

The Real-World Use of Different Anti-Tumor Necrosis Factor Agents in a Northern European Population of Patients with Behçet's Disease

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Abstract

Objective: The aim of this study was to evaluate prescription practices, treatment responses, and serious adverse events of anti-tumor necrosis factor (anti-TNF) therapies in Behçet's disease (BD).

Material and Methods: Patients with BD satisfying the International Study Group for Behçet's Disease or the International Criteria for Behçet's Disease criteria were recruited from a regional rheumatology program. The choice of anti-TNF, treatment response, and adverse events were specified. Response to treatment was evaluated by the detection of new, worsening, or improving clinical features, and management was benchmarked against current The European League Against Rheumatism recommendations published in 2008.

Results: Out of the total of 22 patients, 18 (81.9%) received anti-TNF therapies, resulting in 14 (77.8%) complete and 4 (22.2%) partial remissions. Eleven (61.1%) patients switched to a second anti-TNF, seven patients (38.9%) required three different anti-TNFs, and one required a fourth anti-TNF to achieve remission. Two patients required retrials before their disease was controlled. Anti-TNF therapy included infliximab (IFX): n=15, 83.3%; adalimumab (ADA): n=9, 50%; golimumab: n=6, 33.3%; etanercept: n=5, 27.8%; and certolizumab pegol: n=2, 11.1%. Secondary failure was observed with IFX (4/15; 26.7%) and ADA (2/9; 22.2%), and these (100%) were manifested after at least 2 years of treatment. Five patients with potentially life-threatening laryngeal involvement received anti-TNFs successfully halting disease progression. Five allergic reactions were encountered, and five serious infections were documented involving three patients aged ≥ 50 years, all with the use of IFX.

Conclusion: Anti-TNF treatment induced a clinical response in 100% patients and achieved complete remission in 78% patients. It provides an effective alternative option for first-line therapy in severe BD where many conventional immunosuppressive therapies fail. Patients with BD who do not respond to one or more anti-TNFs because of intolerance, ineffectiveness, or secondary failure might benefit from switching to another drug from this group or even retrial of a previously administered anti-TNF because unsatisfactory results with one biologic is not predictive of response to another anti-TNF. For those with potentially life-threatening destructive laryngeal manifestation, anti-TNF as a first choice may be considered.

Keywords: Behçet's disease, Behçet's Syndrome, Biologics, Anti-TNF, TNF-alpha



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Key Messages

1. Anti-TNF treatment induced clinical response was evident in 100% patients, with 78% achieving complete remission.
2. Patients with BD who do not respond to one anti-TNF might still benefit from switching to other anti-TNFs or a retrial of a previously administered anti-TNF.
3. Patients with BD with severe and life-threatening destructive laryngeal manifestation will likely benefit from anti-TNF treatment.

Introduction

Since the first description of the tri-symptom complex by Professor Hulusi Behçet 80 years ago, there have been major developments in the understanding of the epidemiology, pathogenesis, diagnosis, and therapy in Behçet's disease (BD)(1). Management of BD requires a long-term multidisciplinary approach and is best coordinated by a specialist team with rheumatologists often having a leadership role (2). The current treatment practice for BD focuses on symptomatic treatment, including the prevention of irreversible organ damage and death, suppression of mucocutaneous or joint manifestations, and improvement of the patients' quality of life.

The main treatment for systemic manifestations in BD is tailored based upon the pattern and severity of symptoms and includes corticosteroids together with steroid-sparing immune-modulators, such as azathioprine or cyclosporine, and more recently biological therapies (3-6). Patient selection for biological therapy has, in general, been based upon individual consultant opinion and several open-label studies.

The European League Against Rheumatism (EULAR) Standing Committee for Clinical Affairs (ESCCA) initiative, a collaboration of experts from eight different countries, agreed on a set of recommendations based on the best evidence and expert opinion.

The final set of recommendations identified anti-TNF as an option for patients with severe inflammatory eye disease, gastrointestinal involvement, CNS involvement, and in resistant cases (6). Emerging data support the use of anti-TNF biologics in BD for potentially sight- or life-threatening manifestations due to ocular, neurological, or major vascular involvement (5-8). In one randomized controlled clinical trial, etanercept was effective against mucocutaneous manifestations of BD (9). However, the risk of serious infections, including reactivation of tuberculosis, and high cost remain important concerns (10-12).

