Overview of Late Outcome of Medical and Surgical Treatment for Takayasu Arteritis

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Takayasu arteritis (TA), which is a nonspecific inflammatory disease of unknown origin, causes various types of aortoarterial stenosis/occlusion or dilatation (Figure). Historically, Mikito Takayasu, a Japanese ophthalmologist, described a peculiar wreathlike arteriovenous anastomosis around the papillae of the retina (Takayasu disease) in 1908.1 In the first necropsy case reported in 1940, this ophthalmologic finding was related to cervical vessel occlusion.2,3 Subsequently, this nonspecific panarteritis that affects the intima and the adventitia of the aorta and its main branches was called Takayasu arteritis. Its clinical manifestations are varied and related to the vessel that presents the stenotic or occlusive lesions, such as the aortic arch (pulseless disease),4 descending thoracic or abdominal aorta (atypical coarctation),5 renal arteries,6 coronary arteries,7 and pulmonary arteries. Aortic aneurysm8 and aortic valve regurgitation with ascending aortic dilatation9 may also develop in some instances. Pharmacological treatment with corticosteroids is usually the initial treatment. Some patients require surgical treatment such as bypass grafting and graft replacement or endovascular repair including percutaneous transluminal angioplasty (PTA) and stent grafting, even in the active phase or in the inactive chronic phase with adequate control of the inflammation. Since the 1960s, acceptable early and midterm outcomes of medical and/or surgical treatment have been published. However, the long-term outcome, including that of recently developed endovascular treatment, has not been discussed. In this article, we describe an overview, particularly focusing on the late outcome of treatment for TA.

Methods

Some clinical data in our institute were used in addition to the other authors’ data taken from the references. Our clinical data were published after the approval of the institutional review board in our institute. All of the clinical practices in our institute were performed under the national health insurance program. Each patient gave informed consent to receive the treatment and to serve as a subject under the national health insurance program. Each patient gave informed consent and the approval of the institutional review board in their institutes, as stated in the references.

Results

Incidences and Origin

One of the characteristic features of TA is its predominance in young women. A Japanese nationwide survey demonstrated that 90% of the patients were women,10 although an international survey showed a lower female to male sex ratio even in other Asian countries such as China, India, and Israel and in Western countries.2,3 Another epidemiological feature is the ethnic difference. TA is prevalent in Asian countries and Latin America, although it is reportedly distributed worldwide. It is extremely rare in white people.11 Furthermore, there are also some differences in the sites affected by aortoarteritis among different countries. In Japanese patients, the ascending aorta and aortic arch with its branches are more frequently involved, whereas in patients from Korea, India, and Western countries, the abdominal aorta and renal arteries are most frequently affected.12 Consequently, aortic regurgitation used to be the main cause of mortality of Japanese patients, and cerebrovascular accidents relating to hypertension have been the cause of death in other countries.12–15

Although the pathogenesis of TA has long been studied, its cause remains uncertain. In the early years, infection was advocated as its cause,2,3,16 and the relation between TA and tuberculosis was suspected.17 Since the 1960s, autoimmunity has been considered to be involved in its pathogenesis.18 However, the antigens responsible for inciting these events have not been identified. Currently, TA is widely recognized as a multifactorial disease that occurs predominantly in young women and in the Orient. Furthermore, 10 pairs of identical twins having TA have been reported.18 Its characteristic clinical features indicate an important role of genetic factors in its pathogenesis.20 In fact, a significant association with Bw52 and DR12 antigens was found in 50% of Japanese patients, although the finding was not confirmed in Western countries.21 In addition, a high frequency of the same haplotype of HLA A24-B52-DR2 was found in TA and inflammatory abdominal aortic aneurysm.22 Interestingly, patients with this haplotype are prone to experience an accelerated progression
of the inflammation, which tends to be refractory to antiinflammatory therapy. Further investigations are still required to elucidate the pathogenesis of TA.

Diagnosis
TA is an uncommon disease, even in Asian countries. The disease onset is insidious, and prominent symptoms are nonspecific or absent in two thirds of the patients in the early stage. Diagnosis is then delayed, particularly in the pediatric population. Clues for the diagnosis are hypertension, vascular bruits, asymmetrical arm blood pressure, and other ischemic symptoms. The criteria of Ishikawa in 1988 have been widely applied, which consist of 1 obligatory criterion (age <40 years), 2 major criteria (left and right mid subclavian artery lesions), and 9 minor criteria (high erythrocyte sedimentation rate, common carotid artery tenderness, hypertension, aortic regurgitation or annuloaortic ectasia, and lesions of the pulmonary artery, left mid common carotid artery, distal brachiocephalic trunk, thoracic aorta, and abdominal aorta).

