Screening potential allergy vaccine components.

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Allergen immunotherapy (AIT) is currently performed with aluminum hydroxide-adsorbed allergen extracts. This approach is effective, but requires a long burdensome treatment protocol with a relatively high frequency of allergic side-effects...

Ethical review	Approved WMO
Status	Recruitment started
Health condition type	Allergic conditions
Study type	Observational invasive

Summary

ID

NL-OMON54501

Source
ToetsingOnline

Brief title
Screening potential allergy vaccine components

Condition

- Allergic conditions

Synonym
Allergy, Hypersensitivity

Research involving
Human

Sponsors and support

Primary sponsor: Amsterdam UMC
Source(s) of monetary or material Support: Health Holland,Angany Inc: Canadian biotech company located in lévis, Quebec.

Intervention

- Other intervention

Keyword: Allergen immunotherapy, Allergy, Nanoparticles

Explanation

N.a.

Outcome measures

Primary outcome

Not applicable. Blood from patients will be used to isolate immune cells (PBMCs) and use them in fundamental in vitro experiments. The only value that will be determined directly from blood is the allergen-specific IgE titer to determine how severe the allergy from thet allergic patient is.

Secondary outcome

Not applicable.

Study description

Background summary

AIT is the only causal treatment for allergy that targets the immunological basis of the disease. All other treatments are symptomatic treatments, either typical pharma treatments such as antihistamines or corticosteroids or biologicals such as anti-IgE. Upon cessation of administration of such symptom medication, symptoms return rapidly. AIT is the only treatment with documented sustained reduction of symptoms after stopping the treatment. However, to achieve this state of prolonged tolerance, a very long treatment protocol of 3 to 5 years is required. For subcutaneous AIT this means that patients have to visit an outpatient clinic for their monthly injection for years. This burden is one of the reasons that the majority of patients resort to symptom medication. In addition, current AIT frequently gives allergic side-effects because allergen is administered essentially in its native (symptom-triggering) conformation. To increase acceptance of AIT it is clear that significant reduction of the burden of treatment duration and frequency and of side-effects would be a major step forward.Immunologically, successful AIT transforms an allergen-specific IgE/Th2-dominated inflammatory immune response into an allergen-specific anti-inflammatory response dominated by regulatory T-cells, regulatory B-cells and IgG4 antibodies. During current AIT protocols, allergen extracts, usually adsorbed to aluminum hydroxide, are subcutaneously administered. To induce the desired persistent anti-inflammatory response dominated by

IgG4, this treatment is given for 3 to 5 years. Besides the duration of the treatment, chronic exposure to aluminum hydroxide is increasinglyconsidered as undesirable. In recent years it has become clear that AIT is likely to be more effective at younger age when the immune system may still be more receptive to immune modulation. In addition, it has been shown that AIT in young patients with allergic rhinitis prevents the development of allergic asthma. Although there is not really convincing evidence that chronic exposure to aluminum hydroxide is detrimental, there is a demand for alternatives, in particular when AIT will increasingly be used at younger age.

In summary, there is a need to develop alternatives for current generation AIT products that 1) require less injections to achieve an effective reduction of symptoms and 2) are not dependent on addition of aluminum hydroxide. There are essentially four potential building blocks for the design of an improved AIT vaccine:

- **The allergen**, either as a complete extract or as purified major allergens. The allergen can be modified to a) decrease allergenicity (hypo-allergenicity: less side-effects) and b) target it more effectively to (receptors on) antigen presenting cells.
- **Adjuvants**, to more effectively induce allergen-specific anti-inflammatory immune responses, both with respect to kinetics (quicker) and persistence (memory that can be triggered ideally by natural exposure or by occasional booster injections) than is currently achieved with aluminum hydroxide.
- **A vehicle** for formulation and administration of allergen, to replace aluminum hydroxide as a depot for allergen that helps shielding off IgE-binding sites.
- **Antibody approaches** to more effectively target the allergen to the appropriate antigen-presenting cells in the skin such as dendritic cells (DCs) and Langerhans cells (LCs).

