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RESEARCH LETTER TO THE EDITOR

Long-term effectiveness and safety of switching from originator to biosimilar infliximab in patients with Behçet's disease

Giuseppe Lopalco[1] · Vincenzo Venerito[1] · Luca Cantarini[2] · Giacomo Emmi[3] · Domenico Prisco[3] · Florenzo Iannone[1]

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Behçet's disease (BD) is a chronic multisystem inflammatory disorder clinically characterized by the "triple symptom complex," consisting of recurrent oral aphthosis, genital ulcers, and chronic relapsing bilateral uveitis [1]. Besides this classical clinical pattern, other organs and systems including gastrointestinal tract, musculoskeletal, cardiovascular, and central nervous system may also be involved [2, 3]. The management of BD is often challenging due to its protean clinical features, therefore treatment should be individualized to each patient according to the type and severity of organ involvement [4]. The effectiveness of tumor necrosis factor (TNF) blockers, especially the monoclonal antibody anti-TNF-a infliximab (IFX), for all severe BD manifestations resistant to conventional therapy, has pointed out the critical role of this cytokine in its pathogenesis [5–8]. However, the impending patent expiration and the relatively high costs of anti-TNF agents, have paved the way for biosimilar drugs development, the first of which has been the biosimilar IFX CT-P13. The efficacy and safety of biosimilar IFX has been evaluated in different inflammatory conditions, and approved for all indications of the reference product in several countries [9]. In spite of this, it is still debated whether the biosimilar IFX performs equally to the originator when patients treated with reference IFX are switched to biosimilar in routine care, as small differences in immunogenicity might influence tolerability and outcomes [10]. For this reason, biosimilars remain a hot topic in rheumatology, and some physicians are cautious about their application in clinical practice. To the best of our knowledge, there are scanty data on biosimilar IFX employment in BD [11], some of them with conflicting results, advising caution with regard to the automatic replacement of reference IFX in sustained remission patients [12]. Based on a retrospective chart survey, in the present study we report our experience with biosimilar IFX CT-P13 in patients affected by BD, who were switched from originator IFX.

Thirteen patients diagnosed with BD according to the International Study Group criteria or the International Criteria for BD initially treated with originator IFX were switched to biosimilar IFX CT-P13 from March 1st 2017 to May 31st 2017. Retrieved data including gender, ethnicity, age at diagnosis, HLA-B51 haplotype, clinical manifestations for which originator IFX was started, as well as age and concomitant immunosuppressive drugs at switch were collected (Table 1). The study was approved by the local ethics committee according to the Declaration of Helsinki principles. After obtaining informed consent from all patients, originator IFX was replaced with biosimilar CT-P13 at a dosage of 5 mg/kg every 8 weeks. Clinical assessment was done at the last follow-up visit under originator IFX, subsequently after starting biosimilar, every 3 months, and in case of disease relapse, during a whole follow-up period of 12 months. To assess disease activity accurately, the BD current activity form (BDCAF) was used at each examination during the treatment. BDCAF is a tool for the assessment of BD activity, which scores the history of clinical features including mucocutaneous lesions, joint, blood vessel, gastrointestinal, eye involvement, and central nervous system complications, which present over the 4 weeks prior to the day of assessment. The occurrence of adverse events was

Giuseppe Lopalco and Vincenzo Venerito equally contributed to this work.

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✉ Giuseppe Lopalco
glopalco@hotmail.it

[1] Rheumatology Unit, Department of Emergency and Organ Transplantation, Polyclinic Hospital, Piazza G. Cesare 11, 70124 Bari, Italy

[2] Department of Medical Sciences, Surgery and Neurosciences, Research Center of Systemic Autoinflammatory Diseases, Behçet's Disease Clinic and Rheumatology-Ophthalmology Collaborative Uveitis Center, University of Siena, Siena, Italy

[3] Department of Experimental and Clinical Medicine, University of Firenze, Florence, Italy

Table 1 Demographic and clinical characteristics of our cohort at originator IFX baseline. Data about concomitant treatment at switch. BDCAF distributions at switch and at different follow-up visits

Female, *number* (%)	3 (23.08%)
Age at onset, years, (mean ± SD)	27.15 ± 10.02
Age at switch, years, (mean ± SD)	39.76 ± 7.46
HLA-B51, *number* (%)	3 (75%)[a]
Clinical manifestations for which originator IFX was started	*number* (%)
Uveitis	10 (76.92)
Oral aphtosis	9 (69.23)
Genital aphtosis	7 (53.85)
Cutaneous involvement	7 (53.85)
Concomitant treatment at switch	*number* (%)
Colchicine	5 (38.46)
CsA	3 (23.07)
MTX	1 (7.69)
LFN	1 (7.69)
Corticosteroids	1 (7.69)
BDCAF distributions	Median (IQR)
At switch	0 (0–1)
At 3 months follow-up	0 (0–0)
At 6 months follow-up	0 (0–1)
At 9 months follow-up	0 (0–1)
At 12 months follow-up	1 (0–1)

