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Atorvastatin for unruptured intracranial vertebrobasilar dissecting aneurysm (ATREAT-VBD): protocol for a randomised, double-blind, blank-controlled trial

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ABSTRACT

Introduction Vertebrobasilar dissecting aneurysms (VBDAs) are associated with serious complications and a poor prognosis. It is believed that inflammation of the aneurysm wall may be the main cause of rupture or deterioration. Atorvastatin has been shown to inhibit inflammation and may be a suitable drug candidate. Here, we report a clinical research study protocol to investigate whether atorvastatin inhibits inflammation of the aneurysm wall, as measured by signal index enhancement.

Methods and analysis We have designed a single-centre, randomised, double-blind, blank-controlled clinical trial. 40 patients with non-ruptured VBDAs with enhancement aneurysm walls will be enrolled in Beijing Tiantan Hospital. Eligible patients will be randomly divided into two treatment groups, at a ratio of 1:1, to receive atorvastatin 20 mg orally for 6 months or no treatment. The primary assessment outcome will be the change in aneurysm wall enhancement, as measured by the signal index during the 6-month treatment period. The secondary assessment outcomes will be the aneurysm morphology (intramural haematoma, dissection valve and false lumen) and changes in the concentrations of inflammatory factors, including C reactive protein, tumour necrosis factor-α, interleukin (IL)-1β and IL-6.

Ethics and dissemination The protocol has been approved by the medical ethics committee of the Beijing Tiantan Hospital at which the work will be conducted (Approval No. KY 2019-024-02). Written informed consent will be obtained from all participants. Findings from the study will be submitted for publication in a peer-reviewed journal.

Trial registration number NCT04943783.

Strengths and limitations of this study

- This is the first randomised controlled trial to investigate the feasibility of atorvastatin in the prevention and treatment of unruptured vertebrobasilar dissecting aneurysms.
- This study will test the methodology for providing atorvastatin intervention in two distinct periods (entry and 6 months).
- There is no absolute placebo control.
- The study will lack histological verification of inflammatory changes in aneurysm wall.

INTRODUCTION

Unruptured intracranial vertebrobasilar dissecting aneurysms (UIVBDAs) are a serious health problem and a leading cause of stroke in adults aged <50 years.[1 2] The mortality rate of patients with UIVBDAs ranges between 19% and 50%.[3] However, in recent years, an increasing number of patients with UIVBDA have received medical treatment, including acute stroke treatment and long-term prevention of ischaemic stroke.[4 5] However, no drug treatments to arrest dissecting aneurysm progression and subsequent rupture or occlusion have been established.

With regard to the anatomy of intracranial dissecting aneurysms, the intradural artery is characterised by a well-developed elastic plate, absence of elastic fibres in the media, and few adventitia tissues or absence of an elastic plate in the adventitia.[6 7] In addition, dissecting aneurysms are processed further before the equilibrium between vessel wall repair and extracellular matrix breakdown is reached, and inflammatory cells promote matrix breakdown.[1] As is commonly accepted, inflammatory cell infiltration is one of its characteristics.

High-resolution MRI (HR-MRI) of the vessel wall (HR-VW-MRI) is increasingly used in clinical practice as the only non-invasive imaging method to examine the structure of the vessel wall.[8 9] Aneurysm wall augmentation is a sign of inflammation on HR-MRI and can predict the unstable state of intracranial aneurysms (IAs).[10 11] Studies have shown that

HR-MRI can provide information for the diagnosis and follow-up of UIVBDAs, such as intramural haematomas, double-lumen and endometrial flaps.[12 13]

Statins (3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors) are often used as cholesterol-lowering drugs.[14 15] In addition to their lipid-lowering effects, statins also protect the vascular system by exerting anti-inflammatory effects, stimulating the production of extracellular matrix, and promoting chemotaxis and migration of mesenchymal progenitor cells.[16] Statins also inhibit the expression of several matrix metalloproteinases in smooth muscle cells and macrophages.[17] Researchers believe that statins may also reduce the rate of growth and risk of rupture of abdominal aortic aneurysm and dissection through their pleiotropic effects.[18] In addition, studies have shown that statins and aspirin, through their anti-inflammatory effects, can reduce the rate of growth and the risk of rupture of intracranial cystic aneurysms.[13 19]

We, therefore, hypothesised that atorvastatin could reduce the inflammatory response of the UIVBDAs, mobilise endothelial progenitor cells for vascular repair, and thus inhibit the growth and rupture of aneurysms.

