Endovascular management of symptomatic stenosis of supra-aortic arteries in patients with Takayasu arteritis

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Abstract

Background: Endovascular management is used to treat Takayasu arteritis (TA) involving the supra-aortic branches. However, the long-term outcome of this treatment remains unclear. Here, technical safety, outcomes, and restenosis management of supra-aortic arteries in TA patients receiving endovascular treatment were evaluated.

Methods: TA patients with symptomatic supra-aortic stenosis who underwent percutaneous angioplasty and stenting between 2008 and 2018 at our institute were enrolled in this study. Pre- and post-procedural magnetic resonance imaging (MRI) evaluations, including high-resolution vessel wall imaging (HR-VWI), were performed. Technical efficacy, peri-procedural complications, early post-procedural MRI results, and stent patency were examined.

Results: All six patients successfully received stent placement or percutaneous transluminal angioplasty in a total of 22 treated arteries without neurologic complications. During follow-up (mean, 56.3 ± 41.1 months), no recurrent stroke occurred, yet significant restenosis developed in 12 of 22 (54.5%) of the treated arteries. Three of the patients underwent HR-VWI before surgery. Concentric wall thickening and enhancement of the left common carotid artery was detected in one patient, indicating acute inflammation. Angioplasty with drug-eluting balloon (DEB) successfully treated a case of refractory restenosis. Among 10 early post-procedure MRI performed, only two asymptomatic new lesions were detected with diffusion-weighted imaging.

Conclusion: Endovascular treatment of supra-aortic arteries of TA patients was safe and effective, yet was associated with a high restenosis rate. Thus, close follow-up is needed. HR-VWI is helpful for pre-procedural selection of patients for percutaneous angioplasty and stenting and drug-eluting balloon angioplasty appears to be a promising treatment for refractory in-stent restenosis.

Keywords: Drug-eluting balloon; Endovascular treatment; High-resolution vessel wall imaging; Takayasu arteritis

1. INTRODUCTION

Takayasu arteritis (TA) is a progressive large vessel vasculitis that most commonly involves the aorta and its major branches.[1] TA usually affects young adults during the third decade of life and has a 9:1 female predominance. Granulomatous inflammation is a pathologic finding of TA. In the early stages of disease, patients usually present with non-specific symptoms related to arterial inflammation, such as fever or general malaise, thereby precluding a correct diagnosis. As TA progresses, significant stenosis of the supra-aortic vessels develops and associated ischemic symptoms may manifest. The latter include cerebral ischemia or infarct, visual impairment, vertebrobasilar insufficiency, and diminished radial pulse. Currently, there are no reliable parameters to reflect disease activity.[2] In addition, the systemic inflammatory response does not accurately reflect isolated vessel wall inflammatory activity.[3] There are many therapeutic options for TA, including medical treatments, endovascular interventions, and surgical revascularization procedures. However, no standard treatment has been established.[1,4]

Endovascular management is a valid and less invasive procedure compared with surgical intervention in TA patients with medically refractory symptomatic stenosis of supra-aortic arteries. However, endovascular management of severe stenosis of TA has a high restenosis rate within 2 years.[5] To date, there has been no report of using magnetic resonance (MR) findings to guide patient selection for endovascular management of TA. There has also been no report of optimal management of recurrent/refractory restenosis after percutaneous angioplasty and stenting (PTAS). Therefore, the purpose of this retrospective study was to evaluate the technical safety and outcome of an endovascular treatment strategy for TA based on clinical and imaging findings. Our preliminary experience in treating recurrent restenosis for endovascular management is also described.

2. METHODS

2.1. Study population and data collection

Our institutional review board approved this retrospective study and pre-procedural informed consents were obtained from each patient. TA patients with symptomatic supra-aortic stenosis

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who underwent PTAS between 2008 and 2018 were enrolled. A diagnosis was made according to criteria of the American College of Rheumatology.[6] Clinical findings, including symptoms, laboratory test results, and post-procedural medications, were retrospectively evaluated.

