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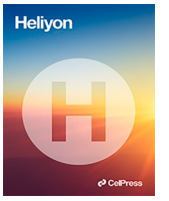

Protective effect of early immunomodulatory treatment on ocular involvement in Behcet's disease: Historical cohort of 1166 patients

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ABSTRACT

Objectives: Eye involvement is a main presentation of Behcet's disease. This study was performed to evaluate possible determinants affecting the occurrence of eye involvement, especially the role of early systemic treatment with immunomodulatory drugs on the incidence of ocular involvement.

Methods: This is a retrospective cohort study performed on 1166 Behcet's patients in the Behcet's Clinic of Rheumatology Research Center. All patients were followed up for at least 10 years and a maximum of 15 years. Data analysis was performed using survival analysis models including Kaplan-Meier Survival analysis, Logrank test, and Cox's proportional hazards regression.

Results: 1166 Behcet's patients were evaluated. 80 patients who had eye involvement as the first manifestation of the disease were excluded and 1086 participants entered the analysis. Among them, 647 patients (59.6%) developed ocular involvement 7.8 ± 6.7 years after the first symptom. Immunomodulatory treatment before ocular involvement reduced the risk by 3 times (P-value <0.001).

Conclusion: This study demonstrated that the initiation of immunomodulatory treatment prior to eye involvement can reduce the risk of eye involvement in Behcet's patients. Therefore, reducing the onset time of disease symptoms and providing appropriate treatment can reduce Behcet's disease ocular complications.

1. Introduction

Originally Hulusi Behçet described Behcet's disease in 1937, who reported three patients with oral and genital aphthpous, uveitis, and skin lesions [1]. Behcet's disease is a systemic autoimmune disease that is classified as systemic vasculitis that can affect small, medium, and large arteries and veins. Oral, genital, skin lesions, eye, and joint involvement are the most common features of the

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disease. Behcet's disease is known as Silk Road disease. The highest incidence of this disease has been reported in Japan, Korea, China, Turkey, and Iran [2–6]. Behcet's disease's prevalence in Iran is 80 per 100,000 population [7–10].

Behcet's disease's early symptoms are skin and mucosa involvement that can affect the quality of life but do not cause permanent damage which is why some references like EULAR recommend that systemic immunosuppressive treatments are not necessary at this stage of the disease [11,12]. However, studies have shown that many of these patients develop organ involvement that can lead to organ dysfunction such as the eye, brain, vessels, and testicles [13]. A study from the BD registry in Iran showed that 55% of patients had ocular involvement in their lifetime [14]. Ocular involvement presents as inflammation of ocular layers (anterior, posterior uveitis, and pan-ophthalmitis) and retinal vasculitis, which can lead to blindness [15]. Treatment of Behcet's disease associated uveitis relies on corticosteroid therapy, immunosuppressive drugs, and or biologic agents [16]. There is an expert opinion that early prescription of systemic immunomodulatory drugs instead of topical treatment for mucocutaneous manifestations can delay the onset of ocular involvement, but there is little evidence to support this opinion.

In this study, we used the database of Behcet's patients in the Rheumatology research center and Shariati Hospital of Tehran university of medical sciences and additional information from outpatient and inpatient medical records, to design and conduct a historical cohort study to assess the correlation between early prescription of immunomodulatory drugs and incidence time of Behcet's disease ocular involvement.

2. Patients and methods

2.1. Participants enrollment

This study is a historical cohort and the data registry of Behcet's patients in the Rheumatology research center in Shariati Hospital was the primary source for data gathering. 1166 participants with Behcet's disease enrolled in this study. The study population included those patients who visited the BD Clinic (inclusive). We excluded the patients who had eye involvement as the first manifestation of the disease for analysis. Retrospectively we followed the patients from the first manifestation and their clinical data were extracted from regular visit reports. These patients were regularly visited by Rheumatologist and ophthalmologist. All the participants had written informed consent to enter the data into Bechet's disease registry. The diagnosis of Behcet's disease in all patients was confirmed using international criteria for Bechet's disease. The ethics in research committee at Tehran university of medical sciences approved this research with the number 16370 (1401/11/53/580). All methods in this study are according to the related guidelines and regulations.

