For our latest Practical Retina column, **Sumit Randhir Singh, MD, Arshad M. Khanani MD, MA,** and **Jay Chhablani, MD,** comment on a unique topic: a review of unsuccessful trials that investigated therapies for age-related macular degeneration (AMD).

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Successful approval of only a handful of anti-vascular endothelial growth factor agents to treat wet AMD have resulted in the paradigm shift in management of wet AMD, and millions of patients have benefitted from our efforts. Much attention in our literature and at the podium has been focused on these positive data and clinical trials.

However, is there anything we can learn from failed trials which are only rarely discussed in our community? Perhaps a deeper analysis of why AMD trials failed can enable us to design better phase 3 trials and increase the chance of approval? As the great Henry Ford said, "The only real mistake is the one from which we learn nothing."

I am certain that the valuable insights and review of this unique topic provided by Drs. Singh, Khanani, and Chhablani will be interesting and valued by our community.

Unsuccessful Trials That Investigated Therapies for Age-Related Macular Degeneration

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Age-related macular degeneration (AMD) is one of the most common causes leading to irreversible visual loss in the elderly population, with an estimated worldwide prevalence rate of 8.69%.[1] Advanced AMD can be classified in two subtypes: geographic atrophy (GA) and neovascular AMD in the form of choroidal neovascularization (CNV). GA is characterized by presence of outer retina and/or retinal pigment epithelium (RPE) atrophy. Neovascular, or wet, AMD presents with subretinal fluid, hemorrhage, or intra/subretinal fluid. Anti-vascular endothelial growth factors (VEGF) therapy have ushered an era wherein at least 50% of patients with neovascular AMD benefit with visual acuity (VA) of 20/40 or greater after a series of successful randomized clinical trials.[2] On the other hand, there is no approved treatment option available for GA. A high rate of failure, particularly trials related to GA, happened possibly due to failure to understand the disease pathogenesis, owing to its multifactorial origin, whereas a few recent failures stem from a faulty study design or inappropriate inclusion criteria.[3] In this article, we discuss a brief overview of the recent unsuccessful clinical trials of AMD that did not move forward or failed to get U.S. Food and Drug Administration (FDA) approvals.

FOVISTA

Pegpleranib, or Fovista, (E10030; Ophthotech, New York, NY) is a 32-merpegylated DNA aptamer with selective anti-platelet-derived growth factor (PDGF) action.[3,4] Following

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TABLE 1
Failed Early Phase Clinical Trials on Age-Related Macular Degeneration

Name	Mechanism of Action	Phase	Comments
Pazopanib	Tyrosine kinase inhibitor against VEGFR-1, 2, 3, PDGFR-a, PDGFRβ, and c-kit	2b	Daily pazopanib eye drops failed to reduce number of PRN ranibizumab injections by ≥ 50%[16]
Rinucumab-aflibercept (CAPELLA study)	Aflibercept co-formulated with rinucumab (anti-PDGFR-beta) antibody	2	At 3 months, combination group showed no additional visual or anatomic improvement compared to aflibercept monotherapy[6,17]
Nesvacumab-aflibercept (ONYX study)	Aflibercept co-formulated with angiopoietin2 antibody	2	Combination therapy failed to meet the clinical endpoint at week 36[18]
Regorafenib	Multikinase inhibitor targeting kinases VEGF-R 2/3 and PDGFR	2a	Post-hoc analysis revealed 2.4 loss of ETDRS letters at week 12 leading to termination of study[19]
Acrizanib (LHA510)	Low molecular weight vascular endothelial growth factor receptor (VEGFR-2) inhibitor	2	Failed to show lower retreatment with anti VEGF injections[20]
NT-503-3 Encapsulated Cell Technology	Intraocular implant delivering VEGF inhibitors	2	Study prematurely terminated[21]
Avacincaptad pegol (Zimura)	Complement factor C5 inhibitor in combination with ranibizumab	2a	Further phase 3 trials about outcomes of combination therapy in wet AMD not planned[22]
Emixustat hydrochloride (ACU-4429)	Oral non-retinoid that inhibits the visual cycle isomerohydrolase, RPE65	2b/3	No significant reduction in growth of GA compared to placebo over 2 years[23]
Eculizumab	Humanized monoclonal antibody derived from the murine anti-human C5 antibody	2	Growth of GA did not vary significantly in intravenous eculizumab or placebo group at 26 weeks[24]

