◆ CLINICAL INVESTIGATION ◆

Endovascular Therapy Combined With Immunosuppressive Treatment for Occlusive Arterial Disease in Patients With Takayasu's Arteritis

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Purpose: To evaluate the feasibility and efficacy of endovascular therapy combined with immunosuppression for the treatment of arterial occlusive disease in patients with Takayasu's arteritis (TA).

Methods: From January 1998 to June 2003, 25 patients (22 women; age 37.8±15.5 years) with TA were treated with angioplasty for symptomatic lesions or with a hemodynamically significant aortic narrowing. The patients with active disease, defined as an increase in inflammatory markers (e.g., erythrocyte sedimentation rate [ESR]), were treated with immunosuppressive agents before intervention. Angioplasty was performed after the ESR had been normalized.

Results: In the 25 patients, 58 vascular territories (7 aortic, 9 carotid, 3 vertebral, 11 subclavian, 2 superior mesenteric, 18 renal, 4 iliac, and 4 coronary arteries) were treated with angioplasty only (19 lesions) or with stents (39 lesions). The mean ESR when the vascular lesions were initially diagnosed was 35.6±26.2 mm/h, which fell to 18.5±7.8 mm/h after immunosuppressive therapy. The endovascular procedure was performed successfully in 52 (90%) of 58 lesions. During the mean 23.7±18.4-month follow-up, 9 (17%) treated segments restenosed; 4 were treated with repeat angioplasty. The overall cumulative primary clinical success rate was 82%; secondary clinical success was 90%.

Conclusions: Endovascular therapy for stenotic lesions in patients with TA is safe and effective when disease activity is strictly controlled with immunosuppressive treatment.

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Key words: Takayasu's arteritis, vasculitis, angioplasty, stents, immunosuppressive agents

Endovascular management has become an established treatment for atherosclerotic occlusive diseases, but relatively few studies have dealt with interventional treatment of vasculitic disorders. Takayasu's arteritis (TA) is a chronic inflammatory disease of unknown etiology that involves the aorta, its major branches, and the pulmonary arteries. The disease leads to stenosis/occlusion or aneurysm formation or both.[1,2] The management of TA is challenging. Steroids and immunosuppressive agents have been used with variable success.[3,4] Revascularization procedures are usually performed for significant stenotic

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lesions.[5] Initial reports revealed excellent results of percutaneous transluminal angioplasty (PTA) in patients with TA.[6–8] However, restenosis remains a major concern with PTA.[9,10] Stent-supported angioplasty achieves better luminal diameter and lowers the rate of restenosis.[11,12] At present, most publications on stent-supported PTA in Takayasu's arteritis are isolated case reports or small series.[13–15] We report our experience with 25 TA patients who underwent endovascular therapy combined with immunosuppressive treatment for stenotic lesions in various vascular territories.

METHODS

Patient Sample and Treatment Indications

Twenty-five patients (22 women; mean age 37.8±15.5 years, range 9–68) with angiographically proven TA underwent endovascular treatment of arterial occlusive disease between January 1998 and June 2003. All patients fulfilled the American College of Rheumatology classification criteria for TA.[16] Angiographic findings based on the International Collaborative Study Group[17] were classified as type I in 4 patients (involving the coronary artery in 2), type IIb in 1, type III in 3, type IV in 5 (1 with a coronary lesion), and type V in 12 (3 had coronary lesions).

Indications for angioplasty included symptomatic stenosis >70% of the reference diameter in arteries or a hemodynamically significant aortic narrowing (peak systolic pressure gradient >50 mmHg across the stenotic lesion). Stenting was performed for ostial lesions, chronically occluded vessels, long-segment lesions, inadequate dilation, or dissection following angioplasty. An informed written consent was obtained from all patients prior to the procedure.

Patients with active disease judged by systemic features, e.g., fever, musculoskeletal pains, or elevated erythrocyte sedimentation rate (ESR), received immunosuppressive therapy before the endovascular treatment. The ESR was measured by the Westergren method (Espette, Korea; reference range <15 mm/h in men and <20 mm/h in women). Prednisolone (1 mg/kg/d) was used as the first-line immunosuppressive drug; in patients unresponsive to steroid, methotrexate (7.5 mg/wk) was added. The doses of immunosuppressive agents were adjusted according to the ESR and clinical status of the patients. Angioplasty was performed after the ESR had been normalized in these patients.

Angioplasty Techniques

All patients undergoing angioplasty were given aspirin (100 mg/d) and ticlopidine (250 mg bid for stenting) prior to the procedure. Using standard catheterization techniques, arterial access was obtained (21 femoral, 1 brachial, and 3 femoral-brachial). Intravenous heparin was administered during the procedure to maintain an activated coagulation time between 250 and 300 seconds. In general, balloons were inflated with increasing pressure until the waist on the balloon disappeared; tandem dilations were used for long-segment lesions. Stents were deployed using the rolling membrane delivery device or over-the-balloon technique; the stents were postdilated with high-pressure inflations.

