An exploratory study to evaluate in vivo, ex vivo and clinical hypersensitivity reactions after first-time treatment with complement-reactogenic infusions

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Primary Objectives• To evaluate in vivo complement activation after first-time treatment with paclitaxel, liposomal doxorubicin (Caelyx) or other complement-reactogenic compounds• To evaluate ex vivo complement activation after incubation of predose...

Ethical review	Approved WMO
Status	Recruiting
Health condition type	Allergic conditions
Study type	Observational invasive

Summary

ID

NL-OMON56981

Source
ToetsingOnline

Brief title
In vivo and ex vivo complement activation

Condition

- Allergic conditions
- Miscellaneous and site unspecified neoplasms benign

Synonym
CARPA, hypersensitivity

Research involving
Human

Sponsors and support

Primary sponsor: Centre for Human Drug Research
Source(s) of monetary or material Support: CHDR

Intervention

Keyword: Clinical hypersensitivity reactions, Complement activation

Outcome measures

Primary outcome

May include, but not limited to:

• Complement activation products in plasma: C3a, C3d, sC5b9. Will be evaluated against baseline.

• Complement levels in serum after ex vivo incubation: sC5b9

Secondary outcome

• Adverse events (AEs)

• Adverse Events of Special Interest (AESIs): symptoms of infusion-mediated reactions including:

o Flushing

o Itching

o Alterations in heart rate and/or blood pressure

o Respiratory symptoms (including dyspnoea, chest discomfort, wheezing)

o Back- or abdominal pain

o Gastrointestinal symptoms

o Skin reactions (including urticaria)

o Angioedema

o Temperature changes

o Dysgeusia (metallic taste)

Study description

Background summary

Complement activation related pseudoallergy (CARPA) is a type of infusion-related reaction (IRR) in which unintentional overactivation of the complement system leads to symptoms of hypersensitivity. CARPA is thought to be primarily caused by the production of anaphylatoxins C3a and C5a, which lead to non-IgE-mediated skin reactions, heart rate and blood pressure alterations and risk of cardiogenic shock.

In vitro studies by Szebeni et al have shown that CARPA reactions may be evoked by a variety of compounds. However, structurally complex formulations such as liposomes and polyethyleneglycol(PEG)ylated-protein structures have been particularly associated with the induction of CARPA in vitro. Paclitaxel, a surfactant-based taxane has been shown to induce CARPA in vitro, which may be an effect of its surfactant excipient rather than the active ingredient. Therefore, albumin-bound paclitaxel (Abraxane) has been developed, with the purpose of relieving these hypersensitivity reactions. A similar response has been described for Amibsome, the liposomal formulation of Amphotericin B. Furthermore, the pegylated liposomal formulation of doxorubicine (Caelyx), has been described to activate complement both in vitro and in vivo. Chanan-Khan et al have shown that first- time exposure to liposomal doxorubicin (Caelyx) leads to elevated levels of complement sC5b-9 in vivo, which was associated with the occurrence of IRRs. The presence of elevated levels of anaphylatoxins C3a and C5a which are thought to be the drivers of CARPA symptoms remains unknown. The contribution of other complement proteins to the development of clinical symptoms also needs to be elucidated.

The first steps in unravelling the role of complement in infusion-related reactions (IRRs) have been taken. However, IRRs in general, and more specifically human in vivo CARPA reactions remain underreported and understudied, whilst the impact of CARPA on clinical trial participants, clinical site staff and the general drug development process is significant. Moreover, infusion reactions severely disrupt routine care, burdening both the patient and the clinical team. Therefore, efforts to recognize and further understand CARPA induction have been made at the Centre for Human Drug Research. We performed in vitro challenge experiments, where serum or plasma is incubated with potentially CARPA reactogenic compounds in line with the approach suggested by Szebeni et al. These ex vivo experiments can be used to evaluate potential complement activation by investigational compounds. Furthermore, the assays can help us gain a deeper understanding of in vivo

CARPA reactions by mapping out the role of individual complement proteins in the development of clinical signs and symptoms. Finally, these challenge experiments may be further developed and standardized with the purpose of assessing individual CARPA sensitivity, with the ultimate goal of establishing the risk of CARPA induction in an individual prior to in vivo dosing. If- and how the ex vivo challenge experiments translate to in vivo induction of CARPA remains to be elucidated.

