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ARUBA – beating natural history in unruptured brain AVMs by intervention

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If you try and take a cat apart to see how it works, the first thing you have on your hands is a non-working cat.

Douglas Adams

The behaviour of brain arteriovenous malformations (AVMs) remains difficult to predict. Host, environmental, and gene susceptibility factors may influence the clinical manifestation. The complication with the most significant clinical sequelae is intracranial haemorrhage. Slowly accumulating data suggest that once the process of bleeding starts, the lesion appears to become destabilized and susceptible to more bleeding [1, 2]. Therefore, the indication for treatment of ruptured AVMs is generally not under dispute.

Unruptured AVMs

Whatever the treatment technique, the crude proportion of treatment-associated morbidity usually ranges around 10% in the most recent reports, but this seems acceptable given the persistent risk of potentially devastating bleeding from an untreated AVM. When it comes to unruptured brain AVMs, however, the long-assumed benefit of interventional therapy seems to have become less clear. Current natural history data from the Columbia AVM Database, the UCSF AVM Study project, and the Scottish Intracranial Vascular Malformation Study suggest the annual risk of spontaneous haemorrhage may be as low as 1% for unruptured AVMs. In addition, the growing availability of MR imaging has led to a substantial increase in the incidental detection of unruptured malformations ranging between 54% and 62% of all diagnosed AVMs in modern population-based data-sets [3, 4]. In the light of these figures, neurovascular 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.

These figures raise concern that invasive treatment may be connected with an unfavourable benefit vs. risk ratio to the degree that some have become reluctant to recommend interventional therapy for many patients presenting with an unruptured AVM. Evidence-

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based guidelines give nonintervention as one option in AVM management [5]. Although current clinical practice favours intervention in most patients, some clinicians understandably prefer to undertake intervention in specific subgroups of patients who are likely to benefit from the intervention. How can these patients be identified?

Besides haemorrhagic presentation, predictors of AVM haemorrhage during natural history follow-up include increasing age, deep brain location, associated aneurysms, and exclusive deep venous drainage [6, 7]. By contrast, the risk of spontaneous haemorrhage may drop below 1% per year in AVMs without these risk factors [2]. These characteristics may guide the interventionalist during case assessment and patient counselling, but the fact that the same factors not only increase the natural history risk but also the hazard of intervention, clearly adds to the complexity. When discussing these details with our patients, careful explanations and sufficient time are needed as they are often otherwise healthy young adults who are actively involved in their working and family life. When evidence is missing, inclusion into a dedicated clinical study protocol may be the ideal choice for most patients, as they will be monitored by a competent team of physicians who are able to react swiftly when clinical symptoms change or new scientific evidence arises.

The ARUBA study

With the initiation of the multidisciplinary international trial ARUBA (A Randomized trial of Unruptured Brain Arteriovenous Malformations, <http://www.arubastudy.org>) we now have the unique opportunity to gather the evidence needed to guide these very tough therapeutic decisions. The study design is a prospective, multicentre trial where the freely chosen best possible invasive treatment strategy (endovascular, neurosurgical, radiation therapy, or any combination) will be randomized against noninvasive management. In the ARUBA model, AVM treatment is considered standard of care, while the noninterventional group constitutes the “experimental” arm as justified by the expected low spontaneous morbidity in unruptured lesions. In its rigorous review, the NIH/NINDS study section found the scientific and ethical balance favouring randomization, and approved ARUBA for international funding. Participating sites include neurovascular teams in North and South America, Australia, and eight European countries. The ARUBA study with its clear focus on long-term follow-up finally offers the opportunity to solve the pressing question of best choice of management.

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

What can endovascular interventionalists expect from ARUBA?

We simply do not know whether endovascular treatment is really beneficial in unruptured brain AVMs. But one day we will be asked by health-care authorities and insurance companies about evidence justifying treatment of unruptured AVMs. Being asked this, we should have something in our hands. It might prove dangerous to consider ourselves as individual artists whose deeds escape standardization or comparison. If the neuroradiological community does not get actively involved in controlled clinical studies, industry and hospital administrators will interpret the available clinical data, design quality standards, and finally decide for us and for our patients.

Still more investigators are welcome to join, especially those from academic institutions with an experienced team of interventional neuroradiologists, vascular neurosurgeons, and stroke neurologists. Some centres are still hesitant and have expressed concerns that participation might reduce the number of invasively treated patients per year. However, based on a projected average enrolment rate of three to four patients per centre per year, only about two patients will be “lost” to interventional therapy—a figure that is certainly tolerable for a busy site in the event that administrative issues such as hospital activity or departmental income pose an obstacle.

ARUBA offers the unique opportunity to address these uncertainties in an investigator-initiated, multidisciplinary, and collegiate study. Several interventional neuroradiologists helped design the trial protocol and are part of the study's steering committee, and many have now started randomizing patients. Eventually, ARUBA will give us much more comfort in the discussion with our patients in relation to three specific expectations:

1. ARUBA will provide the most reliable data on natural history in unruptured brain AVMs. These figures will be the benchmark to beat for any invasive therapy. If the morbidity and mortality in a given centre is below this threshold, treatment is likely to show a positive effect.
2. The results will be transparent and stratified by clinical and morphological subgroups. We will finally be able to group patients either as those who bear an exceptionally high risk of disabling haemorrhage or those who are likely to benefit greatly from treatment—our target population.
3. Some technical insights about staged or targeted embolization can be expected during the long observation period: at least from an externally validated comparison of morbidity and mortality among the strategies. A major advantage of the protocol in this context is that ARUBA will not impose any predefined treatment plan, but relies on the expertise of participating neurovascular teams to establish the best possible treatment algorithm for each individual patient and to document “real life” therapy according to each site's longstanding experience.

One drawback of the study is the need for the inhomogeneous invasive arm to show very low complication rates to be superior to natural history with its expected low haemorrhage risk. Of particular concern may be the relatively short observation period of 5 years after enrolment, knowing that in the “real world” any benefit of AVM treatment relates to the

length of a patient's life with a continuing bleeding risk over time. Nonetheless, these limitations have been considered early and explicitly in order to avoid any misinterpretation by oversimplification of the study results later on. 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, not least because of 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. We also have to acknowledge that even after enrolling 800 patients, the complexity in the biology and treatment response of brain AVMs is not going to be elucidated entirely. Although the most burning questions have been specified in predefined subgroup analyses, the study is not powered to show significant results in all details, especially not within therapy subgroups. New statistical tools are available for individual prediction algorithms that will account for several variables and by doing so allow comparison of a treatment effect in a patient with his or her individual risk [8]. Moreover, after publication of the data every centre will be able to compare its own data after treatment with the natural history data of ARUBA and may evaluate the benefit of its individual strategy.

The more centres are ready to join, the faster we will get the answers we are hoping for. Are you not convinced that you can beat natural history by endovascular intervention?

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