Efficacy and tolerability of Citrus/Cydonia comp.® 1% solution for injection in patients with grass pollen seasonal allergic rhinitis: A randomised, double-blind, placebo-controlled clinical trial

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1. Clinically relevant reduction of symptom severity by use of Citrus/Cydonia comp. subcutaneous injections2. To examine the safety of treatment3. To examine treatment effects on immunological parameters4. To develop and validate an immunological...

Ethical review	Approved WMO
Status	Pending
Health condition type	Other condition
Study type	Interventional

Summary

ID

NL-OMON34862

Source
ToetsingOnline

Brief title
The CiSAR Study

Condition

- Other condition
- Allergic conditions

Synonym
grass pollen allergy, hay fever

Health condition

aandoeningen op keel, neus en oor gebied

Research involving
Human

Sponsors and support

Primary sponsor: Weleda AG
Source(s) of monetary or material Support: Weleda AG

Intervention

Keyword: grass pollen allergy, herbal medicinal product, immuno therapy, placebo controlled clinical trial

Outcome measures

Primary outcome

Days with symptom control defined by:

a)A Total Symptom Score of <= 8 (while exposed to a mean pollen count of 20-50)

or <= 12 (while exposed to a mean pollen count of > 50)

and

b)No use of rescue medication

in the verum group compared to the placebo group in the last two weeks of

treatment

Secondary outcome

1.Total use of rescue medication throughout the whole treatment period.

2.Relevant changes in the following seasonal AR-related immunological

parameters: IL-10, IL-12, IL-1ß, TNFα, IFN-γ, IL-5, IL-13 and IL17A.

3.Number of drop outs between verum and placebo group.

4.Safety: Adverse events and laboratory findings.

5.Development of the immune regulation model that is able to distinguish optimally between (severity of) SAR and non-SAR and predict immunological and clinical outcomes.

Study description

Background summary

Considering the high prevalence of allergic rhinitis and the fact that a significant number of sufferers with severe symptoms are resistant to treatment with usual pharmacotherapy (antihistamines and topical nasal corticosteroids) (Wilson et al., 2005), there still is a space and need for the development of new treatment concepts.
Citrus/Cydonia comp. is an anthroposophic medicine, which contains lemon juice (Citrus limon, succus) and a aqueous extract from quince (Cydonia oblonga, fructus rec., 1:2.1). For over eighty years now, Citrus/Cydonia comp. is being prescribed as a subcutaneous injection or as a nasal spray for patients who suffer from seasonal allergic rhinitis. In several European countries, Citrus/Cydonia comp. is commercially available under the trade name *Gencydo®* for the prophylaxis and treatment of allergic diseases, specifically those affecting the respiratory tract such as hay fever.
A survey on clinical experiences, carried out among a group of 39 general practitioners in the Netherlands, indicates that the subcutaneous treatment with Citrus/Cydonia comp. ampoules is profoundly effective (Bruin et al., 2001). Firstly, a permanent effect from the treatment with Citrus/Cydonia comp. tends to be experienced, which indicates that the patients in question are claiming to lastingly suffer less from hay fever or even that they are free from complaints. Secondly, the effect is occurring within a period of two weeks, up to three months, after the actual treatment. Thirdly, the effect is optimal after a treatment of several years. In a therapeutic causality report, positive effects with Citrus/Cydonia comp. were observed in a group of 13 patients suffering from grass pollen mediated hay fever (Baars et al., 2005). In most patients, Citrus/Cydonia comp. injections were given before the onset of and during the grass pollen season and symptom severity did not increase during the pollen season. Furthermore, 69% of the patients reported an improvement of symptoms. In addition, a prospective, observational study on the effect of Citrus/Cydonia comp. nasal spray on hay fever symptoms reported positive results without side effects in 140 patients (Rother and Oexle, 2008).

Recently, the immunological pathways underlying the positive effects of Citrus/Cydonia comp. in patients with seasonal allergic rhinitis were studied (Baars and Savelkoul, 2008). Therefore, peripheral blood mononuclear cells (PMBCs) were isolated from a healthy and an allergic donor and the effect of Citrus/Cydonia comp. on differentiation capacity and Th1 (e.g. IFN-*) and Th2 (e.g. IL-5) cells was examined. Citrus/Cydonia comp. showed a selective effect on the differentiation of T-cells by producing relatively more IL-10 than IL-12. Furthermore, it also had an effect on the induction of regulatory (IL-10 producing) T-cell subsets. It was therefore concluded that Citrus/Cydonia comp. can potentially restore the disturbed immune state of allergic rhinitis patients by modulation of the Th1-Th2 balance. This immunotherapeutic potency and the positive results from the observed clinical cases, form the rational to further evaluate the effects of Citrus/Cydonia comp. in seasonal allergic rhinitis.
Recently it was demonstrated in a comparative study of two different routes of administration of Citrus/Cydonia comp. 1%, that subcutaneous injections resulted in larger clinical effects on nasal and non-nasal allergic rhinitis symptom severity in patients suffering seasonal allergic rhinitis compared to the nasal administration. The subcutaneous route was also more effective in the differentiation and induction of (regulatory) T-cells and the balancing of the Th1 and Th2 pathways (Baars et al., 2009).

Based on the considerations laid down above, Citrus/Cydonia comp. may be an effective and safe treatment for seasonal allergic rhinitis. Due to its selective effect on immunological pathways, Citrus/Cydonia comp. might restore the disturbed immune state of rhinitis patients by modulation of the Th1-Th2 balance.

