Review Article

Narrative review of risuteganib for the treatment of dry age-related macular degeneration (AMD)

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Abstract: Age-related macular degeneration (AMD) is a leading cause of blindness worldwide. AMD most commonly affects older individuals and is characterized by irreversible degeneration of the retinal pigment epithelium and neurosensory retina. Currently, there are limited treatment options for dry AMD outside of lifestyle modification and nutrient supplementation. Risuteganib [Luminate (ALG-1001), Allegro Ophthalmics, CA, USA] is an intravitreally administered inhibitor of integrin heterodimers αVβ3, αVβ5, α5β1, and αMβ2. It is currently undergoing clinical trials for the treatment of dry AMD and diabetic macular edema (DME). Preclinical studies have shown that risuteganib has an effect on the pathways for angiogenesis, inflammation, and vascular permeability. Ongoing clinical trials have had promising results showing improvements in patient best corrected visual acuity (BCVA) and reduced central macular thickness measured by optical coherence tomography (OCT). There is a pressing need for treatments for dry AMD and while risuteganib appears to have a potential benefit for patients, more data are needed before one can truly evaluate its efficacy. This narrative review provides a concise summary of the most up to date data regarding the proposed mechanism of action of risuteganib in the treatment of nonexudative AMD and DME as well as the results from recent phase 1 and phase 2 clinical trials.

Keywords: Risuteganib; integrin inhibitor; dry age-related macular degeneration (dry AMD); non-exudative age-related macular degeneration (non-exudative AMD)

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General age-related macular degeneration (AMD)

AMD is a leading cause of blindness in developed countries and accounts for 8.7% of blindness worldwide (1). AMD is characterized by degeneration of the retinal pigment epithelium (RPE) and neurosensory retina. This degeneration leads to irreversible vision loss and most commonly effects older individuals. There are two forms of AMD, non-exudative (dry) and exudative (wet). Dry AMD is more prevalent, affecting 85–90% of patients suffering from AMD (2). Exudative AMD is characterized by neovascularization and fluid accumulation within the macula, whereas non-exudative AMD lacks neovascularization. While several treatments exist for the treatment of exudative AMD, there are limited treatment options of non-exudative AMD. Existing recommendations for dry AMD consist of lifestyle modifications and micronutrient supplementation (3,4). While this review will focus on integrin inhibition, several interventions targeting the complement pathway, neuropeptides, mitochondrial protective factors and both induced pluripotent and embryologic stem cells are under investigation and

summarized in *Table 1*. We present the following article in accordance with Narrative Review reporting checklist (available at https://dx.doi.org/10.21037/aes-21-12).

Literature search

We used all available public domains to search for scientific literature published in English. The key words included: risuteganib, luminate, ALG-1001, integrin inhibitor. There was no time limitation for published reports.

What are integrins?

Integrins are heterodimeric receptors composed of 24 unique combinations of α and β subunits. There are 18 types of α subunits and 8 types of β subunits (*Figure 1*). The two subunits interact non-covalently and bind to a wide variety of extracellular matrix components and cell surface receptors. Integrins regulate a multiplicity of cellular roles such as shape, orientation, movement, adhesion, proliferation, invasion, apoptosis and survival (5). As a result of these many roles, integrins are involved in inflammatory, angiogenesis, and fibrosis cascades. Previously approved pharmacologic indications for integrin inhibitors use include Crohn's disease, ulcerative colitis, and multiple sclerosis (6).

Lifitegrast was approved by the Food and Drug Administration in 2016 for the topical treatment of dry eye disease and is the first integrin inhibitor that has been successfully used in ophthalmology. It acts by inhibiting αLβ2 integrin which inhibits intercellular adhesion molecule 1 (ICAM-1) interaction, thereby preventing adhesion, activation, migration, and proliferation of lymphocytes. Left uninhibited, lymphocyte proliferation leads to cytokine secretion, cell destruction, and self-amplification of the inflammatory immune response that furthers the inflammatory mediators implicated in dry eye disease. Lifitegrast has been shown to be efficacious in the treatment of dry eye syndrome with no serious adverse effects (7-9).