Angiography used to be the most valuable tool for the diagnosis and classification of TA. Modern noninvasive diagnostic modalities including computed tomography scanning and magnetic resonance angiography, which have replaced angiography, allow an early and easy detection of the details of vascular lesions in 3-dimensional images. Magnetic resonance angiography is advocated in the pediatric field because it avoids the use of radiation and of an important quantity of nephrotoxic contrast media. It allows the measurement of arterial wall thickness and edema due to acute phase TA. However, it also has some limitations in detecting lesions of visceral and renal arteries and the supra-aortic trunk. As an updated diagnostic tool, fluorodeoxyglucose positron emission computed tomographic imaging coregistered with enhanced computed tomographic imaging has been developed. This tool allows the visualization of the distribution of lesions and inflammatory activity in the aorta, its branches, and the pulmonary arteries in active TA, with weak fluorodeoxyglucose accumulation, which decreases as inflammation disappears in response to therapy. In monitoring TA activity, serum C-reactive protein concentration and an erythrocyte sedimentation rate have generally been used. However, these are nonspecific inflammatory markers and therefore lack sensitivity and specificity. Matrix metalloproteinases are reportedly useful markers of disease activity. Matrix metalloproteinase 2 can be helpful in diagnosing TA, and matrix metalloproteinases 3 and 9 serve as activity markers. It is also important to differentiate TA from other similar diseases such as giant cell arteritis, atherosclerotic disease, congenital coarctation of the aorta, and Behçet’s disease.

Pathology and Classification
Nasu summarized the criteria for the pathological diagnosis of TA. One of the characteristic findings is a “skipped lesion” consisting of a mixture of both active, productive inflammatory lesions and old fibrous lesions. Inflammation originates in the vasa vasorum followed by cellular infiltration composed mainly of T cells invading the outer layer of the media and/or its neighboring adventitia. Once the inflammation invades the intima, edematous changes occur, resulting in infiltration of lipids and blood cells. Eventually, these inflam-
matory changes cause atherosclerosis. Calcification and a thickened intima are also characteristic. It is then difficult to differentiate TA from atherosclerosis. Calcification, a useful index of aging, is found >5 years after the onset of the disease. With the rapid progression of these changes, the artery or aorta becomes dilated, forming aneurysms. Healed lesions show progressive intimal and adventitial fibrosis. The histological pattern is classified into granulomatous type, diffuse proliferative type, and fibrous type.\(^{35}\) Documentation of atherosclerotic complications in young females generally free from atherosclerotic risk factors may constitute clinical evidence of the importance of inflammation as a risk factor for atherogenesis.\(^{33}\) TA has recently been shown to affect the parenchyma of various organs: mesangial proliferative, membranoproliferative, crescentic glomerulonephritis, and amyloidosis.\(^{34}\) Dilated cardiomyopathy, myocarditis, and periarteritis nodosa have also been reported.

The disease is subdivided into the early or active phase and the late, chronic, or inactive phase. Nakao et al\(^{15}\) first proposed a classification based on angiographic findings, and Ueno et al\(^{36}\) revised it, stressing the clinical significance of aneurysms. After that, TA was classified into 4 types:\(^{37}\) lesions in the arch and its branches, “pulsatile disease” (type I), the descending and abdominal aorta and its branches, “ataypical coarctation” (type II), manifestation of features of type I and II (type III), and combination of features type I through III with pulmonary artery disease (type IV). At the XIth International Conference on TA in 1994, a newer classification was established: the aortic branches are involved (type I); the ascending aorta, arch, and its branches (type IIa); the ascending aorta, arch with its branches, and thoracic descending aorta (type IIb); the thoracic descending aorta, abdominal aorta, and/or renal arteries (type III); only the abdominal aorta and/or renal arteries (type IV); and the combined features of type IIb and IV (type V). A comparison of affected lesions showed that the incidence of types I and IIa was higher in Japan, whereas the incidence of type IV was higher in India.\(^{38}\) Among the aortic arch vessels, the left subclavian artery was affected in 60%, followed by the left common carotid artery in 40%, and the innominate artery in 19%. Among the patients, 28% had abdominal aortic lesions, 13% had renal arteries lesions, and 15% had pulmonary arteries lesions.\(^{39}\) Coronary artery involvement was first demonstrated at necropsy in 1951.\(^{40}\) Further postmortem studies have revealed coronary artery disease in 9% to 10% of patients.\(^{40}\) The predominant lesions were on the coronary orifices, as indicated by the presence of intimal hypertrophy. Occlusion of the proximal ostium of the anastomosis resulting from intimal hypertrophy is the most frequent problem in coronary artery bypass grafting. A Japanese institute reported 38.3% of coronary artery involvement in TA.\(^{41}\) The ostium was most frequently affected in 87.5%. Kimoto\(^{2}\) was the first to describe aneurysm as a complication of TA. In the phase of acute progression, destruction of the arterial media leads to aneurysmal dilatation.\(^{42}\) Aneurysmal disease reportedly occurs with much higher frequency in Asian countries than in Western countries.\(^{20,21,43}\) In a Japanese angiographic study of 113 patients with TA,\(^{42}\) fusiform or saccular aneurysms were found in 31.9%. Aortic regurgitation also develops and is a risk factor for mortality in Japan.\(^{8,44}\) In the previous Japanese nationwide epidemiological surveys, the occurrence of aortic regurgitation was 19% for the 1973–1975 period and 24.8% for the 1982–1984 period.\(^{10}\) Aortic regurgitation occurs primarily because of annular or ascending aortic dilatation.\(^{9,44}\) Its secondary mechanism is aortic valve change due to TA, including fibrous thickening, rolling, retraction, and calcification. Aortic regurgitation is progressive, and therefore surgical treatment is often required. Hypertension develops frequently as a result of reduced elasticity of the arterial wall (wind-kettle), atypical coarctation (proximal hypertension), and renovascular stenosis (renovascular hypertension). The association rate of hypertension was 55.7% in Japan during the 1982–1984 period,\(^{10}\) and it constitutes a substantive problem in regard to the long-term prognosis because prolonged hypertension results in cerebrovascular accident, congestive heart failure, aneurysmal dilatation, and rupture.\(^{10}\)

