

Efficacy of adalimumab in patients with Behçet's disease unsuccessfully treated with infliximab

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ABSTRACT

Objective. To evaluate the clinical response after switching from infliximab to adalimumab in patients with Behçet's disease (BD).

Methods. In this ongoing, prospective, longitudinal and observational study, data were collected on efficacy and safety of every patient with BD beginning anti-TNF therapy in the last 8 years. The present analysis was restricted to patients who were switched to adalimumab after failing or not tolerating infliximab.

Results. A total of 69 patients with BD have been treated with infliximab so far. Seventeen of these (25%) have been switched to adalimumab for lack or loss of efficacy or infusion reactions. In 10 out of these 17, the main manifestations requiring switching were the mucocutaneous lesions, in 4 retinal vasculitis and in 3 the neurological involvement. Of the 17 treated patients, 9 showed sustained remission of the disease and 3 a good response. No side effects were observed in any patient.

Conclusion. The results of our study suggest that patients with BD showing a scarce response or adverse events to infliximab may successfully be treated with adalimumab, regardless of the reason for switching.

Introduction

Tumour necrosis factor- α (TNF- α) antagonists have been the most significant advancement in the management of Behçet's disease (BD) (1, 2). Of the currently available TNF- α blockers, infliximab, etanercept, and adalimumab have been shown to be effective on various manifestations of the disease (1-3).

Certainly, infliximab is the most extensively studied anti-TNF- α agent in BD. It is included in the EULAR recommendations for the management of BD and specific recommendations for its use have been suggested by a group

of experts (1, 2). However, a variable percentage of patients with BD do not respond to infliximab or withdraw from treatment due to inefficacy or adverse events. Patients with rheumatoid arthritis (RA), ankylosing spondylitis (AS) and psoriatic arthritis (PsA) who do not respond or do not tolerate a TNF- α blocker may successfully be treated with another. So far, only some articles have been published on adalimumab in BD and only few of these deal with the switching from infliximab to adalimumab (4-7).

The objective of this study was to evaluate the short and long term efficacy and safety of the anti-TNF- α antibody adalimumab in patients with BD in whom infliximab had failed.

Methods

At the Rheumatology Department of Lucania there is an ongoing, prospective, longitudinal and observational study on the efficacy and safety of the anti-TNF- α agents in patients with BD who have started these drugs since 2003. The present analysis was restricted to BD patients who were switched to adalimumab after failing or not tolerating infliximab. The Rheumatology Department of Lucania is a tertiary referral center for BD following the EULAR recommendations for its management (1). These recommendations contemplate that patients with resistant ocular, neurological and mucocutaneous involvement may be treated with TNF- α blockers.

Each patient included in the study met the ISG criteria for BD (9). The decision of beginning anti-TNF- α therapy and of switching to adalimumab was based on clinical considerations only. Generally, patients should have failed at least one conventional immunosuppressive agent and/or high doses of systemic corticosteroids. Thus, these patients represent a "real-life" sample of subjects with BD

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treated with TNF- α blockers. Patients were switched only to adalimumab since the soluble receptor etanercept seems to be less effective than the monoclonal antibodies infliximab and adalimumab on the various manifestations of BD as we have addressed previously (10). Reasons for infliximab discontinuation included lack of efficacy or primary failure (satisfactory response never reached), loss of efficacy or secondary failure (relapse after an initial good response), and adverse events. Infliximab was administered intravenously at weeks 0, 2, 6, and every 6-8 weeks subsequently at a dose of 5 mg/kg and adalimumab was given subcutaneously at a dose of 40 mg fortnightly. The wash-out period between infliximab and adalimumab was 8 weeks. After switching to adalimumab, patients continued concomitant therapies given during the infliximab period. No modification of their dosage was made.

Each patient was evaluated by the same rheumatologist, ophthalmologist and neurologist every month in the first three months and every 2 months, subsequently. Data recorded on a standardised form included demographics, disease duration, clinical manifestations, past and present treatments, and comorbidities. Response to anti-TNF therapy was based on the expert opinion (IO) and was graded as follows: remission, response, no response and worsening. Remission was defined as the complete disappearance of symptoms and signs of inflammation and response as at least 50% of improvement. As far as the remission and response of intraocular inflammation is concerned, the judgement was formulated according to the uveitis scoring system suggested by BenErza and co-workers (11). Remission was defined as scores turning into 0 and response as a decrease by 50%. The study was designed and conducted according to the guidelines of the Helsinki declaration. Local ethics committee approval and patient's written informed consent were obtained before study procedures were undertaken.

