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Earlier and more aggressive treatment with biologics may prevent relapses and further new organ involvement in Behçet's disease

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ABSTRACT

Objective: Immunosuppressives (IS) are the choice of treatment for major organ involvement in Behçet's disease (BD). In this study, we aimed to investigate the relapse rate and new major organ development in BD under ISs during long-term follow-up.

Methods: The files of 1114 BD patients followed in Marmara University Behçet's Clinic were analyzed retrospectively. Patients with a follow-up less than 6 months were excluded. Conventional IS and biologic treatment courses were compared. 'Events under IS' were defined as a relapse of the same organ and/or new major organ development in patients receiving ISs.

Results: Among 806 patients included in the final analysis (male: 56%, age at diagnosis: 29 (23–35) years, median follow-up time: 68 (33–106) months). Major organ involvement was present in 232 (50.5%) patients at diagnosis, and 227 (49.5%) developed new major organ involvement during follow-up. Major organ involvement developed earlier in males ($p = 0.012$) and in patients with a first-degree relative history of BD ($p = 0.066$). ISs were given mostly for major organ involvement (86.8%, $n = 440$). Overall, 36% of the patients had a relapse or new major organ involvement under ISs (relapse: 30.9%, new major organ involvement: 11.6%.) 'Events under IS' (35.5% vs 20.8%, $p = 0.004$), and relapses (29.3% vs 13.9%, $p = 0.001$) were more common with conventional ISs compared to biologics.

Conclusion: Any major event under ISs was less common with biologics compared to conventional ISs in patients with BD. These results suggest that earlier and more aggressive treatment may be an option in BD patients who had the highest risk for severe disease course.

1. Introduction

Behçet's disease (BD) is a systemic inflammatory disorder, marked by recurrent oral and genital aphthous ulcers and skin lesions [1]. In addition to mucocutaneous disease, major organs such as ocular, vascular, gastrointestinal, and central nervous systems (CNS) can be involved [2]. The only diagnostic test, skin prick reaction (pathergy) has a low sensitivity (<50%). Assessment of wall thickness of the femoral vein by Doppler ultrasonography can aid diagnosis and has a sensitivity and specificity above 80% [3]. The disease onset is usually in the third decade. Although both genders are affected at a similar rate, BD runs a more severe course in males [4,5]. The prevalance of vascular involvement ranges from 15% to 50%, ocular around 40–50% and neurological manifestations has been reported to be <5% [6]. Gastrointestinal involvement has a variable distribution in different populations, 5–25% in East Asia, but 0–5% in Mediterranean countries [7]. Major organ involvement, primarily large-vessel disease such as arterial aneurysms and large-vessel venous thrombosis, is the most common cause of mortality. Eye involvement in the form of uveitis, which is the most common cause of morbidity, can lead to permanent vision loss [7].

Studies on the long-term disease activity and relapse in BD is limited. In a small series of 62 patients, Talarico et al. observed that 34% of patients with mild disease developed new major organ involvement in 3-years of follow-up, mainly in male and young patients [8]. Conventional immunosuppressive (cIS) agents (mainly azathioprine) are commonly used as the first-line and are effective in the treatment of major organ

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involvement in BD. However, relapses are common even in patients receiving IS therapy. Among patients with uveitis, relapse rates under cIS treatments was reported from 11% in 12-months [9] to 41.3.% in 38-months of follow-up [10]. Relapses among patients with vascular events were observed in approximately one-third of the patients under cISs in one prospective and another retrospective studies [5,11]. With these data, it is recommended that high-risk BD patients should be followed closely, and even argued that IS treatment can be given prophylactically before the traditional IS treatment indications emerge [12,13].

In this context, the data comparing cISs and biologic treatments (Tumor necrosis factor (TNF) antagonists and interferon-alpha (IFNa)) on the disease course in patients in routine practice in BD is still limited. Therefore, we aimed to explore the rate of relapses and new major organ involvement in BD patients in our large-cohort to clarify whether biologic use lead to a better disease prognosis.

