

Biosimilar infliximab for Behçet's syndrome: a case series

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ABSTRACT

Objective. The efficacy and safety of biosimilar infliximab (bio-IFX) was shown in randomised controlled trials and it was approved for all indications of the reference product in several countries. However, a previous case series of 3 patients with Behçet's syndrome (BS) reported disappointing results. We aimed to share our experience with bio-IFX treatment in different types of organ involvement in patients with BS.

Methods. We reviewed the charts of all BS patients who were prescribed reference infliximab (ref-IFX) or bio-IFX in our BS clinic. Among the 181 BS patients who were prescribed IFX since 2003, 6 (3%) were prescribed bio-IFX due to refractory disease despite conventional immunosuppressives.

Results. A total of 6 patients (mean age: 32.1±6.2, mean disease duration: 5.3±1.8 years, 5 men and 1 woman) received bio-IFX for uveitis, nervous system, vascular and joint involvement. Four of the 6 patients obtained remission and stayed in remission during the 16±6.5 months they used bio-IFX. Among the 4 patients who obtained remission, 2 were switched to ref-IFX due to unavailability of bio-IFX infusion set and did not experience adverse events or loss of efficacy. However, relapses occurred during tapering. The other 2 patients are still in remission with bio-IFX. Among the remaining 2 patients, one had to be switched to ref-IFX after the first infusion, due to a change in the reimbursement policy and the other was non-responsive.

Conclusion. Our limited experience showed that bio-IFX may be a safe and effective alternative for patients with BS, refractory to conventional immunosuppressives.

Introduction

Behçet's syndrome (BS) is a multisystem vasculitis with unknown aetiology.

It is characterised by recurrent oral and genital ulcers, skin lesions, pathergy reaction, arthritis, uveitis, vascular, central nervous system and gastrointestinal (GI) system involvement (1). Treatment should be individualised according to age, gender, type and severity of organ involvement. Colchicine is usually effective for mucocutaneous lesions, whereas immunosuppressives are required for organ involvement (2). Monoclonal anti-tumour necrosis factor (anti-TNF) antibodies are recommended for all refractory and/or severe manifestations and infliximab (IFX) has been the most widely used agent (3-5).

Biosimilar products entered the market in 2006 in Europe and in 2015 in the United States, with the aim of lowering the costs and increasing access to biologic agents. A number of randomised controlled trials (RCTs) showed beneficial results and long-term observational studies suggested sustained efficacy with biosimilar anti-TNFs (6). The updated EULAR recommendations for the management of rheumatoid arthritis suggest that EMA- or FDA-approved biosimilars have similar efficacy and safety to their biological originators and that they should be preferred if they are appreciably cheaper (7).

Despite promising data from RCTs, several concerns were raised over the years regarding the use of biosimilars, due to the complex nature of biopharmaceuticals. Although structural, functional, non-clinical and clinical studies are required to demonstrate the quality, safety and efficacy of a biosimilar for approval, clinicians have sought real-world data. Immunogenicity, loss of efficacy and increased drug discontinuation rates upon switching from an originator to a biosimilar, and increased healthcare resource use and costs despite lower prices of the drug itself have been some of the main concerns (8-10). On the other hand, the recent consensus

based recommendations for the use of biosimilars in rheumatological diseases developed by an international multidisciplinary task force advocate the use of approved biosimilars in the same way as their bio-originators (11). These recommendations suggest that measuring antidrug antibodies to biosimilars is not necessary in clinical practice, since no clinically significant differences in immunogenicity was shown between biosimilars and their bio-originators. Moreover, they propose that a single switch from a bio-originator to its biosimilar seems to be safe and effective, but more data is needed for multiple switching (12).

Biosimilar infliximab (bio-IFX), which was approved by EMA in 2013, was the first biosimilar anti-TNF drug. The efficacy and safety of bio-IFX was shown in randomised controlled trials and it was approved for all indications (rheumatoid arthritis [RA], ankylosing spondylitis [AS], Crohn's disease [CD], ulcerative colitis, psoriatic arthritis, and psoriasis) of the reference product in several countries (13, 14). Experience with bio-IFX in BS was previously reported by Cantini *et al.* They reported 3 BS patients who were successfully treated with reference IFX (ref-IFX), but had relapses of uveitis and of nervous system involvement soon after switching to bio-IFX (15). In contrast to these disappointing results, our experience has shown beneficial results with bio-IFX. In this report, we aimed to share our experience with bio-IFX treatment used as first line in 6 patients with BS with 4 different types of organ involvement.

