Salivary biomarkers for primary Sjögren's syndrome detection. A multi-center study. (Biomarker development study)

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The objectives of this research study are to perform a biomarker development study for salivary pSS biomarker confirmation and panel building. The findings will be analyzed against SS diagnosis based on ACR criteria: Aim 1To test individual...

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Autoimmune disorders
Study type	Observational invasive

Summary

ID

NL-OMON39480

Source
ToetsingOnline

Brief title
Salivary biomarkers for primary Sjögren's syndrome

Condition

- Autoimmune disorders

Synonym
Sjögren's syndrome

Research involving
Human

Sponsors and support

Primary sponsor: Universitair Medisch Centrum Groningen
Source(s) of monetary or material Support: National Institutes for Dental and Craniofacial Research (NIDCR);onderdeel vn de National Institutes of Health (NIH);USA

Intervention

Keyword: Biomarker, Proteomics, Saliva, Sjögren's syndrome

Outcome measures

Primary outcome

This research project will test the hypothesis that there are salivary constituents that are biomarkers that can differentiate SS from non-SS sicca subjects as defined by ACR. Specifically, a biomarker panel could be constructed that has specificity significantly higher than 25% for non-SS patients at a threshold corresponding to 95% sensitivity for SS patients. This panel will be built in Aim 1, to be then tested and refined in Aim 2. If confirmed, it will be fixed for a future independent biomarker validation study.

Secondary outcome

Not applicable

Study description

Background summary

Sjögren*s syndrome (SS) is a progressive, chronic autoimmune disease characterized by sicca symptoms of oral (xerostomia) and ocular dryness (keratoconjunctivitis sicca), which affects ~4 million Americans, mostly women at a ratio of 9:1 with men. Primary SS (pSS) occurs alone while secondary SS (sSS) presents in connection with other autoimmune diseases such as rheumatoid arthritis (RA) or systemic lupus erythematosus (SLE). Five to 10% of pSS patients develop B-cell lymphoma in their salivary glands, usually a mucosa associated lymphoid tissue (MALT) lymphoma.
Current diagnosis of pSS is clinically challenging, as it relies on assessment of criteria established by the 2002 American European Consensus Group (AECG) that contains six components. Sicca patients (those with subjective dry eyes and dry mouth) are evaluated using the six AECG criteria. All three clinical

centers for this study (UMN, OMRF and UMCG) adhere to the AECG criteria for pSS diagnosis. These include: I) establishing ocular symptoms; II) establishing oral symptoms; III) objective evaluation of ocular signs; IV) assessing the histopathology of salivary gland specimens for patterns consistent with Sjögren*s syndrome; V) objective evaluation of salivary gland involvement (such as decreased salivary flow rate); and, VI) determining the presence of anti-SSA and anti-SSB auto-antibodies in the serum. Based on the AECG criteria, pSS is defined as 1) the presence of 4 of the 6 criteria, as long as either histopathology of salivary gland specimen or serology for SSA and SSB auto-antibodies is positive; or 2) the presence of any 3 of the 4 objective criteria items (ocular signs, histopathology, salivary gland involvement, and serology). It should be noted that this clinical research project focuses on pSS and not secondary SS (sSS), as sSS patients are a less coherent cohort with a large component of related autoimmune disorders that will affect salivary biomarkers* behavior and profile.
In April of 2012, the American College of Rheumatology (ACR) gave provisional approval to a new set of classification criteria for SS proposed by the NIH-funded Sjögren*s International Collaborative Clinical Alliance (SICCA). Under the new ACR criteria, SS case definition requires at least two of the following three objective features: 1) positive serum anti-SSA or anti-SSB antibody test or (positive rheumatoid factor and antinuclear antibody titer >=1:320), 2) keratoconjunctivitis sicca (KCS) with ocular staining score >=3, 3) presence of focal lymphocytic sialadenitis with a focus score >=1 focus/4 mm2 in labial salivary gland biopsy samples. In their analyses, the SICCA expert panel noted that the observed agreement with the AECG criteria was high when all objective tests were available to define the AECG criteria. The SICCA analyses, partly due to the inclusion criteria of participants of the SICCA study, also found that subjective complaints lacked diagnostic specificity. Therefore, for study purposes, we will perform primary data analyses of biomarker association with SS diagnosis based on provisional ACR criteria. However, since another professional group, the European League Against Rheumatism (EULAR), is considering whether they either will endorse the new SICCA classification criteria or will ask for modification of these criteria, we will also analyze biomarker performance using the full AECG criteria set. It is possible that future criteria endorsed by both the ACR and EULAR could contain additional elements from the AECG criteria or that elements of the ACR criteria set will be omitted or be replaced by elements from the AECG criteria. Correct diagnosis and classification of SS patients continues to be a substantial problem, sometimes taking 10 years or more. Early and accurate diagnosis of SS is crucial as we look for ways to slow or halt the progressive nature and glandular destruction. The goal of this study is to perform a biomarker development study for salivary SS individual biomarker confirmation. Using the biomarker development findings, a panel will be built and evaluated against diagnosis based on ACR criteria. The final panel, if it achieves its performance criterion, will be fixed for an independent biomarker validation study. The overarching clinical goal of the study is to reduce the number of unnecessary diagnostic workups for non-SS sicca patients. Based on our

