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Oral challenge test with gluten versus placebo to identify patients with nonceliac gluten sensitivity (NCGS)

Submission date	Recruitment status	[_] Prospectively registered
28/06/2014	No longer recruiting	[_] Protocol
Registration date	**Overall study status**	[_] Statistical analysis plan
31/07/2014	Completed	[X] Results
Last Edited	**Condition category**	[_] Individual participant data
24/02/2015	Digestive System	

Plain English summary of protocol

Background and study aims
Non-celiac gluten sensitivity (NCGS) is a condition with symptoms similar to that of celiac disease. These include depression, abdominal pain, bloating, diarrhoea, constipation, fatigue, joint pain and a foggy mind. However, despite the number of symptoms common to both conditions, people with NCGS do not test positive for celiac disease or a wheat allergy. Indeed, there is a debate on whether the disease exists at all. The aim of this study is to test the effect of low amounts (doses) of gluten in patients suspected of having NCGS.

Who can participate?
Adult patients with persistent NCGS symptoms and having eaten a diet containing gluten for at least the last two months.

What does the study involve?
Participants are randomly assigned to one of two groups. Those in group 1 are given a pill containing 4.375 grams of gluten for a week. Those in group 2 are given a dummy (placebo) pill made out of rice starch. Then, after a one week wash-out period (where no treatment is given to either group), the groups cross over with Group 1 taking the placebo and group 2 taking the gluten containing pill for a week. The effects of taking the gluten compared with the placebo are then analysed.

What are the possible benefits and risks of participating?
There are no risks associated with taking part in the trial as participants are not taking drugs but common components of a normal diet. Benefits associated with taking part in our trial might be the diagnosis of true NCGS.

Where is the study run from?
St. Matteo Hospital (Italy)

When is the study starting and how long is it expected to run for?
October 2012 to January 2014

Who is funding the study?
St. Matteo Hospital (Italy)

Who is the main contact?
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Contact information

Type(s)
Scientific

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Additional identifiers

Protocol serial number
20120011203

Study information

Scientific Title
Effect of low gluten doses in patients suspected of having nonceliac gluten sensitivity (NCGS): a randomized, double-blind, placebo-controlled cross-over gluten challenge trial

Acronym
NCGS

Study objectives
We hypothesized that even low gluten doses could worsen overall (intestinal and extraintestinal) symptoms in patients strongly suspected of having NCGS

Ethics approval required
Old ethics approval format

Ethics approval(s)
Ethics Committee of the St. Matteo Hospital Foundation - Pavia (Italy), 19/10/2012, ref. 4468 /2012

Primary study design

Interventional

Study design
Randomized double-blind placebo-controlled cross-over trial

Study type(s)
Diagnostic

Health condition(s) or problem(s) studied
Nonceliac gluten sensivity

Interventions
Patients will be asked to fill in a daily questionnaire in order to assess a rating scale of both intestinal and extraintestinal symptoms over a 5-week period. Participants will be asked to follow a strict gluten-free diet (GFD) starting one week before the randomization and continuing until the end of the study period. After the first week of GFD, patients will be given either gastrosoluble capsules containing purified wheat gluten (10 capsules ingested in no more than two times over the day, corresponding to a daily gluten intake of 4.375 grams, equivalent to about 2 slices of white bread) or gastrosoluble capsules containing rice starch (10 capsules ingested in no more than two times over the day, corresponding to a daily rice starch intake of 4.375 grams) as placebo for one week. At the end of the first treatment week, patients from both arms will continue only their wash-out from gluten, without taking a capsule. Subsequently, individuals belonging to the first arm will be given placebo capsules, while individuals belonging to the second arm will be given gluten capsules. After the second treatment week, all patients will continue with their wash-out from dietary gluten. During the trial, patients will undergo five outpatient weekly appointments, during which patients will provide their filled questionnaires and investigators will count any unused capsules remaining in capsule dispensers.

