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Research article

Functional results one-year following the anti-VEGF therapy in macular pathology

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Abstract: This investigation aims at evaluating the functional results 1-year following anti-VEGF therapy in macular pathology. Material and method: This is a retrospective examination that was carried out on 57 patients with macular pathology out of 108 at Sf. Spiridon Hospital in Iasi. 57 patients with macular pathology were included in the investigation, respectively 57 eyes, 24 eyes with diabetic macular edema and 33 with neovascular age-related macular degeneration. Eyes in which less than 6 intravitreous injections were performed (less than one-year of follow-up) as well as those without oct control examinations and without adequate controls were excluded. Results: Visual acuity improves considerably after the therapy was performed in both patients experiencing diabetic macular edema (370 vs 320 microns) and in those with age-related macular degeneration (320 vs 260 microns), while the average thickness of the central macula decreases considerably after therapy. Conclusions: In this study, the therapy with intravitreal Aflibercept was associated with improving the functional and anatomical outcomes, keeping the increasing trend up to one-year of therapy in those who received a minimum of three injections.

Keywords: anti-VEGF therapy, macular degeneration, diabetic macular edema, aflibercept, intravitreal in-jections, OCT

1. Introduction

Age-related macular degeneration and diabetic macular edema are the leading causes of vision loss and blindness worldwide. As in glaucoma, the visual function can be severely affected, being a keen cause of vision loss. According to studies, the association of glaucoma with diabetes mellitus will determine the progression of both diseases, both the progression of retinopathy as well as the manifestation of diabetic macular edema and neovascular glaucomas [1,2]. Most of the shifts linked to AMD are due to the wet type of macular degeneration.

In the context of macular degeneration, it's projected that by 2040, the European prevalence will potentially reach 21 million individuals affected in the early stages and 4.8 million in the advanced stages. The neovascular type, which is the most common, is characterized by severe vision loss caused by the growth of new vessels under or within the macula [3]. In diabetes, in 2012, there were approximately 21 million patients worldwide diagnosed with diabetic macular edema (DME). This number is likely to increase considering the overall rise in the prevalence of diabetes mellitus, especially among younger individuals [4]. It has been observed in recent decades that anti-VEGF therapy is considered the first line of treatment for both DME and neovascular AMD. The study aims to demonstrate, even on a limited number of patients, the effectiveness of anti-VEGF medication on macular pathology, improving both visual function and reducing fluid in the macular area.

Studies have shown that Intravitreal Injection with anti-VEGF Agents represents the standard of care for the therapy of visual acuity impairment caused by the most common diseases – age-related exudative macular degeneration and diabetic macular edema. Aflibercept is the latest antiVEGF (vascular endothelial growth factor); 1 ml of injectable solution contains 40 mg of aflibercept. The recommended dose of aflibercept (Eylea) is 2 mg aflibercept, equal to 50 microliters. A volume of 0.05 ml is injected at 3.5-4.0 mm behind the limbus in the vitreous cavity, without alluding to the horizontal meridian in the direction of the center of the eyeball. Eylea should only be administered by an ophthalmologist with high expertise in administering intravitreal injections.

Therapeutic indications / administration protocol. It is proper in adults for treating: neovascular (wet) type of age-related macular degeneration (AMD); impairment of visual acuity determined by macular edema secondary to retinal vein occlusion (branch OVR or central OVR); the impairment of visual acuity determined by diabetic macular edema (DME); visual acuity impairment caused by myopic choroidal neovascularization (myopic NVC).

Therapeutic indications. The interval between 2 doses should not be less than one month. If visual and anatomical results show that the patient is not experiencing improvement despite ongoing therapy, aflibercept should be discontinued. The therapy can be continued with a "treat-and-extend" regimen, progressively increasing the therapy administration interval so that the visual and, or anatomical results are kept stable, but the existing data is insufficient to reach a decisive conclusion. The gradual extension of the time between administrations until fluid reappears or AV decreases (e.g.,determining the maximum interval in which there is no fluid infiltrate). If the visual and, or anatomical results deteriorate, the therapy administration interval must be reduced according to diabetic macular and age-related macular degeneration).

The VIVID and VISTA trials showed that in a clinical environment, administering aflibercept, an anti-VEGF therapy, led to an average rise of 10 ETDRS (Early Treatment Diabetic Retinopathy Study) letters in visual acuity (VA), starting from a mean baseline of 60 letters after 1 year in eyes affected by DME. The VIVID and VISTA trials involved the administration of five injections at one-month intervals then 2 monthly for one-year, forming the basis of aflibercept dosing in DME [5,6].

The Altair study was designed to evaluate the safety and effectiveness of aflibercept administered via intravitreal injections (IVT-AFL) in therapy and extension (T&E) dosing regimens in treating-naïve patients with exudative macular degeneration (AMD).

ALTAIR demonstrated that proacive, individualized T&E therapy with aflibercept can considerably improve vision gains from baseline to year 2 [7,8].

Based on the results in the literature, the present investigation evaluates the functional and structural results at one-year of follow-up therapy with aflibercept in macular pathology of patients at St. Spiridon Hospital of Iași.

2. Results

The study group consisted of 57 eyes with retinal diseases which were divided into 2 study groups and examined in the Ophthalmology Clinic of Sf. Spiridon University Hospital of Iași, as follows:

- MDE– 24 eyes with diabetic macular edema
- AMD – 33 eyes with age-related macular degeneration

Patients with diabetic macular edema were aged between 31 and 72 years, mean age 59.54 ± 10.23 years, predominantly female (62.5%), half from rural areas (50%).

