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Original Article

Biological Agent Use in Behcet's Patients who are Resistant to Conventional Treatments: A Multidisciplinary Retrospective Study

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ABSTRACT

Background Comparing treatment modalities is difficult in Behcet's syndrome, even if tumour necrosis factor-alpha (TNF-α) inhibitors are a treatment option for all involvements resistant to conventional therapy. This study evaluated how different departments dealt with treatment, particularly with TNF-α inhibitors.

Material and Methods The study comprised 111 patients from our Behcet's syndrome cohort who were treated with TNF-α inhibitors between 2010 and 2019. Data on patients were retrieved retrospectively from the rheumatology, ophthalmology, and dermatology clinics' patient records.

Results Patients followed up in rheumatology (n: 40) were classified as Group 1, and patients followed up in ophthalmology (n: 49) and dermatology (n: 5) as Group 2. In Group 1, genital ulcers, erythema nodosum (p=0.009, p=0.003, respectively), lower extremity deep vein thrombosis, arterial aneurysm and neurological involvement were more common (p=0.005, p=0.008, p=0.001, respectively). In Group 2, the use of cyclosporine and interferon-□ before the anti-TNF agent was higher (p<0.001, p<0.001, respectively), and the use of cyclophosphamide were higher in Group 1 (p<0.001). Both groups preferred infliximab, and ocular involvement was the most common reason for starting.

Conclusions While TNF-α inhibitors were chosen equally across departments, conventional medicines, including cyclosporine, cyclophosphamide, and interferon-α, were not. This choice was determined by the departments' experience and the clinical traits that predominated.

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Introduction

Behcet's syndrome (BS) is an inflammatory multisystemic complex disease of unknown aetiology.[1-3] Turkey is the most frequent place in the world, with a prevalence of 420/100.000.[4] The course of the disease is in the form of attacks and remissions. While attacks are more frequent and severe in the early years, as time passes, the attacks become milder, and their frequency decreases.[2]

For treating BS, the main objective is to provide remission by ending acute attacks quickly and maintain remission by preventing attacks. While glucocorticoids are the primary drug in treating acute attacks, colchicine or immunosuppressive drugs such as azathioprine, cyclosporine, cyclophosphamide, and tumour necrosis factor-alpha (TNF-α) inhibitors or immunomodulatory drugs such as interferon-α, thalidomide, and apremilast are used for the maintenance of remission.[5]

Disease involvement types and severity of involvement are primarily considered in drug selection.[6] In the 2018 update of the European League Against Rheumatism (EULAR) recommendations, TNF-α inhibitors have found a role in treatment options of all involvements resistant to conventional treatment.[7]

The studies regarding the medication in BS are highly heterogeneous in terms of the patient population included in the studies, study duration, study design, primary/secondary endpoints, and outcome measures used. Therefore, it is challenging to compare different treatment methods with each other. Another significant limitation of the studies is that the number of patients included in many studies is low. Attacks and periods of well-being, characteristic of the natural course of BS, are among the other factors that cause problems in evaluating the efficacy of drugs.[8] Here, we aimed to evaluate clinical differences and treatment approaches in rheumatology, ophthalmology, and dermatology departments where various involvements are prioritised.

Material and Methods

Patient Selection

Retrospective cohort research was conducted between 2010 and 2019. The study included 111 patients with BS treated with anti-TNF agents and evaluated at least once by all three departments and examined for their own involvement. Additionally, selected patients were those in whom each department began with its anti-TNF agent and monitored by the primary self. The ethics committee reviewed and approved the present study protocol (approval no. 2019-8/14, dated 07.05.2019).

Forty-two patients from the rheumatology department, 64 from the ophthalmology department, and five from the dermatology department were included. Seventeen patients with insufficient data in the system were excluded from the study. Patients who followed up at the rheumatology clinic (n: 40) were classified as Group 1, and patients who followed up in ophthalmology (n: 49) and dermatology (n: 5) clinics were included as Group 2.