Box 1 Participant inclusion and exclusion criteria

Inclusion criteria

1. Patient has a UIVBDA identified on imaging (CTA, MRA, DSA).
2. Verification of UIVBDA diagnosis by HR-MRI technique.
3. Written informed consent by the patient.
4. Age >18 years by the time of inclusion.

Exclusion criteria

1. The aneurysm types of non-dissecting aneurysms, such as saccular aneurysms, fusiform aneurysms, traumatic aneurysms, etc.
2. Patients with MRI contraindications: metallic implant, contrast allergy, claustrophobia, etc.
3. Planned treatments of the aneurysm within 6 months.
4. Several impaired liver or renal functions.
5. Retreatment of recurrent aneurysm.
6. Pregnant or lactating women.
7. Patients with malignant diseases and significant cardiovascular risk diseases, such as liver disease, kidney diseases, congestive heart failure, malignant tumours, etc.
8. Poor compliance patients.
9. Patient is taking other vasoactive medicines, such as ACE.

CTA, CT angiography; DSA, digital subtraction angiography; HR-MRI, high-resolution MRI; MRA, magnetic resonance angiography; UIVBDA, unruptured intracranial vertebrobasilar dissecting aneurysm.

METHODS AND ANALYSIS

Trial design and setting

This study is a single-centre, prospective, double-blind, randomised, blank-controlled trial. This study will enrol 40 eligible patients with UIVBDAs showing aneurysm wall enhancement in Beijing Tiantan Hospital. Eligible patients will be randomly divided into two treatment groups at a ratio of 1:1. The case group will receive 20 mg atorvastatin per day and the control group will not take atorvastatin. The treatment duration will be 6 months. Recruitment for the study began in July 2021 with an expected completion date in January 2022.

Study objective

The main purpose of this study is to compare the effect of atorvastatin on UIVBDA wall augmentation between patients who undergo treatment with atorvastatin for 6 months and those who do not. The secondary purpose is to assess the aneurysm morphology (intramural haematoma, dissection valve and false lumen) and changes in the concentrations of inflammatory factors, including C reactive protein (CRP), tumour necrosis factor-α (TNF-α), interleukin (IL)-1β and IL-6.

Study population and sample size

The inclusion and exclusion criteria of the trial are shown in box 1. Written consent from participants will be required before enrolment. The wall reinforcement index of unstable aneurysms is higher than that of stable aneurysms (1.70±1.06 vs 0.89±0.88, respectively).[20] We suspect that atorvastatin will reduce the UIVBDA wall enhancement index (WEI). We estimate that each group will need at least 16 patients to observe any effect of atorvastatin on the aneurysm WEI (≥5%) with an α of 5% and a β of 20%. In addition, we have assumed a drop-out rate of 10%–20%; thus, a maximum of 20 patients will be recruited into each group.

Randomisation

Random numbers will be generated by an independent third party using SPSS software (V.26.0, IBM) to generate a random sequence for blinding and to maintain the integrity of the study. The treatment allocation will be sealed in an envelope. These envelopes will only be opened by field researchers who are not involved in the clinical management or recruitment of participants. The clinical team and the participants will not be aware of the treatment allocation.