Herein, we present our clinical experience with anti-TNF biological therapies for BD in a Northern European population. The aim of the study was to assess prescription practices and treatment response to five different anti-TNF disease-modifying agents in rheumatic disease (DMARD) and to describe adverse event profiles.

Material and Methods

A retrospective study was conducted on all patients with BD who attended the rheumatology department at University Hospital Limerick, Ireland, up to February 2017. Patients satisfied the International Study Group for Behçet's Disease or the International Criteria for Behçet's Disease criteria. Demographic and clinical characteristics were captured on all patients at baseline. Data on symptom complex, organ involvement, inflammatory markers, and treatment strategy, along with response rates and adverse effects, were captured at follow-up

clinic visits and through patient interviews. Patients were trialed up to 16 weeks with an anti-TNF, which included dose optimization/escalation, before switching to a different anti-TNF if there was no improvement of clinical signs and symptoms with the induction therapy or if there were signs and symptoms consistent with clinical relapse. Patients were trialed up to 24 weeks if there was some but insufficient clinical response.

All patients were screened for latent tuberculosis, which included a history of tuberculosis exposure, tuberculin skin test, and chest x-ray prior to commencement of anti-TNF biological therapy.

"Complete responders" were defined as patients who experienced a full disappearance at any time of signs and symptoms as previously described after therapy with or without corticosteroid dose of ≤ 10 mg/day at 6 months.

Table 1. Clinical manifestations of patients with BD and the anti-TNFs used (n=22)

No	G	Age	AOU	GU	OL	CL	PP	VI	GI	ENT	B1	B2	B3	B4
1	F	25	+	+	-	+	-	-	-	+	IFX	ADA	-	-
2	M	71	+	-	+	+	-	-	-	+	IFX	GOL	ADA	-
3	F	35	+	+	-	+	-	-	-	+	IFX	-	-	-
4	M	53	+	+	+	+	+	-	+	+	IFX	ADA	GOL	-
5	F	38	+	+	-	+	-	-	-	+	IFX	ETA	-	-
6	F	24	+	+	-	+	-	-	-	+	IFX	ADA	GOL	-
7	F	19	+	+	+	+	-	-	-	-	IFX	-	-	-
8	M	50	+	+	+	+	-	+	-	-	IFX	-	-	-
9	M	57	+	-	+	+	-	-	-	+	IFX	ADA	IFX-r	-
10	F	38	+	+	-	+	-	-	-	-	IFX	CER	-	-
11	F	39	+	+	-	+	-	-	-	-	IFX	ADA	GOL	-
12	F	39	+	+	-	-	+	-	-	-	-	-	-	-
13	M	35	+	+	-	+	-	-	-	-	ETA	-	-	-
14	F	39	+	+	-	+	-	-	-	-	-	-	-	-
15	F	53	+	+	-	+	-	+	-	-	IFX	ADA	GOL	IFX-r
16	F	83	+	+	+	+	-	-	-	-	IFX	-	-	-
17	F	68	+	+	-	+	-	-	+	-	-	-	-	-
18	M	47	+	+	-	-	-	+	-	-	ETA	-	-	-
19	F	39	+	+	-	+	-	-	-	-	-	-	-	-
20	F	24	+	+	+	+	-	-	-	-	IFX	ADA	GOL	CER
21	F	23	+	+	-	+	-	-	-	-	IFX	ADA	ETA	-
22	F	25	+	+	-	+	-	-	-	-	ETA	-	-	-

AOU: Recurrent aphthous oral ulcers; GU: Genital ulcers; *OL: Ocular lesions CL: Cutaneous lesions; PP: Positive pathergy test; VI: Vascular involvement; GI: Gastrointestinal involvement; **ENT: Otolaryngeal manifestations; B: Anti-TNF biologics; IFX: Infliximab; IFX-r: Retrial with Infliximab ADA: Adalimumab; ETA: Etanercept; GOL: Golimumab; CER: Certolizumab pegol. * OL, this includes six patients with uveitis confirmed by the ophthalmologist and another patient who presented with bilateral painful, red eyes and transient loss of her left lateral vision but had a negative slit-lamp exam for uveitis. **ENT, this includes two patients with nasopharyngeal ulcerations, tonsillar ulcers/hypertrophy, and sensorineural deafness as well as the five patients deemed to have more significant laryngeal destruction.