2.2. Magnetic resonance imaging

Brain and neck magnetic resonance imaging (MRI) was performed as part of the pre-procedural evaluation and post-procedural follow-up for each patient. A 1.5 T scanner (GE Healthcare, Milwaukee, WI, USA) with a standard eight-channel head coil was used. Axial fluid attenuation inversion recovery and diffusion-weighted imaging (DWI) of the brain, time-of-flight MRI of the brain, and contrast-enhanced magnetic resonance angiography (MRA) of the neck were performed. Three patients were additionally subjected to high-resolution vessel wall imaging (HR-VWI). Stenotic lesions in the supra-aortic arteries were visualized with MRA of the neck and were subsequently investigated with HR-VWI. Briefly, a two-dimensional technique was applied to obtain multi-planar images perpendicular to the long axis of the whole stenotic segment of the affected supra-aortic arteries. The sequences included T1 weighted imaging, T2WI, and contrast-enhanced T1WI. The HR-VWI protocol included: slice thickness = 3 mm, number of excitations = 6 (for T2WI) and 4 (for T1WI), field-of-view = 13 × 13 cm^2, matrix = 288 × 224 (on T2WI) and 288 × 192 (on T1WI). Fat suppression and blood flow suppression techniques were applied to enhance resolution of the vascular wall. Two experienced neuroradiologists interpreted the MR images by consensus. On HR-VWI, the relative overall signal intensity of the vascular wall of the stenotic segment of the supra-aortic arteries was compared with the signal intensity of the nearby muscles of the neck or chest wall. High signal intensity was defined as ≥150% of muscle signal intensity, while iso- to low signal intensity was defined as <150%. Enhancement of T1WI following injection of contrast media was defined as either strong (with a signal intensity similar to that of the venous structures) or faint or absent (with a signal intensity less than that of the venous structures). Concentric thickening and enhancement of the vessel wall characterized an acute inflammatory stage. In contrast, less thickening and an absence of enhancement on post-contrast images characterized a chronic stage of inflammation. HR-VWI findings were also correlated with C-reactive protein (CRP) levels.

2.3. Percutaneous angioplasty and stenting

An indication for PTAS was medically refractory symptomatic stenosis (≥50%) of the supra-aortic arteries.[7] Symptoms include cerebral or retinal ischemia, dizziness due to vertebrobasilar insufficiency, and limb ischemia. Stenotic lesions with acute inflammation were not treated. Disease activity of affected vessel walls was evaluated by using biologic markers of CRP and/or level of erythrocyte sedimentation rate (ESR) and an imaging marker of HR-VWI. All patients received 300 mg aspirin and 75 mg clopidogrel for at least 3 days before their procedure. This antiplatelet therapy was maintained for 3 months post-procedurally, followed by maintenance of aspirin alone indefinitely.

Procedures were performed under local anesthesia. A transfemoral arterial approach was used to obtain a complete angiogram of the bilateral carotid, bilateral subclavian, and bilateral vertebral arteries. Briefly, after an intravenous bolus of heparin (3000–5000 IU) was administered, a 6F or 7F guiding sheath (Shuttle Sheath; Cook Co., Bloomington, IN, USA) was placed into the targeted artery. A 0.014 Fr. wire was navigated through the stenotic lesion. Stenotic lesions were pre-dilated with a non-compliant balloon (Sterling; Boston Sci. Co., Boston, MA, USA) before self-expandable stents (Wallstent or Epic stent; Boston Scientific, Natick, MA, USA; or Precise stent; Cordis Co., Bridgewater, NJ, USA) were implanted. Generally, stenotic lesions of the supra-aortic arteries of TA are long and can be compressed externally. Therefore, self-expandable stents were used to treat these types of lesions since they are longer and more resistant to external compression compared with balloon-expandable stents. Any technical complications were recorded. PTAS was considered successful if angiography showed <30% stenosis in the target artery and no major neurologic deficit. All patients underwent clinical and computed tomography angiography/MRA within the first post-procedural month and then every 3–6 months after treatment. Restenosis >50% in treated arteries was defined as significant and requiring re-intervention. In one case, a drug-eluting balloon (DEB) was used to treat recurrent/refractory restenosis.

3. RESULTS

3.1. Patient characteristics

A total of six female TA patients were enrolled in this study. Their demographic features and PTAS are presented in Table 1. The mean age of this cohort was 32.8 ± 12.5 years (range: 14–49). Clinical symptoms included: stroke with hemiparesis (n = 2; 33.3%), upper limb ischemia (n = 2; 33.3%), visual impairment or amaurosis fugax (n = 3; 50%), headaches (n = 4; 66.7%), and dizziness (n = 5; 83.3%). In total, 22 diseased arteries were treated: subclavian arteries (n = 10; 45.5%), common carotid arteries (n = 8; 36.3%), and vertebral arteries (n = 4; 18.2%).

3.2. High-resolution vessel wall imaging

There were three patients who underwent HR-VWI for a pre-procedural evaluation of stenotic vessel disease activity. In one patient, concentric wall thickening and enhancement of the left common carotid artery (CCA) was detected (Fig. 1). In addition,

Table 1

Patient demographics, endovascular procedures, and follow-up results

Characteristics	Total
Sex (M/F)	0/6
Age (y), mean ± SD (range)	32.8 ± 12.5 (14–49)
Symptoms, % (n/total)	
Stroke	33.3% (2/6)
Vertebrobasilar insufficiency (dizziness)	83.3% (5/6)
Upper limb ischemia	33.3% (2/6)
Headache	66.7% (4/6)
Visual impairment	50% (3/6)
Pre-procedural ESR (mg/dL), mean ± SD (range)	20.5 ± 21.3 (4–86)
Pre-procedural CRP (mg/dL), mean ± SD (range)	0.7 ± 0.9 (0.035–2.9)
Treated arteries, % (n/total)	
Common carotid artery	36.3% (8/22)
Subclavian artery	45.5% (10/22)
Vertebral artery	18.2% (4/22)
Technical success rate, % (n/total)	100% (22/22)
Neurologic complications, % (n/total)	0% (0/22)
Restenosis rate (>50% restenosis), % (n/total)	54.5% (12/22)
Common carotid artery	25% (2/8)
Subclavian artery	70% (7/10)
Vertebral artery	75% (3/4)
Follow-up interval of restenosis (months), mean ± SD (range)	12.4 ± 11.6 (7–45)
Re-intervention, % (n/total)	50% (6/12)
Outcome, % (n/total)	16.7% (1/6)
Recurrent symptoms	Limb ischemia with diminished radial pulses
Follow-up interval (months), mean ± SD (range)	56.3 ± 41.1 (9.5–103.5)

CRP = C-reactive protein; ESR = erythrocyte sedimentation rate.

