Randomised, double-blind, placebo-controlled, multi-centre trial on the efficacy and safety of budesonide for induction of remission in incomplete microscopic colitis

Published: 25-02-2014
Last updated: 20-04-2024

* To demonstrate efficacy of budesonide (9 mg budesonide/d) vs. placebo for induction of remission in active incomplete microscopic colitis after 8 weeks of treatment* To study the maintenance of remission after end of treatment* To study safety and…

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

Summary

ID

NL-OMON45182

Source
ToetsingOnline

Brief title
BUG-3/MIC

Condition

- Gastrointestinal inflammatory conditions

Synonym
Incomplete microscopic colitis, inflammation large intestine

Research involving
Human

Sponsors and support

Primary sponsor: Dr. Falk Pharma GmbH
Source(s) of monetary or material Support: Industry - Dr Falk Pharma

Intervention

Keyword: budesonide, incomplete microscopic colitis, placebo

Outcome measures

Primary outcome

* Rate of clinical remission at final/withdrawal visit (clinical remission

defined as a mean of < 3 stools/day and a mean of < 1 watery stool/day during

the week prior to the visit)

Secondary outcome

Double-blind phase:

* Rate of clinical remission at V2 and V3

* Time to remission

* Total number of stools in the week prior to V2, V3, V4/withdrawal and change

from baseline

* Number of formed stools in the week prior to V2, V3, V4/withdrawal and change

from baseline

* Number of soft stools in the week prior to V2, V3, V4/withdrawal and change

from baseline

* Number of watery stools in the week prior to V2, V3, V4/withdrawal and change

from baseline

* Number of days with abdominal pain in the week prior to V2, V3, V4/withdrawal

and change from baseline

* Number of urgent stools in the week prior to V2, V3, V4/withdrawal and change from baseline

* Number of stools with urgency grade 3 (have to go immediately to the toilette) in the week prior to V2, V3, V4/withdrawal and change from baseline

* Number of stools with difficulties staying continent in the week prior to V2, V3, V4/withdrawal and change from baseline

* Number of days with bloating in the week prior to V2, V3, V4/withdrawal and change from baseline

* Changes from baseline of histological signs (inflammation of the lamina propria, thickness of the subepithelial collagen band, number of IELs in the surface epithelium, degeneration of the surface epithelium) at V4/withdrawal

* Rate of histological remission as defined in 6.4.7 at V4/withdrawal

* Rate of histological improvement/no change/aggravation as defined in 6.4.7 at V4/withdrawal

* Physician*s Global Assessment (PGA) at V4/withdrawal

* Short Health Scale (SHS) dimensions symptom burden, social function, disease-related worry and general well-being at V2, V3, V4/withdrawal and change from baseline

Follow-up phase:

* Rate of responders maintaining clinical remission at FU1 and FU2

* Rate of patients with relapse at FU1 and FU2 (relapse defined as a mean of * 3 stools/day and thereof a mean of * 1 watery stool/day during at least one

week)

* Time to relapse

Safety variables

* Incidence and type of Adverse Events (AEs)

* Vital signs (blood pressure, heart rate) at V2, V3, V4/withdrawal and change

from baseline, body weight at V4/withdrawal and change from

baseline

* Haematology, blood chemistry, urinalysis

* Assessment of tolerability by investigator and patient

Study description

Background summary

Microscopic colitis (MC) is a leading cause of repetitive periods of chronic non-bloody diarrhoea, in particular in the elderly, with a profound negative impact on quality of life.
For the individual patient, the clinical symptoms associated with both MC subtypes * collagenous colitis and lymphocytic colitis - cannot be distinguished from other causes of watery diarrhoea including drug induced diarrhoea, irritable bowel syndrome and bile acid diarrhoea. As the colonic mucosa at colonoscopy appears macroscopically normal or nearly normal, the diagnosis MC rests on strict, albeit controversial histopathological findings in colonic biopsies taken from the rectum to the proximal colon, including the caecum.
Abnormal chronic inflammation in the lamina propria is a typical characteristic but does not help to distinguish between the subtypes of MC. Collagenous colitis (CC) is characterised by a thickened subepithelial collagen band, i.e., > 10 *m in well oriented biopsies cut perpendicularly to the surface, and lymphocytic colitis (LC) is characterised by an increased number of intraepithelial lymphocytes (IEL), i.e., * 20 IEL per 100 epithelial cells.
Colonic biopsies are regarded normal when the lamina propria is without chronic inflammation, the number of surface epithelial cells is * 5 IEL/100, and the collagen band is * 5 micrometers. Warren et al. found the original definitions