preliminary study, the salivary biomarkers selected will have 98% sensitivity and at least 50% specificity for SS detection. This will permit at least half of the non-SS sicca patients to avoid the diagnostic workups. Our collective clinical experience indicates that 30-50% of sicca patients will be diagnosed with pSS based on the AECG criteria. The evaluation of salivary markers for pSS detection in primary referral clinics, where clinical impact can be more significant, may reduce the number of diagnostic workups and aid in early detection of pSS.
The salivary biomarkers developed for SS detection in this research project will be clinically impactful in the following ways:
1) Preliminary studies suggest the combination of salivary biomarkers can achieve sensitivity of 98% and specificity of 50%, which could reduce unnecessary diagnostic workups in approximately 50% of the non-SS sicca patients. This will be clinically relevant considering over 60% of sicca patients will not have a SS diagnosis.
2) Clinicians who suspect that a patient has SS first will do a saliva test to see whether the patient*s biomarkers are consistent with SS. The intended use will be as a screening/risk assessment test for a symptomatic, undiagnosed population. If a marker is positive, the diagnostic evaluation for SS is justified to evaluate, assess and treat the patient. If a patient does not fulfill the diagnostic criteria for pSS, they may have components of the disease spectrum (e.g., keratoconjunctivitis sicca (KCS), xerostomia, or extraglandular manifestations or hyposalivation) that need treatment. When a patient is considered for diagnostic work up and a physician/dentist is familiar with the pattern of complaints related to SS, he or she can decide to restrict the diagnostic workup to the saliva test when the patient's history is not very characteristic for SS. This will reduce the number of diagnostic work ups for SS, as the work-up will occur only if there is a strong suspicion that the patient has SS.
3) Assessing the current 6 criteria for AECG diagnosis for pSS as well as the 3 criteria for ACR diagnosis is invasive, time consuming and costly. It often requires months to receive serology and salivary gland biopsy (histopathology) results. The total evaluation time is up to 12 weeks. A salivary pSS test could be completed at a fraction of the time and costs.

Study objective

The objectives of this research study are to perform a biomarker development study for salivary pSS biomarker confirmation and panel building. The findings will be analyzed against SS diagnosis based on ACR criteria:

Aim 1
To test individual biomarker association (OR) with SS diagnosis based on ACR criteria and test an initial panel sensitivity and specificity for diagnosis of SS at the time of interim analysis using paraffin stimulated whole saliva specimens collected from the first 210 recruited subjects.

Aim 2
To confirm the sensitivity and specificity of the panel built from Aim 1, refining the panel and evaluating its sensitivity and specificity on specimens from all 420 subjects.

