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Dawn of the ANTI-VEGF Era in AMD

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Abstract

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Introduction

ABefore the introduction of Anti-VEGF, following treatment options were also available:

Laser photocoagulation was the first effective treatment and its efficacy was shown in the macular photocoagulation studies (MPS)- was initiated in 1970

Photodynamic Therapy (PDT):

First treatment to produce a significant decrease in the rates of visual loss from subfoveal neovascular AMD and still has a role in treatment today.

Transpupillary Thermotherapy (TTT):

Transpupillary thermotherapy (TTT) is an infrared diode laser procedure that uses a subthreshold, low irradiance, prolonged exposure time, and big spot size. Compared to typical short-pulse photocoagulation, retinal temperature rises in TTT for choroidal neovascularization (CNV) are significantly less, but they are maintained for 60 seconds to produce therapeutic effects. Retinal lesion size, chorioretinal pigmentation, macular elevation, and media clarity all affect treatment power. TTT employs infrared radiation with an 810-nm diode laser, which has no phototoxicity to the retina. To guarantee homogeneity of irradiance across treatment spots with a large diameter, a parfocal laser delivery system is necessary. Dense subretinal haemorrhage, previous focal photocoagulation, and serous RPE detachment are relative contraindications for TTT. Retinal arteriole blockage and impaired vision are two uncommon adverse effects.

Anti vascular endothelial growth factor (anti-VEGF) therapy has revolutionized the treatment of neovascular age-related macular degeneration (AMD). This review will summarise the current evidence of anti-VEGF therapy in neovascular AMD

A neurodegenerative eye condition called age-related macular degeneration (AMD) is the main cause of blindness in people who are 50 years of age or older. The anticipated number of AMD cases worldwide by 2040 is 288 million, with the majority of cases occurring in Asia (113 million).[1,2,3]

The treatment of neovascular AMD has undergone a revolution with the introduction of anti-vascular endothelial growth factor (anti-VEGF) therapy in the middle of the 2000s, greatly improving the outlook for those suffering from this illness. The current gold standard of care for neovascular AMD is anti-VEGF therapy. Since the introduction of anti-VEGF medication, registry data from numerous nations have shown a considerable decline in the incidence of AMD-related blindness.[1,2]

Purpose:

In order to review the data on anti-vascular endothelial growth factor (VEGF) therapies' effectiveness in treating neovascular age-related macular degeneration (AMD)

Materials and methods

A literature search was conducted on http://PubMed.gov using two different searches as the foundation for this review. In the initial search, the terms "age-related macular degeneration" were used. The terms "Anti-VEGF" and "age-related macular degeneration" were used in the second search. The review concentrated on pre-clinical studies in English that were found using these criteria, however it was not restricted to those studies. For inclusion, additional research that was thought to be pertinent to the subject of this review were also taken into account.

ANTI-VEGF in AMD:

PEGAPTANIB (Macugen) - First Anti-VEGF agent that was FDA approved for Neovascular AMD.[3.] However, recent experience with ranibizumab (Lucentis), off label use of bevacizumab (Avastin), and aflibercept have shown more favourable visual outcomes and have virtually succeeded pegaptanib in clinical use.[4,5,6,7]

In the VISION Studies RCT, where 1186 participants were enrolled with subfoveal CNVM to Sham, it is an RNA aptamer that binds VEGF-165.

Every six weeks, Pegaptanib intravitreal injections of 0.3 mg, 1.0 mg, or 3.0 mg were administered.

Results: At 48 weeks, the 0.3mg group (70%) had lost at least 15 letters compared to that of the Sham group (55%) (P 0.001).

RANIBIZUMAB (Lucentis) - **GOLD Standard** by which Neovascular AMD is evaluated. Monoclonal Fab fragments against all active VEGF-A isoforms

FDA approved in 2006: ANCHOR and MARINA Trial have been carried out.

The phase 2/3 open-label, multicenter EXTEND studies served as the inaugural evaluation of ranibizumab's effectiveness and safety for treating neovascular AMD in the Asian population (EXTEND I in Japanese patients, EXTEND II in Chinese patients, EXTEND III in South Korean and Taiwanese patients).[8-10]

In contrast to few patients who lost 15 letters or more, all 3 studies showed a significant increase in best corrected visual acuity (BCVA) from the baseline (+9.3 to 12.7 letters).[8-10.]

