A randomized, double-blind, placebo-controlled, study to determine the added value of vitamin D3 to treatment with subcutaneous immunotherapy (SCIT) in patients with moderate to severe allergic rhinitis/ rhinoconjunctivitis caused by birch pollen

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The aim of this clinical phase IIa randomized, double-blind, placebo-controlled study is to investigate tolerability/ safety and clinical and immunological effects of the addition of a subcuteaneous injection of a VD3 analogue in the vicinity of the...

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Upper respiratory tract disorders (excl infections)
Study type	Interventional

Summary

ID

NL-OMON46004

Source
ToetsingOnline

Brief title
Added value of Vitamin D3 to SCIT

Condition

- Upper respiratory tract disorders (excl infections)

Synonym
allergic rhinitis, hayfever

Research involving
Human

Sponsors and support

Primary sponsor: Academisch Medisch Centrum
Source(s) of monetary or material Support: European Commission 7th framework Programme for Research technology development and Demonstration

Intervention

Keyword: Allergic rhinitis, Birch Pollen, Immunotherapy, Vitamin D3

Outcome measures

Primary outcome

The primary objective is the assessment of serological and cellular immunological changes and kinetics thereof induced by SCIT with VD3 compared to SCIT alone in patients with moderate to severe allergic rhinitis/rhino-conjunctivitis caused by birch pollen in a pre-seasonal short-term course of SCIT.

Amongst the immunological outcomes, IL-10 production by PBMCs in response to allergen-specific stimulation after 5 weeks of treatment with VD3 analogue Zemplar® compared to placebo was chosen as primary end-point (visit 7). The rationale behind this is that 1) IL-10 is the key cytokine in the mechanism of SCIT [22, 23] and 2) the hypothesis is that IL-10 induction is more rapid in the presence of VD3 than without, hence visible already after 5 weeks of treatment. At 11 weeks the postulated difference may already not be as significant anymore.

Secondary outcome

* The IL-10 production by PBMCs in response to allergen-specific stimulation

after 11 weeks of treatment with VD3 analogue Zemplar® compared to placebo (visit 10).

* The IL-10 production by PBMCs in response to polyclonal stimulation after 5 and 11 weeks of treatment with VD3 analogue Zemplar® compared to placebo.

* Determination of the difference between cellular composition of PBMC with respect to Th1, Th2, Th17, Th22, and Treg cells, B cells, and antigen-presenting cells (APC) induced by SCIT with VD3 compared to SCIT alone in patients with moderate to severe allergic rhinitis/rhino-conjunctivitis caused by birch pollen after 6 and 12 weeks of treatment (visit 7 and 10).

* Determination of the difference between PBMC proliferation and cytokine production in response to allergen (Bet v 1) induced by SCIT with VD3 compared to SCIT alone in patients with moderate to severe allergic rhinitis/rhino-conjunctivitis caused by birch pollen after 6 and 12 weeks of treatment (visit 7 and 10).

* Determination of the difference between PBMC proliferation and cytokine production in response to polyclonal stimuli (*CD3/*CD28) induced by SCIT with VD3 compared to SCIT alone in patients with moderate to severe allergic rhinitis/rhino-conjunctivitis caused by birch pollen after 6 and 12 weeks of treatment (visit 7 and 10).

* Determination of the difference between intracellular cytokine measurements in response to PMA/ionomycin induced by SCIT with VD3 compared to SCIT alone in patients with moderate to severe allergic rhinitis/rhino-conjunctivitis caused by birch pollen after 6 and 12 weeks of treatment (visit 7 and 10).

* Determination of the changes in IgE, IgG and IgG4 antibody responses in serum

to birch pollen and Bet v 1 induced by SCIT with VD3 compared to SCIT alone in patients with moderate to severe allergic rhinitis/rhino-conjunctivitis caused by birch pollen after 6 and 12 weeks of treatment (visit 7 and 10).

* Determination of changes in a so-called IgE facilitated allergen-binding assay (FAB) and in a rat basophilic leukemia cell (RBL)-based histamine release test after 5 and 11 weeks of treatment, to monitor the functional blocking antibody capacity of induced IgG/IgG4 antibodies.

* Evaluation of changes in a titrated skin prick test (SPT) with birch pollen extract after 5 and 11 weeks of treatment, as a surrogate clinical marker of efficacy.

* Monitoring of epigenetic changes after 6 and 12 weeks of treatment (visit 7 and 10).

* The identification of predictive and efficacy-associated biomarkers by transcriptomics on nasal brushing taken at after 6 and 12 weeks of treatment (visit 7 and 10).