2. Materials and methods

The files of 1114 patients diagnosed with Behçet's disease who were being followed in the outpatient multi-disciplinary Behçet's Clinic of Marmara University Hospital were analyzed retrospectively. Fifty-four patients who failed to meet the International Behçet's Disease Study Group (ISBGD) criteria [14] were excluded from the study. In addition, patients with a follow-up less than six months were excluded, and a total of 806 patients were included in the final analysis. The demographic and clinical characteristics of the patients and their treatment regimens were recorded. Vascular, ocular, CNS, and gastrointestinal involvement were defined as major organ involvement.

A *new major organ involvement* was defined as any manifestation of an organ previously unaffected. The term "relapse" refers to a new manifestation in the same organ that was previously known to be affected during follow-up. Relapse of the same organ and/or new major organ involvement during the follow-up of patients who were initiated IS therapy for any reason (major organ involvement or skin-mucosal and joint symptoms) were defined as *events under IS*.

Azathioprine (AZA), cyclophosphamide, cyclosporine-A, methotrexate (MTX), thalidomide, mycophenolate mofetil (MMF), and corticosteroids were included in the cIS group, and TNF antagonists and IFNa were included in the biologics group.

This study was conducted in accordance with the Declaration of Helsinki and approved by the ethics committee of the Marmara University School of Medicine (No: 09.2019.570). Since our study was a retrospective chart review study, written patient consent was not deemed necessary.

2.1. Statistical analysis

Categorical variables are presented as frequency (n) and percentage (%). According to data distribution, numerical data were displayed as medians, and the 25th and 75th percentile (Q1-Q3) were given in parentheses. Categorical data were compared with Chi-square and Fisher's exact tests. Continuous variables were compared with student *t*-test or Mann-Whitney *U* test.

Kaplan-Meier method was used to estimate for event-free survival.

3. Results

The median age of diagnosis was 29 (23–35) years in the final analysis group ($n = 806$). Male gender was more prominent (56%) (M/F: 452/354). Male patients had a younger age at diagnosis [(Male: 28 (23–34) years vs Female: 30 (24–38) years, $p = 0.004$]. Table 1 shows the disease characteristics of the patients.

Overall, 459 patients (57%) experienced major organ involvement. At the time of diagnosis, major organ involvement was present in 232 (50.5%) of 459 patients and 73.7% were male ($p < 0.001$). Of patients with major organ involvement at the time of diagnosis, 124 (53.5%) had ocular, 91 (39.3%) had vascular, 40 (17.3%) had CNS, and one (0.4%) had gastrointestinal involvement. There was simultaneous organ involvement in 15 patients, including seven patients with vascular and eye involvement, six patients with CNS and vascular involvement and two patients with ocular, vascular and CNS involvement.

Table 1
Distribution of disease characteristics.

Clinical Findings (no.of patients with available data)	n = 806 (%)
Oral aphthae (805)	795 (98.8)
Genital ulcer (797)	609 (76.4)
Erythema nodosum (800)	421 (52.6)
Papulopustular lesions (772)	408 (52.8)
Pathergy positivity (685)	414 (60.4)
Arthritis (806)	80 (9.9)
Family history of Behçet's Disease (797)	185 (23.3)
First-degree relative with Behçet's Disease (790)	110 (14)
Overall Major Organ Involvement (806)	
Ocular involvement*	270 (33.9)
Vascular involvement#	240 (29.8)
Neurological involvement†	78 (9.7)
Gastrointestinal involvement	13 (1.6)

* posterior, panuveitis and retinal vasculitis
# pulmonary thrombus, deep venous thrombosis, superficial thrombophlebitis, inferior vena cava/superior vena cava thrombosis, Budd-Chiari syndrome, upper extremity thrombosis, portal vein thrombosis, renal vein thrombosis, superior mesenteric artery thrombus, subclavian vein thrombus, pulmonary artery aneurysm, femoral artery aneurysm, aortic aneurysm, cardiac involvement (intracardiac thrombus, intraatrial aneurysm, coronary artery aneurysm).
† parenchymal involvement and cerebral sinuses thrombosis.

