An open-label, 8-week, proof of concept trial on thymosin-α1 (thymalfasin) in the treatment of primary antibody deficiency (PAD) associated mood disorders (TIDAM).

Published: 19-01-2022
Last updated: 05-04-2024

Based on the effects of Tα1 on immune cell function, the known disturbances in T lymphocyte numbers and subsets in patients with CVID and the increased prevalence of mood disorders in these patients the following research questions have been...

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

Summary

ID

NL-OMON51992

Source
ToetsingOnline

Brief title
Thymosin-α1 in immunodeficiency associated mood disorders

Condition

- Immunodeficiency syndromes

Synonym
Inborn errors of immunity, Primary immunodeficiency

Research involving
Human

Sponsors and support

Primary sponsor: Erasmus MC, Universitair Medisch Centrum Rotterdam
Source(s) of monetary or material Support: Europese Unie;Horizon2020 project Moodstratification (2017)

Intervention

Keyword: 1, Immunodeficiency, Mood disorder, Thymosin-&alfa

Outcome measures

Primary outcome

Primary endpoint of this study will be the increase in absolute and relative numbers of peripheral blood T regulatory cells, measured after 8 weeks of treatment and 8 weeks after termination of the clinical study

Secondary outcome

Secondary endpoints include:

EFFICACY

1) Change in depression scores (Hamilton Depression Scale (HAM-D) scores) from baseline to week 6 and 12 and at 6 weeks after termination of the clinical study.

2) Change in fatigue scores (Fatigue Severity Scale (FSS)) from baseline to week 6 and 12 and at 6 weeks after termination of the clinical study.

3) Increase/decrease in numbers of Th1, Th2 and Th17 cells

4) Increase in the balance between naïve and memory T helper cells

5) Alterations in the balance between the Th17/T regulatory cells

6) Decrease in inflammatory gene expression (cluster 1 and 2 gene expression) in circulating leukocytes

7) Decrease in circulating levels of hCRP, IL-6, CCL2, PTX-3, sCD25, SCF, BDNF

8) Change in health-related quality of life (as measured by the CVID_QoL

Questionnaire)

SAFETY

9) Frequency and type of adverse events

10) Lab tests: mean change and frequency of values outside the normal range

Study description

Background summary

Primary antibody deficiency (PAD) : Common Variable Immune Deficiency (CVID)

Primary antibody deficiency (PAD) is an umbrella term encompassing a broad array of primary immunodeficiency diseases collectively characterized by a quantitative and/or qualitative impairment of antibody production {Quinti, 2016 #1}. Common variable immune deficiency (CVID) is the most common symptomatic form of PAD in adults {Geha, 2007 #2}.
CVID shows heterogeneous clinical phenotypes with infections, autoimmune disorders, granulomatous and inflammatory diseases and cancers {Chapel, 2008 #3;Verma, 2015 #4}. Current treatment options to prevent infections and treat complications include (prophylactic) antibiotics, immunoglobulin replacement therapy and immunomodulatory drugs {Bonilla, 2016 #5;Hoernes, 2011 #7;Kuruvilla, 2013 #6}.
Although scarcely studied it has been well recognized that patients with CVID are at increased risk for development of depression and/or anxiety disorders. In a cohort of 96 CVID patients it was shown that one-third of CVID patients were at risk for depression/anxiety {Hajjar, 2017 #9}. In a recent survey among over 2500 PAD patients in the United States, depression was also overreported {Hajjar, 2017 #9}. It has been hypothesized that the increased risk of mood disorders in PAD patients is related to disease-associated morbidity (amongst others infections, auto-immune disease) and (subsequent) increased loss of days at work or school and the impact on social life.
However, in recent years it has become more clear that a significant number of patients with CVID (approximately 20-25%) also show disturbed T lymphocyte subset distribution and function {Arandi, 2013 #12;Azizi, 2016 #10;Bateman, 2012 #13;Kutukculer, 2016 #11}, which not only explains the increased risk of

(viral) infections and autoimmune complications in these patients but may also be directly related to the increased risk of mood disorders, as in recent studies it has been demonstrated that in patients with recurrent mood disorders inborn T cell defects are present that elicit an aberrant (auto)inflammatory state of monocytes/macrophages/microglia which in turn results in disturbed normal frontal brain-hippocampus development and communication leading to severe mood dysregulations. Partial T cell defects lead to maturation defects in the CD4+ T helper lineage and in particular to reduced numbers of T regulatory cells and Th17 cells. It has been hypothesized that the dysregulated cellular immune responsiveness in lymphocytes could play a role in mood disorders {Grosse, 2016 #14;Snijders, 2016 #15}. Interestingly, unipolar depressed patients with severe T cell defects do not respond to treatment with conventional anti-depressants like selective serotonin-reuptake inhibitors (SSRIs) and the question arises whether these patients with underlying T cell defects might benefit from a T-cell enforcing treatment strategy, by promoting T cell restoration.

