Published in final edited form as:

Can J Ophthalmol. 2011 August ; 46(4): 322–328. doi:10.1016/j.jcjo.2011.06.008.

Long-term daclizumab therapy for the treatment of noninfectious ocular inflammatory disease

Keith Wroblewski, MD^{*,†}, H. Nida Sen, MD^{*}, Steven Yeh, MD^{*}, Lisa Faia, MD^{*}, Zhuging Li, PhD^{*}, Pushpa Sran, MD^{*}, Sapna Gangaputra, MD^{*}, Susan Vitale, PhD, MHS^{*}, Patti Sherry, BSN^{*}, and Robert Nussenblatt, MD, MPH^{*}

^{*}Laboratory of Immunology, National Institutes of Health, Bethesda, Md

[†]Ophthalmology Service, Walter Reed Army Medical Center, Washington, DC

Abstract

Objective—Safety and efficacy of daclizumab during an 11-year period.

Design—Structured, retrospective chart review.

Participants—Thirty-nine patients.

Methods—Patients with chronic, noninfectious intermediate and/or posterior uveitis.

Results—Thirty-nine patients (78 eyes) were treated for a mean of 40.3 months. Visual acuity improved by ≥ 2 lines in the better eye in 7 patients (18.4%) and worsened by 2 lines in 6 patients (15.8%) with a mean of 2.8 Snellen lines of vision lost per eye. Six eyes with vitreous cell less than grade 2 lost 2 lines of vision and 7 eyes with less than grade 2 vitreous cell improved 2 lines. Mean number of immunosuppressive medications per patient decreased from 1.89 medications/patient to 1.17 medications/patient. The average number of periocular injections per patient was 1.46 (range, 0–9). The mean number of flares was 2.05/patient (range, 0–12), with the rate being 0.62 flares per patient-year. Four patients developed cancer during the course of this study. Mean time to onset of malignancy was 26 months and the mean age in this group was 49 years.

Conclusions—Daclizumab demonstrated efficacy in the reduction of concomitant immunosuppressive medication, stabilization of visual acuity, and the prevention of uveitic flares in most cases. Dermatologic complications were the most frequently observed adverse event in our series. Four patients developed solid tumor malignancies during this 11-year period.

The decision to use corticosteroids, anti-metabolites, signal transduction agents, alkylating agents, corticosteroid intraocular implants, biologic agents, or combinations of these agents in the treatment of uveitis is based on the stage of the disease process, potency of the agents, rapidity of action, the relative contraindications that are often dependent on the systemic health of the patient, the age of the patient, the risks of malignancy, costs of the agents, and the potential for visual rehabilitation. There is, however, a relative lack of evidence from randomized controlled clinical trials on the use of these treatments in noninfectious uveitis. Recent efforts by Galor et al.¹ have helped to increase the available information on the treatment of noninfectious uveitis by conducting a retrospective study that compared 3 antimetabolite drugs at 1 academic center with an emphasis on dosage, use of other drugs,

Correspondence to Col. Keith J. Wroblewski, MD, Chief, Ophthalmology Service, Walter Reed Army Medical Center, Washington, DC 20307; keith.wroblewski@amedd.army.mil.

This study was presented at the 7th International Symposium on Uveitis, International Uveitis Study Group, Lake Constance, Germany, September 2008.

Disclosure: The authors have no proprietary or commercial interest in any materials discussed in this article.

response to therapy, and side effects of the drugs used. There is also little data on the long-term risk of malignancy when these agents are used to treat uveitis. Kempen et al.² recently reported the long-term risk of malignancy associated with the use of immunosuppressive medications used commonly in ocular inflammatory diseases; further efforts will elucidate the risks posed by these medications, but information on the safety of the newer biologic agents remains limited.