Table 2. Choice of anti-TNF biological therapy for patients with BD in the Midwest Region of Ireland

Anti-TNF	1 st	2 nd	3 rd	4 th	Retrial	Secondary Failures
IFX	15	0	0	0	2	4 (all after 2 years)
ADA	0	8	1	0	0	2 (all after 2 years)
ETA	3	1	1	0	0	0
GOL	0	2	4	0	0	0 (but one needed dose increment)
CER	0	1	0	1	0	0

Anti-TNF: Anti-tumor necrosis factor alpha; IFX: Infliximab; ADA: Adalimumab; ETA: Etanercept; GOL: Golimumab; CER: Certolizumab pegol

"Partial responders" were classified as patients with significant improvement in signs and symptoms and reduction of >50% of the initial corticosteroid dose. All other patients were considered as non-responders. The management strategy was compared to current EULAR recommendations published in 2008 (4). We determined the frequency of serious infections and the time between commencement of biological therapies and infection onset. Serious infections were defined as infections that required intravenous antimicrobials and hospitalization. The study was approved by the local ethics committee and is in accordance with the Declaration of Helsinki.

Results

Out of a cohort of 22 Caucasian patients of Irish descent (mean age of 42.0 years), 18 (81.9%) received anti-TNF biologic therapies (6 males, 12 females) (Table 1). The indications to initiate anti-TNF therapy included ocular disease-six patients with uveitis, one resulting in permanent blindness (6/18), destructive laryngeal disease (5/18), vascular manifestations-including one pulmonary embolus and four deep vein thromboses (3/18), severe mucocutaneous lesions with significant impact on the quality of life (15/18), and resistance or intolerance to conventional treatments (8/18). Some patients had more than one indication.

Anti-TNFs included infliximab (IFX): n=15, 83.3%; adalimumab (ADA): n=9, 50%; golimumab (GOL): n=6, 33.3%; etanercept (ETA): n=5, 27.8%; and certolizumab pegol (CER): n=2, 11.1%. Out of the 18 patients, 11 (61.1%) (all of whom were on IFX infusion) were switched to a second anti-TNF, 7 patients (38.9%) needed at least three different anti-TNFs, 1 patient needed a fourth anti-TNF, and 2 patients needed retrial with IFX before their diseases were controlled (Table 2, 3). Currently, all 18 patients have been on a stable dose of anti-TNFs for more than 18 months (Table 3).

All 18 patients on anti-TNF achieved satisfactory remission; 14 (78%) patients were complete

responders achieving complete remission, and the other 4 (22%) patients were partial responders. Secondary failure was observed with IFX (4/15, 26.7%) and ADA (2/9, 22.2%), and all secondary failures were observed after at least 2 years of treatment. Thus far in our experience, ETA has been effective in all five of our patients achieving complete remission.

Five patients (27.7%) developed type I hypersensitivity reactions, all of whom were administered IFX. Three patients (16.7%) presented with acute mild flushing, chest discomfort, and rash, while two patients (11%) developed more severe reactions requiring intravenous hydrocortisone and anti-histamine. We identified five cases of serious infections involving three patients (16.7%), all of whom were administered IFX and all of whom required intravenous antimicrobials and hospitalization. These included one case of pneumonia, two cases of urosepsis, one case of infective cholangitis, and one case of herpes zoster. Only one of these patients was on a concomitant conventional DMARD in the form of methotrexate 15 mg weekly. The lag time between infections and initiation of biologic therapy was 60, 96, and 96 weeks (the same patient at week 96 had two infections, pneumonia and herpes zoster) in one patient and 56 and 214 weeks in the next two patients, respectively. All patients had swift recovery and have been recommenced biological therapy since then. None of our patients developed any other severe adverse events such as reactivation of tuberculosis, malignancies, demyelinating disease, or congestive cardiac failure.

Patients received rapid tapering doses of oral steroid therapy or intramuscular steroid depot injections for flares, and 11 patients were maintained on long-term low steroid doses (5 mg oral prednisolone or less). Only one patient remained on a conventional immune-modulator as a combination therapy in the form of methotrexate 15 mg weekly. Previous unsuccessful immunosuppressant therapies among our patients included azathioprine in seven patients; cyclosporine, methotrexate, and thal-

lidomide in two patients each; and mycophenolate mofetil in one patient (a patient may have been on more than one conventional immunosuppressant at different times) (Table 3).