Materials and methods

We reviewed the charts of all BS patients who were prescribed reference infliximab (ref-IFX) or bio-IFX in our multidisciplinary BS clinic. Among the 181 BS patients who were prescribed IFX in our clinic since the year 2003, 6 (3%) were prescribed bio-IFX due to refractory disease despite conventional immunosuppressives. Bio-IFX (5 mg/kg) was given intravenously at weeks 0, 2 and 6 and then every 6-8 weeks. Patient charts were reviewed for demographic features, types of organ in-

volvement, previous and concomitant treatment modalities, response to bio-IFX, adverse events and follow-up.

Results

A total of 6 patients (mean age: 32.1 ± 6.2 , mean disease duration: 5.3 ± 1.8 years, 5 men and 1 woman) received bio-IFX for uveitis (n=2), central nervous system involvement (n=2), vascular involvement (n=1) and arthritis (n=1). Demographic and baseline disease characteristics are presented in Table I. Among them, 4 patients had remission with bio-IFX and were followed for 16 ± 6.5 months with this agent, without relapse. After 27 and 10 months of treatment with bio-IFX, 2 of these patients had to be switched to ref-IFX due to unavailability of bio-IFX infusion set and did not experience any adverse events or loss of efficacy. IFX was tapered due to sustained remission for 20 and 24 months, by increasing the dose intervals. However, relapses occurred during 12th and 3rd month of tapering- 5 and 17 months after ref-IFX was started. Relapses were managed by increasing the IFX dose and adding corticosteroids. They are currently doing well on ref-IFX. The remaining 2 patients are still in remission with bio-IFX.

Other than these 4 patients, one patient had to switch to ref-IFX after the first infusion due to a change in the reimbursement policy and the other was unresponsive to bio-IFX and was switched to etanercept.

Case 1

The first patient was a 30-year-old man with uveitis who had received azathioprine (AZA), cyclosporine-A and methotrexate for a total of 6 years. AZA was stopped due to liver toxicity, cyclosporine-A for relapses of uveitis and methotrexate for GI adverse events. Six months after these drugs were stopped, he had a right haemiparesis. Cranial magnetic resonance imaging (MRI) revealed hyper-intense areas of restricted diffusion involving the left internal capsule to pons and mesencephalon with moderate contrast enhancement. Spinal cord MRI revealed a hyper-intense lesion extending from C3 to mid thoracic

level. Cranial MR venography excluded sinus thrombosis. He refused lumbar puncture. He received intravenous (IV) pulse methylprednisolone (MP) followed by bio-IFX. He achieved partial clinical remission with right foot weakness as sequela, but almost total radiological regression within 3 months. AZA was added as maintenance therapy, but he never adhered to oral treatment. After 20 months of clinical and radiological stable disease, bio-IFX infusion intervals were increased to 12 weeks with the aim of stopping after sustained remission was ensured. At 27th month of treatment bio-IFX had to be switched to ref-IFX because of unavailability of bio-IFX infusion set in the market; and he continued to have ref-IFX infusions without any adverse events or loss of efficacy. However, while under IFX every 12 weeks for 12 months, he experienced a relapse with an acute onset head and neck ache, and ataxia. Spinal MRI revealed new areas of signal changes and spinal atrophy extending from upper cervical to mid thoracic level. His antidrug antibodies were negative. His signs and symptoms disappeared with pulse 1 g MP for 5 days and IFX dose was increased to 7 mg/kg every 6 weeks. AZA was continued concomitantly and corticosteroid dose was slowly tapered. He has not had any relapses with this regimen for the last 11 months, but right foot weakness is persistent.

Case 2

The second patient was a 25-year-old man with refractory skin lesions despite colchicine, and AZA had been started for these. He developed bilateral external iliac vein and right common iliac vein thrombosis, while on AZA. Bio-IFX and high dose glucocorticoids (GC) was added to AZA. At the 4th month of treatment, his abdominal superficial collateral vein distension regressed and Doppler ultrasonography showed recanalisation in bilateral external iliac veins and residual thrombosis only in the right common iliac vein. At 10th month, bio-IFX was switched to ref-IFX because of unavailability of infusion set. There were no adverse events or loss of efficacy. After 24 months of maintenance, IFX

Table I. Demographic, clinical characteristics and outcomes of patients.

