Review

Anti-cytokine biologic treatment beyond anti-TNF in Behçet's disease

A. Arida, P.P. Sfikakis

First Department of Propedeutic Internal Medicine Laikon Hospital, Athens, University Medical School, Greece.

Aikaterini Arida, MD
Petros P. Sfikakis, MD

Please address correspondence to:
Petros P. Sfikakis, MD,
First Department of Propedeutic and Internal Medicine,
Laikon Hospital,
Athens University Medical School,
Ag Thoma, 17,
GR-11527 Athens, Greece.
E-mail: psfikakis@med.uoa.gr

Received on June 7, 2014; accepted in revised form on September 17, 2014.

Clin Exp Rheumatol 2014; 32 (Suppl. 84): S149-S155.

Key words: Behçet's disease, biological treatment, anti-TNF agents, cytokines, IL-1, IL-6, IL-17, IL-2

Competing interests: none declared.

ABSTRACT

Unmet therapeutic needs in Behçet's disease have drawn recent attention to biological agents targeting cytokines other than TNF. The anti-IL-17 antibody secukinumab and the anti-IL-2 receptor antibody daclizumab were not superior to placebo for ocular Behçet's in randomised controlled trials, comprising 118 and 17 patients, respectively. The anti-IL-1 agents anakinra and canakinumab and the anti-IL-6 agent tocilizumab were given to isolated refractory disease patients, who were either anti-TNF naïve (n=9) or experienced (n=18). No new safety signals were reported. Although a potential for bias to report positive effects and underreport negative cases may exist, Anakinra was partially effective, whereas disease remission was noted after canakinumab in some anti-TNF resistant patients. Tocilizumab appeared effective for neuro-Behçet's, but not for mucocutaneous manifestations. Finally, in a pilot study of 7 patients with relapsing posterior uveitis refractory to azathioprine and/or cyclosporine, the anti-IL-1β antibody Gevokizumab was beneficial. Collectively, it seems that IL-1 and IL-6 are promising targets in patients refractory or intolerant to other regimens including anti-TNFs. However, controlled studies are surely needed.

Introduction

Behçet's disease (BD) is a chronic immune-mediated systemic vasculitis with severe morbidity and increased mortality. Although clinical manifestations of the disease may have great individual variability, BD is characterised by recurrent oral and genital ulcers, pustular skin lesions, arthritis, posterior uveitis attacks which lead to significant visual impairment or visual loss, neurological and gastrointestinal manifestations and thrombotic complications (1-3). Treatment varies according to type and severity of disease manifestations. Corticosteroids, interferon-alpha and conventional immunosuppressive drugs, such as azathioprine, cyclosporine-A, cyclophosphamide and methotrexate, are used either alone or in combination for vital organ involvement. During the last decade there has been increased use of anti-TNF monoclonal antibodies in patients with BD who were refractory to conventional treatment or developed life-threatening complications (4, 5). Anti-TNF treatment has been shown to be beneficial for the majority of these patients (6, 7) but since unmet needs still exist reports on patients who have been treated with biologic agents targeting other cytokines are increasingly appearing in the literature (8).

Herein, we critically discuss the potential usefulness of the IL-1 receptor antagonist anakinra, the anti-IL-1β antibodies canakinumab and gevokizumab and the anti-IL-6 receptor antibody Tocilizumab, which were given in the first 33 patients with BD refractory to currently available treatment regimens. We also summarise the negative results of the 2 randomised placebo-controlled trials performed so far, in which the IL-17 monoclonal antibody secukinumab and the IL-2 receptor binding antibody daclizumab were tested for BD-associated ocular inflammation.

Materials and methods

We searched the Medline/Pubmed database for primary articles published trough April 2014 reporting on the therapeutic use of biological agents targeting cytokines other than TNF in BD. Search terms included: Behçet's in combination with cytokine, interleukin, IL-1, IL-6, IL-17, IL-12/23, IL-2 biologics, monoclonal antibody, anakinra, canakinumab, gevokizumab,

tocilizumab and ustekinumab, secukinumab, daclizumab. We included case reports, case series and research studies, whereas systematic reviews, meta-analyses, comments and duplicate studies were excluded. Abstracts presented in conferences were not considered.

