Preoperative immunosuppressive therapy reduces paravalvular leakage after aortic valve surgery in patients with aortic regurgitation attributable to Behçet's disease

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ABSTRACT

Objective. *Severe aortic regurgitation (AR) attributable to Behçet's disease (BD) is a rare but challenging problem in light of the surgical treatment notoriously complicated with paravalvular leakage (PVL) and high mortality. This study aims to test whether immunosuppressive therapy is effective in reducing the complication of the operation and improve the prognosis.*

Methods. *In a retrospective cohort of 644 hospitalised BD patients who were diagnosed and followed up between January 1998 and September 2014, 18 patients (2.8%) with severe AR due to BD were identified and their medical records were analysed.*

Results. *Among the 18 patients, 15 patients underwent the valve surgery and PVL developed in 7 (47%) at a median interval of 3.5 months. In the median follow-up of 32.5 months from first operations, patients with PVL had a significantly higher incidence of repeat surgery and death (71% vs. 0%, p=0.007). They less likely received preoperative immunotherapy (14% vs. 100%, p=0.001), had a lower cumulative dosage of cyclophosphamide before first operations (2.1±5.7g vs. 13.0±6.4g, p=0.004) and a higher preoperative erythrocyte sedimentation rate (44.4±20.7mm/first hour vs. 25.0±12.1mm/first hour, p=0.04) compared with those without developing PVL. Multivariate analysis showed preoperative immuno-suppressive therapy (hazard ratio 18.58; 95% confidence interval, 2.134–161.81; p=0.008) was an independent factor associated with the absence of PVL. The 5-year PVL-free survival rates were significantly higher in patients receiving preoperative immunotherapy (p=0.0004).*

Conclusion. *In patients with severe AR due to BD, preoperative immunosuppressive therapy, especially cyclophosphamide in conjunction with glucocorticoid, could reduce PVL after the corrective surgery and improve the outcomes.*

Introduction

Behçet's disease (BD) is a chronic, relapsing, systemic inflammatory disorder of unknown aetiology characterised by recurrent oral and genital ulceration, ocular inflammation as well as a variety of cutaneous, musculoskeletal, vascular, gastrointestinal and nervous system manifestations (1, 2). Cardiac involvements in BD has been reported to be rare but regarded as a very severe complication. Among the spectrum of cardiac involvements such as valvular disorders, pericarditis, myocardial infarction and intracardiac thrombosis (3-11), aortic regurgitation (AR) is more frequent reported in Far Eastern countries and challenging for diagnosis and treatment (9-11), while the endomyocardial involvement has been reported mostly in Middle Eastern or European populations as endomyocardial fibrosis (6) or mural thrombi (3-5). The majority of patients with severe AR secondary to BD could not be diagnosed correctly before cardiac operations due to their lack of "typical" presentations needed by the diagnostic criteria of the International Study Group (ISG) for Behçet's disease (12). Moreover, the inevitable aortic valve replacement has an infamously high incidence of valvular dehiscence with paravalvular leakage (PVL), which is associated with reoperation and poor event-free survival (13, 14). Recent studies reported that surgical outcomes of these BD patients with severe AR might be related to initial echocardiographic features, perioperative immunotherapy and levels of postoperative inflammatory markers (15, 16) and could be improved by surgical modifications (17, 18). How-

ever, the timing of perioperative immunosuppressive therapy remained to be elucidated. Here, we investigated whether preoperative immunosuppressive therapy played a pivotal role in reducing the PVL of the prosthetic valve and improving the prognosis.

Patients and methods

Patients

The Ethics Committee of Peking Union Medical College hospital approved this retrospective study and waived the need for individual patient consent.

We retrospectively studied the medical records of 644 hospitalised BD patients who were diagnosed and followed up between January 1998 and September 2014 in Peking Union Medical College hospital. All patients fulfilled the criteria of International Study Group (ISG) for BD (12) or the new International Criteria for Behçet's disease (ICBD) (Revision of the International Criteria for BD) (19). Among them, 18 patients with severe AR secondary to BD were enrolled. AR was considered related to BD if it was contemporaneous with BD flares and other known causes of aortic valve disease had been excluded such as rheumatic, Marfan syndrome, congenital or atherosclerosis-related heart diseases.

The following data of all the 18 patients were collected and analysed: demographic characteristics, the duration between the first involvement of BD and the appearance of severe AR, the main manifestations of BD involvement, electrocardiogram (ECG), echocardiography, erythrocyte sedimentation rate (ESR) and HLA–B5 genotype.

The echocardiographic images of the included patients were reviewed by cardiologists with advanced training in echocardiography and blinded from clinical information. Both transthoracic echocardiographic (TTE) data and transesophageal echocardiographic (TEE) data were analysed if the latter was available. Special attention was paid to evaluate individual aortic cusps, the ascending aorta, the interventricular septum adjacent to the aortic leaflets and the severity of AR (20).

A scoring system suggested by Song *et al*. (16) was used to evaluate the severity of lesions involving aortic cusps and the adjacent structure according to the combining findings of preoperative echocardiography and the first operation.