	Case 1	Case 2	Case 3	Case 4	Case 5	Case 6
Gender	M	M	M	F	M	M
Age	30	25	30	36	28	44
Oral ulcers	+	+	+	+	+	+
Genital ulcers	-	-	+	+	-	-
Erythema nodosum	-	+	+	-	-	+
Papulopustular lesion	+	+	-	-	+	+
Vascular involvement	-	+	-	-	-	-
Gastrointestinal involvement	-	-	-	-	-	-
Arthritis	-	+	-	-	-	+
Uveitis	+	-	+	+	+	-
Disease duration (year)	7	5	7.5	2	4	6
Indication for IFX	Central nervous system involvement	Venous thrombosis	Central nervous system involvement	Uveitis	Uveitis	Arthritis
Previous treatment	GC	AZA	Colchicine	AZA, cyclosporine-A, IFN-alpha	AZA, cyclosporine-A, IFN-alpha	AZA, IFN-alpha, SAZ, adalimumab
Concomitant drugs	GC	AZA	AZA	AZA	AZA	Colchicine
Switch to reference IFX	+ (27 th month)	+ (10 th month)	-	-	+ (2 nd week)	-
Outcome	Partial clinical remission on 3 rd month. 12 months after starting IFX taper he, had a nervous system involvement flare; now on IFX every 6 weeks	Recanalization in 4 months. Soon after tapering IFX, had uveitis; now on IFX every 8 weeks	Partial clinical remission. Currently on Bio-IFX for 14 months, persistent gait abnormality	Remission on 3 rd month. Currently in remission on Bio-IFX for 13 th months.	Switched to reference IFX after the 1 st infusion. Remission for 3 years; had uveitis attacks after he discontinued treatment	Nonresponsive to bio-IFX. Switched to Etanercept, in remission for 3 years

GC: glucocorticoid; AZA: azathioprine; IFN-alpha: interferon-alpha; SAZ: sulphasalazine.

was tapered by increasing infusion intervals to 12 weeks. However, 3 months later he had an anterior uveitis episode. IFX dose was increased back to every 8 weeks and he has not experienced any further uveitis or vascular relapses for the last 9 months.

Case 3

The fifth patient had a past history of uveitis and was treated with AZA. He was in remission and was using only colchicine for the past 5 years. He was admitted with ataxia, right foot weakness on dorsiflexion, dysarthria and cognitive impairment. He had normal protein and cell count in cerebrospinal fluid (on the 2nd day of steroids). Seven pulses of 1 g IV MP were administered and foot weakness regressed at the end of pulse steroids. We started bio-IFX and AZA. He was stable on the 14th month of treatment and he had mild gait abnormality but full muscle strength.

Case 4

The sixth patient had bilateral posterior uveitis refractory to AZA and cyclosporine-A with a visual acuity (VA) of 0.5 in the right eye, and 0.7 in the left eye. She was switched to interferon-alpha, but experienced a left posterior uveitis attack with retinal leakage in fundus angiography. At that time her VA was 1.0 in the right and 0.6 in the left eye. Her laboratory examination showed leukopenia. Bio-IFX and AZA were started. She is stable and in remission with this treatment for the last 13 months. Her current VA is 1.0 in both eyes.

Case 5

The fourth patient had bilateral panuveitis with an initial VA of 0.1 in the right and 0.8 in the left eye. AZA and cyclosporine-A were started. After 2 attacks within 4 months, AZA and cyclosporine-A were switched to interferon-alpha 5 MU/day. However, he was lost

to follow up and did not adhere to treatment. At that time his VA was 0.7 in the right, 0.7 in the left eye. Twenty-one months later he presented with a uveitis attack in the right eye: his VA was 0.2 in the right eye and 1.0 in the left eye. We started bio-IFX concomitant with AZA. The first infusion was bio-IFX but the following infusions were ref-IFX due to a change in the reimbursement policy of the hospital. There were no adverse events after switching and he experienced no relapses and VA was 0.6 in the right and 1.0 in the left eye at the end of one year of biologic treatment. He had a history of illicit drug use and was lost to follow up. We learned that he had stopped his medications for the last 10 months and experienced multiple uveitis attacks.

