A randomized, multicenter study to assess the efficacy on disease activity on enteric-coated mycophenolate sodium (EC-MPS, myfortic) versus continuation of azathioprine in patients with systemic lupus erythematosus on azathioprine maintenance therapy.

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To assess, in patients with systemic lupus erythematosus, the effect on disease activity of a regimen with myfortic® versus continuation of azathioprine.

Ethical review	Approved WMO
Status	Recruiting
Health condition type	Immunodeficiency syndromes
Study type	Interventional

Summary

ID

NL-OMON30478

Source
ToetsingOnline

Brief title
Myfortic versus azathioprine in SLE

Condition

- Immunodeficiency syndromes

Synonym
lupus, SLE

Research involving
Human

Sponsors and support

Primary sponsor: Erasmus MC, Universitair Medisch Centrum Rotterdam
Source(s) of monetary or material Support: Novartis

Intervention

Keyword: Azathioprine, Myfortic, SLE, SLEDAI

Outcome measures

Primary outcome

·Disease activity index measured with SLEDAI

Secondary outcome

·Disease activity index measured with BILAG (numerical score)

·Damage index measured with SLICC/ACR

·(Average) daily dose of prednisone. The dose will be measured from the patient

starting the study and for the whole duration of the study

·Assessment of HRQL using MOS SF-36 (Stoll, et al 1997)

Study description

Background summary

Systemic lupus erythematosus (SLE) is a complex and potentially life-threatening disease that affects about 40 per 10,000 people in the general population (Mills 1994, Brown & Schrieber 1996). SLE is a chronic inflammatory disease characterized by auto-antibody overproduction and other distinct immunological abnormalities (Boumpas, et al 1995, Mohan & Datta 1995). It may affect the skin, joints, lungs, heart, serous membranes, nervous system or other organs. Improvements in treatment over the last decade have increased 10-year survival rates in Western countries to 90% or more, and 20-year survival rates of nearly 70% have also been reported (Abu-Shakra, et al 1995). Newer treatment strategies include the use of novel immunosuppressive agents,

such as mycophenolate mofetil (MMF). MMF has been widely used in solid-organ transplantation (Sollinger 1995, The Tricontinental Mycophenolate Mofetil Renal Transplantation Study Group 1996). MMF also has been used increasingly in autoimmune diseases (e.g., dermatomyositis, primary glomerular disease or psoriasis (Epinette, et al 1987, Gelber, et al 2000, Choi, et al 2002)).
MMF is the morpholinoethylester prodrug of mycophenolic acid (MPA). After oral administration MMF is well absorbed and rapidly hydrolyzed to MPA. MPA is a noncompetitive inhibitor of inosine monophosphate (IMP) dehydrogenase (DH). Inhibition of IMPDH leads to the depletion of deoxyguanosine triphosphate and a consequent decrease in the level of substrate required for DNA polymerase activity. This results in inhibition of DNA production and cell proliferation.
T and B cells are more dependent on this de novo pathway of purine synthesis because alternative salvage pathways are unavailable. Thus, MPA is a selective inhibitor of lymphocyte proliferation, especially in activated lymphocytes (Allison & Eugui 2000).
In the transplant population, the high incidence of GI side effects with MMF that leads to dose reductions or discontinuations may increase the risk of graft failure as a result of sub-therapeutic drug exposure (Knoll, et al 2003, Hardinger, et al 2004). Therefore, it would be useful to be able to avoid MPA-related upper GI side effects without compromising drug exposure or efficacy. Enteric coating has been used with several classes of drugs to reduce the incidence of GI side effects and to protect the drug moiety from inactivation by gastric acid. The coating delays delivery of the active ingredient by preventing its release in the stomach; the coating disintegrates in the intestines to allow absorption in the small intestine. Therefore, it was suggested that enteric coating could improve the GI side-effect profile of mycophenolates by delaying the release of MPA until the small intestine is reached. This lead to the development of the enteric-coated formulation of mycophenolate sodium (EC-MPS, myfortic ®), containing MPA as the active moiety. This drug was developed to reduce MPA-related upper GI AEs by delaying the release of MPA while providing effective MPA immuno-protection. EC-MPS may therefore help avoid MPA-related upper GI intolerability, potentially limiting the number of dose reductions and rate of patient withdrawal from therapy. Unlike MMF, EC-MPS does not contain the added molecular weight of a mofetil ester and therefore a 720 mg dose of myfortic ® contains the same MPA content as 1000 mg MMF (Budde, et al 2002).
A limited number of clinical studies have been performed to study the efficacy of MMF in the treatment of SLE. Most of these studies involved the treatment of nephritis. Chan, et al (2000) showed that the combination of MMF and prednisolone is as effective as a regimen of cyclophosphamide and prednisolone followed by azathioprine and prednisolone. Azathioprine and MMF as maintenance therapy were compared to cyclophosphamide therapy (Contreras, et al 2004) and appeared to be more efficacious and safer than long-term therapy with i.v. cyclophosphamide. In this study, it was also noted that patients treated with MMF had received lower doses of corticosteroids during maintenance therapy as compared to patients treated with azathioprine.
Recent reports suggest that MMF may also be effective in systemic lupus without

