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BRIEF REPORT

Predictors of sustained clinical response in patients with Behçet's disease-related uveitis treated with infliximab and adalimumab

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Abstract

To identify clinical variables capable of predicting long-term treatment duration of TNF-α inhibition in patients with Behçet's disease (BD)-related uveitis. Demographic, clinical, and therapeutic data were retrospectively collected from BD patients treated with the tumor necrosis factor (TNF)-α blockers infliximab and adalimumab. Patients still continuing TNF-α inhibitors at 48-month follow-up visits were classified as long-term responders and were statistically compared to patients discontinuing treatment before the 48-month visit. Forty-five patients (75 eyes) were enrolled. Thirty-two patients continued anti-TNF-α treatment for more than 48 months; 13 patients discontinued the treatment after a mean time of 12.3 ± 10.44 months due to lack (61.5%) or loss (38.5%) of efficacy. Baseline value of BD current activity form was the only variable discriminating long- and short-term responsive patients ($p = 0.048$, OR = 0.656, C.I. 95% 0.433–0.996). Disease activity levels at the start of treatment predict duration of response to monoclonal TNF antagonists in ocular BD.

Keywords Behçet's disease · Disease activity · Long-term efficacy · Treatment · Uveitis

Introduction

Behçet's disease (BD) is a systemic inflammatory disorder recently included in the number of multifactorial autoinflammatory diseases [1, 2]. It is clinically characterized by the classical triad of genital aphthosis, oral ulcers, and ocular involvement. However, skin, central and peripheral nervous systems, gut, and the vascular tree may be variously affected with a wide range of inflammatory manifestations [3–6]. Although BD is generally not directly associated with mortality risk, gastrointestinal, vascular and nervous involvement may induce life-threatening complications, while ocular disease often leads to sight-threatening manifestations which can induce a severely decreased quality of life [7–10].

The protean clinical spectrum of BD and lack of validated serological markers make it difficult to define BD activity

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over time. Therefore, the evaluation of disease activity is currently based on clinimetric assessment and the BD current activity form (BDCAF) represents a validated and reliable tool widely used for evaluating BD activity in clinical practice [11].

Treatment of BD is tailored on the single patient according to the type and severity of organ involvement [12]. Therapy is currently based on the use of corticosteroids and disease modifying anti-rheumatic drugs (DMARDs); nevertheless, during the last decade, an increasing number of evidences have highlighted the pivotal role of tumor necrosis factor (TNF)-α inhibitors in the treatment of multisystem and refractory BD [13, 14]. In particular, excellent results have been obtained with BD-related uveitis in terms of control and prevention of ocular attacks, improvement of visual acuity, systemic corticosteroid-sparing effect, and long-term retention rate [15–20]. However, to date no clinical predictive factors have been identified in order to preventively recognize BD patients likely responsive to anti-TNF-α agents in the long-term.

For these reasons, we herein aimed at identifying clinical and demographic variables that could represent predictive factors of sustained clinical response to TNF-α blockers in patients with BD-related ocular involvement.

Methods

Patients with BD-related uveitis consecutively treated with the TNF-α inhibitors infliximab (IFX) and adalimumab (ADA) were enrolled in the study. Diagnosis of BD was based on the International Criteria for BD (ICBD) [21] and/or the International Study Group criteria (ISGC) [22].

Patients still continuing TNF-α inhibitors at the 48-month follow-up visit were classified as long-term responders; subjects discontinuing treatment before the 48-month visit due to lack or loss of efficacy were classified as comparison group. Patients under anti-TNF-α therapy for less than 48 months at the time of enrollment were not included in the study. Subjects undergoing treatment withdrawal due to adverse events, bureaucratic reasons, and lack of compliance were excluded from the study.

