A pilot study towards a therapy with prednisolone encapsulated liposomes for the treatment of Graves' Orbitopathy with reduced systemic steroid exposure

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Nanocort is safe and effectively reduces the inflammatory signs and symptoms of active Graves' Orbitopathy (GO).

Ethische beoordeling	Positief advies
Status	Werving gestopt
Type aandoening	-
Onderzoekstype	Interventie onderzoek

Samenvatting

ID

NL-OMON24926

Bron
NTR

Verkorte titel
GO Nanocort

Aandoening

Active GO (CAS 3 – 7).

Ondersteuning

Primaire sponsor: Het Oogziekenhuis Rotterdam /
Rotterdam Ophthalmic Institute
PO Box 70030, NL-3000 LM Rotterdam
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Overige ondersteuning: Rotterdamse Stichting Blindenbelangen
Enceladus Pharmaceuticals Naarden

Onderzoeksproduct en/of interventie

Uitkomstmaten

Primaire uitkomstmaten

Number of patients responding to treatment (week 6 and 13), with 'response' defined as: at least two of the following outcome measures improved in one eye, without deterioration in any of these measures in either eyes:
i) reduction in palpebral aperture by at least 3 mm;
ii) reduction in any of the class 2 signs of NOSPECS by at least two grades;
iii) reduction in exophthalmos by at least 2 mm;
iv) improvement of >8 degrees in motility in any duction or improvement in diplopia (disappearance or change in degree);
v) improvement in CAS by at least 2 points.
If a response to treatment is observed at week 6 and at week 13, it is qualified as sustained.

Change of maximum T2RT of EOMs and EOM area at orbital MRI at week 13 relative to baseline.

Safety.
At beginning and end of the study: HbA1C, fasting glucose and insulin, blood pressure, bodyweigth, BMI, WHR.
During entire follow up: (S)AEs, vital signs (blood pressure, heart rate and respiratory rate before, during and after infusion after the patient has been supine for at least five minutes), physical examination and laboratory tests.

Toelichting onderzoek

Achtergrond van het onderzoek

Rationale: The mainstay of treatment for patients with moderate to severe Graves' Orbitopathy (GO) currently consists of various dose schemes of intravenous (IV) methylprednisolone or high doses oral prednisone. To avoid the frequent and potentially serious adverse effects of such treatment, new immunomodulating therapies are required. In a small study, IV administration of long-circulating liposomal prednisolone (Nanocort, LCLP) has been shown effective in rheumatoid arthritis without causing the typical glucocorticoid-related adverse events (AEs). It is hypothesized that GO can also be effectively treated with LCLP and that the number of AEs will be reduced.

Objective: To demonstrate that Nanocort is safe and effectively reduces the inflammatory signs and symptoms of active GO.

Study design: Open label, multicentre, dose-escalating study (phase I/II).

Study population: Maximally 20 patients (18 years or older) with active GO (CAS 3 – 7).

Intervention: The first 10 subjects in this trial will be treated with 150 mg/infusion of Nanocort administered IV at week 0 and 2. Infusion will take approximately 2.5 hours. If three or more of these patients respond to treatment, another cohort of 10 subjects will be treated with 150 mg/infusion of Nanocort administered IV at week 0, 2 and (if applicable) 4.

Main study parameters/endpoints: Number of patients with a predefined response to treatment.

Nature and extent of the burden and risks associated with participation, benefit and group relatedness: The incidence of infusion reactions to liposomes (empty placebo as well as drug-loaded) is not unlike that for other colloidal formulations and biologics: 5-10%. AEs (possibly) associated with Nanocort appear to be manageable.

Compared to conventional therapy, the study regimen (i.e. treatment and control visits together) involves reduced burden (12 hospital visits versus 8) and reduced steroid dose (total 4500/7500 mg methylprednisolone versus 300/450 mg Nanocort). In consequence of the lower steroid dose, it has to be expected that the incidence of AEs which are associated with systemic steroid exposure will be less.

Doel van het onderzoek

Nanocort is safe and effectively reduces the inflammatory signs and symptoms of active Graves' Orbitopathy (GO).

Onderzoeksopzet

presentation (day -3±2)

screening (d -1±1)

baseline (d 0)

d 14±2

d 28±2

d 42±4

wk 13±1

wk 26±1

wk 52±2

Onderzoeksproduct en/of interventie

The first 10 subjects in this trial will be treated with 150 mg/infusion of Nanocort administered IV at week 0 and 2. Infusion will take approximately 2.5 hours. If three or more of these patients respond to treatment, another cohort of 10 subjects will be treated with 150 mg/infusion of Nanocort administered IV at week 0, 2 and (if applicable) 4. (Trial terminated after interim analysis of 10 subjects.)