Patients with age-related macular degeneration were aged between 59 and 82 years, mean age 73.33 ± 6.12 years, predominantly female (69.8%), from urban areas (66.7%). In Table 1 the demographic description of the data is introduced.

Table 1. Descriptive demographic data

Demographic characteristics	MDE (n=24)	AMD (n=33)	Statistical test	p
AGE				
Mean Age ± SD, years (min-max)	58.54 ± 10.23 (31-72)	73.33 ± 6.12 (59-82)	t-Student	0.001
< 60 years, n(%) ≥ 60 years, n(%)	9 (37.5%) 15 (62.5%)	1 (3.0%) 32 (97.0%)	Chi2 test Likelihood Ratio	0.001
GENDER				
Male, n(%) Female, n(%)	9 (37.5%) 15 (62.5%)	10 (30.3%) 23 (69.7%)	Chi2 test Likelihood Ratio	0.570
Areas				
Urban, n(%) Rural, n(%)	12 (50.0%) 12 (50.0%)	22 (66.7%) 11 (33.3%)	Chi2 test Likelihood Ratio	0.206

Evaluation of visual acuity. Both in patients afflicted by diabetic macular edema and in those with age-related macular degeneration, visual acuity improves considerably after therapy. In the MDE group, visual acuity in the first 6 months increased considerably from 0.40±0.30 to 0.50±0.33 (p=0.003), remaining approximately at the same level after one-year of therapy 0.48±0.28 (p=0.085). In the AMD group, visual acuity in the first 3 months considerably increased from 0.17±0.16 to 0.24±0.22 (p=0.016), keeping with the increasing trend until after one-year of therapy 0.27± 0.24 (p=0.030) (Figure 1 a and b).

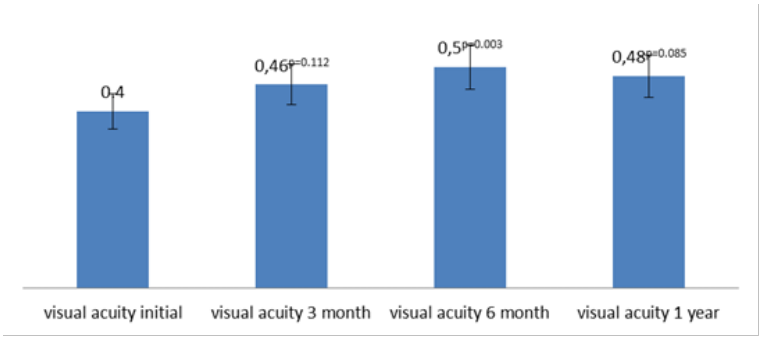


Figure 1a. The changes in visual acuity over time in patients with MDE after 1 year. Initial visual acuity upon enrollment, subsequent assessments at 3 months, 6 months, and 1 year.

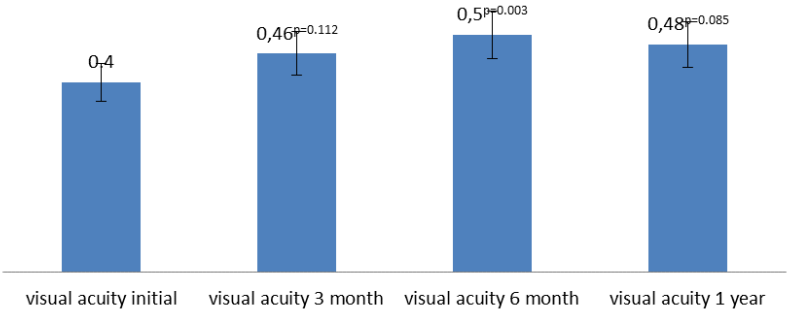


Figure 1b. The changes in visual acuity over time in patients with AMD after 1 year. Initial visual acuity upon enrollment, subsequent assessments at 3 months, 6 months, and 1 year.

The visual acuity improves after therapy both in patients diagnosed with diabetic macular edema (0.40 vs 0.48 ps; p=0.085), but especially in those with age-related macular degeneration (0.17 vs 0.27 ps; p=0.03), (Figure 2).

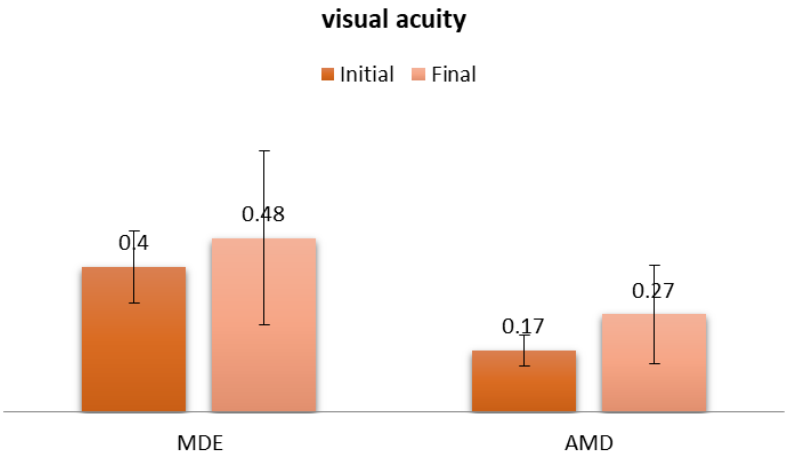


Figure 2. Mean values of visual acuity before and after therapy depending on the diagnosis. The baseline visual acuity and the one-year follow-up show improvement following therapy for both AMD and DME

The average thickness of the central macula decreases considerably after therapy both in patients diagnosed with diabetic macular edema (370 vs 320 microns) and in those with age-related macular degeneration (320 vs 260 microns) (Fig. 3 and 4).

