AMERICAN ACADEMY OF OPHTHALMOLOGY®

Anti–Vascular Endothelial Growth Factor Use and Atrophy in Neovascular Age-Related Macular Degeneration

Systematic Literature Review and Expert Opinion

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Topic: To summarize the rates of atrophy, risk factors, and atrophy-associated visual outcomes in patients with neovascular age-related macular degeneration (nAMD) who received anti–vascular endothelial growth factor (VEGF) treatment for macular neovascularization (MNV).

Clinical Relevance: Age-related macular degeneration is a leading cause of vision loss worldwide, and VEGF inhibitors are the primary treatment for nAMD. However, atrophy is observed frequently in eyes treated with anti-VEGF therapy, prompting questions regarding a causative role for these therapies in atrophy development.

Methods: PubMed was searched for articles published in the past 5 years (January 1, 2014, through January 10, 2019). Studies including atrophy outcome(s) in patients with age-related macular degeneration who received anti-VEGF treatment were included. Review articles, retrospective studies, case reports or studies, preclinical studies, prevalence data reports, and non-English studies were excluded. Randomization was not required.

Results: Overall, 145 studies were identified; 29 publications were included, with cohorts ranging from 8 to 1185 eyes. Imaging methods used to assess atrophy varied across studies. All studies confirmed the occurrence of atrophy, and when available, longitudinal data from the included studies demonstrated an increase in atrophy incidence over time. Key risk factors or phenotypes associated with atrophy were fellow eye atrophy, reticular pseudodrusen, increased injections, and type 3 lesion. In addition, visual acuity loss was noted with foveal atrophy.

Discussion: All studies demonstrated that atrophy occurs in the context of MNV treated with anti-VEGF therapy; however, it is not clear whether anti-VEGF treatment is causative of atrophy versus being associated with atrophy development. The included studies were not designed or powered to assess atrophy as a primary outcome. In addition, it is difficult to determine whether prognostic factors directly affect atrophy. Furthermore, patient populations in clinical trials do not necessarily represent real-world patients. Although phenotypes and risk factors may help to identify those at greater risk of atrophy developing, it is important to recognize that adequately treating exudative MNV remains the best option to optimize vision outcomes in patients with nAMD, particularly given the risk of vision loss with undertreatment observed in the real world. *Ophthalmology 2020;127:648-659 © 2019 by the American Academy of Ophthalmology. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).*

Age-related macular degeneration (AMD) is a leading cause of severe and irreversible vision loss worldwide.[1,2] Vascular endothelial growth factor (VEGF), a critical mediator of neovascular AMD (nAMD), is associated with pathologic vascular permeability and proliferation.[3,4] Phase 3 clinical trials of VEGF inhibitors validated intravitreal VEGF-A as a therapeutic target for nAMD treatment.[5–7]

Studies in mice lacking retinal pigment epithelium (RPE)–derived soluble VEGF demonstrated normal choriocapillaris development; however, an atrophy-like phenotype emerged, with areas of photoreceptor apoptosis and RPE loss.[8] In clinical research, observation of eyes with untreated intermediate AMD revealed that atrophy develops in a certain proportion of eyes.[9] In addition, an association between anti-VEGF treatment and atrophy development has been observed,[10–12] prompting questions regarding a causative role for these therapies in atrophy development. The potential relationship between atrophy and VEGF inhibition—the natural history of atrophy development, anti-VEGF causation of atrophy, or whether atrophy worsens the natural history of AMD—is unclear. Therefore, understanding the evidence behind the potential association between anti-VEGF treatment and atrophy is valuable. The objective of this systematic literature review was to summarize atrophy outcomes in patients with nAMD who received anti-VEGF treatment for macular neovascularization (MNV).

https://doi.org/10.1016/j.ophtha.2019.11.010
ISSN 0161-6420/19

Methods

Eligibility Criteria, Search, and Study Selection

Population, intervention, and outcome characteristics (Table 1) were used to search PubMed for articles published in the past 5 years (from January 1, 2014, through January 10, 2019). Review articles, retrospective studies, case reports or studies, preclinical studies, prevalence data reports, and non-English studies were excluded. Studies were required to report atrophy outcome(s), to include patients with AMD, and to include an anti-VEGF agent currently used to treat AMD (including bevacizumab). Randomization was not required. Abstracts were screened to determine which would undergo full-text review by a single reviewer (A.R.). The selected studies were further screened by an additional reviewer (J.S.) using the inclusion and exclusion criteria. The study adhered to the tenets set forth in the Declaration of Helsinki.

Data Analysis

The principal summary measures were atrophy outcomes and risk or predisposing factors for atrophy development or progression.

Results

Study Characteristics

Overall, 145 publications were assessed (Fig 1). After screening, 29 publications were included in the final analysis; the cohorts ranged from 8 to 1185 eyes.[10–38] Study designs are summarized within the tables. Atrophy was described using nomenclature from the respective trial; the lexicon is addressed in the "Discussion."

Comparison of Age-Related Macular Degeneration Treatments Trials

Thirteen publications from the Comparison of Age-Related Macular Degeneration Treatments Trials (CATT; ClinicalTrials.gov identifier; NCT00593450) assessed atrophy using color fundus photography (CFP) and fluorescein angiography (FA; Table 2).[11,13–24] In the CATT, this atrophy was termed *geographic atrophy* (GA), although atrophy was associated with MNV. Among the 1185 participants, GA was present already in 86 (7.3%) at baseline and developed in an additional 120 (10.1%) and 36 (3.0%) eyes during years 1 and 2, respectively (Table 3).[16] Among eyes with no GA at enrollment (n = 1024), 10.6% demonstrated GA by the end of year 1; this rate of incident GA increased to 18.3% by the end of year 2.[11] Among those who demonstrated GA at year 2, 83% showed extrafoveal GA and 17% showed foveal GA. Among gradable eyes, 41.4% demonstrated GA after 5 years; 16.5% of gradable eyes showed subfoveal GA.[18] The overall GA growth rate was 0.43 mm/year.[16]

Sustained visual acuity (VA) loss (≥15 letters from baseline at weeks 88 and 104) was observed in 61 of 1030 eyes (5.9%) that completed 2 years of follow-up.[13] In an analysis of the 61 eyes with sustained VA loss, it is interesting to note that only 7 (11.5%) sustained that loss as a result of foveal GA (5 of 24 ranibizumab-treated eyes [20.8%] and 2 of 37 bevacizumab-treated eyes [5.4%]). In a multivariate analysis of eyes with available morphologic and VA data at year 5, foveal GA was associated with poor VA outcomes.[24]

A multivariate analysis identified several baseline factors associated with GA development by 2 years, including study eye baseline VA, retinal angiomatous proliferation (RAP) lesion, fellow eye GA, intraretinal fluid, treatment (ranibizumab vs. bevacizumab), and regimen (monthly vs. as needed [PRN]; Table 4).[11] Blocked fluorescence lesion, subretinal thickness at the foveal center, and vitreomacular attachment were associated with decreased GA incidence at 2 years. An increased GA rate also was observed at 1 and 2 years in patients with baseline RAP lesions.[19]

Unresolved subretinal hyperreflective material (SHRM) at baseline was associated with lower GA rates at year 1.[17] Nonfibrotic scar in year 1 was associated with an increased GA incidence at years 2 and 5.[23] Poor baseline VA was associated with an increased risk of development of GA by 5 years.[22] Additional factors associated with a higher incident GA risk at 5 years were older age, hypercholesterolemia, increasing MNV lesion size, RAP lesion, fellow eye GA, and intraretinal fluid. Thicker subretinal tissue complex at the foveal center and subretinal fluid (SRF) at baseline were associated with a lower incident GA risk.

Table 1. Population, Intervention, Comparison, Outcome, and Setting Approach for Defining Eligibility Criteria

Item	Search Terms
Population	
Disease	Neovascular age-related macular degeneration, age-related macular degeneration, or choroidal neovascularization
Intervention	
Anti-VEGF therapy	Anti-VEGF, ranibizumab, aflibercept, or bevacizumab
Comparison	
Not searched	
Outcome	
Atrophy	Atrophy, macular atrophy, or geographic atrophy
Setting	
Study design	Phase 2, phase 3, and phase 4 RCTs; single-arm trials; prospective studies

RCT = randomized controlled trial; VEGF = vascular endothelial growth factor.

