Switching of anti-TNF-α agents in Behçet's disease

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ABSTRACT

Objective. *Recent reports suggest ef-
ficacy of anti-tumour necrosis fac-
tor-alpha (TNF-α) therapy in Behçet's
disease. However, the switching of
anti-TNF-α agents for treatment fail-
ure remains unexplored. Our aims were
to describe the efficacy and safety of a
second anti-TNF-α agent in Behçet's
disease patients after failure of a first
agent.*

Methods. *In this retrospective case
series, 34 Behçet's disease patients
receiving anti-TNF-α agents, 19 of
whom switched to a second anti-TNF-
α agent, were identified. We assessed
the response to anti-TNF-α agents, the
duration of anti-TNF-α therapy, the
reasons for withdrawal, adverse events,
the Behçet's Disease Current Activ-
ity Form (BDCAF), C-reactive protein
(CRP), ESR and concomitant therapies
at the onset of the first and second anti-
TNF-α therapies, and after 6, 12 and
24 months.*

Results. *Clinical improvements were
seen in 26/34 (76%) after the first and
18/19 (95%) after the second anti-
TNF-α agent. Continuation rates at 24
months were 14.4% after the first and
22.3% after the second anti-TNF-α
agent. The most frequent reason for dis-
continuation was secondary failure in
both groups (12 after the first anti-TNF-
α agent and 8 after the second). Adverse
events leading to treatment withdrawal
were seen in 10 after the first anti-TNF-
α agent and three after the second.*

Conclusion. *The second anti-TNF-α
agent in Behçet's disease demonstrated
similar efficacy to that seen with the
first agent without new safety concerns,
supporting switching to a second anti-
TNF-α agent. However, long-term con-
tinuation rates for anti-TNF-α therapy
were low after both the first and second
agents.*

Introduction

Behçet's disease is a chronic, multi-
system inflammatory disorder clas-
sified among the vasculitides (1-2).

There is a consensus that Behçet's dis-
ease is strongly associated with HLA-
B51. However, prevalences of HLA-
B51 in Behçet's disease are different
between different geographic areas (3).
The genetic contribution and the etiol-
ogy of Behçet's disease remain unclear.
Without defined pathogenic mecha-
nisms, colchicine, glucocorticoids and
other immunosuppressants have been
empirically used in the treatment, par-
ticularly for more serious presentations
with ocular, neurologic, vascular and
gastroenterological involvement. How-
ever, these conventional therapies can
be ineffective.
A high secretion of TNF-α by T cells
and monocytes from peripheral blood
has been demonstrated in patients with
active Behçet's disease (4-7). Thus
anti-TNF-α agents have been tried in
refractory and/or severe disease, and
the recent use of these agents has in-
creased. There is a weak evidence base
underlying the efficacy of anti-TNF-α
therapy with only one randomised, pla-
cebo-controlled trial (8), and many case
series and cohort studies suggesting ef-
ficacy (9-10). However, many aspects
of anti-TNF-α therapy remain unex-
plored, such as the lack of long-term
data, comparison between anti-TNF-α
agents, optimal use of concomitant glu-
cocorticoids and immunosuppressants,
and switching of anti-TNF-α agents.
We aimed to describe the efficacy and
the safety of switching to a second anti-
TNF-α agent after failure of the first
anti-TNF-α agent.

Materials and methods

Patients

We performed a retrospective case se-
ries study of Behçet's disease patients
treated with anti-TNF-α therapy. Nine-
ty-seven patients with Behçet's disease
attending the vasculitis clinic at our
Hospital from 2001 to February 2012
were identified. The diagnosis was
based on the criteria of the Internation-
al Study Group for Behçet's disease
(11). Thirty-four out of 97 had received

anti-TNF-α therapy, 19 had received at least two anti-TNF-α agents, and two had received three agents.

Of the 34 patients treated with anti-TNF-α agents, 27 were female and their median age at the time of the first agent was 36 years (21–60 years). 32 were Caucasian and 2 were Asian. The median prior disease duration was 37 months (5–214 months). Of 19 patients treated with a second anti-TNF-α agent, 17 were female, median age 37 years (22–63 years). All were Caucasian with a median disease duration of 52 months (8–238 months). All patients were currently receiving or had previously received both glucocorticoids and immunosuppressants (Table I).

The first anti-TNF-α agents were infliximab in 30, and adalimumab in four. The second anti-TNF-α agents were infliximab in one, etanercept in six, and adalimumab in 12 (Table II).

Definitions

We divided the cases who lacked efficacy of the anti TNF-α agent into two groups, 'primary failure' and 'secondary failure'. 'Primary failure' was defined as a failure to reach a satisfactory response at three months evaluated by an experienced Behçet's disease physician. Organ specific definitions were: uveitis; still having active uveitis or ocular attack, confirmed by an ophthalmologist. Intestinal disease; persistent abodominal pain attributable to active disease (not always re-checked by endoscopy). CNS disease; persistent headache or progressive weakness, memory loss, cognitive disorder (Stability of neurological function was classified as 'satisfactory response'). Joint/Mucocutaneous disease; still having severe manifestations which significantly reduced the patient's quality of life (Mild manifestations were classified as 'satisfactory response').

