Conestat alfa as prophylactic treatment for idiopathic non-histaminergic acquired angioedema

Published: 06-04-2017
Last updated: 12-04-2024

The primary objective of this exploratory study is to test if prophylactic use of conestat alfa decreases the frequency of angioedema attacks in patients with InH-AAE. As secondary objectives, effects on disease severity, quality of life and drug...

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Angioedema and urticaria
Study type	Interventional

Summary

ID

NL-OMON49738

Source
ToetsingOnline

Brief title
Conestat alfa prophylaxis for InH-AAE (CAPI)

Condition

- Angioedema and urticaria

Synonym
angioedema, Idiopathic non-histaminergic acquired angioedema

Research involving
Human

Sponsors and support

Primary sponsor: Universitair Medisch Centrum Utrecht
Source(s) of monetary or material Support: Pharming Group,Pharming Group N.V.

Intervention

Keyword: Angioedema, Conestat alfa, Idiopathic non-histaminergic acquired angioedema, InH-AAE, Ruconest

Outcome measures

Primary outcome

The primary endpoint of this study is the mean monthly attack frequency during the 8-week treatment period as reported by the patient on the AAS form.

This primary parameter will be compared with the patient reported mean monthly attack frequency over the past 6 months (primary outcome) and the mean monthly attack frequency during the 8-week observational period.

Secondary outcome

Secondary endpoints are changes in disease severity, quality of life and occurrence of adverse events. In addition, a panel of biomarkers will be assessed for association with disease severity, proposed disease mechanism, response to treatment and safety.

Study description

Background summary

Conestat alfa, a recombinant human C1 esterase inhibitor (C1INH), is an effective treatment for acute attacks of angioedema in patients with hereditary angioedema (HAE) caused by C1INH deficiency. C1INH inhibits the contact system, this enzymatic system produces bradykinin. Bradykinin mediates swelling attacks in HAE. Another mediator that can drive angioedema is histamine. Histamine is held responsible for angioedema attacks in patients with chronic spontaneous urticaria, anti-histamines can bring relief. In the case of idiopathic angioedema the mediator is unknown, patients that do not responds to anti-histamines are diagnosed with idiopathic non-histaminergic acquired angioedema (InH-AAE). The anti-IgE biological Omalizumab has recently become available for chronic spontaneous urticaria including InH-AAE patients. The

effectiveness of Omalizumab in InH-AAE was not yet investigated.
InH-AAE is suspected to be mediated by bradykinin, however biomarkers to determine if bradykinin is indeed involved are not available. Case reports describe that angioedema in InH-AAE responds well to medication used in HAE. Currently, there is an urgent clinical need for therapy for InH-AAE patients, conestat alfa might be used as a therapy for InH-AAE by inhibiting bradykinin generation.

Study objective

The primary objective of this exploratory study is to test if prophylactic use of conestat alfa decreases the frequency of angioedema attacks in patients with InH-AAE.
As secondary objectives, effects on disease severity, quality of life and drug safety will be reported. Further, potential novel biomarkers for bradykinin mediated disease will be studied.

Study design

This study is a mono-center, open label, uncontrolled exploratory intervention study.

Intervention

Study participants will receive 50IU/kg conestat alfa (max 4200 IU), twice weekly via intravenous infusion for eight weeks. Four weeks prior to treatment, during the 8-week treatment period and four weeks after treatment, attack frequency will be reported. Blood samples will be collected for biomarker studies.

Study burden and risks

There is currently limited therapy available for InH-AAE, this unmet clinical need may be resolved with conestat alfa treatment. Conestat alfa is in general a safe and well tolerated drug as was shown in extensive studies in HAE patients and healthy volunteers.
Patients will be asked to fill in a very concise, daily angioedema activity score reporting attack frequency and severity over the course of 16 weeks. In addition, quality of life will be assessed four times. During the 16 weeks, patients are asked to visit the out-patients* clinic 18 times; 1 visit at inclusion,16 visits during the 8 week treatment period, and 1 visit at the end 4 weeks after treatment. They will receive conestat alfa via an iv bolus every 3 or 4 days during the 16 visits of the treatment period.
A total of 19 blood tubes will be collected at 6 time points, 5 times the venepuncture set for drug infusion can be used , 1 time an extra venepuncture will be performed..

We consider the risks of intervention to be low but acknowledge that participation is demanding. We only include patients with a highly frequent of angioedema attacks. This sub-population may benefit the most; would also be considered eligible for twice weekly prophylactic treatment if therapy was already available; and effect on monthly attack frequency may become apparent fast allowing the relatively short treatment duration of two months.

Contacts

Public
Universitair Medisch Centrum Utrecht

Heidelberglaan 100
Utrecht 3584CX
NL
Scientific
Universitair Medisch Centrum Utrecht

Heidelberglaan 100
Utrecht 3584CX
NL

Trial sites

Listed location countries

Netherlands

Eligibility criteria

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

Inclusion criteria

Age * 18 years. , Diagnosis idiopathic non-histaminergic acquired angioedema (InH-AAE) were *non-histaminergic* is defined as following: insufficient effect of treatment with antihistamines up to 4 times the standard dose (step 2 in CSU-treatment regimen), defined as having breakthrough attacks. , Minimal mean

attack rate of 2 per month during the past six months despite treatment; with at least one attack in the month prior to inclusion. , Written informed consent.

Exclusion criteria

- Presence of recurrent wheals/ urticaria accompanying angioedema. Where wheals are defined as recurrent, itchy, urticarial plaques that tend to appear and resolve quickly (<24). A patient reported incidental wheal, that was unrelated to angioedema is not considered an exclusion criteria. , - Diagnosis other than InH-AAE is deemed more likely e.g. drug-hypersensitivity, HAE, mastocytosis. , - ACE-inhibitor use in the past 6 months., - Treatment with add on therapy Omalizumab (wash-out period 2 months) use in the two months prior to visit 1., - Treatment with add on therapy cyclosporine (wash-out period 1 month) prior to visit 1., - Treatment with add on therapy methotrexate, azathioprine or mycophenolic acid (wash-out period 3 month) before visit 1., - History suggesting allergy for rabbits or rabbit derived products (such as conestat alfa). Defined as allergic symptoms occurring within hours after contact with rabbits, and after every contact with rabbits. , - Currently trying to conceive, pregnancy and women giving breastfeeding., - Inability to comply with study and follow-up procedures., - Presence of clinically significant conditions that could interfere with the interpretation of the study results and or compromise the safety of the patients e.g. severe impaired renal or hepatic function, active malignancy or currently treated for malignancies other than non-melanomal skin cancer., - Participation in an investigational drug or device trial within the last 30 days prior to screening., -*C4 levels lower than 0.10 g/L. In this case additional investigations are necasarry to first exclude the diagnosis HAE by repeating C4 measurement and perform a C1-esterase inhibitor function test.

Study design

Design

Study phase:	2
Study type:	Interventional
Masking:	Open (masking not used)
Control:	Uncontrolled
Primary purpose:	Prevention

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	12-03-2018
Enrollment:	10
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Ruconest
Generic name:	Conestat alfa
Registration:	Yes - NL outside intended use

Ethics review

Approved WMO Date:	06-04-2017
Application type:	First submission
Review commission:	METC NedMec
Approved WMO Date:	23-08-2017
Application type:	First submission
Review commission:	METC NedMec
Approved WMO Date:	01-11-2017
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	06-03-2019
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	24-10-2019
Application type:	Amendment
Review commission:	METC NedMec

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
EudraCT	EUCTR2016-005083-34-NL
CCMO	NL60248.041.16