For aortic angioplasty, the lesion was crossed with a 0.035-inch hydrophilic guidewire (Terumo, Tokyo, Japan), which was exchanged for a similarly sized extra-stiff guidewire (Cook, Bloomington, IN, USA). Angioplasty of the stenotic segment was done using 14 to 18-mm-diameter Medi-tech XXL balloons (Boston Scientific, Natick, MA, USA) or a 7 to 12-mm UDT balloon (Boston Scientific). In the aorta, 10×80-mm SMART stents (Cordis, a Johnson & Johnson company, Warren, NJ, USA) or 22 to 25-mm by 40 to 60-mm nitinol stents (Taewoong, Seoul, Korea) were implanted. High pressure (14 to 18 atmospheres) was required to optimally dilate the lesions.

For aortic arch vessels, a Shuttle sheath (Cook) was placed near the lesion, which was crossed with a 0.018-inch extra-support Roadrunner guidewire (Cook). The lesion was dilated with 4 to 6-mm by 20 to 40-mm balloons (Symmetry or UDT, Boston Scientific; Powerflex, Cordis); a variety of stents ranging from 6 to 8 in diameter by 13 to 43 mm long were used: Palmaz (Cordis), SMART (Cordis), Corinthian (Cordis), Easy Wallstent (Boston Scien-

TABLE
Comparison of Diameter Stenosis Before and After Angioplasty With or Without Stenting in 25 Patients With Takayasu's Arteritis

Arteries	Diameter Stenosis, %		
	Pre	Post	p
Aorta (n=7)	69.6±13.0	34.6±14.8	0.002
	(69.9±36.6*)	(17.0±12.9*)	(0.004)
Carotid (n=9)	82.7±11.4	15.3±18.2	0.002
Vertebral (n=3)	73.3±5.8	20.0±26.5	0.094
Subclavian (n=11)	84.1±12.6	18.2±19.8	<0.001
Mesenteric (n=2)	75.0±7.1	25.0±35.4	0.242
Renal (n=18)	85.8±8.3	17.2±19.3	<0.001
Common iliac (n=4)	75.0±10.0	17.5±12.6	0.014
Coronary (n=4)	79.3±7.1	7.0±3.7	<0.001

* Peak systolic pressure gradient, mmHg.

tific), or Jostent (Jomed GmbH, Rangendingen, Germany). The maximum dilation pressures were 4 to 15 atmospheres; stents were postdilated at 6 to 15 atmospheres. Small vessels or severe lesions <4 mm long were predilated with coronary balloons (Adante; Boston Scientific); later, larger peripheral angioplasty balloons were used. Coronary stents (NIR; Boston Scientific) were used in the vertebral artery. In the patients with renal artery stenosis, a guiding catheter was placed into the renal artery ostium, and a 0.018-inch guidewire was introduced into the lesion. Peripheral balloon catheters ranged from 4 to 7 mm by 10 to 40 mm, and the stents measured 6 to 9 mm by 12 to 20 mm. Maximum inflation pressures were 10 to 18 atmospheres.

In patients receiving stents, ticlopidine was administered for 1 month. Aspirin was continued indefinitely after the procedure in all patients. After endovascular treatment, the dosage of immunosuppressive drugs in patients with active disease was adjusted to maintain the serum ESR level within the normal range.

Definitions and Follow-up

An intervention was considered technically successful if the residual stenosis was <30% or the pressure gradient across the lesion was <50% of the value before treatment. Surveillance was conducted every 3 months in our outpatient clinic. Long-term success of the endovascular procedure was documented by angiography, computed tomography (CT), magnetic resonance angiography (MRA), or color-flow duplex ultrasound (CDU). Symptom recurrence and hemodynamic changes were primary criteria for clinical assessment of restenosis. Detailed criteria for restenosis relative to each vascular territory were: hypertension, lower limb claudication, or congestive heart failure for aortic lesions; syncope, dizziness, transient ischemic attack, or stroke for the carotid and vertebral lesions; arm claudication, decreased pulsation, or systolic pressure differential between the arms for subclavian lesion; nausea, vomiting, or abdominal pain for the mesenteric lesions; hypertension or renal insufficiency for the renal lesions; and chest pain for the coronary lesions.