Many biologic agents are used for the treatment of autoimmune disease but 3 major biologic agents have been widely used to treat uveitis: infliximab (Remicade, Centocor, Horsham, Penn.), daclizumab (Zenepax, Hoffman-La Roche, Nutley, N.J.) and adalimumab (Humira, Abbott, North Chicago, Ill.).^{3,4} There are also early reports within the literature on the use of rituximab in the treatment of Wegener's granulomatosis and primary intraocular lymphoma.^{5,6} Cytokines such as tumor necrosis factor α (TNF α) and interleukin-2 (IL-2) are important factors in the development of intraocular inflammation and the use of biologic agents to inhibit these factors may be considered when standard therapies are insufficient or intolerable to patients.⁷ The risk of malignancy with biologic agents has been described in the etanercept trial.⁸ It is also important to note that there have been concerns raised about autoimmune diseases induced by biologic agents as well as the risks of disseminated tuberculosis, histoplasmosis, fungal infections, and the risk of TNF α inhibitors in patients with congestive heart failure and demyelinating diseases.⁹

In this study, we focus on one biologic agent, daclizumab, which is a humanized monoclonal antibody that binds to the CD25 portion of the IL-2 receptor on activated T-cells at 1 academic center. Waldman¹⁰ first reported the development of this monoclonal antibody in 1981 and recently reported his 25-year experience with this agent at the National Institutes of Health in the treatment of a variety of conditions including renal allograft rejection, multiple sclerosis, and human T-cell lymphotropic virus I (HTLV-1)-associated disease.

The goals of this study were to elicit long-term trends in safety and efficacy in patients with noninfectious ocular inflammatory disease and to provide the basis for a randomized, multicenter trial to study the efficacy of this agent.

Methods

All patients with chronic, noninfectious intermediate and/or posterior uveitis treated with Daclizumab at the National Eye Institute between January 1997 and November 2008 were included. Daclizumab was administered intravenously (IV), subcutaneously (SC), or in high-dose fashion. These studies were approved by the Institutional Review Board of the National Eye Institute and conformed to the tenets of the Declaration of Helsinki. Written informed consent was obtained from all patients.

All patients underwent a thorough history, physical examination, and laboratory studies to rule out uveitis cases due to infectious etiologies. PPD skin tests, syphilis testing, and pregnancy tests were required to be negative before initiation of therapy. CBC with differential, full chemistry panel, and urinalysis were carried out at baseline and before each administration of daclizumab. Information on age, gender, ethnicity, type of uveitis, past and current immunosuppressive treatments, and adverse events were collected at baseline and at each visit.

The ocular examination carried out at each visit included an assessment of best-corrected visual acuity, anterior chamber (AC) cells and flare, vitreous cells and haze, and a dilated fundus examination. The measures in this retrospective review conformed to the Standardization of Uveitis Nomenclature Working Group classification although this was not established until 2005.¹¹

Primary outcome measures for this retrospective review included the number of adverse events, visual acuity at baseline and final examination (converted to logarithm of the minimum angle of resolution [logMar] units for analysis), degree of ocular inflammation at baseline and final examination, and ability to taper concomitant medications (assessed by an immunosuppressive medication grading scheme used at National Eye Institute).¹² The relation of demographic features to diagnosis type, treatments, and complications, including morbidity and mortality, were examined using descriptive statistics. In addition, we computed the number of flares and the number of periocular injections per patient year.

Patients were on standard immunosuppressive therapy and received the following regimens that are found in Table 1 in abbreviated form.

Intravenous regimen

All enrolled patients received an IV dose of daclizumab (1 mg/kg) every 2 weeks for 1 month followed by monthly 1 mg/kg dosages. Intervals between infusions were initially 2 weeks and were increased in a stepwise fashion until week 24, when patients were scheduled to receive infusions every 4 weeks for a period of 12 months.

Subcutaneous regimen

Patients received an induction dose of 2 mg/kg IV (limit 200 mg) every 2 weeks for 1 month followed by maintenance therapy of 1 mg/kg (limit 100 mg) SC monthly. With the first SC dose, the initial immunosuppressive medication load was tapered in a staggered fashion to a target of $\leq 50\%$ of the original load within an 8–12 week period. After the initial 12 weeks, further tapering of the immunosuppressive medication was continued along with the monthly SC daclizumab. The SC regimen continued for an additional 22 weeks.

High dose regimen

All enrolled patients received an initial induction regimen of 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 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.