2.2. Data registry

The data collection sheets contained demographical and clinical characteristics of patients. These forms were filled using medical records. The time of each important clinical event and the time of Immunomodulatory treatment at each visit were also extracted. It should be mentioned that all patients in the BD clinic underwent a full ophthalmological examination by an expert ophthalmologist to diagnose Behcet's ocular involvement in every routine visit. Immunomodulatory treatment was defined as systemic oral treatment with either colchicine or low-dose corticosteroids (less than 15 mg daily). Severity at diagnosis was defined as having any major organ involvement at the time of disease diagnosis. This includes the eyes, nervous system, vascular system, gastrointestinal system, and reproductive system [17].

2.3. Statistical analysis

Based on the exposure participants were divided into two groups, one group with positive exposure (early systemic immunomodulatory treatment) and the other group with negative exposure. Then the survival analysis was performed based on the time of the first eye involvement episode.

Table 1
Patients characteristic.

Disease onset age (Mean ± SD)	25.1 ± 9.4 y
Diagnosis age (Mean ± SD)	32 ± 9.3 y
Sex	
Male	619 (57%)
Female	467 (43%)
Behcet's disease Family history	58 (5.3%)
The pathergy Test (Positive)	537 (49.4%)
HLA-B5 (Positive)	502 (46.3%)
Follow-up Time (Mean ± SD)	11.6 ± 7.6 y
First presentation	
Oral lesions	1032 (95%)
Genital lesions	157 (14.4%)
Pseudo-folliculitis	37 (3.4%)

Data analysis was performed using survival analysis models including Kaplan-Meier Survival analysis and Logrank test. Proportional hazard assumption was checked using both graphical diagnostics and goodness of fit test and Univariate Cox's regression was performed. The variables that were found to have a P-value ≤ 0.2 in the univariate model entered into the multivariate Cox model. All analyzes were performed by Stata software (version 11, StataCorp, LP, TX, USA). A P value < 0.05 was considered as statistically significant.

3. Results

Among 1166 participants that we evaluated we excluded 80 patients who had eye involvement as the first manifestation of the disease and 1086 patients entered the analysis. 619 (57%) were male and 467 (43%) were female. The female to male ratio of