3.1. Follow-up data

The median follow-up duration was 68 months (33–106). Major organ involvement developed in 227 (49.5%) patients within a median of 36 months (12–75) after the first diagnosis of BD. In patients who developed major organ involvement during follow-up, 130 (57.2%) had ocular, 119 (52.4%) had vascular, 24 (10.5%) had neurological, and 9 (4%) had GIS involvement. Male gender was also dominant in this group (57.7%, $p < 0.0001$). In addition, males experienced major organ involvement earlier with a median of 24 months (6–72) after diagnosis compared to females (median 48 months (12–96), $p = 0.012$). Major organ involvement developed after a median of 12 months (6–60) in first-degree relatives with a history of the disease vs. 36 months (12–96) who had no first-degree relative history ($p = 0.066$). Ten patients (1.2%) died during follow-up, 6 of whom had vascular involvement.

In 446 patients, an IS due to major organ involvement or resistant mucocutaneous findings was initiated. Six patients had stopped using IS in the last visit, or the follow-up data was unavailable. The remaining 440 (54.5%) patients were followed under ISs for a median of 47 months (24–80). The leading cause (86.8%) of IS use in both sexes was major organ involvement (92% in males, 76.4% in females). Another 9.3% ($n = 41$) received IS for resistant mucocutaneous disease and the remaining 3.8% ($n = 17$) for joint involvement. The main reason for IS usage was major organ involvement in males and joint involvement in females. (Table 2).

The IS agents used by 440 patients during the follow-up period were AZA ($n = 383$, 87%), cyclophosphamide ($n = 87$, 19.7%), TNF antagonists ($n = 74$, 16.8%), IFNa ($n = 41$, 9.3%), and cyclosporine-A ($n = 34$, 7.7%). Nine (2%) patients used methotrexate, and one patient each (0.2%) used thalidomide and MMF. Corticosteroids were used mostly in combination with other IS drugs. Of patients who received biologic treatments, 74 of 101 used TNF antagonists: 40 infliximab (IFX), 42 adalimumab (ADA) (9 patients received both IFX and ADA, one received IFX and etanercept, and two received ADA and golimumab at different times during follow-up), one etanercept and the data of 2 TNF antagonists were not recorded. IFNa was given to 41 patients and 14 patients

Table 2
Demographic and clinical characteristics of patients followed up under immunosuppressives (IS)*

	Male (%)**	Female (%)**	p	Total (%)**
Gender	292 (66.4)	148 (33.6)	< *0.0001*	440
Indication				
Major Organ	269 (70.4)	113 (29.6)	< *0.0001*	382 (86.8)
Mucocutaneous/Joint	23 (39.7)	35 (60.3)	< *0.0001*	58 (13.2)
Age at diagnosis (Q1-Q3)	28 (23–34)	29 (24–37)	*0.052*	28 (23–35)
Age of IS initiation (Q1-Q3)	30 (25–36)	35 (29–44)	< *0.001*	32 (26–39)

* For age at diagnosis, data were available for 422 patients, and for age of IS initiation data were available for 424 patients.
** Numbers in parentheses denote percentages but for the rows of age at diagnosis and age of IS initiation numbers in parenthese denote Q1 and Q3.

used both IFNa and TNF antagonists (IFNa was switched to TNF antagonists due to a major event in 6 of these patients).

3.2. Events under immunosuppressives

Events under ISs developed in 160 of 440 patients (36.4%) after a median of 23 (9–44) months. Relapse developed in 109 (68.1%) and new major organ development in 24 (15%) with 27 (16.9%) having both a relapse and a new major organ involvement (Fig. 1).

When relapse rates under ISs were analyzed separately for each organ involvement, it was 35.9% as ocular, 25.5% as vascular and 6.8% as neurologic involvement. In 51 patients, totally 54 new major organ involvement developed with simultaneous vascular and ocular disease observed in 3 cases. Thirty (55.5%) vascular, 12 (22.2%) ocular, 9 (16.7%) CNS and 3 (5.6%) GIS events developed under ISs.