Based on the concomitant presence of mood disorders and T lymphocyte subset disturbances in CVID and based on the current knowledge on T lymphocyte subset defects, particularly a decrease in regulatory T cells, in mood disorders we hypothesize that restoration of T lymphocyte subsets in CVID patients could improve mood disorders. We therefore aim to set up a clinical trial with thymosin α1 (thymalfasin).

Thymosin α1 (Tα1, thymalfasin)
Tα1 is a 28-amino acid peptide physiologically present in the human body and originally isolated from the thymus as one of the compounds of a crude thymus hormone preparation responsible for restoring immune function to thymectomized mice characterized by T lymphocyte defects. Tα1 shows strong immune modulating effects. It exerts its immune-modulating activity through the interaction with Toll-like receptors (TLR), a group of proteins involved in the regulation of innate immunity, and in particular with TLR9 and TLR2 on dendritic cells (DCs) and precursor T-cells {Romani, 2007 #24;Romani, 2006 #25}, activating intracellular signaling pathways such as NF-*B, p38 MAPK, and the MyD88-dependent pathway {Bistoni, 1982 #26;Peng, 2008 #27;Zhang, 2005 #28}. Tα1 is also able to prevent a pro-inflammatory cytokine storm and possibly autoimmune events through the activation of indoleamine-2,3-dioxygenase in plasmacytoid DCs resulting in an increase of regulatory T-cells that ultimately inhibit the excess of cytokine production {Romani, 2007 #24;Romani, 2006 #25;Xiang, 2014 #29}. Due to the immune stimulating effects of Tα1, the compound would be expected to show utility for treatment of immune deficiencies, in particular of T lymphocyte mediated immunodeficiencies. Although the compound is produced by Sciclone and has been registered in South-East Asia and China as an enforcement therapy for hepatitis vaccination and in the treatment of certain cancers, it has only sparsely been used in immune deficiency syndromes (due to the non-availability in the US and Europe). A single child with 22q11.2DS was treated with Tα1 {Gupta, 1998 #30}. Blood

cells were taken from this 13-month-old infant before and after 3 months of treatment with Tα1 and examined for evidence of lymphocyte apoptosis compared to an age matched healthy control. Prior to treatment with Ta1, the subject showed increased apoptosis (increased Fas and FasL, decreased Bcl-2 in both CD4 and CD8 cells, increased DNA fragmentation); after treatment with Tα1 the proportion of lymphocytes undergoing apoptosis decreased. The T lymphocyte responses (response to mitogen) also improved after treatment, and the subject showed a marked clinical improvement evidenced by a significant decrease in infections. No adverse experiences associated with Tα1 were reported in this patient.

Study objective

Based on the effects of Tα1 on immune cell function, the known disturbances in T lymphocyte numbers and subsets in patients with CVID and the increased prevalence of mood disorders in these patients the following research questions have been postulated:

1) Does Tα1 restore disturbed T lymphocyte (regulatory T cell) populations in patients with CVID ?

2) Is Tα1 an effective treatment option for mood disorders in CVID patients with disturbed T lymphocyte populations?

Primary objective
The primary objective of this study is to evaluate in CVID patients with mood disorders the effect of Tα1 on the increase in absolute and relative number of T regulatory cells

Secondary objectives
Secondary objectives include:
- Changes in T lymphocyte subset patterns
- Changes in levels of markers of inflammation
- Improvements in depression, fatigue and quality of life scores
- Assessment of adverse events.

Study design

An open-label, single center, 8-week, proof-of-concept trial of thymosin-α1 (thymalfasin) in patients with common variable immune deficiency associated mood disorders will be conducted.

Patients will be treated according to the following schemes:
Thymosin-α1 (Zadaxin) 1.6 mg subcutaneously once daily for 1 week followed by subcutaneous administration twice a week for 7 weeks

Intervention

In this 8-week open-label study, patients will be treated for 8 weeks with Zadaxin, by subcutaneous injections, starting with once daily injections for one week followed by 2 injections per week for 7 weeks,1.6 mg

Study burden and risks

Study participants will be screened for eligibility at the outpatient clinics of their hospital.
Baseline visit and visits 8 and 16 weeks after initiation of study treatment will include blood drawings (43 ml per visit) and questionnaires.