HARBOR

Three subanalyses from HARBOR (pHase III, double-masked, multicenter, randomized, Active treatment-controlled study of the efficacy and safety of 0.5 mg and 2.0 mg Ranibizumab administered monthly or on an as-needed Basis [PRN] in patients with subfoveal neOvasculaR age-related macular degeneration; ClinicalTrials.gov Identifier: NCT00891735) assessed atrophy using CFP and FA.[12,25,26] Among all patients in HARBOR who had no study eye with subfoveal atrophy (n = 1095), new macular atrophy (MA) was detected in 8.53%, 21.06%, and 29.43% of eyes at months 3, 12, and 24, respectively.[12] The mean

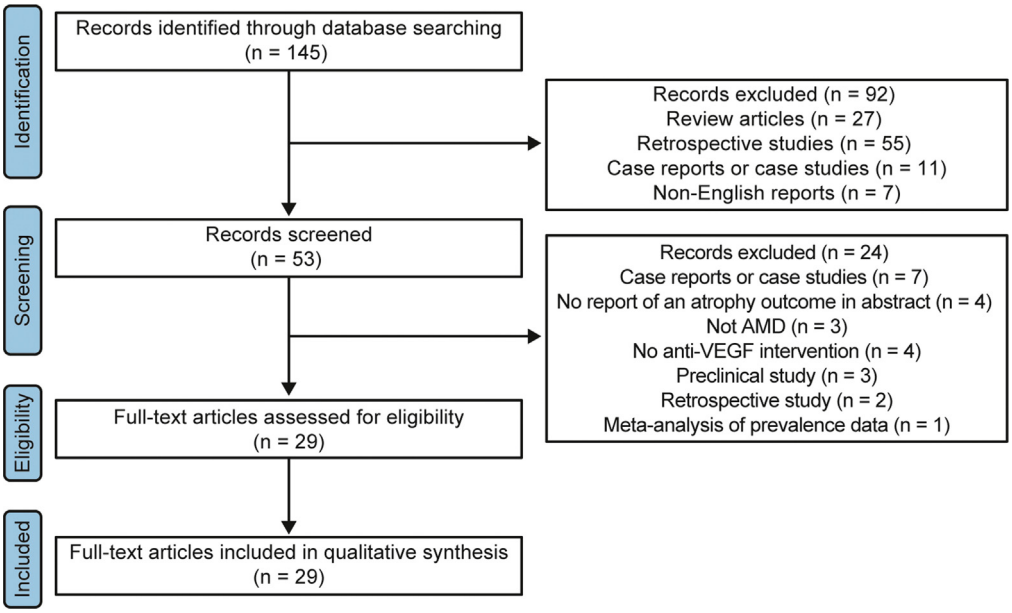

Figure 1. PRISMA flow diagram. AMD = age-related macular degeneration; PRISMA = Preferred Reporting Items for Systematic Reviews and Meta-Analyses; VEGF = vascular endothelial growth factor.

best-corrected visual acuity (BCVA) scores for eyes with and without concurrent baseline MA were 54.1 and 53.9 Early Treatment Diabetic Retinopathy Study (ETDRS) letters at baseline, 60.8 and 62.9 ETDRS letters at month 3, 62.9 and 65.0 ETDRS letters at month 12, and 62.0 and 64.7 ETDRS letters at month 24.

Intraretinal cyst, fellow eye atrophy, and increased age were associated with increased MA incidence.[12] Baseline SRF was associated with decreased MA development. In a pairwise comparison of dose–regimen combinations, a higher risk of MA development was reported with monthly than with PRN ranibizumab (0.5 mg).

IVAN

Two publications reported atrophy outcomes using CFP, FA, and spectral-domain (SD) OCT from IVAN (The Inhibition of VEGF in Age-related choroidal Neovascularisation; Current Controlled Trials ISRCTN92166560).[10,27] Over 2 years, 30% of eyes demonstrated GA.[10] An analysis of

Table 2. Studies Identified by the Systematic Literature Review and Methods Used for Assessing Atrophy in the Included Studies

Study	Methods for Assessing Atrophy
CATT[11,13–24]	Color fundus photography and fluorescein angiography*
HARBOR[12,25,26]	Color fundus photography and fluorescein angiography
IVAN[10,27]	Color fundus photography, fluorescein angiography, and OCT
RESPONSE[28]	Color fundus photography, fluorescein angiography, SD OCT, FAF, and infrared imaging
SEVEN-UP[29,30]	Fluorescein angiography and FAF†
TREX-AMD[31,32]	SD OCT, FAF, and infrared imaging
Chang et al (2015)[33]	Color fundus photography and fluorescein angiography, FAF, and SD OCT
Saito et al (2017)[34]	Color fundus photography and short-wavelength autofluorescence
Thavikulwat et al (2017)[35]	Color fundus photography, fluorescein angiography, FAF, and SD OCT
Zandi et al (2017)[36]	FAF and SD OCT
Mantel et al (2018)[37]	Color fundus photography, fluorescein angiography, FAF, and SD OCT
Mantel et al (2018)[38]	Color fundus photography, fluorescein angiography, FAF, and SD OCT

CATT = Comparison of Age-Related Macular Degeneration Treatments Trials; FAF = fundus autofluorescence imaging; HARBOR = pHase III, double-masked, multicenter, randomized, Active treatment-controlled study of the efficacy and safety of 0.5 mg and 2.0 mg Ranibizumab administered monthly or on an as-needed Basis (PRN) in patients with subfoveal neOvasculaR age-related macular degeneration; IVAN = The Inhibition of VEGF in Age-related choroidal Neovascularisation; RESPONSE = Genetics in Non-response to Anti-VEGF Treatment in Exudative AMD; SD = spectral-domain; SEVEN-UP = Seven-Year Observational Update of Macular Degeneration Patients Post-MARINA/ANCHOR and HORIZON Trials; TREX-AMD = Treat-and-Extend Age-Related Macular Degeneration.
*The study by Lee et al[11] also reported using SD OCT.
†The study by Bhisitkul et al[28] reported using color fundus photography.

Table 3. Atrophy Outcomes in the Included Studies

Study and Treatment Arms	Population	Atrophy Outcomes
CATT*		
Grunwald et al (2014)[11]	Eyes from CATT with no GA visible on CFPs and/or FAs at enrollment (N = 1024)	1 yr: 10.6% demonstrated GA; 2 yrs: 18.3% demonstrated GA
Ying et al (2014)[13]	Cohort study within CATT (N = 1030; patients who completed 2 yrs of follow-up)	Population: eyes with (n = 61) vs. without (n = 969) sustained VA loss at 2 yrs; GA at 2 yrs: 31.6% vs. 20.7% ($P = 0.004$)
Lee et al (2014)[14]	Eyes with SD OCT images at weeks 56 and 104 in CATT (N = 391)	Population: eyes with (n = 64) vs. without (n = 304) ORT at 2 yrs; GA at 2 yrs: 17.2% vs. 19.1% ($P = 0.86$)
Ciulla et al (2015)[15]	Eyes enrolled in CATT (N = 1115; patients with known baseline vitreomacular interface status)	Population: 1-yr outcomes of eyes with baseline VMT or VMA (n = 136) vs. neither (n = 908); GA at 1 yr: 8.82% vs. 16.7% ($P = 0.02$) Population: 2-yr outcomes of eyes with baseline VMT or VMA (n = 128) vs. neither (n = 848); GA at 2 yrs: 11.7% vs. 22.5% ($P = 0.005$)
Grunwald et al (2015)[16]	Eyes enrolled in CATT (N = 1185)	Present at baseline: 7.3%; 1 yr: an additional 10.1% of eyes demonstrated GA; 2 yrs: an additional 3.0% of eyes demonstrated GA; overall GA growth rate was 0.43 mm/yr (among 194 eyes evaluable for growth)
Willoughby et al (2015)[17]	Eyes enrolled in CATT (N = 1184; eyes with baseline OCT images)	Population: baseline SHRM unresolved vs. resolved; baseline SHRM unresolved (n = 385) vs. resolved (n = 312) at 1 yr; GA at 1 yr: 9.4% vs. 14.4% ($P = 0.04$) Population: baseline SHRM unresolved (n = 364) vs. resolved (n = 320) at 2 yrs; GA at 2 yrs: 17.0% vs. 15.6% ($P = 0.68$)
CATT Research Group (2016)[18]	Eyes enrolled in CATT, with a VA measurement in the required interval of 51 (4.3 yrs) to 85 (7.1 yrs) mos after assignment of treatment in the clinical trial (N = 647; 515 gradable eyes)	GA at 5 yrs: 41.4%; subfoveal GA at 5 yrs: 16.5%
Daniel et al (2016)[19]	Prospective cohort study within CATT (N = 1183)	Population: 1-yr outcomes of eyes with (n = 116) vs. without (n = 988) RAP at baseline; GA at 1 yr: 24.1% vs. 14.6% ($P = 0.014$) Population: 2-yr outcomes of eyes with (n = 110) vs. without (n = 922) RAP at baseline; GA at 2 yrs: 31.8% vs. 19.4% ($P = 0.004$)
Sharma et al (2016)[20]	Prospective cohort study within CATT (N = 1185)	GA at 1 yr: 1.9%; GA at 2 yrs: 6.1%
Daniel et al (2017)[21]	Prospective cohort study within CATT (N = 1185)	Population: 1-yr outcomes of eyes with hard exudate present (n = 120) vs. absent (n = 986) at baseline; GA at 1 yr: 18.6% vs. 16.1% ($P = 0.50$) Population: 2-yr outcomes of eyes with hard exudate present (n = 112) vs. absent (n = 922) at baseline; GA at 2 yrs: 26.6% vs. 20.7% ($P = 0.17$)
Grunwald et al (2017)[22]	Prospective cohort study within CATT (N = 1185; 517 with evaluable photographs at yr 5)	Population: patients who completed the 5-yr follow-up; GA at 1 yr: 13%; GA at 2 yrs: 18%; GA at 5 yrs: 39% Population: patients who completed the 5-yr follow-up (n = 112); overall GA growth rate: 0.29 mm/yr
Daniel et al (2018)[23]	Eyes with nonfibrotic scar identified at 1 yr in CATT (N = 39)	GA at 1 yr: 0%; GA at 2 yrs: 5%; GA at 5 yrs: 21% ($P = 0.02$)
Jaffe et al (2018)[24]	Eyes enrolled in CATT among patients who were alive at 5 yrs with VA and image gradings available (N = 523)	GA at yr 5: 16.2%
HARBOR†		
Sarraf et al (2016)[25]	Eyes enrolled in HARBOR (N = 1097)	Population: eyes with no atrophy at baseline, eyes with (n = 404) vs. without (n = 342) PED; MA at 2 yrs: 32% vs. 29% Population: eyes with PED at baseline and no atrophy at baseline, complete PED flattening vs. present PED at 2 yrs; MA at 2 yrs: 44% vs. 17% ($P < 0.0001$)
Rebhun et al (2018)[26]	Eyes with nAMD and PED (N = 28)	OCT-based MA at 2 yrs: 50%
Sadda et al (2018)[12]	Eyes enrolled in HARBOR (N = 1095)	New MA at 2 yrs: 29%
IVAN‡		
Chakravarthy et al (2015)[10]	Eyes enrolled in IVAN (N = 610; ranibizumab [n = 314], bevacizumab [n = 296]; at 3 mos, continuous [n = 305], discontinuous [n = 300])	New GA at 2 yrs: 30%; ranibizumab vs. bevacizumab GA: 28% vs. 31% ($P = 0.46$); continuous vs. discontinuous GA: 34% vs. 26% ($P = 0.03$)

