Double-Blind, Randomized, Placebo-Controlled Phase IIa Clinical Trial to Investigate the Safety and Immunogenicity of RUTI® Therapeutic Vaccination in Patients with Multi-Drug Resistant Tuberculosis after successful intensive-phase treatment.

Published: 19-10-2016
Last updated: 17-04-2024

Primary endpoint: Evaluation of the safety of the novel anti-TB vaccine RUTI® (25*g FCMtb) in patients with MDR-TB favourably responding to second-line, standard MDRTB treatment through clinical, microbiological, and radiological response criteria....

Ethical review	Approved WMO
Status	Will not start
Health condition type	Mycobacterial infectious disorders
Study type	Interventional

Summary

ID

NL-OMON43117

Source
ToetsingOnline

Brief title
Safety of RUTI® vaccine in MDR-TB

Condition

- Mycobacterial infectious disorders
- Respiratory tract infections

Synonym

Infection with Mycobacterium tuberculosis resistant to at least the two first line antibiotics, Multidrug-resistant Tuberculosis

Research involving
Human

Sponsors and support

Primary sponsor: Archivel Farma S.L.
Source(s) of monetary or material Support: Archivel Farma S.L.,Archivel Farma, S.L., Badalona, Spanje, ontwikkelar van het RUTI® vaccine

Intervention

Keyword: Immunotherapy, Multidrugresistant, RUTI vaccine, Tuberculosis

Outcome measures

Primary outcome

The main endpoint of this study is safety. This will be assessed using

clinical, routine laboratory, and radiographic data obtained during follow-up.

- Local tolerability (limited function, swelling, redness, pain, itch) will be

examined daily during the first week and weekly in the remaining 7 weeks of

follow up.

- Systemic tolerability (body temperature, generalized pruritus, rashes,

arthralgia, myalgia, nausea, malaise, headache) will be assessed daily during

the first week and weekly in the remaining 7 weeks of follow up.

- Vital signs (blood pressure, heart rate, respiratory rate, and pulse

oxymetry) will be taken at screening, immediately before vaccination and at

weeks 1, 2, 3, 4, 6 and 8 during the follow-up.

- Adverse Events raised by patients spontaneously or observed by the study

doctor or attending physician during the study

- Chest X-Rays will be taken before vaccination and at week 8 follow up for assessment of nature and extent of lung lesions

- Laboratory tests at screening and at weeks 2 and 8 after vaccination:

o full blood count, haematology;

o serum chemistry (liver and kidney function);

o ESR, CRP;

o Glucose

Secondary outcome

Immunogenicity is the secondary study endpoint and the assays will be performed at the London School of Hygiene and Tropical Medicine, UK. It will be assessed using

i) IFN-* responses of stimulated Peripheral Blood Mononuclear Cells (PBMCs) upon stimulation with a panel of antigens comparing placebo and intervention group at three time points (before vaccination, 2 and 8 weeks post-vaccination). The technique used is ELISPOT (Enzyme-linked immunosorbent spot)

ii) Mycobacterial growth inhibition assay (MGIA). This functional immunogenicity assay measures the summative ability of the patient derived PBMCs to control the mycobacterial growth in an ex vivo system. Mycobacterial growth inhibition will be assessed using a BACTEC MGIT (mycobacterial growth indicator tube; as used for liquid culture) system as well as plate counting to

measure the decrease of bacterial load upon vaccination in the presence of PBMCs. The assessment will be performed after 4 days of PBMC co-culture with Mycobacterium bovis BCG as immune target. This is a novel tool to measure immunogenicity, which has not been used with PBMCs from clinical vaccine trials before.

Exploratory endpoint: Effect on a clinically relevant endpoint

Difference between the intervention and control group in time to sputum culture positivity immediately before vaccination and at 8 weeks post-vaccination grown in liquid culture (MGIT) read at 10 days.

