Five year single blind effectiveness randomised actively controlled Phase III Clinical Trial in New Onset Juvenile Dermatomyositis: Steroids Treatment versus Steroids plus Cyclosporine Treatment versus Steroids plus Methotrexate Treatment

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

Summary

ID

NL-OMON30111

Source
ToetsingOnline

Brief title
Phase III Clinical Trial in New Onset Juvenile Dermatomyositis

Condition

- Muscle disorders

Synonym
(juvenile) dermatomyositis

Research involving
Human

Sponsors and support

Primary sponsor: Universitair Medisch Centrum Utrecht
Source(s) of monetary or material Support: Ministerie van OC&W

Intervention

Keyword: dermatomysitis, juvenile, methotrexate

Outcome measures

Primary outcome

Primary Outcome Measures after 6 months of treatment. According to the PRINTO definition of improvement for JDM, patients will be considered responders to therapy if they will demonstrate at least 20% improvement in at least 3 core set variables with no more than 1 of the remaining variables, (muscle strength excluded), worsened by > 30% .

The PRINTO JDM core set variables are:

1) muscle strength by the mean of the Childhood Myositis Assessment Scale (CMAS);

2) physician*s global assessment of disease activity on a 10 cm VAS ;

3) global disease activity assessment by the mean of the Disease Activity Index (DAS);

4) parent*s/patient*s global assessment of overall well-being on a 10 cm VAS;

5) functional ability assessment by the mean of the Childhood Health Assessment Questionnaire (CHAQ)

6) health-related quality of life assessment by the mean of the CHQ.

Primary Outcome Measures after 24 months of treatment: a) time to clinical

remission on medication defined as normal muscle strength and physician global assessment of disease activity equal to 0; b) time to flare of the disease defined as at least 20%, worsening from the previous evaluation value in 2 of any 6 JDM core set measures with no more than 1 of the remaining improved by more than 30% (muscle strength excluded). Effectiveness: the rate of retention on treatment will be used as main measure of effectiveness.

Secondary outcome

Change over time in the individual components of the JDM core set of variables; time to muscle enzymes normalisation; frequency of drop-out of suggested steroids use; frequency of drop-out for inefficacy of treatment.

Study description

Background summary

Juvenile dermatomyositis (JDM) is a multisystem disease characterised by acute and chronic non-suppurative inflammation of striated muscles and skin. The disease is marked early in its course by the presence of a vasculopathy of varying severity that can be widespread and sometime also fatal, and late by the development of dystrophic calcinosis (that is more frequent in children than in adults) . Although JDM is a rare disease, it is the most common of the pediatric inflammatory myopathies, with an incidence of 3.2 cases/1 million children/year fulfilling the diagnostic criteria of Bohan and Peter. Disease duration in JDM ranges from <1.0 year to persistent disease beginning during childhood but lasting well into adulthood . Death has been reported to occur in up to 39% of children with JDM with most studies reporting mortality rates between 3-18%.
However, even for those surviving the illness, there are often chronic complications and long-lasting disability. In one long-term study that followed childhood onset JDM patients into adulthood, 33% still demonstrated weakness, 39% still had dermatologic manifestations, 22% had persistent contractures, and 39% had subcutaneous calcinosis. In another study of childhood onset JDM patients evaluated at a mean age of 18.8 years, 33% reported limitations in

ability to do daily activities, 78% still had dermatologic manifestations, 58% had additional
nondermatologic abnormalities on physical exam, and 50% had evidence of muscle scarring by ultrasound evaluation .
Current available treatments in children: the treatment of JDM, is unsatisfactory, and corticosteroids are the only agents currently approved by the US Food and Drug Administration for myositis. Prednisone therapy is frequently required for long periods with a mean duration ranging from 25 to 54 months. In some series, over 40% of the JDM subjects remain on prednisone for more than 7 years . Many of JDM patients fail to respond adequately to corticosteroids and require additional immunosuppressive medications, none of which have been tested in controlled trials in this conditions. Indeed no randomised clinical trial with immunosuppressive agents are available for children with JDM, and most of the studies involve single referral centres reporting retrospectively on small numbers of patients followed for relatively brief periods of time. Few examples are reported in the following paragraphs.
The duration of prednisone treatment was studied retrospectively in children with JDM treated by two different methods, PDN alone versus MTX and PDN. The authors concluded that in this short-term comparison, early use of MTX allowed for acceptable clinical outcomes with much shorter duration of prednisone treatment. This study suggests a significant prednisone sparing effect with the early introduction of MTX in the treatment of JDM. Similar conclusions were reported by others.
In other 2 studies cyclosporine A (CsA) has been used to treat patients with refractory JDM. the Authors concluded that CsA represents a promising agent for the treatment JDM.
Although suggestive, these trials have significant design limitations, small sample size, they lack standardised measures to evaluate the outcome, and they do not have a standardised protocols for prednisone tapering. As a conclusion it can be stated that current treatment for JDM has failed to eliminate significant morbidity and mortality and that although several publications describe experience with second line agents no prospective randomized trial has ever been performed
in children with JDM.