The frequency of disease findings, gender, presence of family history, and age at diagnosis was similar among BD patients with and without an event under ISs (data not shown). Among patients having an event under ISs, 91% of the relapses and 75% of new major organ involvement developed under AZA treatment as AZA was the most commonly used IS. In 22% of these patients, AZA was switched to TNF antagonists while majority of them (47.5%) received combination of TNF antagonists and cIS (mostly with AZA). Immunosuppressive treatment courses were then divided into 2 groups as cISs and biologics and 440 patients received 534 treatment courses with either cISs or biologics. Overall, 433 courses of conventional and 101 courses of biologic treatments were used: 60 patients received TNF antagonists, 27 IFNa and 14 patients received both TNF antagonists and IFNa at different times. Conventional immunosuppressive courses lasted for a median of 41.5 months (17–75), and biologic courses a median of 41.5 months (27–68). Patients had more events under cIS compared to biologic agents (35.5% vs 20.8%, $p = 0.004$) (Table 3). When events were separately analyzed as relapses and new major organ disease, relapses were more frequent under cISs compared to biologics (29.3% vs 13.9%, $p = 0.001$), whereas cIS vs biologic treatment assessment for new major organ disease (10.9% vs 6.9%, $p = 0.238$) did not reach significance. Kaplan-Meier survival curve (Fig. 2) showed that there is a significant difference between cIS and biologic treatments in patients having 'events under IS' ($p = 0.014$).

Seven patients treated with biologics had a new major organ involvement after a median of 36 months (Q1:16, Q3:52) after initiation of the biologic treatment. Five vascular, one CNS, and one simultaneous vascular and CNS involvement developed under biologics in seven

Table 3
Effect of treatment courses on events*

	Conventional $n = 433$ (%)	Biologic $n = 101$ (%)	p	Overall $n = 534$ (%)
No event under IS#	279 (64.5)	80 (79.2)	*0.004*	359 (67.2)
Event under IS	154 (35.5)	21 (20.8)		175 (32.8)
New major organ	47 (10.9)	7 (6.9)	0.238	51(9.5)
Relapse	127 (29.3)	14 (13.9)	*0.001*	141 (26.3)

* Addition of new major organ row with relapse row exceeds the numbers in events under IS row since some patients had both a relapse and a new major organ involvement.
# IS, immunosuppressive.

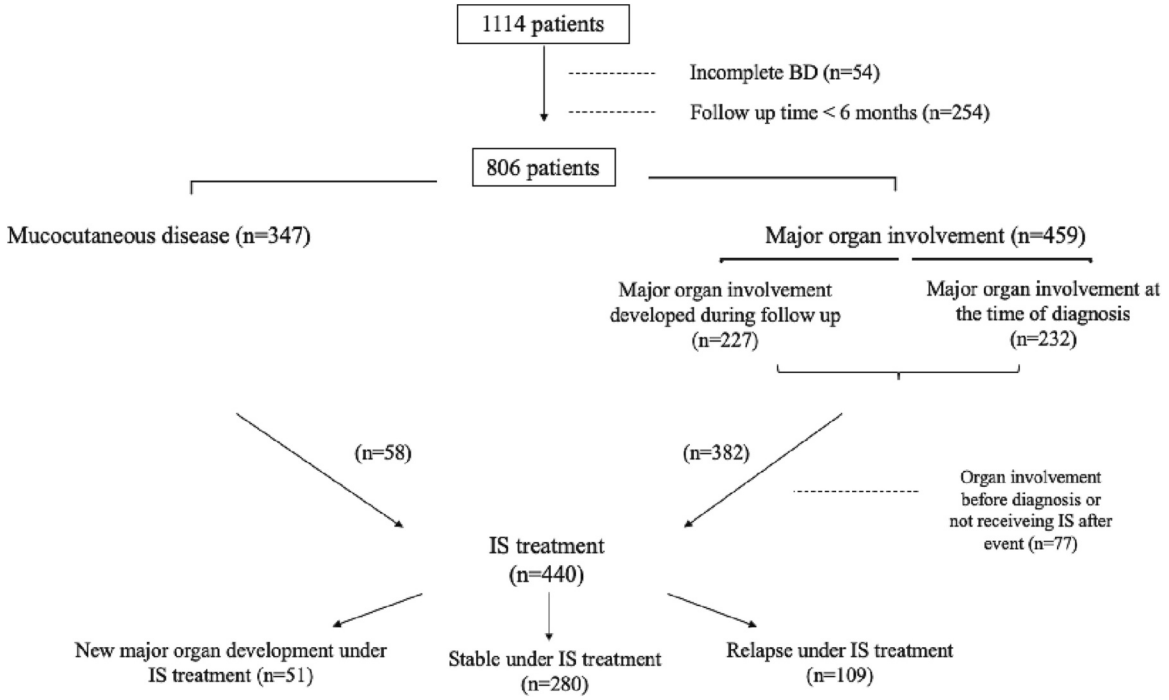

Fig. 1. An overview of patient inclusion, disease course and treatment.