Patient Data

Using the patient files and archive records, age, gender, age at diagnosis, smoking, pathergy positivity, presence of human leukocyte antigen B51 (HLA-B51), family history, and medications used were recorded. The organ and system involvement such as mucocutaneous involvement (oral aphthae, genital ulcer, papulopustular lesion, erythema nodosum [EN]) and ocular involvement, musculoskeletal system involvement, neurological system involvement, gastrointestinal system (GIS) involvement, vascular (venous-arterial) involvement were questioned. The medications used before and after the anti-TNF agents were evaluated. It was examined whether anti-TNF agents and corticosteroids could be discontinued, and factors affecting this situation and differences between departments were assessed

Statistical Analysis

Mean, standard deviation, and median values weMean, standard deviation, and median values were used in the descriptive statistics of the data. The distribution of variables was measured using the Kolmogorov-Smirnov test. An independent sample

t-test was used to analyse quantitative independent parametric data and the Mann-Whitney U test for non-parametric data. The Chi-square test analysed the independent qualitative data. Analysis was performed using SPSS 26.0 program. A p-value of <0.05 was considered statistically significant.

Results

There was no difference between the two groups regarding age, age at the time of diagnosis, and duration of diagnosis. The number of female patients in Group 2 was significantly higher than in Group 1 (p=0.05). There was no difference between Groups 1 and 2 in terms of smoking, presence of BS in the family, and HLA-B51 and pathergy positivity (*Table 1*). The period between diagnosis and the onset of the anti-TNF agent was longer in Group 1 but did not show statistical significance (68.35±56.941 vs 59.06±52.116 months, p=0.363, respectively).

Clinically, mucocutaneous, ocular, vascular (venous-arterial), joint, neurological, and GIS involvements were examined separately in both groups. While the rate of mucocutaneous involvement was similar in both groups, genital ulcers and EN were more common in Group 1. The ocular involvement rate was significantly higher in Group 2 than in Group 1 (90.7% vs 50%, respectively; p<0.001), and this difference was also found when examined separately as posterior, anterior, and panuveitis. In vascular involvement, lower extremity deep vein thrombosis (DVT) and arterial aneurysm frequencies were significantly higher in Group 1 than in Group 2 (p=0.005, p=0.008, respectively). There were no patients with Budd-Chiari and intracardiac thrombosis in both group. While no difference was found between the groups in joint involvement, neurological involvement was more frequent in Group 1 (p=0.001). GIS involvement was not found in both groups (*Table 2*).

In addition to the TNF-α inhibitors used, the treatments they obtained before and after the TNF-α inhibitors were also assessed. The use of cyclosporine and interferon-α before TNF-α inhibitors was significantly higher in Group 2 (p<0.001, for both). Cyclophosphamide use was significantly higher in Group 1 (p<0.001). The use of colchicine after TNF-α inhibitors was higher in Group 1 (p=0.001), while cyclosporine use was significantly higher in Group 2 (p=0.004). Corticosteroid use before anti-TNF agents was 90% in Group 1 and 79.6% in Group 2 (p=0.175). Corticosteroid use after TNF-α inhibitors decreased to 60% in Group 1 and 46.2% in Group 2; however, no significant difference was found between the groups regarding corticosteroid discontinuation (p=0.189) (*Table 3*). In Group 1, the continuation rate of anti-TNF agents was 80%, while it was 81.4% in Group 2 (p=0.464).

The most commonly used TNF-α inhibitors in both groups were infliximab and adalimumab, respectively (*Figure 1*). In both groups, ocular involvement was the most common reason for initiating anti-TNF agents (*Figure 2*). When

Table 1. Patients' demographics and disease characteristics.

Variables	Group 1 (n: 40)	Group 2 (n: 54)[a]	P value
Age (years)	38.7±7.5 (40)	36.6±9.2 (35)	0.234[&]
Gender (female)	8 (25)	21 (38)	0.05[*€]
Smoking	12 (30)	16 (29.6)	0.969[€]
The presence of BS in the family	10 (25)	18 (33.3)	0.382[€]
HLAB51 positivity	26 (65)	42 (77.7)	0.171[€]
Pathergy positivity	15 (37.5)	16 (29.6)	0.422[€]
Diagnosis age (years)	28.5±7.7 (27.5)	27.7±9.3 (26.5)	0.674[&]
Disease duration (month)	121.8±60.0 (108)	108.0±60.6 (96)	0.200[¥]
Period between diagnosis and biological start (month)	68.3±56.9 (60)	59.0±52.1 (36)	0.363[¥]

Data were given as n (%) or mean±SD (median).
BS: Behcet's syndrome, HLA-B51: Human leukocyte antigen B51.
[a]Ophthalmology (n: 49) and Dermatology (n: 5), [&]Independent sample t test, [¥]Mann-Whitney U test, [€]Chi-square test.

