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A Double-masked, Randomized Study to Investigate the Safety and Efficacy of Daclizumab to Treat the Ocular Complications Related to Behçet's Disease

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Abstract

Purpose— To investigate the safety and efficacy of daclizumab (Zenapax, humanized anti-Tac, HAT) in controlling the ocular manifestations of Behçet's disease.

Design— Randomized, placebo-controlled, double-masked clinical trial.

Participants— Seventeen participants with Behçet's disease experiencing at least two prior ocular attacks and requiring treatment with immunosuppressive agents for the ocular complications of Behçet's disease.

Methods— Participants received either intravenous placebo or daclizumab (1 mg/kg) infusions every two weeks for six weeks, then every four weeks while continuing their standard immunosuppressive regimens. If clinically indicated, tapering of the standard immunosuppressive medications was allowed after six months of study enrollment. Complete ocular and physical examinations and an adverse event assessment were performed at baseline and prior to each study infusion.

Main Outcome Measures— Primary safety endpoints were the development of a life-threatening complication or a severe opportunistic infection. Primary efficacy outcomes 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.

Results— Nine participants randomized to daclizumab and eight to placebo were followed monthly. Follow-up ranged from one to 34 months, with a median follow-up of 15 months. Two participants randomized to daclizumab discontinued study therapy prior to the end of the study for personal reasons. No participant experienced a safety endpoint, and visual acuity remained stable in all participants during the course of the study. Ten participants (six daclizumab, four placebo) experienced ocular attacks requiring therapy. The median ocular attack rate during the study was greater in the daclizumab arm than the placebo arm (median 1.27 vs. 0.17 attacks/year, respectively).

Participants in the placebo arm also experienced a greater reduction in the immunosuppressive medication score compared to participants receiving daclizumab (median -4.0 vs. -1.0, respectively).

Conclusions— The observed results in the placebo group demonstrate that careful follow-up and treatment with standard combination immunosuppressive therapy can be effective for the management of the ocular complications of Behçet's disease. In our small study, there was no suggestion that daclizumab was beneficial in comparison with placebo. However, the low observed attack rate limited our ability to make a definitive treatment group comparison.

Keywords

Behçet's disease; uveitis; daclizumab; clinical trial

INTRODUCTION

Behçet's disease (BD) is a multisystem inflammatory disorder defined clinically by intraocular inflammation, oral and mucosal ulcerations, cutaneous lesions and inflammation that may affect other body organs such as the joints, intestinal tract, epididymis, blood vessels, and central nervous system. Although a positive pathergy test and HLA-B51 haplotype support the diagnosis of BD, a specific laboratory test to establish the diagnosis does not exist. Ocular involvement in BD is characterized by recurrent, explosive episodes of intraocular inflammation or uveitis most commonly presenting as an obliterative retinal vasculitis. The recurrent ocular attacks can lead to irreversible alterations of the sensory retina, which are a significant cause of visual impairment in affected patients. Treatment of ocular BD with topical, periocular, or systemic corticosteroids alone or in combination with systemic immunosuppressive medications such as cyclosporine, methotrexate, azathioprine, cyclophosphamide, and chlorambucil can yield ocular protection but is often complicated by the side-effects of therapy.¹ Consequently, an effective and safer therapy for the treatment of ocular BD is needed.

Evidence suggests that the interleukin-2 (IL-2) receptor-bearing T-cells play an important role in the pathogenesis of Behçet's disease and uveitis.² Daclizumab (Zenapax, humanized anti-Tac, HAT) is a recombinant monoclonal immunoglobulin of the human IgG-1 isotype composed of 90% human and 10% murine antibody sequences that recognizes the high affinity IL-2 receptor Tac protein (p55, alpha chain, CD25) and inhibits IL-2-mediated responses of activated lymphoid cells. Initially shown to delay the onset of graft rejection in solid organ transplant recipients, Roberge and colleagues demonstrated the efficacy of humanized anti-Tac in treating S-antigen-induced experimental autoimmune uveitis in non-human primates.³ In a recent report, we described the 4-year results of a nonrandomized, open-label, Phase I/II clinical trial using intravenous daclizumab and the short-term results of a Phase II trial investigating a subcutaneous formulation of daclizumab for the treatment of non-infectious sight-threatening intermediate and posterior uveitis.⁴ These studies suggest that anti-IL-2 receptor blockade could be useful in the treatment of uveitis and other Th1-mediated autoimmune conditions. Herein, we describe a randomized, placebo-controlled, double-masked clinical trial investigating the safety and efficacy of daclizumab in controlling the ocular manifestations of BD.

