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Subconjunctival Palomid 529 in the treatment of neovascular age-related macular degeneration

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Abstract

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Background—Recent evidence suggests that neovascular age-related macular degeneration (AMD) may have an immune mediated component. Palomid 529, an investigational medication involving the immune Akt/mTOR pathway, is unique in dissociating both targets of rapamycin complexes TORC1 and TORC2. This small short-term pilot study assesses the safety of subconjunctival Palomid 529 in the treatment of neovascular AMD, with some limited efficacy information.

Methods—In this 12-week phase I open-label prospective pilot study, five participants with neovascular age-related macular degeneration that were refractory to intravitreal anti-vascular endothelial growth factor (VEGF) received three serial monthly subconjunctival doses of 1.9 mg Palomid 529. All participants were also offered concomitant monthly intravitreal anti-VEGF injections. Safety was monitored via adverse events recording. Additional outcome measures included visual acuity, optical coherence tomography, fluorescein angiography, indocyanine green angiography and fundus photography.

Results—The study drug was well-tolerated by all participants. There were no drug-related adverse events and no serious adverse events. A depot formed at the injection site, which persisted at the end of the study. In these anti-VEGF refractory patients, no clinically important changes in best-corrected visual acuity, fluorescein leakage pattern, choroidal neovascularization size on indocyanine green angiography, or autofluorescence pattern on fundus autofluorescence were observed compared to baseline. The fluid status, assessed with optical coherence tomography showed that central retinal thickness and macular volume remained stable in three participants, while the other two participants clinically progressed.

Conclusions—Serial subconjunctival injections of Palomid 529 were well-tolerated and resulted in depot formation. There were no concerns for any ocular or systemic toxicity during this small short-term study. Larger randomized studies are required to determine efficacy.

Keywords

Akt/mTOR; Choroidal neovascularization; Neovascular age-related macular degeneration; Palomid 529

Introduction

Neovascular age-related macular degeneration (AMD) has a complex etiology affected by multiple factors such as aging, genetic predisposition, environmental elements, oxidative stress, and inflammatory effects [1, 2]. More recent evidence suggests that AMD is immune-mediated [3–6]. Innate immunity and autoimmune components, such as complement factors, chemokines, cytokines, macrophages, and ocular microglia, may be involved in AMD development [7]. Inflammation, however, is a double-edged sword; some studies support the notion that inflammation is a risk for AMD progression [8], while others state that inflammation is actually protective [9]. Others suggest that inflammation has a dual role, with both beneficial and detrimental functions [10].

The immune Akt/mTOR pathway, a multifunctional serine–threonine kinase critical in regulating basic cellular functions, has been well-studied in the field of oncology [11–13], and plays a role in ischemic and vascular endothelial growth factor (VEGF)-mediated

angiogenesis [14, 15]. Inhibition of mTOR results in blockade of interleukin-2 mediated signal transduction pathways, preventing cell cycle progression, as well as upstream blockade of VEGF production. Given this, mTOR inhibition may be beneficial for the treatment of choroidal neovascularization (CNV) [16, 17]. Although anti-VEGF therapy is currently an effective standard-care for neovascular AMD, inflammatory mediation targeting the immune Akt/mTOR pathway may provide an alternative or adjunct pathway for the treatment of neovascular AMD.

Palomid 529 is a non-steroidal, wholly synthetic, small-molecule drug with a molecular weight of 406 Daltons and a mean particle size of approximately 0.8 μm developed by Paloma Pharmaceuticals. Palomid 529 inhibits the Akt/mTOR signal transduction pathway via dissociation of both targets of rapamycin complexes, TORC1 and TORC2, in the immune system. Specifically, Palomid 529 inhibits HIF 1 α and pS6 (TORC 1) and pAKt Ser-473 and pGSK3 β Ser-9 (TORC2) [18]. Unlike the similar compound sirolimus, Palomid 529 is unique in dissociating both TORC1 and TORC2, as opposed to acting primarily via TORC1. Studies are in progress assessing sirolimus with its primary TORC1 blockage as a possible treatment for AMD. However, pursuing the additional TORC2 blockage with Palomid 529 may prove to be efficacious in treatment of neovascular AMD.