In the frame of three projects at Amsterdam UMC, we are exploring possibilities to improve AIT for both respiratory and food allergy. The three projects largely overlap with respect to timelines. We have combined these three projects in a single protocol because experiments to be carried out with moDCs generated from voluntary blood donations will be used in identical experiments. In fact, candidate vaccine components from the three different projects can and will be compared in single experiments to establish which (combination of) approaches is most promising to improve AIT. The three projects are:

1. **Dendritic cell targeting for resetting immune balance (DC4BALANCE).**
   This is a 4 years* project with a start date on January 1, 2019, ending December 31, 2022. Due to Covid-19 restrictions in 2020/21, the end date may move up to one year to December 31 2023. Pilot experiments have been carried out with blood donations from subjects with unknown demographic and clinical background (buffy coats from Sanquin / volunteers through BACON). Since it is known that DCs from allergic and from non-allergic donors possess different immune-skewing properties, it is difficult to draw firm conclusions from the experiments. There is a need to perform these experiments with blood from donors with known clinical background. The project is funded by Health Holland under the TKI-PPP and focuses on several diseases, one being house dust mite

allergy.

2. **Sialylation van allergens - mode of action for improved immunotherapy using novel immune tolerizing pathways (SIALLERGEN)**.
   This is a 4 years* project starting November 1, 2019, ending by December 31, 2023. Due to Covid-19 restrictions in 2020/21, the end date may move up to June 30, 2024. Based on previous findings this project is continued, funded by Eurostars, starting January 2025, ending December 2027.The project is also funded by Health Holland under TKI-PPP and focuses on house dust mite allergy and peanut allergy. The central hypothesis of the project is that sialylated antigens/allergens effectively induce a regulatory anti-inflammatory immune response. This effect is thought to be mediated by Siglec receptors on DCs.

3. **Evaluation of plant-based bioparticles surface-expressing (ANGANY).**
   This project is a 3-year project starting in October 2019 and ending by September 2022. Based on previous findings an additional plant-based bioparticle project is funded by Amsterdam UMC under TKI-PPP starting in August 2024 and ending in July 2026. Based on findings in this project, a cashew nut/pistachio allergy project was started in March 2025 and ending March 2029. The project is funded by a Canadian biotech company from Quebec City, ANGANY Inc. The concept is a plant-based nanoparticle approach. The plant bioparticles are exposing allergens on the surface and are rich in glucosylceramide which is thought to induce anti-inflammatory responses.

Study objective

Allergen immunotherapy (AIT) is currently performed with aluminum hydroxide-adsorbed allergen extracts. This approach is effective, but requires a long burdensome treatment protocol with a relatively high frequency of
allergic side-effects. There is a need to increase safety and to reduce the duration and frequency of administration during treatment protocols. Modification of allergens, application of novel adjuvants, nanoparticles and cell-targeting strategies are amongst the possible strategies to reach improved safety and efficacy. Pre-clinical evaluation of such innovations requires blood samples from allergic patients and appropriate controls. The aim is to enroll volunteers for donation of blood samples for the isolation of PBMCs and collection of serum. This will allow to make steps towards:

1. **Safer AIT:** shielding off allergen from interaction with mast cells by application of nanoparticles, high-density presentation on nanoparticles, sialylation of allergens altering their IgE-binding surface.
2. **More effective induction of an anti-inflammatory regulatory response (Tregs/Bregs/IgG4):** addition of adjuvants, modification by sialylation, presentation in context of glycosylceramide containing plant bioparticles.
3. **Replacement of aluminum hydroxide:** liposomes, PLGA, plant bioparticles.

Study design

The study aims at recruiting healthy subjects (n=20), subjects with allergic rhinitis (n=40),

peanut allergy (n=20), and cashew nut and/or pistachio allergy (n=10) that are prepared to give 50-200 ml of blood on multiple occasions (up to maximally 20 times in 4 years) for pre-clinical evaluation of novel approaches for AIT. Between subsequent blood donations a period of at least 2 months is required. For specific experiments (mass spectrometry of allergen-specific peptides in MHC-molecules), 500 ml of blood is required. A maximal number of 10 subjects from each group (healthy individual (n=10/20), allergic rhinitis (n=10/40), peanut allergy (n=10/20), cashew nut and/or pistachio allergy (n=10/10)), will be recruited for a 500 ml blood donation (up to maximally 2 times in 4 years). After a 500 ml blood donation, a subsequent donation (either 50-200 ml or 500 ml) can only take place after a period of at least 4 months. When subjects donate 500 ml once, the maximum number of blood donations in 4 years of 50-200 ml will be reduced to 17 donations, due to the longer recovery time of the 500 ml blood donation. When subjects donate 500 ml twice, the maximum number of blood donations in 4 years of 50-200 ml will be reduced to 15 donations, due to the longer recovery time of the 500 ml blood donation. For all blood donations the aforementioned recovery times for a subsequent blood donation (2 months for 50-200 ml of blood and 4 months of 500 ml of blood) will be taken into account. Subjects will be provided with a patient information sheet and will be asked to sign informed consent. Subjects will be given 50 euro reimbursement for the blood donation and reimbursement of their travel costs.