The effectiveness of ranibizumab monthly against pro-re-nata (PRN) regimen was recently further compared in the phase 4, randomised, double-masked, multicenter DRAGON research located in China.[11]

Both arms of the study saw a significant improvement in BCVA (+12.1 letters in the monthly arm and +9.4 in the PRN arm).

Patients received ranibizumab 0.5 mg PRN between months 12 and 24 as directed by visual acuity (VA) stability criteria. With a mean of 4.5 to 4.7 more injections, the BCVA gain was mainly maintained at month 24 (+10.6 letters in the monthly arm, +8.7 letters in the PRN arm).

Table1: **Strengths, weaknesses and approaches to missing data in real-world studies of ranibizumab in wet AMD**

Study	Strength	Weakness	Approach regarding missing values	Attrition
Chavan et al[12]	Consecutive enrollment to lessen bias in selection data with/without LOCF	Relatively smaller sample size	review of data with and without LOCF separately for patients who discontinued	30% over 3 years

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	separately analysed for patients who discontinued			
Cohen et al (LUMIERE)[13]	Reduce selection bias through consecutive enrollment	Snellen system was utilised by some ophthalmologists; VA values required to be adjusted to ETDRS-equivalent values. Evaluation of VA improvements was challenging due to low compliance (however, compliance was one of the study outcomes)	Included only patients with 12-month follow-up	NA
Finger et al (WAVE)[14]	Bigger than average sample size Sample must widely represent individuals who have received ranibizumab treatment (no additional selection criteria applied at enrolment)	In the maintenance phase, only around one-third of patients received further injections.	Excluded	25.5%
Frennesson and Nilsson[15]	Comparing the effects of using the LOCF versus ignoring dropout data on VA outcomes	Several patients received treatment in both modalities (not independent samples)	separate data analysis with/without LOCF for patients who discontinued	20.8%

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Gabai et al[16]	____	____	Only included patients with 12-month follow-up	NA
Hjelmqvist et al (Swedish Lucentis Quality Registry)[17]	Both retrospective and prospective components	In 100 of the retrospective patients, Snellen testing was used at baseline and the data were converted to ETDRS values	Excluded	370/471 patients completed 12 months and formed the 'on-treatment' population: 21.4% attrition
Holz et al (AURA)[18]	Large sample size Real-life assessment of anti-VEGF use Monitoring and visual outcomes in consecutively enroled patients across multiple centres and countries Retrospective design (prevents investigator bias)	Different disease management between countries Clinical centres included in AURA might not represent patient management in the entire country Study limited by the observational and uncontrolled nature of the design	To account for missing data, mean change in VA was assessed using LOCF	Overall 2609 patients: Effectiveness analysis set: 2227 First-year completers' set: 1695 Second-year completers' set: 1184
Kumar et al[19]	Prospective study with monthly clinic attendance	Presence of coexisting ocular pathology or time to treatment from first diagnosis not taken into consideration	Excluded	80/81 Patients received 3 loading injections 2 died (although data available for months 3 and 6, respectively)

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				Further 3 patients lost to follow-up So 75/81 completed=attrition: 7.5%
Matsumiya et al[20]	Cohort study of consecutive case series Differential diagnosis of typical AMD and PCV carried out after inclusion To exclude possible influence of previous PDT treatments, visual outcomes were evaluated in sub-population of patients that were treatment-naive	Relatively small sample Possibility of under-treatment	NA	NA
Muether et al[21]	Time course of changes in VA tracked	Relatively small sample size	Excluded	12.7%
Nomura et al[22]	Cohort study of consecutive case series	As B-mode ultrasonography was not performed, some eyes with vitreous completely attached to the retina might have been categorised into the VMA (−) group in the	NA	NA