Several pre-clinical studies have been performed using various routes of Palomid 529. Animal studies were noteworthy for vitreous opacities detected after intravitreal injection, while the subconjunctival studies only demonstrated focal erythema and edema locally at the conjunctival injection site, with spontaneous resolution. No intraocular abnormalities were detected after subconjunctival administration. Subconjunctival Palomid 529 was detectable in the choroid, retina, and vitreous, indicating that the drug reached the targeted tissue via subconjunctival administration [18].

In the current study, the subconjunctival route was chosen due to its ease of administration and improved safety profile, given the mechanical risks of an intravitreal injection and the cloudy-appearing vitreous seen with intravitreal dosing that may interfere with fundus viewing. Based on the results from animal studies and human intravitreal trials, a dose of 1.9 mg was selected for this study. In animal studies, a subconjunctival dose of 1 mg administered to the New Zealand white rabbits was well-tolerated and demonstrated penetration into the chorioretinal tissue. Since the human eye is approximately twice as large as the New Zealand white rabbit eye, a dose of 2 mg was chosen (which is double that given to the rabbits). For ease of administration, the volume of 100 μl was chosen which contains 1.9 mg of Palomid 529 (concentration 10 mg/ml) [18]. Additionally, there is currently a phase I study using Palomid 529 with intravitreal doses of 0.04 mg and 0.10 mg.

The dual effect of Palomid 529 on TORC1 and TORC2 in the AKt/mTOR pathway may prove to be efficacious in the treatment of neovascular AMD; and this five-participant pilot study assesses the safety of subconjunctival Palomid 529 in the treatment of neovascular AMD, with some limited efficacy information.

Materials and methods

This phase I open-label prospective pilot study was conducted at the National Eye Institute, National Institutes of Health, in Bethesda, Maryland. The study protocol adhered to the tenets of the Declaration of Helsinki, and institutional review board approval was obtained.

Study population

Patients with active neovascular AMD in at least one eye (the study eye) were eligible. Study eye inclusion criteria included: (1) CNV in the setting of AMD resulting in fluid or blood within the macula as determined by clinical examination, optical coherence tomography (OCT), and fluorescein angiography (FA), (2) Non-response to conventional anti-VEGF treatment defined as any persistent intraretinal cyst with a greatest linear dimension of at least 100 μm and/or subretinal fluid pocket with a height of at least 100 μm and/or the presence of any foveal fluid after four serial anti-VEGF intravitreal injections determined 2 weeks after the last injection, (3) visual acuity of 20/32 or worse in the study eye, and (4) reasonably clear media and fixation for good quality OCT and fundus photography.

Principal exclusion criteria for the study eye included: (1) evidence of ocular disease other than neovascular AMD that may confound the outcome, (2) retinal pigment epithelial detachment (unless subretinal or intraretinal fluid was present), (3) treatment with anti-VEGF within 12 days prior to enrollment or intraocular steroids 3 months prior to enrollment, and (4) systemic immunosuppressive treatments within 2 months prior to enrollment. If both eyes met the above criteria, the designation of the study eye was chosen by the principal investigator in consultation with the participant.

Study design

In this 12-week prospective, open-label pilot study, five participants with neovascular AMD who were not fluid-free after four serial anti-VEGF injections received three serial subconjunctival injections of Palomid 100 μl (1.9 mg). Participants were enrolled in a stepwise fashion to maximize safety (the subsequent participant was not enrolled until the previous participant had completed week 4). Injections were performed at baseline, week 4, and week 8. Patients were evaluated at baseline, day 1, week 1, week 4, week 8, and week 12. At the baseline visit, a complete medical and ophthalmic history, physical examination, complete blood count, chemistry 14, and complement Factor H genotyping was performed. Complete blood count and chemistry 14 were repeated at the final visit at week 12. At each visit, participants underwent a complete ophthalmological examination, assessment of medications, adverse events, and OCT. All OCTs were reviewed to confirm correct segmentation. Indocyanine green angiography (ICG), FA, and fundus photography were performed at baseline, week 4, and week 12. Fundus autofluorescence was performed at baseline and week 12. Intraocular anti-VEGF treatment was allowed 12 days prior to and 12 days after the investigational produce injection, to allow for participants to continue to receive standard-care monthly intravitreal injections.

