Abstract

Background: Observations in people with cerebral cavernous malformations, and in preclinical models of this disorder, suggest that the β-blocker propranolol might reduce the risk of intracerebral haemorrhage. We aimed to evaluate the safety and efficacy of prolonged treatment with propranolol to reduce the incidence of symptomatic intracerebral haemorrhage or focal neurological deficit in people with familial cerebral cavernous malformations.

Methods: We conducted a randomised, open-label, blinded-endpoint, phase 2 pilot trial (Treat_CCM) at six national reference centres for rare diseases in Italy. People aged 18 years or older with symptomatic familial cerebral cavernous malformation were eligible for enrolment. Participants were randomly assigned (2:1) to receive either oral propranolol (20-320 mg daily) plus standard care (intervention group), or standard care alone (control group), for 24 months. Participants, caregivers, and investigators were aware of treatment group assignment. Participants had clinical assessments and 3 T brain MRI at baseline and at 12 and 24 months. The primary outcome was new occurrence of symptomatic intracerebral haemorrhage or focal neurological deficit attributable to cerebral cavernous malformation over 24 months. Outcome assessors were masked to treatment group assignment. The primary analysis was done in the intention-to-treat population. Because of the pilot study design, we chose a one-sided 80% CI, which could either exclude a clinically meaningful effect or show a signal of efficacy. This trial is registered with EudraCT, 2017-003595-30, and ClinicalTrials.gov, NCT03589014, and is closed to recruitment.

Findings: Between April 11, 2018, and Dec 5, 2019, 95 people were assessed for eligibility and 83 were enrolled, of whom 57 were assigned to the propranolol plus standard care group and 26 to the standard care alone group. The mean age of participants was 46 years (SD 15); 48 (58%) were female and 35 (42%) were male. The incidence of symptomatic intracerebral haemorrhage or focal neurological deficit was 1·7 (95% CI 1·4-2·0) cases per 100 person-years (two [4%] of 57 participants) in the propranolol plus standard care group and 3·9 (3·1-4·7) per 100 person-years (two [8%] of 26) in the standard care alone group (univariable hazard ratio [HR] 0·43, 80% CI 0·18-0·98). The univariable HR showed a signal of efficacy, according to predefined criteria. The incidence of hospitalisation did not differ between groups (8·2 cases [95% CI 7·5-8·9] per 100 person-years in the propranolol plus standard care group vs 8·2 [95% CI 7·1-9·3] per 100 person-years in the standard care alone group). One participant in the standard care alone group died of sepsis. Three participants in the propranolol plus standard care group discontinued propranolol due to side-effects (two reported hypotension and one reported weakness).

Interpretation: Propranolol was safe and well tolerated in this population. Propranolol might be beneficial for reducing the incidence of clinical events in people with symptomatic familial cerebral cavernous malformations, although this trial was not designed to be adequately powered to investigate efficacy. A definitive phase 3 trial of

propranolol in people with symptomatic familial cerebral cavernous malformations is justified.