Results

Five patients received the high dose regimen, 5 patients received the SC regimen, and the other 29 patients received the IV regimen. The demographic data are shown in Table 2. Thirty-nine patients (78 eyes) were treated with daclizumab for a mean of 40.3 months (range, 3–136 months) with the 5 SC patients receiving daclizumab for a mean of 41 months, and the high dose patients receiving the agent for a mean of 34 months. The ages of the patients ranged from 13 to 70 years (mean, 38.8 years); 16 (41%) were male and 23 (59%) were female.

Diagnoses included Behçet's disease-associated panuveitis (8 patients), idiopathic intermediate uveitis (6 patients), sarcoidosis-associated panuveitis (6 patients), birdshot retinochoroidopathy (5 patients), Vogt-Koyanagi-Harada (VKH) disease (5 patients), and other ocular inflammatory diseases (9 patients).

Efficacy outcomes

Baseline vitreous cellularity was less than grade 2 in 37 patients (94.9%) in the better eye, baseline vitreous haze was less than grade 2 in 38 patients (97.4%) and baseline anterior chamber cellularity was less than grade 2 in 39 patients (100%). In regard to the better eye, the visual acuity improved by ≥ 2 lines in 7 patients (18.4%) and worsened by 2 lines in 6 patients (15.8%) with a mean of 2.8 Snellen lines of vision lost per eye. Using visual acuity worsened by 2 lines, 6 eyes with vitreous cell less than grade 2 lost 2 lines of vision and 7 eyes with less than grade 2 vitreous cell improved 2 lines. Using Fisher's exact test the p -value was 0.66 but the numbers were very small and not very useful to make a comparison. There were no patients worse than vitreous cell grade 2+ that worsened by 2 lines or improved by 2 lines. The results were the same as vitreous cell for vitreous haze with a p -value of 0.82 but again the numbers were too small for a definitive conclusion. Anterior chamber cellularity was similar to both vitreous cell and vitreous haze and no statistical comparison could be made.

Vision loss

The temporal relation of vision loss was then analyzed. In those patients in which the better eye worsened by 2 lines, 3 occurred during the first 9 months and 3 occurred after 39 months of treatment (these occurred in 3 idiopathic patients, 1 VKH patient, 1 Behçet's patient and 1 patient with intermediate uveitis). Seven patients gained >2 lines in the better eye and these occurred with the following distribution: 1 at <9 months, 3 at 24 months $\pm$ 3 months, 2 at 36 $\pm$ 3 months and 1 at >39 months. These were distributed as follows: 1 patient with birdshot chorioretinopathy, 1 patient with idiopathic uveitis, 2 patients with intermediate uveitis, and 2 patients with sarcoidosis.

Vision loss >2 lines was attributed to the following causes: refractory intraocular inflammation ($n = 2$), cystoid macular edema, epiretinal membrane formation, glaucoma, and continued corneal decompensation.

Immunomodulatory therapy

The mean number of immunosuppressive medications per patient decreased from 1.89 medications/patient to 1.17 medications/patient during this treatment period.⁶ The range of immunomodulatory therapy (IMT) medications is listed in Table 3 per diagnosis group that is listed as a composite group.

Flare rates

In this area, we estimated any increase in therapy in response to a flare and this included periocular injection, oral corticosteroids or other increase in IMT. The average number of periocular injections per patient in both groups during the study period was 1.46/patient (range, 0–9). The mean number of flares was 2.05 flares/patient (range, 0–12), with the rate being 0.62 flares/patient-year. Flare rates for each uveitis etiology are shown in Table 2. The Behçet's patients had the highest flare rate of 16.6/patientyear over the mean treatment of 21 months, and their IMT reduced from an initial value of 22 medications per treatment group to only 17 medications.

Cystoid macular edema

Nineteen patients had CME at baseline and the mean central macular thickness decreased from a mean of 259 to 235 μm after daclizumab therapy. Fluorescein angiography showed either a 32.5% lessening or no change (61.76%) in the amount of perifoveal leakage compared to baseline.¹³

Extraocular outcomes

Four patients developed cancer during the course of this study (Table 4) that is an important finding of this long-term retrospective analysis. Mean time to onset of malignancy was 26 months and the mean age in this group was 49 years.

A previously described case concerned a 45-year-old female patient who developed renal cell carcinoma with subsequent nephrectomy. She has been followed now for a total of 136 months without recurrence.

