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ORIGINAL RESEARCH

Systemic Immunomodulatory Therapy in Uveitis Related to Behçet's Disease: A 10-year Profile

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Purpose: Behçet's disease (BD) is a systemic vasculitis which is often accompanied by intraocular inflammation. This study aims to determine the efficacy and safety of systemic immunomodulatory therapy (IMT) in Behçet's disease and the optimal timing for its discontinuation in patients who are in remission.

Patients and Methods: A retrospective single center longitudinal study was performed at the Centro Hospitalar Universitário São João (Porto, Portugal). A total of 38 records of patients with uveitis related to BD and on IMT were analyzed for demographic data, characteristics of their uveitis, treatment period, pattern of relapses, and first and final discontinuation outcomes. The statistical analyses were done with IBM SPSS® software.

Results: The mean follow-up duration was 122.5 ± 62.6 months. Anterior uveitis was the most common manifestation (36.8%), followed by retinal vasculitis (31.6%) and panuveitis (13.2%). Azathioprine (36.8%) and cyclosporine (28.9%) were the most used immunomodulatory agents. The median treatment duration was 63.5 months, significantly reducing relapse rates from 2 ± 2.0 to 1 ± 1.2 per year ($p < 0.001$). Biologic therapies showed a slight advantage in reducing relapses ($p = 0.045$). Among 16 patients (42.1%) who discontinued treatment, 30.8% experienced relapse after a median of 13 months. Patients treated for more than 6 years had no relapses.

Conclusion: IMT effectively controls ocular inflammation in BD uveitis, significantly reducing relapse frequency. Azathioprine and cyclosporine remain first-line therapies. Discontinuing IMT after 4–6 years of sustained remission appears to be a safe strategy, particularly after 6 years.

Keywords: uveitis, retinal vasculitis, remission, discontinuation

Introduction

Behçet's disease (BD) is a systemic vasculitis frequently associated with intraocular inflammation. It is characterized by significant clinical heterogeneity and presents with various systemic manifestations, including mucocutaneous, articular, vascular, neurological, and gastrointestinal features. It is most common in regions along the historic "Silk Road", stretching from Eastern Asia to the Mediterranean basin. The highest incidence has been recorded in Turkey.[1,2]

The etiopathogenesis of BD has not been clarified. It usually affects young adults 20 to 40 years of age and is characterized by a relapsing and remitting course.[2] While both genders are affected equally, male patients tend to experience a more severe progression of the disease.

The criteria established by the International Study Group for Behçet's disease requires that patients must have recurrent oral ulcers along with at least two of the following criteria: recurrent genital ulcers, skin lesions, eye lesions, or a positive pathergy test.[3]

Ocular involvement contributes most to the morbidity in BD. Common eye symptoms include blurred vision, reduced visual clarity, redness, periocular or periorbital pain, light sensitivity, tearing, foreign body sensation, and headaches. The

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most common type of ocular involvement in BD is non-granulomatous uveitis, often accompanied by retinal vasculitis and can be the initial manifestation of the disease. Bilateral involvement is generally observed and may affect anterior, posterior or both segments of the eye (panuveitis). Panuveitis and posterior uveitis are the most common forms of involvement, posing a significant threat to vision and a high risk of lasting complications.[4]

In recent years, research in Behçet's disease uveitis (BU) has evolved significantly, particularly through the integration of artificial intelligence (AI) and radiomics into ophthalmic diagnostics. Novel AI-driven models, especially those based on OCT angiography and radiomic biomarkers, have demonstrated high diagnostic performance in identifying BU, providing a promising complement to clinical evaluation and overcoming.[5]

The primary goals in the management of patients are to achieve rapid resolution of intraocular inflammation, to prevent recurrent attacks, and to ensure complete remission and preservation of vision.

Patients with isolated anterior uveitis can be managed using topical steroids. However, systemic IMT (immunomodulatory therapy), such as azathioprine (AZA) could be considered in cases of poor prognostic factors such as hypopyon, early onset of the disease and male gender.