Table 2. Comparison of the patients in terms of organ involvement.

Involvements	Group 1 (n: 40)	Group 2 (n: 54)[a]	P value[€]
Mucocutaneous (n/%)	40 (100)	51 (94.4)	0.259[α]
Oral aphthae	39 (97.5)	48 (88.8)	0.116
Genital ulcers	30 (75)	26 (48.1)	0.009**
Pseudofoliculitis/acneiform skin lesions	20 (50)	31 (57.4)	0.476
Erythema nodosum	16 (40)	7(12.9)	0.003**
Ocular (n/%)	20 (50)	49 (90.7)	<0.001***
Anterior uveitis	4 (10)	38 (70.3)	<0.001***
Posterior uveitis	7 (17.5)	45 (83.3)	<0.001***
Panuveitis	2 (5)	37 (68.5)	<0.001***
Other[∞]	9 (22.5)	9(16.6)	0.477
Vascular-venous (n/%)	15 (37.5)	4 (7.4)	<0.001***
Superficial thrombophlebitis	4 (10)	2 (3.7)	0.217
Lower extremity deep vein thrombosis	9 (22.5)	2 (3.7)	0.005**
Vena cava inferior	1 (2.5)	0	0.426[α]
Budd Chiari	0	0	-
Vena cava superior	1 (2.5)	0	0.426[α]
Intracardiac thrombosis	0	0	-
Dural sinus thrombosis	2 (5)	0	0.178[α]
Others	0	1 (1.85)	0.574[α]
Vascular-arterial (n/%)	5 (12.5)	1 (1.85)	0.037*
Thrombosis	1 (2.5)	1 (1.85)	1[α]
Aneurysm	5 (12.5)	0	0.008**
Musculoskeletal (n/%)	8 (20)	7 (12.9)	0.357
Neurological (n/%)	12 (30)	3 (5.5)	0.001**
Gastrointestinal (n/%)	0	0	

Data were given as n (%). [a]Ophthalmology (n: 49) and Dermatology (n: 5).
[€]Chi-square test, [α]Fischer-exact test, [∞] Active posterior segment findings outside the uveitis (retinitis, occlusive vasculitis, papillitis, vitritis), posterior segment sequelae outside uveitis (optic atrophy), ptosis, and conjunctivitis.
Group 1→ Retinitis: 4, occlusive vasculitis: 1, papillitis: 1, vitritis: 1, optic atrophy: 1, ptosis: 1.
Group 2→ Retinitis: 2, occlusive vasculitis: 5, periphlebitis: 1, conjunctivitis: 1.
Note: One patient had two simultaneous involvements.

patients with ocular involvement (n: 69, 73.4%) and those without (n: 25, 26.5%) were compared, genital ulcers, venous involvement (p=0.05, p=0.004 chi-square test, respectively), and arterial aneurysm (p= 0.017, Fischer exact test) were more frequent in those without ocular involvement. No statistical significance was found in the parameters compared in patients who continued and discontinued anti-TNF agents. Similarly, no statistical significance was found in the parameters compared between the patients who continued and discontinued corticosteroids.

Discussion

Uveitis, recurrent oral and genital ulcers are the most common clinical manifestation of BS.[2,3] In our study, oral aphthae were the most frequent mucocutaneous manifestations in both groups. However, group 1 had a higher prevalence of genital ulcer and EN. The typical ocular involvement of BS is bilateral non-granulomatous panuveitis and retinal vasculitis.[9,10] In our study, posterior uveitis was more common in both groups. Additionally, groups had similar rates of active posterior segment

Table 1. Comparison of the patients in terms of treatments.

Treatments	Group 1 (n: 40)	Group 2 (n: 54)[a]	P value[€]
Before TNF-α inhibitor			
Colchicine	27 (67.5)	26 (48.1)	0.061
Azathioprine	27 (67.5)	42 (77.7)	0.265
Mycophenolate mofetil	2(5)	7(12.9)	0.195
Methotrexate	2(5)	4(7.4)	0.637
Cyclosporine	8(20)	38 (70.3)	<0.001***
Cyclophosphamide	18 (45)	1(1.85)	<0.001***
Interferon-alpha	1(2.5)	30 (55.5)	<0.001***
Corticosteroids	36 (90)	43 (79.6)	0.175
After TNF-α inhibitor			
Colchicine	23 (57.5)	13 (24)	0.001**
Azathioprine	23 (57.5)	27 (50)	0.471
Mycophenolate mofetil	3(7.5)	4(7.4)	0.987
Cyclosporine	0	10 (18.5)	0.004**
Corticosteroids	24 (60)	25 (46.2)	0.189