(*Continued*)

Table 3. (Continued.)

Study and Treatment Arms	Population	Atrophy Outcomes
Bailey et al (2019)[27]	Eyes enrolled in IVAN (N = 610; ranibizumab [n = 314], bevacizumab [n = 296]; at 3 mos, continuous [n = 305], discontinuous [n = 300])	Intralesional MA at baseline: 9.6%; incident intralesional MA at 2 yrs: 24.4%; incident extralesional MA at 2 yrs: 1.54%
RESPONSE[§]		
Sitnilska et al (2018)[28]	Eyes without baseline atrophy that received ≥9 anti-VEGF injections for ≥3 yrs (N = 52)	RPEA at 1 yr: 28.8%; RPEA at 2 yrs: 40.4%; RPEA at 3 yrs: 44.2%; RPEA at final visit in third yr: 57.7%
SEVEN-UP[‖]		
Bhisitkul et al (2016)[29]	Eyes from ANCHOR, MARINA, and HORIZON; 7 yrs after randomization (N = 65)	MA at baseline: 78.6%; MA at yr 7: 97.7%
Kuehlewein et al (2016)[30]	Eyes from ANCHOR, MARINA, and HORIZON; 7 yrs after randomization, with baseline and 7-yr follow-up gradable images (N = 41)	RPEA at baseline: 7.3%; mean area, 0.29±1.50 mm^2: RPEA at yr 7: 70.7%; mean area, 7.42±7.97 mm^2 ($P < 0.001$)
TREX-AMD[¶]		
Abdelfattah et al (2017)[31]	Eyes enrolled in TREX-AMD (N = 60)	Mean ERMA over 18 mos: 0.39±0.67 (every 4 wks), 1.1±1.9 (TREX), 0.49±1 mm^2 (control; $P = 0.12$); mean ERMA (patients with baseline MA; n = 36): 0.9±1 (every 4 wks), 1.9±2.2 (TREX), and 1±1.3 mm^2 (control; $P = 0.31$); ERMA incidence: 40% (every 4 wks), 0% (TREX), and 8.3% (control)
Abdelfattah et al (2018)[32]	Eyes enrolled in TREX-AMD (N = 60)	By month 18: MA + MNV overlap, 84.6%; MA in baseline classic MNV regions, 36.4%; MA in baseline occult MNV regions, 40.9%; MA in both regions, 22.7%
Others		
Chang et al (2015)[33,#]	Eyes with treatment-resistant nAMD (N = 49)	Median RPEA area growth at month 12, 0.48 mm^2
Saito et al (2017)[34,**]	Eyes with AMD (N = 47)	Population: PCV (n = 20) and typical AMD (n = 27); GA at 1 yr: 5.0% and 11.1%
Thavikulwat et al (2017)[35,††]	Eyes with nAMD (N = 69; n = 63 with quality baseline images)	Pre-existing GA (among eyes with quality baseline images): 35%; new-onset GA (among eyes without preexisting GA): 17%; GA growth in eyes with baseline GA vs. new-onset GA: 0.34±0.26 mm/yr vs. 0.19±0.12 mm/yr
Zandi et al (2017)[36,‡‡]	Eyes matching the requirements of MARINA and ANCHOR (N = 84)	Population: gainers (n = 49) vs. poor responders (n = 35); foveal RPEA: 14% vs. 31% ($P = 0.05$); juxtafoveal RPEA: 14% vs. 37% ($P = 0.015$); extrafoveal RPEA: 16% vs. 29% ($P = 0.14$)
Mantel et al (2018)[37,§§]	Eyes without macular atrophy at baseline (N = 149; aflibercept, 70 eyes; ranibizumab, 79 eyes)	MA at 2 yrs: 42%; mean area of new atrophy: 1.9 mm^2
Mantel et al (2018)[38,‖‖]	Eyes with nAMD (N = 109; 101 patients)	Analysis included only eyes with MA at 2 yrs; MA growth rate: 0.54±0.34 mm/yr

AMD = age-related macular degeneration; ANCHOR = Anti-VEGF Antibody for the Treatment of Predominantly Classic Choroidal Neovascularization in Age-Related Macular Degeneration; CATT = Comparison of Age-Related Macular Degeneration Treatments Trials; CFP = color fundus photography; ERMA = enlargement rate of macular atrophy; FA = fluorescein angiography; GA = geographic atrophy; HARBOR = pHase III, double-masked, multicenter, randomized, Active treatment-controlled study of the efficacy and safety of 0.5 mg and 2.0 mg Ranibizumab administered monthly or on an as-needed Basis (PRN) in patients with subfoveal neOvasculaR age-related macular degeneration; HORIZON = pHase 3b Open-Label Extension Trial of Ranibizumab for Choroidal Neovascularization Secondary to Age-related Macular Degeneration; IVAN = The Inhibition of VEGF in Age-related choroidal Neovascularisation; MA = macular atrophy; MARINA = Minimally Classic/Occult Trial of the Anti-VEGF Antibody Ranibizumab in the Treatment of Neovascular Age-Related Macular Degeneration; MNV = macular neovascularization; nAMD = neovascular age-related macular degeneration; ORT = outer retinal tubulation; PCV = polypoidal choroidal vasculopathy; PED = pigment epithelial detachment; PRN = as needed; RAP = retinal angiomatous proliferation; RESPONSE = Genetics in Non-response to Anti-VEGF Treatment in Exudative AMD; RPEA = retinal pigmented epithelium atrophy; SD = spectral-domain; SEVEN-UP = Seven-Year Observational Update of Macular Degeneration Patients Post-MARINA/ANCHOR and HORIZON Trials; SHRM = subretinal hyperreflective material; TREX = treat and extend; TREX-AMD = Treat-and-Extend Age-Related Macular Degeneration; VA = visual acuity; VEGF = vascular endothelial growth factor; VMA = vitreomacular adhesion; VMT = vitreomacular traction.

*Ranibizumab 0.5 mg every 4 wks; bevacizumab 1.25 mg every 4 wks; ranibizumab 0.5 mg PRN; bevacizumab 1.25 mg PRN (for patients with every-4-wks treatment: second randomization to either every 4 wks or PRN treatment at 1 yr with same drug).

†Ranibizumab 0.5 mg every 4 wks; ranibizumab 0.5 mg PRN; ranibizumab 2.0 mg every 4 wks; ranibizumab 2.0 mg PRN.

