Anti-TNF therapy in the management of Behçet’s disease—review and basis for recommendations


Introduction

Behçet’s disease (BD) is a multisystem, chronic-relapsing, inflammatory disorder classified among the vasculitides [1, 2]. It has a worldwide distribution being more prevalent in the Middle East, Far East and the Mediterranean basin [3]. The diagnosis is entirely based on clinical grounds since no pathognomonic laboratory findings exist. International study group classification criteria used for BD patients participating in research protocols depend on the presence of recurrent oral ulceration plus any two of the following: recurrent genital ulcerations, ocular lesions (anterior or posterior uveitis, or cells in the vitreous on slit lamp examination, or retinal vasculitis), typical skin lesions (erythema nodosum, pseudofolliculitis) and a positive pathergy (skin hyperreactivity) test [4, 5]. The clinical picture of BD is diverse and while recurrent mucocutaneous lesions are usually the only symptoms at the onset of the disease, most patients develop ocular and/or articular, vascular, central nervous system and gastrointestinal inflammation later on. Vital organ involvement may lead, despite treatment, not only to severe morbidity but also to increased mortality especially among young males [1, 2, 6].

Adequately powered, randomized, controlled clinical trials are few in BD. This is especially true for the use of anti-tumour necrosis factor (TNF) agents, which reportedly result in impressive remissions in BD patients, especially in those with manifestations refractory to conventional treatments. During the last 6 yrs, over 70 publications have appeared in the English literature suggesting that inhibition of TNF actions, using mainly the anti-TNF monoclonal antibody infliximab, is a promising therapeutic approach for this disease. However, the current evidence of therapeutic efficacy is low grade, and there is only one randomized trial available, which assessed the effects of the soluble TNF receptor etanercept in mucocutaneous manifestations and found it to be very effective [7].

An expert panel meeting was held in May 2006, in order to review the currently available treatment options for BD and the unmet medical needs for those patients with severe disease, and to develop a consensus on the positioning of anti-TNF agents in their treatment. Clinical scientists who have contributed with relevant publications and physicians with specific expertise in BD management participated in the discussion, aiming: (i) to assess the available information on the efficacy of anti-TNF therapies, alone or in combination therapy with currently used regimens, in the treatment of BD; and (ii) to formulate recommendations for optimal use of anti-TNF agents in these patients, filling gaps in evidence with their expert opinion. An extended summary of the discussion and the conclusions reached is presented herein, intended to help physicians in their practice with BD patients. These recommendations do not constitute treatment guidelines but aim to improve the uniformity of clinical practice in the management of BD, until higher grades of evidence are obtained.

Limitations of current therapies and unmet medical needs in Behçet’s disease

Several effective anti-inflammatory and immunosuppressive regimens for BD currently exist, but none results in disease cure [1, 2, 8, 9]. Moreover, the long-term use of these regimens can be associated with significant adverse effects, especially in those patients in whom treatment is introduced at a young age [8, 9]. Physicians taking care of patients with BD should be aware that the disease is intermittent in its manifestations in the majority of patients, and that symptoms vary both in their recurrence rate and healing time; accordingly, the therapeutic approach should be strictly individualized. Although the course of BD is unpredictable, spontaneous remissions often occur and the disease may even burn out in some patients with time [6]. Still, a significant proportion of patients may suffer a progressive disease course resulting eventually in permanent organ damage [1, 6, 9]. No prognostic criteria to identify these patients exist, although there is evidence that young men are at higher risk in general [6], particularly with respect to losing useful vision, or developing vascular and neurological manifestations [10], than women. Moreover, there are no established criteria to define the subgroup of patients with severe BD. However, most physicians consider that patients with vital organs at threat, mainly with ocular, parenchymal, neurological and major vascular involvement have severe disease. In addition, some patients with chronic articular and mucocutaneous manifestations, which significantly impair their quality of life, can also be classified as having severe disease.

