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Clinical Trials

Safety and Tolerability of Intravitreal Carotuximab (DE-122) in Patients With Persistent Exudative Age-Related Macular Degeneration: A Phase I Study

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Purpose: Carotuximab (DE-122) is a novel endoglin antibody that exhibits potent anti-angiogenic activity. The aim of this study was to evaluate the safety and tolerability of a single intravitreal injection of four ascending doses of carotuximab in patients with persistent exudative age-related macular degeneration (AMD).

Methods: In an open-label, dose-escalating, sequential cohort study, patients with persistent exudative AMD were assigned to an intravitreal injection of carotuximab 0.5 mg, 1.0 mg, 2.0 mg, or 4.0 mg ($n = 3$ per group). Safety and change in central subfield thickness (CST), as measured by spectral domain–optical coherence tomography, were assessed from baseline until day 90. Rescue therapy with an anti-vascular endothelial growth factor medication was allowed on days 8, 30, and 60.

Results: Seven patients (58%) experienced at least one adverse event (AE), including five patients (41.7%) who experienced one or more AEs in the study eye and two patients (16.7%) who experienced one or more non-ocular AEs. Posterior eye deposits were reported in one patient 2 days after receiving 1.0 mg, but they resolved spontaneously by day 43. A >50-µm reduction in CST on two consecutive visits was observed in four patients (33%), including one patient in each dose cohort.

Conclusions: In this study, carotuximab was generally well tolerated, with no serious AEs reported, when administered as a single intravitreal injection to patients with persistent exudative AMD.

Translational Relevance: Further characterization of the safety and efficacy of carotuximab will be needed to determine what role it may have in the treatment of exudative AMD.

Introduction

As a progressive chronic disease, age-related macular degeneration (AMD) is the leading cause of irreversible vision impairment and affects an estimated 8.7% of adults worldwide between the ages of 45 and 85 years.[1,2] Experimental and clinical evidence has demonstrated that vascular endothelial growth factor (VEGF) plays a vital role in the formation of choroidal neovascularization. The hallmark clinical finding is the presence of extracellular matrix deposits known as drusen in the subretinal space.[3] In exudative AMD, local injury to retinal pigment epithelial cells

stimulates secretion of pro-angiogenic mediators such as VEGF, which leads to aberrant neovascularization in the macula, as well as increased vascular permeability, causing hemorrhage and accumulation of subretinal fluid.[3–7] The accumulated fluid can lead to retinal detachment and the formation of scar tissue, resulting in permanent impairment of central vision.[5]

Intravitreal injection of anti-VEGF agents has been recommended as a first-line treatment for neovascular AMD and effectively stabilizes vision loss in more than 90% of patients with exudative AMD. However, only one-third of patients experience improvement in vision.[7–9] Despite standardized anti-VEGF therapy, recent evidence suggests that persistent fluid or recurrent exudation still occurs in approximately 30% of patients after 12 months of treatment.[9] Additionally, analysis of long-term data from a large randomized trial evaluating anti-VEGF therapy in patients with AMD showed that retinal fluid was present in 73% and 83% of patients after 2 and 5 years, respectively.[10,11] Until now, there has been no consensus on the definitions of refractory neovascular AMD and recurrent neovascular AMD.[2] However, these findings, coupled with evidence that VEGF inhibition activates alternative angiogenic pathways facilitating therapeutic resistance,[12–14] suggest that inhibition of the VEGF pathway alone does not completely attenuate angiogenesis in patients with exudative AMD. Therefore, there is an unmet medical need for novel therapies, such as combination therapy and multitarget treatment that can overcome this resistance to anti-VEGF therapy.

Endoglin is a pro-angiogenic transmembrane glycoprotein expressed on proliferating vascular endothelial cells that modulates signal transduction via multiple receptors of the transforming growth factor (TGF)-β superfamily, including TGF- β, bone morphogenic protein, activin, and activin-like receptor kinases.[15] Endoglin expression is markedly upregulated on choroidal vascular endothelial cells in patients with exudative AMD[16] and on tumor endothelial cells following treatment with anti-VEGF agents.[17,18] Activation of endoglin induces signaling via the SMAD 1/5/8 pathway to promote endothelial cell proliferation and migration.[19,20] Additionally, endoglin promotes VEGF signaling by forming a complex with VEGF receptor 2 (VEGFR2) on the cell surface, thereby preventing its degradation in lysosomes and potentially mediating escape from VEGF inhibition.[21] Both genetic depletion of endoglin from endothelial cells and pharmacological inhibition of endoglin attenuate VEGF-induced angiogenesis.[22] Combined targeting of endoglin and VEGF pathways has been shown to induce anti-angiogenic effects in both in vitro and animal models.[23]