‡Ranibizumab 0.5 mg every 4 wks; bevacizumab 1.25 mg every 4 wks; ranibizumab 0.5 mg PRN; bevacizumab 1.25 mg PRN.

§Ranibizumab PRN ×2 yrs, then PRN ranibizumab, bevacizumab, or aflibercept.

‖Included eyes from the ANCHOR, MARINA, and HORIZON studies that received ranibizumab.

¶Ranibizumab 0.5 mg every 4 wks; ranibizumab 0.5 mg TREX.

#Aflibercept 2 mg every 4 wks ×3 doses, then every 8 wks.

**Aflibercept every 4 wks ×3 doses, then every 8 wks until 12 mos.

††Ranibizumab 0.5 mg PRN.

‡‡Ranibizumab every 4 wks.

§§Ranibizumab observe and plan; aflibercept observe and plan.

‖‖Ranibizumab observe and plan; aflibercept observe and plan.

Table 4. Risk Factors or Predisposing Factors of Interest in Included Studies

Study	Risk Factors or Predisposing Factors of Interest and Vision Outcomes Associated with Atrophy
CATT*	
Grunwald et al (2014)[11]	Increased risk of GA development (multivariate analysis): worse VA (relative to baseline VA of 20/25–20/40; $P = 0.007$), GA in the fellow eye (relative to none or questionable; $P = 0.0003$), RAP lesion (relative to absence; $P = 0.007$), intraretinal fluid (relative to no fluid; $P = 0.006$), ranibizumab treatment (relative to bevacizumab; $P = 0.02$), monthly treatment (relative to PRN; $P = 0.003$) Lower risk of GA development (multivariate analysis): blocked fluorescence lesion (relative to absence; $P = 0.007$), increasing SRF thickness at foveal center (relative to 0 μm; $P = 0.006$), increasing subretinal tissue complex thickness in the foveal center (relative to >0 to ≤75 μm; $P < 0.0001$), vitreomacular attachment (relative to none; $P = 0.04$)
Ciulla et al (2015)[15]	Eyes with VMA or VMT at baseline (n = 15 [11.7%]) were less likely to demonstrate GA at 2 yrs than were those without VMT or VMA (n = 191 [22.5%]; $P = 0.005$)
Grunwald et al (2015)[16]	Factors for faster GA growth rate (multivariate analysis): ranibizumab treatment (relative to bevacizumab; $P = 0.03$), minimally classic or predominantly classic lesion (relative to occult only; $P < 0.01$), GA in the fellow eye (relative to absence; $P = 0.03$), epiretinal membrane (relative to none; $P = 0.02$), distance to fovea (per 1-mm increase; $P = 0.03$), nonsubfoveal lesion (relative to subfoveal lesion; $P = 0.03$)
Willoughby et al (2015)[17]	GA developed in more eyes with resolved SHRM at wk 52 (n = 45 [14.4%]) than in eyes with persistent SHRM (n = 36 [9.4%]; $P = 0.04$)
Grunwald et al (2017)[22]	Increased risk of incident GA (baseline; multivariate analysis): older age (relative to 50–69 yrs of age; $P = 0.04$), hypercholesterolemia (relative to none; $P = 0.01$), worse VA (relative to baseline VA of 20/25–20/40; $P = 0.02$), larger MNV area (relative to ≤1 DA; $P = 0.01$), RAP lesion (relative to none; $P < 0.001$), GA in the fellow eye (relative to none or questionable; $P < 0.001$), and IRF (relative to none; $P < 0.001$) Decreased risk of incident GA (baseline; multivariate analysis): thicker subretinal tissue complex at foveal center (relative to >0 to ≤75 μm; $P < 0.001$) and SRF (relative to none; $P < 0.001$) Increased risk of GA growth (multivariate analysis): ranibizumab treatment in first 2 yrs (relative to bevacizumab; $P = 0.009$), baseline fellow eye GA (relative to absence; $P = 0.03$), hemorrhage associated with MNV (relative to absence; $P = 0.049$), absence of sub-RPE fluid or nonsubfoveal sub-RPE fluid (relative to subfoveal sub-RPE fluid; $P = 0.003$)
HARBOR†	
Rebhun et al (2018)[26]	MA at 2 yrs was associated significantly with baseline MA or nascent MA ($P = 0.0136$), fellow eye MA at baseline ($P = 0.0467$), baseline intraretinal cysts ($P = 0.0048$), and collapse of PEDs in study eye ($P = 0.0025$)
Sadda et al (2018)[12]	Factors associated with MA at 2 yrs (multivariate analysis): baseline intraretinal cyst (HR, 2.45; 95% CI, 1.76-3.42), baseline fellow eye MA (HR, 2.02; 95% CI, 1.42-2.87), baseline age (5-yr increase; HR, 1.09; 95% CI, 1.0027-1.19) Decreased risk of MA development (multivariate analysis): baseline SRF (HR, 0.50; 95% CI, 0.33–0.74)
IVAN‡	
Bailey et al (2019)[27]	Factors that increased odds of incident intralesional MA in the study eye: fellow eye extralesional MA at baseline ($P < 0.001$) Factors that lowered odds of incident intralesional MA in study eye: >50% classic MNV (baseline; relative to classic MNV accounting for ≤50% lesion area; $P = 0.010$), SRF (final visit; $P = 0.004$), PED (final visit; $P = 0.004$)
RESPONSE§	
Sitnilska et al (2018)[28]	Significant association with RPEA development: total follow-up time (logistic regression analysis; $P = 0.012$), baseline CRT (Cox regression analysis; $P = 0.005$)
SEVEN-UP‖	
Kuehlewein et al (2016)[30]	First model: significantly associated with area of DDAF, area of leaking MNV lesion components ($P < 0.001$), area of other lesion components ($P = 0.038$), and area of RPEA ($P = 0.040$) Second model: significantly associated with area of DDAF, area of RPEA ($P < 0.001$), and area of other lesion components ($P < 0.001$)
TREX-AMD¶	
Abdelfattah et al (2017)[31]	Significant association between decreased choroidal thickness ($P = 0.01$) and increased SHRM thickness ($P = 0.02$) with MA presence at month 18 Risk factors for development of new MA: SHRM ($P = 0.042$), SHRM thickness ($P = 0.014$), PED thickness ($P = 0.045$), and baseline hemorrhage ($P = 0.016$)

(*Continued*)

Table 4. (Continued.)

Study	Risk Factors or Predisposing Factors of Interest and Vision Outcomes Associated with Atrophy
Other	
Mantel et al (2018)[37]	Confirmed associated baseline factors with de novo MA incidence (multivariate analysis): fewer anti-VEGF injections ($P = 0.011$), depigmentation ($P = 0.0004$), reticular pseudodrusen ($P = 0.0005$), lower baseline VA ($P = 0.0006$), and RAP ($P = 0.0011$)
Mantel et al (2018)[38]	Factors associated with faster MA growth (multivariate analysis): lower baseline VA ($P = 0.008$), PED >200 μm ($P = 0.035$) Significant correlation: MA growth rates in neovascular eyes with nonneovascular fellow eyes ($P = 0.003$)

AMD = age-related macular degeneration; CATT = Comparison of Age-Related Macular Degeneration Treatments Trials; CRT = central retinal thickness; DA = disc area; DDAF = definite decreased autofluorescence; GA = geographic atrophy; HARBOR = pHase III, double-masked, multicenter, randomized, Active treatment-controlled study of the efficacy and safety of 0.5 mg and 2.0 mg Ranibizumab administered monthly or on an as-needed Basis (PRN) in patients with subfoveal neOvascularR age-related macular degeneration; HR = hazard ratio; IRF = intraretinal fluid; IVAN = The Inhibition of VEGF in Age-related choroidal Neovascularisation; MA = macular atrophy; MNV = macular neovascularization; PED = pigment epithelial detachment; PRN = as needed; RAP = retinal angiomatous proliferation; RESPONSE = Genetics in Non-response to Anti-VEGF Treatment in Exudative AMD; RPE = retinal pigmented epithelium; RPEA = retinal pigmented epithelium atrophy; SEVEN-UP = Seven-Year Observational Update of Macular Degeneration Patients Post-MARINA/ANCHOR and HORIZON Trials; SHRM = subretinal hyperreflective material; SRF = subretinal fluid; TREX-AMD = Treat-and-Extend Age-Related Macular Degeneration; VA = visual acuity; VEGF = vascular endothelial growth factor; VMA = vitreomacular adhesion; VMT = vitreomacular traction.
*Ranibizumab 0.5 mg every 4 wks; bevacizumab 1.25 mg every 4 wks; ranibizumab 0.5 mg PRN; bevacizumab 1.25 mg PRN (for patients with every-4-wks treatment: second randomization to either every 4 wks or PRN treatment at 1 year with same drug).
†Ranibizumab 0.5 mg every 4 wks; ranibizumab 0.5 mg PRN; ranibizumab 2.0 mg every 4 wks; ranibizumab 2.0 mg PRN.
‡Ranibizumab 0.5 mg every 4 wks; bevacizumab 1.25 mg every 4 wks; ranibizumab 0.5 mg PRN; bevacizumab 1.25 mg PRN.
§Ranibizumab PRN ×2 yrs, then PRN ranibizumab, bevacizumab, or aflibercept.
||Included eyes from the ANCHOR, MARINA, and HORIZON studies that received ranibizumab.
¶Ranibizumab 0.5 mg every 4 wks; ranibizumab 0.5 mg treat and extend.

revised image grading from IVAN revealed no intralesional MA at baseline or at the final visit in 390 eyes (65.4%); no baseline intralesional MA, but intralesional MA at the final visit, in 127 eyes (21.3%); and intralesional MA at both baseline and the final visit in 57 eyes (9.6%).[27] In the analysis of intralesional MA development, no statistically significant difference in visual outcomes was found between eyes that did versus those that did not demonstrate MA over 2 years; however, a rigorous assessment of the foveal MA and vision relationship was not possible because of the imaging protocol.