severe renal involvement.(Pisoni, et al 2005) Yet, the superiority over azathioprine in this patient group has not been established. The aim of this study will be to show a decreased lupus activity in patients treated with myfortic ® compared to therapy with azathioprine. Data so gathered may be useful in planning future developments in this indication

Study objective

To assess, in patients with systemic lupus erythematosus, the effect on disease activity of a regimen with myfortic® versus continuation of azathioprine.

Study design

This is a 12 months, multi-center, 2-treatment arm, parallel-group, randomized, open label study in patients with lupus erythematosus. The patients will be randomized to one of the following two treatment groups:
·Maintenance of previous therapy (including azathioprine)
·Switch to a myfortic ® based regimen: myfortic ® (starting dose of 1440mg/day instead of azathioprine)

Intervention

24 patients will be switched from azathioprine to Myfortic during this study.

Study burden and risks

NA

Contacts

Public
Erasmus MC, Universitair Medisch Centrum Rotterdam

Dr. Molewaterplein 40
3015 GD
NL
Scientific
Erasmus MC, Universitair Medisch Centrum Rotterdam

Dr. Molewaterplein 40
3015 GD
NL

Trial sites

Listed location countries

Netherlands

Eligibility criteria

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

Inclusion criteria

Systemic lupus on azathioprine
SLEDAI score equal or higher than 6

Exclusion criteria

1. Creatinine clearance of < 20ml/min
2. Patients with any clinically significant infection
3. Patients with known hypersensitivity to myfortic ® or to drugs with similar chemical structures
4. Patients with a history of malignancy of any organ system, treated or untreated, within the past 5 years whether or not there is evidence of local recurrence or metastases, with the exception of localized basal cell carcinoma of the skin
5. Patients with SLE active CNS manifestations or a past history of SLE CNS complications (e.g. psychosis, grand mal seizures)
6. Patients who have received prior therapy with mycophenolic acids (MPAs) (e.g. MMF)
7. Patients who have received an investigational drug within four weeks prior to study entry
8. females of childbearing potential who are planning to become pregnant, who are pregnant and/or lactating, who are unwilling to use effective means of contraception

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:	Recruiting
Start date (anticipated):	01-07-2007
Enrollment:	48
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Myfortic
Generic name:	Mycophenolate sodium
Registration:	Yes - NL outside intended use

Ethics review

Approved WMO

Date:	06-04-2007
Application type:	First submission
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)

Approved WMO

Date:	10-04-2007
Application type:	First submission
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	EUCTR2006-006217-33-NL
CCMO	NL15307.078.06