Complement Inhibition: Attacking the Overshooting Inflammation @fter Traumatic Brain Injury (A phase II trial on the safety and efficacy of C1 esterase inhibitor Cinryze for the acute management of severe traumatic brain injury)

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This study has been transitioned to CTIS with ID 2024-514488-24-01 check the CTIS register for the current data. Primary Objective: To determine the safety and efficacy of 6000 IU Cinryze in patients with moderate and severe TBI (GCS 20 mM Hg as...

Ethical review	Approved WMO
Status	Recruiting
Health condition type	Injuries NEC
Study type	Interventional

Summary

ID

NL-OMON52831

Source
ToetsingOnline

Brief title
CIAO@TBI

Condition

- Injuries NEC
- Increased intracranial pressure and hydrocephalus

Synonym

1 - Complement Inhibition: Attacking the Overshooting Inflammation @fter Traumatic B ... 2-05-2025

Traumatic Brain Injury

Research involving
Human

Sponsors and support

Primary sponsor: Leids Universitair Medisch Centrum
Source(s) of monetary or material Support: Hersenstichting ,Takeda

Intervention

Keyword: Clinical trial, Complement system, Inflammation, Traumatic Brain Injury

Outcome measures

Primary outcome

The core problem of failing clinical trials in traumatic brain injury is mainly because included patients and the trauma mechanisms are very heterogeneous in contrast to animal studies. In addition, these studies focus primary on functional outcome, which is as heterogeneous as the pre-morbid population. To address this issue, the primary outcome in this study will be focussed on the therapy*s mechanism of action with function outcome as an important co-primary outcome (60). With the adequate endpoint focussed on Cinryze, we are more accurately informing the clinical trial with the preclinical data. In the past, ICP has been used, either explicitly or implicitly, as a surrogate end-point, especially in early-stage trials in clinical TBI. Many clinical trials using this end-point, particularly those focussed on neuroprotective agents, have prematurely halted or failed the past decade (61). This might be contributed to the fact that ICP is a surrogate marker early during TBI but confounded by the modern neuro-ICU practices through escalating interventions (such as decompressive craniectomies and hyperosmolar therapy) to normalize ICP. This

results in reduction of its sensitivity as an early primarily endpoint (39). As the actual values of ICP might not be clinically relevant, this trial will focus primarily on the intensity of ICP-targeted therapy based on the Therapy Intensity Level (TIL) Scale. The Therapy Intensity Level Scale is designed to integrate all known and relevant ICP directed treatments into a single summary score. The current TIL scale was developed as part of the Interagency Common Data Elements scheme (62). Since introduction, the novel TIL scale have been widely used in neurotrauma research, with excellent inter- and intra-rater reliability with minimal measurement errors (39). The TIL includes eight ICP-treatment modalities, termed items.

The TILmean based on the daily TIL score over four days will be calculated. The daily TIL score will be calculated based on the highest score in each item per day, to provide a metric of the maximal therapeutic intensity for ICP management for that day.

The co-primary efficacy endpoint will be the Extended Glasgow Outcome Scale (GOS-E) at six months after trauma (63). This endpoint can only be tested if the primary difference on the TIL scale is evaluated. If the difference on the TIL scale is not significant after finishing the trial, the co-primary efficacy endpoint will formally be declared *non-significant*. Nevertheless, this endpoint is not used primarily used to declare the study success. The so-called serial gatekeeping approach will be used (described in paragraph 9) (64). These multiple primary endpoints are used to also try to determine the role of

Cinryze in longer term clinical outcome (six months). The use of the GOS-E as a core global outcome measure is recommended by the interagency TBI Outcomes Workgroup and the International Mission for Prognosis and Analysis of Clinical Trials in TBI group (IMPACT Common Data Elements) (65). The GOS-E (66), derived from its precursor the GOS (67), is globally the most commonly used TBI outcome measure. While the GOS grades disability on a 5-point scale and is determined largely by physical deficits, the GOS-E provides a higher sensitivity by defining disability on an 8-point scale and incorporating emotional and cognitive disturbances affecting disability. The GOS-E is designed as a structured interview and can also be applied through telephone (68) and e-mail (69). This allows for a long-term follow-up without a high burden for patients. Although several other primary outcome measures for TBI exist, the GOS(-E) remains the most widely implemented and best validated tool to assess outcome in TBI and permits comparison to much of the world literature on TBI outcome (70, 71). Two research nurses or researchers will independently grade outcomes based on the GOS-E in each patient according to the standardized approach. Disagreements will be resolved by consensus between them or by consultation of a third investigator who is unaware of the trial-group assignment.

