Thiopurines with Low Dose Allopurinol: a prospective one way cross-over study

Published: 17-05-2016
Last updated: 16-04-2024

Primary objective: Investigating whether 50 mg allopurinol is non-inferior to 100 mg in combination with azathioprine or mercaptopurine by measuring and comparing thiopurine metabolites Secondary objectives:-Comparing patient tolerability in terms...

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

Summary

ID

NL-OMON42907

Source
ToetsingOnline

Brief title
ThiLDA-study

Condition

- Gastrointestinal inflammatory conditions

Synonym
Crohn, inflammatory bowel disease

Research involving
Human

Sponsors and support

Primary sponsor: Meander Medisch Centrum
Source(s) of monetary or material Support: Ziekenhuisbudget

Intervention

Keyword: allopurinol, colitis, crohn, thiopurine

Outcome measures

Primary outcome

- 6-TGN and 6-MMP concentrations

These are the metabolites of the thiopurine that is being used by a patient.

The concentrations before and after the intervention will be measured with (a validated) UPLC-analysis.

Secondary outcome

-Incidence of adverse events

The incidence of adverse events before and after the intervention will be compared.

-Allopurinol concentrations

Allopurinol concentrations will be measured with a validated HPLC-analysis.

-Enzyme activity XO, TPMT and HPRT

These enzymes are involved in the metabolism of thiopurines and their metabolites. The enzyme activity of these enzymes will be measured with a validated enzyme assay (HPLC and radioactivity).

-Disease activity (HBI scores for Crohn's and Mayo scores for Colitis Ulcerosa, CRP, faecal calprotecin)

The HBI and Mayo score are validated and widely used scoring tools for defining

disease activity of patients with respectively Crohn's and CU. These two

indices will also be used within this study population to compare disease

activity before and after the intervention.

Other parameters:

-Thiopurine (azathioprine or mercaptopurine) dose

-Duration of previous allopurinol 100 mg usage

-Indication of thiopurine (Crohn's or Colitis Ulcerosa)

Study description

Background summary

Crohn's disease and Colitis Ulcerosa patients frequently use a thiopurine (azathioprine or mercaptopurine) to reduce disease activity. These drugs are metabolised in a few metabolites, including 6-thioguanine (6-TGN) and 6-methylmercaptopurine (6-MMP).

Therapeutic 6-TGN concentrations correlate with the efficacy of thiopurines, while 6-MMP and 6-TGN concentrations that are too high can lead to hepato- en myelotoxicity (liver disease, trombocytopena, anemia, pancreatitis en leucopenia).

About 25% of thiopurine users has non-therapeutic 6-TGN and/or supratherapeutic 6-MMP concentrations with a 6-MMP/6-TGN ratio > 10. These patients are normally treated with additional allopurinol 100 mg once daily, because allopurinol interferes with the metabolism of thiopurines by inhibiting the enzym xanthine oxidase (XO). The dosage of the thiopurine is then lowered to ~25-33% of the original dose. This intervention causes the metabolism to shift from mainly 6-MMP to 6-TGN and causes an improvement of the 6-MMP/6-TGN ratio. A number of studies has shown previously that this intervention is safe and effective in daily practice.

In our hospital, Meander Medical Center, a part of our patients who are using allopurinol 100 mg once a day does not tolerate this drug. A recent study has

shown that 50 mg of allopurinol might be equally effective as 100 mg, and might be better tolerated. In the current study this will be investigated intrapatiënt by giving the same patients 50 mg allopurinol instead of 100 mg.

This study can lead to better understandig of the effectiveness and tolerability of allopurinol 50 mg so that patients are not unnecessarily exposed to a high dose of allopurinol.

Study objective

Primary objective:
Investigating whether 50 mg allopurinol is non-inferior to 100 mg in combination with azathioprine or mercaptopurine by measuring and comparing thiopurine metabolites

Secondary objectives:

-Comparing patient tolerability in terms of adverse events
-comparing allopurinol concentrations
-comparing enzyme activity for XO, TPMT and HRPT
-comparing disease activity (HBI and Mayo scores, CRP, faecal calprotectin)

Study design

a prospective one way cross-over study

Intervention

Reducing the dose of allopurinol: from 100 to 50 mg once a day

Study burden and risks

Evaluation of burden and risks:
-Patients will be seen in our hospital during their regular, existing appointments (polyclinical).
-Only additional blood will be taken from patients during their existing polyclinical and laboratory analysis appointments.
-Patients will be asked about their experience, just as in daily practice.
-Recently performed research has proven the safety of a similar intervention.

Contacts

Public
Meander Medisch Centrum

Maatweg 3
Amersfoort 3813 TZ
NL
Scientific
Meander Medisch Centrum

Maatweg 3
Amersfoort 3813 TZ
NL

Trial sites

Listed location countries

Netherlands

Eligibility criteria

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

Inclusion criteria

-Crohn's disease or Colitis Ulcerosa
-At least one month perior usage of 100 mg allopurinol daily with azathioprine or mercaptopurine
-Stable response and adequate concentrations on combination therapy with a thiopurine and allopurinol
-No recent (<1 month) changes in thiopurine dosage
-At least 18 years old

Exclusion criteria

-Age below 18 years old
-Pregnancy
-Hypersensitivity to azathioprine, mercaptopurine and/or allopurinol
-Severe anemia, leukopenia or thrombocytopenia
-Lesch-Nyhan syndrome

Study design

Design

Study type: Interventional

Masking:	Open (masking not used)
Control:	Uncontrolled
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	01-09-2016
Enrollment:	22
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Allopurinol 100 mg
Generic name:	allopurinol
Registration:	Yes - NL outside intended use

Ethics review

Approved WMO Date:	17-05-2016
Application type:	First submission
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)

Approved WMO Date:	08-07-2016
Application type:	First submission
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)

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	EUCTR2016-001638-84-NL
CCMO	NL57653.100.16