Another patient, a 58-year-old male, developed a cutaneous squamous cell carcinoma that was excised and has been followed now for 72 months with no recurrence. He continued Daclizumab monotherapy after the biopsy and then enrolled in a combination Daclizumab-Sirolimus protocol.

A third patient, a 40-year-old male with birdshot chorioretinopathy and a history of treatment with prednisone and CellCept, received 3 doses of IV daclizumab, after which he complained of increasing dyspepsia. Endoscopy revealed a high grade esophageal carcinoma that resulted in death approximately 6 months after diagnosis.

The fourth patient, a 45-year-old female with multiple sclerosis-associated intermediate uveitis, was treated with daclizumab for 49 months and combination daclizumab-sirolimus for 12 months. This patient had a long history of treatment with prednisone and CellCept. She subsequently developed a vulvar carcinoma and had a partial vulvectomy. She has been in remission now for 10 months and is now only on CellCept and prednisone.

Adverse effects

Cutaneous reactions were the most commonly observed adverse event with daclizumab therapy and included drug eruption, eczema, fibrosis, psoriasis, and folliculitis as reported by Faia et al.¹⁴ Three of these patients had preexisting skin conditions. It should be noted that subsequent infusions were well tolerated in these patients.

Other side effects possibly attributable to daclizumab included elevated liver function tests, lower extremity edema, herpes zoster skin infection, upper extremity neuralgia, lymphadenopathy, isolated chest pain with normal EKG, upper respiratory infections, gastrointestinal infection, and cramping.

One patient complained of extreme lethargy and shortness of breath after the compassionate administration of a high-dose regimen of 4 mg/kg.

Discontinuation

A total of 18 patients discontinued treatment as required by the clinical research protocol meaning that at the end of the protocol they stopped the medication.

Five patients who were able to maintain daclizumab therapy after protocol cessation were able to stop daclizumab after maintaining quiescence of their ocular disease for nearly a year with daclizumab as the sole immunosuppressive agent.

Another seven patients discontinued daclizumab during their protocol or compassionate use for various reasons and these are illuminated as follows. One patient stopped due to worsening sarcoidosis-associated arthropathy and started Infliximab. Two patients died, 1 secondary to esophageal cancer after 3 doses of daclizumab and another secondary to an unrelated accident. Another patient stopped after developing vulvar carcinoma as previously described. One patient became pregnant and stopped the medication and delivered a healthy

newborn. One patient stopped daclizumab after developing anemia associated with uterine fibroids and another patient was lost to follow-up. One patient with Behçet's disease developed cerebellar herniation 1 month after abrupt cessation of daclizumab after termination of the protocol but he resumed daclizumab shortly thereafter. Nine patients currently continue daclizumab therapy for ocular inflammatory disease.

Discussion

This remains as the largest series reported on the use of daclizumab for noninfectious ocular inflammation using a variety of treatment regimens. There have been several pilot studies using daclizumab that at the outset had the goal of taking stable, inactive patients on standard immunosuppressive therapy and then attempting to wean all immunosuppressive agents while initiating monthly daclizumab. These initial studies were later supplanted by taking active patients and treating with high dose daclizumab and then finally using combinations of daclizumab and sirolimus in an attempt to induce immune tolerance.¹⁵ These will be summarized now and are also found in Table 1. In a report by Nussenblatt et al.,¹⁶ a pilot study was initiated to determine the safety and efficacy of intravenous daclizumab in patients with sight-threatening, noninfectious intermediate and posterior uveitis.

This pilot study showed a very favorable side effect profile in patients with intermediate, posterior, or panuveitis and few adverse events. In this year-long study, in 8 of 10 patients, daclizumab appeared to prevent the expression of sight threatening intraocular inflammation and 1 patient met the primary endpoint with a loss of 10 letters from baseline and another discontinued due to increasing intraocular inflammation.¹⁶

This IV study was followed by another study of patients in 2003 with 2 arms, an IV arm and a SC arm. This study showed the feasibility of long-term therapy, the finding of lymphadenopathy in 2 patients, and the evidence that every 4-week infusions was probably better than every 6-week infusions due to reoccurrences.¹⁷

The next method of use was SC daclizumab that was reported to be efficacious in a 6-month 3-center study.¹⁸ The results showed that 10 of 15 patients were able to reduce their immunosuppressive load by 50% while maintaining baseline visual acuity levels at 12 and 26 weeks. The dosage appeared to be well-tolerated although 3 patients had non-serious adverse events.

