Adalimumab for treatment of severe Behçet’s uveitis:
a retrospective long-term follow-up study

E. Interlandi1, P. Leccese2, I. Olivieri2, L. Latanza1

1Uveitis and Ocular Immunopathology Unit, Department of Ophthalmology, “A. Cardarelli” Hospital, Naples Italy;
2Rheumatology Department of Lucania, “San Carlo” Hospital of Potenza and “Madonna delle Grazie” Hospital of Matera, Italy.

Emanuela Interlandi, MD, PhD
Pietro Leccese, MD
Ignazio Olivieri, MD, Professor
Loredana Latanza, MD

Department and Institution to which the work is to be attributed:
Uveitis and Ocular Immunopathology Unit, Department of Ophthalmology, “A. Cardarelli” Hospital, Naples, Italy.

Please address correspondence to: Emanuela Interlandi, MD, PhD, Via della Commenda 31, 20122 Milano, Italy, E-mail: dott.emanuelainterlandi@gmail.com

ABSTRACT

Objective. Behçet’s disease (BD) is a chronic multisystem inflammatory disorder associated to uveitis that may represent a serious sight-threatening condition. The purpose of the present study is to assess the effectiveness of adalimumab as new strategic therapeutic approach in patients affected by severe Behçet’s uveitis.

Methods. Clinical data from twelve selected patients (22 eyes) were retrospectively analysed. All patients received 40 mg of adalimumab subcutaneously, once every 2 weeks, in addition to traditional immunosuppressive on-going therapy and eight of them were switched to adalimumab after failure of infliximab therapy. Primary outcome measures included ocular inflammatory activity, frequency of uveitis attacks and steroid-sparing effect. Secondary outcomes were changes of best-corrected visual acuity (BCVA), impact on traditional immunosuppressive therapy and occurrence of adalimumab-related side effects.

Results. Mean age of patients (11 males and 1 female) at the onset of disease was 24.34 years (±8.62 SD). Ocular involvement resulted bilateral in 83% of cases and mainly consisted in panuveitis (68% of eyes). After mean follow-up of 21 months (±9.63 SD) all patients but one (92%) achieved uveitis remission with BCVA improvement at least in one eye. Average uveitis attacks decreased from 2 to 0.42 during adalimumab (p<0.001) and daily-steroid dose was tapered in all adalimumab responders up to suspension in seven of them. No patient developed related side effects during adalimumab administration.

Conclusions. Our results demonstrate that adalimumab is a very effective and safe option for treatment of patients with severe and resistant Behçet’s uveitis, providing an appropriate and long-term control of ocular inflammation.

Introduction

Behçet’s disease (BD) is a chronic multisystem inflammatory disorder of unknown aetiology and relapsing course characterised by ocular involvement in 30–70% of cases with bilateral non-granulomatous uveitis involving anterior segment, posterior segment or both (panuveitis) (1-4).

Tumour necrosis factor-α (TNF-α) is a cytokine that plays a key role in acute phase of inflammatory immune response in patients affected by BD (5-6) so to make TNF-α-blockers a strategic approach for treatment of BD and related uveitis. Etanercept has been the first anti-TNF-α agent to be approved; it is a dimeric fusion protein binding with high affinity TNF receptor p75 linked to Fc portion of human IgG. Etanercept has been shown to be effective for mucocutaneous manifestations of BD but not for uveitis (7) and it is no longer used in ocular inflammations since it has been proven to exacerbate the uveitis severity (8). Infliximab is a chimeric mouse-human monoclonal antibody that binds the soluble and bound molecules of TNF-α with subsequent deactivation of these, but its chimeric nature may induce antibodies formation with following progressive loss of efficacy after some time (9). Adalimumab is the first fully human anti-TNF-α monoclonal antibody with a structure and function indistinguishable from human IgG1 and binding, similarly to infliximab, both soluble and trans-membrane forms of TNF-α.

Effectiveness of infliximab for treatment of BD and related uveitis has been diffusely described in literature (10-14) and various authors therefore have reported interesting results of adalimumab for treatment of BD even including cases with severe resistant uveitis (15-29).