Risuteganib

Risuteganib [Luminate (ALG-1001), Allegro Ophthalmics, CA, USA] is an intravitreally administered Arginine-Glycine-Aspartate (RGD) oligopeptide that has a molecular weight of less than 1 kDa (*Figure 2*). The RGD domain acts as a binding site for several extracellular matrix proteins such as fibronectin, fibrinogen, and vitronectin. Risuteganib acts by integrin inhibition, binding to 4 of the 24 known integrin heterodimers: αVβ3, αVβ5, α5β1, and αMβ2 (10,11). These integrins, specifically, are thought to be involved in pathways for angiogenesis, inflammation, and vascular permeability.

Takagi *et al.* showed increased expression of integrin αVβ3 and αVβ5 in murine models of ischemic retina. Through their association with vitronectin, these heterodimers are involved in angiogenesis and vascular proliferation (12). Similarly, Friedlander and colleagues found that enucleated eyes from patients with choroidal neovascularization (CNV) expressed αVβ3 while eyes from patients with retinal neovascularization expressed both αVβ3 and αVβ5 (13). These findings make these integrin heterodimers potentially useful therapeutic targets for angiogenic diseases such as AMD and diabetic macular edema (DME) (14-16). Friedlander and colleagues also demonstrated that murine retinal angiogenesis was dramatically reduced by systemic inhibition of αVβ3 and αVβ5 integrins (13).

Ramakrishnan *et al.* determined that integrin heterodimer α5β1 also plays a key role in angiogenesis as it is expressed in proliferating vascular endothelial cells. Inhibition of the α5β1-fibronectin interaction leads to apoptosis of proliferating endothelial cells but spares non-proliferating endothelial cells in vitro. Additionally, α5β1 integrin inhibition has an anti-angiogenic effect through a VEGF-independent pathway. In their study, Ramakrishnan *et al.* used a primate model of angiogenesis to determine that inhibition of α5β1 integrin may show promise in the treatment for ocular neovascularization (17).

Jawhara *et al.* used a murine model deficient in αMβ2 and found that the integrin heterodimer plays a role in the immune response through involvement in chemotaxis, inflammation, phagocytosis, and cell-mediated killing functions (18). Kim *et al.* determined that αMβ2 heterodimer is involved in monocyte adhesion through interaction with transforming growth factor-β-induced gene product (βig-h3/TGFBIp) (19). Transforming growth factor-β accumulation has been shown to be associated with diabetic angiopathy (20). Through intravitreal αMβ2 heterodimer inhibition, there is a potential to decrease inflammatory and pro-angiogenic chemokines.

As demonstrated by Yang *et al.*, hydroquinone (an oxidant found in cigarette smoke and other pollutants) can induce necrosis and apoptosis, decrease mitochondrial bioenergetics, increase reactive oxygen species levels, and

Table 1 List of treatments for dry AMD currently under investigation

Category	Drug	Mechanism of action	Dry AMD/geographic atrophy clinical trials
Integrin inhibitor	Risuteganib; Luminate (Alg-1001)	Inhibits integrin heterodimers αVβ3, αVβ5, α5β1, and αMβ2	NCT03626636 (2018) phase 2
Complement pathway inhibitor	Zimura (ARC-1905)	Inhibits complement C5	NCT00950638 (2009) phase 1; NCT02686658 (2016) phase 2
Complement pathway inhibitor	Lampalizumab	Inhibits complement factor D	NCT02288559 (2014) phase 2; NCT01602120 (2012) phase 2; NCT02247531 (2014) phase 3; NCT02247479 phase 3 (2014); NCT02745119 (2016) phase 3
Complement pathway inhibitor	CLG561	Inhibits properdin	NCT01835015 (2013) phase 1; NCT02515942 (2015) phase 2
Complement pathway inhibitor	APL-2	Inhibits complement C3	NCT000473928 (2017) phase 1; NCT02503332 (2018) phase 1; NCT03525613 (2018) phase 3; NCT03525600 (2018) phase 3; NCT04770545 (2021) phase 3
Complement pathway inhibitor	LFG316; tesidolumab	Inhibits complement C5	NCT01255462 (2010) phase 1; NCT02515942 (2015) phase 2; NCT01527500 (2012) phase 2
Corticosteroid	Iluvien; fluocinolone acetonide	Inflammation suppression	NCT00695318 (2008) phase 2
Gene therapy	AAVCAGsCD59; HMR59	AAV2 gene therapy for transgene product CD59, inhibits membrane attack complex	NCT03144999 (2017) phase 1; NCT04358471 (2020) phase 2
Neuropeptide	Brimonidine tartrate	α2 adrenergic agonist, prevents retinal ganglion cell death	NCT00658619 (2008) phase 1; NCT02087085 (2014) phase 2
Neuropeptide	Ciliary neurotrophic factor	Prevent photoreceptor degradation	NCT00447954 (2007) phase 2
Mitochondrial protection	Elamipretide	Mitochondrial protection	NCT03891875 (2019) phase 2; NCT02848313 (2016) phase 1