Excluding 'primary failure' and early withdrawal by adverse events before we assessed the efficacy of anti-TNF-α agents, the remaining patients were defined as 'responders'. In the 'responders', a case relapsed after initial good response was defined as 'secondary failure'. Symptoms of relapse were defined as one of the following; active uveitis

confirmed by an ophthalmologist, active colitis confirmed by endoscopy, severe headache or progressive weakness, memory loss, cognitive disorder, and severe joint/mucocutaneous manifestations which significantly reduced patient's quality of life (Mild joint/mucocutaneous manifestations were not classified as 'relapse').

These definitions encompassed the range of Behçet's disease manifestations experienced by patients in this study but were not intended to be comprehensive for all possible manifestations.

Indications

In the EULAR recommendations (12), candidates for anti-TNF-α agents are patients with relapsing posterior uveitis, active central nervous system disease, active intestinal disease and

Table I. Characteristics of Behçet's disease patients treated with anti-TNF-α agents.

	1st anti-TNF-α agent (n=34)	2nd anti-TNF-α agent (n=19)
Median age (min-max)	36 (21–60) years	37 (22–63) years
Sex M:F (female rate)	7:27 (79.4%)	2:17 (89.4%)
Ethnicity	32/34 Caucasian 2/34 Asian	19/19 Caucasian
Organ involvement		
Eye	19/34	7/19
Oral ulcer	34/34	19/19
Genital ulcer	30/34	17/19
Skin	24/34	18/19
Nerve	9/34	6/19
Intestine	5/34	4/19
Vascular	4/34	1/19
Median disease duration (min-max)	37 months (5–214 months)	52 months (8–238 months)
Prior treatment		
Glucocorticoids	34/34	19/19
Colchicine	11/34	6/19
Hydroxychloroquine	17/34	10/19
Azathioprine	18/34	9/19
Cyclophosphamide	2/34	NA
Mycophenolate	14/34	9/19
Tacrolimus	14/34	11/19
Cyclosporine	12/34	7/19
Methotrexate	4/34	2/19
Thalidomide	7/34	5/19
Leflunomide	1/34	NA
Alemtuzumab	3/34	3/19
Rituximab	2/34	1/19
Interferon-α	NA	1/19

NA: not applicable.
Data were collected at the onset of the first and second anti-TNF-α therapies. Organ involvements reflected involvements at any stage in the disease course. All patients had prior exposure to both glucocorticoids and immunosuppressants.

Table II. Number of Behçet's disease patients treated with anti-TNF-α agents.

1st agent (n=34)	continued 1st agent (n=4)	withdrew 1st agent (n=30)	Switch to 2nd agent (n=19)			No 2nd agent (n=11)
			IFX (n=1)	ETN (n=6)	ADA (n=12)	
IFX (n=30)	n=3	n=27	NA	n=6	n=12	n=9
ETN (n=0)	NA	NA	NA	NA	NA	NA
ADA (n=4)	n=1	n=3	n=1	NA	NA	n=2

IFX: infliximab; ETN: etanercept; ADA: adalimumab; NA: not applicable.
34 patients received the first anti-TNF-α agents.
4/34 continued to receive the first anti-TNF-α agents and 30/34 withdrew the first anti-TNF-α agents.
19/30 switched to the second anti-TNF-α agents and 11/30 had no more anti-TNF-α agents (They had other therapies).

arthritic and mucocutaneous manifestations that significantly reduce quality of the life. In our series, anti-TNF-α therapy was commenced for similar indications that were also refractory to conventional therapies or were glucocorticoid-dependent. A second anti-TNF-α agent was commenced for primary failure, secondary failure, or for severe infusion reactions with the first anti-TNF-α agent (Table III).

Treatments

Infliximab was administered at 5mg/kg every 4 weeks for 4 doses and then every 6 weeks. Etanercept was administered at 50mg twice a week and adalimumab administered at 40mg every two weeks. 27/34 and 11/19 initially had concomitant glucocorticoids with the first and the second anti-TNF-α agent, respectively. 15/34 and 8/19 initially had concomitant immunosuppressants with the first and the second anti-TNF-α agent respectively. 5/6 with uveitis had concomitant calcineurin inhibitors with their anti-TNF-α agent and one mycophenolate due to an adverese effect with cyclosporine. Following anti-TNF-α therapy the management plan was to reduce and stop glucocorticoids first and immunosuppressants second. It was not planned to maintain patients on long-term glucocorticoids or immunosuppressants in the absence of disease activity.

Assessment

We retrospectively assessed the Behçet's Disease Current Activity Form (BDCAF) (13), CRP, ESR, glucocorticoid and immunosuppressant doses. Each of those items alone was not enough to evaluate the efficacy of the anti TNF-α agent but supported the conclusions of response or failure. Hydrocortisone dosing was converted to the prednisolone equivalent. We classified responders to anti TNF-α therapy and noted the reasons for treatment withdrawal, time to withdrawal and major adverse events. Data was recorded at the time of initiation of an anti TNF-α agent (baseline), and after 6, 12 and 24 months, and was acquired from patients' medical charts and computer records with confirmation of details

Table III. Indications for anti-TNF-α agents, active organs and concomitant drugs at baseline.

