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Pain in anti-GD2 therapy

Submission date
29/01/2025

Recruitment status
Recruiting

Registration date
27/02/2025

Overall study status
Ongoing

Last Edited
28/02/2025

Condition category
Cancer

[X] Prospectively registered
[ ] Protocol
[ ] Statistical analysis plan
[ ] Results
[ ] Individual participant data
[ ] Record updated in last year

Plain English summary of protocol

Background and study aims
Neuroblastoma is the most common cancer in children under five years old. An antibody therapy – called anti-GD2 - has brought hope to those with the highest risk cases, helping children to survive longer than standard therapies and in some cases achieve remission. Unfortunately, the target on cancer cells that makes this antibody so effective - called GD2 - is also found on nerves throughout the body, meaning the antibody causes excruciating pain when delivered to the patient. Despite being given strong painkillers before treatment, these side effects can be so severe that patients have to either reduce the dose of the antibody, meaning it is less effective or stop treatment altogether. The immune response to anti-GD2 treatment has been demonstrated as important in fighting cancer, although the mechanism of action remains unclear. Previous research also suggests that, unfortunately, the immune system also contributes to the nerve-related side effects. The challenge is therefore to reduce the pain of neuroblastoma immunotherapy while still targeting the cancer.

Who can participate?
Children aged 12 months old and over diagnosed with high-risk neuroblastoma

What does the study involve?
This study will collect blood samples from participants receiving anti-GD2 treatment for neuroblastoma. These blood samples will be analysed in detail to understand the levels of inflammation and immune cells at the peak of the pain. The knowledge gained from the patient samples and their pain experience will be brought together and compared using experimental models to identify the antibody properties and immune cell responses that likely cause the painful side effects. Understanding why anti-GD2 causes nerve pain will inform the design of the antibody to better reduce the pain, while still keeping the most important characteristics required to target the neuroblastoma. This will make the therapy more effective, and perhaps allow it to be given earlier in the disease. This study will also learn about the neurological side effects of immune therapies more generally.

What are the possible benefits and risks of participating?
This research study aims to understand what role the immune system plays in causing the pain of anti-GD2 immunotherapy. The data collected will not have any direct implications for the health of participants. Similarly, it is highly unlikely that any genetic analysis will be of medical significance to participants. However, by taking part in this study, participants will be directly

helping to develop a blueprint for future novel cancer therapies with fewer pain side effects and thus improve the quality of life of cancer survivors.

This study is observational, meaning that participants will receive the same treatment whether or not they take part in the study. The risks from the study are therefore minimal. Participants will have extra blood samples taken. The volume of blood taken will be within what is considered safe limits of blood to take for research studies, and it will not involve any additional needles. The pain-related questionnaires will be taken during treatment when participants may be experiencing pain. The clinical research staff are trained to disturb participants as little as possible; however, some attention will be required for a few minutes for this.

Where is the study run from?
Nuffield Department of Clinical Neurosciences, University of Oxford, John Radcliffe Hospital, UK

When is the study starting and how long is it expected to run for?
July 2024 to October 2027

Who is funding the study?
Medical Research Foundation, UK

Who is the main contact?
Alexander Davies, alexander.davies@ndcn.ox.ac.uk

Contact information

Type(s)
Public, Scientific, Principal investigator

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Additional identifiers

Integrated Research Application System (IRAS)
344279

Central Portfolio Management System (CPMS)

66005

Study information

Scientific Title
A study to investigate the immune mechanisms of pain in patients receiving dinutuximab beta (anti-GD2) for the treatment of neuroblastoma

Study objectives
Pain is an almost universal toxicity associated with anti-GD2 immunotherapy, and can be severe despite opioid analgesia. Preclinical evidence suggests that cellular effector mechanisms likely play a role in the acute side effects of anti-GD2 antibody treatment. By understanding why anti-GD2 causes nerve pain, this study aims to design the antibody better to reduce the pain, while still keeping the most important characteristics required to target the neuroblastoma.

Ethics approval required
Ethics approval required

Ethics approval(s)
approved 22/01/2025, London - Fulham Research Ethics Committee (2 Redman Place Stratford, London, E20 1JQ, United Kingdom; +44 (0)20 7104 8084; fulham.rec@hra.nhs.uk), ref: 24/PR/1510

Study design
Multi-centre observational cohort study

Primary study design
Observational

Study type(s)
Quality of life

Health condition(s) or problem(s) studied
Neuropathic pain in patients undergoing anti-GD2 therapy for neuroblastoma.