AMD, age-related macular degeneration.

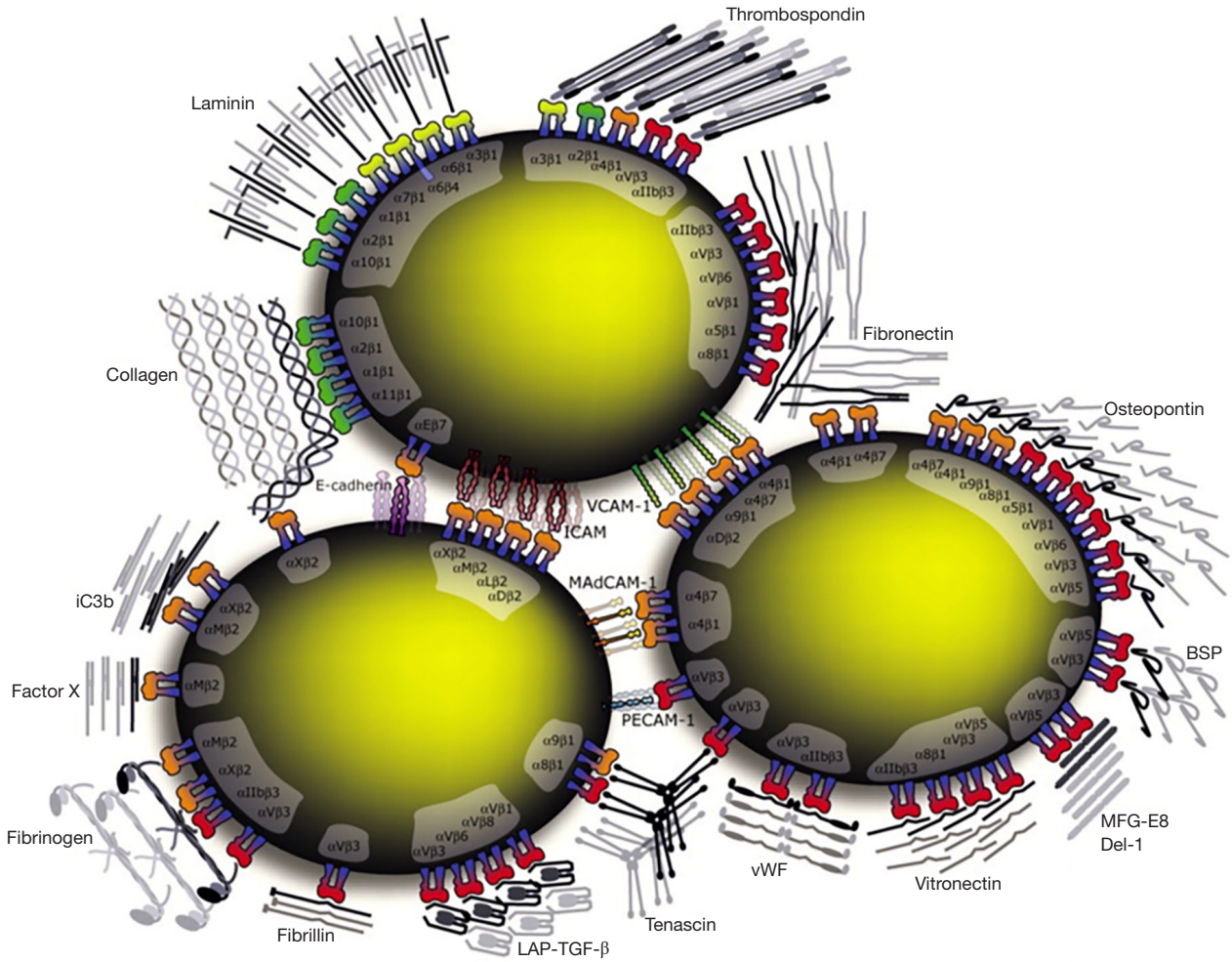

Figure 1 Image of integrin heterodimers presented with examples of their ligands. Edited and reproduced with permission from: Humphries JD, Byron A, Humphries MJ. Integrin ligands at a glance. *J Cell Sci* 2006;119:3901-3. doi: 10.1242/jcs.03098. BSP, bone sialoprotein; ICAM, intercellular adhesion molecule; LAP, latency-associated peptide; MAdCAM-1, mucosal addressin cell adhesion molecule-1; PECAM-1, platelet endothelial cell adhesion molecule-1; TGF-β, transforming growth factor β; VCAM-1, vascular cell adhesion molecule 1; vWF, von Willebrand factor; MFG-E8, milk fat globule-epidermal growth factor-factor VIII.

induce actin reorganization within human cultured RPE cells. They found that healthy RPE cells treated with risuteganib were not adversely affected, while RPE cells injured by hydroquinone but also treated with risuteganib were protected against injury (21). This suggests a potential role for risuteganib to treat diseases of RPE oxidative stress, such as AMD.

Pharmacokinetics and metabolism

