Multicentre, controlled, randomised, investigator-blinded, comparative study of oral Mesalazine 4g per day Once daily versus 4g per day in Two divided doses in patients with active Ulcerative colitiS (MOTUS study)

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Primary objective: To demonstrate that mesalazine po 4g per day once daily (QD.) is non-inferior to the reference regimen, mesalazine 4g per day in two divided doses (BID.) (2g x 2 per day), in patients with active ulcerative colitis treated for 8...

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

Summary

ID

NL-OMON32538

Source
ToetsingOnline

Brief title
MOTUS

Condition

- Gastrointestinal conditions NEC

Synonym
IBD, ulcerative colitis

Research involving

Human

Sponsors and support

Primary sponsor: Ferring
Source(s) of monetary or material Support: Ferring BV

Intervention

Keyword: dosing frequency, mesalazine, once daily, ulcerative colitis

Outcome measures

Primary outcome

Remission at week 8.

Secondary outcome

• Compliance

• Clinical remission at week 4 and week 8

• Clinical variables improvement (stool frequency and bloody stools) at week 4,

8 and 12 separately

• Treatment failure rates at W4 and W8

• Time to remission according patient*s diary (normal stool frequency and

cessation of bleeding)

• Time to cessation of bleeding

• Improvement at week 4 and 8 based on UC-DAI score

• Endoscopic assessment at W0 and W8

• Acceptability of the treatment

• Safety

• Proportion of patients staying in clinical remission at week 12.

Study description

Background summary

Ulcerative colitis (UC), an inflammatory bowel disease (IBD), is a chronic condition of unknown origin. Ulcerative colitis is a relapsing and remitting disease characterised by acute non-infectious inflammation of the colorectal mucosa (14) (Ghosh S., Shand A., Fergusson A. 2000). The estimated incidence of UC is in Europe of 8 new cases per year for 105 inhabitants and 4/105 in France. The estimated prevalence is 21 to 243/105 in Europe and 60/105 in France. Active episodes of UC are marked by passing of blood and mucus, diarrhoea and abdominal pain presenting as urgency and tenesmus (1) (Baumgart and Sandborn 2007). In the most severe forms, systemic signs comprising fever, anorexia and weight loss may occur. Approximately 60% of the patients have a mild form, 25% a moderate form and 15% a severe disease. It is estimated that approximately one of every two patients with UC will experience a relapse within one year and the cumulative probability of relapse is 80% within 2 years and 95% within 10 years (2) (Carter, Lobo et al. 2004).
In this disease, involvement of the rectal mucosa is a constant feature while the inflammation spreads to higher levels in continuous and retrograde fashion, with no sparing of mucosa from the anorectal junction. Hence, UC may be divided in proctitis, proctosigmoiditis, left-sided colitis (the proximal limit being below the splenic flexure), extensive colitis (involving the transverse colon), or pancolitis.
The aim of the treatment is to induce remission and then maintain it. Several therapeutic drug classes are used in UC: aminosalicylate derivatives, corticosteroids, immunosuppressants and anti-TNF* agents. Aminosalicylate derivatives are the chief therapy for mild to moderate episodes of UC and for maintenance treatment (27) (Marteau, Seksik et al. 2004). Rectal administration of salicylate-type drugs constitutes the treatment of choice in proctitis, proctosigmoiditis, and left-sided ulcerative colitis (4, 24, 25), (Cohen, Woseth et al. 2000; Marshall and Irvine 1995; Marshall and Irvine 2000). Oral mesalazine constitutes the treatment of choice in inducing remission of mild to moderate episodes of extensive forms (16,32) (Hanauer 2004; Sutherland and MacDonald 2006).
The optimum dose of mesalazine for induction therapy in order to achieve remission is between 3 and 4 g/d by the oral route and 1 g/d by topical administration (enema) (31) (Riley 1998). The time required to achieve remission in active episodes of UC with oral mesalazine is approximately 8 weeks. The rapidity of action of mesalazine in alleviating symptoms of active UC may be increased by supplementing oral treatment with topical therapy comprising mesalazine enema for the first 4 weeks. A randomised controlled study by Marteau et al demonstrated that combined 4g/d oral mesalazine for 8 weeks and 1g/d topical mesalazine during the initial 4 weeks is superior to oral therapy alone in terms of remission rates at 8 weeks (64% vs 43%, p=0.03)