Study objective

Objectives. The goals of the current protocol is therefore the natural follow-up of the objectives achieved with the previous grants and, in particular, of projects designed to discern new models for the successful conduct of clinical trials in children with rare diseases, and to develop standardized and validated measures for the evaluation of response to therapy in JDM.
The proposed trial in JDM (prednisone [PDN] versus PDN plus methotrexate [MTX] versus PDN plus cyclosporine [CsA]), should serve as a model for the successful running of early phase clinical trials for severe and disabling rare diseases of childhood. The ultimate aim of these trials is to provide evidence-based

information about the clinical utility of drugs in the management of rare paediatric conditions.

Trial Objective. To assess the effectiveness (efficacy, safety, tolerability and compliance to treatment) of the 3 treatment approaches for the treatment of children with JDM. THE OVERALL HYPOTHESIS TO BE TESTED IN THIS TRIAL is that the early introduction of combination therapy of corticosteroids and either MTX or CsA will prove more effective and safe than corticosteroids alone in the treatment of JDM.

Study design

Trial Design and Duration. Two-year single-blind (assessor blinded to treatment arm of subject), randomised, actively controlled, multi-centre, international prospective, non inferiority trial of different combination of drugs. Patients will be then followed for up to 5 years for the evaluation of long term morbidity and mortality.
Dose Regimen: 3 daily pulses of intravenous (iv) methylprednisolone (30 mg/kg/pulse max 1 g/pulse) followed by randomisation into one of these 3 groups.

Group 1 prednisone or equivalent (PDN): PDN 2 mg/kg/day;
Group 2 PDN+cyclosporine A (CsA): PDN 2 mg/kg/day + CsA 5 mg/kg/day in 2 oral doses.;
Group 3 PDN + methotrexate (MTX): PDN 2 mg/kg/day + MTX 15-20 mg/m2 once per week. Patients treated with MTX will receive concomitant folic or folinic acid according to the attending physician decision.

Long term follow up after month 24 until month 60. All patients will be followed for a total of 5 years for the assessment of long term morbidity and mortality rate. After month 24 treatment will be left open to the physician decision based on the clinical status of the patient.

Intervention

none

Study burden and risks

fully compliant with current medical care, i.e. there is no significant burden. Potential benefit is early remission with reduced toxicity and disease damage.

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adolescents (12-15 years)
Adolescents (16-17 years)
Children (2-11 years)

Inclusion criteria

Cirteria according to Bohan and Peters. Muscle biopsy is optional.
Girls with child baring capacity must consent in contraceptive measures (Page 10 of protocol)

Exclusion criteria

neutrophil count less than 1500 and platelet count less than 50.000.
Cutaneous or gastrointestinal ulceration in JDM related pulmonary disease or cardiomyopathy (page 11 protocol).
History of poor compliance.
Live attenuated vaccines not allowed.

Study design

Design

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

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	22-12-2006
Enrollment:	6
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	methotrexate
Generic name:	methotrexate
Registration:	Yes - NL outside intended use
Product type:	Medicine
Brand name:	Neoral
Generic name:	ciclosporin
Registration:	Yes - NL outside intended use

Ethics review

Approved WMO

Date:	21-07-2006
Application type:	First submission

Review commission:	METC Universitair Medisch Centrum Utrecht (Utrecht)
Approved WMO Date:	26-09-2006
Application type:	First submission
Review commission:	METC Universitair Medisch Centrum Utrecht (Utrecht)
Approved WMO Date:	17-10-2006
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Utrecht (Utrecht)

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	2006-05-09
EudraCT	EUCTR2005-003956-37-NL
CCMO	NL12325.041.06