Squalamine and age-related macular degeneration. Did the Shark lose its teeth?

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Abstract

Squalamine is a steroid-polyamine conjugate compound with anti-angiogenic activity. Based on scientific ground work, it started its journey as a potential drug to treat several pathologies including age-related macular degeneration in the mid-1990s. After an odyssey of more than 20 years and clinical trials for neovascular macular degeneration with both systemic and topical application of the compound, by not succeeding in the Phase III trials as of 2018, this journey seems to have reached an end.

Introduction

Squalamine was originally developed by Magainin Pharmaceuticals (subsequently called Genaera), in the mid-1990s based on the work of researcher Michael Zasloff. It is an antiangiogenic natural cationic steroid that has been isolated from tissues of several species of dogfish shark (Squalus acanthias). Squalamine was later owned by Genaera Corp., which closed, and the rights were sold by its liquidator to Ohr Pharmaceutical in 2009. The compound was studied as a potential anti-angiogenic drug, then tested in clinical studies for several types of cancer and received FDA fast track status for the treatment of "wet" age-related macular degeneration (AMD). Though squalamine may have a potential in the treatment of other processes, e.g. infections, this review will primarily focus on its anti-angiogenic capacity that is the present target in treating AMD.

Molecule

Squalamine, a steroid-polyamine conjugate, was first discovered in the tissues of the dogfish shark (Squalus acanthias) and recognized as a broad-spectrum anti-microbial agent in 1993[1,2]. Thereafter it was also identified within the circulating white blood cells of the sea lamprey (Petromyzon marinus) [3]. The chemical structure of squalamine (3β-N-1-N-[3-(4-aminobutyl)]-1,3-diaminopropane)-7α, 24R-dihydroxy-5α-cholestane 24 sulfate; molecular weight = 628) (Figure 1) was determined by fast atom bombardment mass spectroscopy and nuclear magnetic resonance. Squalamine was further characterized as a cationic steroid [4]. Since only trace amounts of squalamine are present in the liver of the shark, obtaining large amounts of the steroidal molecule from its natural source is difficult. Subsequently methods to make it synthetically have been developed [5-7]. The molecule carries a net positive charge by virtue of its spermidine moiety and exhibits a high affinity for anionic phospholipids [8, 9]. This may be a major reason for its potent bactericidal activity against both gram-negative and gram-positive bacteria. Furthermore, it is fungicidal, virucidal, and induces osmotic lysis of protozoa [10,11]. On the other hand, it was also found to have pharmacological activity in endothelial cells, inhibiting several growth factor-dependent processes (such as angiogenesis, migration as well as proliferation) both in vitro and in vivo [12-18].

Figure 1. Squalamine chemical structure

Action mode

Recently, squalamine was discovered to enter cells and cause displacement of proteins that are associated through electrostatic interactions with the inner face of the cytoplasmic membrane [19-21]. Due to its positive charge, on entry into a eukaryotic cell, it neutralizes the negative charge of the surface to which it binds [20]. Surprisingly, this disruption of electrostatic potential can occur without obvious structural damage to the cell membrane as measured by changes in permeability [20]. After entering a cell, squalamine subsequently persists and then exits over the course of hours [22-24]. Activated endothelial cells have been described to intake the drug through structures known as caveolae, which are small invaginations in the cellular membrane. Once it is taken up by the cell, it binds to calmodulin, preventing downstream signaling of the pro-angiogenic factors [25,26].

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Key words: squalamine, VEGF-inhibition, age-related macular degeneration, angiogenesis

Received: November 30, 2018; Accepted: December 10, 2018; Published: December 14, 2018
Intracellularly, squalamine exerts downstream antiangiogenic effects based on a novel intracellular mechanism of action. It has the ability to inhibit several growth factors such as vascular endothelial growth factor (VEGF), basic fibroblast growth factor (bFGF), and platelet-derived growth factor (PDGF). It may also interact with other signaling pathways.

Squalamine interrupts and reverses multiple facets of the angiogenic process. It additionally inhibits integrin expression and reverses cytoskeletal formation, thereby resulting in endothelial cell inactivation and apoptosis. It specifically inhibits brush-border Na⁺/H⁺-exchanger isoform NHE3, a sodium-hydrogen exchanger present on cell surfaces that regulates intracellular pH and is also known to regulate endothelial cell volume and shape. Growth factor related stimulation of the VEGF receptors (VEGFR) activates the MAP kinase pathways involved in blood vessel growth. Inhibition of the sodium-proton exchanger leads to changes in intracellular pH and subsequent inhibition of MAP kinase activity.

**Experimental studies**

The anti-angiogenic effect of squalamine was proven in different experimental models of neovascularization. Using a primate model, Genaidy et al. demonstrated in 2002 that systemic squalamine injection inhibited the development of iris neovascularization and caused partial regression of the pathological vessels. Interestingly, intravitreally injected squalamine did not affect the development of the pathological vessels [16].

Systemically administered squalamine lactate was also able to partially reduce choroidal neovascular membrane development induced by laser trauma in a rat model [27].

Squalamine was also shown to be a very active inhibitor of oxygen-induced retinopathy (OIR) in mouse neonates at doses as low as 1 mg/kg given once subcutaneously. Further, squalamine given late in the course of OIR improved retinopathy by inducing regression of retinal neovessels and aborting invasion of new vessels beyond the inner-limiting membrane of the retina [14,28].

