Intravenous immunoglobulin treatment for encephalitis in children aged 6 months to 16 years: the IgNiTE RCT

Mildred A Iro,[1*] Manish Sadarangani,[1,2,3,4] Michael Absoud,[5,6] Liberty Cantrell,[1] Wui K Chong,[7] Christopher Clark,[8] Ava Easton,[9,10] Victoria Gray,[11] Matilda Hill,[1] Rachel Kneen,[12,13] Ming Lim,[5,6] Xinxue Liu,[1] Mike Pike,[14] Tom Solomon,[12,15,16] Angela Vincent,[17] Louise Willis,[1] Ly-Mee Yu[18] and Andrew J Pollard;[1,2] IgNiTE Study Team

[1]Oxford Vaccine Group, Department of Paediatrics, University of Oxford and NIHR Biomedical Research Centre, Oxford University Hospitals NHS Foundation Trust, Oxford, UK
[2]Department of Paediatrics, Oxford University Hospitals NHS Foundation Trust, Oxford, UK
[3]Vaccine Evaluation Center, BC Children's Hospital Research Institute, University of British Columbia, Vancouver, BC, Canada
[4]Department of Pediatrics, University of British Columbia, Vancouver, BC, Canada
[5]Department of Children's Neurosciences, Evelina London Children's Hospital at Guy's and St Thomas' NHS Foundation Trust, King's Health Partners Academic Health Science Centre, London, UK
[6]Department of Women and Children's Health, Faculty of Life Sciences and Medicine, King's College London, London, UK
[7]Department of Radiology, Great Ormond Street Hospital for Children, London, UK
[8]Institute of Child Health, University College London, London, UK
[9]The Encephalitis Society, Malton, UK
[10]Department of Clinical Infection, Microbiology and Immunology, University of Liverpool, Liverpool, UK
[11]Psychological services (Paediatrics), Alder Hey Children's NHS Foundation Trust, Liverpool, UK
[12]Institute of Infection, Veterinary and Ecological Sciences, University of Liverpool, Liverpool, UK
[13]Littlewoods Neuroscience Foundation, Department of Neurology, Alder Hey Children's NHS Foundation Trust, Liverpool, UK
[14]Department of Paediatric Neurology, Oxford University Hospitals NHS Trust, Oxford, UK
[15]National Institute for Health Research Health Protection Research Unit in Emerging and Zoonotic Infections, University of Liverpool, Liverpool, UK
[16]Walton Centre NHS Foundation Trust, Liverpool, UK

[17]Nuffield Department of Clinical Neurosciences, Weatherall Institute of Molecular Medicine, University of Oxford, Oxford, UK
[18]Nuffield Department of Primary Care Health Sciences, University of Oxford, Oxford, UK

*Corresponding author mildred.iro@nhs.net

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Scientific summary

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Scientific summary

Background

There is significant mortality and morbidity from encephalitis in children despite the current standard of care. Thus, strategies to improve outcomes in patients with encephalitis are urgently required.

Theoretical and empirical evidence suggest a beneficial role of intravenous immunoglobulin (IVIG) for viral and auto-immune forms of encephalitis. Therefore, we set up a prospective randomised controlled trial (RCT) to ascertain the efficacy of early IVIG treatment for all-cause encephalitis in children.

In the study, children with encephalitis were randomised to receive two doses of either IVIG or placebo within five working days from the suspicion of an encephalitis diagnosis, in addition to normal standard of care. They were then followed up for 12 months after randomisation.

We hypothesised that IVIG could have therapeutic benefit for children with encephalitis when administered early in the illness.

Objectives

The primary objective was to evaluate the efficacy of early IVIG treatment in childhood encephalitis. This was assessed by comparing the proportion of children in the 2 treatment groups who made good recovery, assessed using the paediatric version of the Glasgow outcome score extended, at 12 months after randomisation.

The secondary objectives were to: (1) compare clinical, neurological, neuroimaging and neuropsychological outcomes between the treatment groups, (2) evaluate the proportion of participants with autoimmune encephalitis and (3) confirm the safety of IVIG.

Methods

Trial design

This was a phase 3b multicentre, double-blind, randomised, placebo-controlled trial to evaluate the early use IVIG in childhood encephalitis.

Setting

Participants were recruited from 21 NHS Hospitals in the UK.

Participants

Inclusion criteria

Participants were eligible if

- they were aged between 6 weeks and 16 years
- they met the case definition for possible encephalitis based on the International Encephalitis Consensus
- parents/guardians provided written informed consent, or assent if appropriate.