Factors that reduced the odds of intralesional MA developing by the final visit were classic MNV lesions, SRF at the final visit, and pigment epithelial detachment (PED) at the final visit.[27] The odds of intralesional MA being present in the study eye increased significantly when baseline fellow-eye extralesional MA was present. The final total area of intralesional MA was significantly larger in patients with than in those without baseline intralesional fellow-eye MA.

RESPONSE

A post hoc analysis of RESPONSE (Genetics in Non-response to Anti-VEGF Treatment in Exudative AMD [RESPONSE]; ClinicalTrials.gov identifier: NCT01213667) assessed atrophy using CFP, FA, SD OCT, fundus autofluorescence (FAF), and infrared imaging.[28] Retinal pigmented epithelium atrophy (RPEA) developed in 21.2%, 28.8%, 40.4%, 44.2%, and 57.7% of patients at 6 months, year 1, year 2, year 3, and the final visit, respectively. Baseline central retina thickness was the only significant predictor of RPEA development.

SEVEN-UP

Two subanalyses of atrophy from SEVEN-UP (Seven-Year Observational Update of Macular Degeneration Patients Post-MARINA/ANCHOR and HORIZON Trials; ClinicalTrials.gov identifier: NCT01256827) using FA and FAF were included.[29,30] Macular atrophy was present in 22 study eyes (78.6%) at baseline and in 40 study eyes (93.0%) and 43 study eyes (97.7%) at years 2 and 7, respectively.[29] In a separate subanalysis conducted only in patients with gradable baseline images, MA was evident in 3 study eyes (7.3%) at baseline and in 70.7% of study eyes at the 7-year follow up.[30] Fundus autofluorescence imaging at the 7-year follow-up visit revealed definite decreased autofluorescence in 100% of study eyes (comparison over time was not possible because no FAF images were obtained during MARINA [Minimally Classic/Occult Trial of the Anti-VEGF Antibody Ranibizumab in the Treatment of Neovascular Age-Related Macular Degeneration; ClinicalTrials.gov identifier: NCT00056836] and ANCHOR [Anti-VEGF Antibody for the Treatment of Predominantly Classic Choroidal Neovascularization in Age-Related Macular Degeneration; ClinicalTrials.gov identifier: NCT00061594]).[30]

Baseline predictors of increased definite decreased autofluorescence area at 7 years were leaking MNV lesion area components, area of other lesion components (including the

combined area of serous PED, hemorrhage, blocked fluorescence, and staining scar), and RPEA area.[30] Factors associated with definite decreased autofluorescence area at 7 years were RPEA area and area of other lesion components.

TREX-AMD

Two articles from TREX-AMD (Treat-and-Extend Age-Related Macular Degeneration; ClinicalTrials.gov identifier: NCT01748292) used SD OCT, FAF, and infrared imaging to assess atrophy.[31,32] Macular atrophy was present at baseline in 36 eyes (40.9%) overall and developed in 15.4% of eyes (n = 8 [monthly, 6 eyes; TREX, 0 eyes; control fellow group, 2 eyes]) of eyes without MA at baseline over 18 months.[31] A significant correlation was found between increased BCVA and decreased MA area at baseline and months 6, 12, and 18.[31]

At 18 months, a significant association existed between MA presence and decreased choroidal thickness and increased SHRM thickness.[31] Development of new MA by month 18 was associated significantly with SHRM on OCT, SHRM thickness, PED thickness, and hemorrhage on CFP at baseline.

Additional Studies

In a study by Chang et al[33] of aflibercept for treatment-resistant nAMD, atrophy was assessed using CFP, FA, FAF, and SD OCT. The median RPEA area increased significantly at 12 months versus baseline. No association was noted between baseline central RPEA and poor vision, and no significant correlation was found between RPEA area (location not specified) change and BCVA change over 12 months.

A study of aflibercept in Japanese patients, including those with polypoidal choroidal vasculopathy (PCV), assessed atrophy using CFP and short-wavelength autofluorescence.[34] Among 47 eyes (27 with typical AMD, 20 with PCV), baseline GA was detected in 4 eyes (3 with typical AMD, 1 with PCV) and new or progressing GA was detected in 4 eyes (3 with typical AMD, 1 with PCV) at month 12. At month 12, the mean BCVA change was significantly worse in eyes with versus without GA.

In a study of PRN ranibizumab, Thavikulwat et al[35] assessed atrophy using CFP, FA, and FAF (aligned to a CFP, creating a stack of images into a single image). Among 69 evaluable eyes, GA was present at baseline in 22 eyes (31.9%) and developed in 7 eyes (10.1%). Newly developed GA was present within 1 year in 6 eyes (85.7%) and within 2 years in 1 eye (14.3%). Eyes in which new GA developed were older, had poorer baseline VA, received fewer injections in year 1, were less likely to be treatment naive, and were less likely to have occult MNV. Retinal angiomatous proliferation lesions were present in 2 eyes that subsequently demonstrated GA in the area of previous hemorrhage.

A study of early visual response to a single ranibizumab treatment by Zandi et al[36] assessed atrophy using FAF and SD OCT. The assessment of RPEA and VA outcomes, stratified by gainers (n = 49) and early poor responders (n = 35), reported presence of baseline foveal RPEA in 7 eyes (14%) of gainers and in 11 eyes (31%) of early poor responders. Increased RPEA was identified as a predisposing factor to poor ranibizumab response.

In 2 identically designed studies of a modified fixed treatment plan based on exudation (interval capped at 3 months) with either ranibizumab or aflibercept,[39] MA was assessed by CFP, FA, FAF, and SD OCT.[37,38] In year 2, de novo MA was observed in 63 eyes (42%). Newly developed MA overlapped completely with baseline MNV boundaries in 48 eyes (73.8%), occurred completely outside baseline MNV in 7 eyes (10.8%), and showed mixed localization in 10 eyes (15.4%). Risk factors for developing new atrophy over 2 years were depigmentation, reticular pseudodrusen, lower baseline VA, RAP lesion, and fewer injections. Macular atrophy growth rates were associated significantly with lower baseline VA and PED height of more than 200 μm.[38]

Discussion

Data were reviewed from 29 publications reporting atrophy outcomes in studies of anti-VEGF treatment for nAMD, and although not directly comparable, all showed that atrophy occurs. The current review identified numerous risk factors and phenotypes associated with atrophy development or growth, including fellow eye atrophy,[12,16,22,27] reticular pseudodrusen,[37] frequency of injections,[10–12] and type 3 or RAP lesion.[11,19,22,37] In addition, foveal atrophy has been shown to be associated significantly with VA loss.[24] These phenotypes may explain why not all patients with AMD have the same atrophy-related outcomes. For example, patients with type 3 lesions typically demonstrate atrophy in parallel with anti-VEGF treatment; however, those with other lesion types may not demonstrate atrophy as readily with anti-VEGF therapy.[40]

It is important to note that, in the included studies, atrophy was assessed in the context of MNV treated with anti-VEGF agents; therefore, it was difficult to differentiate between atrophy that is part of the AMD natural history and that which is secondary to the MNV process. Furthermore, imaging method may affect interpretation of atrophy outcomes. For example, when images from HARBOR were analyzed with SD OCT, no difference in atrophy with monthly versus PRN was noted, in contrast with previous findings on CFP or FA.[12,41] One possible explanation for these differences may be the presence of fluid confounding the CFP images.