Another 6-month, double-masked, randomized study with the goal of investigating the safety and efficacy of daclizumab in a series of Behçet's patients treated with IV placebo or IV daclizumab suggested that there was no beneficial effect of IV daclizumab versus IV placebo.¹⁹

This particular study showed that the ocular attack rate was actually significantly higher in the daclizumab arm than the placebo arm (1.27 vs. 0.17 attacks/year), and the placebo arm was better able to taper off their immunosuppressive regimen as compared to the daclizumab arm.

The protocols then shifted somewhat toward treating patients with active uveitis with what was considered as a high dose regimen. Yeh et al.²⁰ investigated the use of high-dose daclizumab in a pilot study for the treatment of active disease in 5 patients and found that AC cell decreased in 8 of 9 eyes (88%), vitreous cells decreased in 6 of 10 eyes (60%), and vitreous haze decreased in 8 of 8 eyes.

In this study, the first demonstration that a higher dosage of daclizumab could actually reduce active intraocular inflammation is presented, but this was only a small pilot study with a limited number of patients with noninfectious posterior uveitis. One patient developed a left-lower lobe pneumonia during the study.

Another study at another institution investigated the use of daclizumab in the treatment of 8 patients with birdshot chorioretinopathy and found that over the mean treatment period of 6 months, 7 patients had stabilization or improvement of vision and 6 of 8 patients had improvement in retinal vasculitis.²¹ However, 2 patients experienced adverse events and discontinued the medication and it was noted that ERG 30 Hz implicit times and bright scotopic amplitudes worsened in these patients.

Another study from the same institution by Bhat et al.²² analyzed 17 patients with what was deemed recalcitrant ocular inflammatory disease. These patients received IV daclizumab (1 mg/kg) every 2 weeks for a mean duration of 23.6 months and they reported after a mean of 9.8 ± 11.3 weeks that 15 of 17 patients (88%) were able to control their intraocular inflammation but that side effects included nausea, fatigue, and muscle aches.

These small, initial pilot and case studies reported previously, and the studies by Foster have hinted that daclizumab may be an effective agent in the treatment of noninfectious uveitis, although it may be less effective in the treatment of uveitis associated with Behçet's disease.^{12,13,16,17,20,21}

Simply describing visual changes or inflammation changes from baseline to a final study visit does not capture the entire clinic experience of these patients during an 11-year period. We believe our work here provides useful information on the safety and efficacy of daclizumab in the adult population. The study suffers from the lack of a randomized control group with standard IMT as compared to treatment with this biologic agent. Only the Behçet's group had a placebo arm. It also suffers from selection bias in an academic medical center, but the deficiencies are outweighed by the number of patients, the length of the study, and the wealth of information collected during this time period.

The side effect profile seems acceptable in the context of side-effects associated with more conventional immunosuppressives but the malignancy rate merits further review. Increased duration of immunosuppression has been associated with significantly increased risk of squamous cell cancers of the skin in reports from both transplant and rheumatology patients, although several studies have found no association.²³ In particular, an increased risk of lymphoproliferative disorders and malignancies has been reported in transplant patients on immunosuppression; however, most reports indicate no clear association with immunosuppression use and solid tumors.²⁴ However, the rate observed in this study is not a lifetime estimate of cancer risk and thus is likely to underestimate the total lifetime risk of malignancy. Also, many of the patients who developed malignancy were on other immunosuppressive therapy in addition to daclizumab and that deserves due consideration in this cohort of patients. In our patients, we did not encounter any lymphoproliferative malignancy. The malignancies we did observe were all solid tumors or squamous cell carcinomas of the skin. It is a continuous battle to balance the side-effect profile of the immunosuppressive medications required to treat the eye disease against the burden created by the disease or vision loss caused by treatment. This longitudinal study suggests further review of malignancies associated with biologic therapy.