Controlled studies have shown that colchicine [11], thalidomide [12], dapsone [13], azathioprine [14], interferon-alpha [15] and etanercept [7] are effective to some degree in treating various mucocutaneous manifestations in patients who are not intolerant to these drugs. However, refractory, relapsing oral and genital ulcers are associated with marked physical and psychological morbidity in some patients, while oropharyngeal ulcers are frequently resistant to conventional treatment modalities and even life-threatening pharyngeal stenosis may rarely occur [16]. Scarring of deep vaginal ulcers, in which corticosteroids are not always effective [17], may lead to bladder or urethral fistulae. Vulval ulcerations occasionally may lead to labial destruction, while other cutaneous vasculitic lesions, namely Sweet’s syndrome-like and pyoderma gangrenosum-like lesions, may also cause severe morbidity [16].

In contrast to available data for the management of mucocutaneous manifestations, similar data are more sparse in patients...
with vital organs at threat, such as eye or central nervous system. In these cases, combinations of high doses of corticosteroids and immunosuppressive drugs, including methotrexate, ciclosporin A (up to 10 mg/kg), azathioprine (up to 3 mg/kg), chlorambucil, or cyclophosphamide may be used, albeit not always successfully [8, 9, 18–20]. Importantly, in a 2-yr, randomized, placebo-controlled, double-blind study, restricted to male patients, in those enrolled in the study without eye involvement, azathioprine was significantly better than placebo in preventing the development of ocular disease [14]. In this study, azathioprine was also effective in those patients with eye disease at enrolment by reducing steroid requirements, maintaining visual acuity and reducing the number of hypopyon attacks [14]. A follow-up study of these patients 8 yrs later showed that early treatment with this agent was also efficacious in ocular disease at long term [21]. These results imply that continuous immunosuppressive therapy may control and perhaps, change the course of BD in some patients.

The goal of management should be the initiation of an effective treatment as early as possible to avoid recurrences and irreversible damage to vital organs. With respect to sight-threatening ocular involvement, the first aim must be the effective and rapid suppression of intraocular inflammation to avoid development of permanent lesions in the retina and optic disc and second, the prevention, or decrease in the frequency and severity, of recurrent eye attacks. Two decades ago, 73% of patients with ocular disease developed permanent loss of vision within an average time of 3.5 yrs [22]. This risk has been significantly reduced in the 1990s, following the introduction of immunosuppressive regimens (azathioprine, ciclosporin, interferon-alpha, in combination or as monotherapy), which have improved the prognosis of ocular disease remarkably [6, 8, 9]. Despite this progress, many patients are intolerant to long-term use of these regimens, while corticosteroids, the mainstay of treatment for intraocular inflammation, frequently lead to important co-morbidities during chronic use, such as cataract formation and glaucoma, as well as to systemic side effects [8, 9]. Clearly, the ideal immunosuppressive regimen for patients with severe BD should be not only effective but also safe for long-term use. Accumulating experience on two emerging therapeutic approaches, namely interferon-alpha [23–25] and anti-TNF agents [25, 26] is currently available and justifies optimism for a better outcome of patients with severe BD.

Anti-TNF agents in Behçet’s disease: the current evidence

The anti-TNF monoclonal antibodies infliximab and adalimumab, and the soluble TNF receptor etanercept are widely used in the therapy of rheumatoid arthritis, spondyloarthropathies, Crohn’s disease and psoriasis with an acceptable safety profile. A better understanding of the pleiotropic actions of TNF in chronic inflammatory conditions [27–29], as well as initial evidence implicating TNF in disease pathogenesis [31–33], has prompted trials of anti-TNF agents in patients with BD. The published experience summarized subsequently is derived mostly from independent investigator-initiated trials and uncontrolled case-series, involving about 300 patients with severe disease manifestations. Whilst non-randomized data should be interpreted with caution, in the vast majority of these patients the therapeutic response to anti-TNF treatment has been considered favourable.