Study objective

1. Clinically relevant reduction of symptom severity by use of Citrus/Cydonia comp. subcutaneous injections

2. To examine the safety of treatment

3. To examine treatment effects on immunological parameters

4. To develop and validate an immunological model

Study design

Randomised, double-blind, placebo-controlled comparative clinical trial with two parallel treatment groups and one epidemiological comparison group of healthy volunteers

Intervention

After a 2-week run in period the patients will be randomised to a 6 weeks treatment period.

Either:
6 weeks of subcutaneous injection of Citrus/Cydonia comp.® 1% solution twice a week
or:
6 weeks of subcutaneous injection of 0.9% saline solution (placebo) twice a week

Study burden and risks

Patients:
In the 2 weeks before onset of the study, participants cannot use regular hay fever medication which will result in an increase of hay fever symptoms. (For treatment with cromoglycates it is a period of 4 weeks). They can use rescue medication (antihistaminicum) according protocol guidelines during the 8 weeks of the study.

All participating patients will receive 2 times a week a subcutaneous injection during 6 weeks
There are no known side effects of the subcutaneous administration of Citrus/ Cydonia comp. or placebo injection other than local and small pain symptoms that last for only a short amount of time.

All participating patients will complete an online qeustionnaire once a day (2 minutes) during 8 weeks
Next to this there is an intake visit, where medical history is discussed and a short physical examination is (bloodpressure, heart/ lungs/ ENT) is accomplished. If not available a bloodsample (RAST) will be taken (total visit: about 1 hour), during 2 following visits bloodsample are taken and there will be one telephone call by the investigator.
The risks are the common small risks of venous blood samples.

All participating healthy subjects have an intake visit, where medical history is discussed and a short physical examination is (bloodpressure, heart/ lungs/ ENT) is accomplished. If not available a bloodsample (RAST) will be taken (total visit: about 1 hour), during 2 following visits a bloodsample is taken.
The risks are the common small risks of venous blood samples.

Contacts

Public
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Trial sites

Listed location countries

Netherlands

Eligibility criteria

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

Inclusion criteria

Patients:
•Written informed consent
•Age >= 18 and < 60 years.
•Seasonal AR:
-Duration of respective complaints at least 2 years
-RAST for grass pollen: >= 2
-Suffering from the following nasal symptoms:
sneezing, itching nose, nasal obstruction and watery nasal discharge
-Severity score of at least two of the four nasal symptoms >= 2; ranging from 0 = not present to 3 = severe.
-Suffering from the following non-nasal symptoms: itchy/burning eyes, watery eyes, redness of eyes and itching ears/throat
-Severity score of at least two of the four non-nasal symptoms >= 2; ranging from 0 = not present to 3 = severe
- The necessity to use antihistamines and/or corticosteroids for treatment of symptoms for at least two previous years
- Average Total Symptom Score in the wash-out period >= 9 on days with a pollen count > 20 or use of rescue medication on days with a pollen count > 20;Healthy volunteers:

•Written informed consent
•Age >= 18 and < 60 years
•RAST for seasonal AR related grass and birch pollen = 0
•No history of seasonal AR symptoms for at least 2 years

Exclusion criteria

Patients:
•Chronic autoimmune disease such as Diabetes Mellitus type 1, Rheumatoid Arthritis, Multiple Sclerosis, Psoriasis or Crohn*s disease
•Known hypersensitivity to one of the constituents of Citrus/Cydonia comp.®
•Participation in a further clinical trial at the same time or within 4 weeks prior to enrolment into this study
•Previous use of medicinal products containing Citrus and/or Cydonia
•Pregnancy or lactation
•Severe internal or systemic disease (e.g. cardiac, hepatic, renal diseases)
•A known history of drug, alcohol and/or medication dependence or addiction
•Immunotherapy in the last two years
•Other allergies (non seasonal allergies);Healthy volunteers:
•Nasal seasonal AR related symptoms during the pollen season: sneezing, itching nose, nasal obstruction and watery nasal discharge
•Chronic inflammatory autoimmune disease such as Diabetes Mellitus type 1, Rheumatoid Arthritis, Multiple Sclerosis, Psoriasis or Crohn*s disease
•Participation in a further clinical trial at the same time or within 4 weeks prior to enrolment into this study.
•Pregnancy or lactation
•Severe internal or systemic disease (e.g. cardiac, hepatic, renal diseases)
•A known history of drug, alcohol and/or medication dependence or addiction
•Immunotherapy in the last two years
•Other allergies (no seasonal AR)

Study design

Design

Study phase:	3
Study type:	Interventional
Intervention model:	Parallel
Allocation:	Randomized controlled trial
Masking:	Double blinded (masking used)

Control:	Placebo
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Pending
Start date (anticipated):	01-02-2013
Enrollment:	120
Type:	Anticipated

Medical products/devices used

Product type:	Medicine
Brand name:	Citrus/ Cydonia comp.
Generic name:	Citrus/ Cydonia comp.

Ethics review

Approved WMO Date:	19-02-2010
Application type:	First submission
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	04-11-2010
Application type:	First submission
Review commission:	METC Brabant (Tilburg)

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
EudraCT	EUCTR2009-018112-26-NL
CCMO	NL31097.040.10