The thickness of the macula. In the MDE group the macular thickness reduced considerably in the first 3 months from 366±116 microns to 228±64 microns (p=0.001), remaining approximately at the same level after one-year of therapy 224±79 microns (p=0.001). In the AMD group, the macular thickness reduced slightly from 305±121 to 261±96 (p=0.065) during the first 3 months of therapy reaching an average level of 255±71 (p=0.064) after one-year.

Between 1 and 5 injections were performed in patients diagnosed with diabetic macular edema while between 1 and 6 injections were performed in patients with age-related macular degeneration, the average of the groups being of approximately 3 injections (Figure 3 a and b).

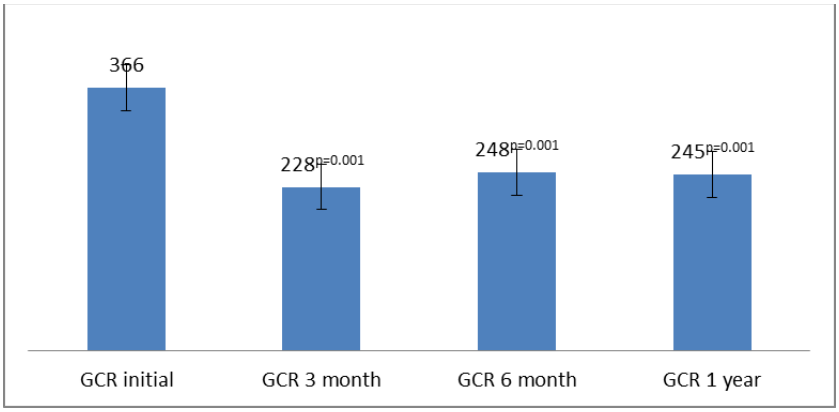


Figure 3a. Evolution of mean values of GCR in patients with MDE after 1 year (initial, 3-month, 6-month, 1 year). The macular thickness reduced considerably in the first 3 months remaining approximately at the same level after one-year of therapy.

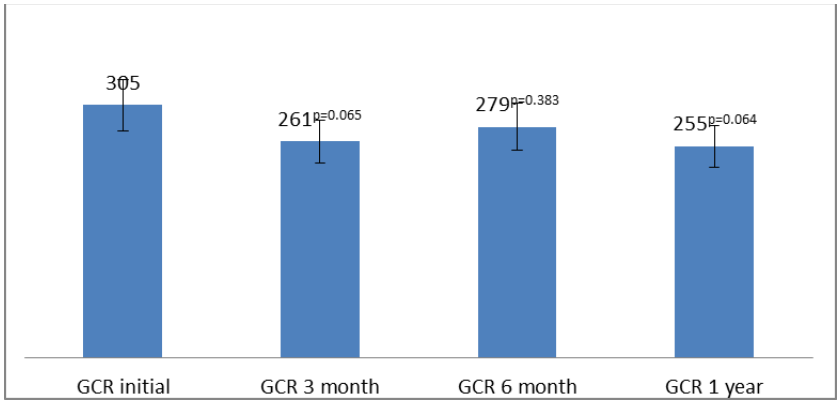


Figure 3b. Evolution of mean values of GCR in patients with AMD after 1 year (initial, 3-month, 6-month, 1 year). The macular thickness reduced considerably in the first 3 months remaining approximately at the same level after one-year of therapy.

The average thickness of the central macula decreases after therapy (fig. 4) in both patients diagnosed with diabetic macular edema (366 vs 245 microns; p=0.001) and in those with age-related macular degeneration (305 vs 255 microns; p=0.065).

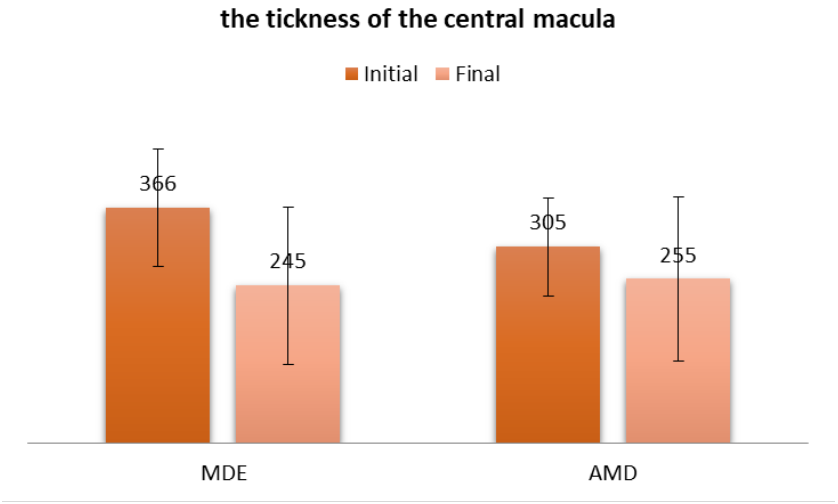


Figure 4. Mean values of central macular thickness before and after therapy depending on the diagnosis (AMD and MDE). There's a noticeable reduction in the average thickness of the central macula after therapy.

Number of injections performed. Between 2 and 10 injections were performed in patients diagnosed with diabetic macular edema while between 3 and 10 injections were performed in patients with age-related macular degeneration, the average of the groups being considerably higher in the MDE group (6.88 vs 5.64; p=0.049) (fig. 5 a and b).

The correlation of the number of injections with the final physical acuity highlights the following aspects (fig. 5):

- in patients diagnosed with diabetic macular edema, the correlation was indirect, reduced in intensity, and statistically insignificant (r= -0.105; p=0.642);

- in patients with age-related macular degeneration, the correlation was direct, moderate in intensity, and statistically significant (r= +0.391; p=0.048).