Infliximab

Of the reported patients with BD who have received anti-TNF agents so far, about 90% have been treated with infliximab, mostly for eye disease, given in parallel to concomitant therapy. Initially, to test the hypothesis that TNF may play a role in BD-associated ocular inflammation, three patients who developed sight-threatening panuveitis despite intensive immunosuppressive therapy were treated with a single infusion of infliximab (5 mg/kg) in addition to their immunosuppressive therapy, which was increased to maximum doses. A rapid and effective suppression of ocular inflammation, i.e. within the first 24 h following the infliximab infusion, was evident in these patients, as well as in two additional patients without increasing concomitant systemic therapy [34]. Such gratifying and rapid results in sight-threatening panuveitis were also reported in additional uncontrolled case series [35–45]. In general, anterior segment inflammation resolved faster than vitritis and retinal infiltrates, while retinal vasculitis healed within 2 weeks in the majority of patients. Infliximab was also successful in sporadic BD patients with scleromalacia perforans [46] and choroidal neovascular membrane [47]. Chronic cystoid macular oedema, one of the most treatment-resistant lesions complicating chronic ocular inflammation, has also been reported to be responsive to a single infliximab infusion in some patients with BD [48].

The long-term effects of repetitive infliximab infusions (used at a dose of 5 mg/kg, every 8 weeks in 33 of 41 patients in total) in preventing ocular relapses, maintaining visual acuity and the ability to taper immunosuppressive therapy in patients who were unresponsive or intolerant to standard immunosuppressive treatment, were evaluated in three independent, open-label, prospective, self-controlled studies [49–51]. It should be noted that two of these studies used historical data from retrospective review of charts but all patients had a pre-defined follow-up period that allowed for reporting the incidence of relapses and the final visual acuity [52]. In the first study, the mean number of ocular attacks in 15 patients during the previous 32 weeks was 2.5. Ocular disease went into complete remission during the following 32 weeks of continuous infliximab infusions in 60% of patients. Overall, the number of relapses during infliximab therapy decreased by 5-fold. Old, atrophic retinal lesions were not affected. The visual acuity in 25 relapsed eyes increased significantly from 0.1 at baseline to 0.4 at 32 weeks [49]. In 13 Japanese patients who were resistant to ciclosporin, the mean number of relapses, based on their frequency per 14 weeks, decreased from 3.96 to 0.98 and from 3.79 to 0.16, for those patients treated for 14 weeks with 5 mg/kg or 10 mg/kg of infliximab, respectively [50]. Similarly, in 13 Turkish patients who were relapsing despite treatment with the combination of azathioprine, ciclosporin and corticosteroids, the mean number of uveitis attacks during 6 months prior to infliximab decreased significantly during the 22-week infliximab infusion period [51]. In the majority of these patients [49–51], as well as in additional case-series [34–45] an immunosuppressive therapy sparing effect of infliximab was evident. In view of the paucity of effective and fast-acting therapies, these results led to the suggestion that infliximab is probably the best currently available treatment for BD patients with acute sight-threatening ocular inflammation [53]. It should be noted, however, that due to the lack of comparative data it is not possible to confirm at present that infliximab has indeed a faster effect in suppressing acute ocular inflammation than ciclosporin, or interferon-alpha.

Infliximab was also efficacious in extraocular manifestations, such as oral and genital ulcers and/or arthritis in the majority of patients in three self-controlled studies [49–51]. Additional case series and case reports suggested that patients with severe mucocutaneous lesions exhibit rapid and good responses to infliximab administration [54–62], mostly using 5 mg/kg, or 3 mg/kg. Some patients with urogenital ulcers unresponsive [56] and/or intolerant [59] to conventional treatments remained disease-free for the first time in years. Almost all patients were resistant to conventional treatments, and were treated with infliximab alone [54, 56] or as an add-on therapy [57, 58, 60, 61]. There is only one report in which erythema nodosum developed during treatment with infliximab [63]. In addition, beneficial effects of infliximab have been reported in sporadic patients with arthritis [36, 54, 57, 58], as well as with severe gastrointestinal involvement [64–66]. Finally, there is very limited published evidence [67–69] and anecdotal data [70] suggesting that infliximab is effective for patients with parenchymal central
nervous system involvement refractory to high-dose steroids and cyclophosphamide. No data exist in patients with vascular thrombosis or aneurysms, except of a single patient with pulmonary artery aneurysms, in whom administration of infliximab was beneficial [71].