In 2012, Ohr Pharmaceutical announced and presented a poster entitled "A Novel Eye Drop Formulation of Squalamine For Exudative AMD: evaluation of ocular distribution and ocular safety in rabbits" at the Association for Research in Vision and Ophthalmology (ARVO) Annual Meeting. The company presented data on the ocular tissue uptake and biodistribution of squalamine eye drops in Dutch belted rabbits when administered once or twice daily in each eye for up to fourteen days. Squalamine concentrations in the posterior sclera/choroid tissues were well above the previously suggested target therapeutic levels and sustained above that level for a full dosing interval. Moreover, the eye drop was found to be safe to ocular tissues, consistent with previous longer-term studies. The results indicated a rapid uptake to the posterior sclera/choroid ocular tissues with slow tissue clearance and sustained concentrations well above threshold antiangiogenic levels, which persist throughout the period in between doses ("trough level"). Safety to ocular tissues with no signs of ocular adverse clinical findings were consistent with previous longer-term toxicity studies. The systemic uptake was negligible which therefore minimizes the risk for systemic adverse events [29].

**Clinical trials**

After having been tested in an exudative AMD phase I study, the absence of any safety concerns led to several phase II trials [30-32]. Patients received a squalamine infusion once a week for 4 weeks. The high dose group (40 mg/infusion) lead to a mean change in BCVA (best-corrected visual acuity) of + 3.8 letters after the second dose and + 5.8 letters 1 week after the final dose. Adding to the positive biological effect with improvement or stability in the study eye of those patients receiving higher doses of the drug, the fellow non-study eyes with advanced macular degeneration also showed significant improvement after drug administration. However, because of pharmacokinetic issues of the intravenous delivery and local infusion site reactions, this route of medication was discontinued [33].

As a consequence of this result, a Phase 2 (IMPACT) study with a topical eye drop formulation (squalamine lactate ophthalmic solution 0.2%) was initiated [34].

The IMPACT trial was a phase II prospective, randomized, double-masked, placebo-controlled, multicenter, interventional study designed to evaluate the safety and efficacy of a topical 0.2% ophthalmic formulation of squalamine in patients with neovascular AMD. A total of 142 patients were enrolled who were treatment naïve with AMD-related choroidal neovascularization with size 12-disc diameters or less and BCVA of 20/40 to 20/320. All patients received ranibizumab at baseline and were then randomized in a 1:1 ratio to receive either topical squalamine 0.2% or placebo drops twice a day. They were followed up monthly with PRN monthly ranibizumab treatments if intraretinal edema or subretinal fluid were noted. The IMPACT study showed that visual acuity gains were related to the size and type of lesions in this study population. A positive benefit in terms of visual acuity outcomes was shown in patients whose lesions had a classic component. Further analysis of lesion type to predict visual acuity gains demonstrated that the smaller the occult CNV size, the greater the effect on visual acuity, with or without classic component. Those patients treated with ranibizumab monotherapy did not show a similar lesion-size dependent effect [35].

In conclusion, the IMPACT trial raised hopes that squalamine could be effective in achieving additional visual gains when used as a topical supplement to anti-VEGF injections. Therefore, the latest effort, the phase 3, MAKO trial for wet AMD was started [36].

The MAKO Study was a multicenter, randomized, double-masked, placebo-controlled clinical trial to evaluate the efficacy and safety of squalamine combination therapy for the treatment of wet AMD. Subjects were randomized 1:1 to receive topical squalamine lactate ophthalmic solution, 0.2%, twice daily and monthly ranibizumab injections or topical placebo twice daily and monthly ranibizumab injections. Eligibility criteria for the study eye included new diagnosed neovascular AMD and no previous treatment, occult neovascularization, if present, measuring less than 10mm as assessed by fluorescein angiography, and visual acuity between 20/40 and 20/320. A total of 237 subjects were randomized. Visual acuity was measured monthly using the Early Treatment of Diabetic Retinopathy Study (ETDRS) eye chart. The primary efficacy endpoint was the mean visual acuity gain at 9 months using a mixed-effects model for repeated measures (MVRM) analysis. Despite the fact that Ohr had used its phase 2 IMPACT trial to select the patient types most likely to benefit from its therapy, at 9 months, patients on ranibizumab monotherapy achieved a mean gain of 10.58 letters compared to a mean gain of 8.33 letters in the combination group.

**Conclusion**

Over the past decade, the only effective treatments that prevented vision loss in most patients with AMD were anti-VEGF agents [37,38].

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**Conclusion**

Over the past decade, the only effective treatments that prevented vision loss in most patients with AMD were anti-VEGF agents [37,38].
Different strategies and treatment regimens tried to balance injections and visits to lower the burden for patients, caregivers, and the health system. But there are still several unmet demands that need to be covered and ophthalmology is at a turning point in the management of this disease. New drug delivery strategies and new ways of interfering with the involved molecular cascades of the disease rise hopes. Squalamine, is or was a compound that carried such a promise and hope over a very long time. It was studied in an eye drop formulation as a potential way to reduce the burden of intravitreal injections [24]. A Phase II trial failed in 2015, but a subpopulation with choroidal neovascularization apparently responded well enough to justify a Phase III trial. The MAKO study, however, erased this last glimpse of hope.

The aminosterol antiangiogenic squalamine, naturally occurring and synthesized from the liver of the dogfish shark, a promising molecule, suggested for the treatment of various diseases (including lung cancer and foot ulcers), with studies undertaken by 3 different companies, may have finally run out of chances. Which is the remaining perspective for squalamine? Focusing on "strategic alternatives to maximize shareholder value" is the financial vision of this story. The mere scientific vision would be to get back to the roots, thrive for a better understanding of the original molecule itself and of its way of action and the various influencing factors that may have jeopardized its effect in humans.

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