Tacrolimus suppositories versus beclomethason suppositories for the treatment of proctitis refractory to local 5-ASA.

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To assess to efficacy of locally applied tacrolimus suppositories compared to beclomethason suppositories in patients with recurrent or refactory ulcerative proctitis.

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

Summary

ID

NL-OMON47129

Source
ToetsingOnline

Brief title
The TSP study

Condition

- Gastrointestinal inflammatory conditions

Synonym
Procitits

Research involving
Human

Sponsors and support

Primary sponsor: Erasmus MC, Universitair Medisch Centrum Rotterdam
Source(s) of monetary or material Support: zon mw goed gebruik geneesmiddelen

subsidie

Intervention

Keyword: proctitis, suppositories, tacrolimus, ulcerative colitis

Outcome measures

Primary outcome

-The primary end point will be the proportion of patients with clinical response at day 28 after treatment with tacrolimus suppositories compared to beclomethasone suppositories. Clinical response is defined as an absolute decrease in Mayo score of >=3 from baseline and a relative decrease from baseline of >=30% with accompanying decrease in the rectal bleeding subscore of >=1 point or absolute rectal bleeding subscore of 0 or 1.

Secondary outcome

-Proportion of patients in clinical and endoscopic remission. Clinical remission is defined as a Mayo score <= 2 and no individual subscore >1, and endoscopic remission is defined as no visible inflammation (i.e. mayo sub-score 0-1).

- Proportion of patients with endoscopic response, defined as a decrease in Mayo sub-score of >= 1 and/or a decrease in extent of inflammation of >= 5 cm from baseline.

-Safety and tolerability of tacrolimus suppositories and beclomethasone suppositories.

-Quality of life (IBDQ).

-Changes in histopathology from biopsies taken before and after treatment (grading scale (0 _ structural changes only, 1_ chronic inflammation, 2 _

lamina propria neutrophils, 3_ neutrophils in epithelium, 4 _ crypt

destruction, 5 _ erosions or ulcers)).

Study description

Background summary

The pathogenesis of ulcerative colitis (UC) is partly understood. Inflammatory bowel disease (IBD) is a multifactorial disease with probable genetic heterogeneity. In addition, several environmental risk factors contribute to the pathogenesis. The incidence rates for UC vary from 0.5 to 24.5 per 100,000 person-years worldwide [1]. Ulcerative proctitis (UP) is a subset of disease limited to the rectum. Similar etiological factors are likely to precipitate distal and extensive colitis. An increasing number of newly diagnosed UC cases in adults presents with disease limited to the distal or descending colon (L-UC), and the subset of UP may encompass up to one-third of all UC cases [2,3].The course of UP varies and most patients experience symptoms in remission-relapse cycles. During the initial work-up, the prevalence of proctitis may be as high as 44- 60% of all patients [4]. Long-term epidemiological studies have revealed that UP often extends to more proximal and even to total colitis. In a study by Moum et al. [5] 22% of proctitis cases progressed in extent within 12- 24 months of initial diagnosis despite medical treatment. Two long-term epidemiological studies [2, 6] showed that 32 and 41% of initial proctitis cases, respectively, progressed within 10 years. The progression was up to the left flexure in half of the patients, to the right flexure in 21%, and there was inflammation beyond the right flexure in 29%. In a recent study by the IBSEN group [7] proximal extension in UP was seen in 28% of patients in five years, with 10% progressing to extensive colitis. Thus, the recognition of UP and L-UC may not be important only because distal disease can generally be treated by topical agents, but also because it has been suggested that treatment may prevent or delay proximal spread of rectal inflammation [8].The first step in UP treatment is 5-ASA administered as suppository. Topical aminosalicylates (5-ASA) induced remission inactive proctitis and distal colitis in 31- 80% of subjects (median 67%) compared to 7- 11% of those given placebo in a meta-analysis of 11 trials in 778 patients [9]. Despite the significant benefits of rectally administered aminosalicylates, some patients with UP fail to improve and require additional medical therapy. In a step up design the following drugs are used for the treatment of recurrent UP: corticosteroids locally or systemic, azathioprine, methotrexate and infliximab. The efficacy of most of the drugs used in refractory or recurrent UP is based on data of patients with a more extended UC (except for infliximab). Overall, these results remain difficult to interpret in the efficacy for specifically recurrent UP. According to the Dutch CBO-guidelines for the treatment of IBD,

local applied corticosteroids are the preferred drugs when 5-ASA suppositories fails, however in a meta-analysis the response to this strategy is around 40% [10]. Furthermore although locally applied patients do experience the side-effects of corticosteroid therapy. We earlier demonstrated that locally applied tacrolimus 2 mg suppositories are effective in approximately 80% of the patients with refractory proctitis and and this strategy also proved to be safe [11]. Others also demonstrated the effect of local tacrolimus, with similar efficacy percentages [12]. With this study we aim to demonstrate the effectiveness of tacrolimus suppositories and we anticipate that these suppositories can be used as second line therapy after failure of 5-asa suppositories in patients with UP.

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ulcerative proctitis. Aliment Pharmacol Ther 2008; 28: 1214Ð20.

