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The Rationale Behind "A Randomized Trial of Unruptured Brain AVMs" (ARUBA)

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Abstract

A Randomized Trial of Unruptured Brain AVMs is a multidisciplinary international randomized controlled clinical trial including 800 adult patients with the diagnosis of an unruptured brain AVM. Patients willing to participate are randomly assigned to either best possible invasive therapy (endovascular, neurosurgical, and/or radiation therapy) or medical management without intervention. The study protocol does not modify any routine treatment strategies in either arm. Patients will be followed for a minimum of 5 years and a maximum of 10 years from randomization.

The primary outcome measure is the composite endpoint of death from any cause or stroke (clinically symptomatic hemorrhage or infarction confirmed by imaging). The secondary outcome measure is long-term clinical status by Rankin Scale, NIHSS, SF-36, and EuroQol.

Patient enrollment was successfully started in 2007. Participating sites currently include multidisciplinary treatment centers in North and South America, Australasia, and Europe (including Australia, Austria, Brazil, Canada, Finland, France, Germany, Italy, Netherlands, Spain, South Korea, Switzerland, UK, and the USA).

The trial is sponsored and monitored by the US NIH/NINDS (NCT00389181).

Keywords

Cerebral arteriovenous malformations; Clinical trial; Epidemiology; Stroke; Intracerebral hemorrhage; Subarachnoid hemorrhage

Introduction

Current invasive treatment for brain arteriovenous malformations (AVMs) is highly specialized and includes neurosurgical removal, endovascular embolization, and stereotactic radiotherapy, either alone or in any combination. Carefully planned intervention generally leads to successful AVM eradication with relatively low treatment-related morbidity and mortality: a systematic meta-analysis of 2,425 from 25 single institutions suggests surgical mortality was 3.3% with a permanent postoperative morbidity of 8.6% for complete AVM eradication [1]. The 2005 overview on endovascular AVM therapy by the World Federation

Conflicts of interest statement There are no conflicts of interest.

of Interventional and Therapeutic Neuroradiology showed frequencies of embolization-related complications in well-established international centers ranging between 9.1% and 11.9% [2]. A large prospective series of 308 patients receiving radiosurgery showed 10% radiation induced deficits and 9% unprevented new intracranial hemorrhages with an overall cure rate of 78% [3]. Another multi-centre analysis of 1,255 patients undergoing stereotactic radiotherapy showed that 8% developed a neurological deficit after radiation [4].

The growing availability of MR imaging has lead to a substantial increase in the detection of unruptured malformations ranging between 54% and 62% of all diagnosed AVM patients in modern population-based datasets [5–7]. Similar to intracranial aneurysms, the natural history of unruptured AVMs seems more favorable with an average bleeding risk of approximately 1% per year, as compared to more than 5% for those discovered after initial hemorrhage [8, 9]. The bleeding risk seems to be particularly low (0.9% per year) in the most frequent subgroup of patients harboring unruptured lobar AVMs with superficial venous drainage [10].

Recent data from the literature have raised the possibility that elective invasive treatment for unruptured AVMs may yield worse outcomes than managing patients with symptomatic therapy alone [11], while other series suggest that long-term outcome may be more favorable after intervention [10]. In the light of these figures, neurosurgical teams face the clinical dilemma of how to balance the inherent risk of intervention against the potentially low haemorrhage rates in patients harbouring an unruptured brain AVM. Unfortunately, no controlled clinical trials have yet been undertaken of the management of unruptured AVMs to address this growing clinical dilemma [12–14].

Methods

Patients and Interventions

A Randomized Trial of Unruptured Brain AVMs (ARUBA) has been designed as a randomized controlled trial in order to compare the long-term outcomes of patients who receive medical management for neurological symptoms (if any-e.g., headache, seizures, etc.) associated with an unruptured AVM to those who receive medical management and invasive therapy to eradicate brain AVM. The study design is a prospective, multi-center trial where the best possible invasive treatment strategy (free choice depending on the patient's individual profile and anatomic AVM characteristics) will be randomized against non-invasive management. The invasive therapy arm of the trial involves best possible standard interventions with a plan for AVM eradication (by means of neurosurgical eradication, endovascular embolization, and/or stereotactic radiotherapy).

