

Behcet's Disease with Uveitis in Taiwan

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Background: Behcet's disease is a multisystemic inflammatory disease which may lead to blindness. The purpose of this study was to describe and compare the clinical features and visual outcome of Behcet's uveitis in Taiwan.

Methods: The medical charts of 227 consecutive patients (414 eyes) with Behcet's uveitis who were seen in the Uveitis Clinic of Taipei Veterans General Hospital were reviewed: 96 patients (group A) between 1984 and 1993 and 131 (group B) between 1994 and 2003.

Results: The male-to-female ratio was 1.6. The mean age at the time of uveitis onset was 30.8 years. Males were most affected in the 3rd and 4th decades and females in the 2nd to 5th decades. There were more skin and gastrointestinal lesions in males, and less skin and genital lesions in group B. HLA-B51 antigen was found in 35.7% of patients. Treatment with cyclosporin, azathioprine and methotrexate was more frequent in group B. Uveitis occurred bilaterally in 83.9% of patients. At the first visit, potential visual acuity (VA) was 0.1 or less in 24.7% of eyes in males and 11.4% in females. The mean time from presentation to loss of useful vision (>0.1) was 51 months in 19.1% of eyes. Kaplan-Meier survival analysis estimated the risks of losing useful vision at 5, 10 and 15 years as being 22.6%, 43.0% and 58.5%, respectively. VA at the first and last visits were better and VA deterioration slower in group B.

Conclusion: Visual outcome is poorer in males than in females and has improved in the recent decade, but still a significant proportion of patients lose their vision quickly. The number of new patients has not decreased. [*J Chin Med Assoc* 2008; 71(10):509–516]

Key Words: Behcet's disease, Chinese, Taiwan, uveitis

Introduction

Behcet's disease (BD) is a multisystemic inflammatory disease characterized by oral and genital aphthosis as well as inflammation of the eye, skin, joints, gastrointestinal tract, vasculature, and even the central nervous system. One of the most common devastating conditions is recurring severe intraocular inflammation (uveitis) involving any area of the posterior segment. Uveitis in BD leads to optic nerve and chorioretinal atrophy and, eventually, blindness.

The geographical distribution of BD, mainly spanning countries between the Mediterranean countries and Japan, led to the synonym of *Silk Road disease*.¹ It is conjectured that Chinese living between the 2 areas are at greater risk. But a detailed search of the

literature via MEDLINE (PubMed) revealed little information regarding the disease in Chinese.^{2–5} A joint survey of 6 major ophthalmological departments performed in 1990⁶ found the prevalence of BD in Taiwan to be about 1 per 10⁵, which is much lower than the prevalence in Silk Road countries.⁷

Recently, the number of patients with newly developed BD decreased in Japan,^{8,9} and the visual prognosis for such patients seems to have improved in Japan and Turkey.^{9,10} In this study, clinical features, treatment, association of the genetic factor of HLA-B51 antigen, and visual outcome were assessed in all Chinese patients who were seen consecutively in a uveitis clinic at a tertiary ophthalmology center in Taiwan during a 20-year period. Furthermore, patients who visited between 1984 and 1993 were compared with patients



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who visited between 1994 and 2003. Our purpose was to describe and compare the disease presentation and visual outcome in these affected groups.

Methods

The study was approved by the Institutional Review Board of Taipei Veterans General Hospital. Diagnosis of BD was made on the basis of the revised criteria of the Behcet's Disease Research Committee of Japan in 2003.¹¹ Recurrent aphthous ulcers of oral mucosa, skin lesions, ocular inflammation, and genital ulcers are the main symptoms. Arthritis without deformity or sclerosis, epididymitis, gastrointestinal lesions, vascular lesions, and central nervous system lesions are additional symptoms. A diagnosis of BD was made for those who manifested 3 main symptoms or typical ocular lesion and another main symptom (1 main symptom was equal to 2 additional symptoms) during the clinical course.