Administration of Palomid 529

Palomid 529 was provided in a ready-to-use single-use rubber septum sealed glass vial containing 0.2 ml at 19 mg/ml. Following administration of topical antibiotics (ofloxacin 0.3 % ophthalmic solution), topical anesthetic (0.5 % proparacaine hydrochloride ophthalmic solution) and speculum insertion, 100 μ l/0.1 ml of Palomid 529 was slowly injected into the subconjunctival space of the study eye. A cotton-tipped applicator was gently placed over the entry site for 1 min following removal of the needle to prevent reflux.

Statistical methods

The primary outcome measure was to evaluate the safety of subconjunctival Palomid 529 as a possible treatment for neovascular AMD. Safety outcomes included the number and severity of ocular and systemic adverse events. Secondary outcome measures included the change in best-corrected visual acuity (BCVA), changes in fluid status, central retinal thickness and retinal volume as measured by OCT, changes in leakage patterns on FA, changes in CNV patterns on ICG, changes in autofluorescence patterns on fundus autofluorescence, and changes in fundus appearance as observed on color fundus photography. Additionally, comparison of complement Factor H polymorphisms with treatment response were evaluated.

Due to the small sample size of five participants, analyses are descriptive, and include tabulation of outcomes over the study period.

Results

The medical and baseline data of the five participants are listed in Table 1. All participants were older adults between the ages of 68 to 87 years at enrollment, which a duration of neovascular AMD ranging from approximately 3 to 11 years. Four were female and one was male. All were Caucasian of non-Hispanic/Latino origin. Two of the participants had a known family history of AMD. None of the participants were current smokers, and two had a previous history of smoking. In the study eye, three patients were phakic without progression in lens opacities during the study period, and two were pseudophakic. All patients had previously undergone treatment with anti-VEGF intravitreal injections in the study eye. Additionally, three participants had previously received intravitreal steroid, and one participant had previously had photodynamic therapy in the study eye. Four of the five participants were treated with concomitant monthly anti-VEGF injections during the study. Three of the participants had neovascular AMD in the fellow eye.

All patients were compliant with the study requirements, and received three serial subconjunctival injections of Palomid 529. A small firm depot formed at the injection site, which remained present throughout the study. One patient was unable to undergo repeat fluorescein testing due to allergic urticaria that developed at the baseline visit during FA testing. None of the patients had a clinically important change in best-corrected visual acuity, FA leakage pattern, choroidal neovascularization size on ICG, or autofluorescence pattern on fundus autofluorescence compared to baseline. The fluid status assessed with OCT central retinal thickness and macular volume essentially remained stable in participants

1, 2, and 4. Participant 3 had an increase in macular volume at week 12, which was accompanied by new retinal hemorrhage. Participant 5, who elected not to receive concomitant intravitreal anti-VEGF injections during the study period, had an increase in both macular volume and central retinal thickness. Participant 4 was homozygous for the high-risk genotype (histidine allele at codon 402) for complement factor H, and the other four participants were heterozygous for the high-risk genotype; no difference in response to treatment was seen. Table 2 summarizes the clinical outcome for all five participants.

Adverse events

The study drug was well-tolerated by all participants. There were no drug-related adverse events. Reported adverse events were deemed not drug-related, and consisted of abnormal lab values such as hypoglycemia and low blood urea nitrogen as well as urticaria due to imaging dye. There were no serious adverse events in our five-participant study.