VEGFR = vascular endothelial growth factor receptor; PDGFR = platelet-derived growth factor receptor; PRN = pro-re-nata; ETDRS = early treatment of diabetic retinopathy study; RPE = retinal pigment epithelium; GA = geographic atrophy

the initial successful phase 1 trial, a phase 2 trial comparing 449 subjects randomized to one of three treatment groups including Fovista (0.3 mg) + ranibizumab, Fovista (1.5 mg) + ranibizumab, and ranibizumab alone was undertaken.[4,5] Phase 3 results at 12 months showed a nonsignificant difference while comparing the combination of Fovista with anti-VEGF or anti-VEGF alone (9.42 vs. 9.04 letters; $P = .74$), leading to premature termination of study.[3,6]

The three groups had a difference in baseline lesion size (1.9 disc areas in the 1.5-mg combination group to 1.5 disc areas in the sham group). This may possibly have affected the difference in baseline VA, as well. Therefore, a potential effect on the change in mean area of CNV during subsequent follow-up visits is a possibility. The main concern that may have led to a failure of phase 3 trial was the use of a retrospective subgroup analysis to report that lesion with subretinal hyperreflective material (SHRM) had the best VA improvement.[5] This prompted them to include all lesions with SHRM instead of only classic CNV, as in phase 2.

LAMPALIZUMAB

Lampalizumab (Roche/Genentech, Basel, Switzerland) is an inhibitor of complement factor D injected through the intravitreal route and presumed to block alternate complement pathway. The phase 2 trial of lampalizumab, known as the MAHALO study, studied its efficacy in GA.[7] Three randomized groups in a ratio of 1:1:1 that received 10 mg lampalizumab each month or on alternate months or sham were evaluated. The progression of lesion size with monthly lampalizumab was 20% lower compared to sham. However, a much higher reduction in progression (44%) of GA area was noted in carriers of complement factor I in comparison to sham.[7] These results led to the initiation of the phase 3 CHROMA and SPECTRI studies. The major concern, however, was that the inves-

tigators had predefined significance at a *P* value of 0.2 or less (ie, an increased alpha error). CHROMA and SPECTRI enrolled more than 1,800 patients but failed to show a statistically significant difference in GA lesion progression between lampalizumab vs. sham at 12 months, leading to premature termination of the study. The possible cause of failure in terms of molecular basis relates to the selective suboptimal inhibition of only alternate pathway with no effect on classical or lectin pathway.

TOPICAL SQUALAMINE

The MAKO study was a phase 3 study to compare the visual outcomes of combination therapy of topical, twice-daily squalamine lactate with ranibizumab (Avastin; Genentech, South San Francisco, CA) against monotherapy of ranibizumab in neovascular AMD.[6] The investigators included patients with classic CNV or occult CNV with an area less than 10mm² — a criterion derived, again, following retrospective analysis of the phase 2 IMPACT trial, results of which showed 11 letters gained in the combination group compared to monotherapy (5.7 letters).[6] The MAKO study failed to meet the primary endpoint.

ABICIPAR-PEGOL

Designed ankyrin repeat proteins (DARPins), a new class of binding proteins, are helpful in mediating protein-protein interactions.[8] Their pharmacokinetics can be modulated and their small size (14 kDa to 18 kDa), high affinity, and stability provided additional advantages. Phase 3 studies were conducted in eyes with neovasvular AMD based on a newer molecule, anti-VEGF DARPin molecule abicipar pegol (also known as abicipar).[9] It has a molecular weight of 34-kDa and is a fusion product of DARPin and polyethylene glycol (PEG) moiety. Previously, phase 1/2 studies showed acceptable outcomes with abicipar.[10,11] However, it failed to gain FDA approval in light of significant intraocular inflammation (8.9% to 15.4%) and an unfavorable risk-benefit ratio.[12,13]

Successful phase 3 clinical trials with anti-VEGF agents to treat wet AMD have resulted in the paradigm shift in management of wet AMD, and millions of patients have benefitted with anti-VEGF drugs. Unfortunately, the success seen with anti-VEGF drugs has been difficult to replicate with these newer drugs for wet AMD.[14,15] In addition, even though there are some potential promising treatments in the pipeline, there are no FDA-approved agents for GA. Table 1 shows a list of phase 1 and 2 clinical trials that either failed to provide successful clinical endpoints, and therefore phase 3 studies were not pursued, or that were prematurely terminated. There have been a few learning experiences from the unsuccessful phase 3 trials, as well. A critical analysis of the phase 2 trial results is needed, and phase 3 trials should be planned based on prospective primary endpoint data from the phase 2 trials. Planning future phase 3 studies on the basis of a retrospective subgroup analysis from phase 2 trials could result in failed phase 3 studies.

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