All the patients included in this study were Chinese, had BD with ocular involvement, and were seen consecutively in the Uveitis Clinic of Taipei Veterans General Hospital during a 20-year period from January 1984 to December 2003. This Uveitis Clinic was established in 1984 and was the first one to be in a Chinese area.¹² The majority of patients were referred from all over Taiwan for further diagnosis and management. A rheumatologist was consulted upon diagnosis of uveitis with BD. A complete ocular examination was performed at each visit. Patients who visited the clinic between 1984 and 1993 were classified into group A, and those who visited between 1994 and 2003 into group B. Ocular manifestations were divided into anterior uveitis, posterior uveitis, or panuveitis when both were involved. When the manifestations of the 2 eyes of the same patient differed, it was defined as asymmetric.

Treatment protocol, which changed during the study period, was based on the severity of the disease. If the uveitis episode was limited in the anterior and/or intermediate segment, then a short course of topical steroid was given. If the uveitis episode was acute and involved the posterior segment, presenting with retinitis with retinal exudates or vasculitis with hemorrhage, then systemic corticosteroids with an evaluated dosage were given. In more severe cases, especially retinitis involving the macula, high-dose intravenous steroid therapy was given. On the other hand, according to disease activity, management was with observation only if the uveitis was mild and rarely recurred. Generally, 1.0–1.5 mg/day colchicine was used as the first choice for preventing the recurrence of uveitis.

When patients were not responsive to colchicine, cyclosporin-A and/or immunosuppressive drugs were used. Cyclosporin A was given in a dosage of 3–5 mg/kg/day since 1990. Immunosuppressive drugs including cyclophosphamide (2.5 mg/kg/day), chlorambucil (0.1–0.2 mg/kg/day), azathioprine (1–2.5 mg/kg/day), methotrexate (7.5–20 mg/week), and plaquenil (200–400 mg/day) were used. Those drugs were used in combination or alternatively according to the eye condition and response, and the potential side effects were closely monitored.

Visual acuities (VAs) of counting fingers, hand movement, light perception (LP), and no LP were given values of 6/1,200, 6/12,000, 6/30,000, and 6/60,000, respectively, to facilitate their conversion into logarithmic values.⁹ VAs better than 6/60 were defined as useful vision. Because VAs were usually severely affected during the inflammatory episodes, we defined potential VA as the best-corrected VA recorded at presentation if the eye was not affected or after the first observed inflammatory episode had resolved and vision had stabilized. For analyses of visual outcomes, only those eyes with potential VAs better than 6/60 were included. A simplified method⁹ was used to determine the stability of vision of those with potential VAs better than 6/60. The potential VA (α) was defined as mentioned above, and the final VA (β) was defined as the best-corrected VA during the month before the last visit or at the time when vision loss was irreversible. The t value is the time interval in months between the α and β measurements. The γ value was calculated using the following equation:

$$\gamma = (\log \text{MAR}\alpha - \log \text{MAR}\beta) / t$$

Data analyses were performed using SPSS version 13.0 (SPSS Inc., Chicago, IL, USA). The normality of each variable was examined using the Shapiro-Wilk test. The Mann-Whitney U test was used to compare nonparametric continuous variables. Categorical variables were analyzed using the χ^2 test or Fisher's exact test. The Kaplan-Meier method was used to estimate survival curves, and the differences between groups and genders were evaluated by the log-rank test. The level of statistical significance was set at less than 0.05.

Results

Demographics

A total of 227 patients were included; their demographic characteristics are shown in Table 1. The male-to-female ratio was 1.6. The mean age at the time of

Table 1. Patients' profiles and comparison between groups A and B

	Total	Group A (1984–1993)	Group B (1994–2003)	<i>p</i>
No. of patients	227	95	132	
Male:female	140:87	64:31	76:56	0.134*
Observation length (mo)	51.6±57.2 (range, 0–227)	83.4±71.2 (range, 0–227)	28.8±27.2 (range, 0–117)	0.000†
Time between uveitis onset and first visit (mo)	26.9±47.3 (range, 0–492)	23.1±28.2 (range, 0–144)	29.7±57.2 (range, 0–492)	0.715†
Average age at uveitis onset (yr)	30.8±10.9 (range, 6–62)	31.7±9.2 (range, 12–55)	30.1±12.0 (range, 6–62)	0.286†
Unilateral:binocular	36:187	10:85	26:102	0.050*
HLA-B51 (positive:negative)†	51:92	27:40	24:52	0.277*

*Calculated by χ^2 test; †calculated by Mann-Whitney U test; ‡based on available data of 143 patients.