Treatment and outcomes

Medical treatment included immunosuppressive agents, diuretics and inotropic drugs if necessary. Immunosuppressive agents included oral prednisone (1mg/kg/day), cyclophosphamide (50–100 mg/day), thalidomide (50 mg/day) and azathioprine (1mg/kg/day). Clinical evaluation and ESR were used to titrate these drugs. The perioperative medication and the timing of surgery were determined by a medical group including rheumatologists, cardiologists and cardiac surgeons. For patients receiving immunosuppressive agents, prednisone was tapered to a maintenance dose (5–10mg/day) before undergoing operations. It was up to the cardiac surgeons to decide the type of surgery that was aortic valve replacement (AVR) or Bentall procedure. Pathologic findings of the excisional specimens showed mixed neutrophilic and lymphoid infiltrates, extensive endothelial loss with fibrin deposition and mucoid degeneration in the valves. Aortic tissue from patients receiving Bentall procedure and those who suffered from serious paravalvular leakage after surgeries showed vasculitis within vasa vasorum, complete endothelial loss, fibrin deposit and infiltration of inflammatory cells and necrosis in media and adventitia; all these characteristics were representative pathologic findings of BD (21).

Follow-up data included symptoms, ESR, TTE every 3 or 6 months depending on each patient's condition, repeated operation and medical treatment. If TTE was insufficient to diagnose PVL, TEE was additionally performed. Data was collected through retrospective review of inpatient records, regular outpatient visits and telephone interviews.

Statistical analysis

Results are expressed as the mean±SD, the median and range, or the percent number (%). Between-group comparisons were performed using the Student's *t*-test or Mann-Whitney test for the continuous variables and using chi-square test or Fisher's exact test for the categorical variables. Variables with p-values <0.20 were selected for multivariate analysis. A Cox regression model using an enter selection process was used to determine parameters associated with development of PVL after first operations. A survival curve was generated using the Kaplan-Meier method, and PVL rates were compared according to preoperative immunotherapy by using the log-rank test. The correlation between the cumulative dosage of cyclophosphamide and preoperative ESR was tested by Spearman's correlation. Receiver operating characteristic (ROC) curve analysis was used to assess the optimal cut-off point of preoperative ESR for predicting PVL; the optimal cutoff value was defined as the value that gave the maximal sum of sensitivity and specificity. All statistical analyses were performed using SPSS version 16.0 (SPSS, Inc., Chicago, IL). p-values <0.05 were considered significant.

Results

Characteristics of the patients with severe AR due to BD

Of the 644 hospitalised BD patients, 18 (2.8%) patients had severe AR caused by BD. Only 8 patients (44.4%) fulfill ISG criteria when the presence of severe AR was demonstrated, but if applying ICBD criteria, 17 patients (94%) could be correctly classified before valve operation. The median interval between the first involvement of BD and the emergence of severe AR was 24 months (range 2–204 months) in the 18 patients. When referred to the hospital for first operation, 3 patients (16.7%) were in class IV according to the New York Heart Association functional classification and the others were in class II to III.

The main features of the patients with severe AR were summarised and compared with those without severe AR in Table I. The mean age of the18 patients was 38.8±9.6years, and 16 of them (88.9%) were male. Associated involvement of BD included oral (100%) and genital (50%) ulcerations, skin (66.7%), articular (16.7%), ocular (11.1%), neurologic (11.1%), gastroin-

Table I. Comparison of clinical features of patients with Behçet's disease (BD) according to the presence or absence of severe aortic regurgitation (AR).

	All patients (n=644) (%)	BD without AR (n=626) (%)	BD with AR (n=18) (%)	*p*
Age (years)	38.0 ± 14.2	37.9 ± 14.3	38.8 ± 9.6	0.47
Male sex	388 (60.2)	372 (59.4)	16 (88.9)	0.01
Clinical features				
Oral ulcerations	631 (98.0)	613 (97.9)	18 (100)	1.00
Genital ulcerations	291 (45.2)	282 (45.0)	9 (50.0)	0.81
Ocular involvement	221 (34.3)	219 (35.0)	2 (11.1)	0.04
Skin involvement	444 (69.0)	432 (69.0)	12 (66.7)	0.80
Neurologic involvement	44 (6.8)	42 (6.7)	2 (11.1)	0.35
Vascular involvement	102 (15.8)	100 (16.0)	2 (11.1)	0.33
Pathergy test	354 (55.0)	348 (55.6)	6 (33.3)	0.09
Articular involvement	190 (29.5)	187 (29.9)	3 (16.7)	0.30
Gastrointestinal involvement	60 (9.3)	58 (9.3)	2 (11.1)	0.68
HLA-B5 positive	37/178 (20.8)	35/162 (21.6)	2/16 (12.5)	0.74

testinal (11.1%) and vascular (11.1%) lesions. Six patients (33.3%) had positive pathergy test. HLA-B5 typing was done in 16 patients and 2 (12.5%) patients were positive. Compared with those without severe AR, these patients were male-predominant (88.9% *vs*. 59.4%, p=0.01) and had less ocular involvement (11.1% *vs*. 35.0%, p=0.04).

