The pharmacokinetics and pharmacodynamics of eculizumab in patients with paroxysmal nocturnal hemoglobinuria.

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To describe the real-world population pharmacokinetics and pharmacodynamics of eculizumab in unselected PNH patients

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Haematological disorders NEC
Study type	Observational invasive

Summary

ID

NL-OMON48010

Source
ToetsingOnline

Brief title
PREPARE

Condition

- Haematological disorders NEC

Synonym
PNH, rare blood disease

Research involving
Human

Sponsors and support

Primary sponsor: Radboud Universitair Medisch Centrum
Source(s) of monetary or material Support: Ministerie van OC&W

Intervention

Keyword: Eculizumab, Pharmacodynamics, Pharmacokinectics, PNH

Outcome measures

Primary outcome

Clearance and volume of distribution

Secondary outcome

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Study description

Background summary

Paroxysmal nocturnal hemoglobinuria (PNH) is a rare hematological disorder which is characterized by hemolytic anemia, cytopenias and thrombosis. PNH is caused by clonal expansion of hematopoietic stem cells with an acquired somatic mutation in the X-linked phosphatidylinositol glycan class A gene (4). This gene encodes a protein required for synthesis of glycosylphosphatidylinositol (GPI) anchors. As a result of the mutation, affected stem cells are deficient in GPI anchored proteins. Clonal expansion leads to the production of hematological cells lacking the expression of GPI anchored complement regulatory proteins CD55 and CD59. This leads to chronic complement-mediated hemolysis of the GPI-deficient erythrocytes. Eculizumab is a humanized chimeric monoclonal anti-C5 inhibitor which is approved for the treatment of PNH and was the first licensed drug targeting the complement system. By binding to C5, eculizumab prevents the activation of C5 into C5a and C5b and subsequent the formation of the terminal complement complex C5b-9. Eculizumab is currently administered in a flat fixed dose for every patient. However, because of the inter and intra individual variability in pharmacokinetics and pharmacodynamics of eculizumab in PNH patients, a tailored treatment approach for the individual is probably preferable. We have recently shown, by means of pharmacokinetic modelling and simulation, based on the drug approval data, that eculizumab dosing in PNH patients can be successfully tailored by means of Therapeutic Drug Monitoring. This approach when implemented in practice will result in overall less pharmacokinetic variability, less under-treatment and an average dose reduction of 11%. It should be noted that the yearly eculizumab drug costs are about 400.000 euro per patient. Considering the fact that in the Netherlands alone approximately 60 patients with PNH are yearly treated with this drug, this indicates that development of a model-informed precision dosing

tool based on the actual pharmacokinetics and pharmacodynamics of eculizumab has the potential to decrease treatment costs with 2.640.000 euro on a yearly basis.

The starting point of a robust tailored dosing approach for eculizumab is the development of a population pharmacokinetic-pharmacodynamic model. The majority of the pharmacokinetic and pharmacodynamic data in PNH patients are derived from controlled clinical studies and may not be representative for general PNH patient population. Therefore, it is pivotal to collect more pharmacokinetic and pharmacodynamic data in PNH patients in the actual clinical setting.

Study objective

To describe the real-world population pharmacokinetics and pharmacodynamics of eculizumab in unselected PNH patients

Study design

This study is a cross-sectional observational pharmacokinetic and pharmacodynamic study

Study burden and risks

The methods of this observational study are considered as minimally invasive with negligible risks. The only risk associated with participation in this study is collection of extra blood. We want to collect approximately 30 ml blood in total, divided over 3 occasions per patient. After the infusion, patients have to wait only 15 minutes before a blood sample can be collected. Furthermore, patients can be benifit form this study, as we can probably optimize their treatment with eculizumab.

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

The patient has a diagnosis of PNH
The patient is treated with eculizumab
Willing to give informed consent

Exclusion criteria

Not applicable

Study design

Design

Study type: Observational invasive

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

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	23-02-2021
Enrollment:	50
Type:	Actual

Ethics review

Approved WMO Date:	22-07-2019
Application type:	First submission
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	05-09-2019
Application type:	First submission
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)

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	EUCTR2019-002928-32-NL
CCMO	NL69637.091.19
Other	Nog niet bekend, wordt bij clinicaltrials.gov ingeschreven

Study results

Date completed:	01-07-2022
Actual enrolment:	27