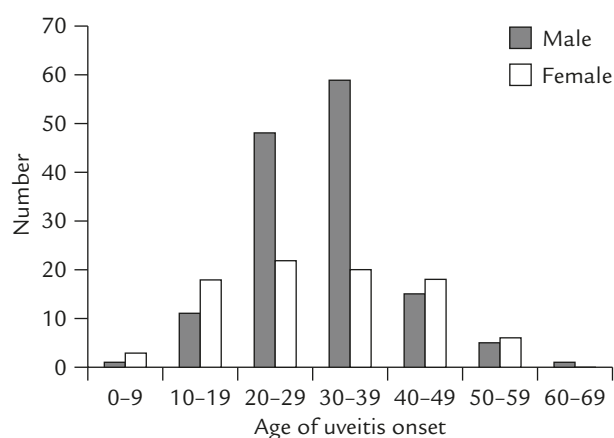


Figure 1. Age of uveitis onset by decade between males and females ($p=0.001$).

uveitis onset was 30.8 ± 10.9 years. Although the differences between sexes and groups were not significant, it was quite remarkable in age distribution by decades, as shown in Figure 1. Association of HLA-B51 antigen was observed in 51 (35.7%) of 143 assessed patients, and there was no difference between genders or groups.

Ocular manifestations

The ocular manifestations are summarized in Table 2. The most common manifestation was panuveitis. Binocular involvement occurred in 82.4% of patients. The percentage of panuveitis, bilateral eye involvement, and symmetric eye presentation was decreased in group B. There was no difference in type of uveitis or symmetry of ocular involvement between males and females.

Extraocular manifestations

The extraocular manifestations are summarized in Table 3. The most common manifestation was aphthous

Table 2. Comparisons of ocular manifestations between groups A and B

	Total	Group A	Group B	<i>p</i>
Type of uveitis				
Anterior	37	7	30	0.001*
Posterior	90	30	60	0.016*
Panuveitis	287	147	140	0.000*
Ocular involvement				
Unilateral vs. binocular	36:187	3:89	33:98	0.000†
Binocular	187	89	98	
Symmetric	167	89	78	0.000†
Asymmetric	20	0	20	
Single eye	4	3	1	

*Calculated by χ^2 test; †calculated by Fisher's exact test.

ulcer, occurring in 221 (97.4%) patients. The remaining 6 patients manifested skin lesions of erythema nodosum in addition to ocular symptoms. The frequencies of skin and gastrointestinal lesions were significantly increased in males, and those of skin lesions and genital ulcers were decreased in group B.

Treatment

The treatment is summarized in Table 4. Usage of colchicine, chlorambucil, and oral corticosteroids was significantly decreased and usage of cyclosporin, azathioprine, and methotrexate was increased in group B.

Visual outcomes

A total of 414 eyes were included (187 patients with bilateral involvement, 36 patients with unilateral involvement, and 4 1-eyed patients). Excluding 5 eyes without follow-up, potential VA was determined in 409 eyes. The visual outcomes of those eyes are summarized in Table 5. Females and patients in group B were more likely to have potential VA better than

Table 3. Comparisons of extraocular manifestations between sexes and groups

	Total (n = 227)	Male (n = 140)	Female (n = 87)	p	Group A (n = 95)	Group B (n = 132)	p
Oral ulcers	221 (97.4%)	136 (97.1%)	85 (97.7%)	0.579*	92 (96.8%)	129 (97.7%)	0.494*
Skin lesions	115 (50.7%)	82 (58.6%)	33 (37.9%)	0.002*	57 (60.0%)	58 (43.9%)	0.017*
Genital ulcers	98 (43.2%)	59 (42.1%)	39 (44.8%)	0.691*	49 (51.6%)	49 (37.1%)	0.030*
Arthritis	149 (65.6%)	92 (65.7%)	57 (65.5%)	0.976*	67 (70.5%)	82 (62.1%)	0.188*
Central nervous system lesions	29 (12.8%)	19 (13.6%)	10 (11.5%)	0.649*	8 (8.4%)	21 (15.9%)	0.095*
Gastrointestinal lesions	9 (4.0%)	9 (6.4%)	0 (0%)	0.012†	3 (3.2%)	6 (4.5%)	0.435†
Vascular lesions	0 (0%)	0 (0%)	0 (0%)	1.000†	0 (0%)	0 (0%)	1.000†
Epididymitis [‡]	13 (5.7%)	13 (24.1%)	0 (0%)	0.783*	5 (33.3%)	8 (20.5%)	0.908†
Complete:incomplete (% of complete type)	65:162 (28.6%)	41:99 (29.3%)	24:63 (27.6%)		36:59 (37.9%)	29:103 (22.0%)	0.009*