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		analysis. The patients were from a single institution (results do not present a general overview of exudative AMD in Japanese patients)		
Pagliarini et al (EPICOHORT)[23]	Mean BCVA	Heterogeneous patient cohort: some patients had previously been treated with ranibizumab	States in methods that analysis was performed with and without LOCF, but LOCF efficacy results are not reported	22.8% over 24 months
Piermarocchi et al[24]	Mean change in BCVA at study end analysed based on patient's genetic characteristics associated with development of AMD	Relatively limited sample size Need for a more prolonged follow-up Clinical risk factors associated with worse prognosis after treatment were not considered	NA	All patients completed the 12-month follow-up
Pushpoth et al[25]	Long duration	High attrition in a long-duration study in an elderly patient group makes later results difficult to interpret	Excluded	No. of patients remaining under follow-up: 12 months: 897/1017 24 months: 730/1017

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				36 months: 468/730 48 months: 110/217
Rakic et al (HELIOS)[26]	Examined effects of no. of injections in maintenance phase	Data collection began soon after approval of ranibizumab in Belgium; thus, results may not reflect current levels of physician expertise	Excluded	255 patients evaluable at baseline 24 months: 184 patients Attrition=27.9%
Ross et al[27]	Examined effects of baseline VA on outcomes Analysed data with and without LOCF but reported only VA data not change in VA data for LOCF analyses	High attrition	Only included patients with 12-month follow-up Analysed data with and without LOCF but reported only VA data not change in VA data for LOCF analyses Data extracted on 700 eyes in 629 patients; 247 eyes in 176 patients did not meet eligibility criteria=453 eyes	47 eyes in 47 patients excluded because no data available at 12 months 198 patients completed 24 months Attrition=1 − (198/453)=56.3 %
Tufail et al[28]	Very large sample size	Missing data excluded	Missing data excluded in main analysis. However, data was also analysed separately for eyes that	12 months: 8598 eyes 24 months: 4990 eyes 36 months: 2470 eyes

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			completed 168 weeks, follow-up (n=1138), vs eyes that received ≥1 injection at time 0 (n=12 951) and n=1138 at Week 168 Change in mean VA was similar for the two groups	
Williams and Blyth[29]		Examined effectiveness of ranibizumab in patients with relatively high baseline VA	Only patients with 12 months' follow-up included	NA
Zhu et al[30]	Strict inclusion and exclusion criteria Standardised retreatment criteria Long duration Retrospective study of consecutive patients treated for AMD All patients treated by a single physician	Difficulties reporting cataract progression due to non-standardised lens grading at each visit Use of multiple OCT devices ICGA screening for PCV was not performed regularly at baseline (PCV patients might have been included in the study)	NA	All patients included in the study (208) had 5-year VA assessment

Anchor Study: The use of anti-VEGF antibodies in the treatment of classic AMD neovascularization.

Design and Duration: Multicentre, randomised, double masked, 2 year study

Participants: Patients who had not previously had PDT or antiangiogenic medications and who primarily had classic, subfoveal CNV.

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Aim: To evaluate whether Ranibizumab, when compared to PDT and verteporfin, can lower the risk of vision loss in classic subfoveal CNVM.

Table 2: There are three groups where 430 patients with classic CNVM were randomly assigned to receive monthly 0.3 mg Ranibizumab or PDT

Group	Visual Acuity Increased	Visual Acuity Decreased
PDT + Sham Injection	35.7%	94.3%
Sham PDT+ 0.3mg Ranibizumab	40.3%	96.4%
Sham PDT+0.5mg Ranibizumab	5.6%	64.3%

Marina Trial:

Neovascular AMD treatment with the anti-VEGF antibody Ranibizumab: a minimally classic/occult cnvm study

Randomized, double-masked experiment with a two-year time frame.

Goal: To ascertain whether ranibizumab can lessen the chance of vision loss in occult, minimally classic, or subfoveal CNVM.

716 patients were enrolled in the study. At 12 months,conclusion of losing fewer than 15 letters were seen most with 0.5mg group similar results were shown by 0.3mg group as compared with of patients receiving sham injections (P<0.001 for both comparisons).

Visual acuity improved by 15 or more letters was marked with 0.5mg group followed by 0.3-mg group as compared with the sham-injection group (P<0.001 for both doses).

Mean increases in visual acuity were 6.5 letters in the 0.3-mg group and 7.2 letters in the 0.5-mg group, as compared with a decrease of 10.4 letters in the sham-injection group (P<0.001 for both comparisons).

The benefit in visual acuity was maintained at 24 months.

