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Telomerase activator TA-65MD® in patients with ACS (TACTIC)

Submission date 30/07/2018	**Recruitment status** No longer recruiting	[X] Prospectively registered [X] Protocol [_] Statistical analysis plan [X] Results [_] Individual participant data
Registration date 30/07/2018	**Overall study status** Completed	
Last Edited 10/10/2024	**Condition category** Circulatory System	

Plain English summary of protocol

Background and study aims
Throughout life, the length of telomeres (the protective caps of the chromosomes) becomes shorter and this is linked to cell ageing and a decrease in cell health. Shorter telomeres in white blood cells (specifically CD8 T cells) are associated with deterioration of the immune system and increased risk of heart attacks and other heart problems. There is a drug called TA-65MD® that has been shown to stimulate cells to add back some of the lost telomeres by activating the enzyme telomerase, which is responsible for elongating and maintaining telomeres. The aim of this study is to see whether TA-65MD® treatment for 1 year increases the length of the protective telomeres and whether this leads to fewer 'aged' CD8 T cells (cells with shorter telomeres) in patients who have coronary heart disease.

Who can participate?
Patients aged 65 years or over with coronary heart disease who have been successfully treated

What does the study involve?
Participants provide blood samples to measure CD8 T cell and immune cell ageing, telomere length, and telomerase activity, and have an echocardiogram (heart scan). They are then randomly allocated to take either TA-65MD® or a placebo (dummy drug) twice daily for 1 year. They attend follow-up visits at 1, 3, 6, 9 and 12 months to have their blood pressure and blood glucose measured, monitor side effects and medications and to return unused study drugs and be given new packs of study drug to take. At the 6 and 12-month follow-up visits the patients provide blood samples again. At the 12-month final follow-up visit the patients also have an echocardiogram (heart scan).

What are the possible benefits and risks of participating?
There may be no immediate personal benefit from taking part in the study but the results may help improve the treatment of people with coronary heart disease in the future. Participants receive additional follow-up assessments compared to routine care including the blood tests and echocardiogram. No serious side effects have been reported by people who have taken TA-65MD® during previous clinical trials and there is currently no evidence to suggest that taking TA-65MD® will cause any serious side effects. There have been non-serious side effects reported by some people who have taken TA-65MD®, which include hyperglycaemia (high blood

sugar) and anxiety. The feeling of being anxious went away when the participants reduced their dose to a level that was still more than double the dose used in this study. Patients with insulin-controlled diabetes are excluded from the study. Participants' blood sugar and blood pressure are also tested at each visit to check for any problems with this. There is a risk that there may be unknown and unpredictable side effects that have not yet been experienced by previous volunteers who have taken TA-65MD®.

Where is the study run from?
The James Cook University Hospital (UK)

When is the study starting and how long is it expected to run for?
July 2017 to January 2021

Who is funding the study?
Telomerase Activation Sciences, Inc.

Who is the main contact?
Dr Karen Nicholson
Karen.nicholson2@newcastle.ac.uk

Contact information

Type(s)
Scientific

Contact name
Dr Karen Nicholson

Contact details
Newcastle Clinical Trials Unit
1-4 Claremont Terrace
Newcastle upon Tyne
United Kingdom
NE2 4AE
No telephone contact available
Karen.nicholson2@newcastle.ac.uk

Additional identifiers

Clinical Trials Information System (CTIS)
2017-002876-26

Central Portfolio Management System (CPMS)
38286

Study information

Scientific Title
Telomerase ACTivator to reverse Immunosenescence in Acute Coronary Syndrome: a double-blind, phase II, pilot randomised controlled trial (TACTIC)

Acronym
TACTIC

Study objectives
Throughout life, the length of telomeres (protective caps of chromosomes) becomes shorter and this is linked to cell ageing and a decrease in cell health. Shorter telomeres in white blood cells (specifically CD8 T cells) are associated with deterioration of the immune system and increased risk of heart attacks and other heart problems. There is a drug called TA-65MD® that has been shown to stimulate cells to add-back some of the lost telomeres by activating the enzyme telomerase, which is responsible for elongating and maintaining telomeres. The main purpose of the TACTIC study is to see whether TA-65MD® treatment for 1 year increases the length of the protective telomeres, and whether this leads to fewer 'aged' CD8 T cells (cells with shorter telomeres) in patients who have coronary heart disease.