Demographic, clinical, and therapeutic data were retrospectively collected. More in detail, data were recorded about age at the start of treatment, age at disease onset, disease duration, gender, human leukocyte antigen-B51 positivity, systemic organ involvement, type of ocular involvement (anterior, intermediate or posterior uveitis, and panuveitis), presence of retinal vasculitis at the start of treatment (as assessed at fluorescein angiography), uveitis activity at the start of TNF-α inhibition, best corrected visual acuity (BCVA) assessed with Snellen charts at the start of treatment, identification of ocular complications at the start of treatment, line of biologic therapy (first line versus second or more line), use of concomitant DMARDs, and disease activity at the start of anti-TNF-α treatment assessed with the BDCAF [11].

Primary aim of the study was to identify demographic, clinical or therapeutic variables capable of predicting a long-term efficacy of monoclonal TNF-α inhibitors in patients with BD-related uveitis. Secondary aim was to identify any significant difference in the frequency or mean/median value of variables between patients showing a long-term treatment duration and subjects discontinuing therapy in an early phase.

Primary endpoint was represented by the identification of demographic, clinical, or therapeutic variables that proved to be significantly related to long-term treatment at binary forward stepwise regression analysis; identifying significant differences at statistical computation of variables assessed in the two groups of patients represented the secondary endpoint.

The study protocol was conformed to the tenets of the Declaration of Helsinki and informed consent was obtained from each patient prior to being enrolled.

Descriptive statistics was assessed for sample size, percentages, mean, median values, and standard deviations. After having evaluated data distribution with the Anderson-Darling test, statistical analysis for pair wise comparisons was performed by using Fisher exact test for qualitative variables and Mann-Whitney U test or Student's t test (as required) for quantitative variables. Binary forward stepwise regression analysis was employed by using the persistence on therapy at the 48-month follow-up visit as dependent variable, while clinical, demographic and therapeutic features specified above as independent variables. Odds ratio (OR), its statistical significance and corresponding 95% confidence interval (CI) were evaluated for predictor variables resulting from regression analysis. SPSS 24.0 software was used for statistical computations and significance was defined as $p < 0.05$.

Results

Forty-five patients were included in the study. Twenty-eight (62.2%) patients were treated with IFX at a dosage of 5 mg/kg every 8 weeks (22 cases), every 6 weeks (4 cases) and every 4 or 10 weeks (each in one case, respectively). ADA was used in 17 (37.8%) patients at the dosage of 40 mg every other week in all cases. At the start of TNF-α blockers uveitis was active in 39/45 (86.7%) patients.

Thirty-two patients continued anti-TNF-α treatment for more than 48 months; 13 patients discontinued the treatment after a mean time of 12.3 ± 10.44 months (median value 8 months). Eight of 13 (61.5%) patients had discontinued TNF-α inhibitors because of lack of efficacy

and 5 (38.5%) due to a loss of efficacy. Ten out of 13 patients (76.9%) had discontinued treatments within 12 months from the start of therapy, 2 (15.4%) during the second year, and 1 patient (7.7%) during the third year. Table 1 summarizes clinical and demographic data of all patients enrolled.

In 36 patients (80%), ADA or IFX had been administered as first-line biologic agent, while 6 patients (13.3%) had been previously administered with another TNF-α inhibitor and 3 patients (6.7%) with 2 TNF-α blockers.

The median BCVA value at the start of TNF-α inhibition was 7/10 (range 0–10). Ocular complications at the start of anti-TNF-α agents were recorded: cataract in 5 cases (11.1%), vitreous detachment in 5 patients (11.1%), ocular hypertension in 4 patients (8.9%), macular atrophy in 1 case (2.2%), and epiretinal membrane in 1 patient (2.2%).

With regard to concomitant treatments, colchicine was taken by 10 patients (22.2%), DMARDs by 23 subjects (51.1%), and systemic corticosteroids by all patients. Twelve patients (26.7%) discontinued corticosteroids during treatment.

Table 2 provides information about the clinical parameters assessed as possible predictors of long-term response to TNF-α inhibition. Table 2 also shows *p* values identified at the statistical analysis, aimed at identifying pair wise differences between patients continuing TNF-α inhibitors for more than 48 months and those discontinuing the treatment at an earlier stage because of lack or loss of efficacy.