**Etanercept**

In a double-blind, placebo-controlled study of 40 male patients with BD, Melikoglu et al. [7] reported that etanercept (25 mg twice/week, for 4 weeks) was effective in suppressing most mucocutaneous lesions. The drug had a clear effect on oral ulcers and nodular lesions, and the response was evident as early as the first week. Almost half of the patients receiving etanercept were free of oral ulcers at the end of the study compared with 5% of the placebo group, whereas the absence of nodular lesions was evident in 85% and 25% of patients receiving the drug and placebo, respectively. Although, the drug decreased the number of genital ulcers and arthritis episodes during the treatment period, the difference was not significant. Because of the small sample size and the relative infrequency of these manifestations during the short study period, a type II error might have affected these results. On the other hand, etanercept did not affect the skin pathology reaction and the cutaneous response to monosodium urate crystals, which were the primary endpoints of the study. Recurrences developed in some patients three months after etanercept was discontinued. During the follow-up period, more patients in the placebo group were prescribed drugs to control disease activity. No data were reported from this study on the efficacy of etanercept in eye involvement [7].

In other reports, rapid resolution of severe mucocutaneous manifestations [62, 72, 73] and arthritis [72] were noted following etanercept treatment, while another patient who failed to respond to etanercept, responded dramatically to infliximab treatment with rapid resolution of orogenital ulcers and erythema nodosum and marked improvement in arthralgia and iritis [57]. Etanercept was also given to two children with BD-associated uveitis. A favourable response was noted in the first, but not in the second patient. The latter patient achieved a moderate response following subsequent treatment with infliximab [74].

**Adalimumab**

Limited anecdotal data (53, 75 and Kaklamanis, unpublished observations) suggests that adalimumab is effective in BD. Mushtaq et al. [76] recently reported BD patients with uveitis, maintained on infliximab who were switched to adalimumab therapy. All remained free of recurrence of uveitis, the main outcome measure of this case-note review, with stable vision.

**Safety issues**

The key safety considerations regarding anti-TNF agents include infections, demyelinating disease, malignancies and congestive heart failure [77, 78]. Either short-term or long-term administration of infliximab was well tolerated in almost all BD patients published so far. The reported side effects were mild and did not require cessation of therapy. However, two patients developed psoriasis [79], two patients developed tuberculosis [38, 50] and one patient developed vitreous haemorrhage, which did not require discontinuation of infliximab [42]. Moreover, infliximab-induced formation of various autoantibodies, which appears to be clinically insignificant, commonly occurs [44, 50, 80].

Importantly, ocular side effects such as cataract formation, infections or increases in intraocular pressure, as well as exacerbation of pre-existing central nervous system signs or vascular thrombotic events have not been reported in patients with BD thus far.

**Anti-TNF agents in Behçet’s disease: recommendations for optimal use**

It is clear that not all patients with BD should be treated with anti-TNF agents, unless randomized trials show that this expensive approach is superior to current therapies in terms of efficacy and safety. As stated above, management decisions should be individualized, focusing on the treatment of the most severe manifestation and balancing the risks of therapy with the putative efficacy of a given regimen. At present, physicians may decide to provide anti-TNF treatment in selected patients (Table 1) as an add-on therapy, with close monitoring for objective improvement. The recommendations for optimal use presented below focus on identification of eligible patients, selection of anti-TNF agents,