Exclusion criteria

The exclusion criteria included: (1) a high clinical suspicion of bacterial meningitis, (2) prior receipt of IVIG during the admission or known contraindication to IVIG, (3) traumatic brain injury, (4) history of metabolic encephalopathy, stroke, toxic or hypertensive encephalopathy, (5) pre-existing demyelinating disorder, (6) significant renal impairment, (7) hypercoagulable state, (8) hyperprolinaemia, (9) participation in another research trial involving an immunomodulatory treatment, (10) known to be pregnant, (11) any significant disease or clinical research that would impact on participation, or interfere with compliance with study requirements.

Randomisation

Participants were randomly assigned 1 : 1 ratio to receive 2 doses (1 g/kg/dose) of either IVIG or matching placebo, in addition to standard care. Randomisation was stratified by age and receipt of steroid treatment.

Interventions

Two doses of 1 g/kg/dose of either IVIG or a matching volume of placebo were given 24–36 hours apart, with the first dose administered as soon as possible after enrolment and within five working days from the suspicion of an encephalitis diagnosis.

The active treatment (IVIG) used in the study was Privigen (100 mg/ml solution), manufactured and provided by CSL Behring. The placebo was a mixture of 0.9% saline + 0.1% human albumin solution, manufactured at the Royal Broadgreen and Liverpool Aseptic Production Unit, Liverpool, UK, under current good manufacturing practice conditions and its Manufacturer's Importer's Authorisation licence. The addition of albumin to saline was necessary to make the placebo visually identical to IVIG.

Blinding

Participants, treating clinicians, parents/guardians and outcome assessors were blinded to the allocated treatment.

Primary outcome

The primary outcome was good recovery (i.e. score of ≤2) on the paediatric version of the Glasgow Outcome Score-Extended (GOS-E Peds) at 12 months after randomisation.

Secondary outcomes

Clinical, neurological and neuropsychological outcomes

Multiple clinical and neurological measures were collected during the hospital admission, at 4–8 weeks after discharge from acute care, and at 6 and 12 months after randomisation. A blinded neuropsychologist assessment of cognitive function was carried out at 12 months after randomisation.

Radiological outcomes

Brain magnetic resonance imaging (MRI) findings at 6 months after randomisation were compared with imaging results obtained during the acute illness.

Safety data

Safety and adverse events (AEs) data were collected until 12 months after randomisation.

Identification of immune-mediated encephalitis

Presence of specific auto-antibodies in serum was assessed.

Statistical methods

The analyses were performed on the intention-to-treat population; this included all participants who were randomised, irrespective of study treatment received. In the analysis of the AEs, all participants

who received study treatment were included. Since 20% of participants were recruited before the trial was halted, all analyses are descriptive.

Results

Recruitment took place between 23 December 2015 and 26 September 2017. Recruitment was paused in September 2017 following withdrawal of funding due to slower than anticipated recruitment. Despite strategies implemented to improve recruitment, funding was not reinstated. Attempts at securing alternative funding were unsuccessful; therefore, the trial was closed on 24 October 2017.

Participants and demographics

At the time of halting the study, 18 participants had been randomised (IVIG *n* = 10; placebo *n* = 8). One participant each from the IVIG and placebo groups were withdrawn from the study before receipt of study treatment and one participant in the placebo arm refused a second dose of study treatment. Therefore 16 participants (IVIG *n* = 9; placebo *n* = 7) received at least one dose of the study treatment and 15 participants (IVIG *n* = 9, placebo *n* = 6) received two full doses of the study treatment.

One participant in the placebo group was lost to follow up after the 6 months visit and 1 participant in the IVIG group withdrew consent prior to the visit 12 months after randomisation.

The median age at randomisation was 4.09 years [interquartile range (IQR) = 2.0–11.8], 44% were male and 89% were of white ethnicity. Baseline characteristics were well matched across treatment arms.

Primary outcome

At 12 months after randomisation, 9 participants [50%; IVIG *n* = 5 (50%); placebo *n* = 4 (50%)] made a good recovery (score ≤2 on the GOS-E Peds) and 5 participants [28%; IVIG *n* = 3 (30%), placebo *n* = 2 (25%)] made a poor recovery (score > 2). Four participants (22%; IVIG *n* = 2 (20%), placebo *n* = 2 (25%)] did not undergo a GOS-E Peds assessment at 12 months after randomisation.

Secondary outcomes

Inpatient data

Ten participants [56%; IVIG *n* = 5 (50%), placebo = 5 (63%)] were admitted to intensive care, and nine of these [90%; IVIG *n* = 4 (80%), placebo *n* = 5(100%)] required invasive ventilation, for a median duration of two days (IQR 2.0–3.0). The median length of stay on intensive care was 4.5 days (3.0–6.8) and the overall median length of hospitalisation for acute care was 11 days (7.8–19.5).