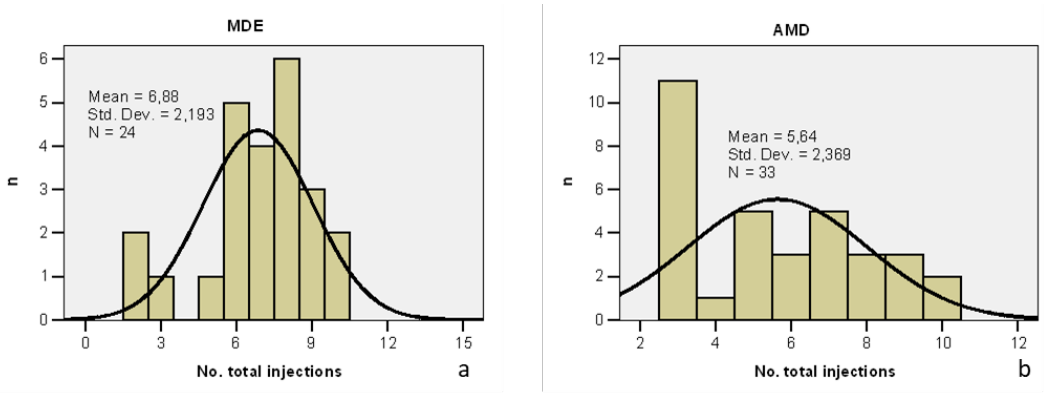


Figure 5. Correlation of the number of injections with the final visual acuity of patients with MDE (a) and AMD (b). The visual acuity is directly correlated with the number of injections in both conditions (increased visual acuity level correlates with a higher number of injections).

The correlation of the number of injections with the final thickness of the central macula highlights the following aspects (fig. 6 a and b):

- in patients diagnosed with diabetic macular edema, the correlation was indirect, reduced in intensity, and statistically insignificant (r= -0.274; p=0.217);

- in patients with age-related macular degeneration, the quantity of administered injections and the final thickness of the macula were apparently independent parameters (r= +0.020; p=0.924).

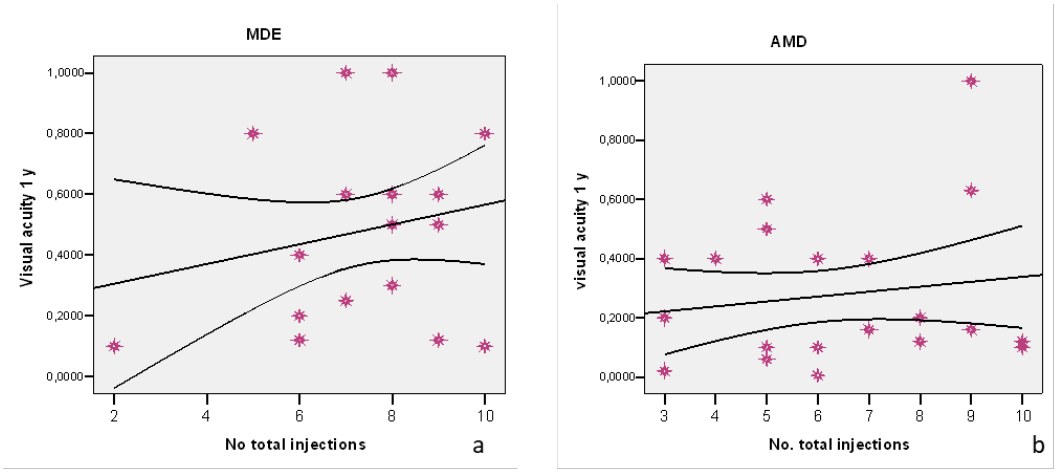
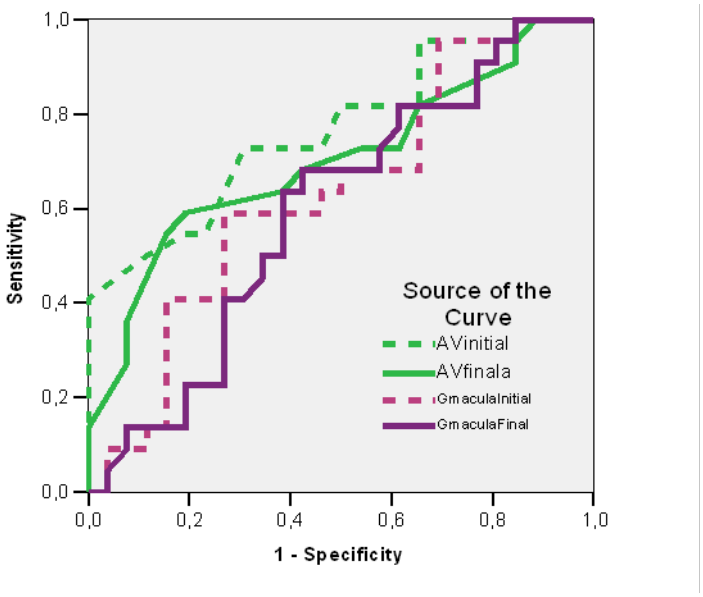


Figure 6. Correlation between number total of injections and CGR after 1 year of therapy MDE (a) and AMD (b). The central macular thickness is indirectly correlated with the number of injections. This decreases with the increase in the number of injections in both conditions. A higher number of injections is correlated with reduced macular thickness.