Patients with allergic (caused by house dust mite, cat or [grass] pollen sensitization) rhinitis and patients with peanut, cashew nut, or pistachio allergy will be approached either retrospectively or prospectively. Retrospective recruitment will take place via the ENT department at the AMC. The database kept at the ENT department, containing a subgroup of patients that have consented to be approached for future allergy-associated research projects, will be used. To comply with GDPR legislation, CTcue will be used to select patients that have consented without jeopardizing the privacy of those that have not provided such consent. For prospective recruitment, allergic subjects will be recruited via the allergy outpatient clinic of the ENT department of Amsterdam UMC or the Internal Medicine department of the Amsterdam UMC and Huid Medisch Centrum Paasheuvelweg, where they will be asked whether they are interested to participate in the study when they come for their normal consultation visits. Likewise, prospective recruitment of allergic subjects also occurs via advertisements (e.g. on notification boards) in the AMC, Amsterdam UMC intranet and social media of the student association of the medical faculty at the AMC (MFAS). Healthy subjects not having chronic inflammatory diseases will be approached via www.link2trials.com, MFAS social media, the Amsterdam UMCintranet and via advertisements on notification boards of outpatient clinic departments not primarily seeing patients with inflammatory diseases (e.g. orthopedic surgery). Advertisements for allergic and healthy subjects will contain contact details from the laboratory of Experimental Immunology. Prospectively recruited subjects do not need to go through the ENT department, which will save them time and effort. All subject that enter the study via the ENT department will receive a skin prick test (SPT). While subject that enter the study via the Department of Experimental Immunology will be characterized via the measurement of allergen-specific IgE serum levels. Subjects that enter via the Internal Medicine-Allergy outpatient clinic at Amsterdam UMC or Huid Medisch Centrum Paasheuvelweg already have a doctor-diagnosed allergy based on history, confirmed with skin prick test and/or IgE levels and/or a provocation test. The choice of methods depends on the material and expertise available at the clinical and laboratory departments, making inclusion into the study

highly efficient for both the subjects and the clinicians/researchers. However, these different methods provide us with the same information regarding the allergic background of the patients. Subjects that enter the study via the Department of Experimental Immunology could still be invited for a SPT to confirm previous IgE serum level results. During the study, subjects may at each moment withdraw from participation, without giving a reason for their withdrawal. Upon withdrawal of subjects, new candidate subjects may be approached for replacement.

Intervention

Products that are being used:

- **Nanoparticles:** Liposomes with different compositions will be used as well as PLGA nanoparticles, both as an alternative for aluminum hydroxide. Loading of liposomes/nanoparticles with allergens prevents contact of the allergens with allergen effector cells (such as mast cells), leading to a reduced chance on side effects of the therapy. Additionally, these particulates could be loaded with anti-inflammatory adjuvants (vitamin D3, retinoic acid, TGF-beta mimetics) or targeted to antigen presenting cells using antibodies. These particulates will be compared to allergen extracts or single natural or recombinant allergens.

  • Purified house dust mite allergens Der p 1 and Der p 2 and house dust mite extract
  • Vitamin D3, retinoic acid and a TGFb mimetic peptide as candidate anti-inflammatory adjuvants
  • Nanoparticles: liposomes of various composition and PLGA nanoparticles as alternative for aluminum hydroxide. By loading the liposomes/nanoparticles with allergen, it is shielded off from contact with mast cells when injected, decreasing the risk of side-effects.
  • Antibodies against receptors on DCs, for more effective targeting to the right antigen-presenting cells.

- **Sialyalted allergens:** Der p 1, Der p 2, Ara h 1, Ara h 2, Ara h 3, Ara h 6, and sialylated versions of these allergens, as well as sialylated liposomes loaded with the above mentioned allergens. These sialylated allergens could shield the allergen froma allergen effector cells, reducing side effects of the therapy.

  • For house dust mite: purified Der p 1 and Der p 2, and sialylated versions thereof
  • For peanut: purified Ara h 1, Ara h 2, Ara h 3 en Ara h 6 and sialylated versions thereof
  • Sialylated liposomes loaded with house dust mite allergens Der p 1 and/or Der p 2 or with peanut allergens Ara h 1 and/or Ara h 2. The advantage of this approach may again be that the allergen is shielded off from contact with mast cells when injected, decreasing the risk of side-effects.