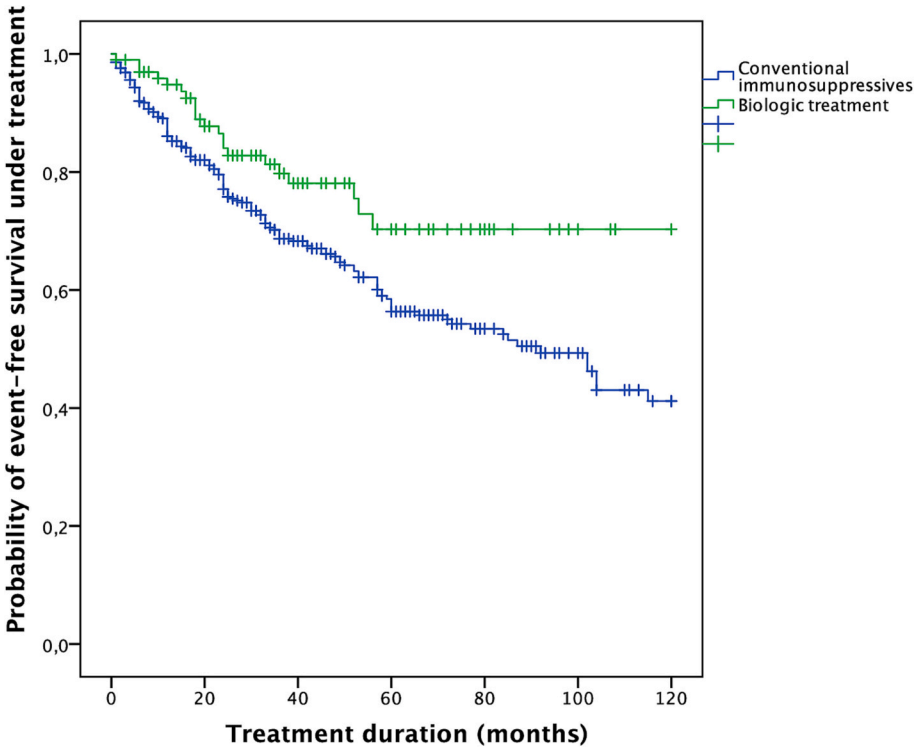

Fig. 2. Kaplan-Meier curves showing the cumulative event-free survival under treatment.

patients, four of whom used to receive biologics due to ocular involvement and three with refractory mucocutaneous disease. These events developed while receiving TNF antagonists in 4 and IFNa in 3 patients.

Fourteen patients relapsed after a median of 16.5 months (Q1:9, Q3:18.5; four patients' data could not be reached) after biologic treatment initiation: Nine patients had ocular relapses, four patients had vascular relapses, and one patient had both ocular and vascular relapses. The 14 relapses under biologics occurred while receiving TNF antagonists in 7 patients, IFNa in 5 patients, and IFNa followed by TNF antagonists in 2 patients.

Forty-seven patients developed a new major organ involvement while on cIS after a median of 24 months (Q1:8, Q3:53) after the initiation of cIS. Of these patients, before a new major organ was involved, 19 were being treated with cIS due to ocular involvement, 14 CNS involvement, 9 vascular involvement, 2 both ocular and vascular involvement, and 3 refractory mucocutaneous disease. These patients' newly developed organ involvements under cISs include 26 vascular involvement, 9 ocular involvement, 7 neurological involvement, 3 GIS involvement, and 2 concurrent ocular and vascular involvement.

After a median of 23 months (Q1:10, Q3:48; sixteen patients' data could not be reached), 127 patients treated with cISs experienced same organ relapse, including 70 ocular involvement, 49 vascular involvement, 4 CNS involvement, 3 ocular and vascular, and one ocular and neurologic involvement.

As a sign of more severe disease, of the 14 patients who had a relapse on biologics, 7 previously had relapsed under cISs, 3 had suffered a new major organ involvement. Additionally, of the 7 patients who had a new major organ involvement, 3 had suffered both a new major organ involvement and a relapse previously on cISs, and 2 had relapsed before the new major organ involvement.