Results

Two randomised double-blind placebo-controlled trials were found, as well as one open-label research pilot study (Table I) and 15 primary case reports or case-series (Tables II and III). The first randomised study, involving a total of 17 patients, focused on the efficacy and safety of daclizumab for ocular manifestations of BD (9). The second study included 118 BD patients assigned to 3 treatment arms and aimed to explore the therapeutic effect and safety of secukinumab for posterior uveitis and panuveitis (10).

There were 8 reports on the use of anti-IL-1 agents; 12 patients were treated with anakinra (11-15), 5 were treated with canakinumab after having received anakinra (14, 16, 17), and 7 patients described in the pilot study, were treated with gevokizumab (18). All patients included in the pilot study were anti-TNF treatment naïve, as were 7 patients treated with anakinra, 5 of whom were subsequently treated also with canakinumab. Of the remaining 10 anti-TNF experienced patients, 5 had been previously treated with Infliximab (11, 14, 15, 17), 3 with adalimumab (14, 17) and 2 with both these anti-TNF agents (13, 16).

The use of IL-6 inhibitor tocilizumab was described in 7 reports including 8 patients (19-25), of whom only one was anti-TNF therapy naive (23), 4 had been treated with infliximab (19-22, 25), one had previously received both Infliximab and adalimumab (22) and one – apart from anti-TNF antibodies – had also been treated with anakinra (24). We found only one report on the use of ustekinumab (anti-IL12/23 antibody) in one psoriasis patient with concomitant BD who had not previously received any biological treatment (26).

Anti-TNF treatment naïve patients

Both randomised controlled studies involved patients with relapsing ocular inflammation despite conventional treatment. Primary efficacy outcomes in the daclizumab study were the number of ocular attacks and an assessment of systemic immunosuppressive medications required during the study, including the ability to taper concomitant immunosuppressive therapy. Primary endpoints in the secukinumab study were reduction of uveitis recurrence or vitreous haze score during withdrawal of concomitant immunosuppressive medication. Daclizumab was not found to be beneficial in comparison with placebo for ocular complications of BD in a total of 17 patients (9). From 9 patients assigned to receive the study drug, none experienced a safety endpoint, but 2 discontinued prior to the end of the study due to personal reasons. Visual acuity remained stable in all participants. Six daclizumab-treated patients experienced ocular attacks during the study period requiring therapy, *versus* 4 receiving placebo, and the median ocular attack rate was greater in the daclizumab treatment group compared to placebo. Moreover, there was greater reduction of concomitant immunosuppressants in patients receiving placebo than daclizumab.

In the secukinumab trial 39 patients received 300mg/2 weeks, 40 received 300mg/4 weeks and 39 patients received placebo; there were more discontinuations due to adverse events in the secukinumab treatment groups compared to placebo group. Overall, 9% of patients discontinued secukinumab because of serious adverse events and the 3 most frequently reported events were

Table I. Therapeutic results of a single infusion of the anti-IL1beta monoclonal antibody gevokizumab given for a unilateral relapse of posterior uveitis despite treatment with azathioprine and/or cyclosporine in 7 patients with Behçet's disease, 4 of whom received a second injection (18).

Gender, Age	Previous treatment suspended at day 0	Concomitant prednisolone dose (mg/d)	Clinical outcome and maximum visual acuity (VA) change after a single gevokizumab intravenous infusion (0.3mg/kg)	Outcome on follow-up to day 95
M, 25	Azathioprine, Cyclosporine	10	Almost complete resolution of hypopyon at day 1, VA improvement at day 21 (20/20 from 20/63)	Exacerbation at day 56 requiring a second infusion and response
M, 37	Cyclosporine	7.5	Resolution of intraocular inflammation, VA stable (20/20)	Exacerbation at day 56 requiring a second infusion and response
F, 33	Azathioprine, Cyclosporine	10	VA improvement at day 56 (20/100 from counting fingers 2m)	Sustained response.
M, 37	Azathioprine, Cyclosporine	5	Resolution of inflammation, VA improvement at day 4 (20/25 from 20/63)	Retinitis attack at day 25 requiring increased doses of prednisolone.
M, 26	Azathioprine	5	Resolution of intraocular inflammation within 1 week. VA improvement at day 14 (20/25 from counting fingers 0.2m)	Cystoid macular edema at day 28 requiring a second infusion and response
M, 29	Azathioprine	20	Resolution of intraocular inflammation, VA improvement at day 28 (20/20 from 20/32)	Exacerbation on day 49 requiring a second infusion and response. Another exacerbation at day 96 treated with corticosteroids
M, 25	Azathioprine, Cyclosporine	10	Incomplete resolution of cystoid macular edema, VA stable at day 7 (20/100)	Beribulbar and intravitreal triamcinolone at days 7 and 22.