Discussion

BD was previously considered to be extremely rare (0.64 per 100,000 population) in Northern European populations such as Ireland and the UK (13). While most physicians in this part of the world encounter very few cases of BD during their entire career, we, currently, care for a total of 22 Irish patients with BD from the catchment areas of Limerick, North Tipperary, and Clare in the Midwest Region of Ireland (population 385,172) (14) who attend our rheumatology outpatient department on a regular basis and whose diagnosis was made in line with international diagnostic guidance (15) (point prevalence of 5.71:100,000 population). The unusually high prevalence in this region may, in part, be due to improved disease recognition and close interactions across multiple specialties including ophthalmology, otolaryngology, maxillofacial surgery, infectious disease, dermatology, hematology, gastroenterology, and general practitioners.

The pathergy phenomenon is an inappropriate hyperreactivity response to minor trauma such as a needle prick. It is more commonly observed among BD populations along the Silk Route and is detected more frequently in patients with HLA-B*51 and active disease (16-17). Its sensitivity has declined over time yet continues to carry significant diagnostic value, especially in the highly prevalent countries (16, 18). The phenomenon is, however, rarely observed within the Northern European populations (19-21). In our cohort, two patients (9%) had a positive response to the skin pathergy test (assessed 48 hours after intradermal injection to the flexor aspect of their forearm), similar to previous studies in this geographical region. Of note, only one of our patients was HLA-B*51 positive, and the patient did not have a positive pathergy reaction (Table 1) (22). We recognize, however, the inherent limitations to the pathergy testing in our cohort, including the small sample size and that the majority of patients were in clinical remission when the test was performed.

Traditionally, BD was an exceptionally difficult disease to treat. While some patients responded reasonably well to topical treatments for mucocutaneous disease, for the majority with systemic disease, response to immunomodulation has generally been poor. Consequently, many patients received regular high doses of corticosteroids for disease flares with resultant

Table 3. Patients with BD, the conventional immune-modulators and anti-TNFs used (n=22)

No	G	Age (YFC)	Conventional immune-modulators	Anti-TNF
1	F	25 (2007)	AZA 50 mg BD PO (Sept 07-Sept 09): ineffective	1. IFX 3 mg/kg, 8/52ly (Nov 10-Dec 13): traveling abroad for a prolonged period 2. ADA 40 mg SC, 2/52ly (Jan 14-N)
2	M	71 (2006)	AZA 75 mg BD PO (Nov 12-Mar 13): ineffective MTX 15 mg weekly PO (Oct 13-N)	1. IFX 5 mg/kg, 6/52ly (Mar 11-Mar 13): secondary failure 2. GOL (Apr 13-Oct 13): ineffective 3. ADA 40 mg SC, 2/52ly (Oct 13-N)
3	F	35 (2011)	-	IFX 5 mg/kg, 6/52ly (July 11-N)
4	M	53 (1999)	AZA 75 mg BD PO (Apr 04-Apr 06): ineffective	1. IFX 5 mg/kg (Jan 09): hypersensitivity reaction 2. ADA 40 mg SC, 2/52ly (Feb 09-Aug 12): secondary failure 3. GOL 50 mg SC 1/12ly (Aug 12-May 15), GOL 100 mg SC 1/12ly (May 15-N) as flares were observed at 50 mg dose
5	F	38 (2010)	-	1. IFX 5 mg/kg 6/52ly (Apr 10-Feb 15): secondary failure 2. ETA 50 mg SC weekly (Feb 15-N)
6	F	24 (2012)	-	1. IFX 5 mg/kg 6/52 (Nov 12): hypersensitivity reaction 2. ADA 40 mg SC, 2/52ly (Jan 13-Jun 13): ineffective 3. GOL 50 mg SC 1/12ly (July 13-N)
7	F	19 (2010)	-	IFX 5 mg/kg 6/52ly (June 11-N)
8	M	50 (1984)	CysA*: treated for 6 months: ineffective THAL*: ineffective	IFX 5 mg/kg, 6/52ly (Dec 08-N)
9	M	57 (2001)		1. IFX 5 mg/kg, 6/52ly (Jan 09): GI upset 2. ADA 40 mg SC, 2/52ly (Feb 09-Aug 09): ineffective 3. IFX-r (Nov 09-N)
10	F	38 (2009)	AZA 50 mg BD PO (Feb 09): skin rash MTX 10 mg weekly PO (Mar 09): GI upset MMF 1 g BD PO (Apr 09-Oct 09): ineffective	1. IFX 5 mg/kg, 6/52ly (Oct 09-Dec 11): secondary failure 2. CER 200 mg SC, 2/52ly (Jan 11-N)
11	F	39 (2013)	AZA 75 mg BD PO (Jan 13-May 13) - ineffective	1. IFX 5 mg/kg, 6/52ly (Jan 13): hypersensitivity reaction 2. ADA 40 mg SC, 2/52ly (Feb-May 13): ineffective 3. GOL 50 mg SC 1/12ly (June 13-N)
12	F	39 (2014)	-	-
13	M	35 (2015)	-	ETA 50 mg SC, 1/52ly (June 15-N)
14	F	39 (1992)	-	-
15	F	53 (1993)	THAL (Jan-Dec 2005): ineffective CysA (July 06): GI upset AZA (Oct 06- Oct 08): ineffective MTX (Feb 09): GI upset	1. IFX 5 mg/kg, 6/52ly (Apr 09-Mar 10): partial remission 2. ADA 40 mg SC, 2/52ly (Mar 10-Sep 10): ineffective 3. GOL 50 mg SC (Oct 10-Mar 11): ineffective 4. IFX-r 5 mg/kg, 6/52ly (Mar 11-N)
16	F	83 (2000)	AZA*: ineffective	IFX 5 mg/kg, 6/52ly (Mar 09-N)
17	F	68 (2012)	-	-
18	M	47 (2014)	-	ETA 50 mg SC 1/52ly (May 14-N)
19	F	39 (2014)	-	-
20	F	24 (2008)	-	1. IFX 3 mg/kg (Mar 09): hypersensitivity reaction 2. ADA 40 mg SC, 2/52ly (Sep 09-Nov 11): secondary failure 3. GOL 50 mg SC, 1/12ly (Jan 12-Jul 12): ineffective 4. CER 200 mg SC, 2/52ly (Feb 13-Sep 13), CER 200 mg SC, 1/52ly (Sept 13-N): as flares were observed at the lower dose
21	F	23 (2006)	-	1. IFX 3 mg/kg (Apr 09): hypersensitivity reaction 2. ADA 40 mg SC, 2/52 (Jul 09-Oct 09): ineffective 3. ETA 50 mg SC, 1/52ly (Nov 09-N)
22	F	25 (2014)	-	ETA 50 mg SC, 1/52ly (June 15-N)