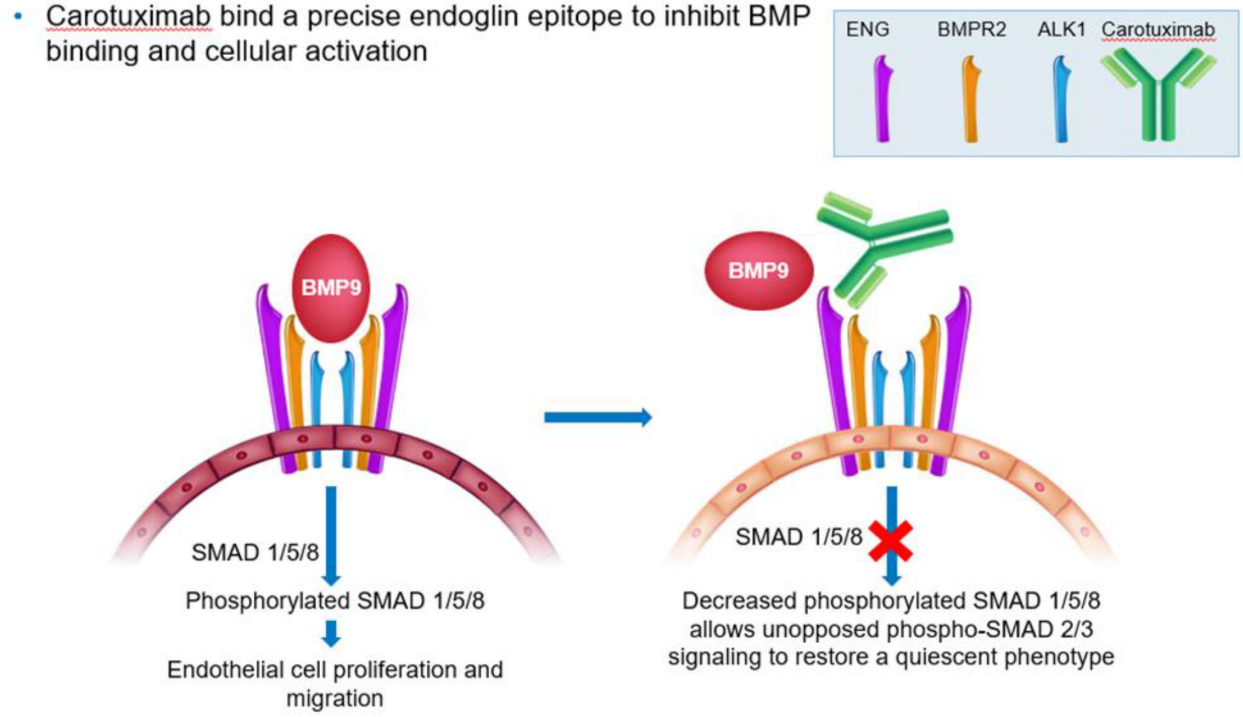


Figure 1. Anti-angiogenic mechanism of action of carotuximab. ALK, activin-like receptor kinase; BMP(R), bone morphogenic protein (receptor); ENG, endoglin. Figure adapted from Nolan-Stevaux O, et al. *PLoS One*. 2012;7(12):e50920.

Carotuximab (DE-122, also known as TRC105)[24] is a novel chimeric antibody against human endoglin that exhibits potent anti-angiogenic activity (Fig. 1). Carotuximab inhibits VEGF-induced and basic fibroblast growth factor–induced endothelial cell proliferation and potentiates the effects of anti-VEGF agents via inhibition of VEGF-induced signaling and promotion of VEGFR2 degradation.[19,21] In clinical studies in patients with various solid tumors refractory to anti-VEGF therapy, carotuximab was safe and well tolerated, showing evidence of durable clinical activity when administered either as monotherapy or in combination with anti-VEGF or chemotherapeutic agents.[24–26] In a multicenter phase I study in patients with histologically proven advanced or metastatic solid tumors refractory to available therapy, 21 of 45 evaluable patients (47%) achieved stable disease or better at 2 months following treatment with carotuximab.[25] A subsequent phase Ib open-label study evaluating combination therapy with carotuximab and bevacizumab in patients with histologically proven advanced solid tumors showed evidence of disease control in 15 of 30 patients (50%) who experienced disease progression during prior treatment with bevacizumab or other anti-VEGF agents.[26]

An ophthalmic formulation of carotuximab injectable solution for intravitreal administration has been developed for evaluation as a potential therapy for patients with exudative AMD, representing the first agent in this class to be designed for use in ophthalmology. The aim of the current study was to evaluate the safety and tolerability of a single intravitreal injection of four ascending dose levels of carotuximab in patients with persistent exudative AMD.

