The University of Nottingham

END OF TRIAL REPORT 15TH JUNE 2013

STUDY TITLE: The Effects of Tetanus Vaccination on Mediators of Autoimmunity in Patients with MS MuST ReIn-1

Trial EudraCT Number: 2007-001496-11

REC ref: 09/HO408/106

R & D ref 10NS003

Project ID: 08020

MREC ref: 03057/0016/002-0001

Marketing Approval: PL06745/0123

Sponsor name and address:

Mr Paul Cartledge
University of Nottingham
Research Innovation Services
Kings Meadow Campus
Lenton Lane
Nottingham
NG7 2NR

Research Ethics Committee:

Dr Martin Hewitt/ Miss Susie Cornick-Willis
Chair/ committee co-ordinator
National Research Ethics Service
Nottingham Research Ethics Committee 2
1 Standard Court
Park Row
Nottingham
NG1 6GN

This study was performed in compliance with Good Clinical Practice.

TABLE OF CONTENTS

1. Study Abbreviations

ADR	Adverse Drug Reaction
AE	Adverse Event
CI	Chief Investigator
CRF	Case Report Form
DMC	Data Monitoring Committee
DAP	Data Analysis Plan
EMEA	European Agency for the Evaluation of Medicinal Products
EOT	End of Trial
GCP	Good Clinical Practice
ICF	Informed Consent Form
MHRA	Medicines and Healthcare products Regulatory Agency
MS	Multiple Sclerosis
NHS	National Health Service
PIS	Patient Information sheet
PI	Principle Investigator at a local centre
REC	Research Ethics Committee
R&D	Research and Development department
SAE	Serious Adverse Event
SAR	Serious Adverse Reaction
SPC	Summary of product characteristics
SUSAR	Suspected Unexpected Serious Adverse Reaction
TMG	Trial Management Group
TSC	Trial Steering Committee

2. Introduction

Multiple Sclerosis is a chronic neurological disease, which is the most common cause of neurological disability in young adults in the UK, with a rate of over 1 per 10000 estimated in a recent study. It is characterised by the development of white matter lesions in the central nervous system, which are disseminated in space and time. The hallmark of MS is an area (a "Plaque") of demyelination, with relatively preserved axons, which have predilection for key areas in the central nervous system, around the optic nerves, cerebellum and periventricular white matter. It is felt that early symptoms e.g. in a relapse are due to the acute demyelination with associated inflammation; as oedema resolves and a smaller area of scar forms, there may be some recovery of symptoms.

The exact cause of MS remains unknown. It is generally agreed that it is likely to be due to a combination of genetic and environmental factors interacting to produce autoimmune destruction of central nervous system myelin. Environmental contributions have also been queried as the rate of MS alters with migration (e.g. the risk has been higher for individuals migrating into a higher prevalence area as children than as adults).

Various treatment options are currently available from Intravenous/oral steroids for acute disabling relapses. Other disease related symptoms can currently be controlled with medications. Patients who suffer regular relapses may be eligible for disease modifying therapy, initially with beta-interferon or glatiramer acetate, which are thought to reduce relapse rate by one-third. Stronger immunosuppressants such as mitoxantrone (chemotherapeutic agent) are an alternative for patients not responding to disease modifying therapy.

The tetanus vaccine was introduced in 1938 for the Armed Forces and was felt to play a significant part in reducing the frequency of the tetanus infection,

The benefit of the reduction of infection rates was so much so that by 1961 a widespread national vaccination programme had been initiated, leading to a substantial decline in death rates. Common side effects are localised redness at injection site, induration and tenderness in up to 70% of patients these are generally self limiting, but rarely abscess formation has been associated. Fever, irritability, vomiting and malaise are common. Severe systemic reactions (which may include anaphylaxis) are rarely reported. Neurological complications are rare, but have been reported. Looking more specifically at MS patients, there are reports described tetanus vaccination proceeding demyelinating events in children, more recent evidence fails to support an increased likelihood of relapse or first events in MS following exposure to tetanus toxoid.