Study description

Background summary

The threat and emergence of multidrug-resistant tuberculosis (MDR-TB) is a European public health priority. While the treatment of MDR-TB can be reduced to 9-12 months under strict circumstances most of the cases of MDR-TB require 20-24 months of chemotherapy with toxic and expensive second/third-line drugs and treatment success. Worldwide this treatment is successful in only 50% of the cases (WHO, Global Tuberculosis Report, 2015, Geneva, Switzerland). Apart from antibiotic development, alternative therapeutic options are therefore needed. MDR-TB is caused by strains of M. tuberculosis that have become drug resistant. With anti TB drugs, most organisms are killed but a sub-population turns into a persister state under antimicrobial pressure. This phenotype is similar to the latent form of TB that infects 23% of the worlds population. Due to their very low metabolism, these persister bacilli cannot be reached by conventional drug therapy and that is why log-lasting treatment is required to prevent failure, relapse and reactivation of disease. This equally represents the key problem why TB is so difficult to eradicate; if immunotherapy should seem to work in eradicating these persister bacilli this would open unprecedented opportunities for the elimination of TB and its latent form worldwide.

The RUTI® vaccine has been developed to evoke an immune response directed at

the molecular signature and antigens expressed by these persister bacilli. It consists of fragmented and inactivated M. tuberculosis cells grown under stress conditions to express persister antigens. RUTI® vaccine has been proven clinically safe and immunogenic in Phase I and II studies in healthy volunteers and latently TB infected individuals, also in HIV co-infected individuals.

The hypothesis of using RUTI® vaccine as adjunct during standard antibiotic therapy is that it stimulates host immune effector cells directed at bacilli that persist under antimicrobial therapy. The ultimate aim is to shorten the (currently 20-months lasting) treatment duration, and to reduce the chances of failure and relapse. The first step is assuring that the RUTI® vaccine is safe in patients with multidrug-resistant (MDR-) TB at two different time points of vaccination.

Study objective

Primary endpoint: Evaluation of the safety of the novel anti-TB vaccine RUTI® (25*g FCMtb) in patients with MDR-TB favourably responding to second-line, standard MDRTB treatment through clinical, microbiological, and radiological response criteria. The safety will be assessed through standard blood testing and physical examination.

Secondary endpoint: Evaluation of the immunogenicity of the novel anti-TB vaccine RUTI® (25*g FCMtb) in patients with MDR-TB favourably responding to second-line, standard MDRTB treatment as evidenced by i) an ex-vivo IFN-y ELISPOT assay and ii) a novel Mycobacterial Growth Inhibition Assay (MGIA).

Exploratory endpoint:
To explore the efficacy as the reduction of bacillary load in the sputum of the novel anti-TB vaccine RUTI® (25*g FCMtb) in patients with MDRTB favourably responding to TB treatment as evidenced by an increase in time-to-positivity of liquid culture.

Study design

Prospective, randomized, double-blind, multicentre, placebo-controlled clinical phase IIa trial to evaluate the safety and immunogenicity of RUTI® vaccine in MDR-TB patients favourably responding to standard MDR-TB treatment. Cohort A will receive the experimental vaccination treatment at time point 16 weeks after start of standard MDR-TB treatment. If clinically safe, as evaluated by an independent panel of experts (DSMB), the second cohort (cohort B) will be vaccinated at time point 12 weeks after start of standard MDR-TB treatment. All the patients will be followed up 8 weeks after vaccination.

Intervention

Study participants will receive once one dose of 25*g of either RUTI® vaccine or Matching RUTI® Placebo that will be injected subcutaneously at the deltoid muscle by the attending pulmonologist at 16 weeks upon start of MDR-TB treatment for Cohort A, and at 12 weeks upon start of MDR-TB treatment for Cohort B.

Study burden and risks

In previous clinical studies, local adverse events such as swelling, itch, and redness have been reported. We prevent the unlikely event of an exacerbated immune response by ensuring that vaccination will be given only when successful antibiotic therapy is guaranteed by clinical, laboratory, microbiological, and Chest X-Ray evaluation.

Clinical evaluation: patients will be assessed daily in the first week post-vaccination and once in week 2, 3, 4, 6 and 8. Each visit will take between 10-30 minutes. For immunogenicity read-out 40 ml (equal to 8 spoons) will be drawn before vaccination and at time points 2 and 8 weeks post vaccination; blood sampling will be combined with routine blood testing whenever possible.

Participants will benefit from state-of-the-art diagnostics, optimized treatment, and possibly boosted immune response directed at persistent and latent bacilli. According to WHO guidelines MDR-TB treatment lasts for 9-20 months, and second line TB drugs cause many unpleasant side effects. Only half the patients qualify for a treatment shortening to 9-12 months, for the remaining patients treatment will take 20-24 months. In less than 50% of the cases this treatment is successful; many fail, die or relapse shortly upon finalizing the treatment. Ever more drug resistances are being recorded and only very few promising new drugs are at the last steps of the development pipeline. Therefore we urgently need to assess novel ways to help these patients. All in all, this patient group will benefit from this investigation with the potential to shorten this lengthy treatment, and to increase treatment success.

