Progress of Clinical Therapies for Dry Age-Related Macular Degeneration: A Literature Review
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Background and Significance
Dry Age-Related Macular Degeneration is the leading cause of irreversible blindness in adults over fifty. It is a progressive and debilitating disease that currently affects millions of people worldwide with no successful treatment available. There are two forms of AMD: Dry (non-exudative) and Wet (exudative). The wet form of the disease has FDA approved therapies to treat it, but the dry form has no approved therapies. Dry AMD accounts for more than 90% of cases. The millions of people suffering from Dry AMD are simply awaiting the slow progression to Geographic Atrophy and blindness. It is anticipated that the number of people with dry AMD will exponentially increase in the next 30 years. Currently much research is being done in the hopes of slowing the progression of this disease or of curing it. This paper endeavors to assess the current status and future direction of therapeutics for Dry AMD.

Research Question
What is the current state of clinical treatments and therapies for Dry Age-Related Macular Degeneration?

Methodology
A thorough search of Embase and Pubmed was conducted for recent and essential literature. A thorough search through the website ClinicalTrials.gov was also conducted to include trials that were in progress and did not have published results.

References
Please Contact Rhianna Rubner at rhianna.rubner@cuanschutz.edu for a complete list of references.

Results: Literature Synthesis
• Cell Based Therapies: Divided into stem-cell based and non-stem-cell based, both of which are delivered into the immune privileged subretinal space. Stem-cell based therapies aim to introduce new RPE cells to preserve the function of remaining photoreceptors. Non-stem-cell based therapies introduce cells that will provide protective factors lacking in the extracellular environment. Concerns include immune rejection, improper differentiation, damage to surrounding tissues, and tumor formation. Also concerning is non-FDA sanctioned treatment offered at clinics using autologous bone marrow-derived stem cells. Trials: MAD20-hRPE, CPCB-RPE1, iPSCs-RPE, CNT0-2476, SCOTS.
• Complement Inhibition: The complement system plays a key role in pathogenesis of geographic atrophy. Several complement system proteins, complement regulatory proteins, and activators are to be components of drusen; also, genetic studies described highly significant statistical associations between AMD and variants of several complement-associated genes. Difficulties for complement inhibition as a therapy include necessity of regular, often frequent, dosing, delivery of therapy to targeted area, method of delivery, etc. Trials: LGF316, Zimura, Lmpalizumab, APL-2.
• Gene Therapy: Designed to replace a deficient or non-functioning protein in order to stop or reverse a disease process. The eye is amenable to gene therapy as is small, transparent, and has a ready control in the other eye. Also, one-time administration, is appealing in terms of patient compliance. Choosing the optimal viral vector requires consideration of cloning capacity, safety, and tissue tropism. Adeno-associated viral vectors are most often used in gene therapy for ophthalmic diseases due to low pathogenicity, prolonged expression profile, and ability to transduce multiple cell types. Method of delivery of the vector (pars plana vitrectomy, intravitreal injection, retinotomy, or via the choroid) poses another debated topic. Trials: AAVCAGs/CDS59, GT005.
• Visual Cycle Modulation: A class of non-retinoid, small molecule compounds that target various enzymes that are part of the phototransduction cascade in the visual cycle. Photoreceptors have a high metabolic demand and increased metabolic waste and inflammatory byproducts. These byproducts are thought to accumulate and lead to inflammation that may contribute to the development of geographic atrophy. Therapies try to reduce inflammation and mitigate the process that may lead to geographic atrophy. Visual cycle modulators oral route of administration is appealing to patients, but the downside of these treatments is that dark adaptation and low-light vision can be adversely affected by modulating the visual cycle. Trials: Emixustat hydrochloride, ALK-001.
• Neuroprotection: Neuroprotection aims to stop progressive cellular damage and necrosis in AMD by utilizing cytoprotective and neuroprotective agents to enhance resilience of neuroretinal tissue against cellular injury. There are various strategies being investigated to achieve neuroprotection, such as, reducing oxidative injury, inhibiting cell death and apoptosis, and adding neuroprotective factors. Trials: Elamipretide, bromodirnine tartrate.
• Anti-Inflammatory Therapies: Sub-antimicrobial doses of tetracyclines can also exhibit anti-inflammatory properties. These antibiotics can prevent complement activation, inhibit cytokine production through effects on microglia and T-cell activation, inhibit caspase activation, reduce reactive oxygen species, and inhibit matrix metalloproteinases involved in the breakdown of the barrier between the RPE and Bruch’s membrane. Trials: Doxycycline, HTR2163.
• Photobiomodulation: This non-invasive treatment option works by using wavelengths of light that can be absorbed by Cytochrome C oxidase in the mitochondria of retinal cells to improve cellular respiration, increased membrane potentials, ATP production; it also leads to reduction in markers of age-related retinal inflammation, reduced free radical production and oxidative stress. The activation of the mitochondrial respiratory chain components leads to this stabilization of metabolic function and can ultimately promote cellular proliferation, in addition to, cytoprotection. Trials: LiteSite I, II, and III, Electrolight.
• Prostheses: The device is used to replace the function of destroyed photoreceptors and to electrically stimulate surviving retinal cells. They provoke neural activity in remaining retinal cells by detecting and converting light into electrical stimuli that can be delivered to the unaffected areas of the inner retinal neurons to evoke downstream visual pathway. All of the retinal implants contain an image capture unit with either a microphoto diode array or an external camera and also an array of electrodes for stimulation of the surviving retinal neurons, increasing the luminance of spatial information of images. Demonstrated benefit of some visual restoration for patients shown. Hurdles being researched include engineering of the devices and biophysical implantation that can make the device outcomes closer to natural vision. Trials: ARGUS II, PRIMA.

Conclusions
Each of the therapies discussed have merit and an important role in elucidating which avenue will provide the best therapeutic treatment. Continued research, not only into possible therapies, but also to gain a better understanding of the processes that lead to the retinal damage seen in Dry AMD will be paramount in diagnosis and treatment of this disease. Further research into improved imaging is also vital, as it will allow for more accurate diagnosis and earlier detection and characterization. Earlier detection may allow even current therapies to be more effective if they are started before substantial disease progression has occurred.

Clinical Implications
The goal of continuing research into pathogenesis, imaging techniques, and therapeutic options, is to find a means of slowing, stopping or even reversing damage caused by Dry AMD. Finding a way to accomplish this goal would spare the vision of millions of people worldwide that are currently suffering from this disease without hope of a cure.

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Conflicts of Interest:
The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Acknowledgments
This work was supported by funding from the Gates Family Fund, the Doni Solich Family Chair in Ocular Stem Cell Research, the CellSight Fund, and an Unrestricted Research Award from Research to Prevent Blindness to the Department of Ophthalmology at the University of Colorado.