Eculizumab (Soliris) for relapsing neuromyelitis optica spectrum disorders

NIHR HSRIC ID: 6091

Lay summary

Eculizumab is a drug to treat neuromyelitis optica spectrum disorders. Neuromyelitis optica is a rare condition that causes damage to nerves of the eye and spinal cord. The main symptoms include muscle weakness, impaired eyesight, nerve pain, spasms and problems with bladder and bowel function. Patients with neuromyelitis optica spectrum disorders have ‘attacks’ of new or worsening symptoms, known as ‘relapses’. Eculizumab is delivered straight into the blood and could reduce the inflammation that causes these relapses.

This briefing is based on information available at the time of research and a limited literature search. It is not intended to be a definitive statement on the safety, efficacy or effectiveness of the health technology covered and should not be used for commercial purposes or commissioning without additional information.

This briefing presents independent research funded by the National Institute for Health Research (NIHR). The views expressed are those of the author and not necessarily those of the NHS, the NIHR or the Department of Health.
TARGET GROUP

- Neuromyelitis optica spectrum disorders: relapsing.

TECHNOLOGY

DESCRIPTION

Eculizumab (Soliris; 5G1-1; anti-C5 monoclonal antibody; h5G1.1) is a first-in-class, long-acting, humanised anti-C5 antibody. It binds to complement protein C5, preventing its cleavage into C5a and C5b, thereby blocking the progression of the complement cascade and the generation of the proinflammatory C5a and cell lytic molecules C5b-9 complex. Complement activation, after binding of an IgG autoantibody to aquaporin 4, is thought to be a major determinant of central nervous system (CNS) inflammation and astrocytic injury in neuromyelitis optica (NMO). In the phase III clinical trial, eculizumab is administered by intravenous (IV) infusion at 900mg weekly for the first 4 weeks, and then 1,200mg every 2 weeks thereafter¹.

Eculizumab is currently licensed in the EU for treatment of paroxysmal nocturnal haemoglobinuria and atypical haemolytic uremic syndrome. Common (≥1% to <10%) reported adverse events include thrombocytopenia, leukopenia, anaphylactic reaction, decreased appetite, dizziness, dysgeusia, hypotension, dyspnoea, cough, nasal congestion, pharyngolaryngeal pain, rhinorrhea, diarrhoea, nausea, vomiting, constipation, alopecia, pruritus, arthralgia, myalgia, muscle spasms, bone pain, oedema, pyrexia, fatigue, asthenia, meningococcal sepsis, aspergillus infection, upper respiratory tract infection, nasopharyngitis, bronchitis, oral herpes, urinary tract infection and viral infection².

Eculizumab is in phase III clinical trials for myasthenia gravis, delayed graft function after kidney transplantation, and antibody mediated rejection after kidney transplantation.

INNOVATION and/or ADVANTAGES

If licensed, eculizumab will offer an additional treatment option for patients with relapsing NMO spectrum disorders, a group who currently have no effective therapies available.

DEVELOPER

Alexion Pharmaceuticals.

AVAILABILITY, LAUNCH OR MARKETING

Eculizumab is a designated orphan drug in the EU and USA for NMO.

In phase III clinical trials.
PATIENT GROUP

BACKGROUND

NMO, also known as Devic’s disease, is a rare inflammatory and demyelinating autoimmune disorder of the CNS characterised by recurrent attacks of optic neuritis and longitudinally extensive transverse myelitis (LETM). Patients present with acute loss of vision, loss of sensation, bladder dysfunction, and weakness and paralysis limbs. Most patients have relapsing attacks, separated by months or years with partial recovery. More rarely, the disease course is monophasic, with nearly simultaneous index episodes of optic neuritis and myelitis.

NMO is associated with the presence of aquaporin-4 antibodies (AQP4-Ab) in approximately 70% of cases. AQP4-Ab positive NMO is more frequently associated with other autoimmune diseases such as myasthenia gravis, systemic lupus erythematosus, Sjogren’s syndrome, coeliac disease, and sarcoidosis. The median age at onset of NMO is 39 years, and nearly 90% of patients are female.

NMO was long considered a clinical variant of multiple sclerosis, though now is regarded as a distinct disease entity. NMO can be distinguished from multiple sclerosis on the basis of several features, including transverse myelitis presenting with longitudinally extensive spinal cord lesions, a tendency to spare the brain in the early stages of disease, and association with seropositivity for NMO IgG (AQP4-Ab).

Diagnostic criteria for NMO require:
- Normal MRI brain.
- Transverse myelitis with MRI changes >3 vertebral segments.
- AQP4 IgG positive.

