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COCOS trial: *CO*rticosteroids for *CO*VID-19-induced loss of *S*mell–protocol for a single-centred, double-blind, randomised, placebo-controlled trial

Emma J A Schepens ,[1,2] Wilbert M Boek,[3] Sanne Boesveldt,[4] Inge Stegeman ,[1,2] Robert J Stokroos,[1,2] Digna M A Kamalski[1,2]

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[1]Department of Otorhinolaryngology, Head and Neck Surgery, University Medical Center Utrecht, Utrecht, The Netherlands
[2]Brain Centre, University Medical Center Utrecht, Utrecht, The Netherlands
[3]Department of Otorhinolaryngology, Gelderse Vallei Hospital, Ede, The Netherlands
[4]Division of Human Nutrition and Health, Wageningen University, Wageningen, The Netherlands

Correspondence to
Emma J A Schepens ;
e.j.a.schepens-2@umcutrecht.nl

ABSTRACT

Introduction Hyposmia and anosmia are common in COVID-19. Most patients regain normal smell within 4 weeks, but severe loss of smell persists roughly in 20% after 2 months and may last up to a year or longer. These persistent smell disorders greatly influence daily life. It is hypothesised that COVID-19 induces inflammation around the olfactory nerve and in the olfactory pathway, leading to smell disorders. Corticosteroids might reduce this local inflammatory response and improve smell.

Methods and analysis We will conduct a single-centre, randomised, placebo-controlled trial to determine the efficacy of a short high-dose treatment of oral prednisolone for persistent loss of smell after COVID-19 in the early phase. We will include 116 patients with persistent (>4 weeks) loss of smell within 12 weeks of COVID-19 diagnosis, based on a positive PCR/antigen test. One group receives 40 mg of prednisolone for 10 days and the other group receives matching placebo treatment. In addition, all patients will perform smell training for 12 weeks. The primary outcome is objective olfactory function measured by means of sniffin' sticks test. Secondary outcomes are objective gustatory function by means of taste strips test and subjective taste and smell ability, trigeminal sensations, quality of life and nasal symptoms, measured by three questionnaires. These outcomes will be measured at inclusion before treatment and 12 weeks later.

Ethics and dissemination The Institutional Review Board of the University Medical Center Utrecht approved the research protocol (21-635/G-D, October 2021). The trial results will be shared in peer-reviewed medical journals and scientific conferences.

Trial registration number NL9635. EUCTR2021-004021-71-NL.

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ This is a double-blinded randomised controlled trial with large sample size to allow for a comparison between prednisolone and olfactory training or only olfactory training in patients with smell loss after COVID-19.
⇒ We use objective measurements for the primary outcome and for one secondary outcome: smell and taste function.
⇒ Multiple outcome measurements besides objective smell and taste function will be assessed, such as quality of life and nasal symptoms.
⇒ To consider the effect in the long term, an extra follow-up measurement after 6–12 months could be considered.
⇒ The Questionnaire of Olfactory Disorders had not been validated in Dutch patients with smell loss after COVID-19.

BACKGROUND

Partial or complete loss of smell ability, respectively, hyposmia and anosmia, are common early features in COVID-19,[1 2] which occur in about two of every three patients.[3 4] Though the vast majority of patients recover within 4 weeks, severe loss of smell persists roughly in one of five patients after 2 months.[5] Reduced ability to smell, hyposmia, persists in 10%–46% after 6 months[6–8] and can last up to a year or longer with 7%–9% being functionally anosmatic.[9 10] Beyond smell loss, patients also report taste disorders and smell alterations, starting after a period of absent smell.[11 12] In parosmia (a distorted sense of smell), odours are perceived different than usual, or phantosmia, odours can be perceived without odour source. Persistent olfactory disorders are associated with a significant reduction in patients' quality of life, including increased depressive symptoms and nutritional issues.[13]

There is no definitive answer yet to the pathophysiology of olfactory disorders during and after COVID-19. In common cold viruses, the loss of smell is typically due to swelling of the nasal mucosa. However, swelling of the nasal mucosa is not observed in SARS-CoV-2

infections.[1 14 15] It is hypothesised that the SARS-CoV-2 causes loss of smell by entering the supporting neural cells in the olfactory epithelium through the ACE2 receptor.[16] In response, a rapid autoimmune response activates lymphocytes and macrophages, and causes release of cytokines. This autoimmune response can differ greatly between patients and may explain the variation in long-term olfactory disorders.[14 17] This inflammatory response during COVID-19 is also seen in certain brain areas, as the olfactory pathway.[18 19]

There is no scientifically proven treatment for post-COVID-19 hyposmia or anosmia yet. In other post-viral loss of smell, involving the olfactory bulb, smell therapy is to date the only proven beneficial treatment to improve olfactory function.[20 21] During smell therapy, a patient sniffs every day a set of known odours over a period of 3 months. Consistent training will speed up and increase the extent of smell recovery.[20 21] Smell therapy is now advised to all patients with persistent loss of smell after COVID-19,[22] however, effects seem limiting on its own.