IFX infliximab, *BDCAF* Behçet's disease current activity form, *SD* standard deviation, *MTX* methotrexate, *LFN* leflunomide, *CsA* cyclosporine-A

[a]Data available for 4/13 patients

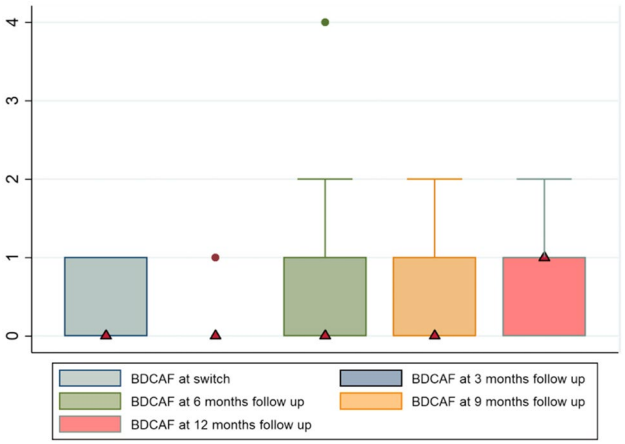

Fig. 1 Distributions of BDCAF after switching at different follow-up periods. Red triangles indicate the median for each distribution. *BDCAF* Behçet's disease current activity form

also recorded. Two-sided Wilcoxon matched-pairs signed-rank test was carried out to evaluate BDCAF distribution differences ($\alpha = 0.05$) between pre-switch and at 3, 6, 9 and 12 months after switching. Drug survival was retrospectively calculated as the time from initiation of biosimilar treatment to discontinuation, or the first missed dose after initiation of IFX CT-P13 therapy. Interruptions were considered definitive when indicated in the records, or when no consecutive re-introduction of treatment was reported. Drug retention rates were analyzed using Kaplan–Meier curves. Statistical and power analysis were carried out with Stata 14.2 (StataCorp, TX, USA) and G*Power 3.1.9.3 (Heinrich-Heine-Universität, Düsseldorf, GER).

Ten male and three female patients (mean age 39.77 ± 7.46 years) with a mean disease duration of 12.54 ± 4.21 years, underwent originator IFX therapy at a dosage of 5 mg/kg every 8 weeks for a period of 117.66 ± 48.01 months. After 106.92 ± 46.37 months of treatment with originator IFX, all of them were switched to biosimilar IFX CT-P13. Table 1 summarizes demographics and clinical manifestations for which originator IFX was started. The majority of patients did not have symptoms at switch, with the exception of four patients who presented arthralgias (2 patients) and folliculitis (2 patients). Ten out of 13 enrolled patients were on combination therapy with biosimilar IFX and immunosuppressant drugs including methotrexate (1 patient), leflunomide (1 patient), cyclosporine-A (3 patients), and colchicine (5 patients). One patient was taking oral prednisone at low doses. BDCAF distributions pre-switch and at different follow-up visits are shown in Table 1. At 3 months after switching, no patient had discontinued biosimilar IFX treatment. No significant difference was observed between BDCAF distributions assessed at switch and 3 months after switching ($p = 0.50$, effect size 0.90, $\beta = 0.20$). At 6 months follow-up, 2/13 patients (15.38%) had stopped biosimilar IFX treatment, both due to relapse of mucocutaneous involvement. Of note, 1/2 patients who discontinued treatment with biosimilar IFX had also previously experienced a mucocutaneous flare under originator IFX therapy, requiring therapeutic adjustment by the addition of colchicine. BDCAF distributions assessed before and 6 months after switching were not significantly different ($p = 1.00$, effect size 1, $\beta = 0.20$). Nine months after switching, two out of the remaining 11 patients were lost at follow-up. Yet, any difference was shown between BDCAF distributions assessed at switch and at 9 months follow-up ($p = 1.00$, effect size 1.12, $\beta = 0.20$) as well as at 1 year follow-up ($p = 0.62$, effect size 1.12, $\beta = 0.20$). Figure 1 shows BDCAF distributions both at switch and at each follow-up visit. No adjustments of biosimilar IFX dose or concomitant drugs were needed throughout the whole period of observation. The overall cumulative survival was 84.6% at 12 months. Globally, mean survival time (MST) was 10.85 months (95% CI 9.37–2.32) (Fig. 2). No adverse event occurred during the entire follow-up period.