Results

So far, a total of 69 patients with BD have been treated with infliximab. Sev-

enteen of these were switched to adalimumab: 7 for lack of efficacy, 8 for loss of efficacy and 2 for infusion reactions (Table I). So far, 230 patients suffering from BD are followed up in the Rheumatology Department of Lucania. Sixty-nine of these have been treated with TNF- α antagonists. The remaining 161 have been treated with conventional therapies: 88 with cyclosporine, 68 with colchicine, 56 with azathioprine, 15 with interferon, 12 with clorambucil, 10 with thalidomide, and 7 with cyclophosphamide.

In 10 out of the 17 (patients nos. 1-10), the main clinical manifestations requiring the switching were the mucocutaneous lesions. Each out of these 10 patients had previously been treated with conventional therapies without any results. Patients nos. 9 and 10, who were switched due to infusion reactions to infliximab, were included in this group since the disease flared with the mucocutaneous lesions. In 5 out of the 10 patients we were able to obtain a complete remission of the disease, in 3 there was a good response (between 50 and 70%) and in the remaining 2 the disease remained unchanged or worsened. We took in consideration in evaluating the response the number of the mucocutaneous lesions and their duration. Patient no. 6 had very severe oral and genital ulcers and patient no. 8 multiple painful and destructive leg ulcers. These two cases have already been published due to their exceptional interest (10, 12). Concomitant therapy included prednisone, colchicine (Col), thalidomide (Thal), azathioprine (Aza), cyclosporine A (CsA) and methotrexate (MTX). After switching to adalimumab, patients continued concomitant therapies given during the infliximab period. No modification of their dosage was performed at the time of the switching. In patients obtaining remission with adalimumab we were able to stop the steroid therapy while the prednisone dose was tapered in patients with good response. Similarly, the dose of thalidomide, colchicine and immunosuppressive agents was reduced.

Patients nos. 11 to 14 were switched because of retinal vasculitis which caused a loss of response to infliximab.

In 3 cases we were able to obtain remission and in 1 the disease remained unchanged. The case of patient no. 11 has already been published due to the extraordinary response to adalimumab (12). In patients with remission, prednisone was stopped and the dose of CsA was reduced.

Patients nos. 15 to 17 were switched due to lack of response of the neurological manifestations to infliximab. Patient no. 15 developed severe neurological manifestations with cerebral lesions on brain magnetic resonance imaging (MRI) while on infliximab therapy. He had a complete recovery with the disappearance of the MRI lesions with adalimumab. His case has already been published due to its exceptional response to the drug (14). Patients nos. 16 and 17 were switched to adalimumab due to seizures. Only the second had cerebral lesions on MRI. These two patients showed no response to adalimumab. They had failed all traditional therapies during the infliximab period and before. They did not receive concomitant therapy during the adalimumab period since seizures were the only clinical manifestations.

So far, the median duration of adalimumab therapy in patients with remission or response was 17.5 months (range 3-54). No adverse events have been observed so far.

However, five (nos. 3, 4, 13, 16 & 17) out of the 17 failed to respond to adalimumab.

Discussion

The recognition of the role of TNF- α in the pathogenesis of BD and the use of TNF- α inhibitors have been a major advance in the management of the disease (1, 2). Infliximab, etanercept and adalimumab have been shown to be effective on the different manifestations of BD. Infliximab is the most widely studied agent and is recommended for patients who have failed traditional immunosuppressive therapy (1, 2). This approach is most likely going to be changed in the near future since some clinical experiences suggest that the use of anti-TNF- α in the early phase of the disease can give a long-lasting remission (15, 16). Our ongoing, longitudinal and observational study permits us to draw the

Table I. Clinical and therapeutic features of the 17 patients switched to adalimumab.