Electrocardiogram and echocardiographic findings

Electrocardiogram and echocardiographic findings before the first operation are summarised in Table II. Before first operations, sinus tachycardia was found in 12 patients (66.7%). Three patients (16.7%) had first-degree atrioventricular block. Two patients (11.1%) showed complete right bundle branch block. One patient (5.6%) was admitted to the hospital for recurrent syncope and was verified intermittent third-degree atrioventricular block. Thirteen patients showed severe AR on initial echocardiography, while the other 5 patients progressed to severe AR during follow-up. Among TTE and/or TEE findings, redundant motion with aneurysmal change of elongated aortic cusp was the most frequently detected feature (83.3%, 15 of 18 patients), and most (80%, 12 of 15 patients) involved the non-coronary cusp. Other findings included dissection into adjacent septum (22.2%, 4 of 18 patients), valvular vegetations (16.7%, 3 of 18 patients), pseudoaneurysm surrounding aortic cusps (16.7%, 3 of 18 patients) and aortic root aneurysm with aortic dissection (5.6%, 1 of 18 patients). As for the 15 patients receiving cardiac surgery, they showed severe aortic valve and adjacent tissue lesions on the echocardiographic and operation findings, with a mean score of 1.9±1.0.

Treatment and follow-up

Treatment and clinical outcomes of all the patients are summarised in Table III. The overall mortality was 16.7% (3 of 18 patients). 15 patients underwent 21 operations, with 4 patients undergoing the second and 2 patients even had the third operation (Fig. 1). Twelve patients underwent AVR, one had replacement of both aortic and mitral valve and two underwent the Bentall operation. All the patients survived first operation; however, prosthetic valve leakage occurred in 7 patients (46.7%).

Twelve patients (66.7%) were correctly diagnosed and received immunosuppressive agents before first operation for a median 6 months (range, 4–48months). All of them took prednisone at 1 mg/kg per day for one month and then gradually tapered to 5–10 mg/day. Meanwhile, cyclophosphamide was given initially in weekly pulse of 1gram for 1to 3 times then followed with 100 mg per day. Thalidomide at the dose of 50 mg/day was added in two of the patients. One patient (patient 9) was complicated by mycobacterial pneumonia and died of septic shock after 8-month treatment with immunosuppressant. Another 2 patients (patient 7and16) became clinically stable after 8–10 months medical treatment and denied cardiac surgery. The remaining 9 patients tolerated cyclophosphamide well and underwent AVR or Bentall procedure after they came into a stable condition which was interpreted as the inflammatory marker, ESR, at a low level (25.0±12.1 mm/first hour). Eight patients maintained good valve function and event-free on postoperative immunosuppressive treatment during follow-up. Only one patient (patient 5) developed infective endocarditis and prosthetic valve leakage in the third month after first operation and died suddenly before reoperation.

The other 6 patients (33.3%), most of whom were treated during the early stage of this study, underwent aortic valve surgery without an accurate diagnosis and preoperative immunosuppressive treatment. Unfortunately, they experienced different degrees of PVL. The median interval between first operation and emergence of prosthetic valve leakage was 3.5 months (range 1-8 months). Four patients (patient 3, 8, 12 and 18) were diagnosed as BD after the presence of PVL and started on immunosuppressive therapy. Medical treatment was sufficient to control symptoms in two patients (patient 8 and 12) and no more operation was performed during follow-up. The other two (patient 3 and 18) went through the second operation and remained in a good valve function on immunosuppressant. Two patients (patient 4 and 15) were not recognised as BD until recurrent severe PVL after the second operation. Patient 15 underwent cardiac transplantation as the third operation successfully; however, patient 4 did not survive the third operation of AVR due to sustained low cardiac output.

Factors associated with PVL

All the patients who did not develop PVL received preoperative immunosuppressive therapy, while only 14% of the patients with PVL received the treatment (p=0.001). The cumulative dosage of cyclophosphamide before first operation was much lower in those with PVL (2.1±5.7g *vs*. 13.0±6.4g, p=0.004). Also, they had a higher pre-

Table II. Electrocardiogram and echocardiographic features of aortic valve lesions in patients with severe aortic regurgitation due to Behçet's disease.

Case no.	Age/Sex	ECG abnormalities	AV lesions	NYHA Functional Class
1	M/18	—	Aneurysmal change and redundant motion of non-coronary and left-coronary cusp, pseudoaneurysm surrounding the two cusps	II
2	M/47	Sinus tachycardia I°AVB	Aneurysmal change and redundant motion of non-coronary and right-coronary cusp	II
3	M/58	Sinus tachycardia	Aneurysmal change, redundant motion and perforation of right-coronary cusp	III
4	M/22	I°AVB	Aneurysmal change and redundant motion of non-coronary and right-coronary cusps with vegetation, dissection into adjacent septum	IV
5	M/46	Sinus tachycardia	aneurysmal change, redundant motion and perforation of non-coronary cusp; moderate PH	III
6	F/42	Sinus tachycardia	Aneurysmal change and redundant motion of non-coronary cusp	II
7	M/38	--	Aneurysmal dilation of aortic root and tubular portion	II
8	M/44	--	Aortic root aneurysm and aortic dissection (Stanford A3)	II
9	M/52	Sinus tachycardia	Pseudoaneurysm surrounding non-coronary cusp and annular abscess;	III
10	M/33	Sinus tachycardia I°AVB	Aneurysmal change and redundant motion of non-coronary cusp; Pseudoaneurysm around non-coronary cusp	II
11	F/39	Sinus tachycardia	Aneurysmal change, redundant motion and vegetation of non-coronary cusp; anterior mitral prolapse and moderate MR, moderate PH	IV
12	M/36	Intermittent III°AVB CRBBB	Aneurysmal change, redundant motion and perforation of right-coronary cusp	III
13	M/46	Sinus tachycardia	Aneurysmal change and redundant motion of non-coronary cusp, dissection into adjacent septum	IV
14	F/37	Sinus tachycardia	Aneurysmal change and redundant motion of non-coronary cusp; moderate PH	III
15	M/34	_	Redundant motion of non-coronary and left-coronary cusps, dissection into adjacent septum	III
16	M/47	Sinus tachycardia CRBBB	Aneurysmal change and redundant motion of left-coronary cusp, severe PH	III
17	M/45	_	Aneurysmal change and redundant motion of non-coronary and right-coronary cusp	II
18	M/43	_	Aneurysmal change, redundant motion and vegetation of right-coronary cusp, dissection into adjacent septum	II