Factors that can influence visual acuity. Good predictors of reduced visual acuity are shown to be patient age (AUC=0.762; CI95%: 0.609-0.914; p=0.003) and gender (AUC=0.625; CI95%: 0.452-0.798; p=0.162)

Factors that can influence central macular thickness. A good predictor of increased macular thickness turns out to be the environment of origin (AUC=0.700; CI95%: 0.539-0.861; p=0.028) of visual acuity (AUC=0.767; CI95%: 0.632-0.903; p=0.002) and its evolution after therapy (AUC=0.702; CI95%: 0.549-0.854; p=0.017) as well as pre-therapy macular thickness (AUC=0.635; IC95 %: 0.476-0.794; p=0.111) prove to be good predictors of diabetic macular edema.



Area Under the Curve

Test Result Variable(s)	Area	Std. Error[a]	Asymptotic Sig.[b]	Asymptotic 95% Confidence Interval	
				Lower Bound	Upper Bound
AVinitial	,767	,069	,002	,632	,903
AVfinala	,702	,078	,017	,549	,854
GmaculaInitial	,635	,081	,111	,476	,794
GmaculaFinal	,597	,083	,251	,435	,759

The test result variable(s): AVinitial, AVfinala, GmaculaFinal has at least one tie between the positive actual state group and the negative actual state group. Statistics may be biased.

a. Under the nonparametric assumption

b. Null hypothesis: true area = 0.5

Figure 7. ROC curve. Visual acuity and thickness of the central macula - prognostic factors of diabetic macular edema.

At the beginning of the investigation, the correlation between visual acuity and the thickness of the central macula highlights the following aspects:

- in 35.8% of patients diagnosed with diabetic macular edema, higher values of visual acuity were associated with lower values of central macula thickness (r= -0.358; p=0.05);

- the correlation was indirect, low in intensity, statistically insignificant (r= -0.105; p=0.642);

- in patients with age-related macular degeneration, visual acuity and central macular thickness were apparently independent parameters (r= -0.124; p=0.548).

At the end of the investigation, visual acuity and central macular thickness were apparently independent parameters both in patients diagnosed with diabetic macular edema (r= -0.087; p=0.700) and in patients with age-related macular degeneration (r= -0.072; p=0.726).

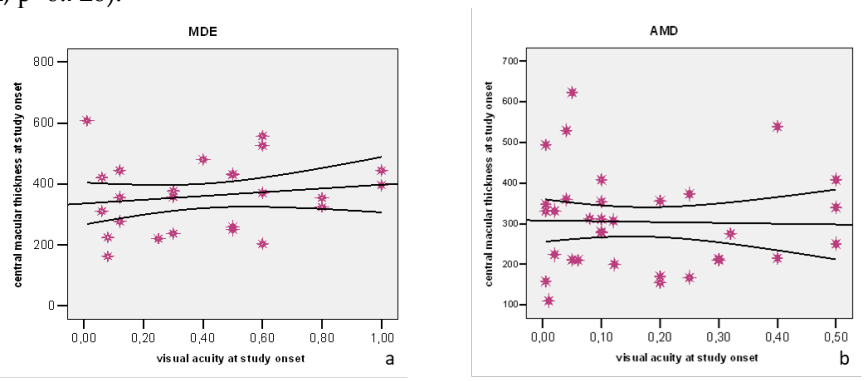


Figure 8. Correlation of visual acuity with central macular thickness during examination onset by diagnosis, MDE (a) and AMD (b). The proximity of the points to the central line indicates a high level of correlation.

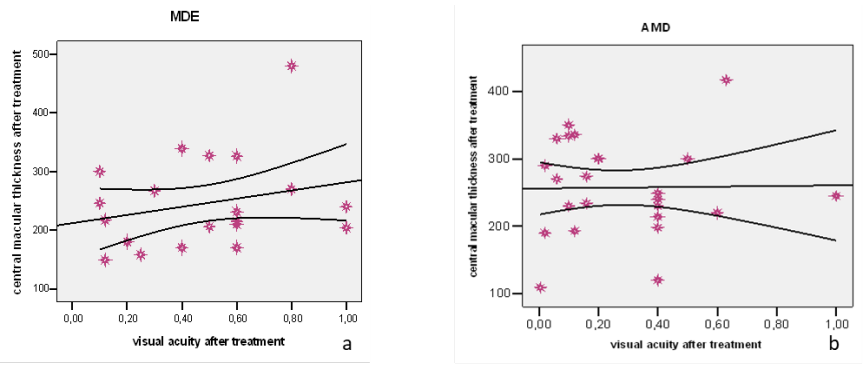


Figure 9. Correlation of visual acuity with central macular thickness during examination onset by diagno-sis, MDE (a) and AMD (b). The proximity of the points to the central line indicates a high level of correlation.

3. Discussion

The results of this investigation show that both in patients with macular degeneration and diabetic macular edema, visual acuity improves considerably after therapy and the average thickness of the central macula decreases considerably after therapy, when at least 3 injections are performed. The wet type of age-related macular degeneration is the most common, characterized by a severe loss of vision caused by the growth of eovascularization under or within the macula. According to studies in the literature, Aflibercept induced a rapid and steady increase in VA in patients with AMD up to week 52 and that was kept until week 96. An increased percentage of patients had a gain in VA ≥ 15 ETDRS letters in week 52, 60-70% of patients presented "dry macula" in week 52, the effect being kept in week 96 [9–11]. Table 2 reports some results of studies using Aflibercept in diabetic macular edema.