The study drug is registered for use in several countries worldwide and side effects/adverse effects in previous studies were found to be limited.
Also in clinical practice, adverse effects are limited.

Benefits for the patients would be the potential clinical improvement in mood disorders, by introducing this immunomodulatory, targeted therapy.

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

Written informed consent must be obtained before any assessment is performed.
Suffering from the following condition
Common variable immunodeficiency (CVID), with an established diagnosis according to the diagnostic criteria from the European Society for Immunodeficiences (ESID) 2014, in accordance with the International Union of Immunological Societies (IUIS).
Presence of a depressive mood disorder as determined by the Hamilton Rating Scale for Depression (HAM-D) (above 12).
Age between 18 and 75.
In case of concomitant use of classical (tricyclic) or non-tricyclic antidepressants (SSRI, SNRI, MAOI, other), with or without mood stabilizer: a stable dosing regimen for a duration of at least 12 weeks prior to inclusion in the clinical study

Exclusion criteria

- Active, concomitant autoimmune disease manifestations
- Renal insufficieny definied by a creatinine clearance of less than 30 ml/min (CKD-EPI or MDRD formula)
- Hepatic impairment, i.e. unexplained persistent liver function abnormalities
- Laboratory parameters at the pre-treatment visit showing any of the following abnormal results: transaminases > 2x the upper limit of normal (ULN) and/or bilirubin > 2x ULN
- Severe cardiac (LVEF < 45%) and/or pulmonary disease (FVC <50%)
- History of heart failure, symptomatic coronary artery disease, significant ventricular
- tachyarrhythmia, stent placement, coronary artery bypass surgery, and/or myocardial infarction
- Use of other investigational drugs, within 5 half-lives of enrollment or within 30 days, whichever is longer
- History of hypersensitivity to any of the study treatments or excipients or to drugs of similar chemical classes.
- Pregnant or nursing (lactating) women, where pregnancy is defined as the state of a female after conception and until the termination of gestation.
- Women of child-bearing potential, defined as all women physiologically

capable of
becoming pregnant, unless they are using highly effective methods of contraception
during dosing and for 2 days after last dose of study medication. Highly effective
contraception methods include:
- Total abstinence (when this is in line with the preferred and usual lifestyle of the patient. Periodic abstinence (e.g. calendar, ovulation, symptothermal, postovulation methods) and withdrawal are not acceptable methods of contraception.
- Female sterilization (have had surgical bilateral oophorectomy with or without hysterectomy) or total hysterectomy or tubal ligation at least 6 weeks before taking study treatment. In case of oophorectomy alone, only when the reproductive status of the woman has been confirmed by follow up hormone level assessment.
- Male sterilization (at least 6 months prior to screening). For female patients on the study, the vasectomized male partner should be the sole partner for that patient.
- Use of oral, injected or implanted hormonal methods of contraception or placement of an intrauterine device (IUD) or intrauterine system (IUS) or other forms of hormonal contraception that have comparable efficacy (failure rate <1%), for example hormone vaginal ring or transdermal hormone contraception., In case of use of oral contraception women should have been stable on the same pill for a minimum of 3 months before taking study treatment.
Women are considered post-menopausal and not in of child bearing potential if they have had 12 months of natural (spontaneous) amenorrhea with an appropriate clinical profile (e.g. age appropriate, history of vasomotor symptoms) or have had surgical bilateral oophorectomy (with or without hysterectomy), total hysterectomy or tubal ligation at least six weeks ago. In the case of oophorectomy alone, only when the reproductive status of the woman has been confirmed by follow up hormone level
assessment she is considered not of child bearing potential., - History of malignancy within the last 5 years, except for resected basal or squamous cell carcinoma of the skin, treated cervical dysplasia, or treated in situ cervical cancer.
- Any psychological, familial, sociological or geographical condition potentially hampering compliance with the study protocol and follow-up schedule. , - Any condition or treatment, which in the opinion of the investigator, places the subject at unacceptable risk as a patient in the trial.

Study design

Design

Study phase:	2
Study type:	Interventional
Masking:	Open (masking not used)
Control:	Uncontrolled
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Pending
Start date (anticipated):	01-03-2022
Enrollment:	20
Type:	Anticipated

Medical products/devices used

Product type:	Medicine
Brand name:	Zadaxin
Generic name:	Thymalfasin

Ethics review

Approved WMO Date:	19-01-2022
Application type:	First submission
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	21-02-2022
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	EUCTR2021-003327-15-NL
CCMO	NL78339.078.21