Imlifidase treatment for acute inflammation in AQP4-IgG associated neuromyelitis optica spectrum disorder

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To analyse in what proportion of NMOSD patients with an episode of acute inflammation circulating pathogenic anti-AQP4 IgG antibodies are depleted below detection limits, as measured with a state-of-the-arts cell-based assay, in the timeframe within...

Ethical review	Approved WMO
Status	Pending
Health condition type	Central nervous system infections and inflammations
Study type	Interventional

Summary

ID

NL-OMON53456

Source
ToetsingOnline

Brief title
DEFEAT NMOSD

Condition

- Central nervous system infections and inflammations

Synonym
devic disease, neuromyelitis optica spectrum disorder

Research involving
Human

Sponsors and support

Primary sponsor: neurologie
Source(s) of monetary or material Support: Erasmus foundation,Hansa Biopharma

Intervention

Keyword: AQP4, attack, Imlifidase, NMOSD

Outcome measures

Primary outcome

- Circulating anti-AQP4-IgG levels at the predefined time points (0h, 0.5h, 1h, 2h, 4h, 6h, 8h, 1d, 2d, 3d, 7d, 14d, 21d, 28d, 64d, 180d) to day 180 as analysed with cell-based flowcytometry assay.

Secondary outcome

- Number of adverse events and serious adverse events within the timeframe to day 180.

- Laboratory abnormalities within the timeframe to day 180.

- Results of physical examination and vital signs

- Samples for Anti-imlifidase IgG (anti-drug antibodies). Aliquoting of each sample and dedicate for PK, PD and ADA.

- Levels of total IgG antibodies at predefined time points to day 180

-Total IgG (pharmacodynamics, PD) and imlifidase concentration (pharmacokinetics, PK) will be determined in serum by Hansa Biopharma, Sweden after inclusion of two patients and after inclusion of five patients.

-Pharmacokinetics and pharmacodynamics of imlifidase at the predefined time-points 0h, 0.5h, 1h, 2h, 4h, 6h, 8h, 1d (24h), 2d (48h), 3d (72h), 7d (168h), 14 d

Other study parameters

Exploratory clinical endpoints

- Mean change in EDSS and from baseline to time 7 days, 28 days, 64 days, 180 days

- Mean change in functional system motor score or functional system visual score from baseline to time 7 days, 28 days, 64 days, 180 days

- Mean change in EQ-5D (patient reported outcome measure, PROM, regarding quality of life) at day 7, day 14, day 28, day 64, day 180

- Requirement of additional plasmapheresis for the treatment of the acute relapse.

Exploratory laboratory endpoints

- Serum levels of neurofilament light chain (NfL) at baseline, day 1, day 7, day 28, day 64 measured using a Siemens assay

- Serum levels of Glial fibrillary acidic protein (GFAP) at baseline, day 1, day 7, day 28, day 64 measured using a Single Molecule Array (SIMOA) assay

Study description

Background summary

Aquaporin-4 IgG seropositive neuromyelitis optica spectrum disorder (AQP4-IgG positive NMOSD) is a rare demyelinating inflammatory disorder presenting with episodes of severe inflammation in typically the optic nerve(s) and/or spinal cord. The AQP4 antibodies are believed to be pathogenic and as such contributing to the inflammation and resulting, often severe, neurological deficits. Since old and new maintenance therapies reduce but not abrogate the overall risk of attacks, persisting attacks remain the most important mediator of persistent disability in NMOSD. In order to reduce neurological damage rapid aggressive treatment of the acute attack of inflammation is indicated. Momentarily standard care to reduce attack related damage includes intravenous methylprednisolone (IVMP) for all patients. Sometimes, in severely affected patients, based on individualized clinical decision making taking in into

account severity of disability, and trends towards recovery, this is followed by a subsequent second course of IVMP and possibly additional treatment with 5 courses plasmapheresis over 2 weeks . The latter treatment is believed to result in a faster recovery and less residual neurological disability by depleting circulating pathogenic anti-AQP4 antibodies. We hypothesize that anti-AQP4 IgG antibodies can be reduced in an early phase of acute attack treatment using imlifidase.

Study objective

To analyse in what proportion of NMOSD patients with an episode of acute inflammation circulating pathogenic anti-AQP4 IgG antibodies are depleted below detection limits, as measured with a state-of-the-arts cell-based assay, in the timeframe within 6h after treatment with imlifidase

Study design

Open label, single arm, single center phase 2 study.