	1st anti-TNF-α agent (n=34)	2nd anti-TNF-α agent (n=19)
Indications		
Uveitis	6/34	NA
Intestinal disease	4/34	NA
CNS disease	8/34	NA
Joint/Mucocutaneous disease	17/34	NA
Primary failure of 1st	NA	2/19
Secondary failure of 1st	NA	11/19
Infusion reaction of 1st	NA	4/19
Patient's convenience	NA	2/19
Active organs		
Eye	7/34	2/19
Oral ulcer	28/34	13/19
Genital ulcer	22/34	11/19
Skin	15/34	6/19
Joint	26/34	11/19
Nerve	9/34	3/19
Intestine	6/34	2/19
Vascular	NA	NA
Concomitant drugs		
Glucocorticoids	27/34	11/19
Hydroxychloroquine	3/34	NA
Azathioprine	5/34	1/19
Mycophenolate	1/34	3/19
Tacrolimus	4/34	3/19
Cyclosporine	3/34	NA
Methotrexate	1/34	1/19
Leflunomide	1/34	NA

NA: not applicable; CNS: central nervous system.
Primary failure meant a case never reached satisfactory response within 3 months.
Secondary failure meant a case relapse after an initial good response. 17 of 34 with the first and 8 of 19 with the second anti-TNF-α agent were also treated with immunosuppressants.
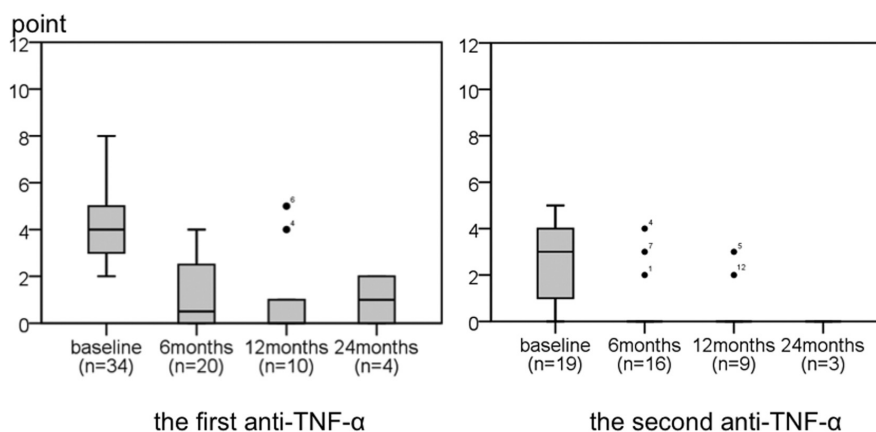

Fig. 1. BDCAF scores during the first and the second anti-TNF-α therapy
BDCAF, Behçet's Disease Current Activity Form.
Data at 6, 12 and 24 months from patients continuing their first and the second anti-TNF-α agents. Median BDCAF scores at baseline, 6, 12 and 24 months were 4.0, 0.5, 0.0 and 1.0 (n=34, 20, 10 and 4) in the first, and were 3.0, 0.0, 0.0 and 0.0 (n=19, 16, 9 and 3) in the second.

where necessary from the patients during routine clinic attendance.

Statistics

The distributions of the following data; age, disease duration, BDCAF, CRP, ESR and dose of glucocorticoids were described by median and ranges. The proportion of patients remaining on therapy was assessed by Kaplan-Meier survival curves. Differences between the first and the second anti-TNF-α

agent groups were assessed by Mann-Whitney U-test for distributions described with median and ranges, Fisher's exact test for response rates and log-rank test for Kaplan-Meier survival curves with a significance level set at <0.05. All analyses utilised IBM SPSS Statistics version 19.

Results

BDCAF

The median BDCAF scores at baseline, 6, 12 and 24 months were 4.0, 0.5, 0.0 and 1.0 after the first anti-TNF-α agent, and 3.0, 0.0, 0.0 and 0.0 after the second (Fig. 1). The BDCAF score fell in both groups between baseline and six months ($p<0.01$).

CRP and ESR

Median CRP levels were in the normal range at baseline and there were no significant changes after initiation of anti-TNF-α therapy (Supplement 1). The ESR followed a similar pattern to the CRP (data not shown).