Methods

Study Design

The Potentiating the Activity of anti-VEGF with anti-Endoglin (PAVE) study was an open-label, dose-escalating, sequential cohort study evaluating the safety and tolerability of a single intravitreal injection of carotuximab in patients with persistent exudative AMD (ClinicalTrials.gov, NCT02555306). A summary of the study design is depicted in Figure 2. Patients were sequentially assigned to one of four dose cohorts (three patients per cohort): low (0.5 mg), medium low (1.0 mg), medium high (2.0 mg), and high (4.0 mg). For each patient, the study included a screening period of up to 7 days and a 90-day observation period. In each dose cohort, the first patient received a single dose of study drug administered via intravitreal injection in the study eye on day 1. After completion of the scheduled study visit on day 8, the safety review committee evaluated safety data to determine if safety and tolerability were acceptable (Table 1). If the criterion for study termination was not met, the remaining subjects in the cohort were treated with the same dose of study drug. After all three patients in a dose cohort completed the day 30 study visit, the safety review committee performed another review of safety data. If neither the criterion for dose adjustment nor the criterion for study termination was met, the

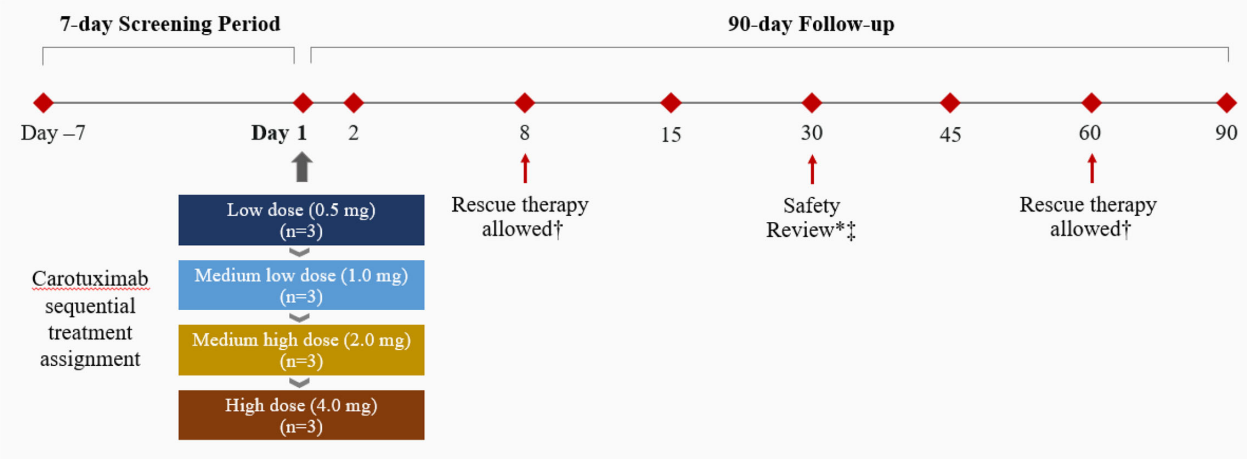


Figure 2. Study diagram. CST, central subfield thickness; ETDRS, Early Treatment Diabetic Retinopathy Study; BCVA, best-corrected visual acuity; SD-OCT, spectral domain–optical coherence tomography.