The way in which tetanus vaccination may protect against MS development or relapse is not entirely clear. It has been hypothesised that tetanus vaccination is protective against the development of MS through as yet unidentified mechanisms (likely to involve T-cells) This trial set out to examine this association further, looking at the action of the tetanus toxoid on the immune system and how it may interact with mechanisms thought to be involved in the pathogenesis of MS. It was hoped that the tetanus toxoid would successfully depress autoimmunity this would then lead to enhancement of our understanding of the aetiology of MS and may have contributed to the development of disease modifying therapies.

3. Trial / Study objectives

The purpose of the study was to test the hypothesis that tetanus vaccine upregulates the activity of T cells, thus reducing the likelihood of developing a relapse in Multiple Sclerosis. The primary objective was to assess the effect of tetanus vaccination on T-regulatory cells, in patients with Multiple Sclerosis. The secondary objective was to assess the effect of tetanus vaccination on natural killer cells in patients with Multiple Sclerosis and to assess the effect of the tetanus vaccination on cytokine production from peripheral blood mononuclear cells and natural killer cells in patients with Multiple Sclerosis. Also to assess the effects of tetanus vaccination, on clinical activity of Multiple Sclerosis as assessed by EDSS and relapse rate.

4. Investigational Medicinal Product

Revaxis is a suspension for injection in a pre-filled syringe. Containing activated Diptheria, Tetanus and polio vaccinations. Injected as a single 0.5ml, dose intramuscularly.

Drug strength:	2*IU*	Purified diphtheria toxoid
	20*IU*	Purified tetanus toxin
	40 D Antigen Unit	Inactivated poilmyelitis virus type 1
	8 D Antigen Units	Inactivated poilmyelitis virus type 2
	32 D Antigen Units	Inactivated poilmyelitis virus type 3
	0.35mg	Aluminium Hydroxide (as absorbent)

From http://emc.medicines.org.uk

(Sanofi-Pasteur MSD Limited, Revaxis summary of product characteristics)

Revaxis has a marketing authorisation and is to be used in accordance with that authorisation therefore standard pharmacy supplies where used.

Placebo was normal saline 0.9%. The marketed product used by NUH pharmacy. Also administered as a single dose 0.5ml intramuscularly.

(known side effects swelling and redness at injection site)

Both products were stored in NUH Trials Pharmacy securely locked in a cupboard and dispensed appropriately as required.

5. Planned/actual enrolment

Planned enrolment was 46. The actual number enrolment was 4. Unfortunately this study was terminated earlier than planned this was due to all 4 of the sub-investigators leaving the department over a period of less than six months, and staff subsequently not being replaced. This left the department with no personnel that had the specialised training that would enable the local task of cell separation techniques. This procedure and other vital blinding roles, such as administration of the investigational medicinal product where an integral part of the on-going investigations in this particular study.

6. A brief description of the population studied

Potentials for recruitment were identified by the PI in MS clinics. Clinically definite MS; Male or female subjects; 18-65 years of age inclusive; Females who are sexually active taking contraception.

7. Discussion of Study Design

The trial was a single centre, Randomised, placebo controlled parallel group design trial. Randomisation occurred at the start of the trial and was 1:1 participants received either Revaxis/placebo, administered as a single dose, 0.5ml intramuscular injection. Patients were randomised by the Clinical Trials Unit using an internet program. Pharmacy remained unblinded and remained responsible for randomisation codes.

Primary Endpoint where to be gained by measuring the number of Treg cells in peripheral blood as measured by expression of foxp3.

Secondary Endpoint where to be gained by measuring the number of Naturals killer cells in peripheral blood as a measure of expression of CD56. The level of pro, and anti-inflammatory cytokines. The number of documented relapse and the change in EDSS score from baseline.

Safety endpoints were to be measured by AE's spontaneously reported throughout the trial.

The stopping rules and discontinuation rules were adhered to, no significant adverse events/ Serious Adverse Events were experienced by the first few patients receiving the vaccine. The aim was to recruit 3 patients initially and observe for adverse events, before proceeding to recruit and treat further patients.