Ethics approval required
Old ethics approval format

Ethics approval(s)
Approved 09/08/2018, NHS HRA REC Newcastle and North Tyneside 1 (NHSBT Newcastle Blood Donor Centre, Holland Dr, Newcastle upon Tyne NE2 4NQ; 0207 104 8089; nrescommittee.northeast-newcastleandnorthtyneside1@nhs.net), ref: 18/NE/0178

Primary study design
Interventional

Study design
Randomized; Interventional; Design type: Treatment, Drug

Study type(s)
Treatment

Health condition(s) or problem(s) studied
Coronary heart disease

Interventions
Design and patient population:
The TACTIC trial will be a single site, double blinded randomised placebo controlled pilot trial. The study will take place at The James Cook University Hospital where the patients' routine care for a heart attack would normally take place under the care of consultant cardiologists in the research team. A total of 90 heart attack patients with a diagnosis of coronary heart disease will be recruited to the study.

The patient journey:
Potentially eligible patients will be identified by the local research team, given a patient information sheet to read, allowed time and opportunity to ask the research team any questions they have before being asked to give written informed consent.

Once consent has been given the patient will have their medical history checked and their blood pressure measured to confirm eligibility.

Eligible patients will have the following baseline assessments:
1. Blood sample for exposure to the cytomegalovirus
2. Blood sample for blood glucose
3. Blood sample for high sensitivity C Reactive Protein and N-terminal pro-brain natriuretic peptide markers of inflammation and heart failure respectively
4. Blood sample for research bloods to measure CD8 T cell ageing (primary endpoint)
5. Blood sample for research bloods to measure immune cell ageing (secondary endpoints), telomere length, and telomerase activity
6. Blood sample to obtain plasma to measure oxidative stress
7. Blood sample to obtain stored serum for further research (with specific consent)
8. Echocardiogram (heart scan)
9. Endothelial function
10. Physical assessment for height and weight
11. Record of patients' medications

Once all of these assessments have been performed the patient may be randomised

All patients will have been successfully treated for their heart attack prior to randomisation to either the test arm (TA65MD) or the placebo control arm with 45 patients in each arm. Once the patient has been randomised they may begin taking their study drug straight away as it will be dispensed by the James Cook University Hospital pharmacy. All patients will take 1 x capsule twice daily for 1 year. This may be the test drug TA65MD (8mg) or the placebo depending on their randomisation allocation.

Patients will attend follow up visits at 1, 3, 6, 9 and 12 months to have their blood pressure and blood glucose measured, monitor adverse events and medications and to return unused study drugs and be given new packs of study drug to take.

At the 6 and 12 month follow up visits the patients will have the following additional assessments:
1. Blood sample for high sensitivity C Reactive Protein and N-terminal pro-brain natriuretic peptide markers of inflammation and heart failure respectively
2. Blood sample for research bloods to measure CD8 T cell ageing (primary endpoint)
3. Blood sample for research bloods to measure immune cell ageing (secondary endpoints), telomere length, and telomerase activity
4. Blood sample to obtain stored serum and plasma
5. Endothelial function

At the 12 month final follow up visit the patient will also have an echocardiogram (heart scan). Once the patient has completed the assessments for the 12 month follow up they have finished their participation in the trial and will have no further follow up from the research team unless there are ongoing Adverse Events that are related to the study drugs which will be followed until resolved/ reached a state of permanence/persistence or the patient dies.

Study management:
Recruitment is expected to take 12 months with the final patient final visit occurring 24 months after the study start. Final data entry, data cleaning and review is expected to take around 6 months. No interim analysis is planned.