HR-VW-MRI protocol

All examinations will be performed using a 3.0 T MRI system (Prisma, Siemens Healthineers; Erlangen, Germany) with a 32-channel head coil. Three-dimensional (3D) time-of-flight magnetic resonance angiography will be used for localisation. VW-MRI will be acquired in the sagittal plane with whole-head coverage and an isotropic resolution of 0.7 mm before and after intravenous gadolinium contrast injection. Multiplanar reformats will be reconstructed for VW-MRI sequences for review. The protocol will include 3D T1-weighted imaging (T1WI; sampling perfection with application-optimised contrasts using different flip angle evolutions) and contrast-enhanced 3D T1WI. Post-contrast T1WI will be performed 3 min after gadolinium injection (0.1 mmol/kg gadopentetate dimeglumine, Magnevist, Bayer Schering Pharma) using parameters identical to those of pre-contrast T1WI. The voxel size for 3D T1W sequences will be 0.7×0.7×0.7 mm. The other

Table 1 Imaging parameters of HR-VW-MRI

	3D TOF MRA	3D T1WI SPACE
TR/TE (ms)	22/3.86	800/22
Flip angle (°)	25	180
Slice thickness (mm)	0.9	0.7
Number of slices	52	48
Field of view (mm)	160×160	240×160
Matrix	256×256	320×240
Scanning time	3'03"	4'17"
In-plane resolution	0.75×1.07	0.70×0.70

3D, three-dimensional; HR-VW-MRI, high-resolution vessel wall MRI; MRA, magnetic resonance angiography; SPACE, sampling perfection with application-optimised contrasts using different flip angle evolutions; TE, echo time; TOF, time-of-flight; TR, repetition time; T1W, T1-weighted imaging.

parameters will be as follows: echo train length: 52, slices: 224, integrated parallel acquisition techniques (IPAT): 2. The parameters of the imaging sequences are listed in table 1.

Image analysis

The image quality will be assessed using a previously described method. Each slice will be graded on a 4-point scale (1=poor; 2=adequate; 3=good; 4=excellent) based on the overall signal-to-noise ratio and the contrast between the vessel wall and the surrounding tissues.[21–23] Imaging data sets with an image quality score of 1 will be excluded. Quantitative analysis of the aneurysm wall on VW-MRIs will be performed using VesselMASS software (V.2014-EXP, MEDIS, Leiden University Medical Center; Leiden, the Netherlands) at a dedicated post-processing workstation. The wall enhancement volume rate (WEVR) analysis of the VW-MRIs will be performed using the latest version of 3D Slicer. We will perform a 3D reconstruction of the aneurysms in 3D Slicer with post-contrast T1W sequences. All VW-MRI data will be analysed independently by two experienced neuroradiologists who are blinded to patients' clinical data and treatment. One neuroradiologist will repeat the image analysis after a 2-week interval. The collected results will be analysed to assess interobserver and intraobserver reliability. The three slices with the most significant enhancement on post-contrast VW-MRI will be selected by the raters who will then trace the lumen and outer boundaries of the aneurysm wall through the optimally displayed angle (coronal, sagittal or axial based on the specific geometry of the aneurysm). The software will be used to automatically match the slice locations of the corresponding pre-contrast images. The inner lumen and outer wall contours of the aneurysm will be automatically segmented by the software, with manual adjustment of the contours if the neuroradiologist considers the tracings to be unsatisfactory. Subsequently, all obtained contours of each layer of the aneurysm will be automatically segmented into four quarters, and the mean enhancement signal intensity (SI) of each quarter (defined as quarter SI) will be calculated automatically. The quarter with the highest mean SI will be selected for each slice, and the average value of the three quarters from the corresponding three slices will be used to represent the SI of the aneurysm wall. This method will permit the evaluation of the most intensely enhanced segments of the aneurysm wall. The average SI of the aneurysm wall at the corresponding position on pre-contrast vessel wall imaging will be obtained using similar methods. To normalise the SI, similar methods will be used to measure the average SI of regions of interest in the adjacent white matter on pre-contrast and post-contrast vessel wall images.[24]

For the 3D aneurysm WEVR analysis, in 3D Slicer, we will manually delineate the outline of each layer of the aneurysm on post-contrast VW-MRI and then reconstruct the entire aneurysm wall volume. After rendering the 3D aneurysm model, the normal vasculature will be isolated by modifying the threshold tool. The threshold level will be adjusted until the major cerebral blood vessels show clear and distinct margins on axial, sagittal and coronal images. According to this threshold setting, the aneurysm volume of the enhanced part will be segmented and reconstructed.