Study objective

Primary Objectives
• To evaluate in vivo complement activation after first-time treatment with paclitaxel, liposomal doxorubicin (Caelyx) or other complement-reactogenic compounds
• To evaluate ex vivo complement activation after incubation of predose samples with paclitaxel or liposomal doxorubicin

Secondary Objectives
• To evaluate the occurrence of clinical CARPA symptoms in relation to in vivo complement levels

Study design

This is a multi-center, exploratory, observational study to evaluate in vivo and ex vivo complement activation after first-time treatment with therapeutic agents, including liposomal doxorubicin and paclitaxel. Up to 60 patients receiving first-time treatment with paclitaxel or liposomal doxorubicin will be included. 60 patients would be a relevant sample size for an exploratory study, as based on the described incidence of clinical CARPA of 5-10% in the pre-medicated population, a minimum of 3 clinical events is expected to occur. The incidence of subclinical events is expected to be at least similar but likely higher, as the limited amount of literature available describes elevated levels of complement in absence of clinical symptoms.

An interim analysis will be conducted after every 15 patients, which will consist of a review of the following relevant events:
1. Observation of clinical CARPA signals after first-time treatment with complement-reactogenic agents including: Flushing, Itching, Alterations in heart rate and blood pressure, Respiratory symptoms, Back- or abdominal pain, Gastrointestinal symptoms, Skin reactions, Angioedema, Temperature changes, Dysgeusia (metallic taste).
2. Observation of subclinical signs of complement activation after first-time treatment with complement-reactogenic agents: post-dose elevated levels of complement-activation products including C3a, C3d and/or sC5b9 in vivo, evaluated against baseline.

If >=1 event occurs, the study will be continued, and another 15 patients will be enrolled. In case of absence of a relevant signal and/or emerging CARPA signals with other therapeutic compounds within the study population, additional subjects may be included. All patients will be treated according to local treatment protocols, including any applicable pre-medication. No modifications will be made to the treatment strategy. Patients will be evaluated for symptoms of IRRs in an observational manner. Serum and plasma samples will be collected pre-infusion and at 10 min, 30 min and 1 hour post-start-infusion. Additional samples may be collected upon signs of IRRs outside of the defined timepoints. Additional samples may also be collected in case the duration of the first treatment is extended (e.g. due to cold cap treatment). The total duration of the study period will correspond with the duration of the treatment per local protocols

Study burden and risks

The overall aim of this study is to study complement activation and CARPA-symptoms in patients that are being treated with complement-reactogenic compounds to gain a deeper understanding of the mechanisms involved in human, in vivo CARPA induction. Additionally, we aim to investigate the relationship between ex vivo complement activation in the assay and in vivo occurrence of CARPA symptoms in an exploratory manner. No medical benefit can be expected form this study for the participating subjects.

No modifications will be made to the treatment protocols or strategies of included patients. Patients will be evaluated for signs of IRRs during the treatment period in an observational manner and will receive an additional intravenous cannula to collect blood for the purpose of this study. Approximately 110mL of blood will be collected which may result in minor discomfort or a bruise but is not expected to have further negative impact on the patient. Any patients who have poor venous access limiting phlebotomy or any other condition that would, in the opinion of the investigator, potentially compromise the safety of the patient will be excluded

Contacts

Public
Centre for Human Drug Research

Zernikedreef 8
Leiden 2333CL
NL
Scientific
Centre for Human Drug Research

Zernikedreef 8
Leiden 2333CL
NL

Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)
Elderly (65 years and older)

Inclusion criteria

1. Patients who have an indication for receiving potentially complement reactogenic treatments (e.g. paclitaxel or liposomal doxorubicin (Caelyx)) according to their clinical treatment protocol as prescribed by their treating medical specialist. Patients eligible for participation may include, but will not be limited to, patients with breast cancer or ovarian cancer.
2. Able and willing to give written informed consent and to comply with the study restrictions.
3. Has the ability to communicate well with the Investigator in the Dutch or English language and willing to comply with the study restrictions.

Exclusion criteria

1. Previous treatment with same complement reactogenic treatment (e.g. paclitaxel or liposomal doxorubicin (Caelyx) (e.g. in case of reintroduction)
2. Subjects with poor venous access limiting phlebotomy.
3. Patients with known complement deficiencies.
4. Patients who received plasma infusions within a week of the first infusion day.
5. Any condition that would, in the opinion of the investigator, potentially compromise the safety of the patient or may preclude the patient*s successful completion of the clinical trial.
6. Patients receiving chemotherapeutic combination therapy during the study

period (first treatment day).

Study design

Design

Study type: Observational invasive

Masking:	Open (masking not used)
Control:	Uncontrolled
Primary purpose:	Other

Recruitment

NL

Recruitment status:	Recruiting
Start date (anticipated):	15-11-2024
Enrollment:	60
Type:	Actual

Medical products/devices used

Registration:	No

Ethics review

Approved WMO

Date:	30-08-2024
Application type:	First submission
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)

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
CCMO	NL87241.056.24