Furthermore, as this is a phase II trial, we use a primary safety endpoint in addition to our primary efficacy endpoint. This safety endpoint will be patient complication rate during hospitalization. This rate include adverse events (including serious adverse events) possibly related to study medication. This includes, but is not limited to, venous thromboembolic events, hypersensitivity

reaction, hyperglycemia, sepsis, mortality. Events will be presented per adverse event type, grade, and seriousness. Patients will be assessed daily by a blinded physician/nurse for these complications. Vital signs will be monitored closely and potential adverse reactions to the experimental treatment will be picked up immediately at the ICU.

Secondary outcome

Secondary outcomes will be measured during hospitalization up to one year follow-up.

During hospitalization:

- ICP burden

- CT scan midline shift

- Mortality

- Neurological damage markers in the blood using BANYAN biomarker assay

- Complement activity using different assays

- Inflammatory markers in serum and CSF

- Gene expression profiling of blood cells

- ICU length of stay, ventilator days

At discharge:

- GOS-E

- Hospital length of stay

- Hospital disposition

During follow-up

- GOS-E

- QoLiBri

- SF 36

- EQ-5D-5L

- Cost-effectiveness

Study description

Background summary

Traumatic Brain Injury (TBI) is a major cause of death and disability across all ages in all countries with the number of elderly people with TBI increasing due to falls and in the younger population due to road traffic incidents (1). In Europe, one million TBI patients are admitted to the hospital yearly, of whom 75.000 people die. This debilitating morbidity leads to enormous societal costs (2, 3). Therapies and guidelines that have been demonstrated to improve outcome after TBI are still limited, especially in the management of severe TBI (s-TBI). Patients with s-TBI have a high mortality rate, estimated at 30-40% in observational studies on unselected populations (1). Survivors of s-TBI experience a substantial burden of physical, psychiatric, emotional and cognitive disabilities, that disrupt their lives and their surroundings. Due to the huge burden after trauma, adequate treatment of these patients is important. TBI comprises a dynamic pathophysiology that evolves in time, consisting of primary injury, followed by systemic disorders which leads to secondary injury (4). These secondary injuries complicate the period of admission and recovery (5).

The human immune system comprises the adaptive and innate immune responses. The complement system forms the first line of defence against microorganisms and is critical in sensing tissue damage. Complement activation can be mediated by three distinct pathways: the classical pathway, the alternative pathway and the lectin pathway (6) Figure 1. Multiple experimental studies have identified a pathophysiologic role of the complement system in contributing to posttraumatic neuro-inflammation, disruption of the blood-brain barrier, secondary neuronal damage and neuronal cell death after traumatic brain injury (7-11). In TBI patients, elevated complement factors have been found in serum (12) and in ventricular cerebrospinal fluid (CSF) directly after the initial trauma (13, 14). Activation of the complement system in TBI results in a cascade of events including increased vascular permeability and activation of microglia and astrocytes, ultimately resulting in inflammatory reactions in and around contusion areas (15, 16). The overshooting inflammatory response, formation of brain edema and elevated intracranial pressures (ICP) cause secondary brain injury and is subsequently related to late morbidity and mortality in TBI (17). The neuro-inflammation can persist for years after the initial trauma and

secondary damage in (sub)acute phase (18) even causing predisposition for other neurological afflictions, like early onset dementia, later in life (19). In TBI patients, elevated complement factors have been found in serum (12) and in ventricular cerebrospinal fluid (CSF) directly after the initial trauma (13, 14).