Data were given as n (%). [a]Ophthalmology (n: 49) and Dermatology (n: 5).
[€]Chi-square test.

manifestations (retinitis, occlusive vasculitis, papillitis, and vitritis) and posterior segment sequelae (optic atrophy). Retinitis, inflammatory macular infiltrate, and vitritis are associated with poor vision.[11] It is vital to recognise active and sequelae findings in the ocular involvement of BS. Ocular involvement is more common in young male patients and has a more severe course. In female patients, involvement begins at older ages, and the prognosis is better.[12] In our study, the rate of women was significantly higher in Group 2. This observation motivated us to conclude that female patient should also be carefully evaluated for ocular involvement.

According to studies, ocular involvement is associated with pathergy positivity and vascular involvement.[12] While DVT is more likely in ocular involvement, pathergy positivity and ocular involvement are more common in patients with DVT.[13,14] In our study, venous involvement, arterial aneurysm, and genital ulcer were found more frequently in patients without ocular involvement. Similarly, ocular involvement was defined as a separate entity in the study by Tunç et al.[13] Different patient admission patterns and different approaches of clinics may be a reason for this inconsistency. Although uveitis alone is a distinctive finding for BS, patients should be carefully evaluated regarding other involvement. GIS involvement is more frequent in Far Eastern countries, especially in Japan.[15] The same feature is observed in the Korean patient group.[16] GIS involvement is rare in Turkish patients.[17] In our study, there were no patients with GIS involvement in both group. In our study, the rates of lower extremity DVT, arterial aneurysm, and neurological involvement were significantly higher in Group 1 compared to Group 2. Because Group 1 has more vascular and neurological involvement, cyclophosphamide is utilised more frequently, and cyclosporine is used less often.

Treatment for BS is based on the type and severity of involvement.[6] Colchicine appears more effective, especially in cases where the predominant lesion is EN or genital ulcer.[5] The higher use of colchicine after the anti-TNF agent in Group 1 was associated with the higher rate of these involvements. Interferon-α is among the treatment options in the EULAR 2018 update for mucocutaneous, ocular, vascular and joint involvement.[18] Although interferon-α is recommended for mucocutaneous, vascular, and joint involvement, the high preference for interferon-α in the ophthalmology department

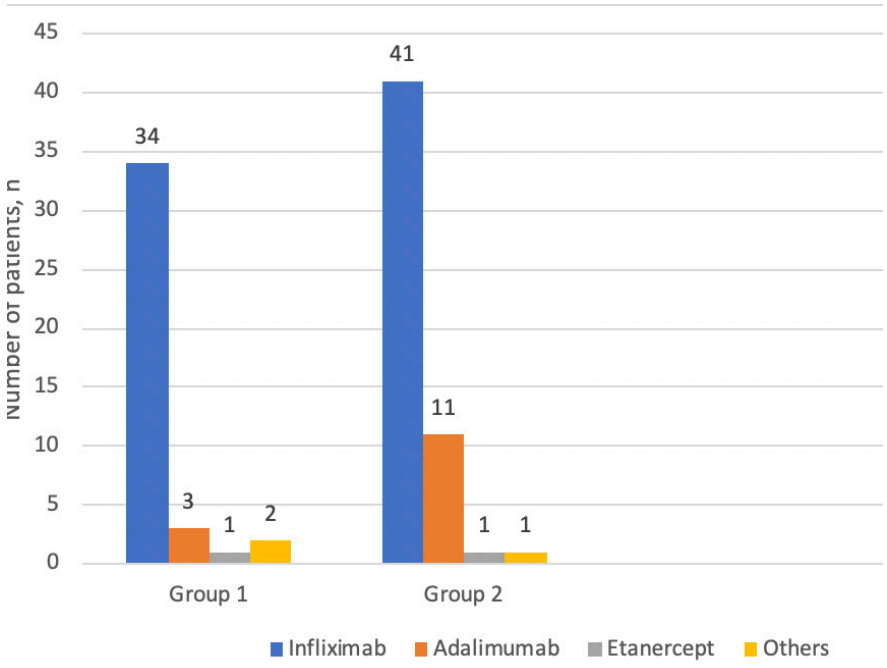

Figure 1. Comparison of TNF-α inhibitors between groups.