*Calculated by χ^2 test with continuity correction; †calculated by Fisher's exact test; ‡based on the available data of 54 male patients.

Table 4. Comparisons of numbers of patients receiving or not receiving agents between groups A and B

	Group A (n = 95)	Group B (n = 132)	p
Patients receiving:patients not receiving			
Colchicine	85:10	84:48	0.000*
Cyclosporine	15:80	55:77	0.000*
Cyclophosphamide	8:87	8:124	0.493*
Chlorambucil	9:86	1:131	0.002†
Azathioprine	2:93	23:109	0.000†
Methotrexate	0:95	11:121	0.002†
Plaqueenil	1:94	1:131	0.826†
Oral corticosteroids	67:28	53:79	0.000*

*Calculated by χ^2 test; †calculated by Fisher's exact test.

6/60. For eyes with potential VA better than 6/60, a total of 63 (19.1%) eyes lost useful vision irreversibly during follow-up, and males and patients in group B suffered more frequently from permanent VA loss. Both at the first and last visits for the 329 eyes with potential VAs better than 0.1, the percentage of eyes with good VA increased and that with poor VA decreased in group B and in females ($p=0.000$ and $p=0.000$, respectively; Figure 2). The mean time to loss of useful vision was 51.0 ± 40.3 months. There was no significant gender or group difference in mean time to this loss. The average γ value was -0.021 ± 0.096 . The speed of deterioration of VA decreased significantly in group B and females.

Kaplan-Meier survival analysis estimated the risk of loss of useful vision to be 22.6% at 5 years, 43.0% at 10 years, and 58.5% at 15 years. A significant gender difference was found (Figure 3). The risk of loss seemed to plateau after around 10 years in females. When comparing the risk of VA loss between groups, there was no significant difference for all patients, males or females.

Discussion

Behcet's disease was named by the Turkish physician Hulusi Behcet,¹³ who in 1937 described the classic trisymptom complex of hypopyon, iritis, and orogenital aphthosis. The Greek physician Adamantiades had reported the disease 6 year earlier, accounting for the alternative eponym Adamantiades-Behcet disease.¹⁴ However, the father of medicine, Hippocrates of Kos (460–377 BC), first described an endemic disease in Asia Minor characterized by “aphthous ulcerations”, “defluxions about the genital parts... watery ophthalmies of a

Table 5. Comparisons of visual outcomes between sexes and groups

	Total	Male	Female	<i>p</i>	Group A	Group B	<i>p</i>
Total eyes with follow-up	409	251	158		178	231	
Potential VA \leq 6/60	80	62	18	0.000*	59	21	0.000*
Potential VA $>$ 6/60	329						
Irreversible vision loss	63	51	12	0.000*	35	28	0.000*
Mean time to vision loss (mo)	51.0 \pm 40.3	49.1 \pm 40.4	59.3 \pm 40.2	0.426 [†]	57.7 \pm 44.4	42.7 \pm 33.3	0.186 [†]
γ value	-0.021 \pm 0.096	-0.032 \pm 0.123	-0.007 \pm 0.028	0.001 [†]	-0.023 \pm 0.066	-0.020 \pm 0.109	0.002 [†]

*Calculated by χ^2 test; [†]calculated by Mann-Whitney U test. VA = visual acuity.

