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High-dose humanized anti-IL-2 receptor alpha antibody (daclizumab) for the treatment of active, non-infectious uveitis

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ABSTRACT

Purpose: This study was designed to provide preliminary data regarding the safety and efficacy of high-dose humanized anti-IL-2 receptor (daclizumab) therapy for the treatment of active intermediate, posterior or panuveitis.

Methods: Five patients were recruited into this non-randomized, prospective pilot study of high-dose intravenous induction daclizumab therapy given at doses of 8 mg/kg at day 0 and 4 mg/kg at day 14. Patients who did not meet a safety endpoint at the 3-week follow-up evaluation were given the option of continuing therapy with subcutaneous daclizumab at 2 mg/kg every 4 weeks for 52 weeks. The primary outcome assessed was a two-step decrease in vitreous haze at day 21. Secondary outcomes evaluated included best-corrected visual acuity, retinal thickness as measured by optical coherence tomography, retinal vascular leakage assessed by fluorescein angiography, anterior chamber and vitreous cellular inflammation.

Results: Four male patients and one female patient were enrolled. Diagnoses included birdshot retinochoroidopathy (two patients), Vogt–Koyanagi–Harada's disease, bilateral idiopathic panuveitis and bilateral idiopathic intermediate uveitis. By the 4th week, four of five patients demonstrated a two-step decrease in vitreous haze. The other participant did not meet this criterion until week 20, but all five patients maintained stability in vitreous haze grade throughout their follow-up periods. At enrollment, mean visual acuity (10 eyes in 5 patients) was 69.2 ETDRS letters and following treatment was 78.2 letters ($p < 0.12$). Anterior chamber cell, vitreous cell, and vitreous haze also improved in the majority of eyes. Adverse events were generally mild except for one episode of left-lower lobe pneumonia requiring hospitalization and treatment.

Conclusion: This is the first demonstration that high-dose daclizumab can reduce inflammation in active uveitis. Daclizumab was well tolerated but there may be a potential increased risk of infection associated with immunosuppression. All five patients demonstrated a decrease in vitreous haze and measures of intraocular inflammation at final follow-up. The results of this small, non-randomized pilot study support the consideration of high-dose daclizumab therapy in cases of active posterior uveitis.

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1. Introduction

Daclizumab is a humanized blocking monoclonal antibody that is directed against an epitope found on the alpha subunit of the interleukin (IL)-2 receptor (CD25), localized on activated T cells and other cells of the immune system [1]. Daclizumab was first shown to be effective in the reduction of acute rejection episodes in patients undergoing renal transplantation [1,2] and has since been utilized for other solid organ transplants including heart [3], lung [4,5], pancreatic[6,7], and hepatic allografts [8,9]. Besides its use in solid organ transplantation, daclizumab has been utilized for the treatment of a subset of patients with human T-cell leukemia virus-1 (HTLV-1) associated T-cell leukemia because of the elevated levels of IL-2 receptor found on leukemic cell populations [10].

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We have previously demonstrated the successful use of intravenous daclizumab as a glucocorticoid and cyclosporin A-sparing agent in the treatment of patients with non-infectious intermediate and posterior uveitis. Patients who required combination systemic immunosuppressive medications to control their disease were successfully tapered off these medications and maintained on daclizumab monotherapy [11]. A subsequent study demonstrated that subcutaneous administration of daclizumab was equally efficacious [12].

While our earlier studies had demonstrated the utility of daclizumab as a corticosteroid and calcineurin inhibitor-sparing agent, we wished to address the question of whether daclizumab might be beneficial in the treatment of patients with active intermediate and posterior uveitis. The primary focus of this feasibility study was to determine whether high-dose daclizumab is effective in the acute reduction of vitreous haze in active, intermediate, posterior and panuveitis of non-infectious origin.

2. Materials and methods

This study was a prospective, open-label, non-randomized, phase II pilot study of daclizumab treatments for participants with active, sight-threatening, non-infectious uveitis. The study was conducted at the Clinical Center of the National Institutes of Health under an Investigational New Drug (IND) application. The study protocol was reviewed and approved by the Institutional Review Board of the National Eye Institute and all procedures conformed to the tenets of the Declaration of Helsinki. Informed consent was obtained from all patients.

2.1. Inclusion and exclusion criteria

Inclusion criteria included a diagnosis of active non-infectious intermediate, posterior, or panuveitis with ≥grade 1 (1+) vitreous haze in at least one eye using the SUN criteria and evidence of retinal vascular leakage or cystoid macular edema (CME) [13], best-corrected distance visual acuity (BCVA) in the poorer seeing eye of 20/400 or better (i.e. Early Treatment of Diabetic Retinopathy Study – ETDRS logMAR < 1.34), and the participant did not plan to undergo elective ocular surgery (e.g. cataract extraction).