Study objective

To assess to efficacy of locally applied tacrolimus suppositories compared to beclomethason suppositories in patients with recurrent or refactory ulcerative proctitis.

Study design

3.1 Setting
Principal center:
Department of Gastroenterology & Hepatology, Erasmus MC Rotterdam, The Netherlands.
Others:
Multiple centers in The Netherlands will participate in this study.

3.2 Number of patients
88 patients will be included, with 44 patients in each treatment group.

3.3 Design (type of trial)
Multicenter, randomized, contolled study with two arms.

3.4 Medication, dosage and duration
Group A receives tacrolimus suppositories 2 mg for 28 days.
Group B receives beclomethason suppositories 3 mg for 28 days.

Intervention

Group A receives tacrolimus suppositories 2 mg for 28 days.
Group B receives beclomethason suppositories 3 mg for 28 days.

Study burden and risks

Burden: an additional of 3 visits is necessary for this study. Furthermore patients have to undergo a maximum of 2 addtional lower endoscopies with biopsies.
From the suppositories only a mild anal irritation is expected. Infrequently beclomethason suppositories do have systemic side effects such as weight gain and emtional instability, no major safety issues are anticipated.
Benifit: remission of the proctitis.

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

Endoscopically or histologically proven ulcerative proctitis at least 3 months before randomization.
Proctitis is defined as: disease activity to 20 cm beyond the anal verge.
Refractory proctitis defined as a failure to at least the use of 5-asa suppositories of a maximum of 1 gram for at least 21 days and recurrent proctitis is defined as relapse within 3 months after stopping of local adequate 5-asa treatment.
Endoscopy may have been performed up to 3 weeks before screening, if the endoscopy was well documented and biopsies were taken.
Age: 18-70 years and written informed consent.
Permitted concomitant therapy: oral aminosalicylates, azathioprine, 6-mercatopurine and methotrexate at stable dose for 12 weeks.

Exclusion criteria

Use of enemas within 14 days prior to randomization
Treatment with tacrolimus prior to randomization
Treatment with any investigational drug in another trial within 12 weeks of randomization
Treatment with any form of corticosteroids within 4 weeks of randomization
Abnormal renal function (eGFR < 30 mL/min)
Presence of toxins or other signs of infectious agents in stool sample (i.e. clostridium, salmonella, shigella, yersinia or campylobacter).
Pre-existent leucopenia or thrombopenia (leucocyte count < 2,000/mm3 or platelets < 90,000/mm3)
Liver function tests abnormalities (>2 ULN).
Other significant medical illness that might interfere with this study:
Current malignancy, immunodeficiency syndromes.
Any known pre-existing medical condition that could interfere with the patient's participation in and completion of the study such as:
- Pre-existing psychiatric condition, especially depression, or a history of severe psychiatric disorder, such as major psychoses, suicidal ideation and/or suicidal attempt are excluded. Severe depression would include the following: (a) subjects who have been hospitalized for depression, (b) subjects who have received electroconvulsive therapy for depression, or (c) subjects whose depression has resulted in a prolonged absence of work and/or significant disruption of daily functions. Subjects with a history of mild depression may be considered for entry into the protocol provided that a pretreatment assessment of the subject*s mental status supports that the subject is clinically stable and that there is ongoing evaluation of the patient*s mental status during the study
- CNS trauma or active seizure disorders requiring medication
- Significant cardiovascular dysfunction within the past 6 months (e.g. angina, congestive heart failure, recent myocardial infarction, severe hypertension or significant arrhythmia).
- Poorly controlled diabetes mellitus
- Significant pulmonary dysfunction/chronic disease (e.g. chronic obstructive pulmonary disease)
- Renal insufficiency (elevated serum creatinine)
- Pregnancy, lactation
- Substance abuse, such as alcohol (80 gram/day), I.V. drugs and inhaled drugs. If the subject has a history of substance abuse, to be considered for inclusion into the protocol, the subject must have abstained from using the abused substance for at least 2 years. Subjects receiving methadone within the past 2 years are also excluded
- Positive stool culture for enteric pathogens
- Any other condition which in the opinion of the investigator would make the patient unsuitable for enrollment, or could interfere with the patient participating in and completing the study.

Study design

Design

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

Recruitment

NL

Recruitment status:	Recruiting
Start date (anticipated):	13-02-2014
Enrollment:	65
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Beclomethason suppositories
Generic name:	Beclomethason suppositories
Registration:	Yes - NL intended use
Product type:	Medicine
Brand name:	Tacrolimus suppositories
Generic name:	Tacrolimus suppositories

Ethics review

Approved WMO

Date:	17-12-2013
Application type:	First submission
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)

Approved WMO Date:	19-12-2013
Application type:	First submission
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	14-02-2014
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	27-02-2014
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	26-05-2014
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	06-06-2014
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	23-04-2015
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	02-07-2015
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	11-12-2015
Application type:	Amendment

Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	07-01-2016
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	26-03-2018
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	30-03-2018
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	06-07-2018
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	25-07-2018
Application type:	Amendment
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	EUCTR2013-001259-11-NL
CCMO	NL44200.078.13