Intervention Type
Other

Phase
Not Applicable

Primary outcome(s)
The primary outcome is the change in the weekly overall symptom score, as assessed by the sum of intestinal and extraintestinal scores, between the 1-week treatment with gluten and the 1-week treatment with placebo. The 15 intestinal symptoms, which patients will be asked to grade daily from 0 to 3 (0=absent; 1=mild; 2=relevant, 3=severe and interfering with daily activities) are:
1. Abdominal pain
2. Abdominal bloating
3. Wind
4. Diarrhea
5. Borborygmus
6. Reduced consistency of stools
7. Increased consistency of stools
8. Constipation
9. Urgency
10. Incomplete evacuation
11. Nausea
12. Heartburn

13. Belching
14. Acid regurgitation
15. Epigastric pain.
The 13 extraintestinal symptoms, which patients will be asked to grade daily from 0 (absent) to 1 (present), are:
1. Tiredness
2. Malaise
3. Headache
4. Depression
5. Anxiety
6. Foggy mind
7. Aphthous stomatitis
8. Paresthesia
9. Arthralgia
10. Myalgia
11. Asthma
12. Rhinitis
13. Skin rash

Key secondary outcome(s)
Secondary outcomes are:
1. The change in individual symptom scores between the 1-week treatment with gluten and the 1-week treatment with placebo
2. The identification of patients with true NCGS
3. To verify whether laboratory parameters at baseline are predictive of true NCGS.
True NCGS patients are defined as having at the end of the trial a delta overall score - calculated by subtracting the weekly overall score under placebo from the weekly overall score under gluten- higher than the mean delta overall score plus two standard deviations. Laboratory predictors include serum IgG AGA, fecal calprotectin, HLA genotyping and intraepithelial lymphocyte density.

Completion date
31/01/2014

Eligibility

Key inclusion criteria
1. Adult patients referred to our outpatients' clinics because of persistence of relevant intestinal and extraintestinal symptoms believed by them to be caused by the ingestion of food containing even low doses of gluten.
2. Under gluten-containing diet at the time of screening since at least two months
3. Happy to undergo ad hoc screening, including:
3.a. Serum determination of IgA anti-transglutaminase and anti-endomysial antibodies
3.b. IgG anti-gliadin antibodies (AGA)
3.c. Total IgA and IgE
3.d. Wheat-specific IgE
3.e. Upper endoscopy with collection of multiple duodenal biopsies
3.f. HLA genotyping
3.g. Fecal calprotectin
3.h. Lactose breath test

Participant type(s)
Patient

Healthy volunteers allowed
No

Age group
Adult

Sex
All

Key exclusion criteria
1. Other significant gastrointestinal diseases, such as inflammatory bowel disease or cirrhosis,
2. Other clinically significant comorbidities such as diabetes, use of nonsteroidal anti-inflammatory agents or systemic immunomodulators
3. Pregnancy
4. Inability to give written informed consent
5. Reported psychiatric disorder
6. Excessive alcohol intake
Only patients, who at the end of the screening are found not to be affected by celiac disease, wheat allergy, lactose or FODMAP intolerance, Helicobacter pylori infection, giardiasis, and who complain of relevant gluten-dependent symptoms that is affecting the overall quality of life, will be randomized according to a computer-generated list of random numbers held by an independent observer to either the gluten or the placebo treatment group.

Date of first enrolment
20/10/2012

Date of final enrolment
31/01/2014

Locations

Countries of recruitment
Italy

Study participating centre
St Matteo Hospital Foundation
Pavia
Italy
27100

Sponsor information

Organisation
St. Matteo Hospital Foundation (Italy)

ROR
https://ror.org/05w1q1c88

Funder(s)

Funder type
Hospital/treatment centre

Funder Name
St Matteo Hospital Foundation, Pavia (Italy)

Results and Publications

Individual participant data (IPD) sharing plan

IPD sharing plan summary
Not provided at time of registration

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
Results article	results	01/09/2015		Yes	No