Study design

From 420 patients complaining of a dry mouth and dry eyes that are referred to one of the three Sjögren's referral centers participating in this study for a diagnostic work-up of Sjögren's syndrome, a whole saliva sample will be collected at the first visit to one of these centers for their oral work-up. These samples will be send to UCLA and analysed according to the UCLA protocol (salivary biomarker test) to rate these samples as matching for Sjögren's syndrome or not.. Separately from this analysis at UCLA, the diagnostic work-up for Sjögren's syndrome will be completed (subjective dry mouth, subjective dry eyes, saliva collection, eye analysis, salivary gland biopsy, serology) to jude whether these patients fulfill the ACR criteria for Sjögren's syndrome. Finally, the UCLA data will be matched with the outcome of the diagnostic work-up for Sjögren's syndrome at the three centers. On basis of this analysis it will be decided whether the newly developed diagnostic salivary biomarker test match the results of the ACR diagnostic work-up in order to judge whethr the salivary biomarker test has a sufficient high sensitivity and specificity to replace (some of) the ACR diagnostic work-up tests. As as part of this study also a full diagnostic work -up according to the AECG criteria will be done, the various analyses will also be done for this criteria set.

Study burden and risks

Saliva is without any burden and risk for the patient. However, as for the ACR criteria yet a labial biopsy is required for diagnosing SS and is has been reported in the literature that there is a slight risk that havesting labial salivary glands can result in some numbness of the biopsy area in the lip, there is an inherent risk of inducing some numbness of the lip in a minority of the patients. It has to be noted that taking a labial biopsy is routine care in all Sjögren's centers worldwide taking the slight risk of inducing numbness of an area of the lip into account. This risk is existent, although very small, when a proper technique is used.

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)
Elderly (65 years and older)

Inclusion criteria

• Subjects greater than or equal to age 18 years of age.
• Subjects must have sicca symptoms, i.e. subjective dry mouth (xerostomia) and dry eyes (keratoconjunctivitis sicca, xeropthalmia) to be enrolled.
• Subjects willing to fill out questionnaire (approximately 10 min).
• Subjects should be willing to donate saliva.
• Subjects should be willing to have a labial biopsy in addition to a parotid biopsy.
• Subjects should be willing and able to give approximately 8 ml of blood.
(for details see pages 15-16 of the protocol)

Exclusion criteria

• Previous radiation to the head and neck (with exception of radioactive iodine for thyoid ablation therapy).
• Confirmed hepatitis C virus infection, which may cause SS-like signs and symptoms.
• Known HIV infection, which can cause salivary gland infiltrates and enlargements similar to SS.
• Sarcoidosis, which may cause SS-like signs and symptoms.
• Graft-versus-host disease, which may cause SS-like signs and symptoms.

• Oral cancer or history of oral cancer.
• Pregnancy based on self-report.
• Previously diagnosed with pSS or sSS using AECG criteria or SS using ACR criteria.
• Previously confirmed diagnosis of autoimmune disease known to be associated with Secondary Sjögren*s syndrome (sSS) (rheumatoid arthritis (RA), systemic lupus erythematosus (SLE)), CREST (Calcinosis, Raynaud's syndrome, Esophageal dysmotility, Sclerodactyly, Telangiectasia), Scleroderma, Mixed connective tissue disease, Polymyositis.

Study design

Design

Study type: Observational invasive

Masking:	Open (masking not used)
Control:	Uncontrolled
Primary purpose:	Diagnostic

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	13-12-2013
Enrollment:	120
Type:	Actual

Ethics review

Approved WMO Date:	12-06-2013
Application type:	First submission
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	18-10-2013
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)

Study registrations

Followed up by the following (possibly more current) registration

No registrations found.

Other (possibly less up-to-date) registrations in this register

No registrations found.

In other registers

Register	ID
ClinicalTrials.gov	NCT01807689
CCMO	NL38920.042.13