In diseases with nerve function loss due to inflammatory response, such as sudden sensorineural hearing loss or Bell's palsy, a short course of high-dose oral corticosteroids is given.[23 24] In early stages of these diseases, the autoinflammatory effects are reversible. Oral steroids have recently been given to patients who suffer from anosmia post-SARS-CoV-2 infection with promising effects: two randomised controlled trials (RCTs) included patients with persistent anosmia 1 month after COVID-19 showed that higher number of patients regained function after corticosteroid treatment, compared with the control group.[25–27] Despite the limited number of cases included, short follow-up and the non-blinded trial design, clinical effects seem promising.

If treatment with prednisolone in combination with smell therapy is efficient, a long-term disability can be prevented. Therefore, we propose to investigate the efficacy of oral corticosteroid treatment in combination with smell therapy in a single-centred, double-blinded, placebo-controlled randomised trial.

METHODS AND ANALYSIS

Study design and setting

The study is a single-centred, randomised, placebo-controlled clinical trial performed in the Otorhinolaryngology Department at the University Medical Center Utrecht (UMCU) in the Netherlands. Patients will be randomly assigned to one of two groups: 10 days of prednisolone or placebo. In addition, all patients will perform smell training for 12 weeks. At first visit, before start of therapy, patients' olfactory and gustatory function will be tested by the sniffin' sticks test (SST) and taste strips test (TST). Subjective measurements consist of questionnaires. After 10 days of treatment, all patients are called by the investigator to check treatment compliance and if they had any side effects. After 12 weeks, evaluation will take place by means of SST, TST and related questionnaires (see figure 1).

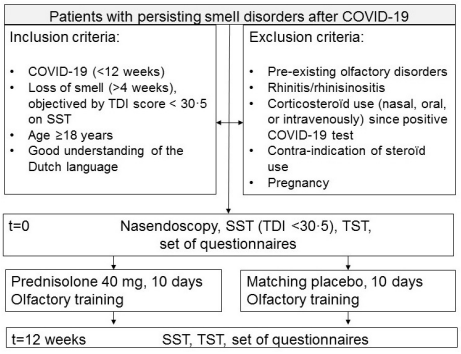

Figure 1 Study flow chart. SST, sniffin' sticks test; TDI-score, threshold, discrimination, identification score; TST, taste strips test.

Patient and public involvement

The National Patients Association was involved in the conduct of the study, applying for the funding and in recruiting patients. Patients who participate in this trial, who prefer, will be informed of the results.

Study objectives

The primary objective of this study is to determine the efficacy of a short high-dose treatment of oral prednisolone for persistent loss of smell after COVID-19. This will be measured with objective SST. Secondary objectives are to investigate the efficacy of prednisolone on objective gustatory function measured with the objective TST and on subjective olfactory, gustatory and trigeminal function, impact of smell/taste changes on quality of life and nasal symptoms by additional questionnaires.

Study population

One hundred sixteen patients will be included (>18 years old) with persistent (>4 weeks) smell loss within 12 weeks after COVID-19 diagnosis based on a positive test (PCR or antigen). For recruitment, we will collaborate with public health services, otorhinolaryngology clinics and the local patient organisation. Inclusions are expected to take a maximum of 18 months, depending mainly on infection numbers in the Netherlands. Inclusions started on 16 November until 10 February. Follow-up outcomes were measured between 2 February and 10 May. Patients need to meet the following criteria to participate:

Inclusion criteria

- Recently diagnosed with COVID-19 (<12 weeks), confirmed with a positive PCR or antigen by the Dutch public health institute.
- Persistent loss of smell (>4 weeks), objectified by threshold, discrimination, identification (TDI) <30.5 on SST.
- Age 18 years or older, and capable of giving informed consent.
- Good understanding of the Dutch language.

Exclusion criteria

- Pre-existing olfactory disorders.
- Chronic rhinitis or rhinosinusitis (with or without nasal polyps).
- Corticosteroid use (nasal, oral or intravenously) since positive COVID-19 test.
- Pregnancy.
- Contraindications of steroid use, which contains the following:
  - Diabetes mellitus for which drugs (either subcutaneously or orally) are used.
  - Stomach ulcers/stomach bleeding.
  - Psychoses.
  - Ongoing oncological disease.