In case of posterior uveitis and panuveitis systemic IMT should be started as soon as possible, such as azathioprine and cyclosporine, in complement to oral corticosteroids.[3,6]

Intra or periocular corticosteroids can be used in addition to systemic treatment for unilateral exacerbations.[7]

In refractory or recurrent cases, biological therapies such as infliximab (IFX) and adalimumab (ADA) are recommended.[8] However, the treatment strategy involving conventional immunomodulators versus anti-TNF agents has not been clearly defined.[9]

Determining whether disease stability results from the treatment itself or the naturally relapsing-remitting course of the disease is challenging. Also, establishing a standardized protocol for discontinuing treatment in all BD patients is complicated because of the higher relapse risk in men and younger individuals. There is no consensus on the appropriate timing to discontinue treatment for BD patients in remission. Current recommendations suggest that in patients with significant organ involvement, as in the case of uveitis, remission may be achieved after 2–5 years of IMT[6] or after more than 6 years.[10]

This strategy aims to maintain remission and limit ocular inflammation. Treatment efficacy is critical to avoid the consequences of long-term ocular inflammation, associated with significant morbidity among an overall young active population, including permanent vision loss. BD uveitis is responsible for an important share of the world's immune-related blindness, so initiating treatment as early as possible can improve this prognosis.[7]

Materials and Methods

Study Design, Setting and Participants

This is a retrospective, single center, longitudinal study of patients with unilateral and bilateral uveitis related to Behçet's disease, followed in the Ophthalmology department of Centro Hospitalar Universitário São João (Porto, Portugal).

Data from all patients under systemic IMT evaluated in the past 10 years were collected by chart review. Initial screening searched for patients under methotrexate, adalimumab, cyclosporine, azathioprine, infliximab and certolizumab, which provided a total of 509 medical processes.

Afterwards, only patients with Behçet's disease were included.

Data Collection

The following information was extracted from each case, based on the patient's electronic medical records and procedure reports: demographic data, characterization of the initial uveitis episode, type of uveitis, total follow period, type and duration of IMT, need for adjuvant corticosteroid therapy and pattern of disease remission and relapses were recorded. Intolerance or toxicity as well as treatment's discontinuation were also documented.

Statistical Analysis

Kolmogorov–Smirnov and Shapiro–wilk tests were used to assess whether each continuous variable followed a normal distribution, with Shapiro–Wilk being preferred for small sample sizes. Normally distributed data is reported as mean ±

standard deviation (SD) while non-normally distributed data is reported as median and interquartile range (IQR). Categorical variables are presented as absolute number and percentage. Parametric tests like student's *t*-test and non-parametric tests like Mann–Whitney or Wilcoxon were used for variables comparison between groups, according to the normality of data. We used Mann–Whitney to compare independent variables and Wilcoxon to compare paired (dependent) variables. Categorical variables were compared using Chi-square or Fishers exact tests.

A p-value<0.05 was considered statistically significant. Statistical analysis was done using IBM SPSS® software (version 26.0).

Results

We analyzed 38 patients with BD under IMT.

Demographic Features and Uveitis Characterization

The mean total follow-up time of patients in this sample was 122.5 ± 62.6 months [10–250]. Patients' mean age was 44.1 ± 11.6 [24–70] and 20 patients were women (52.6%).

Fourteen (36.8%) presented with anterior uveitis, which include iritis, iridocyclitis and anterior cyclitis. Three patients (7.9%) were diagnosed with posterior uveitis, which included choroiditis and/or retinitis. While retinal vasculitis could technically be classified as posterior uveitis, we opted to distinguish it as a separate entity since twelve patients (31.6%) presented specifically with vasculitis. Three patients exhibited with intermediate uveitis (7.9%), which included pars planitis, posterior cyclitis and hyalitis, and five patients had panuveitis (13.2%), which included anterior chamber, vitreous and retina or choroid. One presented with optic neuritis (2.6%).[11,12] Twenty-four patients (63.2%) presented with bilateral uveitis and twenty-six patients (68.4%) had uveitis as their first presentation of the disease (Table 1).

Treatment

The median duration of treatment was 63.50 ± 59.1 [4–201] months. Among the patients, 24 (63.2%) received IMT for at least 48 months, and 16 (50%) were treated for a minimum of 72 months.

