CONCISE REPORT

Interleukin-1β-regulating antibody XOMA 052 (gevokizumab) in the treatment of acute exacerbations of resistant uveitis of Behçet's disease: an open-label pilot study

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ABSTRACT

Objective Uveitis and retinal vasculitis are sight-threatening manifestations of Behçet's disease with limited treatment options. This pilot study aimed to evaluate the safety, pharmacokinetics and clinical activity of XOMA 052 (gevokizumab), a recombinant humanised anti-interleukin 1β antibody, in Behçet's disease patients with uveitis.

Methods Patients with acute posterior or panuveitis, and/or retinal vasculitis, resistant to azathioprine and/or ciclosporin, and receiving 10 mg/day or less of prednisolone, were enrolled into the 98-day study. Immunosuppressive agents were discontinued at baseline. Patients received a single infusion of XOMA 052 (0.3 mg/kg). The safety and uveitis status and pharmacokinetics of XOMA 052 were evaluated.

Results Seven patients enrolled and completed the study. No treatment-related adverse event was observed. XOMA 052 treatment was associated with rapid and durable clinical response in all patients. Complete resolution of intraocular inflammation was achieved in 4–21 days (median 14 days), with a median duration of response of 49 days (range 21–97 days); one patient remained exacerbation free throughout the study.

Conclusions Well tolerated, XOMA 052 resulted in a rapid onset and sustained reduction in intraocular inflammation in patients with resistant uveitis and retinal vasculitis. Moreover, the effect was observed despite discontinuation of immunosuppressive agents and without the need to increase corticosteroid dosages.

Behçet's disease is a multisystem inflammatory disorder characterised by systemic vasculitis with a relapsing/remitting course.[1] Uveitis is an important feature of Behçet's disease. Approximately half of patients develop uveitis, typically affecting both anterior and posterior compartments of the eye.[1–5] Recurrent exacerbations of posterior segment inflammation and retinal vasculitis lead to loss of useful vision. Treatment of uveitis remains challenging, and there are few controlled trials evaluating the efficacy of therapeutic regimens.[2 3 6 7] Corticosteroids and immunosuppressive agents are used to treat the ocular manifestations of Behçet's disease, but remission is difficult, and each of these agents is associated with significant adverse effects.[2 3 7]

Interleukin (IL) 1β is a uniquely pro-inflammatory cytokine fundamental to autoinflammatory diseases.[8] Behçet's disease has many clinical findings overlapping with those of autoinflammatory disorders,[9] and circulating monocytes of Behçet's disease patients produce large amounts of IL-1β.[10] Low concentrations of XOMA 052 (gevokizumab), a recombinant humanised anti-IL-1β antibody, were shown to modulate IL-1β activity.[11] This exploratory study was designed to evaluate the safety, clinical/biological activity and pharmacokinetics of XOMA 052 in Behçet's disease patients with acute intraocular inflammation.

METHODS

Patients

This pilot study was conducted in Behçet's disease patients with acute posterior or panuveitis and/or retinal vasculitis. Patients were required to be resistant to azathioprine and/or ciclosporin. Exclusion criteria included the use of more than 10 mg of prednisolone or equivalents within the previous month of the study (see supplementary data, available online only).

Study protocol

Immunosuppressive treatments and colchicine were suspended on day 0. Patients continued to receive 10 mg or less of prednisolone during the study; one subject receiving prednisolone 20 mg/day was allowed into the study. XOMA 052, 0.3 mg/kg, was administered as a single intravenous infusion. The protocol was amended to allow a second dose of XOMA 052 (0.3 mg/kg) as a rescue for patients developing new uveitis attacks on day 28 or later, if they responded to treatment without any serious adverse events between days 0 and 28. Prednisolone (≤80 mg/day with tapering) was allowed as rescue medication at the discretion of the investigator.