RESULTS

Mean duration of immunosuppressive therapy prior to endovascular treatment in the 16 patients with active disease was 17.6±21.5 days (range 3–66). The mean ESR at diagnosis was 35.6±26.2 mm/h (range 2–106), which fell to 18.5±7.8 mm/h (range 2–32) after the immunosuppressive therapy. In all 25 patients, 54 stenoses and 4 occlusions were treated using endovascular techniques in the aorta (n=7), the coronary arteries (n=4), and various peripheral vessels (n=47, Table). Angioplasty alone was performed in 19 lesions (Fig. 1); 39 arteries received stents (Fig. 2). Final angiography performed immediately after inter-

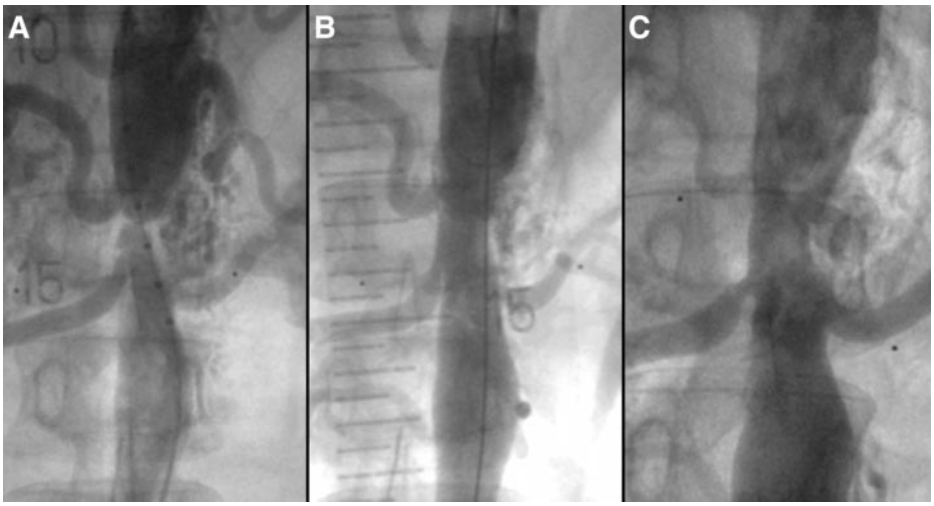

Figure 1 ◆ (**A**) The aortogram of a 30-year-old man with severe hypertension and claudication shows a severe stenosis of the abdominal aorta. The peak pressure gradient across the lesion was 41 mmHg. (**B**) Aortogram after balloon angioplasty with an 18×20-mm Medi-tech XXL balloon revealed marked improvement of the aortic lumen. There was no residual pressure gradient. (**C**) At the follow-up 8 months later, the abdominal aortic lumen is maintained without restenosis.

vention revealed a successful initial result in 52 (90%) of 58 lesions. Three of the 4 total occlusions were successfully recanalized, and 53 (98%) of 54 stenoses were reduced. Angioplasty could not be performed in 1 total occlusion and 1 web-like stenosis. The procedure was also suboptimal (residual diameter stenosis >30%) in 4 stenotic lesions. There were no major complications, such as acute thrombosis, severe dissection, stroke, myocardial infarction, emergency surgery, or death.

During a mean 16.8±12.9-month follow-up (range 6–43), 35 (67%) of the 52 successfully treated lesions were followed using angiography (n=27), CT (n=3), MRA (n=3), or CDU (n=2). Nine patients with 17 lesions declined further imaging. Restenoses occurred in 9 vascular lesions (9/35, 26%). Clinical symptoms recurred in 1 patient in whom restenosis was confirmed angiographically. Six (46%) of the restenoses were in the 13 lesions that were initially successfully dilated; the other 3 recurrences were in-stent restenoses (8% of the 22 stented lesions objectively evaluated). Four of 9 restenoses were treated successfully with repeat angioplasty. The cumulative primary clinical success rate for the 35 successfully treated lesions that were objectively evaluated at a mean 17-month follow-up was 80%±8% (±standard error). Repeat dilation in 4 lesions led to a cumulative secondary success rate of 86%±7%.

DISCUSSION

The treatment modalities of TA usually include medical therapy with steroids or the combination of immunosuppressive agents and revascularization procedures.[3,4,6] In the chronic stage, the principle of treatment is revascularization of the affected organ either by surgery or angioplasty.[6,9,15,18] Surgical bypass of the stenosed segment is oftentimes complicated by graft reocclusion, anastomotic site aneurysm, and morbidity.[5,19] In general, the progressive inflammatory nature of the disease has precluded widespread use of reconstructive surgery. Angioplasty offers a less invasive, cost-effective, and safe method for relief of stenotic lesions in patients with TA.[12]

The initial technical success rate of angioplasty in TA is usually high. Deyu et al.[20] achieved an 89.2% initial success rate and symptomatic improvement in renal stenoses due to TA. Sharma et al.[21] reported a technical