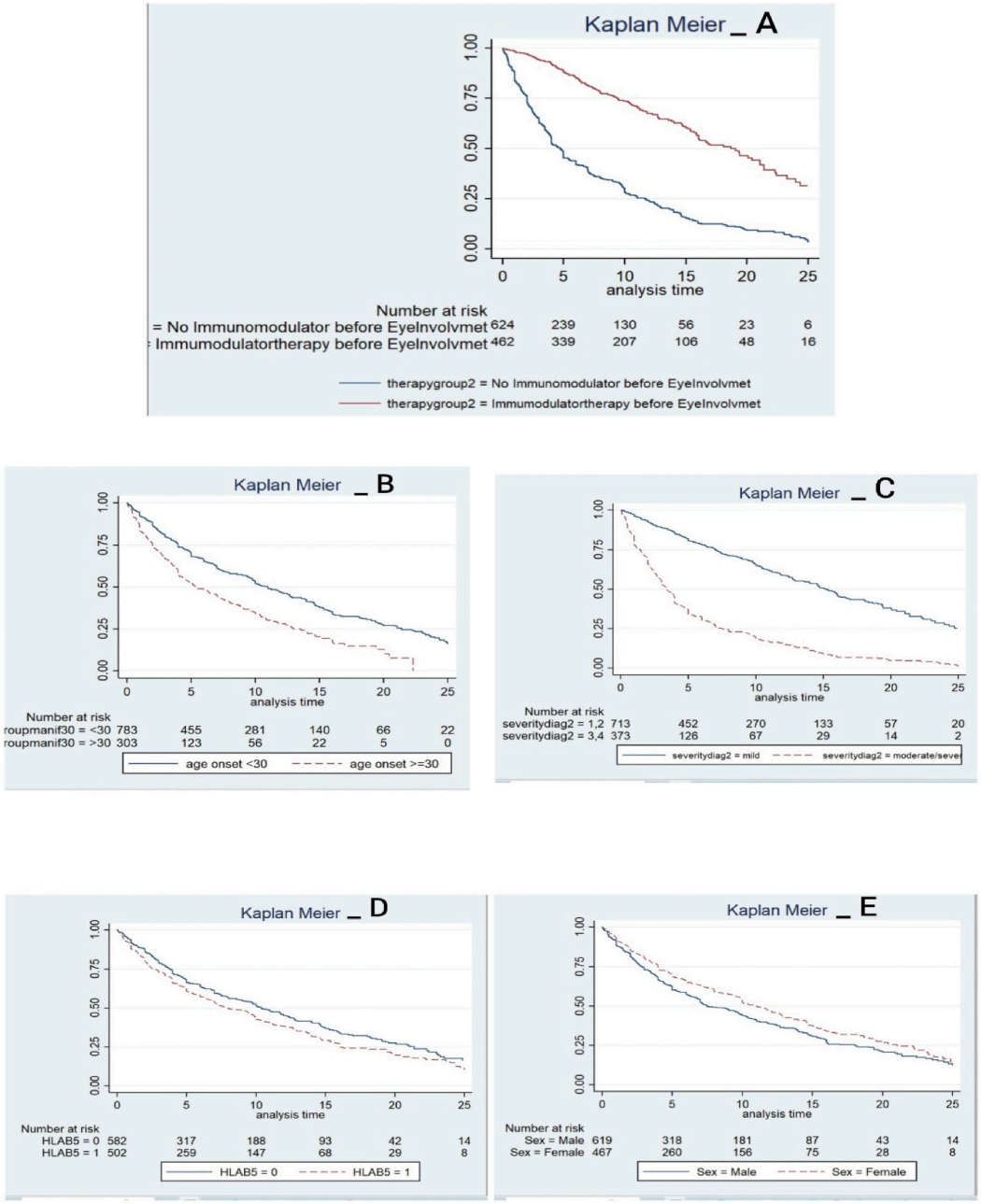

Fig. 1. Kaplan-Meier survival estimate for variables with P-value <0.05 in log rank test (A: Immunomodulatory treatment before eye involvement, B: Age of disease manifestation less than 30 and more than 30, C: Severity at diagnosis, D: positive and negative HLAB5, E: Sex of patients).

participants in our study was 1–1.3. The age of onset was 16 years or younger in 207 patients (17.75%) and 959 (82.25%) patients had age more than 16 at the time of disease onset. Table 1 shows the patient characteristics.

During the study follow up period, ocular involvement occurred in 727 patients (62.3%). The mean ± SD time to ocular involvement from the first presentation of BD was 5.8 ± 6.2years and the median time to ocular involvement was 3.7. Eye involvement led to blindness in 201 patients (28.4%). Among all participants 462 (42.5%) patients had immunomodulatory treatment before eye involvement and 624 (57.5%) did not have immunomodulatory treatment before eye involvement.

Kaplan-Meier survival estimate and log-rank test showed that sex, age of disease onset, HLA B5, severity at diagnosis, and immunomodulatory treatment before eye involvement had a significant effect on survival (P-value was 0.01, <0.001, 0.01, <0.001, <0.001 respectively) (Fig. 1).

Univariate Cox regression also showed that sex, age of disease onset, HLA B5, severity at diagnosis, and immunomodulatory treatment before eye involvement significantly decreased eye involvement. These variables were used in the final multivariate Cox regression which showed that immunomodulatory treatment before eye involvement, age of disease onset, and severity at diagnosis are the prognostic factors of eye involvement. Based on this regression, immunomodulatory treatment before eye involvement reduced the risk of eye involvement by 2.70 times and patients who had severe disease and other major organ involvement at the time of diagnosis had 2.55 times higher risk for developing eye involvement. The analysis also showed that patients with age of disease onset more than 30 years old also had 2.01 times more risk for eye involvement (Table 2).