The primary outcome measure is the composite endpoint of death from any cause or symptomatic stroke, i.e., a clinically symptomatic hemorrhage or infarction confirmed by imaging. The secondary outcome measure is long-term clinical status by Rankin Scale, NIHSS, SF-36, and EuroQal. Should patients in the medical management arm develop a symptomatic stroke related to their AVM, they would then be candidates for any single or combination of invasive therapy.

Statistics

From a statistical standpoint, invasive AVM treatment is considered the current standard of care, while the non-interventional group constitutes the “experimental” arm as justified by the expected low spontaneous morbidity in unruptured malformations [8, 9].

The trial will require 800 patients to detect the hypothesized 36.5% relative risk reduction in the event rate with 80% power in an intention-to-treat analysis. Practically speaking, the trial has been designed to test whether invasive therapy or non-invasive management (“deferred treatment”) will reduce the risk of death or symptomatic stroke by an absolute magnitude of about 7.5% over 5 years.

Results

In its rigorous review process, the NIH/NINDS study section found scientific and ethical equipoise justifying randomization, and approved ARUBA for international funding. The 5-year follow-up is the expected minimum longitudinal study period based on NIH funding cycles and application policies. The overall length of the study will easily double, given alone the time needed to recruit 800 patients world-wide. Moreover, the independent Data and Safety Monitoring Board has already recommended a longer funding period to ensure a valid interpretation of the trial results and long-term projections based on a 10-year longitudinal observation.

Participating sites include neurovascular teams in North and South America (Brazil, Canada, USA), Australasia, and nine European countries including Austria, Finland, France, Germany, Italy, Netherlands, Spain, Switzerland, and the UK (a regularly updated list of sites open to enrollment is available at http://clinicaltrials.gov/ct2/show/NCT00389181). Eligibility criteria for study enrolment are summarized in Table 1.

Discussion

ARUBA offers the unique opportunity to address these uncertainties in an investigator initiated, multidisciplinary international study. An international consortium of vascular neurosurgeons, interventional neuroradiologists, and vascular neurologists helped designing the trial protocol and is overlooking the conduct and the progress of the trial. There is overall consensus that ARUBA will soon be able to provide reliable data on the natural history in unselected patients with unruptured brain AVMs. Major advantages of this collaborative international study design include a sound and statistically robust trial structure based on ethical equipoise. The inclusion criteria are sufficiently large to prevent systematic non-inclusion of eligible patients. The primary endpoint (i.e., symptomatic stroke and death) constitutes an objective, unbiased criterion highly relevant to clinical practice. The power calculations are based on a two-sided model considering invasive AVM treatment as standard of care. Also, the study protocol will not impose any predefined treatment plan, but will be able to document “real life” therapy according to each site’s longstanding experience and expertise of participating neurosurgical and neurovascular teams. Academic treatment centers providing multidisciplinary AVM therapy and treating ten or more AVM patients per

year are welcome to join this clinically important international project. More detailed information and contact addresses are available at www.arubastudy.org.

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Table 1

Predefined inclusion and exclusion criteria for patient enrollment in “A Randomized Multicenter Clinical Trial of Unruptured Brain AVMs” (ARUBA)

Inclusion criteria
1. Patient must have unruptured brain AVM diagnosed by MRI/MRA, CTA and/or angiogram
2. Patient must be 18 years of age or older
3. Patient must have signed informed consent
Exclusion criteria
1. Patient has a brain AVM presenting with evidence of recent or prior hemorrhage
2. Patient has received prior AVM therapy (endovascular, surgical, radiotherapy)
3. Patient has a brain AVM deemed untreatable by local team, or has concomitant vascular or brain disease that interferes with/or contraindicates any interventional therapy type (stenosis/occlusion of neck artery, prior brain surgery/radiation for other reasons)
4. Patient has a baseline Rankin scale score of 2 or more
5. Patient has concomitant disease reducing life expectancy to less than 10 years
6. Patient has thrombocytopenia (<100,000/μL)
7. Patient has uncorrectable coagulopathy (INR>1.5)
8. Patient is pregnant or lactating
9. Patient has multiple brain AVMs or harbours another intracranial vascular malformation (cerebral cavernous malformation, dural fistula, familial hemorrhagic telangiectasia, etc.)[a]

[a]Exclusion criteria truncated to most relevant items