Table 1. Safety Criteria for Dose Adjustment and Study Termination

Decision	Criteria
Planned dose adjusted or stopped *>1 of the following dose-limiting toxicities observed in any one cohort:*	Visual acuity loss • BCVA loss of ≥30 letters not due to vitreous hemorrhage or injection procedure, ***or*** • Transition to no light perception not due to injection procedure Clinically significant inflammation • >3+ vitreous haze as measured by the National Eye Institute grading scheme,[27] ***or*** • Sterile endophthalmitis (including the presence of hypopyon) Severe IOP elevation despite medical therapy[a] • >35 mm Hg, ***or*** • Increase from baseline of >15 mm Hg
Additional patients treated with same or lower dose of study drug	• Retinal non-perfusion of the study eye/vascular occlusion
Any of the following adverse events occurring in any patient in any cohort:	• Vasculitis • Retinitis • >2+ disc edema • >2 quadrants of retinal hemorrhage
Study termination	Pattern of systemic adverse events ***or*** any of the following adverse events in two patients in any cohort:[b] • Retinal non-perfusion of the study eye/vascular occlusion • Vasculitis • Retinitis • >2+ disc edema • >2 quadrants of retinal hemorrhage

[a]Measured by tonometry on two separate exams separated by at least 1 day, excluding the day of injection.
[b]Excluding events assessed as unrelated to the study drug and events related to study drug administration procedures.

first patient in the next cohort was treated with the next dose level of study drug. The same safety review and dose-escalation procedures were followed for each cohort.

Rescue therapy was permitted on day 8 or 60 if either of the following criteria was met: (1) <5 letter increase from baseline in best-corrected visual acuity (BCVA); or (2) <50-µm reduction from baseline in central subfield thickness (CST), as measured by spectral domain–optical coherence tomography (SD-OCT). If rescue therapy was not required on day 8, it was administered on day 30 regardless of the change in BCVA and CST to avoid a prolonged period without treatment. Rescue therapy consisted of the last intravitreal anti-VEGF agent used by the patient prior to study enrollment.

Study drug doses were selected based on evidence from preclinical studies (unpublished data). The range of doses selected for evaluation represents 5% to 40% of the dose determined to be safe in a single-dose toxicity study in cynomolgus monkeys. The lowest dose corresponds to the lowest effective dose in a murine model of laser-induced choroidal neovascularization (0.5 µg), adjusted according to the difference in vitreous volume between humans and mice (approximate ratio, 1000:1).

Study Population

Eligible patients were adult (age, ≥50 years) males and females with a diagnosis of exudative AMD, CST

≥ 300 µm, and persistent subretinal or intraretinal fluid despite continuous anti-VEGF therapy, including at least three intravitreal injections during the preceding 6 months or six intravitreal injections during the previous 12 months, and at least one injection between 30 and 60 days prior to the first study visit. Additional enrollment criteria included a total lesion size of ≤12 disc areas containing ≤50% hemorrhage, ≤50% fibrosis, and ≤50% retinal pigment epithelial atrophy in the study eye; BCVA at baseline between 65 and 20 Early Treatment Diabetic Retinopathy Study (ETDRS) letters, which is equivalent to Snellen fractions from 20/50 to 20/400 in the study eye; and equal or better BCVA in the fellow eye.

Patients were excluded from enrollment if they met any of the following criteria: treatment with intravitreal or periocular corticosteroids, photodynamic therapy, or intraocular surgery within 90 days prior to the first study visit or an intravitreal corticosteroid implant within 12 months prior to the first study visit; uncontrolled or advanced glaucoma in the study eye (intraocular pressure [IOP] > 21 mm Hg or cup/disc ratio > 0.8 while on medical therapy or chronic hypotony [<6 mm Hg]); active ocular or periocular infection in either eye; any ocular malignancy in either eye; and prior treatment with carotuximab, systemic anti-VEGF therapy, or any agent targeting the endoglin pathway (additional medical and laboratory exclusion criteria are summarized in Supplementary Table S1).

Study Drug Administration

Carotuximab was supplied as an aqueous solution for intravitreal injection in single-use glass vials. Study drug was administered using a sterile, single-use 250-µL syringe with a 30-gauge, 0.5-inch needle. Each subject received a single intravitreal injection of 0.5 mg, 1.0 mg, 2.0 mg, or 4.0 mg carotuximab, and fluoroquinolone antibacterial (or equivalent) eye drops were given in the study eye three times daily for 2 days. The volumes injected were 20 µL and 40 µL of a 25-mg/mL solution to deliver the 0.5-mg and 1-mg doses, and 20 µL and 40 µL of a 100-mg/mL solution to deliver the 2-mg and 4-mg doses.

