory disease 1982;2:78–85.
18. Juniper EF, Thompson AK, Ferrie PJJ, et al. Validation of the standardized version of the Rhinoconjunctivitis Quality of Life Questionnaire. J Allergy Clin Immunol 1999;104:364–9.
19. Juniper EF, Guyatt GH. Development and testing of a new measure of health status for clinical trials in rhinoconjunctivitis. Clin Exp Allergy 1991;21:77–83.
20. Sk K, Shin YC, Kwon DY, et al. The Research on evaluation endpoint development for clinical trial of herbal medicinal products about atopic dermatitis and allergic rhinitis. Korean Food and Drug Administration report. 253, 2008.
21. Lee K-J, Kim H-T, Jeong B-H, et al. Assessment of concordance rate in pattern Analysis between pattern diagnosis of KIFDA on allergic rhinitis in 2008 and doctor of Korean medicine. J Korean Med Ophthalmol Otolaryngol Dermatol 2014;27:91–8.
22. Kim N-K, Lee D-H, Choi I-H, et al. An expert survey for developing pattern diagnosis instrument of persistent allergic rhinitis. J Korean Med Ophthalmol Otolaryngol Dermatol 2013;26:1–9.
23. Kim JW, Lee KS, Jeon BH, et al. Characteristics of patients with allergic rhinitis through the pattern questionnaire items. Korean J Prev Med 2014;18:81–90.
24. Kim MH, Yun YH, Sk K, et al. Developing Questionnaire for Pattern Identification of Allergic Rhinitis. J Korean Med Ophthalmol Otolaryngol Dermatol 2017;30:112–25.
25. Church MK, Maurer M, Simons FE, et al. Risk of first-generation H1-antihistamines: a GA2LEN position paper. Allergy 2010;65:459–66.
26. Simons FE. H1-Antihistamines: a GA2LEN position paper. Allergy 2010;65:459–66.
27. Graf P. Adverse effects of benzalkonium chloride on the nasal mucosa: allergic rhinitis and rhinitis medicamentosa. Clin Ther 1999;21:1749–55.
28. Chan RY, Chien WT. The effects of two Chinese herbal medicinal formulae vs. placebo controls for treatment of allergic rhinitis: a randomised controlled trial. Trials 2014;15:261.
29. Chang RS, Wang SD, Wang YC, et al. Xiao-Qing-Long-Tang shows preventive effect of asthma in an allergic asthma mouse model through neurotrophin regulation. BMC Complement Altern Med 2013;13:220.
30. Yang SH, Yu CL. Antiinflammatory effects of Bu-zhong-yi-qi-tang in patients with perennial allergic rhinitis. J Ethnopharmacol 2008;115:104–9.
31. Yang SH, Yu CL, Chen YL, et al. Traditional Chinese medicine, Xin-yi-san, reduces nasal symptoms of patients with perennial allergic rhinitis by its diverse immunomodulatory effects. Int Immunopharmacol 2010;10:951–8.