METHODS

Study Design

The study was a randomized, placebo-controlled, double-masked interventional trial of daclizumab in participants with BD requiring immunosuppression for the treatment of their

intraocular inflammatory disease. The study protocol was reviewed and approved by the Institutional Review Board at the National Eye Institute (NEI) and was monitored by the NEI Data and Safety Monitoring Committee (DSMC) for adverse and/or beneficial effects of the therapy. All enrolled participants gave written informed consent.

Participants over the age of 6 years with BD, as defined using the criteria developed by the Japanese Behçet's Disease Research Committee,⁵ were eligible for the study if they had at least two documented ocular attacks of Behçet's disease involving the posterior segment in either eye and required treatment for at least three months prior to enrollment with prednisone (minimum 15 mg) or cyclosporine, azathioprine, methotrexate, cyclophosphamide, or chlorambucil alone or in any combination for uveitis or retinal vasculitis attributed to BD. Eligible participants also had to demonstrate a neutrophil count above 750 cells per cubic millimeter, have normal or only mild renal or liver function abnormalities, as defined by The World Health Organization criteria for adverse events reporting,⁶ and agree to acceptable use of contraception throughout the study and six months after completion of the study therapy. Participants were excluded from the study if they had an active infection or significant symptomatic neurological disease that would complicate the diagnosis of the neurologic sequelae of BD, a history of cancer other than a non-melanoma skin cancer, known to be pregnant or lactating, end stage ocular disease with no reasonable hope for visual improvement or previously treated with IL-2-directed monoclonal antibody or an investigational agent that would interfere with the ability to evaluate the safety, efficacy, or pharmacokinetics of Zenapax.

Enrolled participants were randomly assigned in a 1:1 allocation to either placebo or 1 mg/kg daclizumab infusions given via an intravenous drip over 30 minutes every two weeks for six weeks (4-dose induction), then once every four weeks for a minimum of 24 months following randomization. All participants were required to continue their standard immunosuppressive medication regimen recorded at enrollment, with no dose reduction while receiving the study therapy for the first six months of the study unless a taper was medically indicated. Ocular examination, including an assessment of best-corrected visual acuity,⁷ anterior chamber cells and flare, vitreous haze,⁸ and dilated fundus examination were performed at baseline, weeks 2, 4, and 6 and, thereafter, every four weeks. Intravenous fluorescein angiography and fundus photography were performed at baseline and weeks 26, 50, 74, and 102. Additional ophthalmic examinations including fluorescein angiography were performed as needed if the participant experienced subjective evidence of an ocular attack or was determined to have an increase in intraocular inflammation by their local treating ophthalmologist. Blood for routine laboratory (complete blood count, serum chemistries including liver and renal functions tests, minerals and lipids, and erythrocyte sedimentation rate) was obtained at baseline, weeks 2, 4, and 6, and then every four weeks. Females were tested for pregnancy at baseline only. Prior to each study infusion, a complete physical examination and an adverse event assessment were recorded.