No: Number; G: Gender; YFC: Year patient fulfilled criteria for BD; F: Female; M: Male; AZA: Azathioprine; MTX: Methotrexate; CysA: Cyclosporine A; MMF: Mycophenolate mofetil; THAL: Thalidomide; IFX: Infliximab; IFX-r: Retrial with Infliximab ADA: Adalimumab; ETA: Etanercept; GOL: Golimumab; CER: Certolizumab pegol; 1/52ly: Weekly; 2/52ly: Fortnightly; 1/12ly: Monthly; N: Still receiving treatment; SC: Subcutaneously; GI: Gastrointestinal

*Medications were prescribed while treated elsewhere (dose/duration/date of treatment unspecified)

long-term side effects, and in severe disease patients historically required thalidomide treatment, despite its strong toxicity profile and lack of license, because it was effective in some of the worst patients who did not respond to other treatments. In our study, a total of eight patients were on conventional immunosuppressants prior to commencement of anti-TNF and were treated for at least 3 months before treatment was deemed ineffective (Table 3). It is also noteworthy that none of our patients treated with conventional immunosuppression alone achieved full remission. Three conventional agents on four occasions involving two patients had to be stopped within a month because of intolerance and side effects (methotrexate caused severe upper gastrointestinal symptoms in two patients, azathioprine was stopped because of a skin rash in one patient, and the final patient could not tolerate cyclosporine because of gastrointestinal side effects).

The advent of biological therapies has changed the whole vista regarding the treatment of the more common autoimmune diseases such as rheumatoid arthritis (RA) in the past decade. More recently, biological therapies have been tried in many of the less common orphan autoimmune diseases such as BD, and in many cases the benefits have been dramatic. In our 10-year experience of using anti-TNF in our cohort, we found it to be generally effective with an acceptable safety profile and tolerability resulting in a clinical improvement in all of our patients. The therapeutic efficacy can be maintained for a prolonged period of time; however, some patients do develop secondary failure with time and may require a switch to a different anti-TNF (or other biological therapy) to re-instate disease control. It is also imperative for us as clinicians to closely monitor our patients and to communicate with them appropriately so as to improve compliance and avoid unnecessary adverse events.