**Treatment**

According to the 1982–1984 Japanese survey, pharmacological treatment was predominantly provided, whereas surgery was attempted in 13.3% (pharmacological in 75.2%, pharmacological and surgical in 11.7%, surgical in 1.6%, no treatment in 3.9%, and unknown in 7.7%).\(^{10}\) Because of recent technical advances, the most common treatment at present has shifted slightly toward prompt surgery or less invasive endovascular treatment such as angioplasty or updated endovascular aneurysmal repair.

**Medical Treatment**

Corticosteroids are still used in the active phase of TA. There is evidence that adequate, long-term prednisolone therapy contributes to an angiographic improvement.\(^{45,46}\) The guidelines established in 1987 by the Systemic Vascular Disorders Research Committee from the Ministry of Health and Welfare of Japan consist of 2 parts: the first deals with antiinflammatory treatment with adrenocorticosteroids and the second with treatments for thrombosis and hypertension.\(^{47}\)

**Antiinflammation**

The guidelines recommend 30 mg/d of adrenocorticosteroids as the initial dose for adult patients with active TA.\(^{47}\) The initial dose is tapered at a rate of 5 mg every 2 weeks down to 10 mg and thereafter at a rate of 2.5 mg every 2 weeks until withdrawal or to the minimum required dose to control inflammation, while the erythrocyte sedimentation rate and serum C-reactive protein concentration are monitored. When withdrawal from corticosteroids is difficult, immunosuppressive drugs such as cyclophosphamide or azathioprine are used.\(^{47}\) The efficacy of other immunosuppressive agents including methotrexate,\(^{48}\) mycophenolate mofetil,\(^{49}\) and infliximab\(^{50}\) has been described. In case of persistent inflammation, even in the chronic phase, the administration of corticosteroids should be continued to control systemic inflammation with <1.0 mg/dL of serum C-reactive protein concentration and 20 mm/h of erythrocyte sedimentation.\(^{47}\)

**Other Treatments Including Antithrombosis and Antihypertension**

The active phase of TA is often complicated by thrombosis in the affected vessels with stenotic/occlusive lesions.\(^{31}\) In the
active phase, platelets may be sensitive not only to collagen but also to prostacyclin because of endothelial dysfunction. Plasma thromboxane B2 levels are higher, whereas cAMP levels are lower. Long-term aspirin therapy is then recommended to prevent thrombus formation in vessels with endothelial damage. Antihypertensive agents are frequently used because 70% of the patients have hypertension related to atypical coarctation or renovascular hypertension. In the 1982–1984 Japanese nationwide survey, the pharmacological treatment was found to include aspirin and antiplatelet agents as well as adrenocorticosteroids (54.1%), hypotensive agents consisting of calcium antagonists, β-blockers, and hypotensive diuretics, cardiac glycoside, coronary vasodilator agents, and other agents.

**Percutaneous Transluminal Angioplasty**

With recent advances in endovascular treatment, PTA has become particularly attractive for inactive stenotic/occlusive arterial or aortic lesions due to TA (Table). Long-term aspirin therapy is then recommended to prevent thrombus formation in vessels with endothelial damage. Antihypertensive agents are frequently used because >70% of the patients have hypertension related to atypical coarctation or renovascular hypertension. In the 1982–1984 Japanese nationwide survey, the pharmacological treatment was found to include aspirin and antiplatelet agents as well as adrenocorticosteroids (54.1%), hypotensive agents consisting of calcium antagonists, β-blockers, and hypotensive diuretics, cardiac glycoside, coronary vasodilator agents, and other agents.