Participants in either treatment group experiencing an ocular attack or manifesting evidence of increased disease activity during the study were managed medically according to standard-of-care for the treatment of uveitis with periocular steroids or an increase in dosage or addition of a systemic immunosuppressive agent. After six months, tapering of the participant's systemic immunosuppressive medications was considered if there was no evidence of active posterior segment inflammation. The objective of the taper was to decrease the participant's overall immunosuppressive therapy while maintaining quiescence of the ocular disease; therefore, the rate of taper and choice of medication decreased first was determined individually for each participant by the study investigators based on the participant's history of disease activity, recurrence, and side-effects associated with therapy. Each immunosuppressive agent was tapered individually, with no more than one agent tapered at a time. The target dose for each agent tapered was at least 50% of the enrollment dose. Once the taper dose was achieved

for the first agent, taper of a second agent could begin with the same target dose of at least 50%. A similar pattern of tapering was followed for participants on three or more immunosuppressive agents. In the event of an ocular attack during the taper, the taper was ceased and the ocular inflammation was managed as clinically indicated according to the standard-of-care for the treatment of uveitis.

Outcome Measures

The primary safety endpoints were either the development of a life-threatening complication, namely an exacerbation of the systemic or neurologic manifestations of BD, or the development of a severe opportunistic infection. The primary efficacy outcomes of the study were based on the number of ocular attacks experienced and the amount of immunosuppressive medications required during the study period, including the ability to taper the standard immunosuppressive medications. An ocular attack was defined as an ocular inflammatory event causing at least one of the following: (1) at least a 10-letter drop in ETDRS⁷ visual acuity from the reference visual acuity score, (2) the need for treatment with a periocular steroid injection, or (3) the need for treatment with an increase in the dose of any systemic immunosuppressive agent by at least 20% from a previously prescribed dose. An ocular attack was considered to be resolved, thereby making the participant eligible for another ocular attack when any one of the following was observed: (1) the return of the visual acuity to within 5 letters of the reference visual acuity score, (2) the dose of the immunosuppressive agent increased to treat the ocular attack is decreased to the pre-ocular attack dose, or (3) the change in anterior chamber cells and vitreous haze attributed to an ocular attack returns to the pre-ocular attack level. An immunosuppressive medication grade was calculated for each participant upon entering the study and recalculated at every follow-up visit to assess the amount of immunosuppressive medications utilized by each participant during the study.

Secondary efficacy outcomes included the degree of intraocular inflammation as measured by vitreous haze and anterior chamber cells and flare, the presence or absence of cystoid macular edema, a change from baseline visual acuity, and quality-of-life issues as measured through the NEI-VFQ25 questionnaire.

Statistical Analysis

The main analysis examining differences in ocular attacks between treatment groups was based on the time to first occurrence of an ocular attack. Ocular attack event rates were calculated using the Kaplan-Meier product-limit method, with a test of overall difference based on a log-rank statistic.⁹ Additionally, analysis for assessing differences in ocular attacks between treatment groups took into account multiple ocular attacks for each participant assuming a Poisson process for the number of attacks per year. A Poisson regression model was fit to determine whether the number of attacks per year were different between the two groups.¹⁰ Due to the small sample size and skewed results, normal assumptions could not be validated, and a non-parametric median test was used to compare continuous variables such as change in medication score, visual acuity, and NEI-VFQ25 score.¹¹ A Fisher's exact test was used to compare proportions.¹²

RESULTS

Between October 1999 and October 2002, 17 participants were enrolled in the study, which was temporarily closed to enrollment between January and September 2000 due to a shortage in the supply of the study medication. Nine participants were randomized to treatment with daclizumab, and eight were randomly assigned to receive placebo infusions. At enrollment, participants were additionally stratified as active or inactive according to the status of the posterior segment ocular disease and as adult or pediatric according to age. Of the 17

participants, two were active at enrollment and three were considered pediatric (less than 18 years of age). The demographic characteristics of 17 enrolled participants are described in Table 1.

The study accumulated follow-up for the 17 participants ranging from 1–34 months. Two participants withdrew from the study prior to the closure date. The first participant (participant 13) withdrew after receiving infusions through week 28 because she wanted to rapidly taper from her prednisone dose and was not willing to adhere to the study-mandated immunosuppressive medication taper schedule. The second participant (participant 16) was withdrawn from the study at eight weeks after receiving only one study infusion at baseline due to abnormal baseline blood results discovered at week 2, indicative of a possible hematological malignancy. While enrolled in the study, neither of these two participants experienced ocular attacks nor ophthalmic problems related to the therapy. Available follow-up for these participants is included in the study tables and analysis of outcomes.