Currently, there is no data available regarding the pharmacokinetics of risuteganib. Without this information, its duration of action or optimal timing of repeat doses remains unknown.

Preclinical studies

Preclinical trials have shown that risuteganib localizes to the RPE and outer retina and remains there for months. Radiolabeled risuteganib has been shown to have a 21-day half-life in rabbit retinal tissue. Retinas pretreated with risuteganib were protected from later exposure to the neurotoxic kainic acid or peroxide (22). Beltran *et al.* showed that RPE cells pretreated with risuteganib had a

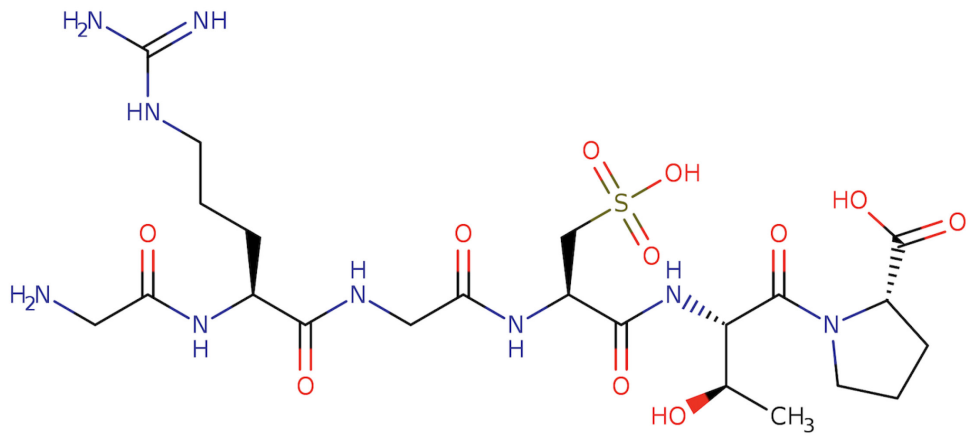

Figure 2 Chemical structure of risuteganib. ChemIDplus. 1307293-62-4. Risuteganib [USAN]. Similar structures search, synonyms, formulas, resource links, and other chemical information. U.S. National Library of Medicine. [Last accessed 2021 March 2]. Available online: https://chem.nlm.nih.gov/chemidplus/rn/1307293-62-4.

significant reduction in oxidative stress caused by hydrogen peroxide. Cells that were not pre-treated did not have the same cryoprotective effects (23).