Azathioprine was the most widely used immunomodulatory agent (n = 14, 36.8%). Cyclosporine was the second mostly used (n = 11, 28.9%). Adalimumab was used in 4 patients, (10.5%) of which three were already on cyclosporine

Table 1 Demographics and Uveitis Characterization

Parameter	Total Subjects (n=38)
Age, years	44.1 ± 11.6 [24–70]
Gender, male/female	18 (47.4) / 20 (52.6)
Total follow-up time, months P25 P50 P75	122.5 ± 62.6 [10–250] 66 131 175
Inflammatory ocular disease Anterior uveitis Vasculitis Panuveitis Posterior uveitis Intermediate uveitis Neuritis	 14 (36.8) 12 (31.6) 5 (13.2) 3 (7.9) 3 (7.9) 1 (2.6)
Unilateral / Bilateral	14 (36.8) / 24 (63.2)
Uveitis was the first presentation of the disease	26 (68.4)

Note: Data presented as mean ± standard deviation; or frequency n (%); [range].
Abbreviations: P25, percentile 25; P50, percentile 50; P75, percentile 75.

and one on azathioprine and infliximab. Infliximab was used in 3 patients (7.9%), of which one was already on cyclosporine, and methotrexate was used in 2 patients (5.3%). Ocular inflammation was effectively managed with a combination of methotrexate and adalimumab in 2 patients (5.3%). In one patient (2.6%), inflammation was controlled using a combination of infliximab and azathioprine. Additionally, azathioprine and cyclosporine were administered in 1 patient (2.6%). Twenty-two patients (57.9%) effectively managed ocular inflammation after the first immunomodulator.

Before IMT patients presented with a median of 2 ± 2.0 [0–10] relapses per year, a number that significantly decreased to a median of 1 ±1.2 [0–4] with the introduction of IMT ($p< 0.001$).

Twenty-eight patients only used non-biological treatment (methotrexate, cyclosporine and azathioprine), 7 patients only used biological treatment (infliximab and adalimumab) and 3 patients used a combination between biological and non-biological treatment. There was a slight superiority of biological IMT compared to non-biological IMT in reducing the number of recurrences after treatment ($p = 0.045$).

Seventeen patients with only non-biological treatment needed adjuvant oral corticosteroids and no patients with biological treatment needed adjuvant oral corticosteroids. Two patients (5.3%) used periocular corticosteroids (Table 2).

In Table 3 LogMAR (Logarithm of the minimum angle of resolution) is the scale used to quantify visual acuity in this population. There was no correlation between LogMAR and the severity of uveitis in Behçet's disease in our sample.

Table 2 Treatment and Inflammation Control. Comparison Between the Number of Relapses per year Before and After IMT

Parameter	Total Subjects N=38
Immunomodulatory agent	
Azatriopine	14 (36.8)
Ciclosporine	11 (28.9)
Adalimumab	4 (10.5)
Infliximab	3 (7.9)
Methotrexate	2 (5.3)
Methotrexate + Adalimumab	2 (5.3)
Infliximab + Azatriopine	1 (2.6)
Azatriopine + ciclosporine	1 (2.6)
Control after the first immunomodulator	22 (57.9)
Control after the second immunomodulator	16 (42.1)
Treatment duration, months	63.50 ± 59.1 [4–201]
≥ 24	29 (76.3)
≥ 36	27 (71.1)
≥ 48	24 (63.2)
≥ 72	16 (50)
Adjuvant oral corticosteroids	17 (44.7)
With biological IMT	0
With non biological IMT	17 (44.7)
Adjuvant intra/periocular corticosteroids	2 (5.3)
Number of relapses/years before IMT	2 ± 2.0 [0–10] p<0.001 1± 1.2 [0–4]

Note: Data presented as median ± standard deviation or frequency n (%), [range].

Table 3 Visual Acuity After Starting Systemic Immunomodulatory Therapy- LogMAR

Right Eye	Left Eye
0	0
0	0
2.7	0.1
0.2	0.1
0	0
0	0
0	0
0	0
0.5	0.4
0.7	1.9
0	3
1.1	0.4
2.3	0.3
0	0
0	0
0	0.5
0.3	0.5
0.2	0.1
0	0
3	2.7
0.9	2.3
0.1	0.1
0	0
1.9	0.1
0.3	0.7
0.3	0
0	0
0	0
0	0.1
0	0
0	0

(*Continued*)

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Table 3 (Continued).

Right Eye	Left Eye
0.1	0
0.1	0.1
0	0
0	0
0.7	1.9
0	0
0.1	0

Treatment Discontinuation and Relapse Profile

Sixteen patients (42.1%) stopped treatment: 6 cases (37.5%) as medical based decision because of long-term remission of the disease, 5 cases (31.3%) because of loss of follow-up, 3 cases (18.8%) because of side effects of the medication and 2 cases (12.5%) because of patient unadvised decision.