However, up to the present, the FDA and the EMEA endorse use of adalimumab in rheumatoid arthritis, psori-
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atic arthritis, ankylosing spondylitis, plaque psoriasis, juvenile idiopathic arthritis and inflammatory bowel diseases but not in BD.

The aim of this study is to assess efficacy of adalimumab in patients affected by severe BD-related uveitis.

Materials and methods

Twelve patients (22 eyes) affected by BD, treated with adalimumab between 2008 and 2012, were selected from our archives and their data retrospectively analysed. In our tertiary referral centre of Uveitis and Ocular Immunopathology, diagnosis of BD is based on ISG criteria (30) and treatment performed according to EULAR recommendations (31).

Primary outcome measures included ocular inflammatory activity, frequency of uveitis attacks and corticosteroid (CS)-sparing effect; secondary endpoints were changes of best-corrected visual acuity (BCVA), impact on traditional immunosuppressive therapy and occurrence of adalimumab-related side effects.

Ocular inflammatory activity and relapses of anterior segment and vitreous were evaluated according to Standardisation Uveitis Nomenclature (SUN) workshop criteria (32) while posterior uveitis was evaluated by fundus ophthalmoscopy and fluorescein angiography (FAG); macular involvement was moreover assessed by Optical Coherence Tomography (OCT). Follow-up visits were performed every one-three months or less depending on clinical course of single case and included BCVA evaluation, full slit-lamp examination, tonometry and when required FAG and/or OCT. Any uveitis reactivation requiring therapy adjustment, independently of ocular-specific localisation and visual function, was considered as uveitis attack. Ocular clinical remission was defined by the absence of active uveitis assessed by full ophthalmic evaluation, FAG and/or OCT analysis, independently of visual outcome and therapy in course. QuantiFERON-TB test (Cellestis Inc, Carneige, Victoria, Australia) was performed in all patients before adalimumab administration and every three months during adalimumab therapy to evaluate exposure to tuberculosis. In addition, full serological assessment testing both renal and hepatic function was performed at baseline and then every three months during adalimumab.

CS daily dosage and BCVA at baseline were compared with final records as resulted at the beginning of data review and were analysed applying a linear mixed model. Number of inflammatory attacks observed during adalimumab administration was compared with that occurred during pre-adalimumab period and then analysed with a generalised linear mixed model of the Poisson family. Because of long-lasting disease of majority of selected patients we referred to pre-adalimumab period as a lapse of time, before adalimumab administration, correspondent for each patient to follow-up period considered from the beginning of adalimumab administration and starting point of the present study. Confidence intervals of average expected values for fixed effect factors were computed by simulation. Complementary significance texts for fixed effect factors were performed with a robust method based on permutations. All values were reported as mean value with related standard deviation (SD). BCVA was expressed as the logarithm of mean angle of resolution (log MAR). T-student test was used to calculate p-values in this study. A p-value less than 0.05 was considered statistically significant. Analyses were done with the R environment (R Development Core Team, 2012) with functions of contributed packages lme4 (Bates et al., 2012), arm (Gelman et al., 2012), lmPerm (Wheeler, 2010) and ggplot2 (Wickham, 2009).

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

The main characteristics of twelve selected patients (11 males and 1 female) are reported in Table I. Mean age at onset of disease was 24.34 years (±8.62 SD; range: 8–39) while mean uveitis duration was 9 years (±5.86 SD). Seven patients (58%) were positive to HLA-B51 antigen. Bilateral ocular involvement resulted in 83% of cases and consisted in severe panuveitis and posterior uveitis respectively in 68% and 32% of eyes. In all cases posterior uveitis consisted in papillitis and retinal vasculitis, while panuveitis was defined by association of posterior uveitis with vitritis and/or anterior non-granulomatous uveitis. Six patients (50%) presented 2 or more systemic lesions in addition to ocular involvement and two of them (17%) had neuro-Behçet pattern of disease with neurological involvement.

