

ACED: Phase II randomised placebo-controlled double-blind study of **a**cetazolamide versus placebo for **c**erebral **o**edema in recurrent and/or progressive high-grade glioma requiring treatment with **d**examethasone

The ACED trial tested a drug, an oral tablet called acetazolamide, to reduce swelling within the brain for people with primary brain tumours. It was conducted in Australia between 2016 and 2019.

We sincerely thank the participants, their caregivers and families and all staff members who contributed to the trial. Here is a summary of the trial and results.

What was the trial about?

High-grade glioma is an aggressive type of primary brain tumour. Examples include glioblastoma, anaplastic astrocytoma and anaplastic oligodendroglioma. The initial treatment for high-grade glioma consists of neurosurgery, then radiotherapy and chemotherapy. High-grade glioma can relapse or progress within a relatively short space of time, and managing symptoms is important for the quality of life for these patients.

High-grade glioma often causes the brain to swell, termed 'cerebral oedema' and this increases pressure inside the skull. This can lead to symptoms including headaches, nausea, drowsiness and blurred vision. Typically a steroid medication called dexamethasone is given to reduce the swelling, with the dose and duration tailored to the individual's situation. However, the prolonged use and/or high doses of steroids can lead to problematic side-effects, such as weight gain, sleep disturbance and muscle weakness.

The ACED trial tested whether a drug called acetazolamide reduces the need for steroids (and thus their side-effects), while still controlling the participants' symptoms caused by brain swelling. Acetazolamide works by reducing the production of fluid around the brain (cerebrospinal fluid) and has been shown to lower the pressure within the brain in other conditions. It is already used to treat conditions which are caused by high pressure such as glaucoma, altitude sickness and benign idiopathic hypertension (a rare condition with high pressure in the brain due to unknown cause).

Another drug called bevacizumab (Avastin™) is known to reduce cerebral oedema, but was not available on the Pharmaceutical Benefits Scheme (PBS) until August 2019. The ACED trial offered an alternative to those who were not able to access bevacizumab. Individuals who received treatment with bevacizumab were not able to enrol in the ACED trial, as it would not be possible to understand the impact of acetazolamide if both medications were given together.

All participants received standard treatment for their high-grade glioma. In addition, they were randomly allocated to receive either:

- a) Acetazolamide 250 mg tablet, taken by mouth twice a day, for 8 weeks; or
- b) 'Placebo' (a pill which contains no active ingredient), taken by mouth twice a day, for 8 weeks.

Thirty (30) participants were enrolled from 7 hospitals across Australia. There were 21 men and 9 women in total, with an average age of 58 years. Twenty-eight (28) caregivers of these participants also contributed to the trial.

How was the effect of treatment measured?

Two main effects were measured:

- 1) The dexamethasone dose required by participants, and
- 2) The 'performance status' of participants (i.e. their function and how well they can do everyday activities)

Participants were considered to have benefitted from the treatment if their dexamethasone dose was lowered while still having a similar performance status.

The side-effects of acetazolamide and dexamethasone were also recorded.

Was the new treatment better?

No. The same number of participants on each treatment achieved the benefit described above:

- a) 2 of 15 participants (13%) who received acetazolamide
- b) 2 of 15 participants (13%) who received placebo.

The trial closed early when 30 participants were enrolled out of a planned 84 participants.

Since the design and opening of the ACED trial several years ago, the treatment options in Australia improved during the trial, with the availability of subsidy via Pharmaceutical Benefits Scheme for bevacizumab (Avastin™) allowing access for a larger number of people living with high grade glioma.

What were the side-effects of the treatment?

Overall, there were few side-effects of acetazolamide.

One participant developed kidney stones needing hospital care which may have been due to acetazolamide. Another participant developed very low platelets (blood cells which help the blood to clot and prevent bleeding). This may have been due to known effects of the chemotherapy the participant was also receiving, but could also be due to acetazolamide.

How will the results help high-grade glioma patients and their treating doctors in future?

The ACED trial has shown that while acetazolamide was well tolerated, it did not consistently relieve the cerebral oedema caused by recurrent and/or progressive high-grade glioma. It is difficult to draw firm conclusions about the use of acetazolamide in this patient group as the study closed early. Despite this, the ACED has still added to our knowledge base about the optimal treatment of patients with primary brain tumours.

The study also provides the self-reported experience of people with high-grade glioma and their caregivers in relation to brain swelling and dexamethasone treatment. This will assist people with glioma, their caregivers and their treating doctors to discuss and address these concerns as an important aspect of care. The standard of care remains unchanged.

What will the researchers do next?

The ACED trial is now closed. The results will inform the design of future trials in this field.

Since August 2019, bevacizumab has become available via the PBS in Australia, with one of the main benefits including the management of cerebral oedema. This use of bevacizumab will need to be considered in future trials of interventions aiming to improve the management of cerebral oedema.

Where can I find out more about the trial?

Your treating health professionals including your oncologist, will be able to further interpret the trial findings in relation to your (or your loved one's) situation.

The preliminary results have been presented at an international conference

Society of Neuro-Oncology Annual Meeting 2020:

Agar MR, Nowak AK, Hovey EJ, Barnes EH, Simes J, Vardy J, Wheeler H, Leonard R, Hall M, Tim E, Spyridopoulos D, Sim H-W, Lwin Z, Dowling A, Harrup R, Jennens R, Kichendasse G, Dunlop T, Gzell C, Koh E-S. QOLP-23: Phase II randomised placebo-controlled double-blind study of acetazolamide versus placebo for cerebral oedema in recurrent and/or progressive high-grade glioma requiring treatment with dexamethasone. *Neuro-Oncology* 2020, volume 22, issue supplement 2, pages ii179–ii180.

<https://doi.org/10.1093/neuonc/noaa215.748>

The final study results have been published in *BMJ Supportive and Palliative Care*:

Agar MR, Nowak AK, Hovey EJ, Barnes EH, Simes J, Vardy JL, Wheeler HR, Kong BY, Leonard R, Hall M, Tim E, Spyridopoulos D, Sim HW, Lwin Z, Dowling A, Harrup R, Jennens R, Kichenadasse G, Dunlop T, Gzell C, Koh ES. Acetazolamide versus placebo for cerebral oedema requiring dexamethasone in recurrent and/or progressive high-grade glioma: phase II randomised placebo-controlled double-blind study. *BMJ Support Palliat Care*. 2023 Feb 17:spcare-2022-004119. doi: 10.1136/spcare-2022-004119. Epub ahead of print. PMID: 36807048.

<https://pubmed.ncbi.nlm.nih.gov/36807048/>

Trial registration:

Australian New Zealand Clinical Trials Registry

Registration number: ACTRN12615001072505

<https://anzctr.org.au/Trial/Registration/TrialReview.aspx?ACTRN=12615001072505>

Cooperative Trials Group for Neuro-Oncology (COGNO):

<https://cogno.org.au/content.aspx?page=currenttrials>

The sponsor of the ACED trial was The University of Sydney. The trial was a collaboration between the Cooperative Trials Group for Neuro-Oncology (COGNO) and the National Health and Medical Research Council Clinical Trials Centre (NHMRC CTC). The trial was funded by Perpetual Funding scheme (2014) through the Cure Brain Cancer Foundation and Cancer Australia via the Priority-driven Collaborative Cancer Research Scheme (2015).

Some authors of the ACED trial have received research funding or have had advisory roles for the pharmaceutical industry. Full disclosures will be listed in the published manuscript when available.