Table 2. Clinical studies that used aflibercept in DME

No. of patients	No. of injections/years	Visual acuity	Macular thickness	Reference
64 eyes of 64 patients	The mean number of aflibercept injections received was 12.59, at month 36	At 36 months, the mean VA (SD) (Snellen) was 68.34 (13.66) (20/50) ETDRS letters (p¼.0003).	The mean CFT (SD) was 303 (106) mm (p<.0001) and the average MV (SD) stood at 8.35 (1.62)mm3 (p¼0.0022) at 36 months	[11] Marko Lukic et. all, 2020
507 patients were enrolled from 35 centers	Mean number (SD) of injections in year one was 6.4	baseline BCVA was 71.4 (12.0) letters. 63.1% of patients presenting with baseline BCVA ≥ 70 letters (mean 78.1).	CST was 448.7 (88.7) μm . CST of −119.1 (116.4) μm was observed at month 12	[12] Sobha Sivaprasad et. all , 2022
402 participants (1 eye per participant), the mean (SD), 133 control group, 134 received aflibercept every 16 weeks after the 3 initials, 135 for 8 weeks		At week 52, the mean (SD) area under the curve (AUC) for the change in BCVA (measured in ETDRS letters) from base line, the average change was 1.7 (3.5) letters (P = .006) in the aflibercept 2q16 group and in the aflibercept 2q8/PRN group, it was 1.3 (3.5) letters (P = .05), contrasting with 0.5 (3.0) letters in the control group.	246.0 (34.3) 246.8 (31.6) By week 52, CST alterations measured -18.9 μm in the aflibercept 2q16 group and -24.9 μm in the aflibercept 2q8/PRN group, contrasting with 5.3 μm in the control group	[13] David M. Brown et. all, 2021
1,742 out of 2,196 eligible patients at one-year, 860 out of 1,270 at two years, and 305 out of 506 at three years	Over spans of 1, 2, and 3 years, the injection frequency was 6, 9, and 12, respectively.	The median visual acuity (VA) increased from an initial 65 to 71, 70, and 70 (ETDRS letters).	Younger age (p = 0.0023) and poorer baseline VA (p < 0.0001) were associated with higher IMD, rather than the total number of injections or VA changes. Lower initial VA, increased IMD, and older age were linked to reduced adherence (p = 0.0010).	[14] SJ Talks et. all, 2022

Randomized, multicenter, double-anonymized, actively controlled clinical trials in patients with DMLV wet type, VIEW 1 (on 1217 patients) [15]; In VIEW 2 (1240 patients), the ratio of patients who kept their vision (defined as loss of <15 letters according to the ETDRS chart was significant at 52 weeks [8]. Central retinal thickness and mean choroidal neovascularization area reduced in all therapy groups to a similar magnitude [14,16,17]. Marko Lukic et. all to evaluate the functional results 4 years after initiating the aflibercept injection, the mean injection count was 19.2 [18]. After 4 years, 33% of eyes saw an improvement of ⩾15 ETDRS letters, while 66 eyes (70%) showed no macular fluid at the end of the follow-up [18]. In a separate study by Wataru Kikushima (2021), 23 patients with neovascular age-related macular degeneration were monitored for 5 years [10]. These patients received nine injections each, administered once per month for three straight months then one injection as required for five years. 92.5% required retreatment. Visual acuity improved considerably after 12 months, the number of injections after the loading dose was 15. In Table 3 clinical studies using aflibercept in AMD are introduced.

Table 3. Clinical studies that used aflibercept in AMD

No. patients	No. of injections	Acuity visual	Macular thickness	Reference
Eighty-two patients with a follow-up period of ≥2 years were included.	The mean number of injections of the patients who completed at least 2 years of therapy was 19.2±9.0 (n=82, mean ± SD).	BCVA (mean±SD, ETDRS letter score) rose from 51.9±25.2 at the start to 63.7±17.7 (p<0.0001) after 1 year, 61.7±18.5 (p<0.0001) after 2 years, 62.4±19.5 (p<0.0001, n=61) after 3 years, and, by the fourth year, stabilized in considerably higher than the baseline at 58.5 ±24.3. (p=0.22)	Central subfield thickness (mean±SD, μm) dropped markedly from 387.5±107.6 (p<0.0001) initially to 291.9±65.5 (p<0.0001) after 1 year, and consistently stayed notably reduced until the fourth year at 289.0±59.4 (p<0.0001).	[16] Damian Jaggi et. all, 2022
53 eyes of 48 patients. A minimum follow-up of 12 months was mandatory. Patients underwent therapy following a modified pro re nata (PRN) approach, omitting the initial monthly loading. Regular visits were scheduled every 4–6 weeks for the patients.	7.36±1.85 bevacizumab/ Ranibizumab The number of injections in the year before the transition was a median of 6 (interquartile range [IR] 6.0–8.5), while in the subsequent year, there was an average of 6.47±2.45 aflibercept injections (median 6, IR 5.0–8.0).	Average alteration in BCVA from the initial measurement was 0.05±0.13 (P=0.01) at M1, 0.04±0.16 (P=0.08) at M3, 0.01±0.22 (P=0.9) at M6, and 0.02±0.28 (P=1) at M12	At the same time the mean changes in CMT from baseline was 64±75 μm (P<0.0001) at M1 (1 month), 42±85 μm (P=0.002) at M3, 47±69 μm (P<0.0001) at M6 (month), and 46±99 μm (P=0.001) at M12 (months). At the start, 77.4% of eyes had SRF, which dropped to 39.6% at M1, then increased to 47.2% at M3, subsequently decreasing to 43.4% at M6, and finally settling at 41.5% by M12 (all p<0.001, compared to baseline).	[17] Mohamed A. Hamid et. all, 2021