Efficacy Outcomes

The primary efficacy outcomes of the study were ocular attacks and the amount of immunosuppressive medications, including the ability to taper, required during the course of the study. At enrollment, the number of ocular attacks recalled by each participant for the prior three years was recorded. Due to one daclizumab participant who reported experiencing monthly ocular attacks (participant 11), the recalled ocular attack rates appear to be significantly different between the two treatment groups ($p = 0.002$). Considering the small number of participants in the study and the subjective nature of the question, this observation was very influential. Momentarily disregarding this observation, the recalled attack rates between the two groups were not significantly different ($p = 1.00$).

Ten of the 17 participants experienced ocular attacks during the study period, six treated with daclizumab and four receiving placebo infusions. The time to first ocular attack was not significantly different between the two treatment groups ($p = 0.620$). The mean time to first attack was 589 days (95% CI [0, 846]) and 732 days (95% CI [0, 1059]) for daclizumab and placebo arms, respectively. The mean (median) ocular attack rate in the placebo group was 1.53 attacks/year (0.17 attacks/year) compared to the ocular attack rate in the daclizumab group 1.57 attacks/year (1.27 attacks/year). Although, observably, the attack rate is much higher in the daclizumab group, since so few attacks were observed in the study period, this difference did not achieve statistical significance ($p = 0.142$). There appeared to be no difference in the severity of the ocular attacks between the two treatment groups as determined by duration of attack before resolution, visual loss, and need for additional immunosuppressive therapy (Table 2).

A grading system for systemic immunosuppressive therapy was established such that each participant could be assigned an overall therapeutic grade based on the number and dosages of prescribed immunosuppressive medications (Table 3). Overall, participants receiving placebo infusions had a greater reduction in their medication grade (mean -2.6 , median -2.5) compared to participants treated with daclizumab (mean -1.2 , median -1.0) (Table 2), but this difference was not statistically significant ($p = 0.47$). The protocol required taper of concomitant immunosuppressive medications beginning at month 6. Adjusting for differential follow-up in the treatment groups, there was still no statistically significant difference in tapering between treatment groups. All placebo participants, with follow-up greater than six months 100% (6/6), were able to begin the taper at month 6, compared to 40% (2/5) of the daclizumab group ($p = 0.02$).

In the worse eye (at baseline), median changes in best corrected visual acuity from baseline to last follow-up visit were +6 and +5.5 letters for daclizumab and placebo, respectively ($p > 0.5$).

In the better eye, the overall median change was -1 and -5 letters for daclizumab and placebo respectively ($p > 0.5$). Similarly, the median change in overall score of the NEI-VFQ25 was $+2$ and $+2.5$ points ($p > 0.5$) for daclizumab and placebo groups, respectively.

Safety Outcomes

No participant experienced a primary safety end-point of a life-threatening complication or a severe opportunistic infection during the course of the study. Although some participants experienced visual loss associated with ocular attacks, overall, the visual acuity remained stable in all participants. Mild infections, primarily upper respiratory and gastrointestinal, of undetermined but presumably viral origin, were reported by participants in both treatment groups. Table 4 summarizes all reported adverse events by severity and perceived relationship to the study therapy for each treatment group. Although the distribution of perceived relatedness is similar in both treatment arms, more adverse events were perceived as greater in severity in the placebo group.

As there was no observed benefit of daclizumab in decreasing the recurrent ocular attacks and reducing standard combination immunosuppressive therapy required for the treatment of the ocular complications of Behçet's disease, in October 2002 the NEI DSMC recommended termination of the study. This recommendation was based on the extremely low rate of observed ocular attacks, which limited and would preclude definitive group comparisons. As a result, the likelihood that the study would provide any evidence supporting the efficacy of daclizumab in controlling the ocular manifestation of Behçet's disease was extremely low, and the study was halted.

