

De rol van corticosteroiden op de coagulatie en inflammatie bij astma.

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We hypothesize that: 1. Patients with mild-moderate and severe asthma have an increased procoagulant activity as compared to healthy controls; 2. Oral corticosteroids activate coagulation in healthy controls and increase the procoagulant activity...

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

Samenvatting

ID

NL-OMON27682

Bron

NTR

Verkorte titel

ROCOCO

Aandoening

Asthma
Corticosteroids
Coagulation
Inflammation

Ondersteuning

Primaire sponsor: Dept. Respiratory Medicine, Academic Medical Center University of Amsterdam the Netherlands
Netherlands Asthma Foundation

Overige ondersteuning: Dept. Respiratory Medicine, Academic Medical Center University of Amsterdam the Netherlands
Netherlands Asthma Foundation

Onderzoeksproduct en/of interventie

Uitkomstmaten

Primaire uitkomstmaten

Primary endpoint will be the change in TATc and PAPc in blood.

Toelichting onderzoek

Achtergrond van het onderzoek

Asthma is a chronic inflammatory disease of the airways characterised by variable airways obstruction and although asthma can be well controlled in most patients by treatment with inhaled corticosteroids, there is a small subset of patients requiring oral corticosteroids for asthma control. High levels of glucocorticoids, either endogenous or exogenous, have been shown to induce hypercoagulability and an increased risk of venous thromboembolism.

In asthma corticosteroids, either inhaled or oral, have been shown to influence hemostasis. In patients with moderate asthma inhaled corticosteroids decrease the activation of coagulation, while in severe asthmatic patients a further activation of coagulation may occur. Oral corticosteroids further activate coagulation during an acute exacerbation.

In addition, asthma itself has also been associated with a prothrombotic state, and preliminary data from our group have shown an increased risk of pulmonary embolism in patients with severe asthma that was associated with chronic oral corticosteroid use and frequent asthma exacerbations.

Therefore, an activated coagulation system might enhance the inflammatory process in the airways of asthmatics and contribute to therapy resistance in those with severe disease.

Doel van het onderzoek

We hypothesize that:

1. Patients with mild-moderate and severe asthma have an increased procoagulant activity as compared to healthy controls;
2. Oral corticosteroids activate coagulation in healthy controls and increase the procoagulant activity in mild-moderate and severe asthmatic patients;
3. Increase of hypercoagulation is correlated with asthma severity and use of high dose corticosteroids.

Onderzoeksopzet

At baseline, day 1 and day 11.

Onderzoeksproduct en/of interventie

Patients will be randomized to receive either prednisolon (once daily 0,5mg/kg) or identical placebo for 10 days.

Contactpersonen

Publiek

Academic Medical Centre

Dept. of Respiratory Medicine (F5-144)

Meibergdreef 9
C.J. Majoor
Amsterdam 1105 AZ
The Netherlands
+31 (0)20 5664356

Wetenschappelijk

Academic Medical Centre

Dept. of Respiratory Medicine (F5-144)

Meibergdreef 9
C.J. Majoor
Amsterdam 1105 AZ
The Netherlands
+31 (0)20 5664356

Deelname eisen

Belangrijkste voorwaarden om deel te mogen nemen (Inclusiecriteria)

All subjects:

1. Age between 18 - 75 years;

2. Non-smoking or stopped smoking more than 12 months ago and 10 pack years or less;
3. Able to give written and dated informed consent prior to any study-specific procedures.

Healthy controls:

1. Baseline FEV1 80% of predicted;
2. Methacholine PC20 > 8 mg/ml²⁹;
3. No usage of steroids by any dosing route;
4. Negative allergy testing by skin prick test or specific IgE;
5. Negative history of pulmonary and any other relevant diseases.

Patients with asthma:

1. All patients have previous evidence of variable airways obstruction within the last 5 years, as documented by at least one of the following:
 - A. Reversibility in forced expiratory volume in one second (FEV1) of $\geq 12\%$ predicted after 4 puffs of a 100 µg salbutamol dose-aerosol, administered via a spacer;
 - B. A mean diurnal variation in peak expiratory flow (PEF) $\geq 15\%$ (highest PEF - lowest PEF) per mean PEF on ≥ 4 days per week for a minimum of 2 weeks;
 - C. An increase in FEV1 of ≥ 400 mL after a course of prednisolone 0.5 mg•kg⁻¹•day⁻¹ for 14 days;
 - D. A provocative concentration causing a 20% fall in FEV1 with histamine or methacholine <8 mg/mL²⁹.
2. Clinically stable, for patients with mild asthma this means no exacerbations within the last 8 weeks prior to the study;
3. No other clinically significant abnormality on history and clinical examination;
4. The use of short and long-acting 2-agonists, leukotriene receptor antagonist, short or long acting anticholinergic agonists are allowed provided that the dose of these drugs remains stable during the study.

Mild/Moderate asthmatic patients:

1. Baseline FEV1 70% of predicted 30;
2. Low- to medium-dose use of inhaled corticosteroids (ICS) (fluticasone $\leq$ 500 μ g/day or equivalent drug).

Severe asthmatic patients:

1. Severe asthma according to the recently published consensus criteria of the Innovative Medicine Initiative (IMI)³¹;
2. High- and ultrahigh dose of ICS (Fluticasone $\geq$ 1000 μ g/day or equivalent drug);
3. On stable doses of inhaled corticosteroids during the previous 4 weeks and during the study.

Belangrijkste redenen om niet deel te kunnen nemen (Exclusiecriteria)

Exclusion criteria for all patient-groups are as follows:

1. Women who are pregnant or lactating or who have a positive urine pregnancy test at screening;
2. Participation in any clinical investigational drug treatment protocol within the preceding 30 days;
3. Use of heparin, LMWH, or vitamin K antagonists;
4. Use of omalizumab during the last 6 months before randomization;
5. Use of prednisolone during the last 8 weeks before randomization;
6. Ongoing use of tobacco products of any kind or previous usage with a total pack year $\geq$ 10 years;
7. General contraindications for the use of corticosteroid use, including a known diagnosis of peptic ulcers, osteoporosis, psychoses, infections, diabetes and hypertension, or symptoms and signs compatible with one of the above diagnoses;
8. Concomitant disease or condition which could interfere with the conduct of the study, or for which the treatment might interfere with the conduct of the study, or which would, in the

opinion of the investigator, pose an unacceptable risk to the patient in this study;

9. Unwillingness or inability to comply with the study protocol for any other reason.

Onderzoeksopzet

Opzet

Type:	Interventie onderzoek
Onderzoeksmodel:	Parallel
Toewijzing:	Gerandomiseerd
Blinding:	Dubbelblind
Controle:	Placebo

Deelname

Nederland	
Status:	Werving gestopt
(Verwachte) startdatum:	01-11-2011
Aantal proefpersonen:	90
Type:	Werkelijke startdatum

Voornemen beschikbaar stellen Individuele Patiënten Data (IPD)

Wordt de data na het onderzoek gedeeld: Nog niet bepaald

Ethische beoordeling

Positief advies	
Datum:	12-10-2011
Soort:	Eerste indiening

Registraties

Opgevolgd door onderstaande (mogelijk meer actuele) registratie

Geen registraties gevonden.

Andere (mogelijk minder actuele) registraties in dit register

Geen registraties gevonden.

In overige registers

Register	ID
NTR-new	NL2953
NTR-old	NTR3101
Ander register	AF / EudraCT number : 3.2.11.021 / 2010-023931-40;
ISRCTN	ISRCTN wordt niet meer aangevraagd.

Resultaten

Samenvatting resultaten

N/A