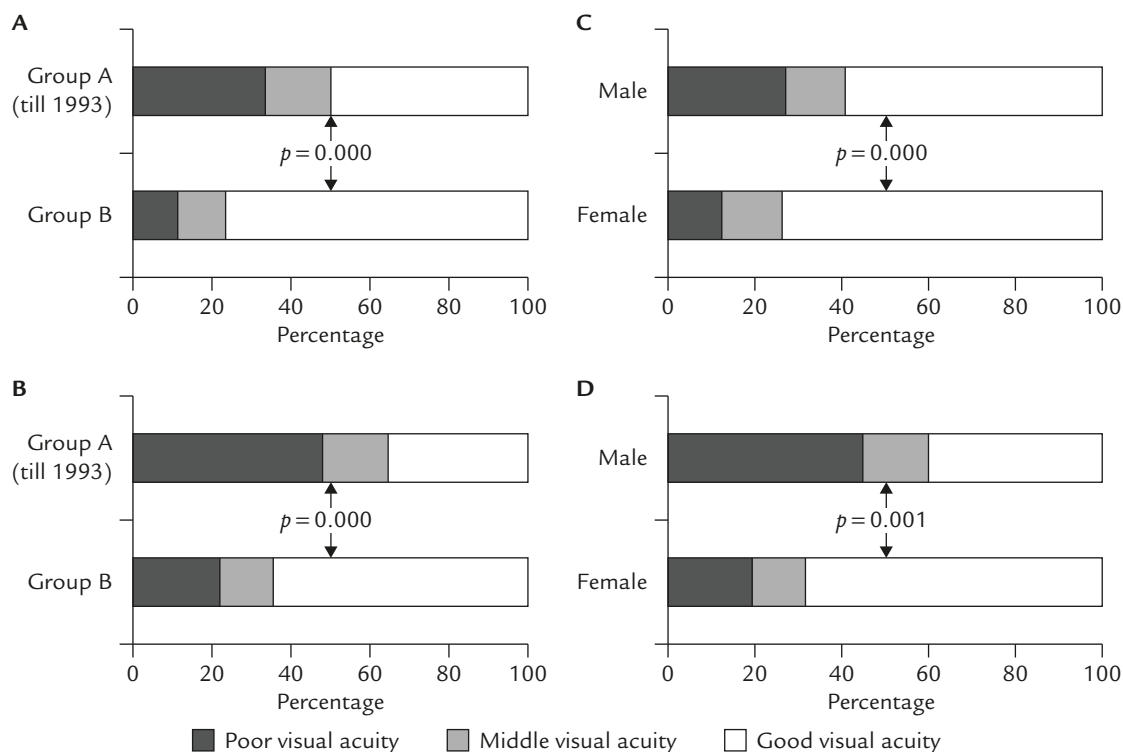


Figure 2. (A, B) Comparison between groups A and B of the number of eyes with poor and good visual acuities (VAs) at the first visit and last visit during the observation period. The end point of follow-up was set in December 1993 for group A in order to have similar follow-up period for both groups. (C, D) Comparison between males and females of the number of eyes with poor and good VAs at the last visit during the observation period. Good, middle, and poor VAs were designated \geq 6/12, $6/60 < VA < 6/12$, and $\leq 6/60$, respectively. The percentage of eyes with good VA increased ($p = 0.01$, χ^2 test), whereas that with poor VA decreased significantly ($p = 0.01$, χ^2 test) in group B and females.

chronic character... which destroyed the sight of many persons".¹⁵ A similar description of a disease named "Hu For" by Dr Chang Chung-Ching (AD 142–220, East Han Dynasty) was also found in ancient China. In the *Chin Kuei Yao Lueh* and *Shang-Han Lun*, Hu For is described as a syndrome comprising several common elements: *Hu* indicates the ulcers involving the genital organs, *For* indicates ulcers involving the oropharynx, "the eyes of the patient may be as red as those of a cushat", and "if the disease extends with the

route of Ki onto the body surface, skin abscesses with pustule formation can be observed".