The research will be overseen by multiple parties. The trial management group consisting of the Chief Investigator, co-investigators, and members of the clinical trials unit will meet regularly throughout the trial to oversee the day to day activities of the trial. There will be a trial steering

committee who will provide overall supervision of the trial, monitoring progress and conduct. The majority of the trial steering committee will be completely independent from the trial. There will also be an independent data monitoring and ethics committee that will review and provide advice on the conduct and safety of the trial."

Intervention Type
Drug

Phase
Not Applicable

Drug/device/biological/vaccine name(s)
TA-65MD

Primary outcome(s)
Immunosenescence determined by flow cytometry (FACS) after 1 year of treatment. The proportion of terminally differentiated CD8+ effector memory cells (%CD8+ TEMRA 'aged') will be calculated from the total number of peripheral blood CD8+ T-lymphocytes in each blood sample; Timepoint(s): End of the study.

Key secondary outcome(s)
1. Leukocyte Telomere Length measured at baseline, 6 months and 1 year; short leukocyte telomere length is a predictor of cardiovascular mortality
2. CD8 T-cell telomere length measured at baseline, 6 months and 1 year; short telomere length is a predictor of cardiovascular mortality, and CD8 telomere length is significantly reduced in patients with coronary heart disease and post myocardial infarction. Isolated peripheral blood mononuclear cells (PBMCs) will be FACS sorted to purify CD8 cells.
3. The proportion of senescent (CD28-) CD4+ T-lymphocytes measured at baseline, 6 months and 1 year and calculated from the total number of CD4+ T-lymphocytes in each PBMC sample. CD28- CD4+ T-lymphocytes have been shown to be significantly increased in patients with acute coronary syndrome
4. The proportion of senescent (CD28-) CD8+ T-lymphocytes measured at baseline, 6 months and 1 year and calculated from the total number of CD8+ T-lymphocytes in each PBMC sample
5. Microvascular Endothelial Function assessed by measuring flow-mediated dilation (FMD) using finger plethysmography (EndoPat) at baseline, 6 months and 1 year of treatment. Using plethysmography at the fingertips of both hands, the EndoPAT system (Itamar Medical Ltd., Caesarea, Israel) will calculate an index of pulse wave amplitude after cuff occlusion to before occlusion of the test arm divided by the same ratio of the control arm, namely the reactive hyperemic index (RHI). FMD has been shown to be compromised in patients with diabetes as well as with coronary artery disease. It is a predictor of adverse clinical outcome. Endothelial dysfunction is seen as the initial step in atherogenesis.
6. Systemic inflammation measured by high sensitivity C-reactive protein (hsCRP) at baseline, 6 months and 12 months of treatment
7. Heart failure and cardiac function assessed by transthoracic echocardiography (TTE) at baseline and 12 months of treatment, and the pro natriuretic peptide NT-proBNP biomarker at baseline, 6 months and 12 months of treatment. Together these measures determine myocardial function, hypertrophy (left ventricular wall thickness), strain (NT-proBNP), and global longitudinal strain, reflecting the pathophysiological targets of heart failure
8. Telomerase activity assessed at baseline, 6 and 12 months following treatment using the TRAP assay. This provides an indication of drug effect
9. Oxidative stress measured at baseline, 6 and 12 months following treatment using the TBARS

colorimetric assay (Oxford Biomedical Research) with frozen plasma. TBARS is an established assay to quantify lipid peroxides. Additionally, the trialists will evaluate whether treatment with TA-65MD® leads to parallel activation of canonical and non-canonical pathways, measuring oxidative stress and endothelial function over time and correlating this with telomere length dynamics and telomerase activity.
10. The effect of CMV seropositivity at baseline will be correlated with study outcomes using an exploratory analysis
11. Adherence to the study drugs determined by counts of returned capsules and packaging at each dispensing visit
12. Adverse events recorded from the time of randomisation to withdrawal or the last study visit. All cause death, stroke and myocardial infarction will also be combined to provide a composite outcome