DISCUSSION

The low ocular attack rate in the placebo group suggests that with careful follow-up treatment with standard combination immunosuppressive therapy can be effective for the management of the ocular complications of Behçet's disease. However, it may not be possible to generalize our results as most Behçet's patients with ocular disease are unlikely to be cared for in a tertiary referral clinical setting by an ophthalmologist with specialized training in ocular immunology and uveitis. Additionally, despite the care provided by the uveitis specialists, participants in the placebo group treated with standard-of-care immunosuppressive medications experienced a higher proportion of adverse events that were perceived greater in severity.

The purpose of the study was to investigate the safety and efficacy of daclizumab in controlling the ocular manifestations of Behçet's disease. We have previously demonstrated the efficacy of daclizumab in other uveitis patients with minimal secondary effects and without the need for other immunosuppressive agents. However, this study highlights the intended utility of a randomized, placebo-controlled trial; using a scientific method, the efficacy of daclizumab in the treatment of ocular complications of Behçet's disease was not demonstrated.

In this randomized, double-masked study there were two main design features that may have improved the ability to determine a potential treatment effect. First, an extensive lead-in period prior to study in-fusions would have provided reliable estimates of each participant's underlying attack rate. Instead, the participant's recall was used to gather information about their ocular attack history. If the underlying ocular attack rates were truly different, this would have significantly impaired the ability of this study to detect a difference between the two groups, especially with the small number of participants. Second, delaying tapering of immunosuppressive medications through month 6 allowed for extensive use and modulation of concomitant medications that can easily confound potential treatment effects. A lead-in period prior to initiating the study treatments would have provided ample opportunity to

stabilize each participant's disease prior to attempting to taper the systemic immunosuppressive medications after the initiation of study infusions.

The need for a safe and effective therapy for participant with Behçet's disease remains an important goal. However, until this goal can be achieved, this study demonstrated that, with careful clinical follow-up, standard systemic immunosuppressive therapy can be effectively used to limit the number of ocular attacks in participants with BD. Although daclizumab was not shown to be beneficial for the treatment of the ocular complications of Behçet's disease in this study, based on its understood mechanism of action and other clinical uses, it still may be a rational treatment strategy for the treatment of uveitis not associated with BD and other putative Th1-mediated autoimmune diseases.^{4, 13, 14}

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TABLE 1
Demographic, treatment group, follow-up, immunosuppressive medication, and ocular attack summary

ID/age/sex/race	Weeks of follow-up	Treatment group	Medication Grade			Ocular attacks/yr	
			Baseline	Last	Change	Prior to treatment	On study
01/46/F/W	145	Placebo	16	11	-5*	0.67	0.34
02/20/M/W	146	Placebo	7	6	-1*	2	1.07
03/51/M/N/Amer	88	Placebo	9	4	-5*	2	0
04/28/F/W	64	Placebo	9	2	-7*	1	0
05/34/M/W	60	Placebo	5	2	-3*	1	0.83
06/47/F/W	33	Placebo	4	2	-2*	1.33	0
07/17/M/W	22	Placebo	11	13	+2	1	0
08/18/F/W	4	Placebo	4	4	NC	1	10
09/40/M/W	96	Dacizumab	7	9	+2*	2.67	3.89
10/31/F/W	95	Dacizumab	15	10	-5*	1.33	1.11
11/69/F/Asian	63	Dacizumab	5	2	-3*	0.33	0.83
12/33/M/W	37	Dacizumab	2	6	+4*	12	1.43
13/27/F/W	28	Dacizumab	17	16	-1*	1	0
14/16/M/W	23	Dacizumab	14	9	-5	1.67	2
15/12/M/W	17	Dacizumab	12	9	-3	1	3.33
16/46/F/B	6	Dacizumab	6	6	NC	1.33	0
17/27/F/W	2	Dacizumab	7	7	NC	0.67	0

* Participants with more than six months of follow-up.