Pt no.	Age/Sex	Main clinical manifestation	Reason for infliximab discontinuation	Response to adalimumab	Concomitant therapy	Duration of adalimumab therapy (months)
1	41/F	Mucocutaneous lesions	Lack of efficacy	Remission	Thal	18
2	33/F	Mucocutaneous lesions	Lack of efficacy	Response	Pred, Aza	17
3	21/M	Mucocutaneous lesions	Lack of efficacy	No response	Col, CsA	3
4	23/M	Mucocutaneous lesions	Lack of efficacy	Worsening	Pred, CsA, Aza	3
5	36/F	Mucocutaneous lesions	Loss of efficacy	Response	Pred	54
6	50/M	Mucocutaneous lesions	Loss of efficacy	Remission	Pred, Colc	34
7	32/M	Mucocutaneous lesions	Loss of efficacy	Response	Pred, Aza	16
8	36/M	Mucocutaneous lesions	Loss of efficacy	Remission	MTX	16
9	33/F	Mucocutaneous lesions	Infusion reaction	Remission	Pred	22
10	38/M	Mucocutaneous lesions	Infusion reaction	Remission	Pred, Aza	31
11	28/M	Retinal vasculitis	Loss of efficacy	Remission	Pred, CsA	25
12	55/M	Retinal vasculitis	Loss of efficacy	Remission	Pred, CsA	14
13	33/M	Retinal vasculitis	Loss of efficacy	No response	Pred, CsA	3
14	39/M	Retinal vasculitis	Loss of efficacy	Remission	Pred, CsA	7
15	39/M	Neurological involvement	Lack of efficacy	Remission	Pred	12
16	56/M	Neurological involvement	Lack of efficacy	No response	–	6
17	41/F	Neurological involvement	Lack of efficacy	No response	–	6

Aza: Azathioprine; Col: Colchicine; CsA: Cyclosporine A; MTX: Methotrexate; Pred: prednisone; Thal: thalidomide.

following conclusions: 1) 25% (17 out of 69) of the patients treated with infliximab fail to respond to the drug due to lack or loss of efficacy and adverse events; 2) patients failing infliximab may successfully be treated with adalimumab; 3) the withdraw rate of adalimumab after switching has been one third. Our study suggests that, as observed in patients suffering from RA, AS and PsA, in the case of treatment failure with one monoclonal anti-TNF- α antibody, switching to the other antibody may also be useful in patients with BD due to the different molecular structures of these drugs.

So far, only few articles have been published on adalimumab in BD patients. In 2007, van Laar and co-workers reported on 6 patients treated with adalimumab for different manifestations of BD (4). Two patients were treated for uveitis, 2 for central nervous system involvement, 1 for colitis and the last for severe oral ulcers and arthritis. Interestingly, each patient had failed traditional immunosuppressive therapy and responded to infliximab. Adalimumab was prescribed after the flare of the disease following the discontinuation of infliximab therapy. The main reason for prescribing adalimumab was the concern about the role of autoantibodies to infliximab at the restart of therapy.

Each patient of this study responded to adalimumab therapy that was given for more than 12 months without any relapse and few side effects. More recently, Bawazeer and Raffa treated with adalimumab 11 male patients with BD showing ocular involvement (7). Ten out of these showed complete resolution of ocular inflammation by 4 weeks. The dosages of corticosteroids and immunosuppressive drugs were reduced or stopped in the majority of patients. Each patient showed a sustained remission of the disease while on therapy with adalimumab without experiencing any side effects. Interestingly, one patient who had not responded to infliximab and methotrexate showed improvement of ocular symptoms after switching to adalimumab. The switching from infliximab to adalimumab was also made by Belzunegui and co-workers in a patient suffering from neuro-Behçet's disease (5). However, this patient was treated with adalimumab because the disease relapsed one year after the end of a successful course of infliximab therapy and because delayed infusion reactions have been reported in patients receiving a second course of infliximab. Another patient was successfully switched to adalimumab after experiencing repeated infliximab-related infusion reactions by Takase *et al.* (6).

The main limitation of our real-life study is that the decision to withdraw infliximab and begin adalimumab was based only on the treating doctor's opinion. Another limitation is the absence of a control group.

In conclusion, the results of our study suggest that patients with BD showing a scarce response or adverse events to infliximab may successfully be treated with adalimumab, regardless of the reason for switching. In view of the limited sample size and the design of our study, larger and controlled trials are necessary in order to confirm our observation.

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