A 24 week multinational multi-center study consisting of a 12-week single blind study to evaluate the efficacy and safety of methotrexate versus azathioprine treatment in adult patients with chronic severe atopic dermatitis and a 12-week follow up period.

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To compare the efficacy and safety of methotrexate versus azathioprine treatment in adult patients with chronic severe AD.

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

Summary

ID

NL-OMON33396

Source
ToetsingOnline

Brief title
MAcAD

Condition

- Allergic conditions
- Epidermal and dermal conditions

Synonym
allergic eczema, Atopic eczema

Research involving
Human

Sponsors and support

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

Intervention

Keyword: Atopic dermatitis, Azathioprin, Methotrexate

Outcome measures

Primary outcome

The primary efficacy variables are difference in mean change of the SCORAD and IGA between groups at week 12.

Also the comparison in the proportion of subjects with a SCORAD reduction of 50% or more and the proportion of subjects with a IGA score of < 3 (clear / almost clear / mild) at week 12 between methotrexaate an azathioprine (Arm 1 and Arm 2).

Secondary outcome

Secondary efficacy parameters assessed at different time points during the study are:

• Frequency and severity of Adverse Events

• Frequency of relapses (>SCORAD75 after response (SCORAD50) was met before)

• Absolute and relative change from Baseline up to weeks 12 on the Eczema area and severity index (EASI), Investigator*s global assessment (IGA), Patient*s global assessment (PGA), Skindex-17, Patient oriented eczema measurement

(POEM), Pruritus visual analogue scale (VAS), Sleeplessness visual analogue

scale (VAS).

Study description

Background summary

Atopic dermatitis is a chronic inflammatory skin disorder secondary to the activation of allergen specific T-cells in the skin. Most patients with AD can be treated effectively with emollients and topical anti-inflammatory agents such as topical steroids and topical calcineurin inhibitors. A subgroup of the AD patients, the more severe cases, require more than topical treatment to control their skin disease.
Cyclosporin (AZA) is considered gold standard for systemic treatment of severe AD and is highly effective. Many patients, however, are contra-indicated for AZA or have to discontinue treatment due to ineffectiveness or side effects such as hypertension and nephrotoxicity. It can be concluded that there is a very limited therapeutic armamentarium for the treatment of severe AD currently. Recent studies showed potential new systematic treatment options for severe AD. Two of which will be investigated in this study.
Methotrexate (MTX) targets several key T-cell activities essential for immunologic responses and inflammation. Recent studies have shown that MTX selectively depletes activated T cells by an apoptosis-dependant mechanism without effect on naïve and memory T-cells. Reported clinical improvement of AD due to MTX treatment in pilot studies suggests a role for MTX in the management of this T-helper 2 mediated skin disease. This study is needed to determine if MTX has a genuine role in the therapy of AD.
Azathioprine (AZA) is a purine synthesis inhibitor, inhibiting the proliferation of cells, especially leukocytes. Two randomized controlled trials (RCTs) have been conducted comparing AZA with placebo. Both showed promising results.

Study objective

To compare the efficacy and safety of methotrexate versus azathioprine treatment in adult patients with chronic severe AD.

Study design

A 24 week multinational multi-center study consisting of a 12-week single blind study to evaluate the efficacy and safety of methotrexate versus azathioprine treatment in adult patients with chronic severe AD and a 12-week follow up

period.

Intervention

During 12 weeks patients will be randomized to weekly oral methotrexaat treatment (Arm 1) or daily oral azathioprine (Arm 2).

Study burden and risks

Patients will visit the clinic one to four-weekly, in total 7 visits including screening-visit. Visits include evaluation of the severity of AD (SCORAD, IGA, PGA, EASI, POEM, SKINDEX-17 and VAS), evaluation of the use of concomitant medications, collection of safety and efficacy data and physical examinations including vital signs. Routine haematology and urine-analysis will be performed at screening, baseline, week 2, 4, 8 and 12. Patients will be provided with diaries detailing intake of MTX or AZA, concomitant medications and AD symptoms. Additional visits may be required between the scheduled visits to assess any AD exacerbations reported or if adverse events require close monitoring.
Participants will be treated with either MTX or AZA. MTX an AZA are medicines in which a lot of knowledge is collected in other treatment indications over the years.