The 4-year follow-up was completed by 94 eyes belonging to 89 patients.	The average count of aflibercept injections received within a span of 4 years was 19.3.	Initially, the average VA (SD) measured 54.1±15.5 (20/100 Snellen) ETDRS letters, with an average CSM (SD) value of 296±81μm. By the fourth year, the average VA (SD) improved to 60.4±20.0 (20/63 Snellen) ETDRS letters ($p<0.0001$).	The average CSMT (SD) measured 218±79μm ($p<0.0001$). At the end of the 4-year period, 33% of eyes exhibited an increase of ⩾ 15 ETDRS letters, and 66 eyes (70%) showed no macular fluid at the conclusion of the follow-up.	[18] Marko Lukic et. all, 2020
479 naïve AMD-related macular neovascularization (MNV) patients were recruited. s. Over a 24-month follow-up, therapy outcomes were assessed in therapy-naïve nAMD patients who underwent intravitreal injections of either aflibercept or Ranibizumab. Each patient received the initial loading dose followed by a PRN regimen.		No significant changes in BCVA were observed at the 1-year and 2-year check-ups compared to the initial evaluations. However, baseline BCVA showed significant correlation with both the 1-year and 2-year follow-up changes ($p < 0.01$). Furthermore, BCVA at 1-year exhibited a significant correlation with BCVA changes at the 2-year follow-up ($p < 0.01$). Patients with better initial visual acuity tended to achieve higher-quality BCVA by the investigation's conclusion.	The CMT showed a significant decrease at both the 1-year and 2-year follow-up evaluations ($p < 0.01$). Classic, polypoidal choroidal vasculopathy, and mixed subtypes were considerably associated with poorer visual outcomes ($p < 0.01$).	[3] Alessandro Arrigo et. all, 2021

According to literature studies, it is demonstrated that antivascular endothelial growth factor agents (anti-VEGF) are effective and safe therapy options for patients with nAMD (wet type) and EMD and have changed the paradigm of disease therapy. A recent meta-analysis [19] conducts a literature review and meta-analysis to evaluate the use of intravitreal aflibercept and real-world outcomes in therapy-naïve neovascular DMLV patients for 2 years. The results of the meta-analysis showed that patients treated with intravitreal aflibercept reported significant gains in visual acuity from baseline after 2 years. Also, related to the number of injections, they argue that the evidence identified indicates that the visual gains achieved in the first year of therapy and in the second year are kept and that they were achieved with a reduction in the average number of aflibercept injections administered in year 2.

Like the results of the specialized literature regarding the functional and structural results after intravitreal aflibercept injections in macular pathologies, our results support an improvement in visual acuity and a reduction in the central macular thickness at 1 year of follow-up.

4. Materials and Methods

This is a retrospective examination that was carried out on 57 patients with macular pathology at the St. Spiridon hospital in Iasi, between September 2020 and March 2021.

The examination enrollment began in September 2020, when Aflibercept was allowed to be used in the hospital. The investigation was approved by the Ethics Commission of University Hospital Sf. Spiridon Iasi, approval no. in compliance with the guidelines related to ethics and moral principles in medical and research practices.

Ethical Considerations: The investigation adhered to the principles outlined in the Helsinki Declaration and with several published principles [20]. All patients signed an informed consent for enrollment in the study, detailing indications, administration procedures, as well as the incidents and side effects of the injections. Those who showed no improvement after a minimum of 3 injections were informed they would be excluded from the follow-up study.

Inclusion criteria: Patients with macular pathologies (wet age-related macular degeneration and diabetic macular edema), treatment-naive individuals (who have not received intraocular injections before). All types of CNV lesions related to neovascular AMD were included in the analysis. Patients who received at least six injections and were followed for a minimum of one year.

Exclusion criteria: Patients with a follow-up period of less than one year, those who received fewer than 6 injections, individuals without regular assessments or OCT examinations were excluded."57 naive patients with macular pathology were included in the investigation, 57 eyes respectively, 24 eyes with diabetic macular edema and 33 with neovascular age-related macular degeneration. Eyes where less than 6 straight intravitreal injections were performed; those without tomography control examinations and without evaluation at one-year of follow-up were excluded.

Protocol details: The recommended dose of aflibercept is 2 mg aflibercept, equal to 50 microliters. A volume of 0.05 ml is injected at 3.5-4.0 mm behind the limbus, in the vitreous cavity, excluding any reference to the horizontal meridian in the direction of the center of the eyeball. Enrolled patients did not previously receive other injections with other anti-VEGF therapies. Inclusion criteria: Patients with macular pathology (diabetic macular edema) and age-related macular degeneration wet type were included.

Therapeutic indications. The interval between 2 doses should not be less than one month. If visual and anatomical results indicate that the patient doesn't show improvement with ongoing therapy, discontinuing Eylea is recommended. The therapy can be continued with a "tritend extend" regimen, progressively increasing the therapy administration interval so that the visual and, or anatomical results are kept stable, still there isn't enough data to reach a definitive conclusion regarding the time of this interval [15,21–23].

Gradual extension of the time between administrations until fluid reappears or AV decreases (e.g., determination of the maximum interval in which there is no fluid infiltrate) [15,22,23].

If the visual and, or anatomical results deteriorate, the therapy administration interval should be reduced accordingly (diabetic macular edema and age-related macular degeneration) [15,22,23].