8. Removal of Patients from the therapy/assessment

The Chief Investigator Professor Cris Constantinescu was advised by the sponsor The University of Nottingham with regards to the formal closure of the study. Hence this report,

participants and GP's have been recently informed of this decision. It was recognised as the only option, as recruitment or follow-up could not be maintained.

9. Treatments administered

All 4 randomised participants received the trial treatment ravaxis/placebo. A 5th person was however randomised, without consent but treatment was not given as the participant did not attend their appointment. This information was gained from the Division's Trial Co-ordinator.

10. Cumulative exposure

Actual cumulative exposure = Unable to assess cumulative exposure due to treatment codes not being broken.

11. Serious Adverse Events

None

12. Overall safety

When it became apparent that the trial would have to be terminated, all of the participants were informed of the closure by letter. All participants were offered support by way of the availability of staff in the division being available to answer questions regarding the trial. Participants GP were also informed as a measure of safety.

13. Study subjects

The four participants where female, aged 44-49.

15. Conclusion

Multiple Sclerosis is a chronic neurological disease, which is the most common cause of neurological disability in young adults in the UK, with a rate of over 1 per 10000 estimated in a recent study. Various treatment options are currently available from Intravenous/oral steroids for acute disabling relapses. Other disease related symptoms can currently be controlled with medications. Patients who suffer regular relapses may be eligible for disease modifying therapy, initially with beta-interferon or glatiramer acetate, which are thought to reduce relapse rate by one-third. Stronger immunosuppressants such as mitoxantrone (chemotherapeutic agent) are an alternative for patients not responding to disease modifying therapy.

The tetanus vaccine was introduced in 1938 for the Armed Forces and was felt to play a significant part in reducing the frequency of the tetanus infection. The benefit of the reduction of infection rates was so much so that by 1961 a widespread national vaccination programme had been initiated, leading to a substantial decline in death rates. Common side effects are localised redness at injection site, induration and tenderness in up to 70% of

of infection rates was so much so that by 1961 a widespread national vaccination programme had been initiated, leading to a substantial decline in death rates. Common side effects are localised redness at injection site, induration and tenderness in up to 70% of patients these are generally self-limiting, but rarely abscess formation has been associated. Fever, irritability, vomiting and malaise are common. Severe systemic reactions (which may include anaphylaxis) are rarely reported. Neurological complications are rare, but have been reported. Looking more specifically at MS patients, there are reports described tetanus vaccination proceeding demyelinating events in children, more recent evidence fails to support an increased likelihood of relapse or first events in MS following exposure to tetanus toxoid.

The way in which tetanus vaccination may protect against MS development or relapse is not entirely clear. It has been hypothesised that tetanus vaccination is protective against the development of MS through as yet unidentified mechanisms (likely to involve T-cells) This trial set out to examine this association further, looking at the action of the tetanus toxoid on the immune system and how it may interact with mechanisms thought to be involved in the pathogenesis of MS. It was hoped that the tetanus toxoid would successfully depress autoimmunity this would then lead to enhancement of our understanding of the aetiology of MS and may have contributed to the development of disease modifying therapies.

This trial aimed to test 'The effects of tetanus vaccination on mediators with autoimmunity in patients with Multiple Sclerosis'. After only four participants were randomised and treated the trial was suspended and then terminated early due to trial staff no longer working in the department. As far as possible all safety standards were met. All participants were informed of the situation participants were offered support by way of the availability of staff in the division being available to answer questions regarding the trial. Participants GP were also informed as a measure of safety. The bloods taken for trial purposes are not as yet analysed due to staff members not being available. The intention is that these bloods will be analysed and so some data may become available at a later date. It may be pertinent to address this question again as the question asked remains yet unanswered.

APPENDIX

Study Staff:

Principle Investigator: Professor Cris Constantinescu

Sub Investigator: Putina Jerca Oltita

Sub Investigator: Radu Tanasescu

Sub Investigator: Laura Edwards

Sub Investigator: Su-Yin Lim

Sub Investigator: Maxine Harrison

Sub Investigator: Juliet Hulse

Sub Investigator: Zoe Rose

Principle Investigators Signature:

Professor Cris Constantinescu_____ Date 5/6/13