of limited use for routine diagnosis. The terms MC *not otherwise specified* (MC nos) and *paucicellular* lymphocytic colitis have been used to describe a subgroup of patients with chronic
diarrhoea and an increased cellular infiltrate in the lamina propria.
Recent results indicate that the present diagnostic criteria may not ensure that all patients with MC receive effective treatment. Histological findings in the individual patient are inconsistent over time, as findings of MC interchange with chronic (non-specific) inflammation or incomplete signs of MC at prior or repeat colonoscopy, and the overlap between CC and LC is significant. Even more important, a large group of patients with chronic diarrhoea, symptoms and findings indistinguishable from those with CC and LC, but with incomplete histological signs of MC appear to have an effect of budesonide treatment similar to that of patients with MC. Furthermore, there is no correlation between symptoms
and neither the thickness of the subepithelial collagenous layer nor the number of intraepithelial lymphocytes. The histological interchange between MC subtypes and the incomplete identification of some patients have led to the introduction of the term incomplete MC (MCi) for this third MC subtype.
The histological criteria for MCi are an abnormally thickened collagenous band (> 5 and < 10 *m), and /or an increased number of intraepithelial lymphocytes (> 5 and < 20 per 100 epithelial cells) without reaching the thickness or number required for the diagnosis of CC or LC.
Controlled trials of interventions to induce remission in patients with MC are few and largely performed with budesonide. Progress has been hampered by restricting most trials to one subtype only (CC or LC). Budesonide has proven consistently effective, although a single definition of remission has yet to be agreed on and validated.
Recently, MCi was proposed as a third subgroup of MC. Patients with MCi display a wider variety of gastrointestinal symptoms and a higher incidence of bile acid malabsorption and lactose malabsorption than cases with CC or LC indicating a more heterogenic group. In addition, a significant subgroup of patients with MCi had in fact LC or CC when subjected to a pathological re-examination or to a new endoscopy with biopsies. Finally, the clinical effect of budesonide in the MCi-group was apparently similar to that of the other MC subtypes in which efficacy was identical to that of controlled trials and independent of coexisting bile acid diarrhoea. Due to the lack of controlled data, prospective therapeutic trials of patients with MCi are needed.
Traditionally, the primary efficacy parameter, clinical remission, has been determined after 4 to 8 weeks of double-blind treatment. However, several studies indicate that the effect is evident already after 2 weeks. To allow for direct comparison with previous studies the primary efficacy parameter will be determined after 8 weeks of treatment and early efficacy will be a secondary efficacy parameter, anticipating that shorter treatment periods will be feasible in future studies.

Study objective

* To demonstrate efficacy of budesonide (9 mg budesonide/d) vs. placebo for induction of remission in active incomplete microscopic colitis after 8 weeks of treatment
* To study the maintenance of remission after end of treatment
* To study safety and tolerability of budesonide
* To assess patients* health related quality of life
* To assess the proportion of patients that fulfil the criteria for irritable bowel syndrome (ROME III criteria)

Study design

The trial is designed as a prospective, double-blind, randomised, placebo-controlled, parallelgroup, multi-centre, multi-national, comparative phase III trial. The trial will be conducted with two arms in the form of a parallel group comparison and will serve to compare oral budesonide and placebo for induction of remission in patients with incomplete microscopic colitis. The trial is subdivided in 3 phases:

- Screening phase, lasting up to two weeks:
Patients considered suitable for entry into the trial will be recorded on a registration log and then informed about the trial, both verbally and by reviewing the patient informed consent.
Once written consent is obtained, patients will be screened for their suitability for entry into
the trial, using the selection criteria.

- 8-weeks treatment phase:
Eligible patients will be randomised in one of the two following treatment groups in conformity with a randomisation list:
A Budenofalk® 9 mg gastro-resistant granules OD
B Placebo granules OD

After randomisation patients will undergo visits at week 2, week 4 and 8 post randomisation, to assess efficacy and safety of the treatment.
It is planned to randomise 53 patients in each group, i.e., a total of 106 patients.

- 24-weeks follow-up phase:
Responders (patients in clinical remission) will be followed up by telephone at week 20 and 32 post randomisation, to assess the maintenance of clinical remission after the treatment phase.

Intervention

8 weeks treatment with either budesonide or placebo. Medication is taken orally and once daily.

