Infliximab top-down in pediatric Crohn's disease

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Ethical review	Approved WMO
Status	Recruiting
Health condition type	Gastrointestinal inflammatory conditions
Study type	Interventional

Summary

ID

NL-OMON39629

Source
ToetsingOnline

Brief title
Infliximab top-down in pediatric Crohn's disease/ITSKids

Condition

- Gastrointestinal inflammatory conditions

Synonym
Crohn's disease, Inflammatory Bowel Disease

Research involving
Human

Sponsors and support

Primary sponsor: Erasmus MC, Universitair Medisch Centrum Rotterdam
Source(s) of monetary or material Support: ZonMw

Intervention

Keyword: Crohn's disease, Infliximab, Pediatric, Top-down

Outcome measures

Primary outcome

The primary endpoint at 52 weeks is steroid free remission.

Secondary outcome

The secondary endpoints will be mucosal healing at 10 weeks assessed by endoscopy. Endoscopy at 52 weeks will be performed to assess mucosal healing in case of persisting complaints. Faecal calprotectin will be performed at both 10, 52 weeks and at flare as an exploratory endpoint. Other secondary endpoints will be duration of clinical remission and clinical response assessed by PCDAI since induction, number of flares, prevention of complications (fistulas, strictures, need for surgery), growth, cumulative use of steroids and cumulative use of IFX and loss of IFX response. In patients with fistulizing disease from onset response will be defined as a reduction of at least 50 percent from baseline in the number of draining fistulas at 52 weeks.

Study description

Background summary

Crohn*s disease (CD) is an incurable, debilitating inflammatory bowel disorder (IBD) and already presents during childhood and adolescence in 25% of all CD patients. CD requires lifelong medication and is accompanied by severe complications. The use of anti-TNF antibodies has dramatically changed CD management. Infliximab (IFX) is the only anti-TNF antibody registered for pediatric CD. Currently, IFX is reserved for immunomodulator refractory patients. Instead of this step-up approach, top-down use, with introduction of IFX at an early stage of disease that may be more susceptible to

immunomodulation, might be more effective. In fact, top-down IFX treatment is able to change the natural course of disease, as shown in immunomodulator naive adult patients. Top-down IFX might prevent or postpone the emergence of strictures and/or fistulas that require surgery. In children, pharmacokinetic (PK) and -dynamic (PD) data on IFX are scarce. Mucosal healing, assessed by endoscopy, predicts a favorable outcome in adults.

Study objective

The primary objective of our study is to determine the efficacy and safety of top-down IFX treatment in moderate-to-severe pediatric CD.
Secundary objectives are determination of PK data and predictors of response to IFX in pediatric CD.

Study design

We will perform an international open-label RCT in 3 academic centers in the Netherlands, 1 academic center in Brussels, Belgium and 1 academic center in Rome, Italy.

Intervention

Patients will be randomized to either top-down IFX treatment or conventional step-up treatment.

a. Treatment arm 1: Top-down IFX treatment will consist of IFX treatment by 5 infusions of 5 mg/kg (IFX induction at week 0, 2 and 6, followed by 2 maintenance infusions every 8 weeks) combined with oral azathioprine (AZA) 2-3 mg/kg, once daily as maintenance treatment. IFX will be discontinued after 5 IFX infusions, while AZA will be continued.

b. Treatment arm 2: Step-up treatment will consist of standard induction treatment by oral prednisolone 1 mg/kg (maximum 40 mg) once daily for 4 weeks, then tapering of prednisolone in 6 weeks until stop, combined with oral azathioprine (AZA) 2-3 mg, once daily, as maintenance treatment. Patients with primary non-response will step-up to IFX induction, followed by maintenance.

c. In both treatment arms, IFX will be (re)started in case of relapse (PCDAI > 30 or increase of PCDAI by 15 or more). Patients starting IFX will be treated with IFX induction followed by maintenance every 8 weeks, patients re-starting IFX (because of flare) will be treated with IFX maintenance every 8 weeks (preceded by re-induction if indicated, at the discretion of the treating physician). Patients with loss of response to IFX will receive intensified IFX treatment by shortening the interval to 6 weeks and/or doubling the dose to 10 mg/kg.

Study burden and risks

The biggest burden for the study participants is the intravenous infusion of infliximab (5 mg/kg in 2 hours; total 5 times) for patients in the top-down treatment arm and undergoing colonoscopy at week 10 for all patients. The standardized study visits will replace regular visits and drawing of blood will be combined with regular drawings, therefore this is a minimal burden.

The benefit of the top-down treatment arm is the possible prevention of complications such as growth failure, fistulas and strictures requiring surgery. The benefit of the colonoscopy for the study participant is the assessment of mucosal healing, which has been shown to predict a favorable outcome in adult Crohn's disease patients.

Potential risks are concerns that infliximab (and other anti-TNF drugs) may increase the likelihood of tumor development. One particular serious type of lymphoma, hepatosplenic T-cell lymphoma (HSTCL) has been reported in 22 cases in association with inflammatory bowel disease and treatment worldwide (see E9).

Considering the very low absolute risk of developing a malignancy and the multiple complications with uncontrolled inflammatory bowel disease, the benefit of adequate treatment from diagnosis seems to outweigh the risk.

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adolescents (12-15 years)
Adolescents (16-17 years)
Children (2-11 years)

Inclusion criteria

Children (age 3-17 yrs) with new-onset CD with moderate-to-severe disease activity assessed by a PCDAI (pediatric Crohn's disease activity score) >= 30 after a diagnosis of Crohn's disease.

Exclusion criteria

Patients with disease limited to the ileocoecal region, immediate need for surgery, symptomatic stenosis or stricture in the bowel due to scarring, severe co-morbidity, infection, a positive tuberculin test or a chest radiograph consistent with tuberculosis or a malignancy. Patients that have already started drug treatment.

Study design

Design

Study type:	Interventional
Intervention model:	Parallel
Allocation:	Randomized controlled trial
Masking:	Open (masking not used)
Control:	Active
Primary purpose:	Basic science

Recruitment

NL

Recruitment status:	Recruiting
Start date (anticipated):	02-01-2013
Enrollment:	50
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Remicade
Generic name:	infliximab
Registration:	Yes - NL outside intended use

Ethics review

Approved WMO Date:	12-07-2012
Application type:	First submission
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	10-10-2012
Application type:	First submission
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	17-01-2013
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	26-02-2013
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	29-07-2013
Application type:	Amendment

Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	12-11-2013
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	20-06-2014
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	20-08-2014
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)

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
EudraCT	EUCTR2012-000645-13-NL
CCMO	NL39203.078.12