Sometimes, if these criteria are not met a diagnosis of NMO spectrum disorders is given. The 2015 International Panel for NMO Diagnosis criteria for NMO spectrum disorders includes:
- At least one core clinical characteristic (optic neuritis, acute myelitis, area postrema syndrome, acute brainstem syndrome, symptomatic narcolepsy or acute diencephalic clinical syndrome with NMOSD-typical MRI lesions, or symptomatic cerebral syndrome with NMOSD-typical brain lesions).
- AQP4 IgG positive.
- Exclusion of alternative diagnosis.

NMO is associated with high mortality and morbidity when not diagnosed early and treated adequately. Relapses usually result in permanent neurologic impairment if not treated in time effectively. Some studies report death in 25-30% of patients after a mean of 5 years from onset. At five years from onset approximately 60-70% of untreated patients have significant visual loss (registered blind) affecting at least one eye.

Prior to NMO-IgG testing many patients with NMO (>20%) were misdiagnosed with multiple sclerosis, and were subsequently treated with disease-modifying therapies. Treatment with some of these therapies can result in worsening of NMO disease, with many patients suffering preventable disability and death.
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CLINICAL NEED and BURDEN OF DISEASE

NMO affects approximately 0.4 per 10,000 population in the EU, which is equivalent to approximately 2,564 people in the UK\(^a\). Expert opinion states that all patients with AQP4-Ab positive NMO receive treatment. If eculizumab becomes available as second line treatment (after azathioprine or equivalent) this will affect approximately 20 new patients a year. If eculizumab becomes available as third line treatment (after azathioprine or equivalent, and rituximab) this will affect approximately 5-10 new patients a year\(^b\).

Expert opinion notes that data regarding hospitalisation for NMO is not currently available for the UK\(^b\).

PATIENT PATHWAY

RELEVANT GUIDANCE

NICE Guidance


NHS England Policies and Guidance


Other Guidance

- International Panel for NMO Diagnosis. Evaluation of the 2015 diagnostic criteria for neuromyelitis optica spectrum disorder. 2016\(^{12}\).
- Neuromyelitis Optica Study Group. Update on the diagnosis and treatment of neuromyelitis optica. 2014\(^7\).
- European Federation of the Neurological Societies. EFNS guidelines on diagnosis and management of neuromyelitis optica. 2010\(^3\).

CURRENT TREATMENT OPTIONS

There is currently no curative treatment for NMO or NMO spectrum disorders\(^4\). Management focuses on remission and improvement of relapse-associated symptoms, long term stabilisation of disease course by means of relapse prevention, and symptomatic therapy of residual symptoms\(^7,13\).

Disability in NMO and NMO spectrum disorders is attack-related, and relapses require a rapid treatment approach\(^3\). If the symptoms of an NMO or NMO spectrum disorder relapse are not due to infection, treatment with a short course of high dose steroids, such as methylprednisolone, is recommended\(^7\). If a patient’s condition does not sufficiently improve

\(^a\) Assuming UK population of 64.1 million.
\(^b\) Expert personal communication.
or the neurological symptoms worsen, therapeutic plasma exchange can be used as rescue therapy\textsuperscript{5,7}.

Following each relapse patients often have incomplete recovery of symptoms and an accumulation of neurological deficits\textsuperscript{7}. Long term immunosuppressive therapies should therefore be initiated immediately upon the diagnosis of NMO to prevent further relapses and disability\textsuperscript{14}. First line treatment options include oral prednisolone in combination with azathioprine, mycophenolate mofetil, or methotrexate\textsuperscript{3,7,13}. Following failure of these treatments, second line therapy can include treatment with rituximab, mitoxantrone, or cyclophosphamide\textsuperscript{3,7,13}. Expert opinion states that some patients continue to relapse despite rituximab; currently these patients are treated with IV immunoglobulin, cyclophosphamide and off-label tocilizumab\textsuperscript{6}.