TABLE 2

All assessed ocular attacks

ID	Treatment group	10-letter VA drop	20% increase in meds	Peri-ocular injection	Resolution criteria	Duration
01	Placebo	No	No	Yes—OS	Meds returned to pre-attack levels	28
02	Placebo	OD VA drop from 80 to 58 letters OS VA drop from 48 to 36 letters OD VA drop from 76 to 59 letters	Yes No No	No Yes—OS No	OD VA returned to 75 letters OS VA returned to 44 letters AC cells and vit haze returned to pre-injection levels	10 133 63
05	Placebo	OD VA drop from 66 to 34 letters	Yes	Yes—OD	OD VA returned to 66 letters	21
08	Placebo	No	No	Yes—OD	Meds returned to pre-attack levels	27
09	Daclizumab	No No No	Yes Yes No	Yes—OD Yes—OD Yes—OD	Meds returned to pre-attack levels AC cells and vit haze returned to pre-injection levels	33 28
10		OD VA drop from 76 to 54 letters No OD VA drop from 62 to 40 letters No OD VA drop from 70 to 55 letters OS VA drop from 66 to 35 letters No	No No Yes No No Yes No	Yes—OD Yes—OD Yes—OD Yes—OD Yes—OS Yes—OS Yes—OD	OD VA returned to 72 letters Meds returned to pre-attack levels OD VA returned to 64 letters Meds returned to pre-attack levels OD VA returned to 65 letters OS VA returned to 61 letters Meds returned to pre-attack levels	44 19 82 54 56 21
11	Daclizumab	OD VA drop from 54 to 42 letters	Yes	Yes—OD	OD VA returned to 63 letters	26
12	Daclizumab	OS VA drop from 77 to 63 letters	No	No	OS VA returned to 73 letters	86
14	Daclizumab	No	Yes	No	Meds returned to pre-attack levels	2
15	Daclizumab	No	Yes	No	Meds returned to pre-attack levels	36 53

TABLE 3

Immunosuppressive medication grading scale

Medication	Grade (based on dose in mg/kg)									
	0	1	2	3	4	5	6	7	8	9
Prednisone *	0	<0.15	0.16–0.30	0.31–0.45	0.46–0.60	0.61–0.75	0.76–0.90	0.91–1.05	1.06–1.20	>1.21
Cyclosporine	0	<0.75	0.76–1.50	1.51–2.25	2.26–3.00	3.01–3.75	3.76–4.50	4.51–5.25	5.26–6.00	>6.01
Azathioprine	0	<0.25	0.26–0.50	0.51–0.75	0.76–1.00	1.01–1.25	1.26–1.50	1.51–1.75	1.76–2.00	>2.01
Cyclophosphamide	0	<0.25	0.26–0.50	0.51–0.75	0.76–1.00	1.01–1.25	1.26–1.50	1.51–1.75	1.76–2.00	>2.01
MMF	0	<10	11–20	21–30	31–40	41–50	51–60	>60		
Steroid	Relative potency									
Cortisone	0.2									
Hydrocortisone	0.25									
Prednisone	1.0									
Prednisolone	1.0									
Methylprednisolone	1.25									
Triamcinolone	1.25									
Dexamethasone	6.7									
Betamethasone	7.0									

* If other systemic corticosteroids are used in place of prednisone, their relative potency factor must be factored in computing the grade.

TABLE 4
Summary of relatedness and severity of all reported adverse events by treatment group

Treatment	Perceived relatedness	Mild	Severity Moderate	Severe	Total
Daclizumab	Not Related	2 (10%)	2 (10%)	1 (5%)	5 (24%)
	Remotely Possibly	10 (48%)	1 (5%)	-	11 (52%)
	Total	12 (58%)	3 (15%)	1 (5%)	16 (76%)
Placebo	Not Related	2 (10%)	4 (19%)	1 (5%)	7 (33%)
	Remotely Possibly	13 (42%)	4 (10%)	1 (3%)	18 (58%)
	Total	15 (50%)	8 (26%)	2 (6%)	25 (84%)