Serum samples were collected at baseline and throughout the study for the determination of serum XOMA 052 concentrations and pharmacokinetics. Whole-blood culture assay was used to measure ex-vivo cytokine production. Also, a cell-based neutralisation assay was used to detect potential anti-XOMA 052 neutralising antibodies (see supplementary data, available online only).

Table 1 Patient characteristics

Patient	Gender	Age	Previous treatment	Prednisolone dose (mg/day)	History
1001	M	25	AZA, CysA	10	Recurrent attacks with hypopyon, experiencing rebound attacks after missing one dose of CysA or prednisolone
1002	M	37	CysA	7.5	Intolerant to AZA and more than 100 mg CysA; recurrent retinitis attacks
1003	F	33	AZA, CysA, Colch	10	No light perception in the right eye, presented with counting fingers from 2 m in the left eye
1004	M	37	AZA, CysA	5	Recurrent uveitis attacks despite the combination of AZA + CysA
1005	M	26	AZA	5	Sight-threatening severe attack involving macula
1006	M	29	AZA, Colch	20	Recurrent attacks of uveitis on 20 mg prednisolone and AZA, intolerant to CysA
1007	M	25	AZA, CysA	10	Recurrent uveitis attacks despite the combination of AZA + CysA

AZA, azathioprine; Colch, colchicine; CysA, ciclosporin.

Table 2 The timing of uveitis exacerbations and second infusions of XOMA 052

Patient	Event, eye (day)	Treatment (day)
1001	Exacerbation, OS (56)	Second infusion (57)
1002	Exacerbation, OD* (56)	Second infusion (57)
1004	Exacerbation, OS (25)	Corticosteroids (25)
	Exacerbation, OU (95)	Corticosteroids (95) and second infusion (98)
1005	CME, OS (28)	Second infusion (29)
1006	Exacerbation, OD* (49)	Second infusion (49)
	Exacerbation, OD* (96)	Corticosteroids (96)
1007	Incomplete resolution of CME, OS* (7)	Peribulbar triamcinolone (7)
	Incomplete resolution of CME, OS* (21)	Intravitreal triamcinolone (22)

*Index eye.
CME, cystoid macular oedema; OD, right eye; OS, left eye; OU, both eyes.

Safety was assessed by recording adverse events, clinically significant abnormal changes in vital signs or laboratory values and infusion reactions.

The primary outcome measure for clinical activity was the progression of uveitis from days 0 to 28. Assessments performed at visits included an ophthalmological examination followed by fundus photography (see supplementary data, available online only). Laser flare photometry was performed to measure the anterior chamber flare.[12] Anterior chamber cells were scored using the SUN Working Group grading scheme.[13] Retinal findings were scored using the uveitis scoring system of Ben Ezra *et al*.[14] A fundus fluorescein angiogram was performed on days 0 and 98.

The current study was an investigator-initiated trial and was conducted with the financial support of XOMA (US) LLC.

RESULTS

Patients

Seven Behçet's disease patients with severe uveitis exacerbations were enrolled. All completed the 98-day study period. Before the study, six patients were receiving azathioprine, combined with ciclosporin in four; and one patient was only on ciclosporin (table 1).

Safety and pharmacokinetics

XOMA 052 was well tolerated with only two adverse events—a mild upper respiratory tract infection and a traffic accident requiring surgical treatment—reported in a single patient. Neither event was considered to be related to XOMA 052. There were no clinically significant changes in vital signs and laboratory values in any patients.

Pharmacokinetic and immunogenicity results are given in the supplementary text and figure S1 (available online only).

Biological activity

In whole-blood culture assay, lipopolysaccharide-induced IL-1β was significantly decreased to 3% at day 28 compared with pre-infusion values ($p<0.001$), whereas IL-1Ra was unaffected. The induction of interferon γ by the combination of IL-12 plus IL-18 significantly increased at day 7 (see supplementary text and figure S2, available online only).