Binary forward stepwise regression analysis was then performed on clinical variables reported in Table 2. BDCAF value at baseline was the only variable discriminating long-term responsive patients from those discontinuing treatment before 48-month follow-up visits ($p = 0.048$, OR = 0.656, C.I. 95% 0.433–0.996).

Table 1 Demographic and clinical features of patients with Behçet's disease enrolled in the study

Clinical and demographic information	
Age (mean ± SD, years)	44.16 ± 11.37
Gender (males/females)	25/20
Age at onset (mean ± SD, years)	29.7 ± 11.8
Disease duration (mean ± SD, years)	14.4 ± 6.3
HLA-B51 positivity	32 (71.1%)
Organ involvement	
Eye	45/45 (100%)
Anterior uveitis	12/45 (26.7%)
Posterior uveitis	15/45 (33.3%)
Panuveitis	14/45 (31.1%)
Retinal vasculitis	25/45 (55.6%)
Skin	35/45 (77.8%)
Musculoskeletal	31/45 (68.9%)
Gastrointestinal	16/45 (35.6%)
Vascular	8/45 (17.8%)
CNS	18/45 (40%)
PNS	6/45 (13.3%)
ISGC fulfillment	36/45 (80%)
ICBD fulfillment	45/45 (100%)
Baseline BDCAF, median value (range)	7 (2–13)

BDCAF, Behçet's Disease Current Activity Form; *CNS*, central nervous system; *HLA*, human leukocyte antigen; *ICBD*, international criteria for Behçet's disease; *ISGC*, International Study Group criteria; *PNS*, peripheral nervous system, *SD*, standard deviation

Discussion

Anti-TNF-α agents have increasingly proved to be useful treatment options for patients with systemic multi-resistant BD and disregarding specific organs involved [12–16]. A considerable experience has been reached by the use of IFX and ADA in BD-related uveitis, while the fusion protein etanercept has been found mostly to control the mucocutaneous manifestations of BD [23], with limited efficacy on uveitis [24–27]. Several studies have explored the effectiveness of the monoclonal TNF-α inhibitors in patients with BD-related uveitis in terms of control of uveitis relapses, resolution of retinal vasculitis, improvement of BCVA, reduction of macular edema and corticosteroid-sparing effect [16–20, 28, 29].

Accordingly, the recently updated EULAR recommendations have proposed the monoclonal anti-TNF-α agents as an alternative to azathioprine, cyclosporine A, or interferon-α for patients with severe eye disease [12].

Recently, retention rates of ADA and IFX on a long-term period have been investigated with excellent results in patients with BD-related uveitis. In particular, IFX retention rate was 47.11% at 10-year follow-up, and ADA retention rate assessed at 4-year follow-up was 63.5%, disregarding the concomitant use of DMARDs in both cases [17, 18]. However, to date predictive factors of long-term response to TNF- α blockade have not yet been identified in patients with BD-related uveitis. In this regard, our analysis has pointed up that a high BDCAF value at the start of treatment is the sole clinical variable capable to predict patients with an early treatment discontinuation.

In particular, the risk for treatment withdrawal due to lack or loss of efficacy increases along with the increase of BDCAF values at baseline. This suggests that a more severe disease activity, as assessed at the clinimetric evaluation, is more difficult to control, and therefore more frequently associated with early treatment failure. Accordingly, at pair-wise statistical analysis, central nervous system involvement, and gastrointestinal manifestations were significantly more

Table 2 Clinical and demographic parameters assessed as possible predictors of long-term response to TNF-α inhibition in patients with Behçet's disease and ocular involvement. Median values, means, and frequency counts are provided distinguishing patients between subjects still treated with TNF-α blockers at the 48-month follow-up evaluation (group 1) and those experiencing treatment withdrawal before 48 months, because of lack or loss of efficacy (group 2). *p* values were obtained with Fisher exact test for frequency counts and with Mann-Whitney *U* test for quantitative data previously assessed as having non-Gaussian distribution