**Table. Balloon PTA for Takayasu Arteritis**

<table>
<thead>
<tr>
<th>Study, Year, and Location</th>
<th>No. of Patients</th>
<th>Site</th>
<th>Site No.</th>
<th>Initial Success Rate, %</th>
<th>Follow-Up</th>
<th>Restenosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Martin et al, 1980, US</td>
<td>2</td>
<td>Renal artery, subclavian artery</td>
<td>2</td>
<td>50.0</td>
<td>1 y</td>
<td>None</td>
</tr>
<tr>
<td>Saddeekni et al, 1980, US</td>
<td>1</td>
<td>Renal artery</td>
<td>1</td>
<td>100.0</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Hodgins et al, 1982, Canada</td>
<td>1</td>
<td>Subclavian artery</td>
<td>1</td>
<td>100.0</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Yagura et al, 1984, Japan</td>
<td>1</td>
<td>Descending aorta</td>
<td>1</td>
<td>100.0</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Khalilullah et al, 1987, India</td>
<td>4</td>
<td>Descending aorta, abdominal aorta</td>
<td>4</td>
<td>100.0</td>
<td>8.5±4.1 mo</td>
<td>None</td>
</tr>
<tr>
<td>Gu et al, 1988, China</td>
<td>9</td>
<td>Abdominal aorta</td>
<td>9</td>
<td>100.0</td>
<td>3–28 mo</td>
<td>None (incomplete data)</td>
</tr>
<tr>
<td>Dong et al, 1987, China</td>
<td>22</td>
<td>Renal artery</td>
<td>22</td>
<td>NA</td>
<td>6 mo</td>
<td>NA</td>
</tr>
<tr>
<td>Park et al, 1989, Korea</td>
<td>8</td>
<td>Coronary artery: 1; renal artery: 9; subclavian artery: 1; abdominal aorta: 3</td>
<td>14</td>
<td>85.7</td>
<td>7–38 mo</td>
<td>21.4%</td>
</tr>
<tr>
<td>Kumar et al, 1989, India</td>
<td>16</td>
<td>Renal artery: 9; subclavian artery: 5; innominate artery: 1; abdominal aorta: 2; descending aorta: 2</td>
<td>19</td>
<td>74.0</td>
<td>2–33 mo</td>
<td>None</td>
</tr>
<tr>
<td>Sharma et al, 1990, India</td>
<td>11</td>
<td>Renal artery: 12; iliac artery: 1; abdominal aorta: 2</td>
<td>15</td>
<td>86.7</td>
<td>1–16 mo</td>
<td>20.0%</td>
</tr>
<tr>
<td>Tyagi et al, 1992, India</td>
<td>36</td>
<td>Abdominal aorta: 26; descending aorta: 14</td>
<td>40</td>
<td>94.4</td>
<td>43.2±4.9 mo</td>
<td>2.8% (incomplete data)</td>
</tr>
<tr>
<td>Tyagi et al, 1993, India</td>
<td>54</td>
<td>Renal artery</td>
<td>75</td>
<td>89.3</td>
<td>14.2±7.8 mo</td>
<td>13.5%</td>
</tr>
<tr>
<td>Rao et al, 1993, India</td>
<td>16</td>
<td>Abdominal aorta: 11; descending aorta: 6</td>
<td>17</td>
<td>100.0</td>
<td>2–41 mo</td>
<td>18.8%</td>
</tr>
<tr>
<td>Sawada et al, 1994, Japan</td>
<td>2</td>
<td>Abdominal aorta</td>
<td>2</td>
<td>100.0</td>
<td>10 mo and 8 mo, each</td>
<td>None (balloon angioplasty with stenting)</td>
</tr>
<tr>
<td>Sharma et al, 1996, India</td>
<td>24 children</td>
<td>Renal artery</td>
<td>40</td>
<td>95.0</td>
<td>33±22 mo</td>
<td>20.0%</td>
</tr>
<tr>
<td>Sharma et al, 1998, India</td>
<td>66</td>
<td>Renal artery</td>
<td>96</td>
<td>95.0 (89)</td>
<td>22±17 mo</td>
<td>16.0%</td>
</tr>
<tr>
<td>Sharma et al, 2000, India</td>
<td>20</td>
<td>Coronary artery: 1; carotid artery: 5; renal artery: 5; subclavian artery: 5; aorta: 13</td>
<td>29</td>
<td>95.0</td>
<td>4–10 mo</td>
<td>10.5% (balloon angioplasty with stenting)</td>
</tr>
<tr>
<td>Bali et al, 2000, India</td>
<td>6</td>
<td>Descending aorta</td>
<td>6</td>
<td>100.0</td>
<td>22.8±4.0 mo</td>
<td>None (balloon angioplasty with stenting); pseudoaneurysm: 1</td>
</tr>
<tr>
<td>Furukawa et al, 2005, Japan</td>
<td>1</td>
<td>Coronary (LMT)</td>
<td>1</td>
<td>100.0</td>
<td>6 mo</td>
<td>None (DES)</td>
</tr>
<tr>
<td>Amir et al, 2006, US</td>
<td>1</td>
<td>Coronary (LMT)</td>
<td>1</td>
<td>100.0</td>
<td>3 mo</td>
<td>None (DES)</td>
</tr>
</tbody>
</table>

NA indicates not available; LMT, left main trunk lesion; and DES, drug-eluting stent.