All patients received 40 mg of adalimumab subcutaneously, once every 2 weeks, in addition to traditional immunosuppressive on-going therapy. Eight patients received infliximab (5 mg/kg/day intravenously), in addition to traditional immunosuppressants, before adalimumab administration. Seven of them (cases n. 1, 2, 4, 6, 10, 11 and 12) were switched to adalimumab following loss of therapeutic effect of infliximab after a mean therapy duration of 41.7 months (±23 SD). In patient n.7 infliximab was suspended, after 58 months of infliximab administration, because of uveitis exacerbation during last six months of therapy, Table II describes main and secondary outcomes analysed in this study. After a mean time of 21 months (±9.63 SD) all patients but one (92%) achieved an improvement of ocular inflammation associated with visual acuity increase, at least in one eye, in all of them. At the beginning of this study all patients had been receiving adalimumab except patient 7 who didn’t respond to therapy. This patient, already switched from infliximab to adalimumab, was switched to Interferon-α (9,000,000 UI/week) after 13 months of adalimumab administration. During adalimumab therapy frequency of uveitis attacks decreased in 11 out 12 patients (Tab. II). Patient n. 4 had a relapse after 24 months of therapy; patient n. 11 had two relapses after 24 months and 48 months. Eight patients (67%) had no uveitis attack during full follow-up period. The average value of uveitis attacks decreased from 2 to 0.42 during adalimumab therapy (p<0.001). In all adalimumab responders daily dose of CS was gradually ta-
Serious sight-threatening condition leading to legal blindness up to 25% of affected patients. Visual prognosis in these patients tends to be severe due to relapsing course of uveitis where recurrent attacks of ocular inflammation result in structural changes that may produce an important sight impairment and even blindness if patients are not promptly and appropriately treated. The main goals of Behçet’s uveitis management are prompt resolution of intraocular inflammation, prevention of recurrent attacks and preservation of vision. TNF-α is a cytokine involved in establishment and maintenance of inflammatory response and, even specific aetiopathogenesis of BD is still unclear, many experimental data suggest that TNF-α may play a key role in development and persistence of ocular inflammation in BD (4-6).

Table II. Main characteristics of patients.

<table>
<thead>
<tr>
<th>Case/sex</th>
<th>Uveitis age at onset</th>
<th>HLA-B51 duration (years)</th>
<th>Systemic lesions*</th>
<th>Eye† uveitis type**</th>
<th>Switch from infliximab</th>
<th>Pre-adalimumab period=follow-up months</th>
<th>BCV A 1</th>
<th>BCV A 2</th>
<th>Concomitant immunosuppressive therapy 1</th>
<th>Concomitant immunosuppressive therapy 2</th>
<th>Uveitis activity</th>
</tr>
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<tr>
<td>1/15</td>
<td>17</td>
<td>negative</td>
<td>OA</td>
<td>BE/PU</td>
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<td>22</td>
<td></td>
<td></td>
<td>AZT†</td>
<td>AZT†</td>
<td>inactive</td>
</tr>
<tr>
<td>2/M/33</td>
<td>8</td>
<td>positive</td>
<td>OA/GU/SL/NB</td>
<td>BE/POST</td>
<td>yes</td>
<td>26</td>
<td></td>
<td></td>
<td>AZT†</td>
<td>AZT†</td>
<td>inactive</td>
</tr>
<tr>
<td>3/F/20</td>
<td>6</td>
<td>positive</td>
<td>OA/SL</td>
<td>BE/POST</td>
<td>no</td>
<td>6</td>
<td></td>
<td></td>
<td>CSA†</td>
<td>inactive</td>
<td></td>
</tr>
<tr>
<td>4/M/26</td>
<td>5</td>
<td>positive</td>
<td>OA</td>
<td>BE/PU</td>
<td>yes</td>
<td>23</td>
<td></td>
<td></td>
<td>CSA†</td>
<td>inactive</td>
<td></td>
</tr>
<tr>
<td>5/M/23</td>
<td>6</td>
<td>positive</td>
<td>OA/GU</td>
<td>LE/PU</td>
<td>no</td>
<td>31</td>
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<td></td>
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<tr>
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<td>BE/PU</td>
<td>yes</td>
<td>18</td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>7/M/31</td>
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<td>OA/SL</td>
<td>BE/PU</td>
<td>yes</td>
<td>13</td>
<td></td>
<td></td>
<td>CSA†</td>
<td>inactive</td>
<td></td>
</tr>
<tr>
<td>8/M/26</td>
<td>2</td>
<td>negative</td>
<td>OA/GU</td>
<td>RE/POST</td>
<td>no</td>
<td>30</td>
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<td></td>
<td>CSA†</td>
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<tr>
<td>9/M/16</td>
<td>11</td>
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<td>OA</td>
<td>BE/POST</td>
<td>no</td>
<td>18</td>
<td></td>
<td></td>
<td>CSA†</td>
<td>inactive</td>
<td></td>
</tr>
<tr>
<td>10/M/25</td>
<td>11</td>
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<td>NB</td>
<td>BE/PU</td>
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<td></td>
<td></td>
<td>CSA†</td>
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</tr>
<tr>
<td>11/M/29</td>
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<td>OA/SL/R</td>
<td>BE/PU</td>
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<td>39</td>
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<tr>
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<td>BE/PU</td>
<td>yes</td>
<td>8</td>
<td></td>
<td></td>
<td>CSA†</td>
<td>inactive</td>
<td></td>
</tr>
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</table>