Glucocorticoids and immunosuppressants

The median prednisolone doses at baseline, 6, 12 and 24 months were 10.0, 3.0, 0.0 and 0.0mg/day after the first anti-TNF-α agent, and 5.0, 2.5, 0.0 and 7.0mg/day after the second (Fig. 2). The falls from baseline to 6 months were significant after the first agent but not after the second ($p=0.02$ and $p=0.51$ respectively).
27/34 at baseline (79.4%), 13/20 at 6 months (65.0%), 2/10 at 12 months (20.0%), 1/4 at 24 months (25.0%) were treated with prednisolone after the first anti-TNF-α agent, five stopping prednisolone. 11/19 at baseline (57.8%), 9/16 at 6 months (56.2%), 4/9 at 12 months (44.4%), 3/3 at 24 months (100%) were treated with prednisolone after the second anti-TNF-α agent, with two stopping prednisolone.
18/34 baseline (52.9%), 13/20 at 6 months (65.0%), 6/10 at 12 months (60.0%), 2/4 at 24 months (50.0%) were treated with immunosuppressants after the first anti-TNF-α agent, with five stopping immunosuppressants. 8/19 at baseline (42.1%), 8/16 at 6 months (50.0%), 4/9 at 12 months (44.4%), 1/3
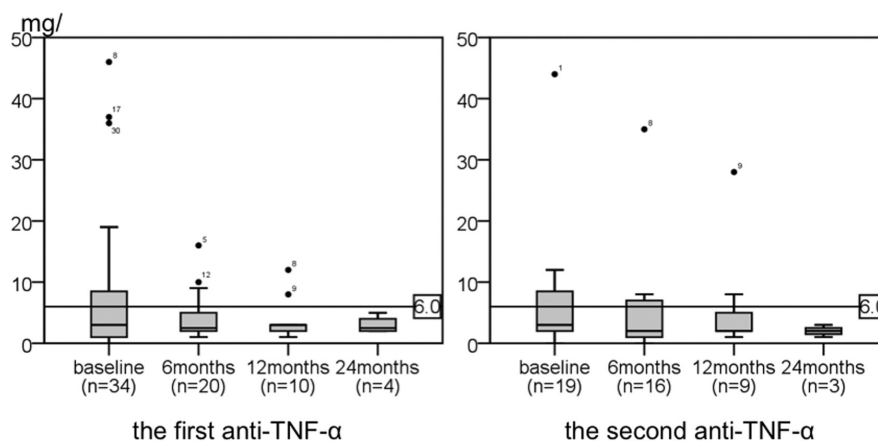
Supplement 1. C-reactive protein during the first and the second anti-TNF-α therapy.
Data at 6, 12 and 24 months from patients continuing their first and the second anti-TNF-α agent. Median CRP values at baseline, 6, 12 and 24 months were 3.0, 2.5, 3.0 and 2.5mg/l in the first (n=34, 20, 10 and 4), and were 3.0, 2.0, 2.0 and 2.0mg/l in the second (n=19, 16, 9 and 3). (Normal <6mg/l, see reference line).
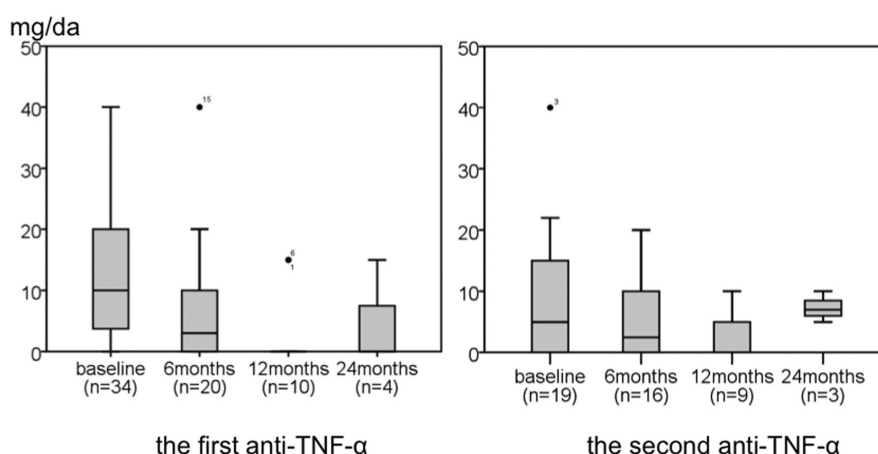

Fig. 2. Dose of prednisolone during the first and the second anti-TNF-α therapy.
Dose of prednisolone at 6, 12 and 24 months from the patients continuing their first and the second anti-TNF-α agent. Median doses at baseline, 6, 12 and 24 months were 10.0, 3.0, 0.0 and 0.0mg/day (n=34, 20, 10 and 4) in the first, and were 5.0, 2.5, 0.0 and 7.0mg/day (n=19, 16, 9 and 3) in the second.
27/34, 13/20, 2/10, 1/4 patients in the first and 11/19, 9/16, 4/9, 3/3 in the second were treated with prednisolone at baseline, 6, 12 and 24 months.
18/34, 13/20, 6/10, 2/4 patients in the first and 8/19, 8/16, 4/9, 1/3 patients in the second were treated with immunosuppressants at baseline, 6, 12 and 24 months.

at 24 months (33.3%) were treated with immunosuppressants after the second anti-TNF-α agent and none stopped immunosuppressants.