and in terms of time to cessation of rectal bleeding (p=0.0025) (26) (Marteau, Probert et al. 2005). Several consensus conferences have recommended a combination of both oral and topical treatment, either after a delay (27) (Marteau, Seksik et al. 2004), either immediately (33) (ECCO 2008).
A key element in therapeutic response in UC is treatment compliance. In daily practice, compliance of UC patients with 5-ASA treatment appears mediocre, particularly in maintenance therapy. In a study of 94 patients with UC in clinical remission, only 40% effectively continued to take their treatment at the prescribed dosage (19) (Kane, Cohen et al. 2001). Poor or non-existent compliance affects not only treatment response but also disease progression. Indeed, the same author detected an increased risk (5-fold greater) of recurrence in non-compliant patients compared with their compliant counterparts (relative risk: 5.5; confidence interval: 2.3-13.0; p<0.001) (18) (Kane, Huo et al. 2003). This issue of treatment compliance with salicylates is thus of crucial importance not only as regards maintenance treatment of UC in remission but also for the treatment of active episodes of the disease. For these reasons, any means of increasing patient compliance with mesalazine therapy are extremely welcome (10) (Evans and Spelman 1983).

An inverse relationship has been found between the number of daily doses prescribed and treatment compliance (3) (Claxton, Cramer et al. 2001). Thus, reduction to a single daily dose of mesalazine is a major factor likely to significantly increase treatment compliance. A non-inferiority study showed that at an identical dose of 4 g/d mesalazine, the efficacy of mesalazine given 2 or 4 times daily is identical with regard to active UC and that the dose frequency was described as optimal in 78% in the twice daily group compared to 26% in the 4 times daily group (11) (Farup, Hinterleitner et al. 2001).
However, reduction of the dosage to twice-daily intake may not be sufficient to improve compliance. In a very recent study, (7) Dignass et al compared a once daily versus a twice daily regimen of patient receiving 2g/d of mesalazine for the maintenance of remission in ulcerative colitis. The authors showed that the once daily regimen was not only equally effective to the twice daily regimen but was also superior in terms of remission rates at 12 months. The compliance assessed with a patient questionnaire was higher in the once daily group (7) (Dignass, Vermeire UEGW 2007). In addition, it was recently demonstrated that QD slow release mesalazine was efficacious in active UC (17, 22) (Kamm, Sandborn et al. 2007; Lichtenstein, Kamm et al. 2007).
Moreover, a very recent double-blind, double-dummy, randomised study (21) (Kruis W., Gorelov A. et al 2007) compared a once daily versus a three-time daily regimen of 3g/d of mesalazine for the induction of remission in ulcerative colitis. The once daily group showed slightly (though not significant) better efficacy in nearly all endpoints at 8 weeks.
These results are supported by a pharmacokinetic study comparing the bioavailability in the intestinal mucosa of mesalazine or its main metabolite (N-acetyl-mesalazine) in a single dose of 4 g and 2 g twice-daily regimen (13) (Gandia, Idier et al. 2007).
In addition, it should be pointed out that the safety and tolerability of these

regimens is acceptable. In the Marteau trial combining 4g/d oral mesalazine for 8 weeks and 1g/d topical mesalazine during the initial 4 weeks in patient with active UC, the occurrence of adverse events was comparable for the 4+1g/d group and the 4g/d group (34% vs 50% respectively). The majority of these adverse events were mild or moderate and the most common were diarrhoea, headache, vomiting, and abdominal pain. During the study period, there were no relevant changes in serum creatinine, urinary protein, urinary haemoglobin, platelet, white blood cells or red blood cells count whatever the treatment group. Elevation of hepatic enzymes was seen in 1 patient/71 of the 4+1/d group and in 3 patients/56 of the 4g/d group (26) (Marteau, Probert et al. 2005).
In the pharmacokinetic study comparing mesalazine in a single dose of 4 g with 2 g twice-daily for 8 days, 3 subjects/30 healthy volunteers reported headache, nausea and asthenia. These AE were all mild or moderate and resolved spontaneously. There were no major changes in vital signs, ECG, renal, hepatic or pancreatic functions. Under the study conditions, both regimens were safe and well tolerated. (13) (Gandia, Idier et al. 2007).
In conclusion, while standard treatment of mild to moderate active episodes of extensive UC using mesalazine is effective in a significant number of patients, response rate and disease progression under treatment is determined by compliance of patients with their therapy. Reducing the dosing rate to a single daily dose for 8 weeks constitutes a simple method of improving treatment compliance but it is necessary to demonstrate at least equivalent efficacy compared to the twice daily dosing.