- **Plant-based bioparticles surface-expressing allergens:** Plant-based bioparltices

express allergens on their surfaces and contain high levels of glucosylceramide, which is thought to be involved in anti-inflammatory responses. The allergens expressed on these bioparticles will be Der p 1, Der p (housedust mit allergens), Ara h 1, Ara h 2 (peanut allergens), Phl p 1, Phl p 5 (grass pollen allergens), and Fel d 1 (cat allergen), which will be compared to soluble single allergens.

• Soluble Soluble plant-expressed Der p 1 and Der p 2 (house dust mite), Ara h 1 and Ara h 2 (peanut), Phl p 1 and Phl p 5 (grass pollen) and Fel d 1 (cat).
• Bioparticles with Der p 1 or Der p 2 (house dust mite), Ara h 1 or Ara h 2 (peanut), Phl p 1 and Phl p 5 (grass pollen) or Fel d 1 (cat) on their surface.

Study burden and risks

Patients will contribute to increasing the knowledge in the field of innovation of AIT for the treatment of allergic diseases. In the future this may provide new safer and more effective treatments that benefit the allergic patient. Disadvantage of volunteering is minimal. Blood drawing can cause a low level of pain and may occasionally results in a hematoma. Skin tests are safe and adverse events are uncommon. Vasovagal reactions (pallor, sweating, faintness) may appear in up to 4 out of 10,000 patients. Systemic allergic reactions (such as e.g. an asthma episode) are even less common and may be seen in 1.5-2.2 out of 10,000 patients. No fatalities have been reported. As this test is performed under the observation of the study personnel, adequate treatment of those
reactions can be effectively initiated.

Contacts

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Trial sites

Trial sites in the Netherlands

Amsterdam UMC
Target size: 90

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)

Inclusion criteria

Inclusion criteria:

- Subjects with doctor-diagnosed allergic rhinitis or convincing history of allergic rhinitis and a positive SPT and/or serum IgE levels for HDM, cat or pollen allergens
  -Subjects with a doctor-diagnosed peanut allergy or a convincing history of peanut allergy and positive SPT and/or serum IgE levels for peanut allergens
- Subjects with a doctor-diagnosed cashew and/or pistachio allergy or a convincing history of cashew nut/pistachio allergy and positive SPT and/or serum IgE levels for cashew nut/pistachio allergens
- Healthy subjects, defined as not having allergic or non-allergic rhinitis, peanut allergy or other inflammatory non-communicable diseases such as rheumatoid arthritis, type 2 diabetes, celiac disease, colitis ulcerosa, Crohn*s disease, and multiple sclerosis.
- Age between 18-65
- Signed informed consent

Exclusion criteria

Exclusion criteria

- History of AIT (SCIT or SLIT) with any allergen within the past year of the time of blood donation.
- Ongoing AIT (SCIT or SLIT) with any allergen at the time of blood donation.

- Vaccination within one week before blood donation.
- Immunosuppressive or biological medication (e.g. IL-5, anti-IgE therapy) within the last six months prior to blood donation.
- Severe immune disorders (including auto-immune diseases) and/or diseases requiring immunosuppressive drugs.
- Active malignancies or any malignant disease during the previous 5 years.
- Active inflammation or infection at the time of blood donation.
- Use of systemic steroids within 4 weeks before the blood donation.
- Treatment with systemic and local β-blockers.
- Volunteers who are students or employees of one of the participating research groups or 1st grade relatives or partners of the investigators.

Study design

Design

Study phase:	N/A
Study type:	Observational invasive
Intervention model:	Other
Allocation:	Non-randomized controlled trial
Masking:	Open (masking not used)
Control:	Other type of control
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruitment started
Start date (anticipated):	09-05-2022
Enrollment:	90
Duration:	48 months (per patient)
Type:	Actual

Medical products/devices used

Product type:	N.a.

IPD sharing statement

Plan to share IPD: No

Plan description
N.a.

Ethics review

Approved WMO Date:	29-10-2019
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	16-12-2020
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	05-10-2021
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	19-09-2023
Application type:	Amendment
Review commission:	MEC Academisch Medisch Centrum (Amsterdam) Kamer G4-214 Postbus 22660 1100 DD Amsterdam 020 566 7389 mecamc@amsterdamumc.nl
Approved WMO Date:	11-12-2024
Application type:	Amendment
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Approved WMO Date:	02-06-2025
Application type:	Amendment
Review commission:	METC Amsterdam

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
CCMO	NL71330.018.19
Research portal	NL-008100