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

- Female or Male patients (aged * 18);- Females of childbearing potential must have a negative pregnancy test at enrolment and must agree to use highly effective methods of birth control during and 30 days after the study;- The patient must provide written informed consent;- The patient must be willing and able to attend all study visits and comply with all study procedures;- diagnosed with active MDR-TB and therefore treated with second-line TB drugs;- MDR-TB patients with Mycobacterium tuberculosis (or Mycobacterium africanum) confirmed by sputum culture;- having successfully completed 16 (Cohort A) or 12 weeks (Cohort B) of MDR-TB treatment, fully supervised, with beneficial initial response to therapy, evidenced by:;1) Clinical response criteria: in patients initially presenting with three classical symptoms (weight loss, chronic cough, fever or night sweats), clinical improvement should be recorded in at least two of three symptoms at least 4 weeks apart; ;in patients with only two of these symptoms present initially, patients should show improvement in at least one symptom, at least 4 weeks apart; and in addition, patients should not develop clinical deterioration * i.e., on-going weight loss, or increased cough, or new-onset fever or night sweats. ;In addition, the attending physician should ascertain an overall clinical beneficial response to treatment. Transient deterioration of chest radiographic abnormalities might be explained by a paradoxical inflammatory response, and this may therefore not necessarily be interpreted as treatment failure; such decision depends on consensus with the DSMB. ;2) Microbiological response criteria: as evidenced by improvement in at least 2 measurements at least 4 weeks apart, using MGIT (liquid culture microbiological assay read at 10 days)

Exclusion criteria

- Inability to provide written informed consent ;- Women reported, or detected, or willing to be pregnant during the trial period;;- Severity of illness precluding full evaluation: expected early death, evidenced by respiratory failure, low blood pressure, WHO performance score 3-4; Central Nervous System involvement of TB (TB meningitis, intra-cranial tuberculomas) as there is too little evidence for effective drug penetration for second-line TB drugs;;- Major co-morbid conditions precluding full evaluation, i.e., active lung cancer, acute coronary syndrome, heart failure exceeding NYHA class 2; a diagnosis of metastasized malignancy; renal failure in excess of creatinine clearance < 30 ml / min calculated by the Cockcroft-Gault formula, which would severely complicate administration of aminoglycosides and capreomycin, considered as the major second-line TB drugs; obesity (BMI>30 kg/m2); chronic liver disease * Child-Pugh class C; ;- Receiving or anticipated to receive a daily dose of * 10 mg of systemic prednisone or equivalent within the period starting 14 days prior to enrolment. Note: patients are allowed to receive an acute, short course of methylprednisolone or prednisone or equivalent for management of an acute exacerbation of COPD or reactive airway disease in asthmatics ;- Cytotoxic chemotherapy or radiation therapy within the previous 3 months;- HIV co-infection, if CD4 count <350 copies/mL; those with 350 copies/mL are expected to be able to mount a sufficient cellular immune response and will therefore be eligible;- Blood transfusion in the last three weeks prior to the trial;- Documented allergy to TB vaccines, notably, to the RUTI® vaccine.;-Any of the following laboratory parameters:
* Aspartate aminotransferase (AST) or alanine aminotransferase (ALT) >3 x upper limit of normal (ULN)
* total bilirubine > 2 x ULN
* Neutrophil count * 500 neutrophils / mm3
* Platelet count < 50.000 cells / mm3

Study design

Design

Study phase:	2
Study type:	Interventional
Intervention model:	Parallel
Allocation:	Randomized controlled trial
Masking:	Double blinded (masking used)
Control:	Placebo
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Will not start
Enrollment:	5
Type:	Anticipated

Medical products/devices used

Product type:	Medicine
Brand name:	RUTI® vaccine

Ethics review

Approved WMO Date:	19-10-2016
Application type:	First submission
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	01-05-2017
Application type:	First submission
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	29-08-2018
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)

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	201600136
EudraCT	EUCTR2016-000850-36-NL
CCMO	NL56995.000.16