Current evidence supports 2 or more explanations for atrophy emergence. First, as individuals age, physiologic changes at the cellular level lead to RPE cell apoptosis (reviewed in Ehrlich et al[42]), suggesting that patients with AMD may be destined to demonstrate atrophy. Phase 3 clinical trial data from patients with GA and no evidence of MNV demonstrated increased GA lesion size over time[43,44]; such increases in the absence of VEGF inhibition support atrophy as part of the natural history of AMD. Recent evidence suggests that atrophy can arise de novo in areas of pre-existing subretinal lesions or in areas with outer retinal atrophy alone or with RPE loss. Continued VEGF inhibition also may increase atrophy development. Studies in mice lacking RPE-derived soluble VEGF

revealed a phenotype resembling atrophy.[8] The 2-year CATT analysis revealed an increased association between atrophy incidence and frequent treatment and also demonstrated a reduced incidence from year 1 to 2 among patients switched from monthly to PRN treatment; at the 5-year visit, the differences were no longer significant.[11,18] It is possible that insufficient data at the 5-year CATT visit precluded a demonstration of significance. Importantly, follow-up analyses of HARBOR and IVAN revealed no difference in atrophy incidence with monthly or continuous versus PRN or discontinuous treatment, in contrast with initial findings.[10,12,27,41]

The relationship between atrophy and neovascularization in AMD remains unclear. One hypothesis is that atrophy is the natural end result of the pathologic processes occurring in AMD. More recently, with the advent of OCT angiography, detection of nonexudative neovascularization in eyes without symptoms and with early or intermediate AMD has become possible. In these cases, it is hypothesized that nonexudative neovascularization is a physiologic response to hypoxia to limit ischemia. However, if the response becomes uncontrolled, then exudation may occur, and treatment becomes necessary. In this scenario, anti-VEGF therapy would be an intervention to a physiologic process gone awry. This scenario also underscores the critical nature of deciding when to treat neovascularization that is detected only on imaging. Currently, no data support intervention before exudation occurs; however, it would seem reasonable to observe patients with nonexudative neovascularization at more regular intervals, because early treatment of exudative MNV, before vision is lost, is associated with better outcomes.

The presence of fluid has become a topic of increasing interest as more becomes known about the presence and persistence of fluid and treatment outcomes. Some studies have suggested that SRF is associated with lower rates of atrophy and better VA.[12,20,22,27] It is important to note that these studies established only an association between SRF and better visual outcomes, and not a causal link. Furthermore, patients with persistent fluid were still being treated with anti-VEGF therapy to achieve the reported visual outcomes. It is also important to note that fluid is one aspect of a lesion, and any predisposing phenotype may be more broadly a result of the lesion type or summation of several characteristics. For example, the presence of a small amount of SRF may be the result of a residual type 1 (sub-RPE) neovascular lesion that is being controlled by anti-VEGF therapy, and it may be that the neovascular lesion itself is conferring the protective effect.

The FLUID (Tolerating Subretinal Fluid in Neovascular Age-Related Macular Degeneration Treated with Ranibizumab Using a Treat-and-Extend Regimen; ClinicalTrials.gov NCT01972789) study was designed to determine the impact of SRF tolerance on VA.[45] At 2 years, BCVA was noninferior with a treat-and-extend regimen that tolerated SRF versus a treat-and-extend regimen with complete SRF resolution. A possible explanation is that a small amount of SRF may indicate persistence of a minimally exudative MNV, and treatment extension under these circumstances may be acceptable. Careful monitoring to distinguish between fluid that is stable and nonresponsive to anti-VEGF treatment and new fluid occurring as a result of high VEGF activity may help to guide treatment decisions. In FLUID, it seemed that treatment intervals could be extended cautiously by a maximum of 2 weeks at a time after treatment, in the presence of SRF, without compromising BCVA. The tolerance of a small amount of fluid over 2 years allowed for fewer injections compared with not tolerating fluid (15.8 vs. 17 injections), suggesting that, at least in the short term, complete SRF resolution is not necessary to achieve good visual outcomes if eyes with minimal unchanging SRF are monitored carefully. These findings have potential implications for definitions of adequate disease control and the end point for titration with anti-VEGF therapy.

A few points relevant to extrapolating these findings to clinical practice are worth emphasizing. First, although the interval to the next treatment was extended, patients were still being monitored carefully for disease activity, and the interval was reduced if any additional signs of activity were noted. Second, the long-term implications of chronically persistent fluid remain undetermined. In other diseases featuring chronic, persistent SRF (e.g., chronic central serous chorioretinopathy), eventual RPE and photoreceptor loss have been noted to occur.[46]

Treatment of MNV with anti-VEGF agents represents the best opportunity to preserve or improve vision. Early analyses using CFP, FA, or both suggest that injection frequency may be associated with atrophy[10–12]; however, analyses with OCT-based approaches suggest this may not be the case.[41] Reducing the frequency of anti-VEGF therapy to allay concerns of atrophy could lead to vision loss; however, titration, or dose adjustment, could be used to mitigate concerns about atrophy development. Results from the RIVAL study (Development of new geogRaphic atrophy In patients with neoVascular [wet] Age-reLated macular degeneration: a comparison of ranibizumab and aflibercept; ClinicalTrials.gov Identifier: NCT02092532) show similar increases in atrophy incidence after 24 months with treat-and-extend ranibizumab or aflibercept, but with improved vision during this time.[47] Nevertheless, an understanding of phenotype, atrophy risk factors, or both may guide when treatment intervals could be extended. Because undertreatment of MNV is deleterious to vision, caution should be taken when extending treatment intervals because of concern regarding atrophy. The CATT demonstrated an association between foveal atrophy and worse VA after 5 years; however, at 5 years, only 17% of atrophy was subfoveal.[18,24] It is also noteworthy that atrophy represents only approximately 10% of vision loss related to AMD.[48] Further, in a real-world analysis of anti-VEGF therapy for nAMD, fovea-involved atrophy was the most common cause of long-term vision loss, but represented only 37% of the cases.[49] Finally, these rates of atrophy in the presence of treated MNV should be viewed in comparison with the established rates of atrophy in the absence of MNV. For example, more than 20% of fellow eyes (without GA or MNV at baseline) in the HARBOR study demonstrated evidence of atrophy at only 2 years.[50]

A clear and consistent description of atrophy is essential. The Classification of Atrophy Meetings program defined a

classification system for atrophy and provided OCT-based criteria to identify atrophy.[51] In the context of AMD, the following terms are recommended to describe atrophy: *complete RPE and outer retinal atrophy*, *incomplete RPE and outer retinal atrophy*, *complete outer retinal atrophy*, and *incomplete outer retinal atrophy*. According to Classification of Atrophy Meetings group recommendations, the term *geographic atrophy* should be used strictly to describe atrophy in the absence of MNV. In the presence of MNV, *complete RPE and outer retinal atrophy* is preferred when atrophy is defined using OCT, whereas *macular atrophy* is preferred when atrophy is observed clinically or defined on CFP (with GA being reserved for atrophy in the absence of MNV). The Classification of Atrophy Meetings group recommends that OCT be used as a reference method to define phenotypes and stages of atrophy, whereas a multimodal approach including FAF would be more informative and should support OCT findings. The importance of imaging is exemplified by the SEVEN-UP study, in which an analysis of only patients with gradable baseline images revealed a lower incidence of atrophy than reported previously.[29,30] Such false-positive results indicate that atrophy could lead to unnecessary treatment reduction and vision loss. With the emergence of OCT angiography, future considerations may include use for detection of early or intermediate atrophy by monitoring choroidal vasculature as a potential atrophy predictor, which highlights the need for the use of OCT angiography in long-term studies.

There are limitations to the current review that should be taken into consideration. First, the included studies were not designed to assess atrophy as a primary outcome. In addition, it is difficult to determine whether prognostic factors truly affect atrophy. For example, atrophy incidence was lower in patients with a nonfibrotic scar than in those with no scar[23]; however, this observation could be a result of the inability of atrophy to develop in these areas. Furthermore, patient populations in randomized controlled trials do not necessarily reflect real-world patients. In addition, we did not have genetic data or information of choroidal thickness. It should be noted that several studies have suggested that patients with thinner choroids (or reduced subfoveal choroidal thickness) may be at higher risk for atrophy.[52–54]

No treatment for atrophy currently exists; therefore, physicians rely on cues from atrophy phenotype and risk factors when making treatment decisions. Although phenotypes and risk factors may help to identify those at greater risk of atrophy, it is important to acknowledge that adequately treating exudative MNV remains the best option for optimizing vision outcomes in patients with nAMD.

