Lengthening Adalimumab Dosing Interval in quiescent Crohn’s disease patients

No registrations found.

Ethical review	Positive opinion
Status	Recruiting
Health condition type	-
Study type	Interventional

Summary

ID

NL-OMON21837

Source
NTR

Brief title
The LADI study

Health condition

In The Netherlands, ~35.000 patients carry a diagnosis of Crohn’s disease (CD). CD is an often incurable, chronic inflammatory disorder of the gastrointestinal tract, characterized by a relapsing/remitting course. Due to the high risk of relapse, the majority of patients require maintenance therapy. Anti-tumor necrosis factor (TNF) therapy, for example with infliximab or adalimumab, is effective for both induction and maintenance of remission. Though effective, adalimumab therapy is expensive. Most frequent adverse events include dose-dependent serious infections and local injection site reactions.

Sponsors and support

Primary sponsor: Radboud university medical center, PO box 9101, 6500 HB Nijmegen Geert-Grooteplein Zuid 10
Source(s) of monetary or material Support: ZonMW

Intervention

Outcome measures

Primary outcome

Cumulative incidence of persistent disease flares in 48 weeks of follow-up. A persistent flare is defined as two of three of the following criteria persisting for > 8 weeks, despite dose escalation of adalimumab; FC >250 µg/g, CRP≥10 mg/L, HBI ≥5. Non-inferiority is reached if the difference in cumulative incidence of persistent flares not exceeds the non-inferiority margin of 15%.

Secondary outcome

 Cumulative incidence of transient disease flares. A transient flare is defined as two of three of the following criteria persisting for ≤ 8 weeks; FC >250 µg/g, CRP≥10 mg/L, HBI ≥5.

 (Serious) adverse event rate. (Serious) adverse events that are (possibly) related to adalimumab and the (Serious) adverse events that are (possibly) related to adalimumab interval lengthening in the intervention and control group, expressed as events/ 100 PYs of follow-up.

 Factors that are associated with successful interval lengthening, e.g. baseline patient and treatment characteristics, FC, CRP, adalimumab drug levels and antibodies to adalimumab

 The decremental cost effectiveness ratio of this interval lengthening strategy. Dividing the difference in costs (based on medical consumption (by iMTA MCQ questionnaire) and work productivity (by iMTA PCQ questionnaire)) by the difference in QALYs (based on EQ-5D).

Study description

Background summary

Rationale

Adalimumab is both an effective induction and maintenance therapy for Crohn’s disease (CD). Due to the risk of side effects (infections, injection reaction) and high costs, an extension of the injection interval is an attractive option. However, this strategy has not been evaluated yet in a randomized controlled trial in CD patients.

Objective

To assess non-inferiority and cost-effectiveness of disease activity guided adalimumab interval lengthening in CD patients in sustained (>9 months) clinical remission, compared to standard dosing of every other week.

Study design

Multicenter, randomized controlled, open label non-inferiority trial, with two treatment arms.

Study population

Crohn’s disease patients, in sustained clinical remission on adalimumab maintenance therapy.

Intervention

Intervention arm: The adalimumab injection interval during maintenance therapy (40 mg per 2 weeks) will be extended through a stepwise disease activity guided manner to 3 weeks and subsequently - after 24 weeks - to 4 weeks. If a step-down leads to recurrence of disease activity patients will return to the preceding effective dosing interval.

Control arm: Patients will continue adalimumab maintenance therapy of 40mg per 2 weeks. Treatment decisions are made at the discretion of the treating physician.

Main study parameters/endpoints

Primary outcome

Cumulative incidence of persistent disease flares in 48 weeks of follow-up. A persistent flare is defined as two of three of the following criteria persisting for > 8 weeks, despite dose escalation of adalimumab; FC >250 µg/g, CRP≥10 mg/L, HBI ≥5. Non-inferiority is reached if the difference in cumulative incidence of persistent flares not exceeds the non-inferiority margin of 15%.

Secondary outcomes include cumulative incidence of transient flares, adverse events, predictors for successful dose reduction and cost-effectiveness.

Nature and extent of the burden and risks associated with participation, benefit and group relatedness:

In this study patients will have to visit the site every 12 weeks which is slightly more than the usual 2-3 times per year. This will allow strict monitoring of disease control and timely intervention in case of flares. In terms of diagnostics, blood tests/ faecal tests and questionnaires will be performed 4 times per year. Additionally, patients in both arms will be

interviewed via telephone every 6 weeks in between clinical visits to assess for symptoms and potential disease activity. The consequence of a confirmed disease relapse includes switching back to the prior injection interval. Risk of interval extension includes a higher risk of disease flare. It is anticipated that most patients will enter remission upon subsequent adjusting of injection interval. Study patients may benefit from reduced exposure to adalimumab, the benefits include reduced risk of injection reactions, and potentially less side effects including risk of infectious complications.