There are more than 7 diagnostic criteria for BD.⁷ The International Study Group Criteria for Behcet's Disease¹⁶ is the most commonly used. But the specificity of ocular inflammation makes it as important as 2 other main symptoms used for diagnosis in the revised diagnostic criteria proposed by the Behcet's Disease Research Committee of Japan.¹¹ So most studies on BD with ocular involvement, including this study, have used

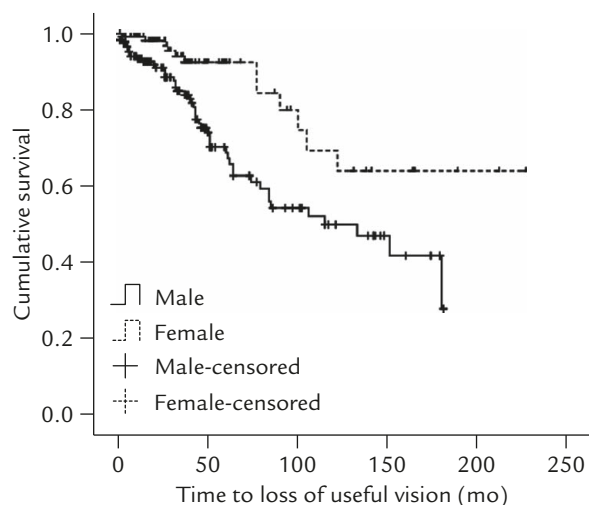


Figure 3. Kaplan-Meier curves showing cumulative survival of eyes with a potential visual acuity of >0.1 in male versus female patients. A censored observation represents irreversible loss of useful vision (≤ 0.1).

the Japanese criteria.^{6,9,17–22} BD is male-predominant in Turkey, Israel, Lebanon, Egypt, Iran and Greece, and female-predominant in Japan, Germany, Brazil, and the United States.⁷ But BD with ocular involvement is male-predominant everywhere, with a male-to-female ratio of 2.1 to 8.^{9,10,17–23} This ratio was relatively low (1.6) in our study, and did not significantly change during the 2-decade period of observation.

There was no significant gender and group difference in average age of uveitis onset (30.8 years), as previously reported.^{9,10,17–23} The most impressive finding (not previously reported) was that prevalence peaked in the 3rd and 4th decades in males, but was evenly distributed throughout the period between the 2nd and 5th decades in females. The frequency of binocular involvement was 84%, which was in the previously reported range of 64–98%.^{9,10,17,21–23}

Uveitis is one of the most devastating conditions in BD. The frequency of bilateral involvement ranged between 78% and 95% in previous reports,^{9,10,19,22,24} and the result of this study fell within this range. Panuveitis was the most common type of uveitis in 2 recent large series, with frequencies of 97.1% and 60.2%, respectively,^{9,10} and it was similar in this study. Furthermore, Tugal-Tutkun and his colleagues found that anterior uveitis was more common in females, while posterior segment involvement occurred more frequently in males.¹⁰ However, similar results were not present in this study. In this study, patients with panuveitis, bilateral involvement and symmetric ocular manifestations were decreased in group B.

Lower frequency of extraocular manifestations has been found in BD patients with ocular involvement

than in the general BD population. Oral ulcers are still the most common lesions (frequency of $>90\%$ to 100%).^{9,10,21–23} In this study, the frequency of skin lesions was 50.7% (previously reported range, 51–80%).^{9,10,21–23} The cause of significantly higher frequency in males and lower frequency in group B is unknown. The frequency of genital ulcers was 43.2% (previously reported range, 41–80%).^{9,10,21–23} Our observation of significantly lower frequency in group B was similar to that reported by Yoshida et al.⁹ The frequency of arthritis was as high as 66%, that is, even higher than the frequency of skin lesions or genital ulcers. The frequency of neuropsychiatric symptoms was 12.8%, which was slightly higher than the reported range (3.8–8.2%).^{9,10} Gastrointestinal lesions occurred in 4.0%, similar to the rate found by Yoshida et al,⁹ but the reason these lesions all occur in males is unknown. The number of patients with complete-type BD appeared to be decreased in the second decade, though this decrease was not statistically significant. The same tendency was found in Japan.⁹

High prevalence of HLA-B51 in BD patients has been found in different ethnic areas.¹ In this study, the incidence of HLA-B51 was 35.7%, much higher than the 6.03% in 7,137 blood samples from the Min-Nan,²⁵ the largest ethnic group in Taiwan. Only one-third of patients had HLA-B51 antigen, which indicates that many factors are still unknown in the pathogenesis of BD.