Clinical activity

Patients experienced rapid and clinically meaningful improvements in visual acuity and reductions in anterior chamber cells and flare, vitreous haze and retinal infiltrates in the index eye (see supplementary table S1, available online only). Intraocular inflammation began to resolve in all patients on days 1–4. Complete resolution of retinal findings was achieved in 4–21 days (median 14 days). Patient 1001 had hypopyon on day 0, and it was almost completely resolved on day 1 following study drug administration, with a concomitant reduction in flare from 467 to 45 ph/ms (figure 1 and supplementary table S1, available online only). In the remaining five patients with anterior chamber cells, a clinically significant improvement was observed within 7–21 days.

Improvement in visual acuity was observed starting from day 1 except in two patients. Patient 1003, who was only able to count fingers from 2 m, experienced vision improvement to 20/200 on day 1 following the infusion. Another patient (1005) presented with a severe uveitis attack causing macular infiltration, widespread retinal oedema, haemorrhages and multifocal retinal infiltrates. Following treatment, his intraocular inflammatory findings resolved within 1 week. As a result of severe macular oedema and vitreous traction, he developed a macular hole, causing a permanent loss of useful vision. On the day 14 visit, re-attachment of the macular flap resulted in an improvement in vision up to 20/25 on the Snellen scale, which excluded ongoing macular ischaemia. As a result of subsequent macular scarring, vision could only be improved up to 20/200. Retinal findings of other patients are summarised in supplementary table S1 (available online only). In five of seven patients, intraocular inflammation was resolved fully without signs of new exacerbation at day 28.

In four patients who were exacerbation free at the second examination, fundus fluorescein angiogram scores were 41–75% lower compared with the day 0 scores.

Responses were durable, with a median duration of 49 days (range 21–97 days). In patient 1003, no exacerbation was observed to the end of the study and up to day 120 after a single infusion. Patient 1004 received increased doses of prednisolone for a new retinitis attack in the contralateral eye on day 25. Patient 1007 received peribulbar triamcinolone acetonide on day 7 and then intravitreal triamcinolone on day 22 as rescue