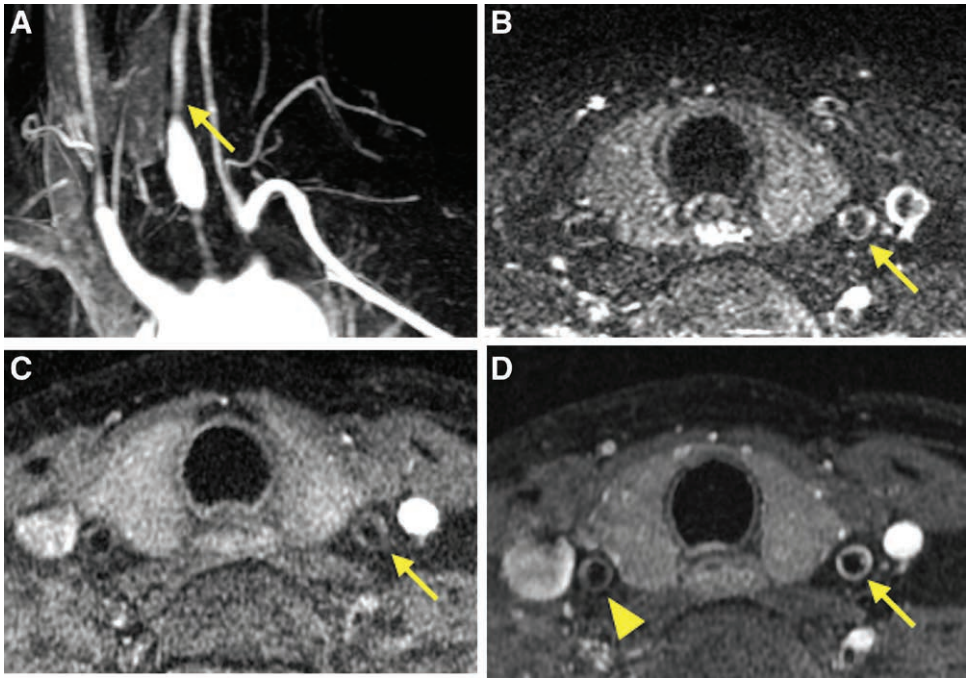

Fig. 1 HR-VWI of a 36-year-old female with TA in an acute inflammatory stage. A, Coronal maximum intensity projection (MIP) three-dimensional MR angiogram shows high-grade stenosis of the left CCA (arrow). B, Axial T2-weighted MR image shows iso- to hyperintense signal in the left CCA wall (arrow). C, Axial T1-weighted MR image shows iso-intense signal of a thickening vessel wall of the left CCA (arrow). D, Contrast-enhanced, axial T1-weighted MRI shows concentric wall thickening and enhancement of the left proximal CCA (arrow), suggestive of an acute inflammatory stage. The chronic inflammatory lesion in the right CCA at the same level shows slight stenosis and nearly no enhancement (arrowhead). CCA = common carotid artery; CTA = computed tomography angiography; HR-VWI = high-resolution vessel wall imaging; MR = magnetic resonance; MRI = magnetic resonance imaging; TA = Takayasu arteritis.

the CRP level of this patient was 0.52 mg/dL. These findings were consistent with an acute inflammatory stage in the left CCA. Thus, PTAS of the left CCA was delayed. When HR-VWI was performed for the other two patients, mild concentric wall thickening and no wall enhancement of the stenotic arteries were observed. These results indicated a chronic stage of TA in both patients. Among these three patients, a total of seven target vessels were evaluated. Only one target vessel exhibited characteristics of an acute inflammatory stage. Based on previous literature, intervention should not be performed during an active stage of disease.[1] Therefore, the other six lesions underwent PTAS after the HR-VWI evaluations. Two of the targeted vessels exhibited no in-stent restenosis, while the other four lesions manifested restenosis within 7–12 months after PTAS.