Study Outcomes

Safety outcomes were assessed during screening and during the protocol-specified study visits from day 1 to day 90. The following assessments were performed on study days 1, 2, 8, 15, 30, 45, 60, and 90: adverse events, BCVA, vital signs, IOP, slit-lamp biomicroscopy, and indirect ophthalmoscopy. A complete schedule of assessments is presented in Supplementary Table S2. The change from baseline in CST, as measured via SD-OCT, was a secondary endpoint in this trial and was evaluated on study days 1, 2, 8, 15, 30, 45, and 60.

Statistical Methods

Data are summarized descriptively by dose level as the distribution (number and percentage) of patients for categorical variables and as the measured value for each patient or the mean value for each cohort for continuous variables. No formal tests of inferential statistics were planned or performed. For the assessment of bioactivity, missing values were imputed using the last observation carried forward method. Adverse events were coded according to system organ class and preferred term using the Medical Dictionary for Regulatory Activities, version 18.0. All analyses were performed using SAS 9.1.3 (SAS Institute, Cary, NC).

All patients provided written informed consent prior to enrollment. The study protocol was approved by the institutional review board or ethics committee at each participating site, and the study was conducted in accordance with the tenets of the Declaration of Helsinki and in compliance with International Conference on Harmonisation guidelines of Good Clinical Practice and applicable local ethical and legal requirements.

Results

Twelve patients were enrolled in the study, and patients were randomly assigned to one of four groups. Each subject received a single intravitreal injection of carotuximab at one of four dose levels. All 12 patients completed the study. Demographic and baseline characteristics are summarized in Table 2. The study population included seven female and five male patients ranging in age from 61 to 90 years (mean, 74.3 years). Anti-VEGF therapies at the time of screening included aflibercept ($n = 6$), bevacizumab ($n = 5$), and ranibizumab ($n = 1$); the median time since the last anti-VEGF injection was 32.5 days (range, 27–54). The baseline median values for CST and BCVA were 420.5 µm (range, 324–1274) and 51 ETDRS letters (range, 29–65; 20/250–20/50 Snellen equivalent), respectively. Rescue therapy with an intravitreal anti-VEGF medication was administered to all 12 study participants: 11 patients received the first dose of rescue therapy on day 8 and one patient received the first dose of rescue therapy on day 30. All but one patient received a second rescue dose on day 60.

Table 2. Patient Demographics and Baseline Characteristics

Patient	Age (yr)	Sex	Anti-VEGF Therapy[a]	Time Since Last Anti-VEGF Injection (d)[b]	CST (µm)	BCVA (Letters)
1001	67	F	Bevacizumab	53	1274	29
1002	61	F	Aflibercept	28	346	46
1003	69	F	Aflibercept	30	324	52
2001	75	M	Bevacizumab	29	451	43
2002	73	F	Aflibercept	32	330	48
2003	73	M	Aflibercept	36	1190	37
3001	69	M	Bevacizumab	29	519	62
3002	72	F	Aflibercept	33	390	65
3003	81	M	Bevacizumab	52	327	55
4001	90	M	Bevacizumab	27	359	50
4002	86	F	Aflibercept	54	774	53
4003	76	F	Ranibizumab	36	458	60

[a]Last intravitreal anti-VEGF therapy at the screening visit.
[b]Assessed at the screening visit.

Safety Assessments

Seven patients (58.3%) reported at least one adverse event (AE), including five patients (41.7%) who experienced one or more AEs in the study eye, and two patients (16.7%) who experienced one or more non-ocular AEs (Table 3). Adverse events were mild to moderate in severity, and all but one (increased lacrimation) resolved without significant clinical consequence.

Mild conjunctival hemorrhage was the most frequently reported AE (three of 12 subjects, 25%) and was observed following intravitreal injection (carotuximab for two subjects and anti-VEGF for one subject). All three cases of conjunctival hemorrhage were assessed as being related to the intravitreal injection procedure; two occurred on day 1 following administration of the study drug and one occurred on day 8 following administration of intravitreal anti-VEGF therapy. Ocular deposits in the posterior segment of the eye were noted on ophthalmoscopy in one patient 2 days after carotuximab administration. The eye deposits were observed on the peripheral