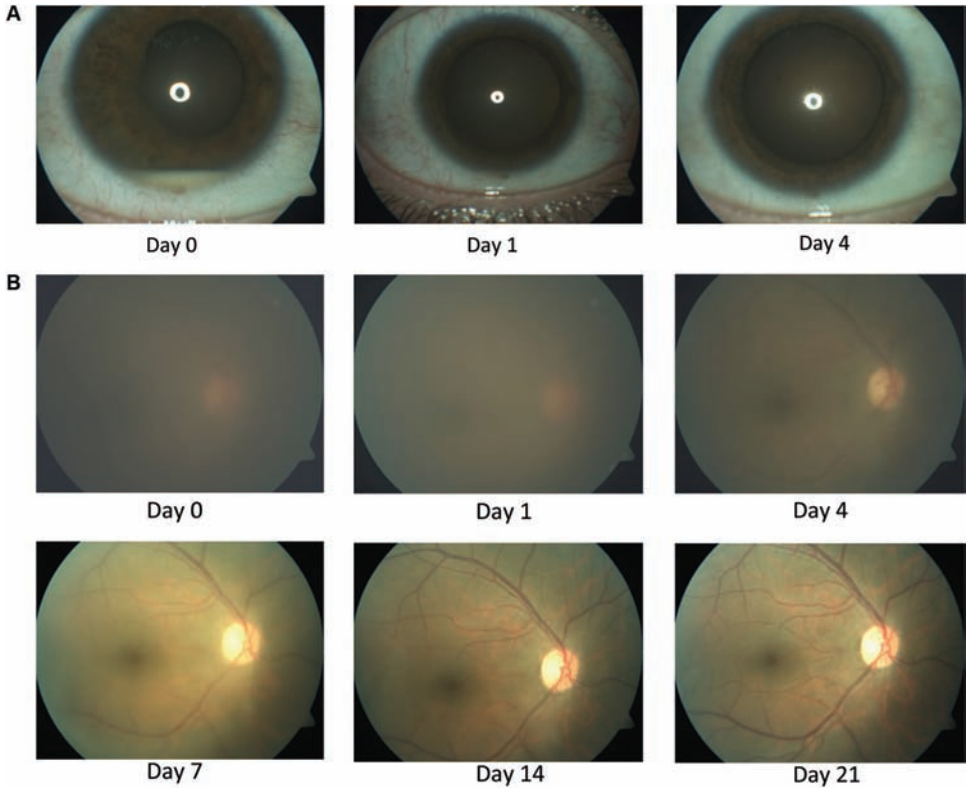

Figure 1 Resolution of panuveitis with hypopyon in the right eye of patient 1001 following XOMA 052 infusion. Anterior eye (A) and retinal (B) images from day 0 to day 21. Please see supplementary table S1 (available online only) for ophthalmological examination findings.

therapy for incomplete resolution of cystoid macular oedema. Four patients received a second infusion of XOMA 052 for new retinal infiltrates between days 49 and 95, and one patient for macular oedema in the contralateral eye on day 29 (table 2). All patients responded to the second infusion. Following the second infusion, they were attack free without the need for any other medication for a median of 115 days (range 41–197 days), a period including post-trial follow-up.

No detailed assessments of extraocular manifestations were performed. However, five patients with recurrent oral ulcers and folliculitis before the trial experienced recurrences. No other Behçet's disease-related manifestations were noted during the study period.

DISCUSSION

Effective treatment of uveitis exacerbations with a rapid resolution of intraocular inflammation is crucial to prevent the partial/total loss of vision. In the current study, XOMA 052 was well tolerated, no XOMA 052-related adverse events were observed in any patient. The treatment resulted in a rapid onset and prolonged reduction in manifestations of intraocular inflammation in all patients.

Standard of care for exacerbation of uveitis or retinal vasculitis often includes an increase in corticosteroid doses with/without intravenous usage in order to reduce intraocular inflammation quickly and limit retinal damage. Discontinuation of immunosuppressive treatments has been associated with the risk of rapid-onset rebound attacks. Notably, current findings suggest that XOMA 052 may be useful for controlling intraocular inflammation without an increase in corticosteroids despite the discontinuation of immunosuppressive agents at baseline.

Active vascular inflammation and disruption of the endothelial barrier might have led to the accumulation of XOMA 052 in ocular tissues allowing it to modulate IL-1β, which resulted in rapid and sustained clinical activity. Available pharmacokinetic data may also allow us to hypothesise that a systemic trough serum concentration (eg, >2 μg/ml) is needed to sustain the therapeutic effect of XOMA 052 in intraocular inflammation by using an infrequent dosing interval (approximately every 4 weeks).

In the present study, we observed 97% less production of IL-1β as well as reduced production of IL-6 and IL-1α upon stimulation with lipopolysaccharide 28 days after the infusion. It appears that after 28 days of neutralisation of endogenous IL-1β, the circulating white blood cells have developed a less inflammatory phenotype compared with baseline. In the same assay there was no reduction in the production of IL-1Ra, suggesting that prolonged neutralisation of IL-1β at this concentration does not dampen the ability to produce this natural inhibitor of IL-1 activity. Also, the observation of increased IL-12/IL-18-induced interferon γ production supports the concept that neutralisation of IL-1β is unlikely to result in an increase in opportunistic infections, including *Mycobacterium tuberculosis*.[15 16]

Overall, the findings described here suggest that IL-1β plays a major role in the ocular manifestations of Behçet's disease. Although this study has limitations resulting from its open-label design and small number of patients, the results support additional studies to evaluate the role of XOMA 052 for the treatment of uveitis and retinal vasculitis and for non-ocular Behçet's disease manifestations as well as other types of non-infectious inflammatory uveitis.

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Ethics approval This study was conducted with the approval of the local ethics committee of Istanbul Faculty of Medicine and the central ethics committee, Ministry of Health, Turkey.

Provenance and peer review Not commissioned; externally peer reviewed.

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