Study objective

Adalimumab is both an effective induction and maintenance therapy for Crohn's disease (CD). Due to the risk of side effects (infections, injection reaction) and high costs, an extension of the injection interval is an attractive option. However, this strategy has not been evaluated yet in a randomized controlled trial in CD patients.

Our objective is to assess non-inferiority of extending the adalimumab dosing interval, under strict disease monitoring in CD patients in sustained (>9 months) clinical remission, compared to adalimumab every other week.

Study design

At week 0, 12, 24, 36 and 48, following endpoints are measured:

- Disease activity (fecal calprotectin, CRP, Harvey Bradshaw Index, PRO-2)

- Pharmacokinetics/ immunogenicity (antidrug antibodies to adalimumab, trough levels) at week 0, 24, 48

- Adverse events

- Quality of life (SIBDQ, EQ-5D)

- Cost-effectiveness (iMTA MCQ, iMTA PCQ)

At week 6, 18, 30 and 42, following endpoints are measured:

- Harvey Bradshaw Index, PRO-2

- SIBDQ, EQ-5D

- Adverse events

Intervention

Intervention arm: The adalimumab injection interval during maintenance therapy (40 mg per 2 weeks) will be extended through a stepwise disease activity guided manner to 3 weeks and subsequently - after 24 weeks - to 4 weeks. If a step-down leads to recurrence of disease activity patients will return to the preceding effective dosing interval.

Control arm:Ppatients will continue adalimumab maintenance treatment of 40mg per 2 weeks. Treatment decisions are made at the discretion of the treating physician.

Contacts

Public
Postbus 9101, Afdeling Maag- Darm en Leverziekten

Lisa J.T. Smits
Geert-Grooteplein Zuid 10 (route 455)

Nijmegen 6500 HB
The Netherlands
T 024-8186626 | M 06-11510557
Scientific
Postbus 9101, Afdeling Maag- Darm en Leverziekten

Lisa J.T. Smits
Geert-Grooteplein Zuid 10 (route 455)

Nijmegen 6500 HB
The Netherlands
T 024-8186626 | M 06-11510557

Eligibility criteria

Inclusion criteria

 Age 18 or older

 Diagnosis of colonic and/or distal ileal CD

 Sustained steroid-free clinical remission for >9 months whilst being treated with adalimumab at a stable dose

 Adalimumab dosed at 40 mg sc every 2 weeks

 Full clinical response and disease control, all three criteria below need to be fulfilled prior to enrollment:

- Absence of active inflammatory intestinal or extra-intestinal symptoms, as judged by both patient and physician

- Fecal calprotectin (FC) < 150 mg/kg and CRP <10 mg/L

- Harvey Bradshaw Index (HBI) <5

Explanation: In order to prevent incorrect exclusion of patients in clinical remission, we decided to change the maximum CRP levels to 10 mg/l as part of the clinical remission definition, according to the most recent ECCO guideline (Gomollón F et al, JCC 2017;11:3-25).

Exclusion criteria

 Absence of written informed consent

 Concomitant corticosteroid usage

 Need for IBD-related surgery

 Actively draining peri-anal fistula

 Pregnancy or lactation

 Other significant medical conditions that might interfere with this study (such as current/recent malignancy, immunodeficiency syndromes and psychiatric illness)

 Impossibility to measure outcomes, e.g. planned relocation, language issues, short life expectancy

Study design

Design

Study type:	Interventional
Intervention model:	Parallel
Allocation:	Randomized controlled trial
Masking:	Open (masking not used)

Control:	Active

Recruitment

NL

Recruitment status:	Recruiting
Start date (anticipated):	03-05-2017
Enrollment:	174
Type:	Anticipated

IPD sharing statement

Plan to share IPD: Undecided

Ethics review

Positive opinion

Date:	29-05-2017
Application type:	First submission

Study registrations

Followed up by the following (possibly more current) registration

ID: 47881
Bron: ToetsingOnline
Titel:

Other (possibly less up-to-date) registrations in this register

No registrations found.

In other registers

Register	ID
NTR-new	NL6237
NTR-old	NTR6417
CCMO	NL58948.091.16
OMON	NL-OMON47881

Study results