Current EULAR recommendations were tailored based on previous data that BD follows a more severe course, especially among young men (6). However, it is becoming more apparent that the disease follows different phenotypes depending on its geographical distribution (23-26). Five of our patients with significant laryngeal and nasopharyngeal involvement were deemed deserving of anti-TNF treatment. One of the central points of a recent study by Fitzgerald et al. is that in a Northern European population with BD and oropharyngeal ulceration, significant and potentially life-threatening pharyngeal damage may be occurring unbeknown to physicians and may be more common than was previously thought (27).

The percentage of patients in our cohort treated with anti-TNF is high (81.9%) when compared to other countries or other approved indications for anti-TNF such as RA (28-30). However, other available treatments for BD have limited efficacy and/or are more toxic, such as thalidomide, cyclosporine, and prolonged use of high-dose steroids. In Ireland, anti-TNF therapies are available to patients deemed suitable by the prescribing physician, and we believe that patients with severe potentially organ- and/or life-threatening disease such as destructive laryngeal or nasopharyngeal involvement are suitable candidates. Moreover, timely treatment with these agents is likely to be cost effective in preventing future hospitalization and or surgical intervention. We also highlight the unusually high disease activity in relatively older patients and among females. Our findings challenge the notion of similar patterns of presentation of BD in Northern European populations. We highlight significant heterogeneity in organ involvement, especially the phenotype of laryngeal and nasopharyngeal destruction. These findings would suggest substantial geographical and genetic variance.

More recently, three new patients in our clinic were commenced on ETA as first choice anti-TNF, and all three patients have had excellent responses and remain in complete remission. IFX and ADA, however, remain the drug of choice for patients with uveitis. We have opted to use regularly scheduled IFX infusion as the main first-line biological therapy option in the majority of our patients because of its proven dramatic sustained efficacy in previous studies, especially for uveitis associated with BD (31-34). In comparison to the 2008 EULAR recommendations that suggested IFX be used as a combination or add-on therapy with azathioprine in refractory eye involvement, our patients who presented with uveitis were treated early with IFX as monotherapy and had favorable outcomes. This early and aggressive approach was also partly because of the unfortunate fact that one of our patients (patient 8) became blind on one eye after his uveitis was unsuccessfully managed with the conventional immunosuppressants cyclosporine and thalidomide prior to the era of anti-TNF (Table 3).

High clinical response rates were observed initially with IFX; however, some patients tended to experience decreased efficacy over a period of time, usually after the 2nd year. Fifteen of our patients were commenced on IFX as the first choice anti-TNF, but among them five patients developed allergic reactions, with two having severe reactions and four developing secondary

failure (all after 2 years). One was switched to a different subcutaneous anti-TNF because they wished to travel abroad for a prolonged period, and a total of four patients achieved sustained prolonged remission and continued to be on treatment. Two patients did have retrials with IFX, one who initially developed upper gastrointestinal symptoms, which settled, and did not develop any further reactions with the retrial and has since achieved complete remission, and one who managed to maintain a low-disease activity, again without further reaction.

We found that with anti-TNF biological therapy, clinical response was evident in 100% of our patients with 78% achieving complete remission. Anti-TNF was extremely effective in suppressing the mucocutaneous oral and laryngeal manifestations thus significantly improving our patients' quality of life. However, resistant genital ulcers were often a difficult symptom to control, with three patients only achieving partial remission.

Our study demonstrated that anti-TNF therapy provides an effective alternative option for first-line therapy in severe BD where conventional immunosuppressive therapy fails. Patients who do not respond to one or more anti-TNFs because of intolerance, ineffectiveness, or secondary failure may benefit from switching to another drug from this group or even retrial of a previously administered anti-TNF because an unsatisfactory result with one biologic is not predictive of response to another anti-TNF. For those with potentially life-threatening destructive laryngeal manifestation, anti-TNF as a first choice may be considered. While we acknowledge the small number of patients as a limitation for this study, we believe nevertheless that these patients are a true reflection of the BD population because of its low prevalence in the Northern European population and that this study provides valuable insights to support the safety and efficacy of anti-TNF biologics in BD, particularly in non-endemic regions.

Ethics Committee Approval: The study was approved by the local ethics committee and is in accordance with the Declaration of Helsinki.

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