Table II. Results of treatment with biologic agents targeting IL-1, IL-6, or IL-12/23 for active Behçet's in 9 anti-TNF treatment naïve patients.

		Gender, Age	Previous treatment	Target clinical manifestations	Biologic agent and concomitant treatment	Clinical outcome	Follow up period
Anti-IL1	Bilginer, 2010	F,17	Methotrexate, Corticosteroids, NSAIDS	Mucocutaneous, arthritis, secondary amyloidosis	Anakinra 1mg/kg/d	Remission for 6 months under treatment. Relapse at discontinuation and re-remission after re-introduction	1 year
	Cantarini, 2013	M, 39	None	Mucocutaneous , fever	Anakinra 150mg/d + Prednisolone 25mg/day	Partial remission of mucocutaneous manifestations; femoral vein thrombosis at 6 months responding to Cyclosporine	18 months
		F, 59	Sulfasalazine, Cyclosporine, Prednisolone, Etanercept	Oral and genital ulcers, unilateral panuveitis	Anakinra 100mg/d + Prednisolone 12.5mg/day	Remission. At 3 months bilateral panuveitis responding to Adalimumab and Prednisolone 25mg/day and Methotrexate	8 months
		F, 29	Azathioprine, Prednisolone	Residual disease activity despite treatment (oral and genital ulcers, arthralgia, bilateral panuveitis)	Anakinra 100mg/d + Azathoprine+Prednisolone 7.5/d	Remission	12 months
		M, 47	Sulfasalazine, Cyclosporine, Azathioprine	Oral and genital ulcers, panuveitis	Anakinra 100mg/d + Prednisolone 25mg/d	Remission of ocular inflammation but persistence of oral aphtosis. Panuveitis relapse at 8 months partially responded to Anakinra 150mg/d +Methotrexate+ Colchicine.	17 months
		M, 21	Prednisolone 10mg/day	Mucocutaneous, arthritis, fever	Anakinra 100mg/d + Prednisolone 10mg/day	Remission or arthritis but not of mucocutaneous manifestations	8 months
	Vitale, 2013	M, 47	Corticosteroids, Sulfasalazine, Cyclosporine, Azathioprine	Mucocutaneous, recurrent deep venous thrombosis, panuveitis, arthritis, fever	Anakinra 100mg/d + Prednisolone up to 25mg/d Canakinumab 150 mg/6 weeks	Remission of panuveitis but not of mucocutaneous lesions. Discontinuation due to adverse event Remission	18 months 6 months
Anti-IL-6	Redondo-Pachon, 2013	F, 51	Corticosteroids low dose for 16 years	Nephrotic syndrome due to secondary amyloidosis	Tocilizumab 8mg/kg/month	Decrease of proteinuria	12 months
Anti-IL-12/23	Baerveldt, 2013	F, 39	Cyclosporine, Steroids	Oral and genital ulcers, skin lesions, concomitant guttate psoriasis and hidradenitis suppurativa	Ustekinumab 45ng at weeks 0, 4 and every 12 weeks thereafter (given for psoriasis)	Remission	36 months

exacerbation of the disease measured by Behçet's disease activity form, uveitis, and folliculitis.

There were no significant differences between secukinumab treatment groups and placebo regarding the rate of recurrent ocular exacerbations in the study eye, however there were smaller proportions of patients with more than 3 exacerbations in the secukinumab treatment groups. Moreover, no difference was noted regarding changes from baseline in best corrected visual acuity of the study eye during study course between either of the secukinumab treatment groups *versus* placebo. Finally, there was significantly greater reduction in mean post-baseline concomitant immunosuppressive medication score in patients of both secukinumab treatment groups compared to placebo (10).