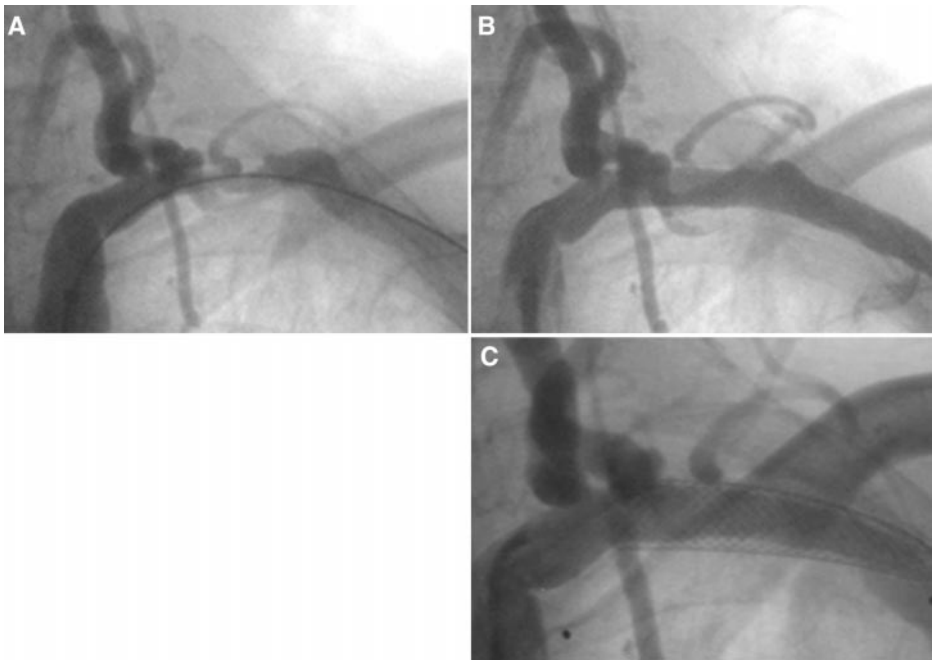

Figure 2 ◆ (**A**) Left subclavian artery stenosis in a 66-year-old woman suffering from left arm claudication. (**B**) Angiogram after a self-expanding Easy Wallstent (8×40-mm) was implanted; there is no residual stenosis. (**C**) The follow-up angiogram 43 months later revealed a patent stent with minimal neointimal hyperplasia. There was no pressure gradient across the stent, and good distal flow was observed.

success rate of ~95% combined with a clinical success rate of 89% after renal angioplasty. In obstructions of the subclavian artery, initial success rates of 86.5%[22] and 81%[8] have been observed after PTA. In a study concerning stent-supported PTA in aortic stenosis due to TA, intervention was initially successful in all treated patients.[13] The 90% technical success rate achieved in our patients is comparable with previous studies involving this pathology.

Our results demonstrate that endovascular treatment of occlusive arterial lesions due to TA is safe and feasible, with high technical success and no procedure-related morbidity. However, atherosclerotic lesions seem to respond better to dilation, as proven in a study by Tyagi et al.[22] They documented a 15.5% residual stenosis after subclavian artery PTA in Takayasu's arteritis compared with only 8.3% residual stenosis in atherosclerotic lesions. In our study, residual stenosis after PTA in subclavian arteries was 18.2%.

Initial technical results in vasculitic lesions are promising, but restenosis still remains a major concern. Both et al.[23] reported a cumulative primary patency rate of 67.6% in different forms of vasculitis. In previous studies concerning PTA in obstructive vascular lesions due to TA, restenosis was seen in 16% to 25% of all lesions treated successfully at initial angioplasty.[20–22] In meta analyses of PTA in atherosclerotic lesions, restenosis rates seemed relatively lower than in TA: 17%[24] after renal artery stenting and 3% after stenting in subclavian arteries.[25]

Thus, our approach included strict control of active disease with the administration of immunosuppressive agents before and after the endovascular treatment. The intensity and duration of the immunosuppressive regimen were determined according to each patient's clinical condition and disease activity. Prednisolone was given to all patients with elevated ESR before endovascular treatment; methotrexate was added if a patient was unresponsive to steroids. Because no single cytotoxic drug appears to be better than any

other in terms of efficacy, side-effect profiles have been an important driving force in determining treatment. Steroid and methotrexate have been reported to be useful and well-tolerated,[26] and this protocol was successful in lowering the ESR before intervention in our study. Moreover, the ≥80% patency rates in the subset of patients undergoing periodic imaging up to a mean of 17 months suggest that endovascular treatment combined with immunosuppressive therapy is a promising therapeutic regimen in TA.

In summary, endovascular treatment is a safe and effective treatment of occlusive arterial disease in patients with TA. Before and after endovascular treatment, disease activity should be strictly controlled with immunosuppressive therapy. However, further long-term study with a larger population is needed to confirm the long-term efficacy of this modality as a treatment for occlusive arterial disease due to Takayasu's arteritis.

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