Contacts

Public
Academisch Medisch Centrum

Meibergdreef 9
1105 AZ Amsterdam
NL
Scientific
Academisch Medisch Centrum

Meibergdreef 9
1105 AZ Amsterdam
NL

Trial sites

Listed location countries

Netherlands

Eligibility criteria

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

Inclusion criteria

1. Subject is 18 years of age or older at inclusion (Day 0); both genders.
2. Subject has a diagnosis of AD based on millennium criteria (with or without IgE) and UK-criteria.
3. Subject has a score of 8-9 on the Rajka and Langeland Criteria which corresponds with a severity of *severe*.
4. Subject is unresponsive, contra-indicated or intolerant to CsA treatment.
5. Female subject is either not of childbearing potential, defined as postmenopausal or surgically sterile or is of childbearing potential and practicing one of the following methods of birth control throughout the study until 3 months after receiving the last study agent:
- Intrauterine device (IUD)
- Contraceptives (oral, parenteral, patch) for three months prior to study drug administration.
- A vasectomized partner
6. Female subjects of childbearing potential must have a negative serum pregnancy test at the Screening visit and a negative urine pregnancy test at Baseline.
7. Sexually active male subjects are able to participate in the study if they use effective contraception during the study and 3 months after discontinuation of the study drug.
8. Have screening laboratory test results within reference values or results without clinical relevance as assessed by the local investigator.
9. Subjects has voluntarily signed and dated an informed consent prior to any study related procedure and is willing to comply with the requirements of this study protocol which has been approved by an Institutional Review Board (IRB/Independent Ethics Committee (IEC)).

Exclusion criteria

1. Subjects is pregnant, nursing, or planning pregnancy (men and women) while enrolled in the study.
2. Subjects has used any investigational drug within the previous 4 weeks or 5 times the half-life of the investigational agent prior to the first administration of study agent, whichever is longer.
3. Subject has ever used azathioprin or methotrexate before
4. Subject has received phototherapy or any systemic medications/treatments that could

affect AD evaluation (including, but not limited to, oral or injectable corticosteroids) within the last 4 weeks of the first administration of study agent.
5. Subject has used very potent topical medications/treatments that could affect AD evaluation within 2 weeks of the first administration of study agent.
6. A history of chronic or recurrent infectious diseases, including but not limited to chronic renal infection, chronic chest infection (eg, bronchiectasis), recurrent urinary tract infection (recurrent pyelonephritis or chronic nonremitting cystitis), or open, draining, or infected skin wounds or ulcers.
7. A history of alcohol abuse
8. A history of latent or active granulomatous infection, including TB, histoplasmosis, or coccodioidomycosis, prior to screening.
9. Subject has or had had herpes zoster infection within 2 months of study day 0.
10. Subject is known to be infected with HIV, hepatitis B, or hepatitis C.
11. A history or current signs or symptoms of severe, progressive, or uncontrolled renal, hepatic, hematological, gastrointestinal, endocrine, pulmonary, cardiac, neurological, cerebral, or psychiatric disease.
12. Subject has a transplanted organ (with exception of a corneal transplant > 3 months prior to the first administration of study agent).
13. Subject has any known malignancy or had a history of malignancy
14. Subject is dependant of a concomitant medication that has interaction with the study medication and thereby should be avoided

Study design

Design

Study phase:	3
Study type:	Interventional
Intervention model:	Parallel
Masking:	Single blinded (masking used)
Control:	Uncontrolled
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	21-07-2009
Enrollment:	32
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Imuran
Generic name:	Azathioprine
Registration:	Yes - NL outside intended use
Product type:	Medicine
Brand name:	Methotrexate
Generic name:	Methotrexate
Registration:	Yes - NL outside intended use

Ethics review

Approved WMO Date:	19-06-2009
Application type:	First submission
Review commission:	METC Amsterdam UMC

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	EUCTR2009-011132-34-NL
CCMO	NL27312.018.09