Intervention

Imlifidase is provided as freeze-dried powder for concentrate for solution for infusion, 11mg per vial. After reconstitution with sterile water for injection the concentrate contains 10mg/mL imlifidase. The concentrate will be added to 50 mL sodium chloride 9mg.mL (0.9%) solution for infusion and administered as an infusion to 0.25mg/kg

Study burden and risks

The study investigates the biochemical effectiveness and safety of an add-on experimental treatment to standard care. Standard care comprises a 5-day course of 1000mg intravenous methylprednisolone daily. The intervention is the addition of a single 15-minute intravenous infusion with imlifidase. The risk of imlifidase treatment comprises infusion related reaction and infection.
Follow up assessment will be done whilst patients are admitted to the Neurology ward, as per standard care, for the first 3 days after imlifidase infusion. During these days there will be 9 blood sampling moments, via intravenous access, follow up of adverse events, vital signs, neurological examination, urine analysis and electrocardiogram.
Subsequently, there will be 7 follow-up visits for which patients, if discharged, will be requested to visit the out-patient neurology department. During these visits there will be blood sampling via vena puncture, which is a low-risk procedure with possible minor risks of pain or local haematoma, and urine analysis. There will also be an assessment of (serious) adverse events, physical examination, recording of vital signs, neurological examination, patient reported outcome measures (EQ-5D and patient determined disease steps).

These visits will replace the visits part of standard care, generally 2-4 visits in the first year after a severe relapse which would also include neurological examination and blood sampling. Except from the burden of extra site visits and minimal risk from blood sampling there will be no additional burden for participants.
This study may be a first step towards a new, fast treatment modality for patients suffering from NMOSD, which may prevent long-term disability.

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

1. Signed Informed Consent obtained before any study-related procedures.
2. Willingness and ability to comply with the protocol.
3. Male or female aged >=18 years at the time of screening.

4. NMOSD diagnosed according to the Wingerchuck criteria[6] with a positive anti-AQP4 IgG serum test using a cell-based assay at presentation or in medical history.
5. Onset of weakness or loss of visual acuity due to the exacerbation of NMOSD is not more than 14 days prior to administration of imlifidase.
6. Exacerbation of myelitis is associated with an increase in functional system motor score of at least 1 point, and requires at least bilateral assistance to walk; exacerbation of uni- or bilateral optic neuritis is associated with an increase in functional system visual score of at least 1 point, and results in a visual acuity of 20/60 to 20/99 (0.33-0.21) or worse.
7. Acute steroid treatment is indicated.
8. Incident cases or prevalent cases treated with maintenance/ prophylactic therapies including azathioprine, mycophenolate mofetil/mycophenol acid, and rituximab, or no maintenance treatment.
9. Negative serological screening test for hepatitis B surface antigen, hepatitis C antibody, or human immunodeficiency virus.
10. Women of child-bearing potential willing or able to use at least one highly effective contraceptive method from the day of treatment until at least 6 months after the dose of imlifidase if not abstinent. In the context of this study, an effective method is defined as those which result in low failure rate (i.e. less than 1% per year) when used consistently and correctly.
11. Men willing to use double-barrier contraception from the day of treatment until at least 2 months after the dose of imlifidase if not abstinent.

Exclusion criteria

1. Previous treatment with imlifidase
2. Subjects who are already on plasma exchange.
3. Intravenous immunoglobulin (IVIg) treatment 28 days prior to administration of imlifidase
4. Women of child-bearing potential unwilling or unable to use at least one highly effective contraceptive method from the screening visit until at least 180 days following imlifidase dosing.
5. Hypersensitivity to IVIg or to any of the excipients.
6. Signs or symptoms suggestive of Thrombotic Thrombocytopenic Purpura
7. Subject known to have a severe concurrent disease, e.g. malignancy, severe cardiovascular disease and severe chronic obstructive pulmonary disease.
8. Any condition that in the opinion of the investigator could increase the subject's risk by participating in the study or confound the outcome of the study.
9. Known mental incapacity or language barriers precluding adequate understanding of the Informed Consent information and the study activities.
10 Subjects with clinical signs of ongoing infectious diseases that requires treatment.
11. Subjects with active SARS-CoV-2 (COVID-19) infection as shown by PCR

12. Subjects should not have received other investigational drugs within 5 half-lives prior to imlifidase dosing.

Study design

Design

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

Recruitment

NL

Recruitment status:	Pending
Start date (anticipated):	01-12-2023
Enrollment:	5
Type:	Anticipated

Medical products/devices used

Product type:	Medicine
Brand name:	Idefirix
Generic name:	Imlifidase
Registration:	Yes - NL outside intended use

Ethics review

Approved WMO

Date:	07-08-2023
Application type:	First submission
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)

Not approved

Date:	04-07-2024
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)

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	EUCTR2022-000654-29-NL
CCMO	NL80681.078.22