**Atypical Coarctation**

The first attempt was reported in 1984, and it was followed by several reports dealing with small series. Tyagi et al reported from India the largest series of 36 patients with favorable initial and midterm outcome, especially in dilatating discrete-type aortic stenoses.

**Surgical Treatment**

Surgery has been associated with low mortality and morbidity except for surgery of aortic aneurysm, especially a ruptured aneurysm. Although <20% of adult patients require surgical treatment, 80% of the patients need surgery for stenotic/occlusive lesions because 70% are in the active phase and on steroid therapy. The major surgical procedures in the Japanese nationwide surveys were aortocervical bypass, cervicosubclavian bypass, aortic re-
placement, aortocoronary bypass, replacement of aortic aneurysm, aortoarterial bypass, aortorenal bypass, reconstruction of renal vessel, and nephrectomy.10

Cerebrovascular Lesion
Ischemic symptoms are common even in the young patient population because of the involvement of the arch vessel.10 Stroke occurs from a reduction in cerebrovascular blood flow due to total occlusion of ≥1 arch vessel rather than from emboli. Aorticocervical bypass originating in the ascending aorta (not in the subclavian artery) and anastomosed to the carotid bulb with the use of saphenous vein grafts is recommended.76

Atypical Coarctation
TA is one of the causes of a much less common variety of aortic coarctation, the middle aortic syndrome, apart from the more common congenital coarctation of the aorta. This atypical coarctation occurs anywhere along the length of the aorta except the ascending aorta, whereas coarctation of the aorta is typically located around the aortic isthmus. An aortoarterial bypass with the use of a 10- to 16-mm prosthetic graft was the most common procedure. The satisfactory long-term survival after surgery was described in 33 patients followed up from 1960 to 2004.77 In that series, the outcome of 29 patients with aortic coarctation proximal to the origin of the renal arteries and hypertension in the upper half of the body was reviewed.

Renal Artery Stenosis (Renovascular Hypertension)
Hypertension is a common occurrence in TA and is related to major complications such as congestive heart failure, cardiomyopathy, hemorrhagic stroke, hypertensive encephalopathy, and myocardial infarction.2,10 Renal artery stenosis as well as atypical coarctation or reduced elasticity of the arterial wall can cause hypertension. Less invasive PTA is today the first choice therapy (Table). If it is unsuccessful or technically impossible, prompt renal artery bypass with the use of a saphenous vein graft with aortic inflow or relief of atypical coarctation with bypass grafting should be performed to lower blood pressure. In renal artery bypass, another available inflow is that from the in situ hepatic or splenic artery close to the kidney.

Coronary Artery Disease
Coronary artery involvement was reported to be 10%.40 The ostium was most frequently involved in 87.5% of the patients, 95.8% of whom were treated surgically.41 In the experience with surgery for stenotic/occlusive lesions at the authors’ institute (1979–1998), obstructive coronary artery disease was found in 41.3% (n = 19).78 Coronary artery bypass grafting was performed in 10 and coronary ostial endarterectomy in 9. There were no hospital deaths. Six patients died from arrhythmia, myocardial infarction,2 cerebral bleeding, surgery for a thoracic aneurysm, or unknown reason during a follow-up of 117 (4 to 240) months. In 9 patients subjected to ostial endarterectomy, only 2 died from arrhythmia or unknown origin, and no restenosis has been found. Coronary ostial endarterectomy is a useful option, particularly in conjunction with ascending aortic surgery. Otherwise, successful angioplasty, especially with a drug-eluting stent, was recently reported for proximal coronary disease in patients with TA (Table).71,72

Aortic Aneurysm
Aneurysm formation is considered one of the major complications related to the prognosis in TA.74 In Japan, the incidence of aneurysmal formation was reported to be higher, between 22.2% and 31.9%,8,42 although the incidence of aneurysm rupture seems to be low.43 Kiefert et al79 reported satisfactory surgical outcome of descending thoracic and thoracoabdominal aortic aneurysm in 33 patients with TA between 1974 and 2001, despite the extent of aneurysmal lesions and high frequency of association with visceral and supra-aortic vessel lesions.