ECG: electrocardiogram; AVB: atrioventricular block; CRBBB: complete right bundle branch block; PH: pulmonary hypertension; MR: mitral regurgitation; NYHA: New York Heart Association.

operative ESR level (44.4±20.7 *vs*. 25.0±12.1mm/first hour, p=0.04) and higher rate of adverse events including reoperation and death than those without PVL (71% [5 of 7] *vs*. 0%, p=0.007). There was no statistical difference in other clinical variables such as age, sex, echocardiographic parameters, the score of lesions, type of surgery and post-operative ESR between those with and without PVL (Table IV). A correlation was identified between the preoperative immunotherapy and preoperative ESR (r=-0.71, p=0.003). Preoperative immunotherapy, left ventricular end-dilated diameter were included in the multivariate analysis, which showed that preoperative immunotherapy (hazard ratio, 18.58; 95% confidence interval, 2.134–161.81; p=0.008) was the only independent factor associated with the absence of recurrent AR. The 5-year PVL-free survival rates were significantly higher in patients with preoperative immunotherapy (89±11% *vs*. 0%, p=0.0004) (Fig. 2). As an effective marker of the immunosuppressive therapy, the optimal cutoff value of preoperative ESR was 32.5mm/first hour with sensitivity and specificity of 85.7% and 75%, respectively, determined by ROC curve analysis. Preoperative ESR had the area under curve (AUC) of 0.839 (p=0.028) in predicting the occurrence of PVL (Fig. 3).

Discussion

The corrective surgery of AR due to BD was characterised by high rates of prosthetic valve dehiscence, which led to reoperation and high mortality. Our study showed that preoperative immunosuppressive therapy, especialy the usage of cyclophosphamide in conjunction with glucocorticoid could effectively decrease the development of PVL, thus improve the prognosis of BD with AR.

Behçet's disease, as a chronic, relapsing and systemic inflammatory disorder,

Table III. Treatment and follow-up data of all the patients with severe aortic regurgitation due to Behçet's disease.

Case no.	Preoperative immunosuppressive therapy	First operation	Complications after 1st operation	Immunosuppressive therapy after 1st operation	Second operation	Complications after 2nd operation	Final results
1	P+CYC+Th for 6 months	Bentall-Me	No	P+CYC+Th	–	–	Survived
2	P+CYC for 36 months	AVR-Me	No	P+CYC	–	–	Survived
3	No	AVR-T	VD 5 months later with interventricular septal dissection	*P+CYC for 3 months	AVR-Me	No	Survived
4	No	AVR-Me	VD and annular abscess 4 months later	No	AVR-Me	VD and recurrent angina 3 months later	Died in 3rd operation 9 months after 1st operation
5	P+CYC for 6 months	AVR-Me	VD and prosthetic valve endocarditis 3 months later	P+CYC	–	–	Died suddenly 6 months after 1st operation
6	P+CYC for 18 months	AVR-Me	No	P+CYC+Th	–	–	Survived
7	P+CYC for 10 months	Denied	–	–	–	–	NA
8	No	Bentall	PVL and vascular anastomotic fistula 8 months later	*P+CYC	–	–	Survived but denied 2nd operation
9	P+CYC for 8 months	No chance	–	–	–	–	Died of recurrent pneumonia and septic shock
10	P+CYC for 6 months	AVR-Me	No	P+CYC	–	–	Survived
11	P+CYC for 4 months	AVR+MVR	No	P+CYC	–	–	Survived
12	No	AVR-Me	PVL 1 month later but no more III AVB	*P+CYC	–	–	Survived but denied 2nd operation
13	P+CYC for 5 months	AVR-Me	No	P+CYC	–	–	Survived
14	P+CYC+Tha for 48 months	AVR-Me	No	P+AZA	–	–	Survived
15	No	AVR-Me	VD 1 months later	No	Bentall	Severe VD 2 months later	*P+CYC for 5 months before the 3rd operation of heart transplant
16	P+CYC for 8 months	Denied	–	–	–	–	NA
17	P+CYC for 6 months	AVR-Me	No	P+CYC	–	–	Survived
18	No	AVR-Me	VD and annular abscess 2 months later	*P+CYC+Th for 14 months	Bentall-Me	No	Survived

P: prednisone; CYC: cyclophosphamide; Th: Thalidomide; PVL: paravalvular leakage; VD: prosthetic valve dehiscence; AVR: aortic valve replacement; Me: mechanical valve; T: tissue valve; MVR: mitral valve replacement; AZA: azathioprine; NA: not apply. *Immunosuppressive therapy start from the confirmation of PVL.

has the highest incidence in countries along the ancient Silk Road connecting China with the Mediterranean Basin. The prevalence has been reported to be 13.5 to 80 /100 000 within the Silk Road whereas only 0.64 to 7.1 /100 000 outside it (22). BD is generally not life-threatening if managed appropriately; however it can be fatal if cardiovascular lesions occur (4, 5). The incidence of cardiovascular complications in BD varies from 16% to 30%, and among them, aortic valve disease occurs rarely but is especially challenging due to the infamously high rate of reoperation and mortality (15, 23).