Patients who discontinued treatment based on medical decisions had a median treatment duration of 77 months. Those who stopped due to side effects were treated for a median of 43 months. Similarly, patients who discontinued treatment because of loss of follow-up or unadvised decision had a median treatment duration of 48 months (Table 4).

Patients were monitored for a median of 57 ± 46.4 months after stopping treatment, during which 4 (30.8%) out of 16 patients developed recurrence after a median period of 13 ± 10.4 months, range [2–27]. Two of these patients were treated for less than 4 years and all of them were treated for less than 6 years.

Eight of the 12 patients who did not relapse had been treated for more than 4 years, and 4 of the 12 patients who did not relapse had been treated for more than 6 years, without any predominance regarding the type of IMT used. Five of the

Table 4 Incidence of Treatment Discontinuation and Relapse Profile

Parameter	Total Subjects N=38
Treatment discontinuation	16 (42.1%)
Reason to stop	
Medical decision	6 (37.5)
Loss of follow-up	5 (31.3)
Side effects	3 (18.8)
Patient's unconsented decision	2 (12.5)
Treatment duration according to stop motive	48 ± 30.3
Medical decision	77 ± 22.9 [36–96]
Loss of follow-up	48 ± 37.8 [18–118]
Side effects	43 ± 23.5 [5–48]
Patient's unconsented decision	48 ± 25.5 [30–66]
Follow-up time after stopping treatment, months	57 ± 46.4 [12–150]
Relapse after stopping treatment	4 (30.8%)
Time between stop and relapse	13 ± 10.4 [2–27]

Note: Data presented as median ± standard deviation or frequency n (%), [range].

6 patients who stopped IMT because of a medical based decision had been treated for a minimum of 4 years and no relapse of ocular inflammation occurred among them.

Discussion

This study aims to provide a comprehensive review of the most significant aspects of systemic IMT for uveitis in the context of Behçet's disease. Behçet's disease uveitis may frequently lead to blindness when left uncontrolled or inadequately treated. Early initiation of appropriate treatment is crucial to improving the prognosis and preventing vision loss and ocular complications.[13] Clear therapeutic guidelines and protocols regarding the appropriate duration of IMT for patients with BD uveitis have not yet been established.

Our study presented a mean follow-up period of patients with Behçet's uveitis of around 10 years. This extensive follow-up period provides valuable insight into the long-term effectiveness of appropriate treatment in controlling the disease. It allows us to see the potential of preventing recurring episodes of intraocular inflammation, which could result in severe complications and permanent visual impairment.

The mean age of the patients was 44 years, with a range between 24 and 70 years, which reflects individuals with Bechet's disease who are monitored at the hospital over varying follow-up periods, highlighting the broad age distribution within this population. The gender distribution in this population was balanced, with 47.4% men and 52.6% women.

Regarding ocular manifestations, anterior uveitis was the most common isolated presentation. Several factors, including, early detection of ocular involvement, and possible regional variations in clinical phenotype may influence this finding.

As a hallmark of Behçet's disease, vasculitis was the second most common type of inflammatory ocular disease. Also, if posterior uveitis is split into its usual subcategories—choroiditis, retinitis, and vasculitis—the combined cases of posterior segment involvement exceed those of anterior uveitis. Therefore, it is of note the predominance of posterior segment involvement, often in the form of retinal vasculitis, which is in line with other publications.[1] Panuveitis is the third most common type of inflammatory ocular disease. Additionally, there is a high proportion of bilateral involvement, which aligns with findings from other studies.[1]

Also, in two-thirds of cases uveitis was the first manifestation of the disease, emphasizing the potential for the screening of early ocular signs as an important diagnostic indicator in Behçet's disease. An early diagnosis often correlates with a more favorable prognosis.

IMT significantly reduces the frequency of relapses as a reflex of its improved control of disease activity in Behçet's disease, preventing long-term complications, including organ damage and disability, which is consistent with existing literature. Azathioprine was the most used systemic immunomodulatory drug for the treatment of uveitis in BD and cyclosporine was the second most widely used agent. Several studies agree with azathioprine and cyclosporine as first-line immunosuppressive options for uveitis in Behçet's disease.[14,15] The introduction of biologic therapies such as infliximab and adalimumab after the failure of non-biological immunomodulatory agents (azathioprine and cyclosporine), are deemed a better approach for refractory cases.[8,16] The combination of biological and non-biological therapies, such as methotrexate and adalimumab or infliximab and azathioprine can be used in certain cases of treatment-resistant uveitis with the intention of reducing the immunogenicity of these biological agents and thus improving their efficacy. More than half the patients were controlled after the first immunomodulator. There was a slight, but not clear, superiority of biological IMT compared to non-biological IMT in reducing the number of recurrences after treatment.[17] This comparison should be interpreted with caution due to the small sample of the biological subgroup.