Sample size

Sample size was calculated based on means and SDs of an earlier pilot study.[26] With a power of 0.90, an alpha of 0.05 and a mean difference of 5.5 (SD 8.0) on SST scores, total sample size is 92. To correct for possible non-parametric testing, the sample size is increased with 15%. As the study is limited in time and effort for the patient, a maximum of 10% dropout is expected. This gives a total sample size of 116 patients, with 58 in every group.

Randomisation, blinding and treatment allocation

Patients will be randomly allocated to one of the two groups. The pharmacy in charge of preparation of treatment and placebo medication made a block randomisation sequence list, on which the patient subject number is linked to the study medication number. This pharmacy is a Dutch state-of-the-art good manufacturing practice compounding pharmacy independent from our department. To minimise seasonal effects between groups, randomisation occurs in blocks of four patients. Both groups carry the same weight.

Patients, physicians and outcome assessors are blinded for treatment allocation.

Only after finishing all analyses, the blinding of researchers and patients to the treatment allocation will be broken. If deblinding is necessary because of medical reasons, this can be done by the clinical drug research pharmacy at any time.

Intervention

Group A will be treated with capsules of 40 mg of prednisolone, once a day for 10 days. Group B will be receive capsules of placebo medication, once a day, for 10 days. Patients in both treatment groups will perform 12 weeks of olfactory training. In this training, patients sniff out four odours (rose, lemon, eucalyptus, clove) twice a day.[20] Training compliance will be monitored by crossing off a daily schedule. Patients receive study medication and olfactory training kits at first visit.

Outcomes to be measured

At inclusion, demographic data, such as gender, age and native language, will be collected. Medical status contains medication use, medical history, date of COVID-19 infection, date of smell loss and vaccination status. Outcome measurements will be collected at the first and second visits to the outpatient department. At the first visit, a nasendoscopy will be conducted, to eliminate other causes for loss of smell. For the primary outcome, SST is performed during this visit and can possibly still lead to exclusion when a TDI score >30.5 is measured. Secondary outcomes will be assessed by the TST and questionnaires. Besides, the patients receive three questionnaires to fill in: the validated Sino-Nasal Outcome Test–22 questionnaire (SNOT-22), self-reported smell, taste, parosmia, trigeminal sensations questionnaire by means of Visual Analogue Scale (VAS),[28] and the translated Questionnaire of Olfactory Disorders (QoD).[29 30] All patients will perform 12 weeks of smell training. Twelve weeks after start of therapy, SST, TST and completing the same questionnaires will be repeated to compare. Both primary and secondary outcomes will be registered in an electronic Case Report Form (eCRF), the UMCU-endorsed system Castor EDC.

Explanation of examinations

Olfactory function will be assessed with the SST, a widely used and well-validated test that is commercially available.[31] The SST is produced by Burghart, a medically certified company (ISO 13485), indicating the odourants and their solvent pose no health risks. This test battery examines nasal chemosensory performance using pen-like odour devices filled with odourants and/or solvent. The test consists of three parts: a detection threshold (THR), discrimination (DIS) test and odour identification (ID) test. The TDI score is the sum of THR, DIS and ID, and ranges from 1 to 48. The higher the score, the better the smell function.

The THR will be measured with a standard series of pens with different concentrations of n-butanol. With a staircase procedure, three pens will be presented to participants in a randomised order. Of these pens, one contains the odour and two contain solvent. Participants have to indicate which pen contains the odourant. To measure DIS ability, 16 triplets of three odourants will be presented. The triplet contains two pens with the same odour and one with a different odour. Participants have to discriminate which pen smells differently. During the ID test, 16 pens with common odours will be presented. Participants have to choose the correct description from a list of four descriptors for each pen.

TST: this validated test uses filter-paper taste strips impregnated with different concentrations of the basic tastes sweet, salt, bitter and sour.[32] The filter papers are impregnated with four concentrations of sweet (0.05, 0.1, 0.2 or 0.4 g/mL sucrose), salt (0.016, 0.04, 0.1 or 0.25 g/mL sodium chloride), sour (0.05, 0.09, 0.165 or 0.3 g/mL citric acid) or bitter (0.0004, 0.0009, 0.0024 or 0.006 g/mL quinine hydrochloride) taste. After placing a paper on the tongue, patients are asked to identify the taste with five possible answers (sweet, sour, salty, bitter or tasteless). Taste strips were presented in

a semirandomised forced choice procedure. Total taste scores range from 0 to 16 since scores for each taste range from 0 to 4. High scores indicate a better taste function.