Colchicine is the preferred treatment and has been widely used in Japan since the 1970s.²⁶ But a double-blind trial of colchicine in BD revealed that it may only be useful for less severe cases.²⁷ In this study, colchicine was the most frequently used drug, but its usage decreased significantly in the last decade, when cyclosporin, azathioprine and methotrexate were used more frequently. Cyclosporin treatment for BD was first reported in 1985,²⁸ and became popular thereafter.^{9,21} Currently, our clinic uses a combination of cyclosporin and low-dose corticosteroid in patients with posterior segment involvement and multiple recurrence. If the combination is not effective enough to prevent recurrence, azathioprine, methotrexate and other immunosuppressants are added. When these immunosuppressive agents are prescribed systemically, their possible side effects should be kept in mind, such as hypertension, hyperglycemia, and hepatorenal toxicity for cyclosporin; leukopenia and thrombocytopenia for azathioprine; leukopenia, hepatorenal toxicity, and central nervous system toxicity for methotrexate; and pulmonary fibrosis, jaundice, renal toxicity, bone marrow suppression, and hemorrhage cystitis for chlorambucil and cyclophosphamide. Therefore, regular follow-up of

liver function, renal function, complete blood count, blood pressure, and serum concentration of certain drugs are mandatory. As the clinical manifestations of this disease are diverse, multidisciplinary coordination is essential for optimal care. Ophthalmologists who take care of these patients should keep close communication with various specialists to achieve successful treatment.

To evaluate the visual outcomes in BD, we compared: (1) the number of patients who had lost useful vision at their last visit and the mean time to this loss; (2) the γ value; and (3) the risk of vision loss using Kaplan-Meier survival analysis. Visual prognosis was better in females regardless of method of evaluation, which is consistent with previous reports.^{10,17,23} However, the difference between groups was less remarkable. Although fewer patients lost useful vision and the γ value was better in group B, Kaplan-Meier survival analysis failed to show a significant between-group difference. The average time to loss of useful vision was even shorter in group B, although the difference was not significant. One possible explanation is that there were more patients with more severe disease in group B. As ours was the first uveitis clinic in Taiwan, most patients with uveitis in Taiwan were referred to this clinic during the first decade of our study. However, as more ophthalmologists began to treat these patients, some patients with milder disease were treated at other medical facilities. One piece of supportive evidence is the average time between uveitis onset and the first visit, which was longer in group B than in group A. We have concluded that the visual prognosis has generally improved in the last decade, but still a significant proportion of patients with more severe disease lose their vision more quickly despite the most aggressive treatment.

Visual outcome in BD was poor before the 1980s. Mamo²⁹ reported that vision was lost in an average of 3.36 years after the onset of ocular symptoms. Mishima et al²⁴ found that more than 50% of Japanese Behcet patients had a visual acuity of ≤ 0.1 in 5 years. BenEzra and Cohen³⁰ reported that in 74% of eyes, useful visual acuity was lost in 6–10 years after the onset of uveitis. In this study, an irreversible visual loss was found in 19.6% of 409 eyes at the beginning of the follow-up period, and useful visual acuity was lost in 19.1% of the other 329 eyes in 6.49 years (4.25 years after the first visit plus 2.24 years from onset to the first visit). Thus, 38.7% of eyes lost useful vision in total. The percentage of vision loss was much lower than that reported 20 years ago.^{24,29,30} But compared to the visual outcomes reported in the 2 largest recent series, 1 from Turkey¹⁰ and 1 from Japan,⁹ the visual

outcome in our series was poorer. Our series had a risk of loss of useful vision of 22.6% at 5 years, 43.0% at 10 years, and 58.5% at 15 years, which was worse than that in Turkish patients.¹⁰ In the Turkish series, survival rate remained stable after around 10 years for both sexes. However, in our study, stable survival of eyes occurred only in females while it continuously declined in males. The rate of visual deterioration was also worse than that in the Japanese series.⁹

The number of new patient with BD is decreasing in Japan.^{8,9} But our study found no such tendency. Our data confirm the generally held beliefs that the prognosis is worse in male patients and that the disease severity has become milder.^{9,10} Nevertheless, uveitis in BD remains a severe sight-threatening disease. Overall, we think the current information concerning uveitis with BD in Chinese patients is instructive.

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