Aortic Regurgitation
Aortic regurgitation, which is another major complication influencing prognosis, is also prevalent in Japan.80–82 It is often associated with ascending aortic or root dilation, which requires concomitant root and aortic valve replacement. Composite graft root replacement has been considered a gold standard procedure.80–82 However, prosthetic graft detachment (anastomotic false aneurysm) including a coronary artery disorder is the most serious morbidity in the long term, particularly in patients with persisting inflammation.80–83 Since 1987, we have used a novel “miniskirt technique,” in which the prosthetic valve is not attached directly to the fragile annulus, for the composite graft root replacement to treat aortic regurgitation with root dilatation.81,82 Ando et al81 and Matsuura et al82 published details of surgical series of aortic regurgitation with or without root dilatation due to TA. In the latter report,82 prosthetic valve detachment (periavalvular leakage) occurred in 11.1% of the patients after aortic valve replacement alone and in only 3.7% of those subjected to composite graft root replacement. Thus, compared with aortic valve replacement alone or composite graft root replacement with the standard technique, the mechanical stress to the fragile inflamed annulus is expected to be less with the miniskirt technique. On the other hand, homograft root replacement83–86 is one option to prevent the detachment by reducing the mechanical stress to the fragile aortic annulus due to inflammatory diseases. In particular, with the use of steroidal antiinflammatory therapy, a longer durability of homograft might be expected, although there have been no studies on this. Full root replacement with a stentless aortic xenograft is another option for this setting;87 however, none has described its long durability. In our experience with more troublesome Behçet’s disease, valve detachment after aortic valve replacement occurred in 4 (40%) of 10 patients.88 Proximal anastomotic detachment occurred in 1 (20%) of the first 5 patients who underwent composite graft root replacement with the standard technique, whereas there was no detachment in the later 5 patients operated on with the miniskirt technique. At other anastomotic sites such as those for coronary and distal aortic reconstruction, no anastomotic false aneurysms occurred, presumably because of routine external Teflon (polytetrafluoroethylene) felt reinforcement.81,82 In addition, late dilatation of the residual ascending aorta occurred in 10.3% after isolated aortic valve replacement compared with 3.7% after composite graft root replace-
Thus, for aortic regurgitation with some root dilatation, composite graft root replacement is preferable. The size threshold of the root for composite graft root replacement is \( \approx 45 \) mm. On the other hand, modern aortic valve-sparing surgery is not recommended very often for root dilatation with or without aortic regurgitation due to TA. There have been no reports regarding this issue. In our experience with 4 patients, 3 of them subsequently required aortic valve replacement due to aortic regurgitation within 5 years. Aortic regurgitation associated with TA primarily develops not only as a result of annular dilatation but also as a result of secondary aortic valve changes such as fibrous thickening, rolling, retraction, and calcification.\(^\text{44}\) In patients requiring aortic valve replacement, the aortic valves had looked normal at the initial valve-sparing surgery. However, at the time of reoperation, the aortic valves showed typical secondary valve changes due to TA. Aortic valve-sparing surgery is indicated only for selected patients without active inflammation of the aortic valve and wall.

### Late Outcome

#### Staging and Prognosis

To investigate the natural history of TA, Ishikawa and Maetani\(^\text{74}\) followed up, for a median of 13 years, 120 patients whose survival rate at 15 years after the diagnosis was 82.9%, and they proposed a prognostic classification of TA. There were 4 significant predictors: (1) major complications of Takayasu's retinopathy, hypertension, aortic regurgitation, and aneurysm; (2) a progressive course; (3) age; and (4) calendar year of diagnosis. The 15-year survival was 66.3% and 96.4% with and without major complications, 67.9% versus 92.9% with and without a progressive course, 58.3% versus 92.7% for age \( \geq 35 \) years and \(< 35 \) years, and 79.9% versus 96.5% for early patients (1957–1975) and late patients (1976–1990). A high erythrocyte sedimentation rate was of marginal significance. In the multivariate analysis, major complications, progressive course, and high erythrocyte sedimentation rate were independent predictors. With the use of these 3 predictors, a 3-stage classification (I, II, and III) was established. Stage III referred to the presence of major complications and progressive course and showed the worst prognosis of only 43% survival at 15 years, whereas stage I referred to TA without manifestations and showed the best prognosis with no death. The report concluded that the long-term outcome seemed to be predicted best on the basis of the presence/absence of major complications, a progressive course, and high erythrocyte sedimentation rate. Aggressive medical and surgical treatment should be considered for patients in stage III. However, this report dealt with only 14 surgical cases (11.7%) treated, and the follow-up period was between 1957 and 1990. In recent series, the frequency of prompt interventions such as surgery and PTA might be at least 20%\(^\text{74,75}\). Presumably, recent earlier diagnosis followed by earlier and aggressive medical and surgical treatment has changed the clinical conditions. The clinical base in the series of Ishikawa and Maetani including patients in the early period before 1990 might be different from the recent one, even though calendar year of diagnosis was included as a factor in the analyses. This is a difficult matter when we are dealing with the late outcome of uncommon diseases such as TA. Using the staging system of Ishikawa and Maetani, Miyata et al\(^\text{89}\) also recently investigated the long-term outcome of surgery for TA in 106 patients between 1955 and 1995. That report showed that surgical treatment seemed to increase the long-term survival even for patients in stage III, whereas conservative treatment was recommended for those in stage I or II because of some surgical complications. Consequently, it is thought that more aggressive surgical treatment including PTA and aortic root surgery for aortic regurgitation would have changed the outcome in the series of Ishikawa and Maetani. In Western countries, this staging system is difficult to use because the incidence of retinopathy, aortic regurgitation, and aneurysm is lower. In regard to this issue, Fields et al\(^\text{75}\) reported that the long-term survival was excellent up to 10 years and was not affected by disease activity or the use of steroids.