References

1. Wong WL, Su X, Li X, et al. Global prevalence of age-related macular degeneration and disease burden projection for 2020 and 2040: a systematic review and meta-analysis. *Lancet Glob Health*. 2014;2(2):e106–e116.
2. Schmidt-Erfurth U, Chong V, Loewenstein A, et al. Guidelines for the management of neovascular age-related macular degeneration by the European Society of Retina Specialists (EURETINA). *Br J Ophthalmol*. 2014;98(9):1144–1147.
3. Miller JW, Le Couter J, Strauss EC, et al. Vascular endothelial growth factor A in intraocular vascular disease. *Ophthalmology*. 2013;120(1):106–114.
4. Chappelow AV, Kaiser PK. Neovascular age-related macular degeneration: potential therapies. *Drugs*. 2008;68(8):1029–1036.
5. Heier JS, Brown DM, Chong V, et al. Intravitreal aflibercept (VEGF Trap-Eye) in wet age-related macular degeneration. *Ophthalmology*. 2012;119(12):2537–2548.
6. Rosenfeld PJ, Brown DM, Heier JS, et al. Ranibizumab for neovascular age-related macular degeneration. *N Engl J Med*. 2006;355(14):1419–1431.
7. Brown DM, Kaiser PK, Michels M, et al. Ranibizumab versus verteporfin for neovascular age-related macular degeneration. *N Engl J Med*. 2006;355(14):1432–1444.
8. Saint-Geniez M, Kurihara T, Sekiyama E, et al. An essential role for RPE-derived soluble VEGF in the maintenance of the choriocapillaris. *Proc Natl Acad Sci U S A*. 2009;106(44):18751–18756.
9. Christenbury JG, Folgar FA, O'Connell RV, et al. Progression of intermediate age-related macular degeneration with proliferation and inner retinal migration of hyperreflective foci. *Ophthalmology*. 2013;120(5):1038–1045.
10. Chakravarthy U, Harding SP, Rogers CA, et al. A randomised controlled trial to assess the clinical effectiveness and cost-effectiveness of alternative treatments to inhibit VEGF in age-related choroidal neovascularisation (IVAN). *Health Technol Assess*. 2015;19(78):1–298.
11. Grunwald JE, Daniel E, Huang J, et al. Risk of geographic atrophy in the Comparison of Age-Related Macular Degeneration Treatments Trials. *Ophthalmology*. 2014;121(1):150–161.
12. Sadda SR, Tuomi LL, Ding B, et al. Macular atrophy in the HARBOR study for neovascular age-related macular degeneration. *Ophthalmology*. 2018;125(6):878–886.
13. Ying GS, Kim BJ, Maguire MG, et al. Sustained visual acuity loss in the Comparison of Age-Related Macular Degeneration Treatments Trials. *JAMA Ophthalmol*. 2014;132(8):915–921.
14. Lee JY, Folgar FA, Maguire MG, et al. Outer retinal tubulation in the Comparison of Age-Related Macular Degeneration Treatments Trials (CATT). *Ophthalmology*. 2014;121(12):2423–2431.
15. Ciulla TA, Ying GS, Maguire MG, et al. Influence of the vitreomacular interface on treatment outcomes in the Comparison of Age-Related Macular Degeneration Treatments Trials. *Ophthalmology*. 2015;122(6):1203–1211.
16. Grunwald JE, Pistilli M, Ying GS, et al. Growth of geographic atrophy in the Comparison of Age-Related Macular Degeneration Treatments Trials. *Ophthalmology*. 2015;122(4):809–816.
17. Willoughby AS, Ying GS, Toth CA, et al. Subretinal hyperreflective material in the Comparison of Age-Related Macular Degeneration Treatments Trials. *Ophthalmology*. 2015;122(9):1846–1853.e5.
18. Comparison of Age-Related Macular Degeneration Treatments Trials (CATT) Research Group, Maguire MG, Martin DF, et al. Five-year outcomes with anti-vascular endothelial growth factor treatment of neovascular age-related macular degeneration: the Comparison of Age-Related Macular Degeneration Treatments Trials. *Ophthalmology*. 2016;123(8):1751–1761.
19. Daniel E, Shaffer J, Ying GS, et al. Outcomes in eyes with retinal angiomatous proliferation in the Comparison of Age-

Related Macular Degeneration Treatments Trials (CATT). *Ophthalmology*. 2016;123(3):609–616.
20. Sharma S, Toth CA, Daniel E, et al. Macular morphology and visual acuity in the second year of the Comparison of Age-Related Macular Degeneration Treatments Trials. *Ophthalmology*. 2016;123(4):865–875.
21. Daniel E, Grunwald JE, Kim BJ, et al. Visual and morphologic outcomes in eyes with hard exudate in the Comparison of Age-Related Macular Degeneration Treatments Trials. *Ophthalmol Retina*. 2017;1(1):25–33.
22. Grunwald JE, Pistilli M, Daniel E, et al. Incidence and growth of geographic atrophy during 5 years of Comparison of Age-Related Macular Degeneration Treatments Trials. *Ophthalmology*. 2017;124(1):97–104.
23. Daniel E, Ying GS, Kim BJ, et al. Five-year follow-up of nonfibrotic scars in the Comparison of Age-Related Macular Degeneration Treatments Trials. *Ophthalmology*. 2019;126(5):743–751.
24. Jaffe GJ, Ying GS, Toth CA, et al. Macular morphology and visual acuity in year five of the Comparison of Age-Related Macular Degeneration Treatments Trials. *Ophthalmology*. 2019;126(2):252–260.
25. Sarraf D, London NJ, Khurana RN, et al. Ranibizumab treatment for pigment epithelial detachment secondary to neovascular age-related macular degeneration: post hoc analysis of the HARBOR study. *Ophthalmology*. 2016;123(10):2213–2224.
26. Rebhun CB, Moreira-Neto C, Gune S, et al. Macular atrophy in neovascular age-related macular degeneration: a pilot post hoc analysis of patients with pigment epithelial detachments. *Retina*; 2018 Dec 24. https://doi.org/10.1097/IAE.0000000000002402 [Epub ahead of print].
27. Bailey C, Scott LJ, Rogers CA, et al. Intralesional macular atrophy in anti-vascular endothelial growth factor therapy for age-related macular degeneration in the IVAN trial. *Ophthalmology*. 2019;126(1):75–86.
28. Sitnilska V, Altay L, Enders P, et al. Onset of retinal pigment epithelium atrophy subsequent to anti-VEGF therapy in patients with neovascular age-related macular degeneration. *Ophthalmologica*. 2019;241(3):154–160.
29. Bhisitkul RB, Desai SJ, Boyer DS, et al. Fellow eye comparisons for 7-year outcomes in ranibizumab-treated AMD subjects from ANCHOR, MARINA, and HORIZON (SEVEN-UP study). *Ophthalmology*. 2016;123(6):1269–12677.
30. Kuehlewein L, Dustin L, Sagong M, et al. Predictors of macular atrophy detected by fundus autofluorescence in patients with neovascular age-related macular degeneration after long-term ranibizumab treatment. *Ophthalmic Surg Lasers Imaging Retina*. 2016;47(3):224–231.
31. Abdelfattah NS, Al-Sheikh M, Pitetta S, et al. Macular atrophy in neovascular age-related macular degeneration with monthly versus treat-and-extend ranibizumab: findings from the TREX-AMD trial. *Ophthalmology*. 2017;124(2):215–223.
32. Abdelfattah NS, Hariri AH, Al-Sheikh M, et al. Topographic correspondence of macular atrophy with choroidal neovascularization in ranibizumab-treated eyes of the TREX-AMD trial. *Am J Ophthalmol*. 2018:19284–19290.
33. Chang AA, Broadhead GK, Hong T, et al. Intravitreal aflibercept for treatment-resistant neovascular age-related macular degeneration: 12-month safety and efficacy outcomes. *Ophthalmic Res*. 2015;55(2):84–90.
34. Saito M, Kano M, Itagaki K, et al. Efficacy of intravitreal aflibercept in Japanese patients with exudative age-related macular degeneration. *Jpn J Ophthalmol*. 2017;61(1):74–83.
35. Thavikulwat AT, Jacobs-El N, Kim JS, et al. Evolution of geographic atrophy in participants treated with ranibizumab for neovascular age-related macular degeneration. *Ophthalmol Retina*. 2017;1(1):34–41.
36. Zandi S, Weisskopf F, Garweg JG, et al. Pre-existing RPE atrophy and defects in the external limiting membrane predict early poor visual response to ranibizumab in neovascular age-related macular degeneration. *Ophthalmic Surg Lasers Imaging Retina*. 2017;48(4):326–332.
37. Mantel I, Dirani A, Zola M, et al. Macular atrophy incidence in anti-vascular endothelial growth factor-treated neovascular age-related macular degeneration: risk factor evaluation for individualized treatment need of ranibizumab or aflibercept according to an observe-and-plan regimen. *Retina*. 2019;39(5):906–917.
38. Mantel I, Zola M, De Massougnes S, et al. Factors influencing macular atrophy growth rates in neovascular age-related macular degeneration treated with ranibizumab or aflibercept according to an observe-and-plan regimen. *Br J Ophthalmol*. 2019;103(7):900–905.
39. Mantel I, Niderprim SA, Gianniou C, et al. Reducing the clinical burden of ranibizumab treatment for neovascular age-related macular degeneration using an individually planned regimen. *Br J Ophthalmol*. 2014;98(9):1192–1196.
40. Dhrami-Gavazi E, Balaratnasingam C, Lee W, et al. Type 1 neovascularization may confer resistance to geographic atrophy amongst eyes treated for neovascular age-related macular degeneration. *Int J Retina Vitreous*. 2015;1:15. eCollection 2015.
41. Sadda SR, Morgenthien E, Gune S. A longitudinal SD-OCT analysis of macular atrophy in the HARBOR trial. *Invest Ophthalmol Vis Sci*. 2018;59:4481.
42. Ehrlich R, Harris A, Kheradiya NS, et al. Age-related macular degeneration and the aging eye. *Clin Interv Aging*. 2008;3(3):473–482.
43. Holz FG, Sadda SR, Busbee B, et al. Efficacy and safety of lampalizumab for geographic atrophy due to age-related macular degeneration: Chroma and Spectri phase 3 randomized clinical trials. *JAMA Ophthalmol*. 2018;136(6):666–677.
44. Jaffe GJ, Schmitz-Valckenberg S, Boyer D, et al. Randomized trial to evaluate tandospirone in geographic atrophy secondary to age-related macular degeneration: the GATE study. *Am J Ophthalmol*. 2015;160(6):1226–1234.
45. Guymer RH, Markey CM, McAllister IL, et al. Tolerating subretinal fluid in neovascular age-related macular degeneration treated with ranibizumab using a treat-and-extend regimen: FLUID study 24-month results. *Ophthalmology*. 2019;126(5):723–734.
46. Nicholson B, Noble J, Forooghian F, et al. Central serous chorioretinopathy: update on pathophysiology and treatment. *Surv Ophthalmol*. 2013;58(2):103–126.
47. Gillies MC, Hunyor AP, Arnold JJ, et al. Macular atrophy in neovascular age-related macular degeneration: a randomized clinical trial comparing Ranibizumab and Aflibercept (RIVAL Study). *Ophthalmology*. 2020;127(2):198–210.
48. Yonekawa Y, Miller JW, Kim IK. Age-related macular degeneration: advances in management and diagnosis. *J Clin Med*. 2015;4(2):343–359.
49. Gillies MC, Campain A, Barthelmes D, et al. Long-term outcomes of treatment of neovascular age-related macular degeneration: data from an observational study. *Ophthalmology*. 2015;122(9):1837–1845.
50. Nassisi M, Lei J, Abdelfattah NS, et al. OCT risk factors for development of late age-related macular degeneration in the