Several factors have been identified contributing to the surgery failure and even death in patients with AR due to BD. One is the low diagnostic rate and short of proper treatment of BD prior to aortic valve surgery. Since there are no specific diagnostic tests, BD is diagnosed by a range of clinical findings, with ISG criteria being the most popular. The ISG criteria include oral aphthosis which is mandatory and two of the followings: genital ulcers, skin lesions, ocular lesions and pathergy phenomenon. Even though the application of ISG criteria is pretty good in general BD patients, it has been reported to be clinically limited in evaluating the patients with AR secondary to BD. Most of such patients failed to meet the standard criteria before undergoing aor-

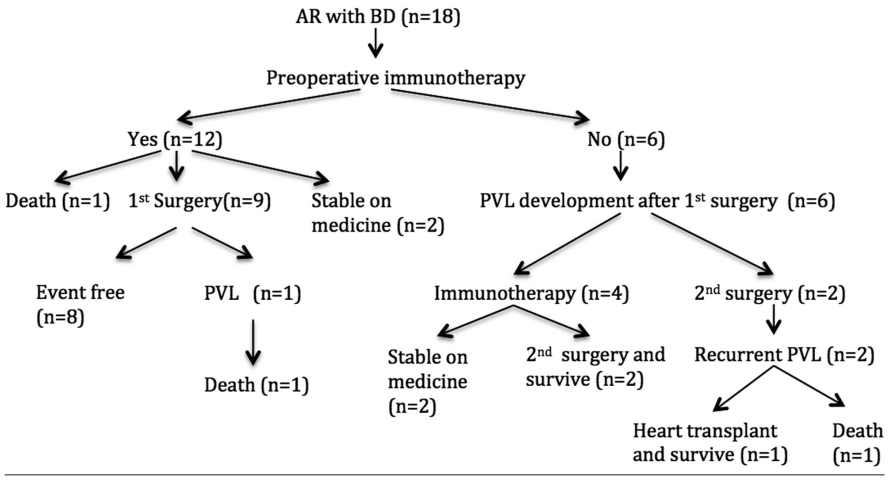

Fig. 1. Summary of the clinical outcomes of patients with aortic regurgitation (AR) due to Behçet's disease (BD). PVL: Perivalvular leakage.

Table IV. Clinical variables and outcomes in patients who had and had not perivalvular leakage (PVL) after first operations.

Variable	Total (n=15)	PVL (n=7)	Without PVL (n=8)	*p*
Age (year)	37.6 ± 9.9	39.1 ± 11.3	36.3 ± 9.0	0.59
Male	12 (75%)	7 (100%)	5 (55.6%)	0.20
Surgical procedure				1.00
Bentall	2 (13%)	1 (14%)	1 (13%)	
AVR	13 (87%)	6 (86%)	7 (86%)	
Immunosuppressive therapy before 1st operation	9 (60%)	1 (14%)	8 (100%)	0.001
Accumulative CYC dosage before 1st operation (g)	7.9 ± 8.1	2.1 ± 5.7	13.0 ± 6.4	0.004
ESR before 1st operation (mm/1st hr)	34.1 ± 18.9	44.4 ± 20.7	25.0 ± 12.1	0.04
Echocardiographic Parameters before 1st operation				
LVEDd (mm)	60.7 ± 5.8	58.4 ± 6.2	62.6 ± 5.0	0.17
LVEF (%)	63.9 ± 4.2	65.0 ± 5.5	63.0 ± 2.6	0.37
AAo (mm)	37.4 ± 7.4	38.4 ± 5.6	36.4 ± 9.5	0.69
Aortic root (mm)	35.9 ± 7.7	37.6 ± 5.5	33.8 ± 10.4	0.49
Total score of the lesions before first operation	1.9 ± 1.0	2.0 ± 1.2	2.0 ± 0.9	1.0
ESR after 1st operation (mm/1st hr)	35.38 ± 23.33	42.33 ± 33.28	29.43 ± 8.67	0.34
Reoperation or death	5 (33%)	5 (71%)	0 (0%)	0.007

AR: aortic regurgitation; CYC: cyclophosphamide; AVR: aortic valve replacement; LVEDd: left ventricular end-diastolic diameter; LVEF: left ventricular ejection fraction; AAo: ascending aortic diameter; ESR: erythrocyte sedimentation rate.

tic valve surgery (13, 14, 16). The delay in diagnosis and medical treatment could lead to a totally different clinical situation. Likewise, this is true for our cohort. Only 44.4% patients satisfied the ISG criteria before operations. The poor sensitivity in this situation may be on account of the lower incidence of ocular lesions. However, if applying the ICBD criteria that provides genital ulcerations more diagnostic value and adds vascular manifestations as a diagnostic item, 94% patients in our cohort can be diagnosed correctly before operations. These findings implied that ICBD criteria might be more applicable in evaluating the patients with AR suspicious of BD. Nevertheless, a controlled clinical study is necessary to test this finding among patients having AR due to BD and other causes.

