A randomized placebo-controlled trial comparing cyclosporine plus steroids with or without Myfortic as primary treatment for extensive chronic graft-versus host disease

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To improve response rate of primary treatment of extensive chronic GvHD with the addition of MPA to the reference treatment CsA+PDN (comparator)Primary ObjectiveTo improve remission rates with cyclosporine A+ prednisone + Myfortic® (CsA+PDN+MPA)...

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Other condition
Study type	Interventional

Summary

ID

NL-OMON30458

Source
ToetsingOnline

Brief title
Myfortic - GvHD

Condition

- Other condition

Synonym
chronic graft versus host disease ; chronic rejection

Health condition

allogene hematopoetische stamceltransplantatie bij diverse maligniteiten

Research involving
Human

Sponsors and support

Primary sponsor: European cooperative group for Blood and Marrow Transplantation (EBMT)
Source(s) of monetary or material Support: EBMT: European cooperative group for Blood and Marrow Transplantation

Intervention

Keyword: Chronic Graft versus Host disease, Cyclosporine, Myfortic

Outcome measures

Primary outcome

The primary endpoint for the determination of sample size is the response evaluated 1 year after the inclusion. A sample of 332 patients is estimated, based on the ability to detect an improvement of the response at 12 months from an anticipated 60% in the control arm (CsA +PDN) to 75% in the experimental arm (CsA+PDN+ Myfortic®) with a significant level of 5% and a 80% power. However, due to potent GvHD-linked infectious death, it has been estimate that the number of patient per arm will be targeted to 200 (total number 400).

Efficacy success is defined as the response rate (CR+PR) at 12 months post randomisation, with no secondary systemic therapy (defined below) at any time.

Death or dropout with lack of follow-up information after response of chronic GvHD but before the final analysis is expected to occur infrequently and will not be used to negate categorization as efficacy success for purposes of this study, since the treatment had been effective in controlling chronic GvHD.

It is possible that systemic immunosuppressive treatment will be discontinued before resolution of all reversible manifestations of chronic GvHD in some patients. Topical therapy may be continued in this situation, at the discretion of the managing physician.

Discontinuation of immunosuppressive medications for the purpose of inducing an anti-tumor response after the development of recurrent or secondary malignancy will not be categorized as efficacy success.

Secondary outcome

-

Study description

Background summary

CsA+PDN remains the gold standard 1st line therapy of chronic GvHD, the most frequent long-term complication of allogeneic stem cell transplantation. However, CsA+PDN lead to objective response in only 60% of the patients (at most) and steroid-induced side effects, including life threatening infections, are of major concern.
Mycophenolate mofetil (MMF) is currently the second drug used in the treatment of chronic GvHD and results of few phase II trials suggest its efficacy. A randomised trial testing improved response with the addition of MPA to CsA+PDN is timely and warranted.

Study objective

To improve response rate of primary treatment of extensive chronic GvHD with the addition of MPA to the reference treatment CsA+PDN (comparator)

Primary Objective
To improve remission rates with cyclosporine A+ prednisone + Myfortic® (CsA+PDN+MPA) combination as compared to the reference treatment with CsA+PDN

Secondary Objectives
• To spare patients from long-term use of corticosteroids (and of their long-term side effects)

• To decrease transplant-related morbidity (infectious and noninfectious)
• To study time to cessation of any immunosuppressive therapy
• To test prospectively the NIH severity index for chronic GvHD

Study design

Multicentre, randomised placebo-controlled clinical trial

Intervention

Patients are randomised between the following two treatment arms:

ARM A: Cyclosporine A (3mg/kg/D) + prednisone 1.5 mg/kg/D + Placebo BID

ARM B: Cyclosporine A (3mg/kg/D) + prednisone 1.5 mg/kg/D + Myfortic® 720 mg BID

Study burden and risks

Occurence of extensive chronic GvHD has a high mortality.
This study investigates the value of addition of MPA to the reference treatment CsA+PDN in the treatment of extensive chronic GvHD
This combination is possibly more effective en could thus lead to a shorter treatmentperiod.

There are no extra procedures for this study, patientvisits and laboratory are according to local practice.

There may be an increased risk on side effects with the addition of Myfortic compared to the reference treatment.

Contacts

Public
European cooperative group for Blood and Marrow Transplantation (EBMT)

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

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

Inclusion criteria

• Age 18 - 60
• Any primary diagnosis requiring treatment by hematopoietic stem cell transplantation (HSCT)
• Recipient of a single allogeneic stem cell transplant (bone marrow or peripheral blood stem cells, or cord blood) minimum 80 days ago
• Transplant from a related or unrelated donor
• Conditioning regimen: Myeloablative (MA) or non-myeloablative (NMA)
• Patients with a first episode of extensive chronic GvHD, without recurrent disease
• The diagnosis of chronic GvHD as defined by the NIH diagnostic and scoring system:
-With clear distinction from acute GvHD
-With presence of at least one diagnostic clinical sign of chronic GvHD or presence of at least 1 distinctive manifestation confirmed bypertinent biopsy or other relevant diagnostic tests
-Exclusion of other possible diagnoses
• Receiving a standard prophylaxis regimen for acute GvHD: CsA alone, CsA plus methotrexate or CsA+MMF for NMA, or a T-cell depleted transplantation (Patients may be started on CsA + steroids pre randomisation but may not be on treatment for more than 3 days pre randomisation)
• Negative pregnancy test in females of child-bearing potential - see section 5.4
• Patient gives written informed consent prior to randomisation

Exclusion criteria

• Age less than 18 or over 60 years old
• GvHD prophylaxis by tacrolimus plus methotroxate
• Delayed onset acute GvHD following NMA or DLI

• Second allogeneic stem cell transplant
• Not the first episode of chronic GvHD needing systemic immunosuppressive therapy
• Limited chronic GvHD (Seattle criteria)
• MMF used to prevent or treat GvHD in the previous 4 weeks
• Neutropenia (<1.0 x 109/l)
• Uncontrolled systemic infection which in the opinion of the investigator is associated with an increased risk of the patient*s death
within 1 week of randomisation
• In the opinion of the investigator, if the patient has significant medical or psychosocial problems or unstable disease status
• Pregnant or lactating females, - see section 5.4

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):	21-01-2008
Enrollment:	10
Type:	Actual

Medical products/devices used

Registration:	No
Product type:	Medicine
Brand name:	Cyclosporine A
Generic name:	Cyclosporine A

Registration:	Yes - NL outside intended use
Product type:	Medicine
Brand name:	Myfortic
Generic name:	mycophenolic acid
Registration:	Yes - NL intended use
Product type:	Medicine
Brand name:	nvt
Generic name:	prednisone
Registration:	Yes - NL intended use

Ethics review

Approved WMO Date:	13-07-2007
Application type:	First submission
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)
Approved WMO Date:	30-09-2008
Application type:	Amendment
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)
Approved WMO Date:	30-09-2008
Application type:	First submission
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
EudraCT	EUCTR2005-006178-86-NL
CCMO	NL15594.068.07