

Azithromycin Based Therapy for Induction of Remission in Active Pediatric Crohn's Disease

Published: 08-03-2013

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Evaluate the efficacy of the combination therapie with azithromycin and metronidazole in a randomized trial

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

Summary

ID

NL-OMON39861

Source

ToetsingOnline

Brief title

AZCRO

Condition

- Gastrointestinal inflammatory conditions

Synonym

Crohn's disease, Inflammatory bowel disease

Research involving

Human

Sponsors and support

Primary sponsor: Wolfson Medical Center

Source(s) of monetary or material Support: medical research en development fund for health services; Wolfson Medical Center Israel. Dit instituut (PI Prof Arie Levine) heeft een grant gekregen van de BROAD FOUNDATION.

Intervention

Keyword: Antibiotic therapy, Crohn's disease, Pediatrics

Outcome measures

Primary outcome

Response rate at 8 weeks defined as a drop in PCDAI of at least 12.5 points (or remission without steroids, intention to treat principle)

Secondary outcome

Clinical remission defined in PCDAI less than 10

Study description

Background summary

Recent reviews and guidelines no longer recommend antibiotic therapy for induction of remission in Crohn's disease (CD) due to studies showing lack of efficacy. Genetic and microbiological findings have demonstrated that CD is characterized by a defective innate immune response to bacteria and defective apoptosis of T cells. Bacteria have been shown to reside on, and invade epithelial cells, are present in granulomas and to replicate inside macrophage phagolysosomes in susceptible individuals. A defect in bacterial triggering from the luminal epithelial and intracellular compartments, while simultaneously trying to induce apoptosis, has never been explored. Azithromycin is an antibiotic with excellent intracellular penetration, high luminal concentrations, and is also effective against biofilms which have been described in CD. It is a potent activator of apoptosis of T cells. Preliminary data in pediatric patients with short duration of disease have shown a remission rate of 60% and normalization of CRP in about 50% of patients treated with azithromycin and metronidazole in combination. We hypothesize that a 2-month antibiotic course of azithromycin combined with metronidazole is effective for inducing remission in active pediatric Crohn's disease (CD). We also hypothesize that remission will be accompanied by normalization of CRP in a high proportion of patients with active CD. The goal of the present study is to evaluate the efficacy of this combination in a randomized controlled trial (RCT).

Study objective

Evaluate the efficacy of the combination therapie with azithromycin and metronidazole in a randomized trial

Study design

After inclusion and signed informed consent will be randomized eithe in group 1 (azithromycin and metronidazole) or group 2 (only metronidazole).

Intervention

Group 1: Oral Azithromycin 7.5 mg/kg once daily (maximum 500mg) 5 consecutive days a week for the first 4 weeks and 3 consecutive days a week for the last 4 weeks

+ metronidazole 10mg/kg X2/day (maximum 1000mg) for 8 weeks

Group 2: Oral metronidazole 10mg/kg X2/day (maximum 1000mg) for 8 weeks

Study burden and risks

Risks associated with participation are minimal. We hypothesize that a 2-month antibiotic course of azithromycin combined with metronidazole is effective for inducing remission in active pediatric Crohns disease (CD). We also hypothesize that remission will be accompanied by normalization of CRP in a high proportion of patients with active CD.

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

1. Children 5-17 years of age; 2. Diagnosis of active Crohn's disease; 3. Patients with a PCDAI equal of more than 10 and equal or less than 40 (mild to moderate disease); 4. Have involvement of the colon and/or terminal ileum; 5. Disease defined as L1, L2, L3 or any of the above and may have gastric, duodenal or esophageal disease (L4a) according to the Paris classification for site of disease; 6. The CRP is equal or more than 0.6 mg/dL; 7. Duration of disease since diagnosis equal or less than 3 years; 8. Negative stool culture, Clostridium Difficile Toxin from current flare

Exclusion criteria

1. Duration of disease since diagnosis more than 3 years.
2. Positive stool culture or O&P last 30 days.
3. Presence of Clostridium difficile toxin in stool.
4. Azithromycin or Metronidazole allergy or known intolerance.
5. Diagnosis of IBD-U
6. Presence of macroscopic disease involving the proximal ileum or jejunum (L4b)
7. Continuous macroscopic disease of the colon appearing as typical ulcerative colitis and Crohn's diagnosed only by focality or granuloma on biopsies.
8. Presence of extraintestinal manifestations (such as arthritis, uveitis, or sclerosing cholangitis). Aphthous lesions of mouth can be included.
9. Presence of fibrostenotic disease (strictures with prestenotic dilatation).
10. Presence of penetrating disease (fistulas or abscess).
11. Presence of current perianal disease defined as fistula or abscess.
12. Patients receiving concurrent corticosteroids or biologics.
13. Patients who have received steroids in the past 14 days.
14. Immune deficiency (CGD, GSD1, IL10R etc).
15. Known allergy or intolerance to any of the study medications.
16. Concurrent disease such as hepatitis, ALT more than 2 times, UNL, renal failure.
17. Pregnancy,
18. Patients with known heart disease.

19. Prolonged QTc by ECG at baseline.
20. Patients after surgical intestinal resection.
21. Present use of medications known to prolong QTc, such as cisapride, terfenadine, domperidone, erythromycin, and ergotamines.
22. Present use of acenocoumarol or digoxin.

Study design

Design

Study phase:	3
Study type:	Interventional
Intervention model:	Parallel
Allocation:	Randomized controlled trial
Masking:	Single blinded (masking used)
Control:	Active
Primary purpose:	Treatment

Recruitment

NL	
Recruitment status:	Recruitment stopped
Start date (anticipated):	28-10-2014
Enrollment:	6
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Azithromycin
Generic name:	Azithromycin
Registration:	Yes - NL outside intended use
Product type:	Medicine
Brand name:	Metronidazole
Generic name:	Metronidazole
Registration:	Yes - NL outside intended use

Ethics review

Approved WMO

Date: 08-03-2013

Application type: First submission

Review commission: METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)

Approved WMO

Date: 11-11-2013

Application type: First submission

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	EUCTR2012-005226-29-NL
ClinicalTrials.gov	NCT01596894
CCMO	NL42267.078.12