Table 3: comparison in terms of gain or loss in Visual Acuity

Group	Visual Acuity Increased	Visual Acuity Decreased
0.3mg Ranibizumab	24.8%	94.5%
0.5mg Ranibizumab	33.8%	94.6%
Sham injection	5.0%	62.2%

During 24 months, presumed endophthalmitis was identified in five patients (1.0%) and serious uveitis in six patients (1.3%) given ranibizumab.

PrONTO TRIAL:

Prospective OCT Imaging of patients with Neovascular AMD treated with intra ocular Ranibizumab.

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Aim: The goal is to see if dosage based on fluid in the macula as detected by OCT could lead to fewer injections while still achieving visual acuity outcomes similar to those attained with monthly dosing.

Method

1. Intravitreal Ranibizumab 0.5mg injections were given three months in a row.
2. Then, from months third month, patients were checked with an OCT every month, and more injections were only given if necessary.

Age of 50 years or more: active primary or recurrent macular With signs of disease progression: central retinal thickness >300 micrometers on OCT, neovascularization secondary to AMD included the centre fovea in the study eye.

Safety Profile:

1. positive safety data
2. Minor local complication such as SCH, irritability
3. conditions that seriously impair vision (VH, RD, Endophthalmitis was uncommon.
4. Systemic thromboembolic incidents: No definite occurrences

Conclusions: The VA outcomes from the PrONTO Study, which used an OCT-guided variable-dosing regimen with intravitreal ranibizumab, were equivalent to those from the phase III clinical studies, but required fewer intravitreal injections.

3. Bevacizumab (Avastin)

The parent molecule of Ranibizumab and a monoclonal anti-VEGF antibody,

developed as a methodically administered chemotherapeutic drug that the FDA has currently approved for use in the treatment of RCC, glioblastoma, non-small cell lung cancer, and colorectal cancer.

Used off-label to replace Ranibizumab for a variety of retinal pathologies since it is more affordable.

The 1208 participants in the NEI-funded CATT Study, which compared BEVACIZUMAB with Ranibizumab for Neovascular AMD, were randomly assigned to receive either Ranibizumab or Bevacizumab on a monthly or "as needed" basis. Ranibizumab and monthly BEVACIZUMAB demonstrated comparable efficacies.

Bevacizumab's effectiveness has been assessed in the Comparison of Age-Related Macular Degeneration Treatments Trials (CATT), which compared ranibizumab and bevacizumab utilising monthly versus PRN dosing, despite the drug's lack of a licence to treat neovascularization.[31]

According to the CATT research, bevacizumab is noninferior to ranibizumab within the predetermined noninferiority margin when taken with the same dose schedule. Ranibizumab and bevacizumab are equally effective in treating neovascular AMD, according to two further randomised studies (GEFAL and IVAN).[32,33]

Disadvantage: off label nature, Legal issues.

Four Dosing Regimen of Anti-VEGF treatment for Neovascular AMD:

1. Fixed Regimen using monthly or bimonthly injection
2. A Pro Re Nata (PRN) strategy
3. Treat and Extend regimen
4. Obscure and plan regimen

Conclusion: They found that 50 percent of eyes had 20/40 vision or better. Researchers also found that treating patients as needed rather than on a monthly basis may possibly yield better outcomes. Overall, the long-term study confirms the fact that Avastin performs just as well as Lucentis for treating wet AMD

4. Aflibercept (Eylea)

1. FDA-approved in 2011
2. An alternative approach of VEGF suppression—when administered once every two months rather than on a monthly basis—has equal efficacy to ranibizumab.
3. Greater binding affinity is the primary cause of the extended impact.

For the first time, the Phase III VIEW trials for aflibercept's year 1 findings showed that injections of the anti-VEGF treatment (aflibercept; 2 mg) every eight weeks improve vision similarly to ranibizumab given every four weeks.[34]

Patients who get aflibercept instead of ranibizumab during the first year of treatment need fewer

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outpatient visits and injections (7 versus 12), as per the labelling recommendations (based on the Phase III study procedures).

Conclusions. It is notable that there was a modest difference in the average frequency of treatment in year 2 of the study— 4.2 for aflibercept vs 4.7 for ranibizumab—and this appears to be driven by the fact that fewer patients needed more intensive therapy with aflibercept.