In a small pilot study a single intravenous infusion of the anti-IL1β-regulating antibody gevokizumab was tested in patients with posterior uveitis, panuveitis and/or retinal vasculitis. Gevokizumab resulted in rapid resolution of inflammation in 6 of 7 patients and amelioration of visual acuity in most of them (Table I). The patient in whom resolution of ocular inflammation was incomplete responded to peribulbar and intravitreal triamcinolone. During the 98-day study period one patient remained relapse-free, whereas 5 patients required a second infusion due to exacerbation, retinitis attack or cystoid macular edema, resulting again in resolution of ocular inflammation (18).

We found 3 reports on a total of 7 anti-TNF naïve patients who received Anakinra (Table II). In one patient with bilateral panuveitis and neurological involvement, partial remission was achieved with azathioprine and corticosteroids, and anakinra was added for optimal disease control, leading to complete remission for 12 months (14). In an adolescent patient with BD and concomitant familial Mediterranean fever with secondary amyloidosis Anakinra led to sustained clinical remission and the patient remained free of fever attacks and mucosal or skin lesions (12). Another patient with unilateral panuveitis and bipolar aphthosis, initially responded to anakinra but experienced bilateral panuveitis while on therapy. That patient was subsequently switched to adalimumab resulting in complete remission of manifestations (14). Anakinra was discontinued due to urticaria in a patient presenting with panuveitis, recurrent deep vein thrombosis, mucocutaneous manifestations, arthritis and fever, after partial remission. This patient was subsequently switched to canakinumab at a dose of 150mg every 6 weeks, resulting in complete remission within days (17). In the remaining patients Anakinra at conventional doses, even along with high-dose corticosteroids, resulted in only partial disease remission or relapse (Table II).

Another patient, whose mucocutaneous manifestations and iridocyclitis had responded to corticosteroid treatment for 9 years, presented with secondary amyloidosis and started therapy with tocilizumab in combination with colchicine. After the 2nd infusion, there was a marked and durable improvement of blood and urine examinations

Table III. Results of treatment with biologic agents targeting IL-1 or IL-6 for active Behcet's in 18 anti-TNF treatment experienced patients.