Central imaging analysis

All baseline and follow-up HR-VW-MRIs from the study participants will be collected at a centre of excellence for neuroimaging, where intensive image analysis will be performed. This will include a review of the UIVBDA diagnosis through a consensus reading by two experienced researchers and a central analysis of the initial and follow-up MRIs of the brain by the independent core imaging laboratory. The latter will consist of two experienced neuroradiologists who will evaluate the imaging component of the comprehensive result measurement. The reviewers from the core imaging laboratory will not know about treatment allocation or the clinical results.

Follow-up

After participating in the study, the participants will be scheduled for the first clinical and imaging (HR-VW-MRI) follow-up examinations. The second clinical and imaging examinations will be performed 180±30 days after registration.

Outcome events

Primary outcome measures

The primary outcome measure will be the change in aneurysm wall inflammation, as measured by HR-VW-MRI. The quantitative WEI and WEVR from HR-VW-MRI will be compared between the treatment and control groups at the end of the 6-month treatment period. The WEVR will be calculated as follows[21]:

$$\text{WEVR} = \frac{\text{aneurysm enhancement volume}}{\text{whole aneurysm volume}} \times 100\%$$

Each voxel will be defined as enhanced when its SI is higher than the SI of the adjacent normal vessel wall.

The quantitative WEI will be calculated as follows (where SI denotes the signal intensity)[25]:

$$WEI = \frac{\frac{SI\_Wallpostcontrast}{SI\_White\ matterpostcontrast} - \frac{SI\_Wallprecontrast}{SI\_White\ matterprecontrast}}{\frac{SI\_Wallprecontrast}{SI\_White\ matterprecontrast}}$$

Secondary outcome measures

The secondary outcome measures will be:

1. The change in aneurysmal morphology from before treatment to the 6-month follow-up (a maximum diameter increase of ≥1 mm or the appearance of a daughter sac will be defined as a change in aneurysmal morphology).
2. The change in aneurysmal wall features from before treatment to the 6-month follow-up (an intramural haematoma decrease of ≥1 mm or disappearance of the false lumen will be defined as a change in aneurysmal wall features).
3. The changes in CRP, TNF-α, IL-1β and IL-6 concentrations in patients with unruptured IAs from before treatment to the 6-month follow-up. CRP, TNF-α, IL-1β and IL-6 concentrations will be measured twice (before treatment and at the 6-month follow-up). A turbidimetric immunoassay will be performed to measure the CRP concentration, and an ELISA will be performed to measure TNF-α, IL-1β and IL-6 concentrations. A blood sample will be drawn from the brachial vein of each participant at a fixed time in the morning before breakfast.

Data management

The final data collection and storage will be done through the electronic case report form using an electronic database that is fully compliant with data protection legislation (Health Insurance Portability and Accountability Act/Personal Information Protection and Electronic Documents Act). In addition to the electronic case report form, the data will be stored along with associated supporting documents, such as scans, medical records, care reports and blood tests. All research papers and documents will be kept at all test centres that participate in the research for at least 10 years. Upon completion of the research, the data will be reviewed by the research ethics committee, the quality assurance committee and other regulatory agencies. Research documents in paper form (consent forms, questionnaires and source data set from the diagram coordinator) will be properly stored at the Department of Neurosurgery. All computerised files will be password protected.

Safety considerations

Serious adverse drug reactions/events are related to the following conditions: death, disability and hospitalisation for emergencies. Although drug-related morbidities are rare, once the series of adverse drug events are confirmed in a patient, the patient will be removed from the study and a report should be completed within 24 hours.