Exclusion criteria included patients who had received IL-2 or IL-2 receptor-directed therapy within 90 days, lens or media opacities that would hinder evaluation and grading of the posterior segment, pregnant or lactating patients, history of active herpes or varicella infection within 6 months or chickenpox exposure within 21 days before enrollment, known history of human immunodeficiency virus (HIV) infection, current enrollment in another trial involving the use of immunotherapy for a non-uveitic condition or any investigational therapy within 30 days, significant systemic infection requiring treatment, history of cancer within 5 years, or any other non-ocular comorbid conditions with significant risks to health or the patient's ability to follow-up in the study protocol.

All participants, male or female, with reproductive potential and who were sexually active agreed to use double-barrier contraception methods throughout the course of the study (minimum of 52 weeks) and for an additional 6 weeks after completion of the protocol treatment period.

2.2. Medication dosing and administration

All enrolled patients received an initial induction regimen of intravenous (IV) daclizumab, 8 mg/kg on day 0 followed by a second IV dose of 4 mg/kg on day 14 ± 1 day, provided a safety endpoint had not already been met. Daclizumab was provided by PDL BioPharma (Redwood City, CA). Participants who showed improvement without serious adverse events, and who did not experience a ≥3-line drop (15 letters) in visual acuity during the induction treatments, had the option to receive extended treatments of 2 mg/kg subcutaneous (SC) daclizumab treatments at 4-week intervals for up to 1 year. Meeting the safety failure criterion (i.e. ≥15-letter loss of visual acuity) or having a serious adverse affect directly attributed to daclizumab therapy was cause for termination from further daclizumab therapy.

2.3. Ophthalmic and medical evaluation

All patients underwent baseline medical and ophthalmologic examinations. Ophthalmic examination included best-corrected visual acuity measurement using the standardized ETDRS refraction protocol at 4 m, intraocular pressure by applanation tonometry, slit lamp biomicroscopic examination, dilated funduscopic examination, fluorescein angiography, and stereoscopic fundus photography. Imaging with optical coherence tomography (OCT-3) was performed and mean central retinal thickness (area A1 with a 1-mm diameter) was recorded at interval visits. Medical examination included physical examination and laboratory measurements including the following values: hemoglobin, hematocrit, platelets, leukocytes, serum electrolytes (sodium, potassium, chloride, bicarbonate, blood urea nitrogen, creatinine), serum bilirubin, alkaline phosphatase, alanine aminotransferase, and aspartate aminotransferase.

2.4. Primary and secondary outcome assessment

The primary outcome measure was the reduction of vitreous haze by at least two steps (e.g. 2+ to trace, or 1+ to 0) from baseline at day 21 in both eyes. Participants were considered treatment failures if at any time during the study, a ≥3-line (≥15 letters or >0.30 logMAR) decrease in best-corrected visual acuity (BCVA, ETDRS method) was observed when compared to baseline.

Secondary outcome measures included distance BCVA, ocular inflammation grades for anterior chamber (AC) cells and vitreous cells, the amount of retinal vascular leakage measured by fluorescein angiography, the presence or extent of cystoid macular edema (CME) determined by optical coherence tomography and/or visualized by fluorescein angiography, and weighted grading score of immunosuppressive medications (i.e. immunosuppression load). During the maintenance phase of the protocol (i.e. following day 28), concomitant systemic immunosuppressive medications could be tapered as clinically indicated. However, medications were not tapered during the initial 21-day induction phase.

2.5. Safety assessment and adverse event reporting

Safety outcomes were tabulated by observing the nature, severity and frequency of systemic toxicities, adverse events (AE), and infections throughout the study. Safety assessments were made routinely during the study, with a review of the previous visit interval performed at each scheduled visit. Each participant was encouraged to report any apparent adverse events between scheduled visits, and returned for additional evaluations and appropriate treatment between scheduled visits if needed. Safety failure criterion that would result in suspension and potentially permanent withdrawal of study treatments included a drop of ≥3 lines (≥15 letters) from baseline visual acuity, a serious adverse event, drug reaction or complication (whether related or unrelated to daclizumab) with an impact on visual function or any other organ system that would preclude continuation of study treatment (e.g. hypersensitivity, allergic response, or serious drug reactions), and pregnancy.

Adverse medical events were evaluated and treated by an Internal Medicine service when clinically indicated, and appropriate