View Trial:

1. Two parallel studies that randomly assigned 2419 subjects to receive either 0.5 mg or 2.0 mg of aflibercept. After the first three monthly doses, take 2.0 mg every two months, or take 0.5 mg of ranibizumab every month.
2. The entire aflibercept group has been demonstrated to be comparable to monthly Ranibizumab.

However, the majority of practitioners employ "treat and observe" or "treat and extend" tactics to lessen the burden of clinic visits and intravitreal injections. Although neither of these approaches was specifically evaluated in the VIEW trials, in the second year a "treat and observe" approach with a 3-month gap (requiring injection) was adopted.

Both ranibizumab and aflibercept functioned well throughout year 2, according to the product's manufacturer Regeneron, with patients using either medication losing an average of just 0.8 letters of vision. Aflibercept had marginally greater durability for each group studied compared to ranibizumab, indicating that the interval between injections for aflibercept may be increased by 2-4 weeks in comparison to ranibizumab.

In contrast, most patients probably won't be able to double their injection intervals, as suggested by the year 1 outcome.

Aflibercept lowers expenditures and patient visits by 42% as compared to ranibizumab for patients who are treated in accordance with the VIEW standards. The savings will be much less for individuals following "treat and observe" or "treat and extend" regimens.

Newer Anti- VEGFs

Brolucizumab (Pagenax)

Brolucizumab, a single chain antibody fragment that inhibits VEGF-A, and aflibercept were evaluated in 2 similarly constructed phase 3 trials, Hawk and Harrier, for the treatment of Neovascular AMD. In comparison to other anti-VEGF medications, brolucizumab's distinctive molecular design resulted in a low molecular weight of only 26 kDa, enabling a concentrated molar dose of just one intravitreal injection. Results of the phase I and phase II clinical trials supported the efficacy of brolucizumab in the treatment of nAMD and showed signs of a more long-lasting therapeutic impact. Brolucizumab can be given every three months while still maintaining disease control, according to the pivotal phase III trials HAWK and HARRIER, which involved a combined 1,817 patients.

Conclusion:

1. At 48 weeks, the visual function of brolucizumab was comparable to that of aflibercept, and >50% of the eyes treated with brolucizumab 6 mg were still receiving it on a q12w schedule at that point.
2. Brolucizumab outperformed Aflibercept in terms of anatomic results.
3. As with aflibercept, overall safety was comparable.

Faricimab*:* (Roche's Vabsymo): FDA approved in January 2022

Non humanized bio specific antibody inhibiting the angiopoietin-2 and VEGF-A Pathways, Blocking both pathways- stabilise blood vessels and potentially improve vision outcomes

Conclusion: The rapid approval of the drug is based on promising result of phase-3 clinical trial that demonstrated Vabysmo given at interval of upto 4 months achieved a non inferior vision gain vs aflibercept given 2 months in first year.

Abicipar Pegol:

However, due to these molecules' short intraocular half-life, many injections are necessary on a regular basis, usually every 4 to 12 weeks when a treat and extend injection technique is used.[35]

The visual improvements achieved with current anti-VEGF monotherapy are +8 to +10 ETDRS letters, according to the anti-VEGF clinical trials.

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However, this important advantage does not seem to get better with higher doses or more frequent injections, suggesting a potential therapeutic ceiling.[36]

Based on the therapies for designed ankyrin repeat proteins (DARPins), abicipar Pegol is an anti-VEGF drug (Molecular Partners AG, Switzerland). Ankyrin protein repeats that exist in nature are the source of DARPins. The repeats are typically four to six, resulting in a right-handed solenoid structure with a hydrophobic core and a sizable, grooved binding surface that is accessible to solvents. [37]

A unique approach of protein engineering and recombinant DNA technology has been used to create libraries of DARPin molecules with different amounts of repeats.

The Stage 3 REACH study determined that the molecule's 2-monthly dose was noninferior to ranibizumab's monthly schedule.[38]

Ranibizumab showed stronger visual improvements compared to abicipar in a second, smaller cohort phase 2 study made up of two trials with 25 patients each, BAMBOO and CYPRESS. [39]

The SEQUOIA and CEDAR phase 3 studies of abicipar for nAMD showed comparable efficacy of 2 mg abicipar in 6 and 8 injections compared to 13 injections of ranibizumab at the primary end goal of 52 weeks in terms of visual improvements. For the first time, a treatment group was enrolled in these phase 3 pivotal trials and given a baseline 12-week dose regimen (after a series of loading injections).