Discussion

In this prospective five-participant phase I pilot study, repeated subconjunctival injections of Palomid 529 were well-tolerated and formed a depot at the injection site. There were no concerns for any ocular or systemic toxicity during this study. While our study was primarily investigating safety, the investigational drug did not appear to benefit the participants in terms of visual acuity or macular fluid status during this short-term pilot study. Given the limited sample size and short follow-up duration, conclusions cannot be drawn regarding the efficacy of Palomid 529 in neovascular AMD. Our participants were refractory to anti-VEGF treatment, and it is possible a response to treatment could have been seen in those with newer onset disease or in those who demonstrated a response to anti-VEGF treatment. Additionally, while the subconjunctival route is advantageous in comparison to intravitreal injection in terms of ease of administration and reduced mechanical complications, an intravitreal route may be more efficacious. Intravitreal injection of Palomid 529 for the treatment of neovascular AMD is currently being evaluated by other investigators.

The small sample size of our study was the key limitation, and a larger randomized clinical trial with longer follow-up is needed to evaluate any potential efficacy of Palomid 529 and continued understanding of any safety issues. Treatment strategies based on inflammatory modulation through immunosuppression have a scientific theoretical basis; however, further studies will be required to assess whether immunomodulation can be an effective approach in clinical practice for neovascular AMD.

References

1. Coleman HR, Chan CC, Ferris FL III, Chew EY. Age-related macular degeneration. *Lancet*. 2008; 372(9652):1835–1845. [PubMed: 19027484]
2. Klein R, Cruickshanks KJ, Nash SD, Krantz EM, Nieto FJ, Huang GH, Pankow JS, Klein BE. The prevalence of age-related macular degeneration and associated risk factors. *Arch Ophthalmol*. 2010; 128(6):750–758. [PubMed: 20547953]
3. Nussenblatt RB, Ferris F III. Age-related macular degeneration and the immune response: implications for therapy. *Am J Ophthalmol*. 2007; 144(4):618–626. [PubMed: 17698021]

4. Nussenblatt RB, Liu B, Li Z. Age-related macular degeneration: an immunologically driven disease. *Curr Opin Investig Drugs*. 2009; 10(5):432–442.
5. Patel M, Chan CC. Immunopathological aspects of age-related macular degeneration. *Semin Immunopathol*. 2008; 30(2):97–110. [PubMed: 18299834]
6. Liu B, Faia L, Hu M, Nussenblatt RB. Pro-angiogenic effect of IFN γ is dependent on the PI3K/mTOR/translational pathway in human retinal pigment epithelial cells. *Mol Vis*. 2010; 16:184–193. [PubMed: 20157617]
7. Wang, Y.; Wang, VM.; Chan, CC. Eye. Vol. 25. Lond: 2011. The role of anti-inflammatory agents in age-related macular degeneration (AMD) treatment; p. 127-139.
8. Tarallo V, Hirano Y, Gelfand BD, Dridi S, Kerur N, Kim Y, Cho WG, Kaneko H, Fowler BJ, Bogdanovich S, Albuquerque RJ, Hauswirth WW, Chiodo VA, Kugel JF, Goodrich JA, Ponicsan SL, Chaudhuri G, Murphy MP, Dunaief JL, Ambati BK, Ogura Y, Yoo JW, Lee DK, Provost P, Hinton DR, Nuñez G, Baffi JZ, Kleinman ME, Ambati J. DICER1 loss and Alu RNA induce age-related macular degeneration via the NLRP3 inflammasome and MyD88. *Cell*. 2012; 149(4):847–859. [PubMed: 22541070]
9. Doyle SL, Campbell M, Ozaki E, Salomon RG, Mori A, Kenna PF, Farrar GJ, Kiang AS, Humphries MM, Layelle EC, O'Neill LA, Hollyfield JG, Humphries P. NLRP3 has a protective role in age-related macular degeneration through the induction of IL-18 by drusen components. *Nat Med*. 2012; 18(5):791–798. [PubMed: 22484808]
10. Rosenbaum JT. Eyeing macular degeneration—a few inflammatory remarks. *N Engl J Med*. 2012; 367(8):768–770. [PubMed: 22913688]
11. Janes MR, Limon JJ, So L, Chen J, Lim RJ, Chavez MA, Vu C, Lilly MB, Mallya S, Ong ST, Konopleva M, Martin MB, Ren P, Liu Y, Rommel C, Fruman DA. Effective and selective targeting of leukemia cells using a TORC1/2 kinase inhibitor. *Nat Med*. 2010; 16(2):205–213. [PubMed: 20072130]
12. Shor B, Gibbons JJ, Abraham RT, Yu K. Targeting mTOR globally in cancer: thinking beyond rapamycin. *Cell Cycle*. 2009; 8(23):3831–3837. [PubMed: 19901542]
13. Xue Q, Hopkins B, Perruzzi C, Udayakumar D, Sherris D, Benjamin LE. Palomid 529, a novel small-molecule drug, is a TORC1/TORC2 inhibitor that reduces tumor growth, tumor angiogenesis, and vascular permeability. *Cancer Res*. 2008; 68(22):9551–9557. [PubMed: 19010932]
14. Ackah E, Yu J, Zoellner S, Iwakiri Y, Shurk C, Shibata R, Ouchi N, Easton RM, Galasso G, Birnbaum MJ, Walsh K, Sessa WC. Akt1/protein kinase B α is critical for ischemic and VEGF-mediated angiogenesis. *J Clin Invest*. 2005; 115(8):2119–2127. [PubMed: 16075056]
15. Fulton D, Gratton JP, McCabe TJ, Fontana J, Fujio Y, Walsh K, Franke TF, Papapetropoulos A, Sessa WC. Regulation of endothelium-derived nitric oxide production by the protein kinase Akt. *Nature*. 1999; 399(6736):597–601. [PubMed: 10376602]
16. Humar R, Kiefer FN, Berns H, Resink TJ, Battegay EJ. Hypoxia enhances vascular cell proliferation and angiogenesis in vitro via rapamycin (mTOR)-dependent signaling. *FASEB J*. 2002; 16(8):771–780. [PubMed: 12039858]
17. Dejneka N, Kuroki AM, Fosnot J, Tang W, Tolentino MJ, Bennett J. Systemic rapamycin inhibits retinal and choroidal neovascularization in mice. *Mol Vis*. 2004; 10:964–972. [PubMed: 15623986]
18. Paloma Pharmaceuticals, Inc. Palomid 529 investigator's brochure (3rd). 2009 Brochure.