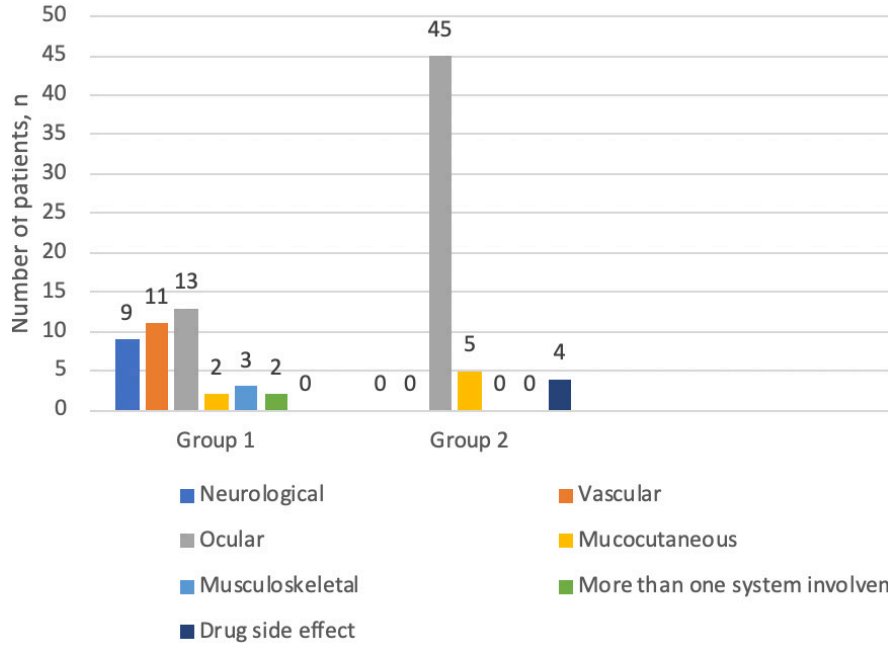

Figure 1. The reasons of initiation of the TNF-α inhibitors.
The order of involvement shown in colour at the bottom and graphic bars is the same from right to left. No patient in group 2 received TNFi for neurologic, vascular, musculoskeletal, or multiple organ involvement.

and the low preference for interferon-α in the rheumatology department in our study suggests that departments' experience may be important in drug selection.

There are no randomised controlled trials on 2nd line agents to be used in patients resistant to conventional therapy in ocular involvement. As there are clinicians who prefer interferon-α first, there are also clinicians who directly switch to anti-TNF agents.[12] In the EULAR 2018 update, although TNF-α inhibitors have found a place in any involvement resistant to conventional treatment, the most common reason for starting anti-TNF agents in our study was ocular involvement in both groups. Many studies have shown the effectiveness and reliability of infliximab[19-21] and adalimumab.[22] Similar to the literature, in our research, the most commonly used anti-TNF agents in both groups were infliximab and adalimumab, respectively.

Our study had some limitations. Our retrospective study and the small number of patients in the dermatology department made it difficult to evaluate the dermatology approach. On the other hand, our research is crucial because it sheds light on prospective studies in which patients were examined by three divisions, allowing for recognising symptom clusters and sharing treatment experiences.

Conclusions

Ocular involvement, a significant cause of morbidity in BS, is the most common reason for initiating TNF-α inhibitors. No difference was found in the agents selected between departments in our study. However, it was observed that there was a difference in the preference for conventional agents such as cyclosporine, cyclophosphamide, and interferon-α. In addition to the difference in the dominant clinical phenotype, it was thought that the departments' experience determined this preference, as it became prominent, especially in the selection of interferon-α. We can better treat BS with collaboration between departments and sharing experiences.

Conflict of interest

The authors have no conflicts of interest to declare.

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Authors' Contribution

Study Conception: BY, SY, HS, GUG, OY, YP; Study Design: BY, BNC, ZKC; Supervision: BY, ED, YP, HS, OY; Literature Review: KFB, KB; Critical Review: All Authors; Data Collection and/or Processing: GUG, SY; Statistical Analysis and/or Data Interpretation: BY, BNC, ZKC; Manuscript preparing: BY.

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