		Gender, Age	Previous treatment	Target clinical manifestations	Biologic agent and concomitant treatment	Clinical outcome	Follow-up period
Anti-IL1	Botsios 2008	F, 75	Cyclosporine intolerance, Azathioprine+ Prednisolone, Infliximab+Methotrexate	Oral and genital ulcers, arthralgias, fever	Anakinra 100mg/d + Prednisolone 5mg/d	Remission	20 months
	Ugurlu 2012	F, 16	Azathioprine+ Cyclospirine+ Prednisolone, Interferon, Infliximab, Adalimumab	Bilateral panuveitis, retinal vasculitis	Anakinra 2mg/kg/d Canakinumab	No response Remission	1 month 2 months
	Emmi 2013	F, 27	Azathioprine, Prednisolone, Infliximab intolerance, Adalimumab, Rituximab	Mucocutaneous, arthralgia, abdominal symptoms, bilateral panuveitis (visual acuity 20/50 and 20/32)	Anakinra 100mg/d	Remission and restoration of visual acuity	12 months
	Cantarini 2013	M, 47	Leflunomide, Cyclosporine, Azathioprine, Etanercept, Infliximab	Mucocutaneous, uveitis, retinal vasculitis	Anakinra 150mg/d+ Prednisolone 25mg/d	Partial remission	unknown
		F, 21	Sulfasalazine, Methotrexate, Cyclosporine, Azathioprine, Etanercept / Infliximab intolerance	Mucocutaneous, arthritis, abdominal symptom, fever	Anakinra 100mg/d +low dose Prednisolone	Remission, deep vein thrombosis after 16 months	28 months
		M, 7	Thalidomide+ Mycophenolate Mofetil + Prednisolone, Adalimumab	Mucocutaneous, abdominal symptoms, arthralgias	Anakinra 2.5 mg/kg/d + Prednisolone 15mg/d	Partial remision	7 months
		F, 41	Corticosteroids, Methotrexate, Azathioprine, Etanercept, Adalimumab	Oral and genital ulcers, arthralgias, fever, abdominal symptoms	Anakinra 100mg/d Canakinumab 150mg/ 8 weeks	No response Partial remission	8 weeks 2 weeks
	Vitale 2013	F, 20	Prednisolone high dose, Sulfasalazine, Methotrexate, Cyclosporine, Azathioprine, Leflunomide, Etanercept/ Infliximab intolerance	Mucocutaneous, arthritis, abdominal symptoms, fever	Anakinra 100mg/d Canakinumab 150mg/8 weeks	Partial remission; discontinuation due to adverse event Remission within days. At 16 months deep vein thrombosis. Remission with modification of Canakinumab dosage every 6 weeks	Few weeks 22 months
		F, 41	Corticosteroids, Methotrexate, Azathioprine, Etanercept, Adalimumab	Oral and genital ulcers, fever, abdominal symptoms, arthralgia	Anakinra 100mg/d Canakinumab 150mg/6 weeks	No response Remission	8 weeks 12 months
	Caso, 2013	M, 36	Cyclosporine, Corticosteroids, NSAIDs, Infliximab	Oral and genital ulcers, sacroiliitis	Anakinra 100mg/d + Prednisolone 5mg/d	Remission	6 months
	Caso, 2013[1]	F, 41	Prednisolone Azathioprine, Cyclosporine+, Adalimumab Methotrexate, Cyclophosphamide, Infliximab	Mucocutaneous, fever, uveitis, arthralgias, pemphigus foliaceus	Anakinra 100mg/d	Partial remission. Relapse.	20 days
	Sfikakis, unpublished [2]	F, 56	Prednisolone Azathioprine Methotrexate, Cyclosporine, Cyclophosphamide, Infliximab, Adalimumab	Posterior uveitis	Anakinra 100mg/d	No response	4 months
Anti-IL-6	Hirano 2012	F, 47	Corticosteroids, Cyclosporine, Ifmiximab	Mucocutaneous, posterior uveitis	Tocilizumab 8mg/kg/4 weeks	Remission, occasionally oral ulcers	12 months
	Shapiro 2012	M, 35	Methotrexate, Azathioprine, Mycophenolate, Cyclosporine, Interferon, Daclizumab, Cyclophosphamide, Infliximab	Aseptic menengo-encephalitis (chronic Neuro-Behçet's with positve MRI)	Tocilizumab 8mg/kg/4 weeks	Resolution of neurological symptoms, negative MRI but recurrence of oral ulcers	7 months
	Urbaniak 2012	M,46	Azathioprine, Corticosteroids, Infliximab	Neuro-Behçet's (positive MRI) relapse	Tocilizumab 8mg/kg/4 weeks +Prednisolone 15mg/d+ Azathioprine 150mg/d	Remission, stable MRI, discontinuation after 4th infusion because of scrotal abscess	8 months
	Diamanto-poulos, 2013	F, 55	Methotrexate, Azathioprine, Etanercept, Infliximab	Mucocutaneous	Tocilizumab 8mg/kg + Azathioprine 150mg	Deterioration	1 month
		F, 26	Cyclosporine, Azathioprine, Methotrexate, Infliximab, Adalimumab	Oral and genital ulcers	Tocilizumab 8mg/kg/month	Partial initial remission and relapse of genital ulcers after 3rd infusion	3 months

Table III. (*continued*)

	Gender, Age	Previous treatment	Target clinical manifestations	Biologic agent and concomitant treatment	Clinical outcome	Follow-up period
Caso, 2013 [1]	F, 41	Prednisolone, Azathioprine, Cyclosporine+ Adalimumab, Methotrexate, Cyclophosphamide, Infliximab, Anakinra	Mucocutaneous, fever, uveitis, arthralgias, pemphigus foliaceus	Tocilizumab 480mg/month + Prednisolone 25mg/d	Remission	14 months
Cantarini 2014	F, 43	Prednisolone, Cyclosporine, Cyclophosphamide, Methotrexate, Infliximab	Mucocutaneous, knee arthritis	Tocilizumab 8mg/kg/dose + Prednisolone	Deterioration of oral and genital ulcers and 2 weeks papulopustular eruption of both arms and chest. Response to Golimumab+ Methylprednisolone	
Sfikakis, unpublished [2]	F, 56	Prednisolone Azathioprine Methotrexate, Cyclosporine, Cyclophosphamide, Infliximab, Adalimumab, Anakinra	Posterior uveitis	Tocilizumab 8mg/kg/4 weeks	No response	3 months

[1]Same patient; [2]Same patient.

(23). Finally, in a BD patient with ocular and intestinal involvement and concomitant psoriasis the anti-IL12/23 agent ustekinumab was initiated and resulted in complete remission of both psoriasis and BD skin manifestations for 36 months without adjunctive immunosuppressive treatment (26).