Echocardiography seems to be useful for the differential diagnosis of BD before surgery. Consistent with previous studies (15, 21), the characteristic echocardiographic findings of aortic valve lesions in BD were redundant motion with aneurysmal changes of elongated aortic cusps and periannular pseudo-aneurysm. It should be borne in mind of the possibility of BD when these findings are encountered. Once these pathognomonic findings were detected, TEE should be suggested and performed in all the patients. The number of involved aortic cusps, the extension of pseudo-aneurysm around ascending aorta as well as the presence of interventricular dissection could be more accurately detected and evaluated by TEE. These are useful in determining the severity of lesions involving aortic valve and adjacent structure that has been suggested helpful in predicting recurrent AR after operations (16). Thus we carefully checked the anatomic feature of our patients but found no difference in the severity of lesions between the two groups with and without PVL after first operation.

In our study, preoperative usage of cyclophosphamide and glucocorticoid seems effective in preventing the progression of PVL and improving the prognosis. Pathologically, AR in BD is related with valvulitis and aortitis. Histologic examinations demonstrated characteristic myxoid degeneration in the aortic valve and perivascular infiltration of neutrophils and lymphocytes in adventitia, media as well as vasa vasorum of ascending aorta. All of these leave the aortic wall fragile and vulnerable to the prosthesis dehiscence (24). Theoretically, controlling aortitis by immunosuppressive agents may help to strengthen the aortic annulus and adjacent tissue, thus decrease the incidence of PVL. A few previous studies had proposed the possibility that perioperative immunosuppressive therapy (most were prednisone combined with azathioprine or colchicine) might be helpful in reducing PVL and reoperation (15, 16, 24, 25). However, whether preoperative immunosuppressive therapy is beneficial remains unclear. A recent study failed to demonstrate the favourable effect of preoperative use of prednisolone and colchicine (16). However, cyclophosphamide was applied to the patients instead of colchicine in our study. Since cyclophosphamide had

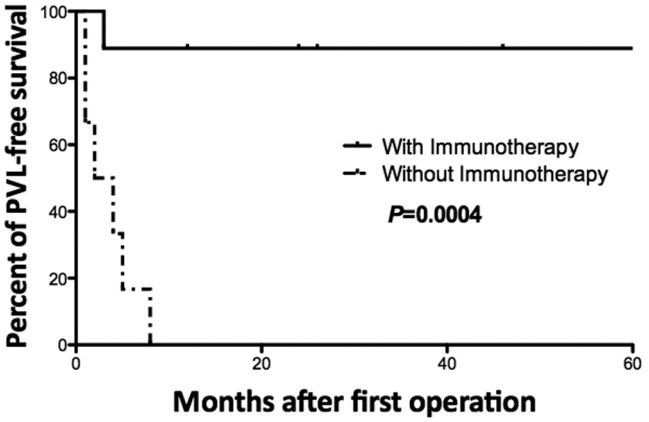

Fig. 2. Perivalvular leakage (PVL)-free survival curves after the first operation in all 15 patients.

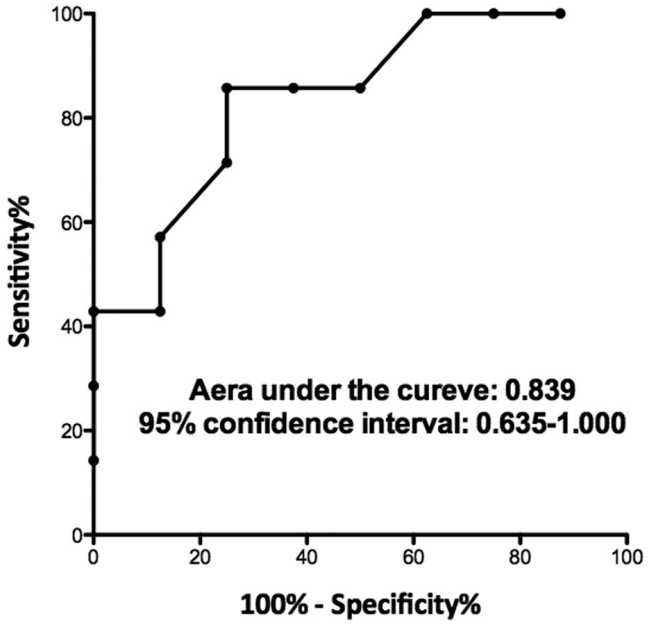

Fig. 3. Receiver operating characteristic curve testing the diagnostic value of preoperative ESR level in predicting perivalvular leakage (PVL).

been well documented for induction of remission of systemic vasculitis (26, 27) and organ-threatening situations in BD (28, 29), it is not surprising that this medicine was more effective in suppressing aortitis and preventing the development of PVL in BD patients. Even if PVL occurred, this therapeutic regimen seemed still valid in stabilising the progression. Furthermore, the median interval between the operation and the emergence of PVL was only 3.5 months which was too short for immunosuppressant to take effect if this treatment starts after cardiac surgery, so postoperative immunotherapy might not as effective as the preoperative strategy. It is true that sometimes AR occurred in an emergent or urgent condition so that administering immunosuppressive agents and delaying the operation might put the patients at great risk. In our study, three patients (patient 4, 11 and 13) came to the hospital with severe heart failure. One patient (Patient 4) underwent an urgent surgery without receiving immunosuppressant and the prognosis was poor. The other two were stabilised by use of diuretics and inotropic agent and then survived cardiac surgery after adequate immunosuppressive treatment. Hence, treating heart failure with conservative therapy, perhaps using assistive devices when necessary, might be the first choice in these patients for getting the opportunity to receive immunosuppressant before proceeding with surgery.