Case 6

The third patient had severe mucocutaneous and joint involvement and had

used colchicine, AZA, sulfasalazine, interferon-alpha and adalimumab for refractory right knee arthritis episodes that lasted 2 weeks and recurred every 2 to 3 months. He had initially benefited from adalimumab, but later stopped due to secondary non-responsiveness. Bio-IFX was started in addition to colchicine. During 9 months of treatment with bio-IFX, he had 3 arthritis attacks and had intra-articular glucocorticoid injections. Treatment was switched to etanercept 50 mg/week due to inadequate response. For the last 3 years he only experienced an attack while tapering etanercept, however he is still in remission under weekly treatment.

Discussion

This case series showed that among our 6 patients who were prescribed bio-IFX with central nervous system, ocular, joint and vascular involvement, 4 had remission with bio-IFX, one was non-responsive to bio-IFX and one was immediately switched to ref-IFX due to reimbursement issues. During the maintenance period, 2 of the patients who were in remission were switched to ref-IFX due to unavailability of infusion sets, without any adverse reactions or loss of efficacy. The other 2 patients were still in remission with bio-IFX.

A recent systematic review of RCTs and observational studies of switching between biosimilar and originator anti-TNFs did not identify significant increases in risks regarding safety, efficacy and immunogenicity with a single switch (8). This was also the case in our 2 patients who were switched to ref-IFX due to technical reasons. They stayed in remission until tapering due to sustained remission. There is no data to guide the timing and schedule of tapering in BS patients who obtain sustained remission with biologic agents. The two cases of relapses in our series were seen after tapering of biologics. The recommended duration and tapering strategies of biologics in BS is unclear. There are studies in RA and spondyloarthritis (SpA) evaluating the outcomes of decrease in the dose or extension in the dosing interval. Although the level of evidence is moderate, it may be reasonable to start

tapering only in patients with remission of at least 6 to 12 months and after withdrawal of steroids. However, half of the patients with RA and SpA experienced flare within a year of discontinuation of anti-TNF (16). A longer duration of sustained remission may be necessary for patients with BS. Sfika-kis *et al.* assessed maintenance of remission after withdrawal of anti-TNF treatment in BS patients with major organ involvement (17). Anti-TNFs were stopped after a median of 2 years of successful treatment and 12/29 patients remained in complete remission for at least 3 years. However, 17/29 patients experienced a relapse within 1 year after discontinuation. We propose that it may be safer to continue biologics in major organ involvement of BS for at least 2 years after remission, considering the risk of organ/life threatening relapses.

To the best of our knowledge, the only reported experience in the literature regarding the use of biosimilars in BS is by Cantini *et al.* (15). They reported 3 BS patients who were successfully treated with ref-IFX for 5 to 6 years and who experienced relapses of uveitis and of neuro-Behçet soon after switching to bio-IFX. Relapses were at first, second and third infusions of bio-IFX. Whether this was due to development of anti-drug antibodies against ref-IFX, was not determined in those patients. Development of anti-drug antibodies has been an important concern for patients switching from a reference anti-TNF to a biosimilar anti-TNF and *vice versa*. However, this may not be a major issue in patients with BS. It was previously shown in a study of 66 patients with BS, 27 with RA and 25 with CD who were prescribed IFX, the number of patients who developed anti-IFX antibodies was lower among BS compared to RA and CD patients (4/66, 5/27 and 3/25, respectively) (18). In RA and SpA patients, it was shown that anti-IFX antibodies of ref-IFX-treated patients cross-react with bio-IFX (19). Switching between reference and bio-IFX resulted in similar efficacy, immunogenicity and safety outcomes in RA. However, few studies defined relapses in inflammatory bowel disease (20).

There is evidence in RA and CD that concomitant DMARD use may attenuate the frequency of anti-drug antibodies and improve biologic drug survival. However, there is insufficient data in BS to suggest that DMARDs show the same effect in patients with BS. In two different multicenter studies of refractory BS patients; no significant difference was found with respect to efficacy among patients who use anti-TNFs as monotherapy or in association with an immunosuppressive agent (4, 21).

In conclusion, in contrast to what was previously reported, our limited experience with this small case series showed that bio-IFX may be safe and effective for BS patients refractory to conventional immunosuppressives. This data on biosimilar use in BS needs to be confirmed in a larger number of patients for efficacy, safety and other outcomes after switching from and to originator biologics.

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