### Table 1. Recommendations for the prescription of anti-TNF agents in BD

<table>
<thead>
<tr>
<th>Subset</th>
<th>New manifestation</th>
<th>Recurrent/refractory cases</th>
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<tbody>
<tr>
<td>Posterior segment intraocular inflammation</td>
<td>In unilateral involvement with visual acuity &lt;0.2 Infliximab&lt;sup&gt;a&lt;/sup&gt; can be used as first line treatment</td>
<td>In patients with two or more relapses/year despite, or intolerant to, adequate doses&lt;sup&gt;b&lt;/sup&gt; of AZA and/or Cs, or interferon α-2a, combined with prednisolone (&lt;7.5 mg/day), infliximab&lt;sup&gt;c&lt;/sup&gt; can be used</td>
</tr>
<tr>
<td>Anterior segment intraocular inflammation</td>
<td>Not recommended</td>
<td>Not recommended</td>
</tr>
<tr>
<td>Parenchymal CNS involvement</td>
<td>Not recommended</td>
<td>In patients refractory to treatment with pulse cyclophosphamide and prednisolone (1 mg/kg/day), or in those who relapse while on maintenance with AZA&lt;sup&gt;a&lt;/sup&gt; and prednisolone (&lt;7.5 mg/day) infliximab&lt;sup&gt;c&lt;/sup&gt; may be tried</td>
</tr>
<tr>
<td>Intestinal inflammation</td>
<td>Not recommended</td>
<td>In patients that have failed two immunosuppressive agents&lt;sup&gt;b&lt;/sup&gt; and require prednisolone at a dosage &gt;7.5 mg/day, infliximab&lt;sup&gt;c&lt;/sup&gt; may be used</td>
</tr>
<tr>
<td>Major vessel involvement</td>
<td>Not enough data</td>
<td>Not enough data</td>
</tr>
<tr>
<td>Mucocutaneous manifestations</td>
<td>Not recommended</td>
<td>In patients with poor quality of life despite, or intolerant to, adequate doses&lt;sup&gt;b&lt;/sup&gt; of AZA, colchicine or thalidomide and require prednisolone at a dosage &gt;7.5 mg/day, etanercept&lt;sup&gt;c&lt;/sup&gt; or infliximab&lt;sup&gt;c&lt;/sup&gt; may be used</td>
</tr>
<tr>
<td>Arthritis</td>
<td>Not recommended</td>
<td>In patients that have failed two immunosuppressive agents&lt;sup&gt;b&lt;/sup&gt; including MTX and require prednisolone at a dosage &gt;7.5 mg/day, etanercept&lt;sup&gt;c&lt;/sup&gt; or infliximab&lt;sup&gt;c&lt;/sup&gt; may be used</td>
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<sup>a</sup>A single i.v. infusion of 5 mg/kg.

<sup>b</sup>AZA (azathioprine): 2.5 mg/kg/day; Cs (cyclosporin): 3–5 mg/kg/day; MTX (methotrexate): 20 mg/week; colchicine: 1.5 mg/day; thalidomide: 300 mg/day; interferon-α-2a: 3.000.000 IU SC three times/week.

<sup>c</sup>i.v. infusions of 5 mg/kg, at week 0, 2, 4 and subsequently every 6–8 weeks for up to 2 yrs.

<sup>s</sup>c., 25 mg twice/week for up to 2 yrs.
monitoring, and treatment adjustments. Particular emphasis is
given on the use of infliximab in patients with sight-threatening
ocular disease. These recommendations will be updated in the
future based on emerging evidence.

Identification of patients likely to benefit from anti-TNF
treatment
Criteria for selecting patients eligible for anti-TNF treatment of
BD should include: (i) a definite diagnosis of BD; (ii) presence
of active disease, including objective signs of inflammation;
(iii) previous failure of drugs that have a documented efficacy in
controlling BD manifestations, combined or not, with low dose
corticosteroids (equivalent to prednisolone dose ≤7.5/day);
(iv) presence of contraindications or intolerance to these conven-
tional regimens; (v) absence of contraindications to anti-TNF
treatment.

Patients fulfilling the first three criteria usually belong to the
severe disease subgroup and are likely to benefit from anti-TNF
therapy. Although no established criteria to define the subgroup
of those patients with severe BD exist, patients with two or more
relapses of posterior uveitis or panuveitis per year, patients with
low visual acuity due to chronic cystoid macular oedema, or
patients with active central nervous system parenchymal disease
would certainly fit this category. Selected patients with intestinal
inflammation, chronic arthritis and/or mucocutaneous manifesta-
tions significantly impairing the quality of life could also benefit
from anti-TNF treatment. Although patients with major vessel
involvement are also considered as having severe disease with an
increased mortality, not enough data are available about the
efficacy of anti-TNF agents in this situation (Table 1).

Selection of anti-TNF agent, monitoring and treatment
adjustments
Available anti-TNF agents have not been compared directly with
each other in controlled trials in any disease. Indirect evidence
indicates that the anti-TNF monoclonal antibodies and the
soluble TNF receptor etanercept have overall comparable efficacy
in the treatment of rheumatoid arthritis [77], but their efficacy is
clearly different in Crohn’s disease [81], and perhaps in uveitis
associated with other rheumatic diseases [82, 83].