Statistical analysis

The association between independent parameters will be evaluated using the X^2 test or Fisher's exact test for categorical variables and the non-parametric Mann-Whitney U test for continuous variables. The Wilcoxon signed-rank test will be used to compare the pretreatment and post-treatment variables. The bivariate non-parametric correlation between HR-VW-MRI wall enhancement and blood inflammatory markers will be tested using Spearman's r coefficient. The intraclass correlation coefficient will be calculated to measure the interobserver and intraobserver reproducibility in the measurements of WEI, WEVR and aneurysm size. All statistical analyses will be performed by a statistician using SPSS software (V.26.0, IBM).

Patient and public involvement

There was no patient or public involvement in the study. Study results will not be disseminated to participants specifically. However, if participants are interested in the results of the research, they will receive any information, the manuscript and published research on this topic in the future.

Ethics and dissemination

The study has been approved by the Ethics Committee of Beijing Tiantan Hospital (Approval No. KY 2019-024-02). This clinical trial will be conducted following the principles laid down by the 18th World Medical Assembly (Helsinki, 1964) and all applicable amendments laid down by the World Medical Assemblies and the International Conference on Harmonization Guidelines for Good Clinical Practice. Written informed consent will be obtained from all participants (online supplemental material). Findings from the study will be submitted for publication in a peer-reviewed journal.

DISCUSSION

ATREAT-VBD is a clinical study based on atorvastatin for the treatment of UIVBDAs. To our knowledge, this is the first conservative treatment study to completely exclude the effects of intervention, while previous studies have focused on reducing the recurrence of UIVBDAs after the intervention. This study is based on our previous research[26 27] and the known effects of statins in regulating inflammation and promoting angiogenesis in chronic subdural haematoma.[15]

At present, there is a lack of effective prevention and treatment measures for the causes and risk factors of UIVBDAs. There have been reports of bypass grafting and decompression surgery for vertebrobasilar artery extension and compression of the brain stem, as well as case reports on the effectiveness of endovascular therapy when drug therapy fails.[28 29] However, no drugs, endovascular therapies or surgical approaches have been systematically studied on a large scale.

We, therefore, believe that this study is necessary because conservative treatment options for UIVBDAs are very limited. Although some studies have shown that anti-thrombotic or platelet-inhibiting drugs are effective, they often result in a high rate of complications.[3 4] These complications include gastric ulcer and bleeding, intracranial haematoma and worsening of UIVBDAs.[30] In contrast, studies have shown that atorvastatin has a high curative effect in the treatment of unruptured IAs with few side effects. The most common side effect with atorvastatin is myopathy, which is considered dose related and is self-relieving when atorvastatin therapy is terminated.[31] Therefore, atorvastatin is considered to be safer than currently available conservative treatments. In addition, several studies have shown that a 20 mg dose of atorvastatin can have anti-inflammatory effects and reduce the biomarkers of inflammation in the vessel wall and the abundance of inflammatory cells. If the ATREAT-VBD Study proves the effectiveness of atorvastatin, we believe that atorvastatin could be a useful complementary treatment option to traditional interventions that are independent of drug intervention. However, the study considers a variety of clinical control factors, and research progress may be reduced as a result.

We recognise that the trial has some potential limitations. According to modern practice, early surgery may be the preferred option for patients with high risk of bleeding or ischaemic stroke, so this study included only patients with mild to moderate aneurysms and mild symptoms. Additionally, the trial does not include a placebo in the control group and the study will be conducted at a single centre in China, potentially limiting generalisability.

Trial status

Recruitment started in July 2021 and ended in January 2022. Follow-up is ongoing at the time of preparation of this manuscript.

Contributors MT performed the manuscript writing. XY and YisenZ made a critical revision to the manuscript for important intellectual content. HK, JH, ML, JL, YingZ and KW participated in the final design of the study. XY and YisenZ conceived and designed the research, and handled funding and supervision. All authors read and approved the final manuscript.

