A multicentre randomiSed controlled TRial of IntraVEnous immunoglobulin compared with standard therapy for the treatment of transverse myelitis in adults and children (STRIVE)

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Scientific summary

The STRIVE study

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Scientific summary

Background

Transverse myelitis (TM) is a rare inflammatory disorder of the spinal cord affecting approximately 350 children and adults annually in the UK. TM attacks usually develop over 24 hours and, in some cases, can progress rapidly to a potentially devastating and sometimes life-threatening condition. The severity of symptoms depends on the spinal cord level affected, with patients with high cervical lesions often requiring intensive care support to maintain respiratory function. Patients can recover fully from TM but a large number are left with significant disability. Among patients who recover, recovery occurs within weeks of the onset of symptoms and is most rapid during the first 3–6 months, although further improvement may be seen for up to 2–4 years.

A proportion of patients initially diagnosed with TM will subsequently relapse, often with the involvement of other parts of the central nervous system (CNS), and may often be diagnosed with either multiple sclerosis or neuromyelitis optica (NMO). NMO is a relapsing subset of TM, usually caused by antibodies to aquaporin 4. Clinically, patients have recurrent episodes of predominantly myelitis and optic neuritis. Initial presentation may be with myelitis alone, making it clinically and radiologically indistinguishable from TM, and patients are thus subjected to the same acute therapeutic strategies.

No robust controlled trials have been carried out in children or adults to inform the optimal treatment of TM. Standard treatment with intravenous methylprednisolone (IVMP) is based on class IV evidence that it shortens the relapse duration and speeds recovery in exacerbations of adult multiple sclerosis. Given the disease severity and poor outcomes, plasma exchange (PLEX) has been used in addition to standard therapy with some effect. However, PLEX is not universally available in the NHS, particularly at short notice and at weekends, and can be technically difficult and costly to administer. Randomised controlled trials (RCTs) have demonstrated intravenous immunoglobulin (IVIG) efficacy in a number of neurological conditions. In steroid-unresponsive CNS demyelination, IVIG is often used, although supporting data are limited to small case series and single case reports. IVIG appears to inhibit complement binding, neutralise pathogenic cytokines, down-regulate antibody production, enhance remyelination and modulate phagocytosis and T-cell function. The majority of these factors are common across inflammatory disorders of the CNS, including TM, providing a strong rationale for its use. Its availability, ease of administration, familiarity and safety also make IVIG an attractive option in the acute setting.

Objective

The primary aim of this study was to evaluate whether or not additional, and early, treatment with IVIG is of extra benefit in TM compared with the current standard therapy of IVMP.

The secondary objectives were to investigate the following potential benefits:

- The clinical and para-clinical data collected from patients will provide a robust resource and platform for other clinical studies, including the identification of early predictors of poor outcome.
- Biobanked samples from patients recruited to the study will be collected and used for carefully designed biological studies by a consortium of established basic science researchers in the field.

Method

The randomiSed controlled TRial of IntraVEnous immunoglobulin compared with standard therapy for the treatment of transverse myelitis in adults and children (STRIVE) study was a multicentre, single-blind, parallel-group RCT with follow-up visits at 3, 6 and 12 months following randomisation.

Patients were considered for recruitment if they were aged ≥ 1 year, had been diagnosed with either acute first-onset TM or NMO, had an American Spinal Injury Association (ASIA) Impairment Scale score from A to C (categories range from A to E, with category E describing normal function and category A describing complete lack of motor and sensory function below the level of injury) and were within 5 days of commencing steroid treatment.

Randomisation was 1 : 1 to treatment with IVMP (control arm) or IVMP plus 2 g/kg of IVIG in divided doses (treatment arm). The sample size calculation yielded a target sample size of 170 participants (85 participants per arm).

The primary outcome was assessed at 6 months post randomisation, with a good outcome defined by a two-grade change in ASIA Impairment Scale score.

The following additional outcomes were measured:

- secondary end-point measures:
    - ASIA motor scale (0–100) and ASIA sensory scale (0–112) at 3, 6 and 12 months post randomisation
    - Kurtzke Expanded Disability Status Scale assessment using Neurostatus scoring at 3, 6 and 12 months
    - EuroQol-5 Dimensions youth version at 3, 6 and 12 months for patients aged 8–12 years (at presentation)
    - EQ-5D five-level version at 3, 6 and 12 months for patients aged ≥ 13 years (at presentation)
    - International Spinal Cord Injury Quality of Life (SCI-QOL) Basic Data Set at 3, 6 and 12 months for patients aged ≥ 13 years (at presentation)
    - Client Service Receipt Inventory at 3, 6 and 12 months
- tertiary end-point measures:
    - patients aged ≥ 13 years (at presentation): International SCI-QOL, Pain, Bladder and Bowel Function Basic Data Set at 6 and 12 months post randomisation
    - patients aged 2–4 years (at presentation): Paediatric Quality of Life Inventory (PedsQL™) Parent Report for Toddlers at 6 and 12 months
    - patients aged 5–7 years (at presentation): PedsQL Parent Report for Young Children at 6 and 12 months
    - patients aged ≥ 13 years (at presentation): International SCI-QOL Pain Basic Data Set at 6 and 12 months.

Results

Of the 28 patients screened for eligibility, two were randomised into the study between 4 March 2015 and 8 February 2016, precluding any statistical analysis of the data, and, consequently, any differences in treatment outcomes between the two study arms could not be determined. However, we identified multiple barriers to accrual into the study. These included the strict inclusion criteria, the short enrolment window, challenges associated with the use of the ASIA Impairment Scale as the primary outcome measure, an inaccurate estimation of the incidence of TM and the spectrum of severity within the target population and the variability of research funding of individual sites.

Conclusions

The clinical and health economic impacts of the use of IVIG in addition to standard therapy with IVMP in the treatment of adults and children with TM/NMO could not be determined in the study. As the study question is crucial to inform the acute treatment of TM/NMO patients, and thus one that necessitates further investigation, we recommend additional research to establish the incidence and the spectrum of severity of the disorder within the intended study population, alongside evaluating the utility of alternative primary outcome measures such as the ASIA motor score and other patient-derived outcome measures. The success of future intervention trials in TM will be contingent on being able to overcome recruitment barriers identified in this study, which may have broader implications for investigators embarking on similar studies in other rare disorders.

Trial registration

This study is registered as EudraCT 2014-002335-34, ClinicalTrials.gov NCT02398994 and Current Controlled Trials ISRCTN12127581.

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