Completion date
30/04/2021

Eligibility

Key inclusion criteria
1. Able to give written informed consent
2. Patients aged 65 years or over with an index presentation of an acute coronary syndrome* within the previous 6 months
3. Successfully completed revascularisation** or managed medically following ACS
4. Angiographic evidence of coronary heart disease (at least one major epicardial vessel stenosis ≥70%)
5. More than 24 hours after presentation with the index event
*Acute coronary syndrome (ACS) defined as either a non-ST elevation acute coronary syndrome (NSTEMI), or ST elevation MI (STEMI) only.
**PCI/angioplasty (eligible the following day) or surgery (eligible 3 months later)

Participant type(s)
Patient

Healthy volunteers allowed
No

Age group
Adult

Lower age limit
65 Years

Sex
All

Total final enrolment
90

Key exclusion criteria

Updated participant exclusion criteria (as of 12/09/2018):
1. Patients with any disorder associated with immunological dysfunction (acute or chronic inflammatory or neoplastic co-existing disease, known positive serology for HIV, or hepatitis)
2. Clinically unstable patients (haemodynamically unstable, cardiogenic shock, unconscious)
3. Severe, uncontrolled hypertension (Blood Pressure > 170/110 mmHg, or ambulatory BP of 150 /95 mmHg)
4. Severe comorbidity that has an impact on outcome over next 2 years
5. Taking immunosuppressants
6. Known malignancy
7. Insulin-controlled diabetes
8. Judgment by the Investigator that the patient should not participate in the study, for example, if the patient is unlikely to comply with study procedures, restrictions, and requirements or if the patient had a previous diagnosis of a serious psychiatric disease
9. Participation in any other interventional medicinal studies in the past 6 months
10. Previous known substance addiction
11. Current use of nutritional supplements derived from roots of the Astragalus species

Previous participant exclusion criteria:
1. Patients with any disorder associated with immunological dysfunction (acute or chronic inflammatory or neoplastic co-existing disease, known positive serology for HIV, or hepatitis)
2. Clinically unstable patients (haemodynamically unstable, cardiogenic shock, unconscious)
3. Severe, uncontrolled hypertension (Blood Pressure > 170/110 mmHg, or ambulatory BP of 150 /95 mmHg)
4. Severe comorbidity that has an impact on outcome over next 2 years
5. Taking immunosuppressants
6. Known malignancy
7. Insulin-controlled diabetes
8. Judgment by the Investigator that the patient should not participate in the study, for example, if the patient is unlikely to comply with study procedures, restrictions, and requirements
9. Participation in any other interventional medicinal studies in the past 6 months

Date of first enrolment
12/01/2019

Date of final enrolment
31/03/2020

Locations

Countries of recruitment
United Kingdom

England

Study participating centre
The James Cook University Hospital
South Tees Hospitals NHS Foundation Trust
Marton Road

Middlesbrough
United Kingdom
TS4 3BW

Sponsor information

Organisation
South Tees Hospitals NHS Foundation Trust

ROR
https://ror.org/02js17r36

Funder(s)

Funder type
Industry

Funder Name
Telomerase Activation Sciences, Inc.

Results and Publications

Individual participant data (IPD) sharing plan
The anonymised datasets generated during and/or analysed during the current study are available upon request from Newcastle Clinical Trials Unit by accessing the following link https://www.ncl.ac.uk/nctu/work-with-us/data-sharing/
A data request form will need to be completed and this asks for the following:
1. Study design
2. Study objectives
3. Data required
4. Ethical approval and consent requirements
5. Proposed analysis
6. Planned outputs
7. Funding and resources needed and support available

Requests will be considered in conjunction with the chief investigator, senior members of the Clinical Trials Unit, and sponsor. Data will be available for the archive period of the trial, which is 15 years following the end of the trial. Participants have given consent for this data sharing.

IPD sharing plan summary
Available on request

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
Results article		22/04/2023	10/10/2024	Yes	No
Protocol article	protocol	23/09/2020	24/09/2020	Yes	No
HRA research summary			26/07/2023	No	No