#### Percutaneous Transluminal Angioplasty

Tyagi et al\(^\text{63}\) reported on the largest series of 36 patients with favorable initial and midterm outcome, especially in dilatating discrete-type aortic stenoses (Table). Persistent relief was observed during the follow-up of 43 ± 9.4 months, except for 1 case (2.7%) of restenosis. Interestingly, further relief of the stenosis was also observed, presumably because of late remodeling of the ruptured fibrous band or release of superimposed spasm. In contrast to PTA for congenital coarctation of the aorta, no aneurysm developed even after forced balloon dilatation. However, because the stenosis is rigid and noncompliant in TA, higher balloon inflation pressure is required to stretch and split the thick and more rigid fibrous tissue compared with atherosclerotic aortic stenosis. Pressure gradient might remain after PTA alone in some instances. Even after initially successful angioplasty, restenosis also occurs quickly. It develops in 15% to 20% of the cases during the midterm follow-up and is most likely to occur in the renal arteries or in stenotic lesions involving a long segment of the vessel. It was reported from India that male gender, stenosis beginning at the origin of the renal artery, and >20% residual stenosis after PTA were predictors of restenosis.\(^\text{57}\) To prevent marked restenosis, stenting is currently added, especially for ostial lesions, long-segment lesions, or incomplete dilatation of stenosis and dissection after PTA.\(^\text{67,69,70}\) The long-term impact of PTA is still uncertain because there have been no reports describing the outcome of PTA with and without stenting after a longer period of \( \geq 10 \) years. In a recent US cohort study involving 75 patients, a discouragingly high occurrence (78%) of restenosis, even after initially successful PTA, was reported.\(^\text{90}\) Consequently, at present, it appears reasonable to attempt less invasive PTA with stenting for stenotic/occlusive lesions of the renal artery or other branches of the aorta, including discrete stenosis of the aorta, with close long-term observation.

#### Anastomotic False Aneurysm

After surgery for TA, anastomotic false aneurysms (anastomotic detachment) occur anytime in the long term, although the incidence seems to be low even in the active phase of TA compared with that in Behçet' disease.\(^\text{88}\) In Western coun-
tries, the development of anastomotic false aneurysm is reportedly rare.\textsuperscript{91} In the largest series from Japan, the incidence of anastomotic false aneurysm was 8.5% (22/259).\textsuperscript{92} However, of the 22 aneurysms, 18 occurred in early cases in which silk threads were used. In recent cases in which synthetic suture material was employed, only 1.8% of the patients at 10 years and 3.5% at 20 years developed anastomotic false aneurysms. These low incidences were comparable to those observed after more common surgeries for atherosclerotic lesions. In addition, its development was not influenced by any factor specific to this disease, except for the presence of an aneurysmal lesion.\textsuperscript{93} Reportedly, the pathology of the anastomotic site is not reflected in serum inflammatory parameters. The incidence of anastomotic false aneurysm seems to be unrelated to systemic inflammatory reactions. Even if corticosteroids suppress inflammatory reactants, the pathological status of the arterial wall does not change.\textsuperscript{94} In regard to anastomotic stenosis related to intimal hyperplasia, the incidence was also reasonable,\textsuperscript{92,94} although the incidence was found to be much higher (36%) after bypass surgery in a recent US cohort study.\textsuperscript{90} Consequently, Ando et al\textsuperscript{78} summarized the characteristics of surgery for TA as follows: abrasion around the aorta or artery is difficult because of dense adhesion to the surrounding tissue, which makes extraanatomic bypass frequent. Anastomotic false aneurysms forming because of suture insufficiency are the most serious complications. To prevent this complication, reinforcement of sutures with the use of a Teflon felt strip or prophylactic suture with silk threads was used. In recent cases in which nonabsorbable sutures were used, the incidence of TA-like aneurysms has reportedly decreased.\textsuperscript{95} In the largest series from Japan, the incidence of TA-like aneurysms was 0.8% (8/954 patients). The mean follow-up periods of these reports were 6 years. Furthermore, the results of a recent US cohort study were rather discouraging.\textsuperscript{90} According to that study, both PTA and vascular surgery were initially successful, but restenosis occurred frequently in 78% of the lesions treated by PTA and 36% of those subjected to bypass/reconstruction procedures.