Table 3. Summary of Adverse Events

	Dose Cohort, *n* (%)				
	Low, 0.5 mg (*n* = 3)	Medium Low, 1.0 mg (*n* = 3)	Medium High, 2.0 mg (*n* = 3)	High, 4.0 mg (*n* = 3)	Total, *n* (%) (*N* = 12)
Patients with any adverse event	0	2 (66.7)	2 (66.7)	3 (100)	7 (58.3)
Eye disorders	0	2 (66.7)	1 (33.3)	2 (66.7)	5 (41.7)
Conjunctival hemorrhage	0	1 (33.3)	1 (33.3)	1 (33.3)	3 (25.0)
Deposit eye	0	1 (33.3)	0	0	1 (8.3)
Foreign body sensation	0	0	0	1 (33.3)	1 (8.3)
Lacrimation increased	0	0	0	1 (33.3)	1 (8.3)
Photophobia	0	0	0	1 (33.3)	1 (8.3)
Retinal hemorrhage	0	0	0	1 (33.3)	1 (8.3)
Blurred vision	0	0	0	1 (33.3)	1 (8.3)
Musculoskeletal and connective tissue disorders	0	0	1 (33.3)	1 (33.3)	2 (16.7)
Neck pain	0	0	0	1 (33.3)	1 (8.3)
Spinal pain	0	0	1 (33.3)	0	1 (8.3)
Vascular disorders	0	0	0	1 (33.3)	1 (8.3)
Hypertension	0	0	0	1 (33.3)	1 (8.3)

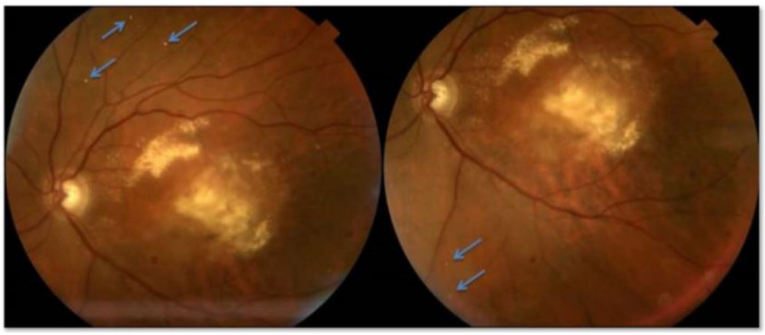
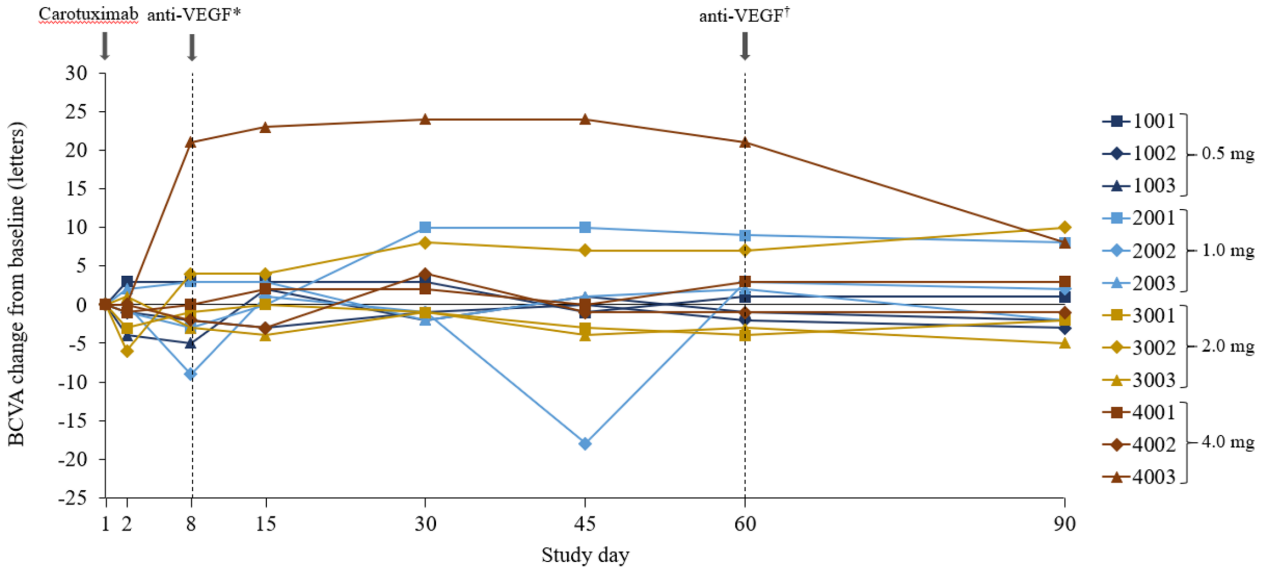


Figure 3. Ocular deposits reported in a patient in the 1.0-mg cohort.