Interventions
This non-intervention, multi-centre, observational study will investigate the mechanisms contributing to pain in patients receiving anti-GD2 monoclonal antibodies. Patients receiving dinutuximab beta (anti-GD2) monoclonal antibody (Qarziba) as part of their neuroblastoma treatment will be recruited at Oxford University Hospitals and University Southampton Hospital NHS Trusts. Patients will receive dinutuximab beta continuous infusion according to the SmPC and standard of care. Analgesics (opioids, gabapentin) will be given prophylactically with dosing titrated according to clinical need as per the institutional standard of care. Clinical observations will also be made as per institutional standards of care.

Clinical data will be collected by physicians using an electronic case report form designed to gather data from the medical records at baseline and during treatment. The pain experienced by participants during their treatment (pain scores and analgesia required recorded by questionnaires) will be correlated with clinical parameters, as well as detailed immune profiling and biomarkers of neural damage performed on serial blood sampled at baseline (pre-infusion)

and peak neuropathic pain (mid-infusion, e.g. days 2-3) during the first cycle of treatment. This process will be repeated upon the third treatment cycle (approximately 5 weeks later) when pain is expected to be lower.

Intervention Type
Drug

Phase
Not Applicable

Drug/device/biological/vaccine name(s)
Dinutuximab beta (Qarziba)

Primary outcome(s)
Changes in immune cell abundancies in peripheral blood measured using flow cytometry will be correlated with measures of pain using the Modified Objective Pain Score (KUSS, MOPS) (pre-verbal) or Revised Faces Pain Scale (verbal infants) before and after infusion

Key secondary outcome(s))
1. Changes in immune cell abundancies in peripheral blood measured using flow cytometry will be correlated with analgesic dosing measured using an electronic case report form (CRF) designed to gather data from the medical records as an indirect measure of pain before and after infusion
2. Neural damage measured using clinical assessment or molecular assay will be correlated with measures of pain using the Modified Objective Pain Score (KUSS, MOPS) (pre-verbal) or Revised Faces Pain Scale (verbal infants) before and after infusion
3. Patient clinical characteristics as recorded in the CRF will be correlated with measures of pain using the Modified Objective Pain Score (KUSS, MOPS) (pre-verbal) or Revised Faces Pain Scale (verbal infants) before and after infusion
4. Immune-related genetic sequencing (e.g. HLA type) will be correlated with clinical and diagnostic phenotypes at the individual patient level

Completion date
31/10/2027

Eligibility

Key inclusion criteria
1. Diagnosed with high-risk neuroblastoma
2. Scheduled to undergo treatment with dinutuximab beta
3. A parent/guardian willing and able to give informed consent for participation in the study, if under 16
4. In the Investigator’s opinion, is able and willing to comply with all study requirements

Participant type(s)
Patient

Healthy volunteers allowed
No

Age group
Child

Lower age limit
12 months

Sex
All

Key exclusion criteria
An individual may not enter the study if ANY of the following apply:
1. Patients with moderate to severe pain from other causes that may confound assessment or reporting of pain from events such as recent severe injury.
2. Patients with concurrent severe psychological or psychiatric disorders.
3. Any other significant disease or disorder which, in the opinion of the Principal Investigator, may either put the patients at risk because of participation in the study, or may influence the result of the study, or the individual's ability to participate in the study.
4. Patients who are in the opinion of the Principal Investigator unsuitable for participation in the study.

Date of first enrolment
01/03/2025

Date of final enrolment
01/09/2027

Locations

Countries of recruitment
United Kingdom

England

Study participating centre
Oxford University Hospitals NHS Foundation Trust
John Radcliffe Hospital
Headley Way
Headington
Oxford
United Kingdom
OX3 9DU

Study participating centre
University Hospital Southampton NHS Foundation Trust
Southampton General Hospital
Tremona Road
Southampton

United Kingdom
SO16 6YD

Sponsor information

Organisation
University of Oxford

ROR
https://ror.org/052gg0110

Funder(s)

Funder type
Charity

Funder Name
Medical Research Foundation

Results and Publications

Individual participant data (IPD) sharing plan
Access to original patient data will be strictly controlled by the clinical research teams at OUH and UHS.

The study will comply with the UK General Data Protection Regulation (UK GDPR) and Data Protection Act 2018, which require data to be anonymised as soon as it is practical to do so.

Following data processing into standard data fields, fully anonymised (de-identified) research data, as well as donated samples for which consent is given, may be shared with other researchers in the University of Oxford, or those based in the UK or abroad, including countries outside the European Economic Area.

Once results are published, large, de-identified datasets (i.e. lacking ID codes) will be uploaded to online public databases to enable cross-referencing and validation of the data by the wider scientific community. Smaller datasets will be submitted to journals as supplementary data in easily accessible Excel files, or made available on request.

IPD sharing plan summary
Stored in publicly available repository, Available on request, Published as a supplement to the results publication