* Determination of a difference in clinical efficacy of SCIT with VD3 compared to SCIT alone, as analysed for the upper airways by titrated nasal provocation test (TNPT), including an objective read-out i.e. peak nasal inspiratory flow (PNIF), after 6 and 12 weeks of treatment (visit 7 and 10).

* Determination of a difference in clinical efficacy of SCIT with VD3 compared to SCIT alone, assessed by monitoring symptoms and medication in the birch pollen season with the combined symptom medication score (CSMS) of EAACI and the use of an electronic diary (e-diary). In a subset of patients with allergic

asthma, asthma control will be evaluated during birch pollen season.

Study description

Background summary

For decades, allergen immunotherapy (AIT) is being used as a causal therapeutic option in the treatment of IgE-mediated allergic diseases such as allergic rhinitis (AR), allergic rhinoconjunctivitis (ARC) or allergic asthma (AA). Efficacy of this therapeutic principle is well documented for allergen extract-based products, but the required duration of the treatment of at least three years of monthly injections and the (controlled) risk of severe side-effects are experienced to be significant drawbacks. There is a need for a treatment with a lower risk of side-effects and a more rapid onset of longlasting efficacy, i.e. less injections. Vitamin D3 (VD3) is a promising adjuvant to more rapidly skew the allergic immune response towards a protective anti-inflammatory immune status.

Study objective

The aim of this clinical phase IIa randomized, double-blind, placebo-controlled study is to investigate tolerability/ safety and clinical and immunological effects of the addition of a subcuteaneous injection of a VD3 analogue in the vicinity of the SCIT administration site in birch pollen allergic patients with moderate-severe allergic rhinitis.
A total of 40 birch pollen allergic patients with allergic rhinitis (AR)/allergic rhinoconjunctivitis (ARC) with/without concomitant controlled allergic asthma (AA) will be included. The treatment will be performed as a pre-seasonal course of 12 weeks with a total of 13 injections with Alutard and 9 injections with VD3/Placebo.

Study design

This trial is planned as a randomized, double-blind, placebo-controlled Phase IIa study.

Intervention

A total of 40 patients will be randomized to 2 treatment groups in a 1:1 manner as follows: 20 patients receiving SCIT/VD3, 20 patients receiving SCIT/placebo (=placebo matching VD3).

Study burden and risks

Venapunction 4 times 57 ml
Subcutaneous injection 22 times 0.5-1 ml
Nasal provocation 3 times
Nasal brush 3 times
Titrated skin prick test 3 times

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

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

Inclusion criteria

1. Signed informed consent
2. Age *18 * 65 years
3. Moderate to severe birch-pollen-induced AR/ARC of at least 2 years according to the Allergic Rhinitis and its Impact on Asthma (ARIA) guidelines (Appendix 1, see manual) with or without concomitant mild to moderate persistent asthma

4. FEV1>70% for patients with a history of asthma, FEV1>70% or PEF>80% for patients without a history of asthma
5. A positive SPT (mean wheal diameter * 3mm compared to negative control and negative control should be negative) for birch pollen assessed within 1 year before randomization
6. A positive ImmunoCAP (>0.7 kU/L) for birch pollen

Exclusion criteria

1. Clinically relevant co-sensitization (others than hazel, alder and elm) expected during the birch-pollen season.
2. Chronic asthma with an FEV1<70 % of predicted value.
3. History of AIT (SCIT or SLIT) with any allergen within the past 5 years
4. Ongoing AIT (SCIT or SLIT) with any allergen(s) during the study period
5. Current Treatment with VD3 analogue.
6. Vaccination within one week before or during the treatment phase.
7. Immunosuppressive or biological medication (e.g. IL-5, anti-IgE therapy) within the last six months prior to inclusion and up to end of trial (EoT).
8. Severe immune disorders (including auto-immune diseases) and/or diseases requiring immunosuppressive drugs.
9. Uncontrolled asthma or other active respiratory diseases.
For the rest of the exclusion criteria see protocol

Study design

Design

Study phase:	2
Study type:	Interventional
Intervention model:	Parallel
Allocation:	Randomized controlled trial
Masking:	Double blinded (masking used)
Control:	Placebo
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	11-09-2018

Enrollment:	40
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Zemplar
Generic name:	paricalcitol
Registration:	Yes - NL outside intended use

Ethics review

Approved WMO Date:	07-06-2018
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	05-07-2018
Application type:	First submission
Review commission:	METC Amsterdam UMC

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	EUCTR2018-001339-33-NL

Register	ID
CCMO	NL65758.018.18