	Group 1	Group 2	*p* value
Age, years (mean ± SD)	45.81 ± 10.17	40.08 ± 13.46	0.082
Gender, males/females	18/14	7/6	> 0.999
Age at disease onset, years (mean ± SD)	30.4 ± 12.02	28 ± 11.66	0.660
HLA-B51 positivity	23/32	9/13	> 0.999
Skin involvement	24/32	11/13	0.698
Articular involvement	21/32	10/13	0.724
PNS involvement	5/32	1/13	0.656
CNS involvement	9/32	9/13	0.018
Gastrointestinal involvement	8/32	8/13	0.037
Vascular involvement	5/32	3/13	0.672
Anterior uveitis	9/32	3/13	> 0.999
Posterior uveitis	9/32	6/13	0.304
Panuveitis	10/32	4/13	> 0.999
Retinal vasculitis	18/32	7/13	> 0.999
Active ocular involvement at baseline	27/32	12/13	0.656
Retinal vasculitis at baseline	7/32	6/13	0.149
Ocular complications at baseline	5/32	6/13	0.053
BCVA, median (range)	8 (1–10)	7 (1–10)	0.177
First-line/s (or more) line biologic treatment	24/8	5/8	0.037
Baseline BDCAF, median (range)	6 (2–10)	7 (3–13)	0.071
Concomitant DMARDs	15/32	8/13	0.514

BCVA, best corrected visual acuity; *BDCAF*, Behçet's Disease Current Activity Form; *CNS*, central nervous system; *DMARDs*, disease modifying anti-rheumatic drugs; *HLA*, human leukocyte antigen; *PNS*, peripheral nervous system, *SD*, standard deviation

frequent in the group discontinuing anti-TNF-α agents before 48-month follow-up, confirming that a severe systemic disease activity is a clinical setting that may anticipate an early treatment failure.

The presence of ocular complications at the start of anti-TNF-α therapy tended to be more frequent among patients discontinuing treatments before 48 months with a borderline statistical significance. Consequently, in accordance with EULAR and American Academy of Ophthalmology recommendations [12, 30], our study confirms that early use of anti-TNF-α treatment should be warranted in case of severe uveitis in BD patients.

Indeed, an early treatment with anti-TNF-α inhibitors could limit ocular inflammation before the appearance of sight-threatening complications. Interestingly, no statistical differences were identified in relationship with both the type of uveitis and the presence or absence of active uveitis at baseline, confirming that effectiveness of TNF-α blockers is not influenced by these variables. Of note, most patients with a poor retention rate discontinued anti-TNF-α treatment within the first 12 months. Conversely, the vast majority of patients exceeding 12 months of treatment showed to persist on therapy up to the 48-month follow-up visit, thus suggesting that patients persisting on anti-TNF-α treatment at 12-month follow-up will likely continue therapy during the following years.

Noteworthy, anti-TNF-α therapy as second (or more) line biologic approach was significantly more frequent among patients with an early discontinuation than among those continuing treatment for more than 48 months. This is probably related to the higher number of patients treated with IFX in the present study. Indeed, we recently found that 10-year retention rate on IFX was significantly higher in patients undergoing their first biologic agent [17]. Conversely, different lines of ADA treatment did not affect its cumulative retention rate in patients with BD-related uveitis [18]. Nevertheless, the higher frequency of early discontinuation among patients previously administered with other biologics may also be explained by a high disease activity, possibly leading to multi-drug resistance.

In conclusion, BDCAF value at baseline represents the sole clinical variable capable of preventively identifying BD patients with a higher risk for early discontinuation of anti-TNF-α treatment. Moreover, early withdrawal of TNF-α inhibitors is more frequent among patients undergoing TNF-α inhibition as second- or more-line biological therapy and is usually more frequent when sight-threatening ocular complications are present at the start of treatment.

Compliance with ethical standards

Disclosures None.

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