Notably our patients received a large amount of cyclophosphamide with an average cumulative dosage of 13.0 g during averagely 6-month preoperative period. This dose is employed because strong inflammatory reaction is always present in these BD patients with cardiovascular involvement. Though this dose is higher than the usual prescribed in vasculitis patients, most of the patients tolerated this high dose well in the present study except two. One (patient 5) had infective prosthetic endocarditis after aortic valve replacement, and the other (patient 9) suffered atypical mycobacterial and fungal pneumonia in the 3rd month of therapy and died of septic shock which might be affiliated with the immunosuppression. So it should be alert to severe adverse reactions especially opportunistic infections when practicing our treatment strategy.

Conventional inflammatory markers such as ESR, which could reflect BD activity, are proposed be helpful in predicting the prognosis and modifying the treatment strategy of BD. Here, we suggested that ESR might be an effective indicator of the timing of surgery. According to the present study, preoperative levels of ESR were significantly lower in non-PVL patients and those with ESR<32.5mm/first hour before the operations had much better outcomes.

Even preoperative immunosuppressant was crucial for the outcome of cardiac BD patients, continuity of the intensive immunosuppressive therapy is also important. BD is a chronic and relapsing autoimmune disorder with unpredictable exacerbation and remission. In our cohort, all the patients continued to use cyclophosphamide for more than half a year after surgery and gradually tapered the dosage or switched to other immunosuppressant.

It has been suggested that different surgery procedures may result in different event-free survival rate (15). However, only two patients underwent Bentall operation in our study: one developed PVL and vascular anastomotic fistula while the other was stable in good valvular function. Among those undergoing AVR, PVL occurred in 100% of patients without preoperative immunotherapy, which is as high as previous studies (70–100%) (11, 13, 16, 25), while only in 12% of those receiving preoperative immunosuppressive treatment. It is hard to find out the role of surgery procedure in determining the outcomes in this condition.

Limitations

We acknowledge some limitations in our study. First, this was a retrospective study and the number of patients enrolled was small. However, prospective enrolment and data collection from the time of diagnosis would be quite difficult considering the rare incidence and detection of severe AR in BD. Secondly, we were unable to collect complete longitudinal data of patients who were followed up only on an intermittent consultation basis. Finally, although we demonstrated the superiority of preoperative use of cyclophosphamide and glucocorticoid in the small number of patients, a larger clinical trial is necessary to test our findings.

Conclusion

In patients with severe AR due to BD, surgical treatment carries a high risk of postoperative morbidity as a result of perivalvular leakage at anastomosis sites because of the fragilities of aortic structure and tissue inflammation. Preoperative immunosuppressive therapy, especially cyclophosphamide in combination with glucocorticoids, might be essential for preventing the development of these serious postoperative complications and subsequently improving the outcome. In addition, preoperative ESR might be an effective marker in determining the timing of operation. We suggest that early detection of Behçet's disease and the start of an effective immunosuppressive therapy before first operation might provide the best means of improving clinical outcomes in AR attributable to Behçet's disease.