Conclusion: Participants who received abicipar for 8 weeks (94.8% in SEQUOIA, 91.7% in CEDAR) and for 12 week 91.3%, 91.2%) showed stability of visual gains similar to those who received ranibizumab for 4 weeks (96.0%, 95.5%).[40]

Conbercept:

conbercept, approved in China in 2013 based on results from the PHOENIX study.[41]

In addition to the VEGF binding domains of VEGFR1 and VEGFR2, Conbercept has the fourth binding domain of VEGFR2.[42]

The added binding domain is considered to reduce the molecule's positive charge and lessen its ability to adhere to the extracellular matrix. Conbercept's safety and effectiveness were evaluated in the AURORA study, a 12-month, randomised, double-masked, controlled-dose, interval-ranging phase 2 clinical trial carried out in China for people with CNV secondary to AMD.[43]

Conclusion: The results of the trial showed statistically significant functional and anatomical improvement after the first three doses, and these outcomes were either maintained or improved through month 12 whether either a monthly or PRN regimen was used. Mean BCVA changes at month 12 relative to baseline varied from 9.31 letters (0.5 mg monthly) to 15.43 letters (2.0 mg monthly).

Anti-VEGF in type 3 Neovascularization

Anti-VEGF therapy has been demonstrated to be beneficial for treating type 1 and type 2 neovascularization (occult and classic pattern leaks based on fluorescein angiography findings), however type 3 neovascularization (also known as retinal angiomatous proliferation, or RAP) has less conclusive evidence.[44]

A distinct form of neovascular AMD called retinal angiomatous proliferation has been estimated to account for up to 15% of cases in white people, but may be less common in Asian populations. This subtype's clinical characteristics stand out due to the development of geographic atrophy, thin choroid, and connection with reticular pseudodrusen (GA). Although anti-VEGF medication is routinely utilised in this subtype of neovascular AMD, the majority of RAP studies have been constrained by the sparse patient populations and inconsistent follow-up times. Additionally, it is now obvious that therapy response is largely dependent on the stage of the lesion and that no single treatment is equally beneficial in all stages because to developments in imaging that increase the accuracy of staging RAP lesions.

Following treatment with ranibizumab, aflibercept, and bevacizumab, numerous case series indicated stabilisation or improvement of visual acuity and decreased macular thickness in eyes with RAP. [45,46,47]

Safety In Anti-Vegf Therapy

Although early outcomes with anti-VEGF were positive for up to two years, studies with extended follow-up have shown that the long-term visual outcome may be less positive. The ANCHOR,

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MARINA, and HORIZON subset of patients were followed up by the SEVEN UP study, which discovered that after seven years, the mean BVCA had fallen to 8.6 letters worse than baseline.[48]

After receiving extensive anti-VEGF medication for two years, the majority of patients did not see a long-lasting halt of exudative AMD 7–8 years later, indicating that treatment may need to last for many years. Similar to this, most of the visual gain at 2 years was lost in the 5-year follow-up of the CATT research (mean change in VA was 3 letters from baseline and 11 letters from 2 years).[49]

After the clinical trial was completed, the average number of treatments was 15.4. Better long-term outcomes were observed in a separate study utilising the Fight Retinal Blindness database after a mean follow-up period of 53.5 months, which the authors hypothesised to be the result of more injections given in 3-5 years.[50]

After receiving anti-VEGF therapy, a considerable percentage of patients developed macular atrophy (MA). 98% of participants in the SEVEN UP research displayed RPE atrophy. The CATT and IVAN studies' follow-up reports revealed that the emergence of MA was linked to worse visual outcomes.[51]

Few studies in Asian patients provide functional or anatomical outcomes beyond the first two years. Incidence of RPE atrophy progression was reported by Kuroda et al[52] to be 3.8% at 12 months and 5.4% at 26.7 months in Japanese patients receiving ranibizumab. These numbers appear to be less than those that have been published for the white population.

Therefore in conclusion, These studies established that these Anti-VEGF agents are safe and improve vision in ARMD.

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