Complement inhibition is therefore considered to be a potentially important aspect of TBI treatment. Most modalities of complement inhibitions have focussed on interfering with the cascade at the central level of the C3 or C5 convertases (20-22). The Membrane Attack Complex (MAC), the final product of the terminal pathway, initiates the NLRP3 inflammasome causing production of IL-1B, which activates microglia, astrocytes and causing infiltration of macrophages from the periphery (23). As shown in our previous experiments in TBI animal models (Baas group), inhibition of MAC formation appears to be sufficient to prevent secondary neurologic damage and improve neurologic performance in mice by reducing microglia activation, apoptosis and axonal loss (24). Studies directed at MAC formation are therefore promising as potential therapeutic intervention after TBI (25). Although specific MAC inhibition might seem a good approach to prevent secondary brain injury, there are also studies showing that C3 activation (upstream of MAC) is negatively influencing the inflammation overshooting of TBI. Activation of C3 triggered a sustained degenerative mechanism of microglial and astrocyte activation, reduced dendritic and synaptic density and inhibited neuroblast migration several weeks after TBI in animal models (26).

Complement 1 inhibitor (C1-INH) controls activation of multiple plasma mediator pathways by binding to two of the active sub-units of the first component of the complement system (C1r and C1s). In addition, it is a known inhibitor of kinin generation (kallikrein), fibrinolytic (plasmin) and contact activation (factor XIIa, XIIf, X1a) (27). It has also been shown to be an inhibitor of the mannan-binding lectin pathway of complement activation, inhibiting mannan-binding lectin-associated serine proteases (MAPSs) in the pathway (28). C1 inhibitor also interacts with C2b to inhibit binding of factor B to C3b and therefore it is also a down-regulator the alternative pathway convertase (29).

Cinryze is a human C1 esterase inhibitor (serine protease inhibitor), isolated from human plasma and is approved for treatment of hereditary angioedema (30). Because of its excellent safety profile, it has also been used to treat other inflammatory diseases, such as sepsis or ischemic reperfusion injury (31, 32). C1 esterase inhibitors are the only approved drugs that can inhibit most of the complement pathway activity. An alternative for Cinryze is to use the recombinant C1 esterase inhibitor Ruconest (33). However, the cost per treatment is higher for Ruconest and the elimination half-life of the recombinant C1 esterase inhibitor Ruconest is 2.5 hours, compared to 56-62 hours in the natural human protein Cinryze (34, 35). Due to the longer circulation time and the lower cost of treatment, Cinryze is the preferred treatment to use in this clinical trial to reduce ICP and secondary brain

injury.

Currently, there is clinical and preclinical evidence available regarding the role of the complement system in developing secondary brain injury in TBI patients. Moreover, high quality pre-clinical evidence exists for years concluding that interfering in this complement cascade alters the brain damage dramatically. Complement inhibition is considered to be a potentially important aspect of TBI treatment. Therefore, C1-INH can be beneficial in treatment of s-TBI, downsizes the detrimental and overshooting inflammation and preventing secondary brain injury to ensure a more favorable functional outcome and quality of life for patients with TBI.

Study objective

This study has been transitioned to CTIS with ID 2024-514488-24-01 check the CTIS register for the current data.

Primary Objective: To determine the safety and efficacy of 6000 IU Cinryze in patients with moderate and severe TBI (GCS <13 with a clinical indication for ICP measurements).

Primary hypothesis: The hypothesis is that random assignment to Cinryze in patients with moderate and severe TBI will experience a reduction in ICP directed therapy intensity levels (TIL) compared to random assignment to placebo (difference of 2.2). Secondary, if efficacy is proven on the TIL scale, a difference of the GOSE at six months will be evaluated. Furthermore, no difference should be detected in complication rate after one month between the two groups.

Secondary Objective: To determine differences between Cinryze and placebo treatment in the following outcomes for patients with moderate and severe TBI:
- Clinical outcomes: ICP burden, CT midline shift, GOSE, mortality, hospital and ICU length of stay, ventilator days, hospital disposition, quality of life (as expressed by QoLiBri), health-related quality of life (as expressed by SF-36 and EQ-5D-5L)
- Cost-effectiveness
- Neurological damage: BANYAN (GFAP/UCHL-1) blood biomarker
- Complement activation: human serum (WIESLAB assay) and total terminal complement activity levels (CH50) and protein levels of complement component.
- Level of Cinryze (C1 inhibitor activity) in plasma and RNA expression

Specifically, it is hypothesized that patients randomly assigned to Cinryze will have a lower ICP burden, measured as minutes of ICP>20 mM Hg as compared to the control group. Furthermore, we hypothesize that random assignment to Cinryze in patients with TBI will change the proportion of patients with a favourable long-term neurologic outcome compared to random assignment to placebo, based on the GOS-E at six months. The outcome biomarkers (complement

activation and BANYAN) serve to get a better mechanistic understanding of the pathophysiological neuro-inflammation and of the possible therapeutic effect of Cinryze.