Response rate, continuation rate and reasons for withdrawal

8/34 after the first and 1/18 after the second anti-TNF-α agent withdrew anti-TNF-α therapy within 3 months. 5/8 after the first and 1/1 after the second anti-TNF-α agent did not improve within 3 months and were classified as primary failures. 3/8 after the first agent withdrew with early adverse events (2 systemic drug reactions and

one malignancy) before we assessed the efficacy of the anti-TNF-α agents. We classified the remaining patients as responders. Falls of BDCAF were seen in all responders. 26/34 (76%) after the first and 18/19 (95%) after the second anti-TNF-α agent were responders, $p=0.26$. However 22/26 after the first and 13/18 after the second anti-TNF-α agent withdrew from anti-TNF-α therapy after 3 months. The most frequent reason was relapse after initial good response, classified as secondary failure, in 12 after the first anti-TNF-α agent at 14 months (4-26), and eight after the second at 13 months (7-54) (Table IV).

14.4% and 22.3% were still receiving a first or second anti-TNF-α agent respectively at 24 months, *p*=0.23 (Fig. 3).

Adverse events
Severe infusion reactions occurred with the first anti-TNF-α agent, infliximab, in four. Other adverse events leading to withdrawal of an anti-TNF-α agent were seen in six after the first anti-TNF-α group and three after the second. These included rash (2), infections (5) and malignancy (2), multiple basal cell carcinoma and acute lymphocytic leukaemia (Table V).

Discussion

In this study, we observed falls in disease activity permitting glucocorticoid reduction after both first and second anti-TNF-α agents when used for Northern European patients with Behçet's disease who had failed conventional therapy (Fig. 1). Not all patients responded with 5/34 (15%) and 1/19 (5%) having no benefit after the first or second agent respectively, three withdrawing their first agents due to adverse events before efficacy could be assessed. However, 26/34 (76%) after the first anti-TNF-α agent and 18/19 (95%) after the second responded to the therapy. These response rates reflect the clinical utility of anti-TNF-α therapy in refractory Behçet's disease, permitting better disease control and reductions of glucocorticoids and immunosuppressants, and are in line with previous reports.

A frequent problem with anti-TNF-α therapy in Behçet's disease has been discontinuation due to a return of disease activity or intolerance of the medication. This inspired our study into the efficacy and safety of switching to a second anti-TNF-α agent after failure of the first. We found a similar pattern of response to the second anti-TNF-α agent indicating that this is a worthwhile strategy after failure of the first agent. However, the mean activity was lower at the time of commencement of the second agent than the first. The duration of response after the second agent was also short with only 22% remaining on therapy at 24 months. We found a similar pattern of adverse drug

Table IV. Responder and withdrawal of anti- TNF-α agents.

	1st anti-TNF-α agent n=34	2nd anti-TNF-α agent n=19
Early withdrawal	8/34	1/19
Primary failure	n=5	n=1
Systemic drug reaction	n=2	NA
Malignancy	n=1	NA
Responder to the treatment	26 /34	18/19
Later withdrawal	22/34	13/19
Secondary failure	n=12	n=8
Systemic drug reaction	n=2	NA
Rash	n=2	NA
Infection	n=3	n=2
Malignancy	NA	n=1
Patient's convenience	n=2	n=2
Unclear	n=1	NA
Continued	4/34	5/19

NA: not applicable.
Early withdrawal was withdrawal within 3 months from the commencement of anti-TNF-α therapy and later withdrawal was withdrawal after 3 months. Primary failure meant a case never reached satisfactory response within 3 months. Secondary failure meant a case relapse after an initial good response. 26/34 (76.4%) after the first and 18/19 (94.7%) after the second anti- TNF-α agents responded to the treatments at first (*p*=0.26). Then, 22/26 after the first and 13/18 after the second anti- TNF-α agents had later withdrawal.
 "Malignancy" included 1 acute lymphocytic leukaemia after the first and 1 basal cell carcinoma after the second anti-TNF-α agents.
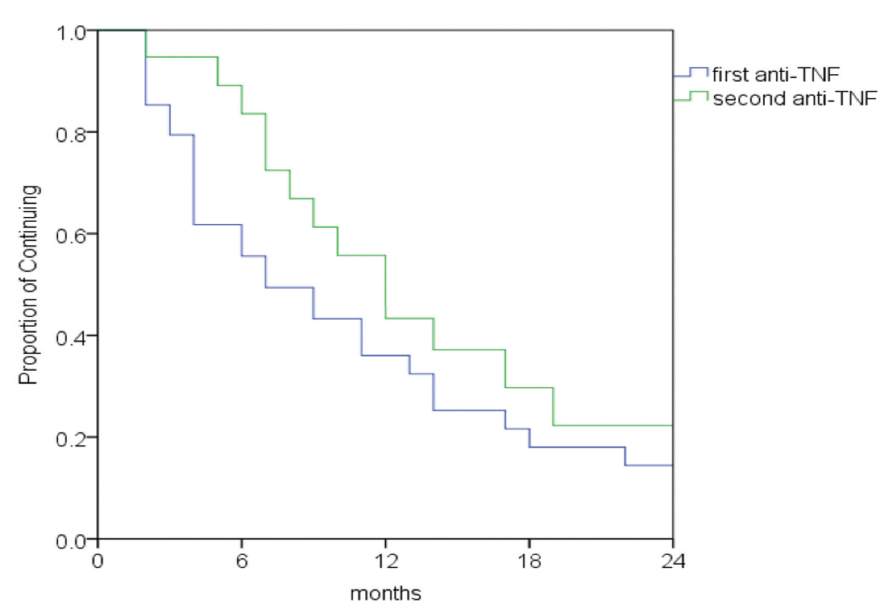