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Competing interests None declared.

Patient and public involvement Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

Patient consent for publication Not required.

Provenance and peer review Not commissioned; externally peer reviewed.

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Informed consent

Research Proposal Name: Application of atorvastatin in the treatment of intracranial vertebrobasilar artery dissecting aneurysm

Department: Beijing neurosurgical Institute

Version: V1.0

Version data: 2021/05/24

Informed consent

Informed consent Version: V 1.0 Version date: 2021/5/24

Dear patients:

We invite you to participate in the research project "The Application of Atorvastatin in the Treatment of Patients with Intracranial Vertebral Basilar Aneurysm" under the Youth Innovation Fund Project of Beijing Institute of Neurosurgery. The study will be conducted at Beijing Tiantan Hospital, and an estimated 40 subjects will volunteer to participate. This study has been reviewed and approved by the Ethics Committee of Beijing Tiantan Hospital.

1. Why conduct this research?

Endovascular treatment and surgical treatment are commonly used treatments for unruptured intracranial aneurysms. However, some patients temporarily choose conservative treatment and regular imaging follow-up because the risk of aneurysm rupture is low or the risk of treatment is greater than the risk of rupture. Conservative treatment of unruptured aneurysms The risk of aneurysm development and rupture is generally reduced by controlling risk factors such as hypertension and hyperlipidemia.

Studies have shown that the inflammatory response of the aneurysm wall, especially oxidative stress, plays a crucial role in the occurrence, development, and rupture of aneurysms. High-resolution magnetic resonance imaging can determine the occurrence and degree of inflammation by observing the enhancement of the blood vessel wall. Atorvastatin has been found in other diseases to be effective in reducing the inflammatory response in the body. Therefore, the subjects of this study were patients with unruptured intracranial aneurysms who were treated conservatively and showed signal enhancement in the aneurysm wall by MRI.

Therefore, in this study, we evaluated whether atorvastatin can effectively inhibit the vascular wall of the intracranial aneurysm by comparing the MRI images of patients without intracranial aneurysm taking atorvastatin at the time of enrollment and after six months of follow-up. Inflammation, as well as slowing the development of aneurysms and reducing the probability of aneurysm rupture and bleeding.

Through the implementation of this study, it is expected to provide a new treatment model for the conservative treatment of intracranial unruptured aneurysms.

2. How many people will participate in this study?

All patients with unruptured intracranial aneurysms who underwent conservative treatment in the Neurointerventional Department of Beijing Tiantan Hospital and showed signal enhancement in the aneurysm wall by MRI will be invited to this study. About 40 people were invited to participate in this study by the Neurointerventional Department of Beijing Tiantan Hospital.

3. How long will this study last?

The primary endpoint of this study was the changes in the enhancement of the aneurysm wall at the time of patient enrollment and 6 months after taking the drug, and the secondary endpoint was ① morphological indicators of the aneurysm (size, size, Aneurysm neck width, tumor area, tumor volume, etc.); ② Probability of aneurysm rupture and hemorrhage 6 months after operation; ③ Changes of serum inflammatory indexes (CRP, TNF-α, IL-1β, and IL-6) at 6 months after the operation. Therefore, this study is expected to last for 18 months.

You may opt-out of the study at any time without forfeiting any of the benefits you should have received. However, if you decide to withdraw from the study during the study, we encourage you to discuss this with your doctor first. Considering your security issues, there may be a related check after you log out.

4. What does this study include?

If you agree to participate in this study, first, we will ask you about your medical history and review all the medicines you are currently taking. Secondly, record the results of routine laboratory tests and auxiliary

examinations during your hospitalization, including blood tests, blood biochemical examinations, coagulation examinations, and other laboratory examinations, as well as auxiliary examinations such as electrocardiogram and head magnetic resonance (MRI). In addition to routine laboratory tests, we will draw about 10ml of blood from your arm vein and store it in this research specimen bank for etiology and other related research. We can perform a urine test for you (for women of childbearing age only), women who are pregnant cannot participate in this study. Finally, if we believe you are suitable to participate in this research, we will proceed with the following research procedures with your consent.