Table II. Main and secondary outcome measures.

<table>
<thead>
<tr>
<th>Case n.</th>
<th>CS 1 (mg/day)</th>
<th>CS 2 (mg/day)</th>
<th>Attacks 1 (n.)</th>
<th>Attacks 2 (n.)</th>
<th>BCVA 1 b/w eye*</th>
<th>BCVA 2 b/w eye</th>
<th>Concomitant immunosuppressive therapy 1</th>
<th>Concomitant immunosuppressive therapy 2</th>
<th>Uveitis activity</th>
</tr>
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<tbody>
<tr>
<td>1</td>
<td>12.5</td>
<td>5</td>
<td>3</td>
<td>0</td>
<td>0.00/0.05</td>
<td>0.00/0.1</td>
<td>AZT†</td>
<td>AZT†</td>
<td>inactive</td>
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<tr>
<td>2</td>
<td>50</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>0.60/1.0</td>
<td>1.00/1.0</td>
<td>AZT†</td>
<td>AZT†</td>
<td>inactive</td>
</tr>
<tr>
<td>3</td>
<td>50</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>0.90/0.7</td>
<td>1.0/1.0</td>
<td>CSA†</td>
<td>/</td>
<td>inactive</td>
</tr>
<tr>
<td>4</td>
<td>10</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>0.1/1.0</td>
<td>0.9/1.0</td>
<td>CSA†</td>
<td>/</td>
<td>inactive</td>
</tr>
<tr>
<td>5</td>
<td>10</td>
<td>0</td>
<td>3</td>
<td>0</td>
<td>- /1.0</td>
<td>/1.0</td>
<td>CSA†</td>
<td>/</td>
<td>inactive</td>
</tr>
<tr>
<td>6</td>
<td>25</td>
<td>0</td>
<td>2</td>
<td>0</td>
<td>0.9/0.2</td>
<td>0.9/1.0</td>
<td>AZT†</td>
<td>/</td>
<td>inactive</td>
</tr>
<tr>
<td>7</td>
<td>50</td>
<td>10</td>
<td>2</td>
<td>1</td>
<td>0.6/0.1</td>
<td>0.1/0.1</td>
<td>CSA†</td>
<td>INF-α**</td>
<td>active</td>
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<tr>
<td>8</td>
<td>25</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>0.8/-</td>
<td>1.1/-</td>
<td>CSA†</td>
<td>/</td>
<td>inactive</td>
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<tr>
<td>9</td>
<td>25</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>0.60/0.8</td>
<td>1.0/1.0</td>
<td>CSA†</td>
<td>/</td>
<td>inactive</td>
</tr>
<tr>
<td>10</td>
<td>50</td>
<td>12.5</td>
<td>1</td>
<td>0</td>
<td>0.00/0.6</td>
<td>0.00/0.6</td>
<td>AZT†</td>
<td>/</td>
<td>inactive</td>
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<tr>
<td>11</td>
<td>5</td>
<td>7.5</td>
<td>4</td>
<td>3</td>
<td>0.00/0.01</td>
<td>0.00/0.08</td>
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<td>AZT†</td>
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<tr>
<td>12</td>
<td>10</td>
<td>5</td>
<td>5</td>
<td>1</td>
<td>0.9/0.6</td>
<td>1.0/0.7</td>
<td>AZT†</td>
<td>AZT†</td>
<td>inactive</td>
</tr>
</tbody>
</table>