Fig. 3. Proportion of patients continuing their first and second anti-TNF-α agents.
At 12 and 24 months, the proportion of patients continuing were 36.0 and 14.4% with the first anti-TNF-α agent and 43.3 and 22.3% with the second anti-TNF-α agent (n=34 and 19 respectively). There was no differences between the groups (*p*=0.23).

reactions, infection and malignancy to that previously observed with anti-TNF-α agents in Behçet's disease with no evidence that the second anti-TNF-α agent caused more frequent or severe adverse events than the first.
In this study, dose schedules of infliximab and etanercept were different from what are generally used (infliximab; 5mg/kg every 8 weeks, etanercept 25mg twice or 50mg once every week). Higher doses of anti- TNF-α agents were not likely to deteriorate response rates or relapse rates, but might influence adverse events, though adverse events in this study were similar

to previous reports. The selection of anti-TNF-α agent may have influenced our results. Infliximab was most commonly used as the first agent and is more frequently associated with infusion reactions and anti-human chimeric antibody (HACA) responses can lead to secondary treatment failure (14-15). HACA levels were not investigated in this study. Adalimumab, a fully humanised antibody, is better tolerated and this may have been reflected in the trend to longer continuation when compared to infliximab (Continuation rates at 24 months were 10.1% in the infliximab group and 33.3% in the adalimumab group, *p*=0.03 (Supplement 2). Adalimumab might be better than infliximab for maintenance therapy for Behçet's disease, especially in the absence of glucocorticoids and immunosuppressants. However, the long-term continuation rate of adalimumab was still low. Our results may also have been influenced by the sequence of anti-TNF-α agents used, 12/19 switched to adalimumab from infliximab in this study, reflecting local practise at the time, and different results may have been obtained with a different sequence of agents.

Concomitant drugs may also have influenced our results. The combination of anti-TNF-α agents and immunosuppressants remains controversial due to a paucity of data. The EULAR recommendations only refer to this issue in uveits (12) recommending the combination of azathioprine and infliximab. Inliximab is an approved therapy for uveitis of Behçet disease in Japan based on a trial performed with monotherapy (not published). In a systematic review with 369 patients, only the combination of cyclosporine and infliximab, not azathioprine and infliximab, for uveitis showed superiority against the monotherapy (10). It was noted that there was a lack of data on combination therapy for other indications and with other anti-TNF-α agents. Our management plan aimed to withdraw glucocorticoids and immunosuppressants after successful remission induced by an anti-TNF-α agent because these initial agents had been perceived to have failed. This is in contrast to other indications for anti-TNF-α agents, such as

Table V. Adverse events of anti-TNF-α agents.

	1st anti-TNF-α agent (n=34)	2nd anti-TNF-α agent (n=19)
systemic drug reaction	n=4	NA
injection site reaction	n=1	n=1
rash	n=3	n=1
infection	n=4	n=6
abnormal liver function	n=1	NA
malignancy	n=1	n=1
alopecia	n=1	NA

NA: not applicable.
Patents made a good recovery from all adverse events except for one case of leukaemia.
Infections were systemic herpes zoster, severe pneumonitis, groin abscess and skin abscess with the first anti-TNF-α agent, and six airway infections cases including three with pneumonia, with the second anti-TNF-α agent.
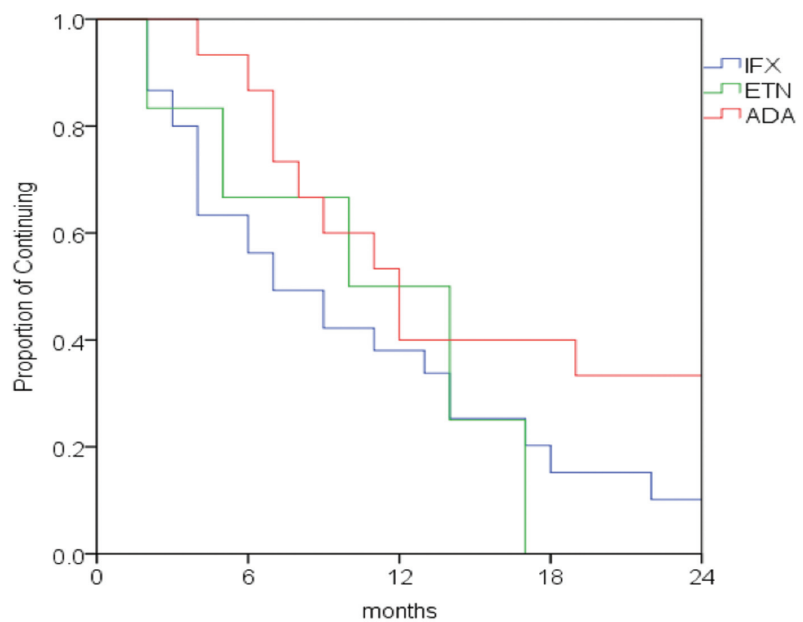
Supplement 2. Proportion continuing anti-TNF-α therapy according to the agent.
IFX: infliximab; ETN: etanercept; ADA: adalimumab.
At 24 months, the proportion of patients continuing were 10.1% with IFX, 0% with ETN and 33.3% with ADA (n=31 with IFX, 7 with ETN and 16 with ADA). The proportion continuing ADA was significantly higher than with IFX (*p*=0.03).