According to the plan, we randomly divided the participants into groups, one group received oral atorvastatin and the other group received no atorvastatin. Regardless of which group you're assigned to, we'll control for aneurysm-related risk factors, such as high blood pressure, high blood lipids, and more. This study is a "double-blind" study, which means neither you nor your study doctor knows which drug you are taking. Subjects randomized to atorvastatin will receive oral atorvastatin, and patients randomized to no atorvastatin will receive a placebo in the same form as atorvastatin. A placebo is a tablet that looks identical to the study drug but does not contain the active ingredient. We use placebos in our studies to understand whether the beneficial or detrimental effects observed in subjects are actually from the study drug. All study drugs will be blinded, meaning neither you nor your study doctor can tell which drug you are taking. However, in an urgent and necessary situation, your doctor will be able to know which medicines you are taking.

On days 1-7, you will receive atorvastatin 20mg orally once a day. All study medication will be provided to you in a box. The study doctor will record in writing how many pills you take from which box at a time. The daily dose must be following the study requirements under the guidance of the study doctor. The study doctor will give you enough of the study drug to last until the next visit; at the follow-up visit, you will return the entire kit and any unused study drug to the doctor. If you decide to participate in this study, you must agree to take the medicine as directed by the study doctor and not to give the study medicine to anyone else. Do not take any other medicines or receive other treatments, whether prescribed or purchased from a pharmacy or supermarket, until approved by your study doctor. In addition, any special diet must be determined after discussion with the study physician.

During this period, we will plan to request the collection of basic information and imaging information of patients and relevant information during follow-up. You need to assist the doctor to complete the items required in the questionnaire, and you also need to leave reliable contact information (including phone number and address) so that the doctor can arrange a follow-up for your disease after surgery.

5. Do I have other treatment options?

Participation in this study may or may not inhibit the inflammatory response of the aneurysm, thereby inhibiting the progression and rupture of the aneurysm. If you do not participate in this study, you can choose other treatment options, and your doctor will give you the best treatment according to your condition.

6. Who was selected for the study?

(1) Aged over 18 years old;

(2) Patients with intracranial unruptured vertebrobasilar artery dissection aneurysm with a diameter of ≥3mm;

(3) Aneurysm patients without clinical indications for surgery and conservative treatment: asymptomatic aneurysm; Aneurysm diameter < 7mm; no aneurysm morphological risk factors (such as ascus, lobulated aneurysm);

(4) High-resolution MRI showed aneurysm wall enhancement;

(5) All subjects or their proxies People need to sign informed consent.

Whether you can participate in the study will be decided after a doctor's examination.

7. Who should not participate in research?

(1) Aneurysms whose pathological mechanisms are inconsistent with dissecting aneurysms, such as cystic and fusiform;

(2) No contraindications to MRI (such as contrast agent allergy, claustrophobia, or implantation of metal foreign bodies, etc.);

(3) Diagnosis Patients with other serious diseases or Hunt-Hess grade ≥3 will significantly affect the follow-up;

(4) patients with recurrent aneurysm and retreatment;

(5) pregnant women;

(6) combined with other serious systemic diseases, expected survival Patients with a time less than 1 year;

(7) Abnormal liver and kidney function;

(8) Patients with other immune diseases

If you are one of the conditions, it is not within the scope of this study.

8. What are the risks of participating in research?

The use of all drugs carries risks and may lead to adverse effects, whether or not it was part of this study. During the study, we will promptly notify you of any new findings related to atorvastatin that may affect your participation or continued participation in this study. You will also be notified promptly of any drug-related information that may negatively affect your health. If you wish to withdraw from the study because of new findings, your doctor will arrange for other treatment for you.