Study burden and risks

Microscopic Colitis is a condition associated with chronic watery diarrhoea, abdominal pain, weight loss and a high impact on health related quality of life and social life. As a first step, drugs suspected of being able to cause MC (e.g., NSAIDS or proton-pump inhibitor) should be tried to stop. Also, generic anti-diarrhoeal drugs can be given. If these measures are unsuccessful, more specific medical treatment is indicated.
Budesonide is currently the best-documented treatment in CC and LC and seems to be effective also in MCi. Budesonide is a well-known, highly potent non-halogenated glucocorticosteroid. Its highly anti-inflammatory action makes it ideal for the treatment of asthma and gastrointestinal disorders. Budesonide is licensed since 1998 and clinical experiences are abundant for various indications and also for diverse preparation forms.
A daily dose of 9 mg OD was chosen, because in four previous placebo-controlled trials in CC and in one trial in LC this dosage turned out to be effective and safe. Due to its rapid inactivation by biotransformation in the liver, budesonide has a very low bioavailability when absorbed through mucosal surfaces. This minimises systemic side effects and leads to a high ratio of topical versus systemic activity. The steroid action of budesonide is mainly restricted to the target organs, so that even low dosing leads to a good therapeutic outcome and long term treatment is well tolerated.
Patients randomised to the verum group of this clinical trial will be treated with a well-known drug, shown to be safe and efficient for the treatment of inflammatory bowel disease. With the proven effectiveness of budesonide in CC and LC (see above), it is expected that the drug will be efficacious also in MCi.

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

1. Signed informed consent,
2. Man or woman between 18 and 80 years of age,
3. Histologically established diagnosis of incomplete microscopic colitis (MCi) defined as the following findings in at least two segments of the colon:
* increased lymphoplasmacellular infiltrate in the lamina propria and
* thickened subepithelial collagenous band > 5 *m and < 10 *m and/or
* abnormal intraepithelial lymphocytes > 5 and < 20 per 100 epithelial cells,
4. History of chronic non-bloody, watery diarrhoea for at least 4 weeks,
5. Clinically active disease (defined as a mean of * 3 stools/day, thereof a mean of * 1 watery stool/day during the week prior to randomisation),
6. Women of child-bearing potential have to apply during the entire duration of the study a highly effective method of birth control, which is defined as those which result in a low failure rate (i.e., less than 1% per year) when used constantly and correctly such as implants, injectables, combined oral contraceptive method, some IUDs, sexual abstinence or vasectomised
partner. The investigator is responsible for determining whether the patient uses adequate birth control for study participation.

Exclusion criteria

1. Other significant abnormalities in colonoscopy that may have been the cause of diarrhoea except for colonic diverticulosis and non-dysplastic polyps < 2 cm,
2. Infectious cause of diarrhoea (local routine stool samples, Clostridium difficile included) or history of infectious diarrhoea within the last 3 months prior inclusion or local intestinal infection,
3. Clinical suspicion of drug-induced diarrhoea,
4. Prior and present MC (i.e., all histological criteria for collagenous colitis or lymphocytic

colitis fulfilled),
5. History of bowel resection,
6. Radiation therapy of the abdominal or pelvic region,
7. Positive antibody titres for celiac disease (tGT IgA + serum IgA),
8. Untreated active thyroid dysfunction,
9. Any severe concomitant cardiovascular, renal, endocrine, or psychiatric disorder reducing life expectancy,
10. Abnormal hepatic function (ALT or ALP > 2.5 x upper limit of normal [ULN]), liver cirrhosis, or portal hypertension,
11. Tuberculosis, hypertension, diabetes mellitus, osteoporosis, peptic ulcer disease, glaucoma, cataract, or infection if careful medical monitoring is not ensured,
12. History of colorectal cancer,
13. History of cancer (other than colorectal) in the last 5 years,
14. Therapy with immunomodulators (e.g., azathioprine, 6-mercaptopurine, or methotrexate) within 3 months prior to baseline,
15. Treatment with budesonide or other steroids within 4 weeks prior to baseline,
16. Treatment with antibiotics within 4 weeks prior to baseline,
17. Treatment with anti-diarrhoeal drugs (e.g., loperamide, ispaghula, codeine, and opium), cholestyramine, bulking agents, and spasmolytics within 2 weeks prior to baseline,
18. Known intolerance/hypersensitivity/resistance to the trial drug or drugs of similar chemical structure or pharmacological profile,
19. Current or intended pregnancy or breast-feeding,
20. Doubt about the patient*s cooperation, e.g. because of addiction to alcohol or drugs,
21. Participation in another clinical trial within the last 30 days, simultaneous participation in another clinical trial, or previous participation in this trial.

Study design

Design

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

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	03-12-2015
Enrollment:	6
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Budenofalk
Generic name:	Budesonide
Registration:	Yes - NL outside intended use

Ethics review

Approved WMO Date:	25-02-2014
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	22-05-2014
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	12-08-2016
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	03-02-2017
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	12-07-2017
Application type:	Amendment
Review commission:	METC Amsterdam UMC

Approved WMO Date:	18-07-2017
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	26-07-2017
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	05-07-2018
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	19-07-2018
Application type:	Amendment
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	EUCTR2013-001912-31-NL
CCMO	NL46786.029.14

Study results

Results posted:	08-04-2021
Actual enrolment:	1

Summary results
Trial ended prematurely

First publication
18-03-2021