*Patient 2003 received first dose of rescue therapy on Day 30.
†Patient 3003 did not receive rescue therapy on Day 60.

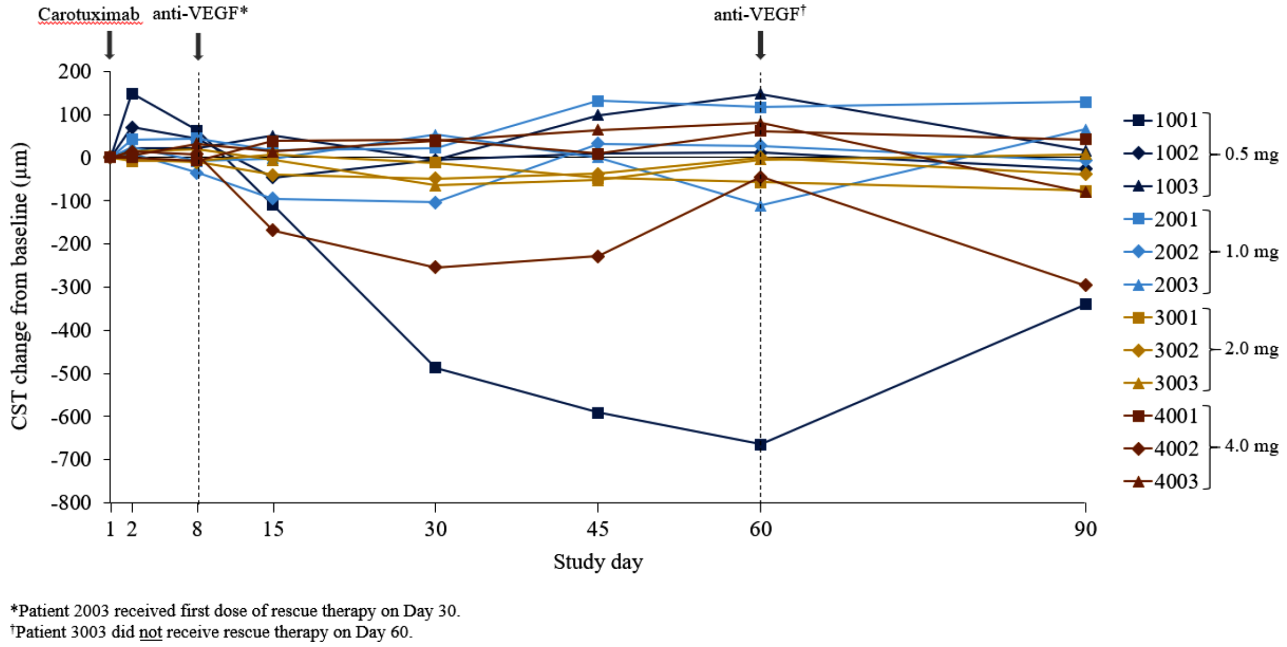
Figure 4. Change from baseline in BCVA.

area, which is not normally captured in standard (i.e., not widefield) fundus photographs taken at baseline (Fig. 3). Improvement in these eye deposits was noted on day 14, and spontaneous resolution occurred by day 43, without clinical consequence. No signs of vitreous haze or inflammation were noted. The patient did not exhibit any symptoms and had stable visual acuity throughout the 90-day observation period.

All other AEs (preferred terms) were reported in a single subject. There were no serious AEs. One AE (hyphema, mild) met the protocol definition for events of special interest. All AEs were of mild to moderate severity, and all were resolved or resolving on or before the last study visit (day 90). During the study, no clinically significant changes were observed in IOP, clinical laboratory evaluations (hematology, serum chemistry, and urinalysis), electrocardiograms (EKGs), or vital signs.

BCVA generally remained stable during the 90-day observation period (Fig. 4). One patient receiving the medium-low dose (1.0 mg) had a >5-letter decline from baseline on more than one study visit; the maximum decline of –18 letters occurred on day 45 and was followed by an improvement to +3 letters compared with baseline on the subsequent study visit (day 60) and a gain of +2 letters compared with baseline on day 90. Three of 12 patients experienced a >5-letter gain in BCVA compared with baseline, including one patient each in the medium-low (1.0 mg), medium-high (2.0 mg), and high (4.0 mg) dose cohorts. The maximum improvements in BCVA by cohort were +3, +10, +10, and +24 letters in the low (0.5 mg), medium-low (1.0 mg), medium-high (2.0 mg), and high (4.0 mg) dose cohorts, respectively.