### EFFICACY and SAFETY

<table>
<thead>
<tr>
<th>Trial</th>
<th>PREVENT; NCT01892345, ECU-NMO-301; eculizumab vs placebo; phase III.</th>
<th>NCT02003144, ECU-NMO-302, 2013-001151-12; eculizumab; phase III extension.</th>
<th>NCT00904826, 09-001240; eculizumab; phase I/II.</th>
</tr>
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<tbody>
<tr>
<td>Sponsor</td>
<td>Alexion Pharmaceuticals</td>
<td>Alexion Pharmaceuticals.</td>
<td>Mayo Clinic.</td>
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<tr>
<td>Source of information</td>
<td>Trial registry\textsuperscript{1}.</td>
<td>Trial registry \textsuperscript{15}.</td>
<td>Publication \textsuperscript{16}, trial registry \textsuperscript{17}.</td>
</tr>
<tr>
<td>Location</td>
<td>EU (incl UK), USA, Canada and other countries.</td>
<td>EU (incl UK), USA, Canada and other countries.</td>
<td>USA.</td>
</tr>
<tr>
<td>Participants</td>
<td>n=132 (planned); aged 18 yrs and older; NMO or NMO spectrum disorder; ≥2 relapses in last 12 mths or ≥3 relapses in last 24 mths; Expanded Disability Status Score (EDSS) ≤7.</td>
<td>n=132 (planned); aged 18 yrs and older; pts completed the ECU-NMO-301 trial.</td>
<td>n=14; aged 18 yrs and older; NMO or NMO spectrum disorder; ≥2 relapses in last 6 mths or ≥3 relapses in last 12 mths; no progressive neurological deterioration unrelated to relapses of optic neuritis or myelitis.</td>
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<tr>
<td>Schedule</td>
<td>Randomised to eculizumab 900mg IV weekly for 4 wks, then 1,200mg every 2 wks thereafter; or matched placebo.</td>
<td>Pts receive eculizumab 1,200mg every 2 wks.</td>
<td>Pts receive eculizumab 600mg IV weekly for 4 wks, 900mg IV at wk 5 and 900mg IV every 2 weeks thereafter.</td>
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<tr>
<td>Follow-up</td>
<td>Active treatment until relapse.</td>
<td>Active treatment for maximum of 4 yrs.</td>
<td>Active treatment for 12 mths.</td>
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<tr>
<td>Primary outcomes</td>
<td>Time to first relapse.</td>
<td>Safety.</td>
<td>Annual relapse rate.</td>
</tr>
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<td>Secondary outcomes</td>
<td>Safety; annual relapse rate (ARR); disability as measured by EDSS and modified Rankin Scale (mRS) scores; neurology function as measured by Functional System Scores</td>
<td>ARR; disability as measured by EDSS and mRS scores; neurology function as measured by FSS; Quality of Life as measured by EQ-5D and SF-36; pharmacodynamics.</td>
<td>Disability as measured by EDSS; visual acuity subscale of the Opticospinal Impairment Score; Hauser Ambulation Index; pharmacokinetics.</td>
</tr>
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\textsuperscript{c} Expert personal communication.
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(FSS); Quality of Life as measured by EuroQol five dimensions questionnaire (EQ-5D) and Short Form Health Survey (SF-36); pharmaco-dynamics.

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<th>Key results</th>
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<th>After 12 mths of treatment, 12 of the 14 pts were relapse free. Median number of attacks per yr fell from three before treatment to zero during treatment. EDSS improved from 4.3 before treatment to 3.5 during treatment.</th>
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<td>Adverse effects (AEs)</td>
<td>-</td>
<td>-</td>
<td>One pt had meningococcal sepsis and sterile meningitis 2 mths after eculizumab infusion. No other drug-related serious adverse effects occurred.</td>
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<td>Expected reporting date</td>
<td>Study completion date reported as Dec 2016.</td>
<td>Study completion date reported as Dec 2018.</td>
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**ESTIMATED COST and IMPACT**

**COST**

Eculizumab is already marketed in the UK for the treatment of paroxysmal nocturnal haemoglobinuria and atypical haemolytic uremic syndrome: a 30mL vial (10mg/mL) costs £3,150, and treatment with 1,200mg every 2 weeks for 1 year would cost £327,600.

**IMPACT - SPECULATIVE**

**Impact on Patients and Carers**

- Reduced mortality/increased length of survival
- Reduced symptoms or disability: *expert opinion states that there is need for this drug to be available for patients who continue to relapse despite rituximab*.
- Other
- No impact identified

**Impact on Health and Social Care Services**

- Increased use of existing services
- Decreased use of existing services
- Re-organisation of existing services
- Need for new services
- Other
- None identified

*d Expert personal communication.
Impact on Costs and Other Resource Use

☑ Increased drug treatment costs: expert opinion states that due to the high cost of this drug it may be best used as third line treatment in rare cases of rituximab failure.

☐ Reduced drug treatment costs

☐ Other increase in costs

☐ Other reduction in costs

☐ Other

☐ None identified

Other Issues

☑ Clinical uncertainty or other research question identified: expert opinion states that there are several drugs currently being trialled in NMO which may also offer alternative treatment. A trial of rituximab to confirm benefit in NMO is also required to make this standard first line treatment.

☐ None identified

REFERENCES


* Expert personal communication.