Phase 1 studies

In a phase 1b study, 25 participants with exudative AMD received three monthly injections of either 1.5, 2.5, or 4.0 mg risuteganib and were followed for 6 months. The primary objective of the study was to observe for toxicity and to determine the maximally tolerated dose. Currently, there are no published results from this trial (24).

In a phase 1b/2a study, patients with DME received a monthly injection of either 1.5, 2.5, 5.0, or 7.0 mg risuteganib for 3 months and were followed for a total of 180 days. The primary endpoint of the study was to observe for toxicity and determine the maximally tolerated dose. Peak reduction in central macular thickness (CMT) by optical coherence tomography (OCT) ranged from 20% to 80% with a mean reduction of 31%. The treatment effect held for 3 additional months after the completion of treatment. Of the 15 patients enrolled, 53% had best corrected visual acuity (BCVA) improvement with a mean gain of nine or more letters (25,26).

Phase 2 studies

Forty patients were enrolled in a double masked, randomized, placebo controlled, multicenter trial evaluating the efficacy and safety of risuteganib treatment for intermediate-stage dry AMD. To be included in the study, patients needed to have non-exudative AMD with a BCVA between 20/40 and 20/100 (EDTRS between 33 and 73 letters). There was no mention of geographic atrophy in the inclusion or exclusion criteria. Patients were randomized to 1 of 2 study arms: two intravitreal injections of 1.0 mg risuteganib versus one sham injection in a 1.7:1 ratio. The risuteganib group received injections at week 1 and week 16 of the study. The study's primary endpoint was to determine the proportion of patients in the risuteganib group with ≥8 ETDRS BCVA improvement at week 28 compared to the control group at week 12. The study found that more patients in the treatment group had a visual acuity improvement of eight or more letters (48%) compared to the control group (7.1%) (P=0.013) (27,28). There was no explanation as to the mechanism of vision gain in the treatment group.

A randomized, prospective, triple-masked phase 2 trial compared the safety and efficacy of risuteganib to bevacizumab in treating DME. For stage 1 of the trial, 138 participants were randomized to risuteganib monotherapy with 1.0, 2.0, or 3.0 or 1.25 mg bevacizumab. Injections were delivered monthly at weeks 0, 4, and 8 with an as needed injection at week 20 for the risuteganib groups and as needed injection at weeks 12, 16, or 20 for the bevacizumab groups. Patients who did not receive an as needed treatment at weeks 12, 16, or 20 were given a sham injection. A sham laser treatment was also administered

at baseline and at week 16 for the patients receiving risuteganib. The risuteganib groups were compared to the bevacizumab groups at week 24. The primary endpoint was change in BCVA at week 24 compared to baseline. Risuteganib was found to be non-inferior to bevacizumab for the BCVA and CMT endpoints.

For stage 2 of the trial, 80 participants were randomized to 1 of 5 treatment groups. Group one was a control group and received monthly injections of 1.25 mg of bevacizumab for 5 months. Groups 2 and 3 received a single treatment of 1.25 mg bevacizumab at week 0 followed by three 1.0 mg (group 2) or 0.5 mg (group 3) risuteganib injections, at weeks 1, 4, and 8. Groups 4 and 5 received a combination of 1.0 or 0.5 mg of risuteganib, respectively, combined with bevacizumab 1.25 mg at weeks 1, 4, and 8. The most effective treatment was group 2 (1.25 mg bevacizumab at week 0 and three doses of 1.0 mg of risuteganib at weeks 1, 4, and 8), which met the primary endpoint of noninferiority in BCVA gain when compared to bevacizumab. There was a mean gain in BCVA of 7.1 letters for patients in the risuteganib with bevacizumab pre-treatment group (groups 2 and 3) compared to 6.7 letters for patients in the bevacizumab control group. Additionally, sequential risuteganib injections (groups 2 and 3) demonstrated 12-week durability. Sixty percent of patients treated in the trial had been chronic anti-VEGF users, which suggests that risuteganib may successfully treat patients who don't respond to anti-VEGF. Inclusion criteria included BCVA of 20/50 to 20/320 (ETDRS equivalent 65 letters to 23 letters), treatment naïve, and clinically significant DME with central subfield thickness ≥350 µm by spectral domain OCT. Patients were excluded from the trial if they had active proliferative diabetic retinopathy, uncontrolled hypertension, or screening HbA1c blood test greater than 10.0% (29-31).