fellow eyes of patients enrolled in the HARBOR study. *Ophthalmology*. 2019;126(12):1667−1674.
51. Sadda SR, Guymer R, Holz FG, et al. Consensus definition for atrophy associated with age-related macular degeneration on OCT: classification of atrophy report 3. *Ophthalmology*. 2018;125(4):537−548.
52. Giannaccare G, Pellegrini M, Sebastiani S, et al. Choroidal vascularity index quantification in geographic atrophy using binarization of enhanced-depth imaging optical coherence tomographic scans. *Retina*; 2019 Jan 22. https://doi.org/10.1097/IAE.0000000000002459 [Epub ahead of print].
53. Sacconi R, Corbelli E, Carnevali A, et al. Optical coherence tomography angiography in geographic atrophy. *Retina*. 2018;38(12):2350−2355.
54. Perlee LT, Bansal AT, Gehrs K, et al. Inclusion of genotype with fundus phenotype improves accuracy of predicting choroidal neovascularization and geographic atrophy. *Ophthalmology*. 2013;120(9):1880−1892.

Footnotes and Financial Disclosures

Originally received: August 6, 2019.
Final revision: November 7, 2019.
Accepted: November 12, 2019.
Available online: November 22, 2019. Manuscript no. D-19-00113.

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Financial Disclosure(s):
The author(s) have made the following disclosure(s): S.V.R.S.: Consultant − Novartis, Roche/Genentech, Centervue, Iconic, Allergan, Thrombogenics, Topcon, Bayer, Amgen, Heidelberg, Optos, Carl Zeiss Meditec.

R.G.: Advisory board − Novartis, Bayer, Roche/Genentech, Apellis.

J.M.M.: Consultant − Cellcure, Novartis, Roche, Bayer, Kodiak, Reneuron; Financial support − Novartis, Roche, Ophthotech, Bayer, Reneuron; Equity owner − Ophthotech, Notalvision.

A.T.: Financial support − Bayer, Allergan, Kanghong, Novartis, Roche, Oxurion.

G.J.J.: Consultant − Novartis, Sanofi, Heidelberg Engineering, pSivida, Regeneron, Neurotech, Sandoz, Bayer, EyePoint Pharmaceuticals.

Supported by Novartis Pharma AG, Basel, Switzerland. The sponsor or funding organization participated in the review of the manuscript (for accuracy only). Medical writing assistance was funded by Novartis Pharma AG under the direction of the authors.

HUMAN SUBJECTS: No human subjects were included in this study. All research adhered to the tenets of the Declaration of Helsinki.

No animal subjects were included in this study.

Author Contributions:

Conception and design: Sadda, Guymer, Monés, Tufail, Jaffe

Analysis and interpretation: Sadda, Guymer, Monés, Tufail, Jaffe

Data collection: Sadda, Guymer, Monés, Tufail, Jaffe

Obtained funding: N/A

Overall responsibility: Sadda, Guymer, Monés, Tufail, Jaffe

Abbreviations and Acronyms:
AMD = age-related macular degeneration; **ANCHOR** = Anti-VEGF Antibody for the Treatment of Predominantly Classic Choroidal Neovascularization in Age-Related Macular Degeneration; **BCVA** = best-corrected visual acuity; **CAM** = Classification of Atrophy Meetings; **CATT** = Comparison of Age-Related Macular Degeneration Treatments Trials; **CFP** = color fundus photography; **DA** = disc area; **DDAF** = definite decreased autofluorescence; **ERMA** = enlargement rate of macular atrophy; **ETDRS** = Early Treatment Diabetic Retinopathy Study; **FA** = fluorescein angiography; **FAF** = fundus autofluorescence; **GA** = geographic atrophy; **HARBOR** = pHase III, double-masked, multicenter, randomized, Active treatment-controlled study of the efficacy and safety of 0.5 mg and 2.0 mg Ranibizumab administered monthly or on an as-needed Basis (PRN) in patients with subfoveal neOvasculaR age-related macular degeneration; **HORIZON** = pHase 3b Open-Label Extension Trial of Ranibizumab for Choroidal Neovascularization Secondary to Age-Related Macular Degeneration; **HR** = hazard ratio; **IRF** = intraretinal fluid; **IVAN** = The Inhibition of VEGF in Age-related choroidal Neovascularisation; **MA** = macular atrophy; **MARINA** = Minimally Classic/Occult Trial of the Anti-VEGF Antibody Ranibizumab in the Treatment of Neovascular Age-Related Macular Degeneration; **MNV** = macular neovascularization; **nAMD** = neovascular age-related macular degeneration; **OCT-A** = OCT angiography; **ORT** = outer retinal tubulation; **PCV** = polypoidal choroidal vasculopathy; **PED** = pigment epithelial detachment; **PRN** = as needed; **RAP** = retinal angiomatous proliferation; **RESPONSE** = Genetics in Nonresponse to Anti-VEGF Treatment in Exudative AMD; **RPE** = retinal pigmented epithelium; **RPEA** = retinal pigmented epithelium atrophy; **SD** = spectral-domain; **SEVEN-UP** = Seven-Year Observational Update of Macular Degeneration Patients Post-MARINA/ANCHOR and HORIZON Trials; **SHRM** = subretinal hyperreflective material; **SRF** = subretinal fluid; **TREX-AMD** = Treat-and-Extend Age-Related Macular Degeneration; **VA** = visual acuity; **VEGF** = vascular endothelial growth factor; **VMA** = vitreomacular adhesion; **VMT** = vitreomacular traction.

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Title:
Anti-Vascular Endothelial Growth Factor Use and Atrophy in Neovascular Age-Related Macular Degeneration Systematic Literature Review and Expert Opinion

Date:
2020-05-01

Citation:
Sadda, S. R., Guymer, R., Mones, J. M., Tufail, A. & Jaffe, G. J. (2020). Anti-Vascular Endothelial Growth Factor Use and Atrophy in Neovascular Age-Related Macular Degeneration Systematic Literature Review and Expert Opinion. OPHTHALMOLOGY, 127 (5), pp.648-659. https://doi.org/10.1016/j.ophtha.2019.11.010.

Persistent Link:
http://hdl.handle.net/11343/252336

File Description:
Published version