4. Discussion

Our study explored major organ involvement and the effects of immunosuppressives on new major organ events in patients with BD. We observed that more than half of BD patients had major organ involvement, and had a high event rate despite IS treatments. Overall, around a third of patients had an event under immunosuppressives during a follow-up of approximately 4 years. Among the events, relapses were more common than new organ disease.

Our results were similar to published data on major organ relapses in BD. In a cohort of 882 patients from Turkey with vascular involvement, 35.4% of patients experienced relapses under IS [15]. In two other studies, venous relapses under IS were observed in 20% [16], and 25.3% of the patients [5]. In a study in which patients treated with IFNa due to eye involvement resistant to cIS were examined, recurrent uveitis was reported in 63.6% [17]. Another retrospective study showed that 43.7% of patients had a relapse with cIS before being treated with IFNa [10]. In our study, 30.9% of 440 patients relapsed under IS, and the event rate was significantly higher in patients using cIS compared to biologic treatments.

Recent case series with biologic use support our data in BD patients with major organ involvement. There is increasing data showing the efficacy and safety of monoclonal TNF antagonists in BD patients with severe or resistant ocular, vascular, GIS or parenchymal CNS involvement that is resistant to cISs [1,18–22]. Therefore, monoclonal TNF antagonists are recommended for refractory cases [18].

It was shown that the frequency of relapses with ADA [23] and IFNa [24] in patients with eye involvement resistant to cISs is significantly reduced compared to the period when they received cISs. In another study in which retinal vasculitis relapses were compared in patients receiving cISs and patients receiving IFX, the relapse rate was significantly lower with IFX [25]. TNF antagonists also controlled ocular inflammation earlier in a group with 68% relapse rate under cISs [26,27].

In patients with deep vein thrombosis a relapse rate of 45% was observed under AZA compared to 12% under IFNa [11]. A multicenter observational study of patients with major vessel involvement showed nine months risk of relapse was 35% with cISs vs. 6% with TNF antagonists [28]. A retrospective study comparing cISs and ADA in patients with vascular BD reported relapse in 40% under cISs and 8.5% under ADA [22].

New organ involvement under biologics is unsufficiently reported in the literature. A recent study showed a rate of 7% new manifestations in BD patients receiving IFX [29]. Our study similarly showed that only 6.9% of the patients in the biologic group had a new major organ involvement. These very similar results suggest that biologic treatments reduce new major organ disease very prominently in BD which should be taken into consideration in especially high-risk patients.

Many studies emphasized that the disease is more severe in male and younger patients [7,13,30–32]. In a study from Turkey, BD findings developed earlier in the second generation than their parents' [33]. In another study, it was observed that patients with a family history attained the disease criteria at a younger age than sporadic cases [34]. Similarly, in our study, major organ involvement was more common in males. Male patients suffered major organ involvement more and received IS treatment at a younger age. Our patients who had a first-degree relative history of BD also developed major organ involvement earlier.

The limitations of our study were its retrospective design, being a single-center study, and the small number of patients receiving biologics. Grouping several IS and adding IFNa to the biologic group may also seem controversial. However, as the aforementioned study suggests [11], IFNa seems to be a more effective drug than AZA and accepted in the same efficacy level as TNF antagonists for uveitis. Another issue is the heterogeneity, prognosis and treatment approaches in different disease manifestations. Use of biologics such as TNF antagonists are given in different stages of BD, such as earlier use in ocular vs. refractory disease in vascular manifestations. Sequential or combinational use of cISs and biologics might also effect the outcome of disease flares. All these differences can influence the assessment of efficacy in different therapeutic regimens.

In conclusion, major organ involvement developed in more than half of the patients in our retrospective cohort. The disease course was more severe in patients diagnosed at a younger age and in males. Patients with a family history of BD also had major organ involvement earlier. In one-third of patients under cIS treatment, a relapse or a new major organ developed despite cIS use, mainly under AZA. Events under IS were less common with biologics compared to cISs.

Our results suggest that earlier and more aggressive treatment of major organ involvement with biologics may be an option in young male patients with familial BD history who had the highest risk for severe disease course.

Declaration of Competing Interest

None Declared.

Data availability

No data was used for the research described in the article.

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