Risks of using atorvastatin:

1) Allergic reaction and angioedema;

2) Progressive multifocal leukoencephalopathy;

3) Lymphocyte decrease, increasing the risk of infection;

4) Liver damage;

5) Other adverse reactions: facial flushing, abdominal pain, diarrhea, nausea, etc.

9. What are the benefits of participating in research?

Since the safety and efficacy of atorvastatin in patients with multiple sclerosis have been confirmed, its mechanism of action is related to the inhibition of inflammatory response in the human body, and the development and rupture of the intracranial aneurysm have been confirmed to be related to the inflammatory response in vivo. Closely related, therefore, participating in this study may potentially control aneurysm growth and reduce the risk of aneurysm rupture, although no guarantee participating in this study may improve your health for the better. At the same time, during the research process, the research doctor will pay close attention to your physical condition and make corresponding assessments promptly.

10. Do I need to pay for the study?

You will receive the study drug for free.

You will not be paid for participating in this research.

11. What happens if I am harmed while participating in the study?

Any research has implications for patients, and any treatment is risky rather than completely safe. In addition, any treatment may be ineffective, and the disease may continue to develop due to ineffective treatment or due to other diseases. Our hospital and the centers are all Grade III A hospitals, and the hospital personnel and medical

equipment are qualified to rescue patients. If your health does suffer from study-related damage as a result of your participation in this study, please notify the study physician immediately and they will be responsible for appropriate treatment for you. Beijing Tiantan Hospital will bear the cost of treatment and give you corresponding financial compensation following relevant national regulations.

For patients taking atorvastatin, we regularly test liver and kidney functions. Once adverse drug reactions occur, the drug should be stopped immediately and relevant symptomatic treatment will be given. If the patient has changed in the shape of the aneurysm during the follow-up period, the patient should be comprehensively evaluated and conservative or surgical treatment should be decided. If the aneurysm ruptures and hemorrhages in the patient, we will open the green channel and carry out surgical treatment as soon as possible. After the treatment, we will transfer the patient to the intensive care unit to closely monitor and treat the patient.

Even if you have signed this informed consent form, you still retain all your legal rights.

12. Is my personal information confidential?

Your medical records will be kept in the hospital, and investigators, research authorities, and ethics committees will have access to your medical records. Any public reporting of the results of this study will not disclose your identity. We will make every effort to protect the privacy of your personal medical information to the extent permitted by law.

13. Do I have to participate in research?

Participation in this study is entirely voluntary, and you may refuse to participate in the study, or withdraw from the study at any time during the study without any reason. This decision will not affect how your doctor treats you.

If you decide to withdraw from this study, please contact your doctor in advance.

14. How will participate in this study affect my life?

During the study period, in addition to the treatment and follow-up visits during your normal medical visits, we will only contact you when arranging follow-up visits, the purpose of which is to arrange your follow-up matters (review time, bed arrangements, etc.), you may feel that these arrangements will cause inconvenience.

You can ask your study doctor if you have any questions about the tests and procedures in the study.

You cannot participate in any other clinical studies of drugs or medical devices during the entire study period.

15. Related consultation.

If you have any questions related to this research, please contact Yisen Zhang and Mirzat Turton, landline and mobile phone 01059975936, 15001232615, 18699158800.

If you have any questions related to your rights, or if you would like to express your dissatisfaction and concerns during your participation in this research, please contact the Ethics Committee Office of Beijing Tiantan Hospital at 010-59978555.

Patient Statement:

I have read the above description of this study and am fully aware of the possible risks and benefits of participating in this study. I volunteered to participate in this study.

I agree□ or disagree.□ Studies other than this study utilized my medical records and examination specimens.

Patient signature：_____ Date：_____

Patient name：_____ Contact number：_____

Signature of legal representative：_____ Date：_____

Legal representative name：_____ Contact number：_____

Physician's Statement: I confirm that the details of this study have been explained to the patient, particularly the possible risks and benefits of participating in this study.

Doctor's signature.：_____ Date：_____

Doctor's name：_____ Contact number：_____