Along this line, etanercept had no significant efficacy over
placebo in preventing uveitis relapses in patients with non-
infectious uveitis controlled by low-dose methotrexate [84]. The
only randomized short-term trial in BD indicated that etanercept
was efficacious in controlling mucocutaneous disease [7].
Available data suggest that infliximab might be efficacious in
severe mucocutaneous manifestations as well. At present, there is
a general sense that infliximab may be a better choice than
etanercept in severe BD. A clear advantage of infliximab
(intravenous infusion of 5 mg/kg) over etanercept is its fast
onset of action, which is considered to be critical in case of sight-
threatening ocular disease [18, 85–87]. Whether a superior efficacy
of infliximab over etanercept would hold true for non-ocular
disease manifestations remains unclear due to the relative paucity
of etanercept-related data. Available experience with adalimumab
is too limited for comment.

Before starting anti-TNF therapy a thorough baseline clinical
evaluation should be conducted to exclude cardiac insufficiency
and demyelinating disease, as well as screening for latent
tuberculosis with appropriate tests. Anti-TNF as a first line
treatment should be started in conjunction with an appropriate
immunosuppressive drug to try to maintain disease control once a
remission is induced. Upon administration of an anti-TNF agent
as an add-on therapy, an immediate decrease of the dose of
concomitant immunosuppressive drugs is not recommended.

Patients should receive standardized follow-up at regular
intervals and occurrence of a remission should lead to reduction
in concomitant medications, most notably glucocorticoids when
used; in the event of a prolonged remission, the dosage of either
the anti-TNF agent or the concomitant immunosuppressive
drug(s) may be further reduced. Such a decision-making process
should be strictly individualized. Notably, in the three prospective
studies using repetitive infliximab infusions every 8 weeks, there
were BD patients who relapsed just before the next scheduled
infliximab infusion [49–51], suggesting that shorter periods
between infusions are needed for some patients to maintain
remission, as also happens in other diseases in which infliximab
has been used. Development of antibodies against infliximab in
long-term treated patients may be associated with reduced
duration of response to treatment [50], as happens in patients
with RA [88] or Crohn’s disease [89]. Therefore, the fine-tuning
of TNF neutralization is important to maintain long-term remission,
especially in patients with a chronic-relapsing inflammatory
disease course such as BD.

Infliximab for ocular disease
Regarding the use of anti-TNF agents in patients with acute ocular
inflammation, the available evidence and expert opinion suggest
the following: anterior uveitis is usually treated effectively with
topical therapy alone. In acute, unilateral, posterior uveitis with
significant reduction of visual acuity (<0.2), as well as in those cases
with inflammation of the macular area, an intravitreal injection of
triamcinolone or a single infusion of infliximab, 5 mg/kg, may be
superior to other approaches because a rapid resolution of
inflammation is critical. In cases of bilateral posterior eye segment
inflammation, where high doses of i.v. corticosteroids are used by
many, a single infusion of infliximab could be used as a first-line
agent to achieve a fast-onset response, along with the initiation of
an appropriate immunosuppressive drug.

When the suppression of ocular inflammation is achieved,
immunosuppressive drugs such as ciclosporin, or azathioprine,
combined with low-dose corticosteroid can be used long-term to
control recurrent attacks. Interferon-alpha can also be an
alternative treatment. In the event of recurrence, addition of
azathioprine to ciclosporin, or vice versa may be a reasonable
step. However, if the ocular disease remains uncontrolled,
a combination of these immunosuppressive regimens with
repetitive infusions of infliximab 5 mg/kg every 6–8 weeks for up
to 2 years should be considered. It should be noted that there are
no data supporting continuous use of infliximab as monotherapy.
In some patients efficacy of infliximab may weaken with its
prolonged use, thus the dosing interval may need to be decreased
with close monitoring to confirm a sustained efficacy. Whether
patients with an inadequate response, or intolerance to infliximab
can be switched to another anti-TNF agent is unknown, since
current experience is limited [75, 76].