Anti-TNF treatment experienced patients

We found reports on 17 patients with primary (n=3) or secondary inefficacy or intolerance to anti-TNF monoclonal antibodies, who were subsequently treated with anti-IL-1 or anti-IL-6 agents (Table III). Anakinra was given in 3 patients not responding Infliximab or Adalimumab and proved effective in one with remission of all disease manifestations for 20 months of follow-up (11), induced partial remission of mucocutaneous manifestations, with improvement of frequency and intensity in the second (a 7-year-old boy) (14), and proved ineffective in the third patient (24). In this latter patient, presenting with ocular involvement and pemphigus foliaceus, subsequent administration of Tocilizumab achieved complete remission of clinical symptoms and normalisation of inflammatory markers within days from administration and for a follow-up period of 14 months (24).

Of the 14 patients who initially responded to anti-TNF treatment but experienced secondary failure or intolerance, 8 received initially Anakinra and 6 received tocilizumab (Table III). Anakinra was given at a dose of 100 mg/d, except for a patient to whom dosage was adapted at 2mg/kg/d. Sustained disease remission for up to 28 months at this dosage was achieved in 3of 8 patients (13-15); all had recurrent oral and genital ulcerations and pseudofolliculitis, one had uveitis and anakinra therapy induced remission of ocular inflammation and restoration of visual acuity, and one presented with sacroiliitis. The anakinra dose was increased to 150mg/day in a patient with mucocutaneous and ocular involvement, but only partial remission was accomplished even in combination with high-dose prednisolone (14). Anakinra was discontinued in 4 patients: in 3 due to inefficacy and in one due to diffuse pruritic urticarial lesions of increasing severity and was switched to canakinumab. This human monoclonal antibody targeting interleukin-1 beta, was found to be effective in all 4 patients, but dose was modified to 150 mg every 6 rather than 8 weeks for long-term remission (17).

The anti-IL6 antibody tocilizumab was given at the conventional dose of 8 mg/kg/month in 6 patients. Two patients had neuro-Behçet's disease and tocilizumab resulted in rapid amelioration of neurological symptoms (20, 21). Notably, one of them had previously also received daclizumab, with no response (20). Tocilizumab was discontinued because of scrotal abscesses and inguinal condyloma accuminata after the 4th infusion in one patient, but no exacerbation was observed for 8 months of follow-up (21). In another patient with mucocutaneous manifestations, posterior uveitis and impaired visual acuity tocilizumab lead to sustained remission and vision improvement (19). In three patients with mucocutaneous manifestations, tocilizumab was ineffective (22, 25). One of them, who had experienced secondary failure to Infliximab given initially for bipolar apthosis and pseudofolliculatis, tocilizumab resulted in deterioration of oral and genital ulcers and development of generalised papulopustular eruption (25). Finally, we also report our experience on a patient with posterior uveitis, who relapsed despite initial response to both infliximab and adalimumab. Anakinra and subsequently tocilizumab were started, but both failed to induce remission (Table III).

Discussion

The number of biological agents, beyond anti-TNF, that target specific molecules and pathways of inflammation constantly increases. Immune system abnormalities, with disturbed T cell homeostasis and pro-inflammatory cytokine imbalance, are thought to be involved in BD pathogenesis (27). Along this line significantly higher levels of IL-1β and IL-1 receptor antagonist have been found in the serum

of patients with active or inactive BD compared to control subjects (27, 28), suggesting that IL-1 inhibitors, such as anakinra, canakinumab and gevokizumab could have a place in treatment. Also, tocilizumab inhibits IL-6 mediated actions and IL-6 levels have been found increased in the cerebrospinal fluid of neuro-BD patients and perhaps correlate with long-term outcome and disease activity (27, 29). In addition to the classical proinflammatory cytokines, IL-1 and IL-6, IL-12 and IL-23 play important roles in the inflammatory response by stimulating the production of IFN-γ and the differentiation of T cells to Th17 cells, which in turn stimulate the production of other pro-inflammatory molecules. IL-12 has been shown to be upregulated in BD and to prevent expression of the CD95 death receptor (27). Ustekinumab is directed against interleukin 12 and interleukin 23 and has been proved effective in psoriasis and psoriatic arthritis (30). Moreover, high levels of IL-17 have been found in the peripheral blood of BD patients with active uveitis (31), and secukinumab is a monoclonal antibody against IL-17 currently in clinical trials for plaque psoriasis (32). Finally, since there is evidence suggesting that activated T cells which express IL-2 receptor are involved in BD pathogenesis (33), daclizumab, an anti-IL-2 receptor agent used in transplantation (34) and studied for multiple sclerosis (35), could be a candidate drug for BD.