Study design

The CIAO@TBI trial is a prospective, multicenter, randomized, double-blind, placebo-controlled phase II trial, with one group receiving one dose of Cinryze intravenously (IV) and one group receiving a placebo injection IV. The study will be performed in different Dutch level 1 trauma centers. Patients diagnosed with TBI on admission to the emergency departments between 01/08/2020-01/08/2022 with a Glasgow coma score of < 13 (with intracranial deviations on scan) and indication for ICU treatment with ICP monitoring will be eligible for inclusion. If informed consent can be obtained within 12 hours after the accident, patients are randomly assigned to one of the two study arms and will receive a single dose of 6000 IU Cinryze or placebo IV. (1 IU = the average endogenous level C1-esterase inhibitor in 1 ml human plasma). Neither the participants, nor the experimenters will know who is receiving the Cinryze or placebo. All patients will receive standard care. Blood and CSF samples (CSF only when drain is placed) will be taken from both patient groups before administration of Cinryze or placebo. Additional blood samples will be taken at 6, 12, 24, 48, 72, 96 hours after dosing of the Cinryze or placebo. Additional CSF samples will be taken at 24, 48, 72, 96 hours after dosing of the C1-INH or placebo. The timing of these blood samples is based on the estimated activity and elimination time of the test compound and the timing of the onset of neuroinflammation. In most TBI patients a crisis can occur due to the onset of neuro-inflammation about 3 days after the trauma (*troisième jour*) (36). The brain tends to swell the most on the third day after a traumatic injury. The patients* blood samples will be used to asses biomarkers for neurological damage (BANYAN), to measure qualitative levels of functional classical, MBL and alternative complement pathways in human serum, total terminal complement activity levels, protein levels of complement component using different assays and additional inflammatory markers like TNF-alpha and intraleukin. Patients will receive routine CT scans as part of the standard care.

Clinical scores routinely used in the standard clinical care and follow-up during recovery of TBI will be registered up to one year after discharge. Most patients that will match the inclusion criteria are most likely not able to give informed consent themselves due to the nature of the injury (incapacitated due to loss of conscience, mental confusion). Informed consent can therefore be obtained by patient or proxy or deferred consent. Informed consent must be obtained within 12 hours as the efficacy of the C1-INH is suspected to be limited 12 hours after trauma. The LUMC will function as a data coordination and analysis center. All neurosurgeons, intensive care physicians/nurses and other people concerned will be instructed with regard to the study.

Intervention

- CINRYZE is a heat-treated, nanofiltered C1 inhibitor product, purified from human plasma for fractionation. It is presented as lyophilized powder and solvent for solution for injection for the proposed indication. The product is reconstituted with Water for Injections (5 ml) resulting in 100 U/ml C1-inhibitor, with one unit (U) of C1-inhibitor corresponding to the C1-inhibitor activity in one millilitre of normal human plasma.
The starting material for the manufacturing process of CINRYZE active drug substance is "plasma for fractionation" according to Ph. Eur. monograph 07/2008:0853. Plasma is provided in the Netherlands by Sanquin, and in Belgium by CAF-DCF cvba-scrl (CAF-DCF, a subsidiary of Sanquin) and in Finland by the Finnish Red Cross Blood Service (FRC). Information on the source, collection, separation and control of the human plasma used as the starting material of CINRYZE is provided in the relevant Plasma Master Files of Sanquin and CAF-DCF, respectively.
The primary function of Cinryze is to regulate the activation of the complement and contact pathways. This regulation is performed through the formation of pathway-specific complexes that result in inactivation of the target protease and consumption of C1 INH. C1 inhibitor inhibits the complement system by binding C1r and C1s, two of the active enzyme subunits of the first component of the complement system (C1) in the classical pathway. The primary substrate of the activated C1 enzyme is C4; uninhibited C1 results in diminished C4 levels. An increase in C4 levels is therefore a surrogate measure of the biological effect of Cinryze.
C1 inhibitor regulates the contact system and the intrinsic coagulation (kallikrein-kinin) pathway by binding to and inactivation kallikrein and factor XIIa. Because these pathways are part of enzyme amplification cascades, without C1 INH, spontaneous or trigger-induced activation of these pathways leads to production of the vasoactive peptide bradykinin.