References

1. SAKANE T, TAKENO M, SUZUKI N, INABA G: Behçet's disease. *N Engl J Med* 1999; 341: 1284-91.
2. HATEMI G, SEYAHI E, FRESKO I, TALARICO R, HAMURYUDAN V: Behçet's syndrome: a critical digest of the 2013-2014 literature. *Clin Exp Rheumatol* 2014; 32 (Suppl. 84): S112-122.
3. ARSLAN C, ARAPI B, SEYAHI E, TEL C, TÜZÜN KH: Right ventricular thrombus and tricuspid valve dysfunction in a patient with Behçet's syndrome. *Clin Exp Rheumatol* 2014; 32 (Suppl. 84): S109-111.
4. AKSU T, TUFEKCIOGLU O: All Behçet's cases with intracardiac thrombus should be evaluated for pulmonary and vasculary involvement. *Clin Exp Rheumatol* 2015 Jan 20 [Epub ahead of print].
5. EMMUNGIL H, YAŞAR BILGE NŞ, KÜÇÜKŞAHIN O *et al*.: A rare but serious manifestation of Behçet's disease: intracardiac thrombus in 22 patients. *Clin Exp Rheumatol* 2014; 32 (Suppl. 84): S87-92.
6. HUONG DL, WECHSLER B, PAPO T *et al*.: Endomyocardial fibrosis in Behçet's disease. *Ann Rheum Dis* 1997; 56: 205-8.
7. HAMZAOUI A, BEL FEKI N, BRAHEM SFAXI A *et al*.: Chest pain in patients with undiagnosed Behçet's disease. *Clin Exp Rheumatol* 2012; 30 (Suppl. 72): S76-79.
8. YUAN SM: Cardiothoracic interventions in Behçet's disease. *Clin Exp Rheumatol* 2014; 32 (Suppl. 84): S130-9.
9. CHIKAMORI T, DOI YL, YONEZAWA Y, TAKATA J, KAWAMURA M, OZAWA T: Aortic regurgitation secondary to Behçet's disease. A case report and review of the literature. *Eur Heart J* 1990; 11: 572-6.
10. GONZALEZ T, HERNANDEZ-BERIAIN JA, RODRIGUEZ-LOZANO B *et al*.: Severe aortic regurgitation in Behçet's disease. *J Rheumatol* 1993; 20: 1807-8.
11. LEE CW, LEE J, LEE WK *et al*.: Aortic valve involvement in Behçet's disease. A clinical study of 9 patients. *Kor J Intern Med* 2002; 17: 51-6.
12. CRITERIA FOR DIAGNOSIS OF BEHÇET'S DISEASE: International Study Group for Behçet's Disease. *Lancet* 1990; 335: 1078-80.
13. HAN JK, KIM HK, KIM YJ *et al*.: Behçet's disease as a frequently unrecognized cause of aortic regurgitation: suggestive and misleading echocardiography findings. *J Am Soc Echocardiogr* 2009; 22: 1269-74.
14. ANDO M, KOSAKAI Y, OKITA Y, NAKANO K, KITAMURA S: Surgical treatment of Behçet's disease involving aortic regurgitation. *Ann Thorac Surg* 1999; 68: 2136-49.
15. JEONG DS, KIM KH, KIM JS, AHN H: Long-term experience of surgical treatment for aortic regurgitation attributable to Behçet's disease. *Ann Thorac Surg* 2009; 87: 1775-82.
16. SONG JK, KIM MJ, KIM DH *et al*.: Factors determining outcomes of aortic valve surgery in patients with aortic regurgitation due to Behçet's disease: impact of preoperative echocardiographic features. *J Am Soc Echocardiogr* 2011; 24: 995-1003.
17. TANG Y, XU J, XU Z: Supra-annular aortic replacement in Behçet's disease: a new surgical modification to prevent valve detachment. *Int J Cardiol* 2011; 149: 385-6.
18. AZUMA T, YAMAZAKI K, SAITO S, KUROSAWA H: Aortic valve replacement in Behçet's disease: surgical modification to prevent valve detachment. *Eur J Cardiothorac Surg* 2009; 36: 771-2.
19. INTERNATIONAL TEAM FOR THE REVISION OF THE INTERNATIONAL CRITERIA FOR BEHÇET'S DISEASE (ITR-ICBD): The International Criteria for Behçet's Disease (ICBD): a collaborative study of 27 countries on the sensitivity and specificity of the new criteria. *J Eur Acad Dermatol Venereol* 2014; 28: 338-47.
20. ZOGHBI WA, ENRIQUEZ-SARANO M, FOSTER E *et al*.: Recommendation for evaluation of the severity of native valvular regurgitation with two-dimensional and Doppler echocardiography. *J Am Soc Echocardiogr* 2003; 16: 777-802.
21. LEE I, PARK S, HWANG I *et al*.: Cardiac Behçet disease presenting as aortic valvulitis/aortitis or right heart inflammatory mass: a clinicopathologic study of 12 cases. *Am J Surg Pathol* 2008; 32: 390-8.
22. MOHAMMAD A, MANDL T, STURFELT G, SEGELMARK M: Incidence, prevalence and clinical characteristics of Behçet's disease in southern Sweden. *Rheumatology* (Oxford) 2013; 52: 304-10.
23. FEI Y, LI X, LIN S *et al*.: Major vascular involvement in Behçet's disease: a retrospective study of 796 patients. *Clin Rheumatol* 2013; 32: 845-52.
24. SEYAHI E, MELIKOGLU M, YAZICI H *et al*.: Clinical features and diagnosis of Behçet's syndrome. *Int J Adv Rheumatol* 2007; 5: 8-13.
25. AHN JK, KIM H, LEE J *et al*.: Treatment outcomes in patients with non-infectious aortic valvulitis undergoing aortic valve replacement: implication for the treatment of aortic valve involvement in Behçet's disease. *Rheumatol Int* 2009; 29: 1391-3.
26. EVEREKLIOGLU C: Current concepts in the etiology and treatment of Behçet disease. *Surv Ophthalmol* 2005; 50: 297-350.
27. SHARMA P, SHARMA S, BALTARO R, HURLEY J: Systemic vasculitis. *Am Fam Physician* 2011; 83: 556-65.
28. AIT BEN HADDOU EH, IMOUNAN F, REGRAGUI W *et al*.: Neurological manifestations of Behçet's disease: evaluation of 40 patients treated by cyclophosphamide. *Rev Neurol* (Paris) 2012; 168: 344-9.
29. DAVATCHI F, SADEGHI ABDOLLAHI B, SHAMS H *et al*.: Combination of pulse cyclophosphamide and azathioprine in ocular manifestations of Behçet's disease: longitudinal study of up to 10 years. *Int J Rheum Dis* 2014; 17: 444-52.