One patient in the high-dose cohort (4.0 mg) tested positive for anti-drug antibodies. The patient was a



*Patient 2003 received first dose of rescue therapy on Day 30.
†Patient 3003 did not receive rescue therapy on Day 60.

Figure 5. Change from baseline in central subfield thickness.

76-year-old female receiving concomitant anti-VEGF therapy with ranibizumab. Anti-drug antibodies were detected in serum samples collected at baseline (prior to administration of the study drug) and on day 30. The patient experienced three mild AEs on day 1 (foreign body sensation, photophobia, and lacrimation), all of which were classified as unrelated to the study drug. Laboratory values, vital signs, and EKG findings were unremarkable.

Secondary Outcomes

The change from baseline in CST in each of the 12 study participants is presented by cohort in Figure 5. Four patients, including one patient in each dose cohort, had a ≥50-µm reduction in CST on at least two study visits from day 15 to day 60.

Discussion

Several anti-VEGF agents have been approved in the field of ophthalmology since 2004.[2] These agents have brought dramatic changes in the treatment of neovascular AMD, with fewer patients losing their vision and a reasonable proportion showing vision improvement. Despite the outstanding advances made by anti-VEGF therapy, most patients require frequent, repeated injections and regular long-term follow-up. Although anti-VEGF agents represent a dramatic breakthrough in the treatment of neovascular AMD, some patients have a poor response or no response to standardized treatment with these agents, or they experience a slow loss of efficacy after repeated administration over time. Persistent fluid is still common after regular therapy.

This is the first clinical study to evaluate the safety and tolerability of intravitreal injections of carotuximab in patients with exudative AMD. The study population included patients with advanced disease who had been treated with multiple injections of anti-VEGF therapy and not expected to have improvement in BCVA, thus representing a population of suboptimal therapeutic responders. Evaluation of safety data showed that treatment with a single intravitreal injection of carotuximab at doses ranging from low to high was safe and generally well tolerated. Ocular adverse events were consistent with those commonly observed in patients with exudative AMD or receiving intraocular injections. There were no serious adverse events and no significant changes in IOP, clinical laboratory values, or vital signs. Evaluation by cohort revealed no apparent dose-related trends in safety outcomes. The identification of potential dose-related trends was limited by the small sample size and the low frequency of adverse events.

There was a single case of ocular deposits in the posterior segment of the study eye in an asymptomatic patient with stable visual acuity. The deposits were observed outside of the region recorded in baseline fundus photographs; therefore, it could not be determined whether they were pre-existing or attributable to

either carotuximab or anti-VEGF therapy. The patient experienced no other adverse events, and the deposits resolved spontaneously without clinical consequence.

Visual acuity was generally stable during the 90-day observation period, with only one patient experiencing a >5-letter decline on more than one study visit. This patient was found to have a maximum decline of –18 letters on day 45 and was followed by an improvement to +3 letters compared with baseline on the subsequent study visit (day 60) and a gain of +2 letters compared with baseline on day 90. Three of 12 patients experienced a >5-letter gain in BCVA compared with baseline. Although modest, the magnitude of improvement in BCVA was thought to be potentially clinically relevant, given the advanced nature of disease in the study population. However, topline results from the phase 2a AVANTE study of patients with exudative AMD found no improvement in visual acuity after 6 months of treatment with a combination of intravitreal injections of carotuximab and the anti-VEGF agent ranibizumab compared with ranibizumab alone (press release).

In the current phase I PAVE study, there was evidence of a clinically significant (>50 µm) reduction of CST in some patients. Although these findings may possibly reflect a complementary effect of carotuximab and anti-VEGF therapy consistent with observations from studies evaluating intravenous carotuximab in patients with solid tumors refractory to anti-VEGF therapy,[25,26] we cannot discount the possibility of chance.

In conclusion, this open-label, dose-escalating, sequential cohort study showed that all four tested doses of carotuximab were generally well tolerated when administered as a single intravitreal injection to patients with persistent exudative AMD. Additional research is required to understand dose response and duration of effect and to investigate the optimal frequency and timing of administration of carotuximab relative to anti-VEGF therapy. Gaining insight into the causes of resistance to anti-VEGF therapy via other complementary pathways (such as endoglin-based angiogenic pathologies) would be helpful for developing novel strategies to improve the efficacy of anti-angiogenic therapies as a whole.

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