The influence of adalimumab on thiopurine metabolism in Crohn's disease patients.

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Ethische beoordeling	Positief advies
Status	Werving gestart
Type aandoening	-
Onderzoekstype	Observationeel onderzoek, zonder invasieve metingen

Samenvatting

ID

NL-OMON24966

Bron
NTR

Verkorte titel
N/A

Aandoening

interaction, adalimumab, azathioprine, 6-mercaptopurine, 6-thioguanine, thiopurines, 6-TGN, 6-MMPR

Ondersteuning

Primaire sponsor: none
Overige ondersteuning: none

Onderzoeksproduct en/of interventie

Uitkomstmaten

Primaire uitkomstmaten

The influence of adalimumab therapy on the red blood cell levels of the active thiopurine metabolites (6-TGN and 6-MMPR) in Crohn's disease patients treated with stable azathioprine, 6-mercaptopurine or 6-thioguanine monotherapy.

Toelichting onderzoek

Achtergrond van het onderzoek

The influence of adalimumab on thiopurine metabolism in Crohn’s disease (CD) patients.

Background:
The novel anti–tumor necrosis factor monoclonal antibody adalimumab was significantly superior to placebo for long-term treatment of CD irrespective of concomitant immunosuppressive therapies, including the thiopurines azathioprine (AZA) and 6-mercaptopurine (6-MP). In 2003 Roblin et al. provided evidence for a drug interaction between infliximab and azathioprine in CD patients.
The mean erythrocyte level of the active thiopurine metabolites, the 6-thioguanine nucleotides (6-TGN), was comparable before and 3 months after the first infusion, but a significant increase was observed within 1–3 weeks after the first infusion. A mean increase of 50% of the basal level was seen.
An increase of the active thiopurine metabolites, 6-TGN, may on one hand result in a greater efficacy, but on the other hand may result in more (dangerous) adverse events, for instance myelotoxicity.

Objective:
To investigate the influence of adalimumab on the level of the active thiopurine metabolites, 6-TGN and 6-methylmercaptopurine ribonucleotides (6-MMPR), in CD patients treated with a stable maintenance therapy of azathioprine, 6-mercaptopurine or 6-thioguanine (6-TG).

Methods:
CD-patients treated with standard dose AZA (2-2,5mg/kg), 6-MP (1-1,5mg/kg) or 6-TG (10-40mg/day) who require adalimumab for active Crohn’s disease are included prospectively.
Patients receive adalimumab induction therapy with 160mg s.c. (week 0), 80mg s.c. (week 2), and subsequently 40mg s.c. every two weeks.
Efficacy, safety (adverse events), active thiopurine metabolite red blood cell levels and hematological and biochemical safety parameters will be evaluated at week 0 (inclusion), week 2, week 4, week 6 and week 12. The clinical outcome is evaluated by the Crohn’s Disease Acitvity Index (CDAI) at week 0 (inclusion), week 4 and week 12. The duration of the study is twelve weeks. The dose of concomitant medication will be maintained, except for predniso(lo)ne, which can be dosed based on disease activity.

Outcome measures:
The alteration, which means a significant rise or decrease, of 6-TGN and/or 6-MMPR red blood

cell levels resulting from concurrent adalimumab therapy.
Efficacy of therapy is evaluated at week 0, week 4 en week 12 by CDAI.
Safety is evaluated by measurement of hematological and biochemical parameters at week 0, 2, 4, 6 and 12 and clinical evaluation.

Doel van het onderzoek

The novel anti–tumor necrosis factor monoclonal antibody adalimumab was significantly superior to placebo for long-term treatment of CD irrespective of concomitant immunosuppressive therapies, including the thiopurines azathioprine (AZA) and 6-mercaptopurine (6-MP). In 2003 Roblin et al. provided evidence for a drug interaction between infliximab and azathioprine in CD patients. The mean erythrocyte level of the active thiopurine metabolites, the 6-thioguanine nucleotides (6-TGN), was comparable before and 3 months after the first infusion, but a significant increase was observed within 1–3 weeks after the first infusion. A mean increase of 50% of the basal level was seen. An increase of the active thiopurine metabolites, 6-TGN, may on one hand result in a greater efficacy, but on the other hand may result in more (dangerous) adverse events, for instance myelotoxicity. Objective. To investigate the influence of adalimumab on the level of the active thiopurine metabolites, 6-TGN and 6-methylmercaptopurine ribonucleotides (6-MMPR), in CD patients treated with a stable maintenance therapy of azathioprine, 6-mercaptopurine or 6-thioguanine (6-TG).

Onderzoeksopzet

Week 0, 2, 4, 6 en 12.

Onderzoeksproduct en/of interventie

None.

Contactpersonen

Publiek

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Wetenschappelijk

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Deelname eisen

Belangrijkste voorwaarden om deel te mogen nemen (Inclusiecriteria)

1. Adult patients, aged between 18 – 70 years;

2. Diagnosis of CD for at least 6 months (histological and endoscopically confirmed);

3. AZA, 6-MP or 6-TG use for at least 3 months;

4. Steady state AZA, 6-MP or 6-TG use, with an unchanged thiopurine regime for at least 6 weeks (in combination with Infliximab);

5. Normal liver and kidney function (ALAT / AP / creatinin < 2 x upper normal limit, MDRD>60ml/min.);

6. 5-ASA use for at least 8 weeks, and an unchanged dose regime for at least 6 weeks.

Belangrijkste redenen om niet deel te kunnen nemen (Exclusiecriteria)

1. Bone marrow suppression (platelets / leucocytes < 1 x lower normal level);

2. Presence of tuberculosis or active infection (fever and CRP > 1 x upper normal limit);

3. Anemia (hemoglobine < 6 mmoll);

4. Symptomatic stenosis of the ileum;

5. Small bowel surgery interfering significantly with resorptive area;

6. Known intolerance to Humira compounds;

7. Moderate-severe congestive failure (NYHA III/IV);

8. Current use of Humira;

9. Current use of methotrexate;

10. Start or dose regime change of 5-ASA compounds within the last 45 days;

11. Concomitant use of allopurinol, 5-ASA, mycofenolate, furosemide within the past 6 weeks;

12. Pregnancy, expected pregnancy or lactation within 6 months.

Onderzoeksopzet

Opzet

Type:	Observationeel onderzoek, zonder invasieve metingen
Onderzoeksmodel:	Anders
Toewijzing:	N.v.t. / één studie arm

Controle: N.v.t. / onbekend

Deelname

Nederland

Status:	Werving gestart
(Verwachte) startdatum:	03-01-2008
Aantal proefpersonen:	40
Type:	Verwachte startdatum

Ethische beoordeling

Positief advies

Datum:	05-08-2009
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	NL1826
NTR-old	NTR1936
Ander register	n/a : n/a
ISRCTN	ISRCTN wordt niet meer aangevraagd.

Resultaten

Samenvatting resultaten
N/A