3.3. PTAS and follow-up

All of the patients were successfully treated with PTAS without neurologic complications. For the eight stenotic common carotid arteries identified, 14 Wallstent (Boston Scientific) and two Precise stents (Cordis Co.) were used. For the 10 stenotic subclavian arteries identified, three Carotid Wallstents (Boston Scientific), two Wallstent RP (Boston Scientific), one Epic stent (Boston Scientific), one Precise stent (Cordis Co.), and one Protégé (ev3; Endovascular, Inc., Plymouth, MA, USA) were used. For the stenotic lesion in the vertebral artery, a Wallstent RP (Boston Scientific) was used, while percutaneous angioplasty was performed for three other vertebral lesions. Procedural details are summarized in Table 2. Relief of symptoms was reported as soon as the procedures were completed, including improved visual impairment, dizziness, and limb ischemia. Among the 22 treated arteries, significant (>50%) restenosis was noted in 12 (54.5%). Reintervention with PTAS or angioplasty was performed for six of these restenotic arteries. Re-intervention was not performed for the other six arteries due to patient preference or total occlusion of the stenotic artery.

One patient manifested refractory restenosis after reintervention. The patient exhibited moderate stenosis at the right proximal CCA and severe stenosis at the right subclavian artery. Initially, PTAS was performed in both arteries. One year later, in-stent restenosis was observed in both arteries. Therefore, DEB (Ranger Paclitaxel-coated balloon catheter; Boston Sci. Co.) angioplasty was performed on the right subclavian artery, while uncoated balloon angioplasty was performed on the right CCA. After 32 months, the right subclavian artery remained patent (Fig. 2A–E), while the right CCA exhibited in-stent restenosis after 5 months. DEB angioplasty was subsequently performed on the right CCA. After 27 months, the right CCA remained patent (Fig. 2F–L).

Of the 16 procedures performed without cerebral embolic protection devices (three procedures involving only the subclavian artery and 13 procedures involving the carotid artery and subclavian/vertebral artery simultaneously), early post-procedural MRI follow-up was only performed for ten. In addition, DWI only detected two asymptomatic new lesions.

4. DISCUSSION

TA is difficult to manage since an early diagnosis is not straightforward and there are no reliable parameters to evaluate disease activity. Generally, treatment of TA includes suppression of systemic and vascular inflammation by corticosteroids, immunosuppressive agents, or biologic agents, followed by revascularization of affected organs either by surgery or endovascular interventions in the chronic stage.[1] Meanwhile, imaging modalities are used to evaluate lesion distribution and monitor disease activity. However, it has been reported that systemic inflammatory responses do not consistently show good correlation with inflammatory activity in vessel walls. For example, an elevated ESR or serum CRP level does not always indicate an

Table 2

Stents used among the treated patients

Case no.	Age/ sex	Treated artery	Procedural details	Total number of stents
1	28/F	LCCA	8 × 66 mm Wallstent	1
		LSA	8 × 47 mm Wallstent	1
		RCCA	8 × 38 mm Wallstent	1
		LVA	PTA: 3.5 × 20 mm Maveric	0
		RSA	PTA: 8 × 40 mm Wanda	0
2	23/F	RVA	8 × 38 mm Wallstent RP	1
		RCCA	7 × 50 mm, 7 × 30 mm, 7 × 30 mm Wallstent	3
		LCCA	6 × 46 mm Wallstent RP, 7 × 30 mm Wallstent	2
		RSA	PTA: 7 × 20 mm Wanda	0
		LVA	PTA: 2.5 × 20 mm Rafale	0
		LSA	8 × 39 mm Wallstent RP	1
3	14/F	RSA	PTA: 3 × 40 and 6 × 40 mm Wanda	0
		LCCA	8 × 39 mm Wallstent RP, 7 × 50 mm Wallstent, 6 × 47 mm Wallstent RP	3
		LSA	8 × 47 mm Wallstent, 6 × 59 mm Wallstent RP, 8 × 66 mm Wallstent RP	3
4	49/F	RCCA	8 × 66 mm Wallstent RP	1
		LSA	9 × 36 mm Wallstent	1
5	47/F	LSA	8 × 38 mm Wallstent RP	1
6	36/F	RSA	8 × 61 mm Epic PTA: Ranger DEB 8 × 80 mm	1
		RCCA	7 × 40 mm Carotid Wallstent, 8 × 40 mm Precise, PTA: Ranger DEB 8 × 80 mm	2
		LSA	9 × 30 mm Precise, 9 × 60 mm Protégé, PTA: Ranger DEB 8 × 80 mm	2
		LCCA	7 × 50 mm, 7 × 50 mm Carotid Wallstent, 8 × 40 mm Precise PTA: Ranger DEB 7 × 100 mm	3
		LVA	PTA: 5 × 20 mm Sterling	0

DEB = drug-eluting balloon; LCCA = left common carotid artery; LSA = left subclavian artery; LVA = left vertebral artery; PTA = percutaneous angioplasty; RCCA = right common carotid artery; RSA = right subclavian artery; RVA = right vertebral artery.

inflammatory state of vasculitis.[1] However, inflammatory markers of ESR or CRP level can be used to evaluate the systemic status of a patient rather than the disease activity of each stenotic vessel. When patients have poor responses to medical treatment and progress to chronic steno-occlusive arterial disease, revascularization is performed. However, neither endovascular interventions, nor bypass surgery, should be performed during an active inflammatory phase of TA.[8] Endovascular or surgical interventions can be attempted after inflammation in a vessel wall is suppressed, and this can be followed by a post-interventional immunosuppressive treatment to achieve strict control of disease activity.[1] In the present study, all six patients had poor responses to medical treatment and were in a chronic stage of supra-aortic artery stenosis. Thus, endovascular interventions were needed. To date, there are criteria defined for assessing disease activity in TA, although no standardized consensus has been established to evaluate vascular activity for patient selection of PTAS.