4. Discussion

Our results showed that immunomodulatory treatment before eye involvement can reduce the risk of eye involvement occurrence. Univariate analysis showed that sex, age at onset of clinical symptoms, HLA B5, severity of disease at diagnosis time, and early immunomodulatory treatment are associated with eye involvement. However, in the final Cox regression model, treatment with immunomodulators prior to the onset of eye involvement, age of first clinical symptom, and severity of disease at the time of diagnosis remained as prognostic factors in survival without eye involvement.

Based on our results immunomodulatory treatment before eye involvement is the most important prognostic factor for which medical intervention is possible; and reduced the hazard of eye involvement up to 2.7 times. Although immunomodulatory drugs (systemic steroid and colchicine) are used for eye involvement treatment [18]; However, no other study has evaluated the effect of immunomodulatory treatment prior to the onset of ocular involvement on ocular outcome. A study performed on male patients with BD showed that colchicine appeared to decrease the requirement for immunosuppressive use among older onset patients [16]. This may indirectly show the effect of early colchicine treatment on decreasing major organ involvements that need immunosuppressive treatment. Another small trial on both male and female patients showed no relationship between early initiation of colchicine with decreasing the use of other immunosuppressive drugs in late stages of the disease [19].

Also, based on the final Cox model, the risk of eye involvement was twice as high in patients with an age of onset greater than 30 years than in patients with an age of onset less than 30 years. In another retrospective study that was aimed to evaluate the natural course of BD; eye involvement was higher in the patients whose disease onset was at < 40 years which is incoherent with our results [13]. Also in another retrospective study there was no relationship between age of onset and eye involvement [15]. These differences could be due to different diagnosis and treatment delays in these studies and performing prospective cohort studies can give a better understanding of the effect of the age of onset on ocular involvement.

Ocular involvement in patients who had more severe disease and organ involvement at the time of diagnosis is about 2.5 times more than patients who had milder disease at the time of diagnosis. This shows the importance of BD diagnosis before major organ involvement.

In this study, female sex was a protective factor for eye involvement in univariate but in the final regression model, sex did not have

Table 2
Univariate and multivariate Cox regression model.

Variable		Univariate cox regression		Multivariate cox regression	
		Hazard ratio	P value	Hazard ratio	P value
Immunomodulatory treatment before eye involvement	no	1 (base)	–	1(base)	–
	yes	0.29	<0.001	0.37	<0.001
Sex	male	1 (base)	–	1 (base)	–
	female	0.80	0.007	0.89	0.16
Age of disease manifestation	<30	1 (base)	–	1(base)	–
	≥30	1.74	<0.001	2.01	<0.001
Disease severity at diagnosis	Not severe	1 (base)	–	1(base)	–
	Severe	3.84	<0.001	2.55	<0.001
HLA B5	negative	1 (base)	–	1(base)	–
	positive	1.24	0.006	1.15	0.07
HLA B27	negative	1 (base)	–	–	–
	positive	1.05	0.75	–	–
Pathergy Test	negative	1 (base)	–	–	–
	positive	0.94	0.42	–	–

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a significant effect on eye involvement. Previous studies also showed that men had a more severe course of the disease and a higher risk of losing vision than women [12,20].

5. Conclusion

Our study showed that early use of immunomodulatory treatments such as corticosteroids and colchicine may decrease the incidence of ocular lesions in Behcet's patients. Ocular involvement is one of the most common organ involvements in Behcet's disease. The results of this study show the promising efficacy of corticosteroids and colchicine in reducing eye involvement. Regarding the importance of preventing ocular involvement in reducing disease morbidity and mortality, further studies with prospective and interventional designs are needed to assess this association.

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Author contribution statement

Arash Tehrani-Banihashemi: Conceived and designed the experiments; Analyzed and interpreted the data; Wrote the paper.
Seyedeh Tahereh Faezi: Conceived and designed the experiments; Performed the experiments
masoud Solaymani-Dodaran: Analyzed and interpreted the data; Contributed reagents, materials, analysis tools or data.
Faezeh Mohammadi: Performed the experiments; Wrote the paper.
Farhad Shahram and Pedram Paragomi: Contributed reagents, materials, analysis tools or data.
Kamran Moradi: Performed the experiments.
Fereydoun Davatchi: Conceived and designed the experiments.

Data availability statement

Data will be made available on request.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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