Periocular corticosteroids injections were needed in 2 patients as adjunctive therapy because of acute severe recurrences to alleviate symptoms. Patients on non-biological treatments only required more adjuvant corticosteroids in comparison to those on biological therapies. This finding suggests that biological treatment may act as superior corticosteroid-sparing agents, effectively controlling ocular inflammation without the need for prolonged corticosteroid use, and usually with better tolerance (fewer well-documented side effects).[16,18]

Regarding tolerance, only 3 of 38 patients stopped treatment. One patient discontinued treatment because of side effects from azathioprine, including diarrhea and hepatic toxicity, while two others chose to stop treatment due to a desire to become pregnant. This represents an overall favorable safety profile.

In our study, about two thirds were treated for more than 4 years and half were treated for more than 6 years. IMT was associated with a statistically significant decrease in the number of relapses per year, defined as an increase in inflammatory activity following a period of remission.

The patients who stopped IMT because of medical decision (6 out of 38 patients) had a median treatment duration around 6 years. Eight out of twelve patients who stopped treatment and were treated for more than 4 years did not relapse and all the patients who stopped treatment and were treated for more than 6 years (4 patients) did not relapse.

Regarding the 4 patients (30.8%) with relapse after stopping treatment, 2 of these have been treated for less than 4 years and all of them had been treated for less than 6 years. The median time for recurrence after discontinuation was 13 months, ranging from 2–27 months, and it did not appear to be influenced by the duration of treatment among those who relapsed (maximum 66 months). This result must be outlined in the median period of surveillance of 57 months after IMT cessation.

The medical decision to stop IMT after 4–6 years of complete remission appears to be a safe approach, especially in patients who were treated for 6 years, without increasing the incidence of recurrence.

Our study limitations include its small sample size and single-center design. The data collected focused on ophthalmological parameters, and information on extraocular manifestations, such as mucocutaneous or visceral lesions, was not consistently or systematically available. This limitation restricts the analysis of the systemic complexity of the disease and should be taken into account when interpreting the results.

Nonetheless, as a tertiary hospital, we were able to analyze a cohort of patients with uveitis in the context of a rare but sight-threatening disease with a significant length of follow-up, which is an advantage regarding long-term evaluation and follow-up of these patients. This kind of revision may possibly shed some light into specific characteristics of each group, thus allowing for the definition of management protocols in the future.

Conclusion

Most of the patients with Behcet's uveitis needed IMT to effectively control the ocular inflammation and thus achieve durable remission. Azathioprine and cyclosporine were the most used systemic immunomodulatory drugs for the treatment of uveitis in the context of Behcet's disease and are a safe first line approach for Behcet's uveitis.

A medical decision to discontinue treatment after 4 to 6 years of sustained inflammation control appears to be safe, particularly in patients who were treated for 6 years.

Abbreviations

BD, behçet disease; IMT, immunomodulatory therapy.

Data Sharing Statement

Access to any information such as the study protocol or anonymized data can be available upon reasonable request.

Ethics/Ethical Approval

The study was approved by the Institutional Ethics Review Board of Centro Hospitalar Universitário de São João, Porto, Portugal. The protocol conformed with the canons of the declaration of Helsinki for research involving human participants, as well the European Union's General Data Protection Regulation. Informed consent was waived due to the retrospective nature of the study and the protection of patient data confidentiality. This article was redacted according to the recommendations of the Reporting of Studies Conducted using Observational Routinely-collected health Data (RECORD) statement.

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Only the named authors have collaborated in the writing of this paper.

Author Contributions

All authors contributed to the study conception and design. Material preparation was performed by Luís Figueira, Joana Rodrigues Araújo and Ana Margarida Ferreira. Data collection was performed by Ana Margarida Ferreira and Mariana Almeida. Analysis was performed by Mariana Almeida and Luís Figueira. The first draft of the manuscript was written

by Mariana Almeida, and all the authors took part in revising or critically reviewing the article. All authors read and approved the final manuscript.

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Disclosure

The authors have no conflicts of interest to declare for this work.

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