Contactpersonen

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Deelname eisen

Belangrijkste voorwaarden om deel te mogen nemen (Inclusiecriteria)

1. Male or female ≥ 18 years old.

2. Informed consent.

3. Patients are able and willing to complete the study (12 months follow-up).

4. Active GO, defined as Clinical Activity Score (CAS) ≥ 3.

5. Moderate to severe GO (Bartalena et al. 2016):

Patients without sight-threatening GO whose eye disease has sufficient impact on daily life to justify the risks of immunosuppression (if active) or surgical intervention (if inactive). They usually have two or more of the following: lid retraction ≥ 2 mm, moderate or severe soft-tissue involvement, or exophthalmos ≥ 3 mm above normal for race and gender, inconstant or constant diplopia.

6. Euthyroidism for at least 3 months with antithyroid drugs or following thyroidectomy, or 6 months following radioiodine administration. (Euthyroidism is defined as normal serum free thyroxine, total or free triiodothyronine, and thyrotropin levels below 4 mU/Liter.)

Belangrijkste redenen om niet deel te kunnen nemen (Exclusiecriteria)

1. Sight threatening GO due to optic neuropathy (decrease of (pinhole) vision, visual field loss, prolonged VEP, diminished colour vision) or severe keratopathy.

2. Any concurrent illness, disability or clinically significant abnormality that may, as judged by the investigator, affect the interpretation of clinical efficacy or safety data or prevent the subject from safely completing the assessments required by the protocol.

3. Current participation in another interventional clinical trial (with subjects having received an investigational drug within 30 days prior to the baseline visit).

4. Treatment with oral, rectal or injectable (including intra-articular) glucocorticoids within 6 weeks prior to baseline visit. Inhaled glucocorticoids are allowed. Topical steroids are allowed, however subjects should not have received more than 100 gram of a mild to moderate topical corticosteroid cream per week, 50 gram of a potent corticosteroid cream per week or 30 gram of a very potent topical corticosteroid cream per week in the 4 weeks

prior to the baseline visit.

5. Patients who are unlikely to adequately comply with the trial¡¯s procedures (due for instance to medical conditions likely to require an extended interruption or discontinuation, history of substance abuse or noncompliance).

6. Women who are lactating, pregnant (positive pregnancy test at screening) or planning to become pregnant during the course of the study.

7. Unwillingness to use reliable and acceptable contraceptive methods untill 3 months after last study medication except for female patients who are surgically sterile (bilateral tubal ligation, bilateral oophorectomy or hysterectomy) or at least 1 year postmenopausal
8. Uncontrolled Diabetes Mellitus.

9. History of a psychiatric disease (psychosis, depression, mania).

10. History of or active hepatitis or Human immunodeficiency virus.

11. Abnormal hepatic function (ALT/AST or bilirubin > 2 x upper limit of normal) at screening.

12. Abnormal renal function (Blood Urea Nitrogen or creatinine >1.25 x upper limit of normal) at screening.

13. Signs of active infection, requiring systemic treatment.

14. Major surgery within the 60 Days prior to screening or planned surgery during study period.
15. Malignant disease, unless cured.

16. Clinically significant out-of-range values on hematology panel, at discretion of the Principal Investigator.

17. Poor peripheral venous access (as per Investigator or site personnel opinion).

18. Current substance abuse or alcohol abuse.

19. Contraindications for MRI.

Onderzoeksopzet

Opzet

Type: Interventie onderzoek

Onderzoeksmodel:	Anders
Toewijzing:	N.v.t. / één studie arm
Blindering:	Open / niet geblindeerd
Controle:	N.v.t. / onbekend

Deelname

Nederland

Status:	Werving gestopt
(Verwachte) startdatum:	28-11-2017
Aantal proefpersonen:	20
Type:	Werkelijke startdatum

Voornemen beschikbaar stellen Individuele Patiënten Data (IPD)

Wordt de data na het onderzoek gedeeld: Ja

Ethische beoordeling

Positief advies

Datum:	21-07-2017
Soort:	Eerste indiening

Registraties

Opgevolgd door onderstaande (mogelijk meer actuele) registratie

ID: 45340
Bron: ToetsingOnline
Titel:

Andere (mogelijk minder actuele) registraties in dit register

Geen registraties gevonden.

In overige registers

Register	ID
NTR-new	NL6404
NTR-old	NTR6579
CCMO	NL61298.078.17
OMON	NL-OMON45340

Resultaten

Samenvatting resultaten

Paridaens D, Detiger SE, Kremer T, Dalm VASH, de Keizer ROB, Dik WA, Wubbels R, Peeters RP. Nanocort in the medical treatment of moderate-to-severe Graves' orbitopathy: A pilot study. Acta Ophthalmol. 2020; 98(Suppl. S264): 10.
[Abstract]

Detiger SE, Kremer TM, Dalm VASH, de Keizer ROB, Wubbels RJ, Metselaar JM, van Hagen PM, Peeters RP, Paridaens D. A pilot study on the use of prednisolone encapsulated liposomes for the treatment of moderate-to-severe Graves' orbitopathy with reduced systemic steroid exposure. Acta Ophthalmol, 2021; 99: 797-804.
PMID: 33423386