Epilepsy diagnosis

Three participants [17%; IVIG *n* = 1 (10%), placebo *n* = 2 (25%)] had a new diagnosis of epilepsy during the study period. Five participants [28%; IVIG *n* = 2 (20%), placebo *n* = 3 (38%)] had incomplete data for this outcome.

Glasgow Outcome Score-Extended-Peds at 6 months after randomisation:

Eight participants [44%; IVIG *n* = 4 (40%), placebo *n* = 4 (50%)] made a good recovery at 6 months after randomisation, whereas seven participants [39%; IVIG *n* = 4 (50%), placebo *n* = 3 (38%)] made a poor recovery. Three participants [17%; IVIG *n* = 2 (20%), placebo *n* = 1 (13%)] did not undergo a GOS-E Peds assessment at 6 months after randomisation.

Liverpool outcome score

At 4–8 weeks after discharge from acute care, 5 participants [28%; IVIG *n* = 3 (30%), placebo *n* = 2 (25%)] made a full recovery [defined as a Liverpool Outcome Score (LOS) of >4], whereas 10 participants

[56%; IVIG *n* = 5 (50%), placebo *n* = 5 (63%)] had minor to severe sequelae. Three participants [17%; IVIG *n* = 2 (20%); placebo *n* = 1 (13%)] did not have LOS data collected at this timepoint.

At 12 months after randomisation, six participants [33%; IVIG *n* = 4 (40%), placebo *n* = 2 (25%)] made full recovery on the LOS assessment, while 8 participants [44%; IVIG *n* = 4 (40%), placebo *n* = 4 (50%)] reported minor to severe sequelae. Four participants [22%; IVIG *n* = 2 (20%); placebo *n* = 2 (25%)] did not have LOS data collected at this timepoint.

Paediatric quality of life assessment

Paediatric quality of life scores were available for seven participants [39%; IVIG *n* = 5 (50%), placebo *n* = 2 (25%)] at 4–8 weeks after discharge from acute care and for eight participants [44%; IVIG *n* = 6 (60%), placebo *n* = 2 (25%)] at 12 months post randomisation.

At 4–8 weeks after discharge from acute care, the mean PedsQL score was 77.9 (standard deviation, SD, 11.10) and 56.5 (SD 7.8) for the IVIG and placebo group, respectively. At 12 months, mean PedsQL scores were 79.9 (SD 21.6) and 63.7 (SD 30.1) for the IVIG and placebo groups, respectively.

Gross motor function classification system

At 4–8 weeks after discharge from acute care, seven participants [39%; IVIG *n* = 5 (50%); placebo *n* = 2 (25%)] had mild impairment of gross motor functioning. These data were not available for 11 participants [61%; IVIG *n* = 5 (50%), placebo *n* = 6 (75%)] at this timepoint.

At 12 months after randomisation, eight participants [44%; IVIG *n* = 6 (60%); placebo *n* = 2 (25%)] experienced mild or severe impairment of gross motor function. These data were not available for ten participants [56%; IVIG *n* = 4 (40%), placebo *n* = 6 (75%)] at this timepoint.

Strengths and difficulties assessment

Strengths and Difficulties Questionnaire (SDQ) results were available for seven participants (IVIG *n* = 5, placebo *n* = 2) at 4–8 weeks after discharge from acute care and eight participants (IVIG *n* = 6, placebo *n* = 2) at 12 months after randomisation.

At 4–8 weeks after discharge from acute care, five participants [28%; IVIG *n* = 4 (40%); placebo *n* = 1 (13%)] had a close to average SDQ score, one participant [6%, IVIG *n* = 1 (10%), placebo *n* = 0] had a slightly raised SDQ score and one participant [6%, IVIG *n* = 0, placebo *n* = 1 (13%)] had a very high SDQ score.

At 12 months after randomisation, the same number of participants had a close to average score and slightly raised score, but two participants [11%; IVIG *n* = 1 (10%), placebo *n* = 1 (13%)] had a very high SDQ score.

Adaptive Behaviors Assessment System – second edition

At 4–8 weeks after discharge from acute care, five participants [28%; IVIG *n* = 4 (40%), placebo *n* = 1 (13%)] had an Adaptive Behaviors Assessment System-second edition (ABAS-II) score that was either similar or higher than the average score of the normative population. At the same time point, three participants [17%; IVIG *n* = 2 (20%), placebo *n* = 1 (13%)] had a score that was lower than the average score. Ten participants [56%; IVIG *n* = 4 (40%), placebo *n* = 6 (75%)] did not have ABAS-II assessment at this timepoint.