For this study, HR-VWI was performed to evaluate the vascular inflammatory status of target vessels and for patient selection for PTAS among TA patients with symptomatic supra-aortic stenosis who required revascularization of affected organs. If PTAS is performed on an actively inflamed vascular wall, there is a risk of vascular injury or acute thrombosis and occlusion. Moreover, vascular complications such as restenosis are more likely to occur when vessel inflammation is observed at the time of vascular intervention.[9] Therefore, it is essential that a combination of serologic markers and imaging studies be used to prevent progressive arterial injury.[10] HR-VWI allows morphologic changes in the vascular walls of TA patients to be observed, including vessel wall thickening and luminal narrowing. During the acute inflammation phase, concentric mural enhancement of a thickened arterial wall is usually demonstrated.[1,3,11] TA is a systemic disease and diffusely involves the main aortic branches. Since each branch can have different phases of disease activity, laboratory data may not precisely reflect regional disease activity. However, HR-VWI of each involved vessel can potentially provide more detailed information regarding disease activity based on morphology and enhancement patterns.[12] For example, Papa et al.[13] demonstrated that vessel wall enhancement significantly correlates with clinical signs of disease activity and CRP concentration in TA patients. Therefore, we propose that both HR-VWI and CRP level be used to evaluate disease activity for each target vessel and for patient selection for endovascular therapy.[1] Endovascular intervention is recommended in the chronic phase of TA when ESR and CRP levels are normal and no concentric thickening or contrast enhancement of a target vascular wall are observed on pre-procedural HR-VWI.

In the present study, although not every patient underwent a pre-procedural HR-VWI evaluation, serum ESR and CRP levels were checked in every patient before each procedure. Fortunately, acute thrombosis or other acute vascular injuries were not encountered during, or immediately after, the procedures performed, yet the restenosis rate was high. The high restenosis rate may be related to sites of active inflammation not detected by the serologic markers examined.[10] However, one target vessel was revealed to be in an acute inflammatory stage during one of the pre-procedural HR-VWI evaluations, yet the serum biomarker level for this patient was within normal limits. We delayed PTAS of this target vessel based on the general principle of TA treatment that intervention, neither endovascular therapy nor surgical bypass, should be performed during acute inflammatory disease.[1,14] HR-VWI is a novel technique, yet it has been broadly used in evaluations of vascular steno-occlusive diseases. Based on the limited experience obtained in the present study, we propose that HR-VWI is a better tool for evaluating disease activity of individual target vessels in TA. If this is confirmed, severe acute complications in relatively young patients after a procedure could be avoided, satisfactory patient outcomes could be obtained, and better pre-procedural plans could be established for TA patients who are going to receive endovascular treatment. With stricter patient selection, success rates and reduced incidence of restenosis after PTAS could also be improved.

In the present study, the rate of restenosis and re-occlusion was approximately 54.5%, consistent with a previous report.[5] The most common vessel with lesion re-stenosis was the subclavian artery. Only one of our patients with medically refractory restenosis accepted re-intervention with a DEB. DEBs have been reported to successfully treat restenosis of atherosclerotic carotid stenosis. However, the technical safety and efficacy of using a DEB to manage restenosis of vasculitis are not well clarified. By applying strict selection criteria to the refractory restenosis cases at our institute, a DEB was applied to one of our TA patients and a favorable outcome was achieved. This result suggests that use of DEBs represents a promising method of restenosis management in TA patients. However, additional prospective studies are needed to confirm the long-term outcome of this approach.

Both endovascular treatment and bypass surgery are therapeutic options for supra-aortic arterial occlusive disease due to TA. Kim et al.[5] reported that arteries reconstructed after bypass surgery exhibit superior patency compared to those reconstructed by endovascular intervention. However, the common