It is important to caution against the abrupt termination of this medication, as illustrated by a patient with Behçet's disease who developed cerebellar herniation 1 month after cessation of daclizumab. Based on this patient, we now slowly extend daclizumab therapy to 6 weeks and then 8 weeks before considering cessation of the drug.

This is the first study to show the development of cancer in patients treated long-term with daclizumab for intraocular inflammation. In this study, 4 patients developed cancer. However, if we exclude the skin carcinoma and esophageal cancer that developed after only 3 doses, we observed 2 cancers in 2 female patients treated with 51 and 50 doses of IV daclizumab before the development of cancer. Obviously, one cannot eliminate the confounding effects of treatment with cyclosporine, sirolimus, and CellCept. Further data on the use of biologics will have to be pooled to see if there is a long-term higher risk of malignancy as has been observed to occur with alkylating agents, and certainly the use of this agent long-term should be reviewed in the context of a well-designed randomized clinical trial.

The highest long-term flare rates were observed in the Behçet's patients (16.5/patient year), followed by the VKH patients, but as described previously, this may be more of a function of the protocol design and the disease process that forcibly attempted to quickly wean patients off their initial immunosuppressive regimen and not the medication in isolation.

Despite longer overall follow-up rates, the patients with birdshot chorioretinopathy and sarcoidosis had very low flare rates during the treatment period and this may reflect the disease process. It is not the purpose of this review to compare standard IMT versus daclizumab therapy because many of these patients continued their IMT while on daclizumab.

Typically, we commence patients on monthly IV (1 mg/kg or 2 mg/kg) doses in 4-week intervals, but Yeh et al.²⁰ has shown that the high-dose regimen may be effective, especially when started during the active disease phase. However, 1 other patient within our series did not tolerate daclizumab at 4 mg/kg dosage and described lethargy, fatigue, and shortness of breath. Certainly, further studies with larger number of patients are needed to provide clear evidence of which dosage regimen and interval are best for patients with active disease.

There seemed to be no need for dose escalation as is seen with other biologic agents such as infliximab. Our previous work with standard IV therapy and not the high dose regimen has shown that daclizumab was able to saturate all of the available receptors assessed in a lymph node biopsy. Furthermore, there is little evidence to suggest that patients develop auto-antibodies to this medication.²⁵

Finally, a small pilot study with high dose daclizumab for the treatment of juvenile idiopathic arthritis-associated active anterior uveitis has been shown by Sen et al.²⁶ to reduce active anterior uveitis. In this study, 4 of 6 patients showed a decrease in AC inflammation within 12 weeks in the absence of any increase in concomitant immunosuppressives or topical steroids but 2 of 6 patients required re-induction at 12 weeks. One of those patients failed to respond to the re-induction and 1 of 2 re-induction patients had previous history of uncontrolled inflammation while on infliximab. One patient developed a herpes zoster infection and another a skin rash that supported the previous work of Faia et al.¹⁴ Further studies in children will need to establish the safety as well as the efficacy.²⁶

Finally, Imrie and Dick²⁷ have established recently that despite the experimental rationale for the use of these agents there is lack of evidence from randomized controlled studies that establish when to commence therapy, which agent to choose, and how long to continue treatment. In summary, in this large long-term review of this agent, daclizumab demonstrated efficacy in the reduction of concomitant immunosuppressive medication in our series of patients, as well as stabilization of visual acuity and the prevention of uveitic flares in most cases. Visual acuity remained stable in most patients. Dermatologic complications were the most frequently observed adverse event in our series and 4 patients

developed solid tumors during therapy. Further multicenter trials are needed to determine the optimal dosing strategy and efficacy and data should be collated to see if there is a higher rate of malignancy as compared to standard immunosuppressive therapy.

Acknowledgments

Support: Dr. Yeh received a Heed Ophthalmic Fellowship Grant for research.