The monitored parameters were: initial visual acuity with correction and at the last control, central macular thickness at the initial OCT and at all controls. The study protocol was the one recommended by the manufacturer following the results of the evaluations carried out by us: it complied with the Eylea indications, administration regimen according to the protocol 1 monthly injection, 3 straight months for DMLV, then every 2 months and 1 monthly injection for 5 straight months of EMD, then after 2 months. Perioada de urmarire va continua conform protocolului si pe perioada de peste un an cu evaluarea acuitatii vizuale si grosimii maculare centrale la fiecare doua luni si injectarea de anti VEGF atunci cand persista lichidul, absenta injectarii in abesnta lichidului. Scopul acestor injectari este obtinerea [15,22,23].

Patient Follow-Up. The ongoing assessment protocol after one year will consist of ongoing evaluations of visual acuity and central macular thickness measurements using OCT every 2 months, with the possibility of extending or shortening the interval to 16 weeks if there are no indications of persistent fluid

Statistical analysis

The data were centralized in SPSS 18.0 databases and processed using statistical functions suitable at a significance threshold of 95% (95% CI). Both descriptive and analytical methods were employed in the statistical analysis.

Derived indicators serve to highlight the qualitative aspects of a set, aiming to demonstrate the relationship between different parts of a patient group or various characteristics, unveiling interdependencies between variables. The following derived indicators were utilized:

- Indicators of central tendency: simple arithmetic mean, median, mode.
- Indicators of dispersion: standard deviation, variance.

ANOVA (Analysis of Variance) involved analyzing the dispersion of the dependent variable intra- and inter-group.

The coefficient of variation (CV%) highlights the percentage deviation between two means, providing insights into the homogeneity of the value series, and the Skewness test ($-2 < p < 2$) validates the normality of the value series, applied when the examined variable has continuous values.

The t-Student test - a parametric test that compares mean values recorded in 2 groups with normal distributions. The widely accepted significance threshold is 95%, i.e., p=0.05. The smaller the p-value compared to this value, the stronger the significance.

The F test (ANOVA) is used when comparing 3 or more groups with normal distributions, coupled with the application of the Bonferroni correction (post-hoc Bonferroni) to reduce the error rate when testing multiple hypotheses.

The Chi-Square test (Likelihood Ratio) is a non-parametric test comparing 2 or more frequency distributions from the same population. It is applied when expected events are exclusive. If the obtained p-value is smaller than the tabulated one at the 95% significance threshold, the events are not exclusive - in this case, the question arises if they are dependent.

The "Pearson" correlation coefficient (r) represents the correlation between 2 variables within the same group (direct/indirect correlation). The closer the value of r is to 1 (direct correlation) or -1 (indirect correlation), the more dependent the parameters are on each other.

Multiple linear regression using the method of least squares is the most commonly used modeling method. The purpose of multiple regression (a term used by Pearson, 1908) is to highlight the relationship between a dependent variable (explained, endogenous, resultant) and a set of independent variables (explanatory, factorial, exogenous, predictors).

By employing multiple regression, the aim is often to obtain an answer to questions such as "what is the best prediction for...?" or "who is the best predictor for...?"

The ROC curve (Receiver Operating Characteristics) is a two-dimensional curve where the Y-axis represents sensitivity and the X-axis represents specificity. This curve helps us measure the effectiveness of a model by plotting the specificity/sensitivity balance as a prognostic factor. The larger the area under the curve (maximum is 1), the better the model:

- Area > 0.9 - excellent
- 0.9 > Area > 0.8 - very good
- 0.8 > Area > 0.7 - good
- 0.7 > Area > 0.6 - fair
- Area < 0.6 - the model is rejected

Study limitations

There is a retrospective examination on a small number of patients. The outcomes are only after 1 year compared to the other studies that show results after 3 or 4 years. Among the mentioned limitations, the most significant is the study's one-year duration and its retrospective nature. For diabetic patients, clear evidence of glycemic fluctuations during the study period is lacking. Additionally, details regarding the degree of retinal involvement according to ETDRS and the type of retinopathy associated with macular edema were not provided. Studies demonstrating the long-term effects of injections indicate follow-up periods of up to 4 years. We are interested in understanding the injections' effects on both visual acuity and the macular region (such as drying of the macula and absence of subretinal fluid) with a reduced number of injections and increased injection intervals. Results showed that improvements in visual acuity and reduction in macular thickness depended on both the number of injections and the initial macular thickness. The statistical outcomes of our study align with those in the literature. Positive results observed at the one-year follow-up indicate potential outcomes after 3 or 4 years, with a significantly reduced number of injections due to decreased necessity caused by the absence of intraretinal and subretinal fluid. Our findings indicate that aflibercept treatment for nAMD and DME can yield impressive long-term efficacy using an initial proactive treatment approach with predefined dosages in the first year followed by an extended treatment regimen.

5. Conclusions

Within this investigation, the therapy with intravitreal Aflibercept was associated with improving functional and anatomical outcomes in those who received at least three injections. It is an effective drug and the most essential aspect for our patients free of charge through CAS. The results are similar to those in the literature. Visual gains following the use of aflibercept are additionally linked to improving patients' quality of life. For this reason, the aflibercept seems to be an appropriate first line of therapy for MDE and neovascular AMD, in addition to other anti-VEGF therapies currently available in Romania in our patients. It is necessary to re-evaluate the patients over a more extended follow-up period (minimum 1 year) to reach statistically significant results.

Future directions: Given that these conditions severely impact visual function in the absence of treatment, the identification of the most effective anti-VEGF in treating both conditions to improve vision and macular thickness while sustaining results over long periods with a reduced number of injections is crucial. Future studies should aim to enroll a larger number of participants over an extended follow-up period.

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Informed Consent Statement: Informed consent was obtained from all subjects involved in the study.

Data Availability Statement: The data published in this research are available on request from the first author and corresponding authors.

Conflicts of Interest: The authors declare no conflict of interest.

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