Effect of N-acetylcysteine on thiopurine related hepatotoxicity in IBD patients

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1. Determine the influence of acetylcysteine on thiopuirine related hepatotoxicity2. Determine the relation between hepatotoxicity, thiopurine metabolism, amino acid availablility and markers for oxidative stress3. Determine the effect of...

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

Summary

ID

NL-OMON33536

Source
ToetsingOnline

Brief title
NACTOX

Condition

- Gastrointestinal inflammatory conditions

Synonym
hepatotoxicity, liver damage

Research involving
Human

Sponsors and support

Primary sponsor: Vrije Universiteit Medisch Centrum
Source(s) of monetary or material Support: HLW,HLW bv Helmond

Intervention

Keyword: hepatotoxicity, inflammatory bowel diseases, N-acetylcysteine, thiopurines

Outcome measures

Primary outcome

1. alteration of the livertests including aspartate aminotransferase (ASAT), alanine aminotransferase (ALAT), alkaline phosphatasem (AP), gamma-glutamyl transferase (GGT) and bilirubine (Bili).

Secondary outcome

1. To determine the influence of co-administration of N-acetylcysteine (NAC) on thiopurine metabolite levels (6-MMP and/or 6-TGN), xanthine oxidase (XO) activity, amino acid availability and parameters of oxidative stress in thiopurine using IBD patients.

2. To ascertain a correlation between thiopurine metabolite levels (6-TGN and 6-MMP), parameters of oxidative stress, XO activity, amino acid levels and liver test abnormalities in thiopurine using IBD patients.

Study description

Background summary

Thiopurines such as azathioprine (AZA), 6-mercaptopurine (6-MP) and 6-thioguanine (6-TG) are frequently prescribed drugs for the treatment of inflammatory bowel diseases including ulcerative colitis and Crohns disease. Hepatotoxicity is a frequently encountered adverse event of thiopurines. The pathophysiology is not completely elucidated. Rodent models showed that thiopurine related hepatotoxicity correlated with glutathion depletion leading to livercell injury. These models also showed that suppletion of glutathion via N-acetylcysteine increased glutathion and cell viability by reducing oxidative

stress.
This principle is has not been studied in vivo. Hypothetically supplementation of N-acetylcysteine could attenuate thiopurine related hepatotoxicity. If supplementation of N-acetylcysteine reduces hepatotoxicity than thiopurine therapy could be continued. This keeps the risk of relapse low and saves the use of expensive biological rescue drugs.

Study objective

1. Determine the influence of acetylcysteine on thiopuirine related hepatotoxicity

2. Determine the relation between hepatotoxicity, thiopurine metabolism, amino acid availablility and markers for oxidative stress

3. Determine the effect of acetylcysteine co-administration on thiopurine metabolites, amino acid availability and markers for oxidative stress

Study design

Open label phase II paralell group cross-over intervention study with a duration of 16 weeks. The aimed total of participants to include is 30. After screening ,within these 16 weeks the patients will visit the outpatient clinic five times. During four out of the 16 weeks, acetylcysteine will be administered in a dose of 1200mg twice daily.

Intervention

Group 1: Thiopurine therapy will be continued during the first eight weeks of the study. During the fisrt four weeks acetylcysteine 1200mg twice daily will be co-administered. Weeks 5 to 8 no acetylcysteine will be administered. During the weeks 9 to 12 thiopurine therapy will also be discontinued. Rechallenge of thiopurine therapy is during the weeks 13 to 16.

Group 2: Thiopurine therapy will be continued during the first eight weeks of the study. During the weeks 5 to 8 acetylcysteine 1200mg twice daily will be administered. Both thiopurine therapy and acetylcysteine will be discontinued during the weeks 9 to 12. Rechallenge of thiopurine therapy is during the weeks 13 to 16.

All patients, after screening, visit the outpatient clinic the first day of weeks 1, 5, 9, 13 and 17 for blood drawing and urine colection. Any adverse events will be reported and disease activity will be scored. The study visit in week one, also body weight and length will be ascertained.

Study burden and risks

Patients will visit the outpatient clinic five times with an interval of four weeks if the outcome of screening tests permits enrolment in the study. In case of mild hepatotoxicity, thiopurine therapy continues for the first eight weeks and the last four weeks of the study. This could result in worsening of liver test abnormalities. In addition, patients receive 2400mg NAC for four weeks daily during the first or the second four week period of this study. Every visit blood will be drawn and the patient will be asked about adverse events. The potential benefit of participation in this study is that NAC may attenuate hepatotoxicity, hence patients might be able to continue thiopurine therapy when indicated. This is particularly interesting when alternative (medicinal) therapies lack.

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)
Elderly (65 years and older)

Inclusion criteria

written informed consent; adult patients, aged between 18 and 70 years; Crohn's disease or ulcerative colitis; azathioprine, 6-mercaptopurine or 6-thioguanine therapy, Grade 1 or 2 on the CTCAE v3.0 of at least one of the following liver tests: aspartate aminotransferase (ASAT), alanine aminotransferase (ALAT), alkaline phosphatase (AP), gamma-glutamyl transferase (GGT) or total bilirubine (Bili).

Exclusion criteria

Serological findings consistent with active viral hepatitis A, B, C EBV or CMV; findings suggesting auto-immune hepatitis (AIH); cholestasis; known liver diseases inlcuding: Hepatitis A, B or C, cirrhosis, AIH, primary sclerosing cholangitis, primary biliairy cirrhosis, hepatocellular carcinoma, metastatic liver disease or symptomatic cholecystolithiasis; Use of methotrexate or other chemotherapy within the last three months; use of N-acetylcysteine during thioipurine therapy; allergy to N-acetylcysteine; lactation; pregnancy; 6-TGN level >1200 pmol

Study design

Design

Study phase:	2
Study type:	Interventional
Intervention model:	Crossover
Allocation:	Randomized controlled trial
Masking:	Open (masking not used)

Primary purpose: Treatment

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	02-12-2009
Enrollment:	30
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	N-acetylcysteine
Generic name:	N-acetylcysteine
Registration:	Yes - NL outside intended use

Ethics review

Approved WMO Date:	24-02-2009
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	13-05-2009
Application type:	First submission
Review commission:	METC Amsterdam UMC

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	EUCTR2008-005015-17-NL
CCMO	NL24682.029.09