rheumatoid arthritis, psoriatic arthritis and ankylosing spondylitis where anti-TNF-α agents have better sustained efficacy (16-19). These diseases are usually treated with a combination of anti-TNF-α agents and long-term methotrexate or alternative. Our results might have been improved by the prolonged use of an immunosuppressant both by modifying disease activity directly and by reducing the frequency of anti-globulin responses. An alternative hypothesis is that the disease 'escapes' from anti-TNF-α therapy, a concept reported in anti-neutrophil antibody (ANCA)-associated vasculitis with infliximab and etanercept (20-21).

There has been only one study that has discussed the switching of anti-TNF-α agents in Behçet's disease from Southern Italy (22) and there have been few studies that discussed long-term anti-TNF-α therapy (22-27). Some of the studies showed a longer efficacy of anti-TNF-α therapy in Behçet's disease than in this study. However, ethnicities, indications and protocols for reducing steroid and concomitant immunosuppressants were different between studies and most had small sample sizes (less than 10 cases). In their 8-year study, the Southern Italian group reported that 17 of 69 Behçet's disease patients treated with infliximab switched to adalimumab

for primary failure (7), secondary failure (8) or infusion reactions (2). 12/17 responded to adalimumab and 12/12 were continuing adalimumab after a median of 17 months. Interestingly, a Japanese group reported the long-term efficacy of infliximab and methotrexate combination therapy in entero-Behçet's disease (23). At 24 months, 10/10 patients continued their combination therapy in their study. Methotrexate has the best evidence base and is the most frequent concomitant drug with anti-TNF-α agents in rheumatoid arthritis (29-30). We believe methotrexate requires further evaluation in combination with anti-TNF-α agents for Behçet's disease.

In conclusion, we found that a second anti-TNF-α agent was as effective as a first anti-TNF-α agent in the treatment of Behçet's disease without new safety concerns. The high discontinuation rate seen in both groups may have reflected the patient cohort and concomitant therapy or be an underlying feature of this treatment approach in Behçet's disease.