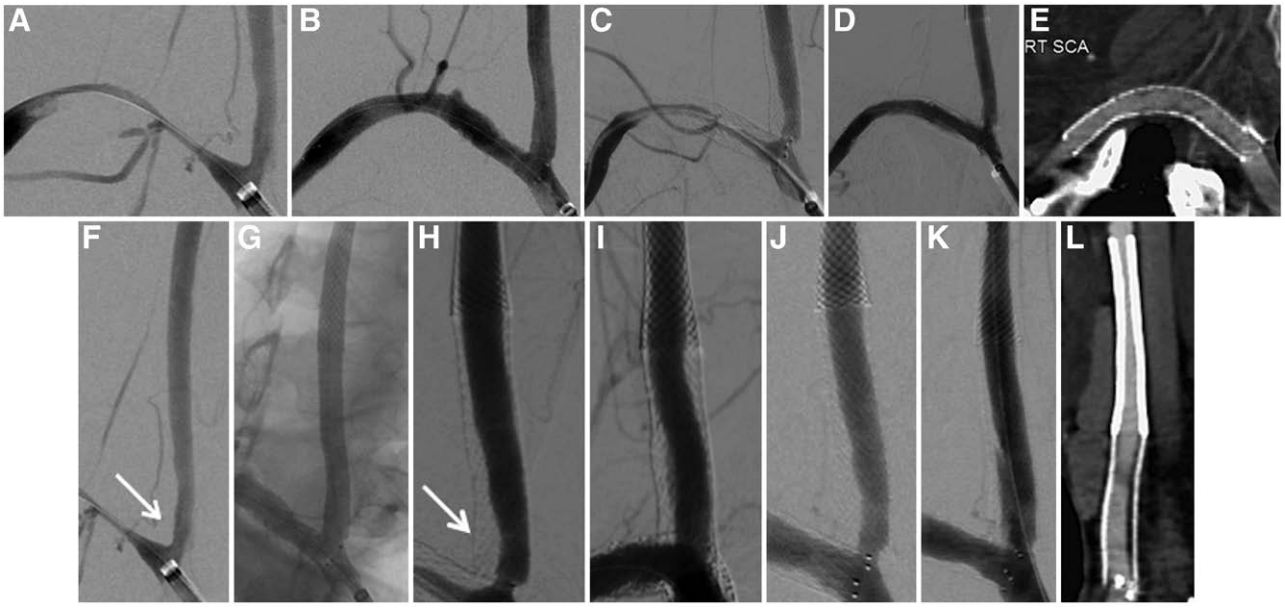

Fig. 2 A 36-year-old female with TA who experienced ipsilateral limb ischemia and visual impairment underwent PTAS in the right subclavian artery (A–E) and right CCA (F–L). A, Initial angiogram shows 95% stenosis in the right subclavian artery. B, Control angiogram after the first PTAS. C, At 1-year follow-up, in-stent restenosis is observed. D, Control angiogram after DEB angioplasty. E, CTA with curved multiplanar reconstruction (MPR) was performed at 32-month follow-up and the right subclavian artery appears patent. F, Initial angiogram shows 50% stenosis in the right proximal CCA (arrow). G, Control angiogram after the first PTAS. H, At 1-year follow-up, in-stent restenosis is observed (arrow). I, Control angiogram after uncoated balloon angioplasty. J, Follow-up angiogram at 5 months after uncoated balloon angioplasty shows restenosis at a proximal site. K, Control angiogram after DEB angioplasty. L, CTA with curved MPR was performed at 27-month follow-up and the right CCA appears patent. CCA = common carotid artery; CTA = computed tomography angiography; DEB = drug-eluting balloon; PTAS = percutaneous angioplasty and stenting; TA = Takayasu arteritis.

lesion location in TA differs from that in atherosclerosis. Bypass surgery of multiple intra-thoracic occlusive arteries is invasive and can be associated with more serious early postoperative complications than endovascular treatment. Meanwhile, endovascular treatment is a less invasive and reproducible method for relief of symptoms caused by stenotic lesions in TA patients, and is also more suitable for short-segment stenotic lesions in TA patients. Thus, to date, PTAS is recognized as an effective treatment of symptomatic stenosis of TA, although post-interventional immunosuppressive treatment is also strongly recommended.[1] Among the present cases, only half of the patients received short-term corticosteroid treatment, and none of the patients received immunosuppressive agents such as methotrexate. This may have contributed to the high incidence of restenosis that was observed.

In 2010, 50% of patients with symptomatic carotid artery stenosis who were enrolled in the International Carotid Stenting Study developed new DWI lesions after carotid stenting.[15] In addition, more than half of these patients were treated with cerebral embolic protection devices.[15] In the present study, all of the TA patients underwent unprotected PTAS, and only 20% of the patients had asymptomatic lesions detected by DWI afterwards. This rate is lower than that reported for patients with atherosclerotic carotid stenosis.[15] TA involves large vessel characterized by granulomatous inflammation of the vessel wall.[16] In its chronic stage, affected vessels are characterized by adventitial fibrosis, smooth muscle proliferation in the arterial intima, and arterial stenosis.[17] During PTAS for TA patients, neither thick subintimal plaques nor lipid cores are exposed to blood. Thus, unprotected PTAS in TA patients appears to be a safe procedure.

Reported rates of restenosis after endovascular treatment of supra-aortic arteries of TA patients range from 10% to 53%.[5,18,19] In the present study, the long-term follow-up restenosis rate was 54.5%. Meanwhile, depending on the definition of restenosis and the duration of follow-up, the rate of restenosis after atherosclerotic carotid artery stenting has been reported to range from 3% to 20%.[20–22] It has also been observed that restenosis is more frequently associated with carotid stenosis of TA patients than atherosclerotic carotid stenosis.[14] Based on these findings, close follow-up of TA patients after PTAS is strongly recommended.