Explanation of questionnaires

- *SNOT-22:* this questionnaire consists of 22 questions about nasal symptoms and health-related quality of life. Patients need to score these symptoms on a 5-point Likert scale; higher scores implicate worse symptoms.[28] In patients with chronic rhinosinusitis, an improvement of 8.9 points after surgery is considered as a clinically significant difference.[33]
- *Self-reported smell, taste, parosmia and trigeminal sensations by means of VAS:* this questionnaire subjectively measures olfactory, gustatory and trigeminal function. Subjects will fill out a brief questionnaire on a 100-unit VAS, with questions pertaining to their current ability to smell, taste and perceive trigeminal sensations.[1] Recovery is considered as an improvement of at least 80% of their pre-illness function.
- *QoD:* to asses olfactory-specific quality of life, the translated QoD of the English validated version will be used. For the first 24 questions, answers are ranked by four options: agree, partly agree, disagree partly, disagree. Two questions require a yes or no answer and nine questions are answered using a 10-point Likert scale.[29 30]

Statistical analyses

All statistical analyses will be performed using IBM SPSS Statistics V.27.0 software and R statistical computing. A test for normality will be used to assess whether variables are normally distributed. We expect limiting missing data. Potentially missing data will be handled with multiple imputation, if the assumption for multiple imputation is met. Analyses will be performed on an intention-to-treat basis.

Primary study parameters: the primary study parameter is the difference on the TDI score post-treatment on the SST, between the two groups (prednisolone or placebo). A difference of 5.5 on TDI score is determined as a clinically relevant difference for the primary outcome.[34] Mean (or median) and SD (or the range) will be reported. Depending on the distribution of the outcome, we will use the unpaired t-tests or the Mann-Whitney U tests to determine the statistical differences between intervention and control group.

Secondary study parameters: objective gustatory function by means of TST, assessing recognition thresholds and identification for the four basic tastes scores range 0–16.[32] Clinical improvement is set at >2 points.[35] The TST score and the scores on the different questionnaires are measured at start and 12 weeks after start. Mean (or median) and SD (or range) will be reported. Depending on the distribution of the outcome, we will use the unpaired t-tests or the Mann-Whitney U tests to determine the statistical differences between intervention and control group.

ETHICS AND DISSEMINATION

The Institutional Review Board of the UMCU approved the research protocol (protocol number: 21-635/G-D, October 2021). This study will be conducted according to the principles of the Declaration of Helsinki (2013, Fortaleza) and in accordance with the Medical Research Involving Human Subjects Act, the European Union General Data Protection Regulation, and other guidelines, regulations and acts, for example, 'Code goed gebruik'. For this protocol, the Standard Protocol Items: Recommendations for Interventional Trials checklist is used. The Consolidated Standards of Reporting Trials will be used for the full RCT report.

All substantial amendments will be notified to the Medical Ethical Committee and to the competent authority. Data handling and protection is conducted according to the ISO standards (27001 and 9001), International Conference on Harmonisaton of Good Clinical Practice (ICH-GCP) and applicable regulations. Confidentiality will be maintained at all times and participant information will not be disclosed to third parties. Only investigators directly involved in this study will get access to all of the collected research data. Patients will receive a unique identifier, after which the members of the research team will extract all necessary clinical parameters into the eCRF Castor EDC and IBM SPSS Statistics V.27.0, which is secured by a password and located in a locked room. A local monitor (UMCU) will monitor trial quality. Adverse events (AEs) will be recorded in Castor EDC and serious AEs (SAEs) will be reported to the sponsor. The sponsor will report the SAEs through the portal *ToetsingOnline* to the accredited Medical Ethical Committee that approved the protocol.

Contributors EJAS—writer of the manuscript and executive investigator. DMAK—writer of the manuscript, head investigator, head of the Otorhinolaryngology Department and co-promoter of COCOS Study. IS—epidemiology check. SB—input testing set-up and testing materials. WMB—clinical set-up check. RJS—promoter of COCOS Study.

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Competing interests None declared.

Patient and public involvement Patients and/or the public were involved in the design, or conduct, or reporting, or dissemination plans of this research. Refer to the Methods section for further details.

Patient consent for publication Not required.

Provenance and peer review Not commissioned; externally peer reviewed.

ORCID iDs
Emma J A Schepens http://orcid.org/0000-0001-7753-0470
Inge Stegeman http://orcid.org/0000-0001-5154-7178

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