Study objective

Primary objective:
To demonstrate that mesalazine po 4g per day once daily (QD.) is non-inferior to the reference regimen, mesalazine 4g per day in two divided doses (BID.) (2g x 2 per day), in patients with active ulcerative colitis treated for 8 weeks, in terms of remission evaluated with the UC-DAI score and defined as * 1. Both groups (4g QD and 2gx2) will receive an enema containing 1g of mesalazine at bedtime during the initial 4 weeks.
Secondary objectives:
To compare the following between the two groups:
• Compliance
• Clinical remission at week 4 and week 8
• Clinical variables improvement (stool frequency and bloody stools) at week 4, 8 and 12 separately
• Treatment failure rates at W4 and W8
• Time to remission according patient*s diary (normal stool frequency and cessation of bleeding)
• Time to cessation of bleeding
• Improvement at week 4 and 8 based on UC-DAI score
• Endoscopic assessment at W0 and W8
• Acceptability of the treatment
• Safety

• Proportion of patients staying in clinical remission at week 12.

Study design

METHODOLOGY
Multicentre, controlled, investigator-blinded design, randomised, parallel-group study.
The randomisation will be done centrally, based on a central computer-generated randomisation scheme.
The patients will be treated for 8 weeks, with clinical evaluations at baseline, week 4, 8 and 12 and endoscopic evaluations (sigmoidoscopy) at baseline and week 8.
400 patients.

Intervention

Mesalazine (orally) 4 grams once daily or 2 grams twice daily.

Study burden and risks

Risk: AEs of mesalazine (i.e. diarrhoea, nausea, pain in stomach, headache, vomiting and skin rash) and (small) risk of endoscopy.
Burden: 5 visitsin in 12 weeks. Diary during 12 weeks. Total amount of blood to be drawn approx. 30 ml.
Physical examination 2x, preganancy test (if relevant) 1x, blood tests 2x, endoscopy 2x, VAS 2x.

Contacts

Public
Ferring

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Scientific
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Trial sites

Listed location countries

Netherlands

Eligibility criteria

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

Inclusion criteria

• Male and female patients, aged over 18 years.
• Active mild to moderate ulcerative colitis (new or relaps) with disease extension beyond rectum
• at least one total colonoscopy in their disease history (within the previous 5 years.
• UC-DAI score 3-8.
• Women with childbearing potential must be using a contraceptive method judged effective by the investigator.
• Oral maintenance treatment with azathioprine or 6-mercaptopurine (taken for at least 6 months at stable dose and continued at the same dose throughout the study) is permitted.

Exclusion criteria

• Previous colonic surgery.
• Previously failed to respond to steroids within the previous year.
• Non-response to rectal 5-ASA therapy or to oral 5-ASA therapy at a dose > 3/day for induction of remission within the previous year.
• Current relapse lasting more than 6 weeks.
• Pregnancy or breast-feeding.

Study design

Design

Study phase: 3

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

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	05-02-2009
Enrollment:	40
Type:	Actual

Medical products/devices used

Product type:	Medicine
Registration:	Yes - NL intended use
Product type:	Medicine
Registration:	Yes - NL outside intended use

Ethics review

Approved WMO

Date:	19-08-2008
Application type:	First submission
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)

Approved WMO

Date:	06-10-2008
Application type:	First submission
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)

Approved WMO

Date:	08-12-2008
Application type:	Amendment

Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)
Approved WMO Date:	07-01-2009
Application type:	Amendment
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)
Approved WMO Date:	14-01-2009
Application type:	Amendment
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)
Approved WMO Date:	22-01-2009
Application type:	Amendment
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)
Approved WMO Date:	22-04-2009
Application type:	Amendment
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)
Approved WMO Date:	26-05-2009
Application type:	Amendment
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)
Approved WMO Date:	04-11-2009
Application type:	Amendment
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)
Approved WMO Date:	10-11-2009
Application type:	Amendment
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)
Approved WMO	

Date:	09-02-2010
Application type:	Amendment
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)
Approved WMO Date:	10-02-2010
Application type:	Amendment
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)

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
Other	clinicaltrials.gov; regsitratienummer nog niet bekend.
EudraCT	EUCTR2008-000045-59-NL
CCMO	NL24580.068.08