At 12 months after randomisation, the same number of participants had a score that was below the average, but four participants [22%; IVIG *n* = 3 (30%), placebo *n* = 1 (13%)] had a score that was either

similar or higher than the average score, and 11 participants [61%; IVIG *n* = 5 (50%), placebo *n* = 6 (75%)] did not have ABAS-II assessment at this timepoint.

Neuropsychology assessment

Thirteen participants (72%; IVIG *n* = 8 (80%); placebo *n* = 5 (63%)] had blinded neuropsychology assessment at 12 months after randomisation; four [30%; IVIG *n* = 2 (25%), placebo *n* = 2 (40%)] of these participants were unable to complete the full battery of assessments due to attention or behavioural needs. Five participants [28%; IVIG *n* = 2 (20%), placebo *n* = 3 (38%)] did not undergo neuropsychology assessment.

Five participants [28%; IVIG *n* = 4 (40%), placebo *n* = 1 (13%)] had a score of ≥85 (indicating normal development) for Full-Scale IQ, six [33%; IVIG *n* = 4 (40%); placebo *n* = 2 (25%)] for Verbal Comprehension Index (VCI), five [28%; IVIG *n* = 4 (40%), placebo *n* = 1 (13%)] for visual spatial; four [22%; IVIG *n* = 4 (40%), placebo *n* = 0 (0%)] for working memory index (WMI); and four [22%; IVIG *n* = 3 (30%); placebo *n* = 1 (13%)] for Perceptual Reasoning Index (PRI). Two participants (one in each treatment arm) were assessed using the Bayley scale of infant and toddler development, one participant (IVIG arm) had severe neurodevelopmental impairment while the other (placebo arm) had a normal neurodevelopmental outcome.

Neuroimaging

Nineteen acute neuroimaging scans were available for 13 participants. Five scans (for five unique participants) had abnormal findings; all of these were MRI scans. Four of the abnormal scans showed bilateral lesions. There were nine follow-up scans for eight unique participants of which six scans (for five unique participants) were normal and unchanged from the acute scan. Three follow-up scans (for three unique participants) had abnormal findings; two of these were unchanged from the acute scans and an acute scan was not available for comparison one participant.

Autoantibody testing

Twelve participants had autoantibody testing. One participant (placebo *n* = 1) was positive for LGI1 antibodies, and one participant (placebo *n* = 1) was positive for myelin oligodendrocyte glycoprotein (MOG) antibodies. Two additional participants (IVIG *n* = 2) were positive for IgG to live neurons, indicating the presence of IgG antibodies binding to neurons, but negative for antibodies to the specific antigens tested for in the study.

Safety reporting

One participant in the IVIG group reported an AE of special interest; the participant developed a fever during IVIG infusion; however, this was judged to be unrelated to the study treatment. Ten serious AEs occurred in three participants in the placebo group and none in the IVIG group. None of the serious adverse events (SAEs) were judged to be related to the study treatment. No deaths occurred during the study period.

Conclusions

ImmunoglobuliN in the Treatment of Encephalitis (IgNiTE) was the first RCT to prospectively evaluate the efficacy of IVIG in childhood encephalitis. It was anticipated that data from IgNiTE would provide definitive evidence on which to base the management of children with encephalitis in the UK and worldwide. However, due to slow recruitment, the trial was terminated early. Therefore, the trial did not reach its pre-determined sample size and was underpowered, making it impossible to reach a conclusion on the role of IVIG in treatment of childhood encephalitis.

Nonetheless, IgNiTE has highlighted several key learning points. Firstly, IgNiTE has demonstrated the feasibility of setting up a large multi-centre trial efficacy trial in a cohort of children with a rare condition such as encephalitis. Secondly, data from IgNiTE, albeit derived from a small sample size, suggest the

safety of IVIG and provide some insight into the burden that encephalitis places on children and the NHS. Over half of the study participants were admitted to the intensive care unit with 90% of those admitted requiring invasive ventilation, with a prolonged overall length of hospitalisation. In addition, a notable proportion of children experienced some degree of disability at follow-up, highlighting the need to prioritise studies aimed at identifying strategies to alleviate the burden from this rare but debilitating disease.

For future studies aimed at addressing the efficacy of early IVIG treatment in childhood encephalitis, consideration should be given to practical challenges with setting up RCTs for rare diseases. These include the necessity to recruit from multiple sites to achieve the sample size, the importance of clinical equipoise amongst treating clinicians, and the trade-off between having a stringent but robust set of entry criteria and the impact of this on recruitment.

Trial registration

This trial is registered as Clinical Trials.gov (NCT02308982) and ISRCTN15791925.

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