Phase 3 studies

Allegro Ophthalmics was preparing to enter the drug into phase 3 trials for AMD and DME starting in Q4 of 2020. As of the writing of this paper, no further information on timeline or study design was available (32).

Comparison studies

Schneider and colleagues created cybrid cells, which are cell lines created by fusing human RPE cells that lack mitochondrial DNA with platelets isolated from exudative and non-exudative AMD patients or age-matched normal subjects. A major factor in the development of AMD is mitochondrial damage and dysfunction. By isolating the mitochondria in the cybrid cells, the investigators were able to determine the consequences of patient-derived AMD mitochondria on RPE cells. They found that AMD cybrid cells treated with risuteganib had lower gene expression of the apoptotic regulator BAX, angiogenesis marker VEGF-A, and integrin *ITGB1* genes than cells treated with bevacizumab and untreated control cells (33). This study demonstrated that monoclonal antibodies like bevacizumab may affect AMD RPE differently than risuteganib. Since risuteganib displayed more anti-apoptotic properties, it may be a promising therapy.

Safety and tolerability

There were no serious adverse events (SAE) attributed to the administration of intravitreal risuteganib in the trials for nonexudative AMD (25,30). The phase 2 trial for DME reported a total of 36 SAEs in the groups treated with at least one injection of risuteganib. The report detailed 6 cardiac disorders, 8 eye disorders, 2 general disorders, 6 infections, 2 metabolism and nutritional disorders, 1 musculoskeletal and connective tissue disorder, 1 neoplasm, 4 nervous system disorders, 1 renal and urinary disorder, 3 respiratory, thoracic, and mediastinal disorders, 1 surgical and medical procedure, and 1 vascular disorder (29). At this time, the detailed SAE data is not available for the nonexudative AMD trial. Longer term data regarding adverse events are currently not available and will be important to keep note of as risuteganib continues down the pipeline.

Conclusions

Integrins are heterodimeric receptors that play a role in the regulation of cellular adhesion, migration, proliferation, invasion, survival, and apoptosis. They have been shown to play a role in pathogenesis of DME and AMD. Integrin inhibition has been shown to be efficacious in the treatment of inflammatory diseases and provides an approach to impede the pathologic pathways of angiogenesis, inflammation, and vascular permeability in AMD and DME (6). Preclinical and early clinical studies show that risuteganib targets a novel integrin mediated pathway implicated in angiogenesis and inflammation. While intravitreal anti-VEGF treatments have had a dramatic impact on patient outcomes and quality of

life, there is still an unmet clinical need for the treatment of non-exudative AMD.

An expert review of risuteganib by Shaw *et al.* concluded that while the current clinical results of risuteganib appear encouraging, clinicians should be skeptical about whether the clinical improvement in BCVA was truly an effect of risuteganib, especially given the short timeline of the studies and lack of pre-clinical data to explain the improvement in BCVA (34). A review by Samanta *et al.* also brings up concern with the crossing over of the phase 2 clinical trial occurring before the primary endpoint (35). Since these review, new non-clinical results remain promising, but there has been no further clinical data regarding risuteganib (21,33).

It is exciting that risuteganib improved BCVA in patients with dry AMD, but longer and larger trials will be needed to determine its true efficacy and mechanism of action. To date, studies assessing the actions of αVβ3 and αVβ5 integrins and preclinical trials, do not seem to offer an explanation for why risuteganib reverses retinal damage caused in non-exudative AMD, especially in such a short period of time. However, Elamipretide, another drug undergoing clinical trials for the treatment of dry AMD, also demonstrated an increase in BVCA for patients with dry and exudative AMD after a short study period (28 weeks) (36). With its novel mechanism of action, risuteganib has potential in the treatment of non-exudative AMD as monotherapy, and in DME and exudative AMD as adjunctive therapy to anti-VEGF agents or secondary therapy in refractory cases.

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Footnote

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Reporting Checklist: The authors have completed the Narrative Review reporting checklist. Available at https://dx.doi.org/10.21037/aes-21-12

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