Anti-TNF agents in Behçet’s disease: caution considerations
Absolute and relative contraindications of anti-TNF agents,
namely acute and chronic infections, solid cancer or haematolo-
gical malignancies, demyelinating disease, congestive heart failure,
pregnancy and lactation, have been extensively reviewed elsewhere
[77, 78]. Those BD patients with extensive mucocutaneous ulcers
may carry an increased risk of infection, therefore special caution
is needed [16]. Given the geographic distribution of BD in the
world, an increased risk of tuberculosis with anti-TNF agents
might be critical in decision-making. This risk could be especially
important for those patients with sight-threatening posterior
uveitis who will have no time for a proper tuberculosis screening.
Therefore, it is recommended that any patient diagnosed with BD,
who is likely to require immunosuppressive drugs and/or high-
dose corticosteroids, should undergo a proper screening for latent
tuberculosis infection and be managed according to the local
guidelines [90]. Acute allergic reactions are seen in approximately
5% of intravenous infusions of infliximab, but using appropriate treatment protocols these reactions are effectively managed in nearly all [77, 78]. Finally, when considering anti-TNF therapy, it is important to provide full information to the patient on the potential benefits and risks of such treatment and to involve patients as much as possible into the decision-making process.

Summary and conclusions

The published evidence on the use of anti-TNF agents in BD consists mainly of reports of the open use of infliximab, principally evaluated as an add-on therapy. The majority of patients suffered from relapsing, posterior segment ocular inflammation, inadequately controlled with available immunosuppressive therapy. With infliximab, a fast-onset therapeutic effect was repeatedly observed in patients with sight-threatening inflammation, including patients with retinal vasculitis. The paucity of effective and fast-acting therapies particularly for patients with eye disease underscores the importance of these findings. As suggested by three independent, open-label, prospective, self-controlled studies, repetitive infliximab infusions were also effective in preventing ocular relapses, maintaining visual acuity and tapering immunosuppressive therapy in the majority of patients who had an inadequate response or were intolerant to conventional therapy. Infliximab was effective for extra-ocular manifestations in these patients, as well as in other patients with recalcitrant orogenital ulcers, arthritis, intestinal or central nervous system involvement and in a single patient with pulmonary artery aneurysm. With short-term use, there were no serious side effects reported. The only randomized controlled trial was a 4-week study of etanercept in patients with mucocutaneous manifestations. Etanercept was beneficial for most of these manifestations, but no data are at hand from this study on eye involvement.

Anti-TNF agents have a number of disadvantages, including induction of potentially serious adverse events and high cost. However, based on the available evidence, physicians may decide to provide anti-TNF therapy to patients with definite BD. However, until results from adequately powered, randomized controlled clinical trials are available, TNF blocking agents should be used with caution only for selected patients with severe disease. Patients with two or more relapses of posterior uveitis per year, low visual acuity due to chronic cystoid macular oedema, or active CNS disease and/or selected patients with intestinal inflammation, or arthritic and mucocutaneous manifestations that reduce significantly the quality of life, would fit this category. According to the experience accumulated so far, infliximab seems to be more efficacious than etanercept in disease manifestations other than mucocutaneous or joint involvement, while data on adalimumab are very limited. Infliximab or etanercept is recommended as an add-on therapy for selected patients with BD, who are refractory or intolerant to traditional immunosuppressive regimens. Moreover, a single infusion of infliximab (5 mg/kg), can be used as a first-line agent for sight-threatening, bilateral posterior eye segment inflammation, when the fast-onset of response is considered to be critical to prevent fixed retinal lesions and thus permanent visual loss. In those cases whose ocular relapses are not controlled by azathioprine and/or ciclosporin, a maintenance therapy with infliximab at the dose of 5 mg/kg every 6–8 weeks could be used for up to 2 years, provided no relapses occur between intervals. These recommendations do not constitute treatment guidelines but are intended to improve practice uniformity and to help physicians in the management of BD patients, until higher grades of evidence are available.

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Conflicts of interest statement: MS has received honoraria for lectures given at (international) events by all companies involved.

Note added in proof: Infliximab was recently approved in Japan for the treatment of "Behcet’s disease complicated with refractory uveoretinitis which does not respond to conventional therapies" (Osa, Japan, Jan 26, 2007, JCN Newswire).

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