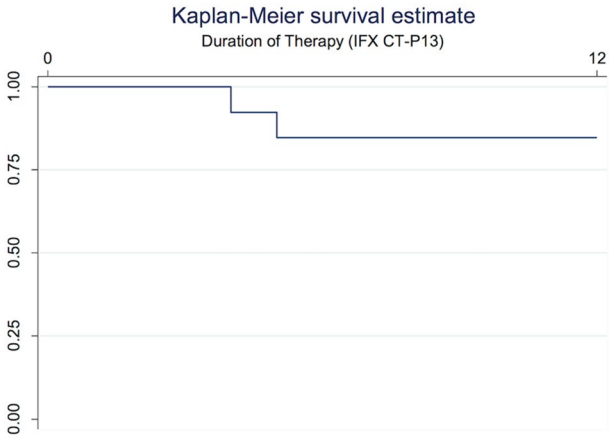

Fig. 2 Kaplan–Meier curve showing retention rate of biosimilar IFX CT-P13 in our cohort

The present study is aimed at evaluating the effectiveness and safety of switching from originator to biosimilar IFX in BD patients. We observe in our cohort that biosimilar IFX CT-P13 is characterized by a good safety and effectiveness profile. The main goal of therapy in patients with BD is to induce and maintain disease remission, and to improve quality of life. In this regard, biologics are rapidly becoming effective alternatives to conventional treatments. In 2007, originator IFX was approved in Japan for the treatment of BD-associated refractory retinitis/uveitis, on the basis of the results of a clinical study [13], and more recently, a prospective, open-label, single-arm phase 3 study has advocated this biologic agent as a new therapeutic option for patients with life-threatening manifestations such as intestinal, neurological, and vascular involvements [6]. The introduction of biosimilar drugs brought the promise of new sources of value. The perspective of more affordable options that are safe and effective has opened up opportunities for health systems to expand access to biologics for more patients, thus bringing relief to pressured healthcare budgets. In this regard, the phase III randomized PLANETRA and the randomized, parallel-group PLANETAS studies show a comparable efficacy, immunogenicity, safety profile, pharmacokinetics and pharmacodynamics of biosimilar IFX CT-P13 and the originator in patients with active rheumatoid arthritis and ankylosing spondylitis, respectively [14, 15]. However, concerns have been raised regarding whether bioanalytical similarity coupled with proven clinical safety and efficacy in one or more indications can ensure safety and efficacy in other indications. To the best of our knowledge, only a few studies have been performed about the use of biosimilar CT-P13 in BD. First, Turkish researchers report their experience with biosimilar IFX (5 mg/kg) in four BD patients refractory to conventional immunosuppressants. The first patient who received biosimilar IFX for neurological involvement, achieved clinical remission at month 3 showing almost total regression of the neurological lesions. In the second one, biosimilar IFX was added to azathioprine for managing refractory skin lesions and vein thrombosis. In the third and fourth patients, biosimilar was started for refractory arthritis and panuveitis, respectively, with only a partial response in joint involvement [11]. Recently, Cantini et al. describe their experience with three BD patients successfully treated with reference IFX who had relapses of uveitis and neuro-Behçet after switching to CT-P13, thus raising concerns with regard to the interchangeability and automatic replacement of reference IFX with the biosimilar. The authors hypothesize that the rapid loss of efficacy might be related to the development of anti-drug antibodies (ADAs) against originator IFX, although circulating ADAs and drug serum levels in these patients were not assessed [12]. To date, our experience represents the largest study suggesting that switching reference IFX to biosimilar CTP-13 in BD patients is feasible and uneventful. In this regard, we demonstrate that only a small percentage of patients experience relapse of symptoms, whereas no significant change of BDCAF pre-switch and post-switch is observed. The literature data show a similar rate of relapse during treatment with originator IFX compared with biosimilar in BD patients. Indeed, it has been demonstrated that originator IFX is effective in controlling ocular inflammation related to BD in the long term, albeit a small percentage of patients up to 15% may experience relapse unresponsive to treatment adjustments [16]. A possible explanation of disease relapse under biosimilar IFX treatment may lie in the different cytokine pathways capable of inducing specific clinical manifestations. In this regard, some disease subsets may be caused by inflammatory mediators different from TNF such as the cytokines deriving from activation of Th17 cells that might discriminate BD patients with ocular and mucocutaneous involvement from patients with only mucocutaneous disease [5]. Additionally, biosimilar IFX CT-P13 was well-tolerated, and no significant adverse events were reported. Nevertheless, some limitations of this study must be pointed out: statistical analysis is not strong enough to detect subtle differences between BDCAF distributions due to the small sample size. Moreover, we cannot draw conclusions about CT-P13 immunogenicity, as serum ADAs in our patients were not assessed before and after switching to biosimilar IFX.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Statement of human and animal rights All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed consent Written informed consent was obtained from all the patients.

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