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Table 1

Previous daclizumab studies

Study	Reference	Pts/Duration	Goals	Results	Comments
Phase I/II Trial IV	16	10/12 months	Wean IMT, daclizumab 1 mg/kg monthly	8/10 Pts successfully tapered off IMT	1 Pt 10 letter loss 1 Pt worse inflammation
Phase I/II single arm IV/SC	17	10/48 months	Wean IMT, daclizumab 1 mg/kg monthly	7/10 Pts successfully tapered off IMT	Every 4 weeks dosing best
Multicenter nonrandomized open label SC	18	15/6 months	SC daclizumab 2 mg/kg $\times$ 2 for 2 weeks, then 1 mg/kg monthly	10/15 Pts tapered off IMT by 50% while maintaining baseline VA	No serious adverse events Lymphadenopathy in 2 patients
Double masked randomized Behçet's patients	12	Daclizumab: 7/mean follow-up 15 months Placebo: 8/mean follow-up 15 months	Daclizumab 1 mg/kg IV $\times$ 3 every 2 weeks then monthly versus placebo Wean IMT over 6 months as indicated	Stable vision in both arms Median ocular attack rate higher in daclizumab arm (1.27 vs. 0.17)	No suggestion that daclizumab was beneficial compared to placebo Low observed attack rate
Pilot high dose	20	5/52 weeks	Daclizumab 8 mg/kg IV at Day 0, 4 mg/kg IV Day 14, then 2 mg/kg SC every 2 weeks for 52 weeks	Mean ETDERS letters 69.2 at enrollment versus 78.2 Inflammation improved	Left lower lobe pneumonia in 1 Pt
Pilot pediatric JIA	18	6/52 weeks	Same as high dose except monthly dosing was IV	4/6 Pts 2-step reduction in AC cellularity Mean ETDERS baseline (68 vs. 79.6)	Three failed due to rash treatment failure and uncontrolled systemic manifestations of JIA

Note: AC, anterior chamber; ETDERS, Early Treatment of Diabetic Retinopathy Study; IMT, immunomodulatory therapy; IV, intravenous; JIA, juvenile idiopathic arthritis; Pt, patient; SC, subcutaneous.

Table 2

Demographic data

Demographic Data	Duration of Daclizumab Treatment
39 patients (16 male, 23 female)	<9 months = 8 patients
Mean age 38.8 years (13–70)	12 ± 3 months = 2 patients
Behçet's (n = 8)	24 ± 3 months = 6 patients
Intermediate (n = 6)	30 ± 3 months = 2 patients
Sarcoidosis (n = 6)	36 ± 3 months = 2 patients
Birdshot (n = 5)	>39 months = 8 patients
VKH (n = 5)	
Idiopathic (n = 9)	

Note: VKH, Vogt-Koyanagi-Harada.

Table 3

Treatment flare rates

Diagnosis	Mean Follow-up (months)	Flares	Flare Rate Per Patient Year	Range	Pre-IMT (per group)	Post-IMT (per group)
Sarcoidosis (n = 6)	72.3 (7–122)	5	0.82	0–3	9	2
Birdshot (n = 5)	46.8 (3–121)	3	0.76	0–3	3	3
Behçet's (n = 8)	21.0 (5–65)	29	16.5	0–12	22	17
Intermediate (n = 6)	35.5 (19–68)	15	5.14	0–5	13	8
VKH (n = 5)	20.6 (3–28)	13	7.57	0–6	9	5
All patients (n = 39)	40.3 (3–136)	81	0.62	0–12	56	35

Note: IMT, immunomodulatory therapy; VKH, Vogt-Koyanagi-Harada.

Table 4

Malignancies

Malignancies	Medications at Commencement	Cancer	Therapy	Dosages/Months	Sequelae
54-year-old female: idiopathic	Cyclosporine/prednisone	Renal cell carcinoma	Nephrectomy	51 IV/restarted 9 months later	None for 86 months of treatment
58-year-old male: retinal vasculitis	Cyclosporine/prednisone	Skin squamous cell	Excision	2 IV/continued 46 months	None for 47 months of follow-up
40-year-old male: birdshot	CellCept/prednisone	Esophageal cancer	Excision/chemo/radiation	3 IV/discontinued	Death 6 months after diagnosis
45-year-old female: intermediate	CellCept/prednisone/sirolimus	Vulvar carcinoma	Excision	50 IV/discontinue	None, 3 months follow-up

Note: IV, intravenous.