References

1. SAKANE T, TAKENO M, SUZUKI N, INABA G: Behçet's disease. *N Engl J Med* 1999; 341: 1284-91.
2. YAZICI Y, YURDAKUL S, YAZICI H: Behçet's syndrome. *Curr Rheumatol Rep* 2010; 12: 429-35.
3. DEMENTHON M, LAVALLEY MP, MALDINI C, GUILLEVIN L, MAHR A: HLA-B51/B5 and the risk of Behçet's disease: a systematic review and meta-analysis of case-control genetic association studies. *Arthritis Rheum* 2009; 61: 1287-96.
4. KANEKO S, SUZUKI N, YAMASHITA N *et al.*: Characterization of T cells specific for an epitope of human 60-kD heat shock protein (hsp) in patients with Behçet's disease (BD) in Japan. *Clin Exp Immunol* 1997; 108: 204-12.
5. YAMASHITA N, KANEOKA H, KANEKO S *et al.*: Role of cd T lymphocytes in the development of Behçet's disease. *Clin Exp Immunol* 1997; 107: 241-7.
6. MEGE JL, DILSEN N, SANGUEDOLCE V *et al.*: Overproduction of monocyte derived tumor necrosis factor alpha, interleukin (IL) 6, IL-8 and increased neutrophil superoxide generation in Behçet's disease A comparative study with familial Mediterranean fever and healthy subjects. *J Rheumatol* 1993; 20: 1544-9.
7. FRASSANITO MA, DAMMACCO R, CAFFORIO P *et al.*: Th1 polarization of the immune response in Behçet's disease: a putative pathogenetic role of interleukin-12. *Arthritis Rheum* 1999; 42: 1967-74.
8. MELIKOGLU M, FRESKO I, MAT C *et al.*: Short-term trial of etanercept in Behçet's disease: a double blind, placebo controlled study. *J Rheumatol* 2005; 32: 98-105.
9. SFIKAKIS PP, MARKOMICHELAKIS N, ALPSOY E *et al.*: Review Anti-TNF therapy in the management of Behçet's disease—review and basis for recommendations. *Rheumatology* (Oxford) 2007; 46: 736-41.
10. ARIDA A, FRAGIADAKI K, GIAVRI E, SFIKAKIS PP: Anti-TNF Agents for Behçet's Disease: Analysis of Published Data on 369 Patients. *Semin Arthritis Rheum* 2011; 41: 61-70.
11. INTERNATIONAL STUDY GROUP FOR BEHÇET'S DISEASE: Criteria for diagnosis of Behçet's disease. *Lancet* 1990; 335: 1078-80.
12. HATEMI G, SILMAN A, BANG D *et al.*; EULAR EXPERT COMMITTEE: EULAR recommendations for the management of Behçet disease. *Ann Rheum Dis* 2008; 67: 1656-62.
13. BHAKTA BB, BRENNAN P, JAMES TE, CHAMBERLAIN MA, NOBLE BA, SILMAN AJ: Behçet's disease: evaluation of a new instrument to measure clinical activity. *Rheumatology* (Oxford) 1999; 38: 728-33.
14. WOLBINK GJ, VIS M, LEMS W *et al.*: Development of antiinfliximab antibodies and relationship to clinical response in patients with rheumatoid arthritis. *Arthritis Rheum* 2006; 54: 711-5.
15. BARTELDS GM, WIJBRANDTS CA, NURMOHAMED MT *et al.*: Clinical response to adalimumab: relationship to anti-adalimumab antibodies and serum adalimumab concentrations in rheumatoid arthritis. *Ann Rheum Dis* 2007; 66: 921-6.
16. KIEVIT W, FRANSEN J, ADANG EM *et al.*: Long-term effectiveness and safety of TNF-blocking agents in daily clinical practice: result from the Dutch Rheumatoid Arthritis Monitoring register. *Rheumatology* (Oxford) 2011; 50: 196-203.
17. GLADMAN DD, MEASE PJ, RITCHLIN CT *et al.*: Adalimumab for long-term treatment of psoriatic arthritis: forty-eight week data from the adalimumab effectiveness in psoriatic arthritis trial. *Arthritis Rheum* 2007; 56: 476-88.
18. SMOLEN JS, EMERY P: Infliximab: 12 years of experience. *Arthritis Res Ther* 2011; 13 (Suppl. 1): S2.
19. HYRICH KL, LUNT M, WATSON KD, SYMMONS DP, SILMAN AJ: British Society for Rheumatology Biologics Register. Outcomes after switching from one anti-tumor necrosis factor alpha agent to a second anti-tumor necrosis factor alpha agent in patients with rheumatoid arthritis: results from a large UK national cohort study. *Arthritis Rheum* 2007; 56: 13-20.
20. BOOTH A, HARPER L, HAMMAD T *et al.*: Prospective study of TNF-alpha blockade with infliximab in anti-neutrophil cytoplasmic antibody-associated systemic vasculitis. *J Am Soc Nephrol* 2004; 15: 717-21.
21. WEGENER'S GRANULOMATOSIS ETANERCEPT TRIAL (WGET) RESEARCH GROUP: Etanercept plus standard therapy for Wegener's granulomatosis. *N Engl J Med* 2005; 352: 351-61.
22. OLIVIERI I, LECCESE P, D'ANGELO S *et al.*: Efficacy of adalimumab in patients with Behçet's disease unsuccessfully treated with infliximab. *Clin Exp Rheumatol* 2011; 29 (Suppl. 67): S54-7.
23. IWATA S, SAITO K, YAMAOKA K *et al.*: Efficacy of combination therapy of anti-TNF-α antibody infliximab and methotrexate in refractory entero-Behçet's disease. *Mod Rheumatol* 2011; 21: 184-91.
24. TOGNON S, GRAZIANI G, MARCOLONGO R: Anti-TNF-alpha therapy in seven patients with Behçet's uveitis: advantages and controversial aspects. *Ann N Y Acad Sci* 2007; 1110: 474-84.
25. HANDA T, TSUNEKAWA H, YONEDA M *et al.*: Long-term remission of ocular and extraocular manifestations in Behçet's disease using infliximab. *Clin Exp Rheumatol* 2011; 29 (Suppl. 67): S58-63.
26. KIKUCHI H, ARAMAKI K, HIROHATA S: Effect of infliximab in progressive neuro-Behçet's syndrome. *J Neurol Sci* 2008; 272: 99-105.
27. CALVO CATALÁ J, CAMPOS FERNÁNDEZ C, RUEDA CID A, GONZÁLEZ-CRUZ CERVELLERA MI, BAIXAULI RUBIO A, PASTOR CUBILLO MD: Efficacy of adalimumab in Behçet's disease. Description of 6 cases. *Rheumatol Clin* 2011; 7: 258-61.
28. ISHIGATSUBO Y, SAMUKAWA S: Behçet's disease from the aspect of autoinflammatory disease. *Nihon Rinsho Meneki Gakkai Kaishi* 2011; 34: 408-19.
29. NAM JL, WINTHROP KL, VAN VOLLENHOVEN RF *et al.*: Current evidence for the management of rheumatoid arthritis with biological disease-modifying antirheumatic drugs: a systematic literature review informing the EULAR recommendations for the management of RA. *Ann Rheum Dis* 2010; 69: 976-86.
30. SOLIMAN MM, ASHCROFT DM, WATSON KD, LUNT M, SYMMONS DP, HYRICH KL; BRITISH SOCIETY FOR RHEUMATOLOGY BIOLOGICS REGISTER: Impact of concomitant use of DMARDs on the persistence with anti-TNF therapies in patients with rheumatoid arthritis: results from the British Society for Rheumatology Biologics Register. *Ann Rheum Dis* 2011; 70: 583-9.