Rapid loss of efficacy of biosimilar infliximab in three patients with Behçet’s disease after switching from infliximab originator

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Abstract

Three patients affected by Behçet’s disease (BD) with severe uveitis and neurological involvement in stable clinical remission and who rapidly relapsed after switching from reference infliximab (re-IFX) to biosimilar infliximab (bio-IFX) are reported. In order to observe the rules of local health authorities, two males and one female (38, 26, and 40 years old, respectively) with BD complicated by severe uveitis and neuro-Behçet and who were in prolonged remission, were switched from re-IFX to bio-IFX, with the same dosing regimen of 5 mg/kg intravenous infusions every 8 weeks. All three patients experienced disease flare-ups, with recurrence of uveoretinitis in the first patient, neuro-Behçet in the second, and uveitis and neuro-Behçet in the third after 1, 3, and 2 infusions, respectively. After appropriate washout of re-IFX, all three patients were administered subcutaneous adalimumab, with a dosing regimen of 40 mg/fortnight, and a good response was achieved. Our three patients with BD experienced a rapid disease relapse after switching from re-IFX to bio-IFX, possibly due to cross-reaction of anti-IFX antibodies. This outcome suggests the necessity to exercise caution regarding the automatic substitution of re-IFX with bio-IFX in patients achieving remission with re-IFX.

Keywords: Behçet’s disease, infliximab, biosimilar infliximab, interchangeability, automatic substitution

Introduction

Behçet’s disease (BD) is a chronic, relapsing, systemic vasculitis of unknown cause involving veins and arteries of all sizes. Eye and neurological inflammatory involvement (neuro-Behçet) represent severe clinical manifestations of BD that may lead to blindness or permanent neurological deficits (1, 2). Both uveitis and neuro-Behçet may be refractory to therapy with corticosteroids (CS) and traditional immunosuppressive drugs. In recent years, the efficacy and safety of infliximab (IFX, trade name: Remicade®, Centocor, Inc.) in patients with refractory BD has been widely reported, with the drug leading to a remarkable suppression of ocular inflammation, visual acuity improvement, and resolution of neuro-Behçet manifestations (3-5). Given this evidence, IFX obtained the approval for the treatment of severe BD in Japan, where the disease is very prevalent (MHLW, Japan. Osaka August 24, 2015).

In June 2013, anti-TNF CT-P13 (biosimilar IFX; trade names: Remsima®, Inflectra®, Celltrion, Inc.) was licensed by the European Medicines Agency (EMA) for the treatment of rheumatoid arthritis and ankylosing spondylitis on the basis of two trials demonstrating the comparable efficacy and safety of CT-P13 (bio-IFX) and reference IFX (re-IFX; trade name: Remicade) (6). According to these data, and based on a strict comparison of in vitro and ex vivo pharmacological and biological characteristics, bio-IFX was considered biosimilar to re-IFX (6).

As bio-IFX has a lower cost than re-IFX, in order to reduce the economic impact of biological therapies, the health authorities of some regions in Italy pronounced local rules for the automatic substitution of re-IFX with bio-IFX.

Herein we report three cases of BD patients with long-term stable remission who relapsed soon after switching from re-IFX to bio-IFX.

Case Presentations

The Rheumatology Department of Prato is a tertiary referral center for rare rheumatic diseases. Since 2005, in this center, BD patients with refractory uveitis or neuro-Behçet undergo the standard therapeutic schedule previously described (7). Briefly, all immunosuppressive therapy is suspended, and treatment with prednisone (PDN) at a dose of 1 mg/kg/day is started. In addition, all subjects receive 2-hour intravenous...
infusions of infliximab at a dose of 5 mg/kg at weeks 0, 2, 6, and every 8 weeks thereafter. In responders, treatment with CS is rapidly tapered over 8-10 weeks until withdrawal. As of October 2015, 26 BD patients with uveoretinitis and/or neuro-Behçet were in stable remission while receiving re-IFX infusions. However, a local health authority issued a rule stating that patients who did not reside in Prato should receive the current intravenous treatment in the hospitals of the area where they lived, and our institution would only conduct scheduled follow-up visits. Over the next few months, of 26 patients, 3 were switched to bio-IFX in their local hospitals and, as described below, all of them rapidly relapsed. Informed consent concerning all treatments was obtained from the three patients.

Case 1
A 32-year-old male presented in 2008 with a 6-year history of recurrent oral and genital ulcers, 1 episode of thrombophlebitis of the left leg, arthritis in the left knee and right ankle, and thrombosis of the central retinal vein of the right eye with visual loss. In the past, the patient had been diagnosed with BD in other hospitals, and had been treated with corticosteroids (CS), methotrexate (MTX) and Ciclosporin A (CsA) with frequent disease flare-ups requiring CS dose escalation. During the first visit in our center, the patient, who was still receiving CsA 5 mg/kg/day and prednisone 25 mg/day, presented severe uveitis and retinal vasculitis of the left eye with reduced best-corrected visual acuity (VA) (Snellen chart of 0.1–1.0 at a distance of 5 meters: 0.2), oral aphthosis, and left knee and left wrist arthritis. Treatment with re-IFX at a dose of 5 mg/kg was started and all clinical manifestations subsided after the third infusion. VA of the left eye improved to 0.7, and over the following 6 years treatment with re-IFX was continued, with sustained clinical remission.