CS: corticosteroids at base-line (1) and at the end of follow-up (2). Attacks during pre-adalimumab period (1) and during whole follow-up period (2); BCVA: best-corrected visual acuity at base-line (1) and at the end of follow-up (2). *b/w: best/worst eye. Concomitant immunosuppressive therapy at base-line (1) and at the end of follow-up (2). *AZT: azathioprine (1-2 mg/kg/day); °CSA: cyclosporine A (3-5 mg/kg/day); **INF-α: interferon-α (9.000.000 UI/week)
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In our study 92% of treated patients achieved uveitis inactivity associated to a significant decrease of frequency of uveitis attacks in most of them, even in patients who failed infliximab treatment. Similarly, steroid-sparing effect was significant considering that 7 out 12 patients discontinued their administration. The effect of adalimumab on BCVA, instead, resulted from this study less significant than previous outcomes. This is quite reasonable considering that acute or chronic ocular complications like macular lesions, cataract and retinal or optic atrophy, occurring during such severe and long-lasting disease, may have a considerable and permanent impact on visual acuity independently of therapy effectiveness. Moreover we could not find a linear or significant correlation between most of patients-related (sex, age, etc.) or disease-related (duration, severity, etc.) and response to therapy, suggesting that a different genetic and immunologic characterisation may influence individual response to therapy.

Thus far, the majority of studies have reported efficacy of adalimumab in BD and related uveitis as effective second-choice anti-TNF-α after failure of infliximab therapy. Our study confirms these data considering that seven out eight patients (87.5%), switched from infliximab to adalimumab, achieved a sustained long-term clinical remission (Table II). Therefore, TNF-α-blockers naive patients responded lightly better than patients switched from infliximab. Although this tendency was no statistically significant (Fig. 1), this may suggest that prompt treatment with adalimumab might have more chances in terms of effectiveness but this hypothesis should be better and properly assessed by a comparative prospective analysis between two groups. In addition, subcutaneous administration provides more stable and continuous plasma levels comparing with intravenous administration of infliximab resulting, moreover, much easier for patients who can receive therapy at home while infliximab requires intravenous administration in the hospital.

Thus far, use of anti-TNF-α has been related to many side effects like opportunistic infections (33), latent tuberculosis reactivation (34), inflammatory neurological disease as multiple sclerosis or similar demyelinating disease (35) and even malignancy (36-37). On the contrary in our study adalimumab showed an excellent safety profile since no patient developed any adalimumab-related side effect.

Finally adalimumab permitted a satisfactory control of ocular inflammation and relapses in our patients, stabilising clinical course and improving visual prognosis. Also according to recent expert panel recommendations (29) it may be considered a very effective and safe option for treatment of patients with severe Behçet’s uveitis refractory to traditional immunosuppressive and infliximab therapy or even as first-choice TNF-α-blocker considering lower risk of developing anti-chimeric antibodies, with consequent loss of efficacy, and easier administration respect with infliximab.

Nevertheless, randomised, controlled trials, including a larger number of patients for a longer follow-up are strongly desirable to better delineate safety and efficacy profile of adalimumab in patients affected by severe Behçet’s uveitis.

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