**Surgery for Atypical Coarctation**

The acceptable long-term survival rate after surgery was described in a series of 33 patients followed up from 1960 to 2004.\textsuperscript{77} In 29 patients with aortic coarctation proximal to the origin of the renal arteries and hypertension in the upper half of the body, aorto- or renal bypass with the use of a 10- to 16-mm prosthetic graft was the most commonly performed procedure. The outcome was favorable, with 4 hospital deaths (12.1%) only in the early period before 1968. However, hypertension was not relieved in 55.6% of the 27 survivors. Long-term complications after surgery included anastomotic false aneurysms, congestive heart failure, cerebrovascular accident, graft deterioration, abdominal aortic aneurysms, and renal failure at any time after surgery. The survival and event-free survival rates at 20 years were 62.3% and 58.4%, respectively. In this series, the presence of postoperative residual hypertension likely influenced the event-free and survival rates. As for the surgical procedure, we believe empirically that large grafts of at least >12 mm in diameter should be used to relieve the stenosis or to prevent residual proximal hypertension in Japanese patients. Lifelong follow-up with full management of persistent hypertension, which is a poor prognostic factor, is also mandatory even after surgery.\textsuperscript{77}

**Surgery or PTA for Renal Artery Stenosis**

Kieffer et al\textsuperscript{95} reported a satisfactory early and long-term outcome in 24 patients. Renal artery revascularization was unilateral in 46% and bilateral in 54%. During follow-up for 61.3 months, repeated renal artery revascularization was required in only 4 patients. Hypertension was cured in 63%, improved in 31%, and unchanged in 6%.\textsuperscript{95} In 2004, Weaver et al\textsuperscript{68} described more details of the long-term effects of revascularization for renal artery stenosis on blood pressure and on renal and cardiac functions. They performed 40 interventions, including aortorenal bypass in 32, repeat implantation in 2, nephrectomy in 4, and PTA in 2. During the 68-month follow-up, 3 graft stenoses due to intimal hyperplasia and 3 graft occlusions occurred. As for hypertension, the interventions resulted in a decrease of blood pressure and a decrease in the need for antihypertensive medication. In regard to renal function, the mean glomerular filtration rate increased, and 2 patients no longer required hemodialysis. In regard to cardiac function, congestive heart failure resolved in 2 patients. There were 3 deaths, and the 5- and 10-year actuarial survivals were 96% and 80%, respectively. On the other hand, Sharma et al\textsuperscript{68} published the midterm results of PTA for renovascular hypertension in 66 patients (Table). The indications included uncontrollable hypertension, evidence of >70% stenosis of the renal arteries with a peak systolic gradient of >20 mm Hg, and clinically inactive disease. Technical success was obtained in 91 stenotic lesions in 62 patients. Clinical success was seen in 89%. The stenosis decreased, systolic pressure gradient decreased, blood pressure improved, and drug requirement decreased. At 22±17 (4 to 84) months of follow-up, the restenosis rate was 16%. However, the mean follow-up periods of these reports were <6 years. Furthermore, the results of a recent US cohort study were rather discouraging.\textsuperscript{90} According to that study, both PTA and vascular surgery were initially successful, but restenosis occurred frequently in 78% of the lesions treated by PTA and 36% of those subjected to bypass/reconstruction procedures.

**Surgery or Endovascular Repair for Aortic Aneurysm**

In surgical repair of aortic aneurysm due to TA, the outcome has been improved with technical advances. Recently, successful endovascular aneurysmal repair (stent grafting) for dilated lesions due to TA was reported.\textsuperscript{96} However, reintervention for ruptured aneurysm after endovascular treatment was also reported.\textsuperscript{97} The long-term efficacy of endovascular aneurysmal repair remains uncertain even for atherosclerotic pathology. In the inflammatory lesions due to TA, a positive but cautious approach might be necessary.

**Pharmacological Treatment**

With active or chronic systemic inflammation, it is essential to suppress it pharmacologically, with determination of serum C-reactive protein concentration and erythrocyte sedimentation rate. Numano et al\textsuperscript{13,33} have advocated that the inflammation due to TA would result in atherosclerotic lesions of the aorta and arteries. Hypertension associated with a high incidence of TA accelerates atherosclerosis in the long term. It is therefore mandatory to prevent some potential complications due to atherosclerotic disorders for improvement of the prognosis in patients with TA.
Conclusions

TA is a nonspecific inflammatory disease and causes arterial stenoses/occlusion or dilatation. TA is widely recognized as a multifactorial disease, although a genetic factor has been suggested as its cause because of predominance in young females from the Orient. There were also some differences in vascular involvement and the incidence of aneurysm among different countries; Asian people tend to develop proximal or aneurysmal lesions from the aortic root to the arch with a higher frequency than that in Western people. Early and less invasive diagnosis is feasible with computed tomographic scan or magnetic resonance angiography. Recent advances of medical and surgical treatments, including endovascular interventions, have improved the prognosis of patients with stenotic/occlusive or dilated lesions. The incidences of potential vascular complications after surgery or endovascular treatment were low because of technical advances or adequate antiinflammatory treatment. A longer follow-up of >20 years is still mandatory to draw any statistically valid conclusion on the impact of current medical and surgical therapies on the natural history of TA. In addition, further studies on updated endovascular therapies, including PTA with stenting and endovascular aneurysmal repair with the use of a stent graft, are also necessary.

Disclosures

None.

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