- Placebo: physiological saline (0.9%) in equal volume dosed intravenously (60 ml)

Study burden and risks

The treatment itself consists out of a single intravenous injection (6000 IU) Cinryze or equal injection volume of placebo (physiological saline. Cinryze is a C1 esterase inhibitor isolated from human plasma. As such it is a *human blood product* and cannot be used by people sensitive for human blood products. When medicinal products prepared from human blood or plasma are administered, the possibility of transmitting infective agents cannot be totally excluded. This also applies to unknown or emerging viruses and other pathogens. Nevertheless, this risk is considered very low. The risks associated with short term complement inhibition by Cinryze are a theoretical increase in susceptibility for bacterial meningitis. This is controlled in this study by

the short term of the treatment with complement inhibitors and careful monitoring of the patient for such infections. This risk is considered low. A decrease in coagulation time because of Cinryze treatment is possible. This can result in thrombosis and might pose extra risks in patients with indwelling catheters. However, most TBI patients experience increased coagulation times due to the consumption of coagulation factors after trauma. Since the drug is given only once this risk is considered low and patients with a history of thrombosis will be excluded. The potential benefit for the patient is that complement inhibition will delay neuroinflammation. The delay of the neuroinflammation might improve the clinical outcome and leads to a decrease of secondary brain injury in the TBI patient. Closely monitoring of the patients can be beneficial in the treatment of TBI and the information gathered from this research project will help to introduce better treatment of TBI patients in the future. Furthermore, C1-inh has been investigated to have an excellent safety profile in multiple trials.

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

In order to be eligible to participate in this study, a subject must meet all of the following criteria:
- Age at admission >= 18 years;
- Clinical diagnosis of traumatic brain injury with GCS < 13 (with intra cranial deviations);
- Catheter placement for monitoring and management of increased ICP for at least 24 hours;

Exclusion criteria

A potential subject who meets any of the following criteria will be excluded from participation in this study:
- A clear, non-traumatic cause of low GCS (e.g. toxic, cardial) on admission;
- Not expected to survive more than 24 hours after admission;
- Brain death on arrival in the participating centres;
- Severe pre-trauma disability, defined as being dependent on other people;
- Known prior history of sensibility to blood products or Cinryze;
- Patients with a history of hereditary angioedema;
- Patients with a history of thrombosis
- Pregnant women.

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:	Recruiting
Start date (anticipated):	02-04-2021
Enrollment:	106
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	C1-esterase inhibitor
Generic name:	CINRYZE
Registration:	Yes - NL outside intended use

Ethics review

Approved WMO

Date:	25-02-2020
Application type:	First submission
Review commission:	METC Leiden-Den Haag-Delft (Leiden) metc-ldd@lumc.nl

Approved WMO

Date:	23-07-2020
Application type:	First submission
Review commission:	METC Leiden-Den Haag-Delft (Leiden) metc-ldd@lumc.nl

Approved WMO

Date:	23-10-2020
Application type:	Amendment
Review commission:	METC Leiden-Den Haag-Delft (Leiden) metc-ldd@lumc.nl

Approved WMO

Date:	19-11-2020

Application type:	Amendment
Review commission:	METC Leiden-Den Haag-Delft (Leiden)
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Approved WMO Date:	01-03-2021
Application type:	Amendment
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Application type:	Amendment
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Approved WMO Date:	01-06-2021
Application type:	Amendment
Review commission:	METC Leiden-Den Haag-Delft (Leiden)
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Approved WMO Date:	13-08-2022
Application type:	Amendment
Review commission:	METC Leiden-Den Haag-Delft (Leiden)
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Approved WMO Date:	30-08-2022
Application type:	Amendment
Review commission:	METC Leiden-Den Haag-Delft (Leiden)
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Study registrations

Followed up by the following (possibly more current) registration

No registrations found.

Other (possibly less up-to-date) registrations in this register

ID: 29423
Source: NTR
Title:

In other registers

Register	ID
EU-CTR	CTIS2024-514488-24-01
EU-CTR	CTIS2024-514488-24-02
EudraCT	EUCTR2020-000140-58-NL
CCMO	NL72551.058.20
OMON	NL-OMON29423