Table 1

Baseline characteristics of study participants

Participant	Study eye	Sex	Age (years)	Duration of neovascular AMD (years)	Prior ocular treatment	
					Study eye	Non-study eye
1	OD	Male	78	3	Intravitreal steroid, Avastin, Lucentis	None
2	OD	Female	68	3.5	Avastin, Lucentis	Avastin, Lucentis
3	OD	Female	74	11	Intravitreal steroid, Avastin, Lucentis	Photodynamic therapy
4	OD	Female	87	8	Photodynamic therapy, Intravitreal steroid, Avastin	None
5	OD	Female	77	4	Avastin	Avastin

Table 2
Study outcomes at baseline, week 1, week 4, week 8, and week 12

Participant	Baseline	Week 1	Week 4	Week 8	Week 12
1					
Best-corrected visual acuity	20/160	20/160	20/200	20/200	20/160
OCT central retinal thickness (microns)	284	296	281	280	286
OCT macular volume (microliters)	9.30	9.50	9.40	9.20	9.10
2					
Best-corrected visual acuity	20/40	20/40	20/40	20/40	20/40
OCT central retinal thickness (microns)	226	221	239	222	221
OCT macular volume (microliters)	9.80	9.70	9.60	9.70	10.20
3					
Best-corrected visual acuity	20/200	20/160	20/160	20/200	20/160
OCT central retinal thickness (microns)	325	309	317	293	330
OCT macular volume (microliters)	11.20	11.90	11.00	11.80	12.80
4					
Best-corrected visual acuity	20/320	20/320	20/320	20/320	20/320
OCT central retinal thickness (microns)	753	773	973	970	703
OCT macular volume (microliters)	16.00	16.10	17.20	16.70	16.10
5					
Best-corrected visual acuity	CF 1'	HM	20/800	20/800	20/800
OCT central retinal thickness (microns)	768	848	813	949	980
OCT macular volume (microliters)	15.50	15.50	15.80	16.10	16.50