The patient was a resident of the Lombardia region, and in December 2015 received the first infusion of bio-IFX (Remsima). Two weeks after the infusion of bio-IFX, the patient developed cutaneous vasculitis with papulopustulosis, oral and genital ulcers and worsening of visual acuity. At the follow-up visit in our center, active uveitis and retinal vasculitis of the left eye were found (Figure 1). Treatment with subcutaneous Adalimumab 40 mg/eow was started and the patient experienced clinical remission after 6 injections, with resolution of retinal vasculitis (Figure 2).

Case 2
A 40-year old woman with BD complicated by bilateral posterior uveitis and cerebral vasculitis had been treated in our center with IFX at 5 mg/kg iv since 2010. The patient achieved a stable disease remission and IFX infusions were continued until November 2015. The patient was a resident of another city of Tuscany, where she was switched to bio-IFX (Remsima) at a dose of 5 mg/kg. After the third infusion, she experienced a loss of response with relapse of bilateral posterior uveitis, fever, pulsating headache, dysarthria, loss of balance, right-sided hemiparesis and cognitive impairment. An MRI of the brain enhanced with gadolinium showed the presence of a large involving the pons and extending to the midbrain. Treatment with intravenous methylprednisolone (1 g daily for 5 days) concomitantly administered with adalimumab 40 mg/eow/sc was started. All clinical manifestations remitted within 1 month and the patient is still in clinical remission.

Case 3
A 26-year old male with BD complicated by neurological and intestinal involvement has been followed at our center since 2009. The patient was resistant to MTX, and cyclophosphamide, and a high dose of CS was required to control clinical manifestations. In early 2010, IFX 5 mg/kg was administered to the patient, and a rapid response and complete disease remission was observed. Treatment with CS was withdrawn over a 4-month period and IFX treatment was continued with maintenance of remission during the following 5 years. As he was a resident of the Piemonte region, from November 2015 he was switched to bio-IFX (Remsima), with infusions of 5 mg/kg administered every 8 weeks. After the second infusion, oral aphthosis, papulopustulosis, and neurological and intestinal manifestations recurred. In February 2016, at the follow-up visit in our center, the flare-up was confirmed and after treatment with intravenous methylprednisolone (1 g daily for 5 days) and adalimumab (40 mg/eow/sc), a rapid improvement of the signs and symptoms of BD was observed, with complete remission after 2 months.

Discussion
The exchangeability and automatic substitution of re-IFX with bio-IFX is debated, and in Europe the decision is entrusted to a single country (8).

There are a few studies on switching from re-IFX to bio-IFX in rheumatoid arthritis, spondyloarthritis, and inflammatory bowel diseases. Most of these studies seem to be reassuring in terms of efficacy maintenance and safety (9-11). However, in a recent report, of 23 patients with stable disease remission who were switched from re-IFX to bio-IFX, 7 experienced disease flare-ups after a mean interval of 2 months (12). Therefore, the authors raised concerns regarding the exchangeability of treatments in the absence of consolidated data from real cases. The same concerns have also been expressed by the Canadian Agency for Drugs and Technologies in Health, which has recently stated that the current evidence does not show a sustained effectiveness and long-term safety of bio-IFX, and that there is not enough data on the occurrence and impact of anti-drug antibodies (ADAs) over time (13).

Our experience with the 3 BD patients who were successfully treated with re-IFX and who experienced recurrence of uveitis and of neuro-Behçet soon after switching to bio-IFX appears to reinforce skepticism regarding the exchangeability and automatic substitution of reference re-IFX with the biosimilar drug.
In the absence of a valid explanation, we could only hypothesize that the rapid failure of bio-IFX in our 3 patients might be related to the development of ADAs against re-IFX. In our clinical practice, we do not examine circulating ADAs and drug serum levels in patients receiving re-IFX, but the hypothesis of ADA-induced loss of efficacy for bio-IFX seems to be confirmed by a recent paper showing cross-reactivity of anti-re-IFX antibodies and bio-IFX (14). The higher proportion of antibody molecules with truncated C-terminal lysines, the differences in site-specific deamination, the lower level of afucosylated glycans, and other minor molecular and pharmacological differences of bio-IFX found in the EMA comparability exercise [6] may enhance the neutralizing action of anti-re-IFX antibodies in patients switched to the biosimilar drug.

Technical problems including defective transport, storage and drug solution preparation could be an alternative explanation for the loss of efficacy of bio-IFX. This possibility was duly investigated, and it was found that all procedures had been properly conducted.

In conclusion, the rapid disease relapse observed in our 3 patients with BD soon after switching from re-IFX to bio-IFX further reinforces the claims that suggest caution concerning the automatic substitution of one treatment with the other. The loss of efficacy of bio-IFX may be related to the development of ADAs, and in order to verify this hypothesis, further investigations need to be conducted.

Informed Consent: Written informed consent was obtained from the patients who participated in this study.

Peer-review: Externally peer-reviewed.

References
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