The mechanistic details of in-stent restenosis after atherosclerotic carotid artery stenting involve neointimal proliferation and vascular remodeling which occur during the early postoperative stage (eg, 6 months to 2 years).[23] Recurrent atherosclerosis can subsequently develop during later stages of disease. In contrast with atherosclerotic carotid artery restenosis, restenosis in patients with TA is usually associated with reactive fibrosis, intimal thickening, neo-vascularization, and disease activity.[14] Stenotic lesions in TA, which tend to contribute to restenosis, also tend to be longer, proximally located, and complicated, rather than short and distal as observed in atherosclerotic carotid stenosis.[24] Vascular inflammation that is initiated by an antigen-specific immune reaction can also play a key role in restenosis after stenting.[25] After endovascular treatment, strict control of active disease is of paramount importance to influence long-term outcome. Use of a paclitaxel-coated balloon with stent implantation has been shown to effectively inhibit restenosis after coronary angioplasty.[26] Paclitaxel acts on the arterial wall by altering cytoskeleton proteins in cells and irreversibly inhibiting proliferation of arterial smooth muscle cells. Similarly, restenosis in patients with TA is caused by smooth muscle cell proliferation. Therefore, use of a DEB may be appropriate for treatment of refractory restenosis in TA. In 2012, Spacek et al.[27] treated a TA patient with refractory in-stent restenosis in carotid artery with a DEB angioplasty. Thirty months later, the stent remained patent. Similarly, Yamamoto et al.[28] reported a 19-year-old TA female patient with refractory renal artery in-stent restenosis who underwent treatment with DEB angioplasty. At the 2-year follow-up, the patient had achieved a good clinical outcome. In the present study, we also applied DEB angioplasty

to treat a TA patient with refractory restenosis. Overall, these results and the mechanism of restenosis in TA patients indicate that DEB angioplasty is a promising therapy for TA patients.

A key limitation of the present study was the small number of cases examined. This is primarily due to the rarity of medically refractory TA cases. Different locations and varying severity of the stenotic lesions examined, as well as non-standardized follow-up periods for each patient, also made an analysis of the cases difficult. However, the present findings do indicate that PTAS is a safe and effective method for relieving symptoms of symptomatic stenosis of the supra-aortic arteries in TA patients, despite a high restenosis rate. We suggest that a prospective study employing a standard clinical and imaging protocol, as well as use of DEBs for treatment of restenosis, should be conducted to evaluate and confirm the present results.

In conclusion, the present results indicate that PTAS for supra-aortic arteries stenosis in TA patients is a safe and effective method, yet is accompanied by a high restenosis rate. It is recognized that TA patients should receive aggressive medical treatment upon diagnosis, with a subsequent goal of achieving strict control of disease activity before and after endovascular intervention. Our present results suggest that use of both inflammatory marker detection and HR-VWI for pre-procedural patient selection will facilitate treatment when a patient needs intervention. We also recommend DEB angioplasty for treatment of refractory in-stent restenosis.