Herein, we have reviewed the so far accumulated published experience of the use of biological agents which target cytokines beyond TNF in BD. Interferon therapy, also considered as biologic therapy, has been recently discussed in detail elsewhere (36) and was not within our review's scope. Three randomized placebo-controlled trials of anti-cytokine treatment for BD, one testing the anti-TNF agent etanercept (37), have been completed. The 2 other studies focused on the efficacy and safety of daclizumab and secukinumab for BD-associated ocular inflammation in anti-TNF naïve patients. Although both safe, neither agent proved to be superior to placebo in reducing the rate of ocular attacks or improving visual acuity (9, 10). One pilot study focused on the therapeutic effect of a single gevokizumab infusion, administered as monotherapy for BD uveitis and/or retinal vasculitis refractory to azathioprine and/or cyclosporine. The ocular result was positive but the efficacy of this agent, which was well tolerated, on other disease manifestations was not studied (18).

In the majority of case reports and small case-series anakinra was used for refractory or naive disease, but with concomitant high-dose corticosteroids in most patients (14, 17). Its effect seemed better on ocular involvement and systematic manifestations; its efficacy on mucocutaneous manifestations was limited on a number of patients, whereas in many patients a relapse of ocular involvement often occurred (14, 24). In cases of residual or relapsing disease, anakinra dosage was increased to 150mg/kg, but usually this only resulted in partial remission of symptoms even after addition of an immunosuppressive drug. There was a report of an anti-TNF naïve patient who received Anakinra for ocular and mucocutaneous involvement and had to be switched to a TNF inhibitor in order to achieve remission (14). Some patients received canakinumab after failure of anakinra (14, 16, 17), resulting in long-term remission. Canakinumab dosage interval in BD was either initially or subsequently – in cases of relapsing disease – reduced from 8 to 6 weeks in order to achieve better disease control.

Tocilizumab seems also promising for BD based on a limited experience deriving from case reports (20, 21). Tocilizumab was used in the same dose as rheumatoid arthritis and induced rapid long-lasting remission in both patients with neuro-BD, but it had to be discontinued in the one due to infections (21). Tocilizumab's effects on other disease manifestations, particularly mucocutaneous and ocular involvement, are controversial. Overall, apart from a patient who developed severe diffuse pruritic urticarial lesions while on anakinra (17) and one patient in whom a scrotal abscess requiring surgical drainage occurred during treatment with Tocilizumab (21), no new safety signals were reported.

Conclusion

As is the case for all chronic inflammatory conditions, cytokines other than TNF may be involved in the pathogenesis of BD (27), thus, the respective biological agents could be beneficial for these patients. Blockade of IL-17- and IL-2- mediated actions by secukinumab and daclizinumab, respectively, was not efficacious on BD ocular manifestations in two placebo-controlled trials (9, 10). In case reports and small case series, although a potential for bias to report positive effects and underreport the negative cases may exist, the therapeutic blockade of IL-1 by conventional doses of anakinra seemed partially effective. Similarly, canakinumab may have beneficial results on various disease manifestations, especially when dosage interval is limited to 6 weeks (14, 16, 17). The newer anti-IL-1b agent gevokizumab could be a promising drug for ocular inflammation, based on the positive outcome of 7 anti-TNF naïve patients included in a pilot study (18). Finally, in 2 anti-TNF treatment experienced patients with CNS involvement, IL-6 blockade by tocilizumab was beneficial (20, 21). Collectively, it seems that IL-1 and IL-6 are legitimate targets in severe BD despite the limited experience. In our opinion, anti-IL-1 and anti-IL-6 agents can be tried in patients refractory or intolerant to combination regimens which include an anti-TNF antibody, but controlled and comparative studies are badly needed, particularly in a relapsing condition like BD which has a natural course of exacerbations and remissions on its own.

Acknowledgments

We thank very much Professor Hasan Yazici for his critical review of the manuscript.

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