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REFERENCES

1. Keser G, Direskeneli H, Aksu K. Management of Takayasu arteritis: a systematic review. *Rheumatology (Oxford)* 2014;**53**:793–801.
2. Direskeneli H, Aydin SZ, Merkel PA. Assessment of disease activity and progression in Takayasu's arteritis. *Clin Exp Rheumatol* 2011;**29**(1 Suppl 64):S86–91.
3. Nastri MV, Baptista LP, Baroni RH, Blasbalg R, de Avila LF, Leite CC, et al. Gadolinium-enhanced three-dimensional MR angiography of Takayasu arteritis. *Radiographics* 2004;**24**:773–86.
4. Chen B, Yu HX, Zhang J, Li XX, Wu XG, Yang SJ, et al. Endovascular revascularization for carotid artery occlusion in patients with Takayasu arteritis. *Eur J Vasc Endovasc Surg* 2015;**49**:498–505.
5. Kim YW, Kim DI, Park YJ, Yang SS, Lee GY, Kim DK, et al. Surgical bypass vs endovascular treatment for patients with supra-aortic arterial occlusive disease due to Takayasu arteritis. *J Vasc Surg* 2012;**55**:693–700.
6. Johnston SL, Lock RJ, Gompels MM. Takayasu arteritis: a review. *J Clin Pathol* 2002;**55**:481–6.
7. Kernan WN, Ovbiagele B, Black HR, Bravata DM, Chimowitz MI, Ezekowitz MD, et al; American Heart Association Stroke Council, Council on Cardiovascular and Stroke Nursing, Council on Clinical Cardiology, and Council on Peripheral Vascular Disease. Guidelines for the prevention of stroke in patients with stroke and transient ischemic attack: a guideline for healthcare professionals from the American Heart Association/American Stroke Association. *Stroke* 2014;**45**:2160–236.
8. Wen D, Du X, Ma CS. Takayasu arteritis: diagnosis, treatment and prognosis. *Int Rev Immunol* 2012;**31**:462–73.
9. Saadoun D, Lambert M, Mirault T, Resche-Rigon M, Koskas F, Cluzel P, et al. Retrospective analysis of surgery versus endovascular intervention in Takayasu arteritis: a multicenter experience. *Circulation* 2012;**125**:813–9.
10. Perera AH, Mason JC, Wolfe JH. Takayasu arteritis: criteria for surgical intervention should not be ignored. *Int J Vasc Med* 2013;**2013**:618910.
11. Sueyoshi E, Sakamoto I, Uetani M. MRI of Takayasu's arteritis: typical appearances and complications. *AJR Am J Roentgenol* 2006;**187**:W569–75.
12. Choi YJ, Jung SC, Lee DH. Vessel wall imaging of the intracranial and cervical carotid arteries. *J Stroke* 2015;**17**:238–55.
13. Papa M, De Cobelli F, Baldissera E, Dagna L, Schiani E, Sabbadini M, et al. Takayasu arteritis: intravascular contrast medium for MR angiography in the evaluation of disease activity. *AJR Am J Roentgenol* 2012;**198**:W279–84.
14. Min PK, Park S, Jung JH, Ko YG, Choi D, Jang Y, et al. Endovascular therapy combined with immunosuppressive treatment for occlusive arterial disease in patients with Takayasu's arteritis. *J Endovasc Ther* 2005;**12**:28–34.
15. Bonati LH, Jongen LM, Haller S, Flach HZ, Dobson J, Nederkoorn PJ, et al.; ICSS-MRI study group. New ischaemic brain lesions on MRI after stenting or endarterectomy for symptomatic carotid stenosis: a substudy of the International Carotid Stenting Study (ICSS). *Lancet Neurol* 2010;**9**:353–62.
16. Serra R, Butrico L, Fugetto F, Chibireva MD, Malva A, De Caridi G, et al. Updates in pathophysiology, diagnosis and management of Takayasu arteritis. *Ann Vasc Surg* 2016;**35**:210–25.
17. Espinoza JL, Ai S, Matsumura I. New insights on the pathogenesis of Takayasu arteritis: revisiting the microbial theory. *Pathogens* 2018;**7**.
18. Lee TH, Chen IM, Chen WY, Weng CF, Hsu CP, Shih CC. Early endovascular experience for treatments of Takayasu's arteritis. *J Chin Med Assoc* 2013;**76**:83–7.
19. Kim HJ, Lee CS, Kim JS, Know SU, Kim JL, Park JW, et al. Outcomes after endovascular treatment of symptomatic patients with Takayasu's arteritis. *Interv Neuroradiol* 2011;**17**:252–60.
20. Bonati LH, Ederle J, McCabe DJ, Dobson J, Featherstone RL, Gaines PA, et al; CAVATAS Investigators. Long-term risk of carotid restenosis in patients randomly assigned to endovascular treatment or endarterectomy in the Carotid and Vertebral Artery Transluminal Angioplasty Study (CAVATAS): long-term follow-up of a randomised trial. *Lancet Neurol* 2009;**8**:908–17.
21. Arquizan C, Trinquart L, Touboul PJ, Long A, Feasson S, Terriat B, et al; EVA-3S Investigators. Restenosis is more frequent after carotid stenting than after endarterectomy: the EVA-3S study. *Stroke* 2011;**42**:1015–20.
22. Eckstein HH, Ringleb P, Allenberg JR, Berger J, Fraedrich G, Hacke W, et al. Results of the stent-protected angioplasty versus carotid endarterectomy (SPACE) study to treat symptomatic stenoses at 2 years: a multinational, prospective, randomised trial. *Lancet Neurol* 2008;**7**:893–902.
23. Dai Z, Xu G. Restenosis after carotid artery stenting. *Vascular* 2017;**25**:576–86.
24. Jeong HS, Jung JH, Song GG, Choi SJ, Hong SJ. Endovascular balloon angioplasty versus stenting in patients with Takayasu arteritis: a meta-analysis. *Medicine (Baltimore)* 2017;**96**:e7558.
25. Furukawa Y, Tamura T, Toma M, Abe M, Saito N, Ehara N, et al. Sirolimus-eluting stent for in-stent restenosis of left main coronary artery in Takayasu arteritis. *Circ J* 2005;**69**:752–5.
26. Scheller B, Speck U, Abramjuk C, Bernhardt U, Böhm M, Nickenig G. Paclitaxel balloon coating, a novel method for prevention and therapy of restenosis. *Circulation* 2004;**110**:810–4.
27. Spacek M, Zimolova P, Veselka J. Takayasu arteritis: use of drug-eluting stent and balloon to treat recurring carotid restenosis. *J Invasive Cardiol* 2012;**24**:E190–2.
28. Yamamoto T, Shirai K, Okamura K, Urata H. Two years efficacy of paclitaxel-coated balloon dilation for in-stent renal artery restenosis due to Takayasu arteritis. *Am J Case Rep* 2019;**20**:1089–93.