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Original Research Article

Study on the efficacy of different injection regimens of aflibercept in the treatment of diabetic macular edema

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Abstract

Purpose: *To determine the efficacy of different regimens of aflibercept injection in the treatment of diabetic macular edema (DME).*
Methods: *A retrospective analysis was performed on 78 DME patients admitted to Affiliated Hospital of Hebei University, China from January 2021 to December 2022. The patients, categorized into control group (39 patients) and study group (39 patients), received varying regimens of aflibercept injections pro re nata (PRN); 3 + PRN regimen and 5 + PRN regimen, respectively. Best-corrected visual acuity (BCVA) and central macular thickness (CMT) were measured at baseline, 1, 3, 6, and 12 months following treatment. The proportions of BCVA improvement by 10 and 15 letters at 12 months and incidence of visual acuity instability during the as-needed period were calculated. Adverse events were also recorded.*
Results: *The BCVA significantly improved in both groups at 3, 6, and 12 months ($p < 0.05$), with no significant difference between the groups ($p > 0.05$). The proportions of BCVA improvement by 10 and 15 letters at 12 months were similar between the groups. Study group had a significantly lower rate of visual acuity instability during the as-needed period ($p < 0.05$) compared to control group. The CMT significantly reduced in both groups at all time points ($p < 0.05$), with no significant difference observed between the groups. Study group had significantly fewer injections during the as-needed period ($p < 0.05$) compared to control group. Adverse events did not significantly differ between the two groups.*
Conclusion: *Both 3 + PRN and 5 + PRN regimens of Aflibercept injection are effective in treating DME. However, the 5 + PRN regimen demonstrates a lower rate of visual acuity instability and requires fewer injections during the as-needed period. Future studies are needed to analyze the efficacy and differences between various injection regimens for treating DME.*

Keywords: *Diabetic macular edema, Aflibercept, 3 + PRN, 5 + PRN, Best corrected visual acuity, Central foveal retinal thickness*

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INTRODUCTION

With the aging population and improved living standards, there has been a yearly increase in the incidence of diabetes mellitus accompanied by a rise in diabetic-related complications [1]. Diabetic retinopathy, characterized mainly by diabetic macular edema (DME), is one of the

most common complications of diabetes [2]. Clinical studies have confirmed that the incidence of DME increases with the duration of diabetes and it is a major cause of visual impairment in patients [3]. Intravitreal injection of anti-vascular endothelial growth factor (anti-VEGF) agents is a first-line treatment for DME [4].

Aflibercept, a humanized recombinant fusion protein, has been approved for the treatment of retinal diseases, including DME [5]. Previous large-scale randomized controlled trials (RCTs) have shown that monthly injections of anti-VEGF drugs such as Aflibercept, followed by as-needed treatment (pro re nata, PRN), known as the 3 + PRN regimen, are the standard treatments for DME [6,7]. However, with longer follow-up periods, requirement for repeated injections in the later stages coupled with high cost of medication as well as low patient compliance, the treatment advantage of the 3 + PRN regimen is not significant and the prognosis is not ideal.

International guidelines suggest that early intensive treatment with anti-VEGF drugs for 4 - 6 months in DME patients leads to a majority of patients not requiring additional injections starting from the third year [8]. This implies that early intensive anti-VEGF treatment may represent a new approach for DME. Therefore, the primary objective of this study is to conduct a comparative analysis of the therapeutic outcomes associated with two Aflibercept injection regimens, namely, the 3 + PRN and 5 + PRN approach, in patients with diabetic macular edema (DME). The "3+" regimen typically means that patients receive Aflibercept injections regularly at specified intervals or after certain events. The "5+" regimen implies a different dosing strategy where patients receive Aflibercept injections more frequently, typically a scheduled injection is given every five months or after every fifth visit or event.

METHODS

Study population

Clinical data of 78 patients with diabetic macular edema (DME) admitted to the Eye Hospital Affiliated to Hebei Medical University from January 2021 to December 2022 were retrospectively analyzed. According to different initial treatment regimens, patients were equally divided (n = 39) into a control group and a study group. This study was approved by the Hospital Ethics Committee (approval no. RB-2023-104), and informed consent was obtained from all participants. All procedures were conducted in line with the Declaration of Helsinki [9].

Inclusion criteria

Inclusion criteria were as follows: Patients diagnosed with DME according to the diagnostic criteria [10] and having type 2 diabetes; age ≥ 18 years; patients with unilateral disease manifestation; central macular thickness (measured by optical coherence tomography, OCT) exceeding 300 μm and best-corrected visual acuity (BCVA) ranging from 31 to 80 letters.

Exclusion criteria

Patients were excluded from the study based on the following criteria: Patients with macular edema caused by other reasons; Inability to perform fundus examination due to corneal opacity or other reasons; patients with history of previous retinal surgery or laser or drug treatment within the past 3 months; patients with presence of intraocular infection, glaucoma or intraocular pressure > 21 mmHg; presence of concomitant severe heart, liver, kidney, or other diseases as well as pregnant or lactating women.

Treatments and procedures

Both groups were treated and examined by the same medical team, following the same preoperative and postoperative procedures. All patients received intravitreal injections of Aflibercept (registered under the number S20180010 by Bayer Pharmaceutical Co., Ltd.), at a dosage of 2 mg per injection. Before the procedure, routine ocular examinations such as slit-lamp biomicroscopy and optical coherence tomography (OCT) were performed. Preoperatively, 2 drops of 0.5 % moxifloxacin hydrochloride eye drops (China Resources Zizhu Pharmaceutical Co. Ltd) were administered for 3 - 5 days at a frequency of 4 - 6 times per day.

Intravitreal injections were performed according to the requirements for intraocular surgery based on the following steps: the patient assumed a supine position, routine disinfection and draping were carried out, and proper anesthesia (isoflurane) was achieved. After thorough pupil dilation, surface anesthesia of the eye was performed using proparacaine hydrochloride eye drops. After irrigation of the conjunctival sac with povidone-iodine solution and normal saline, a 3.5 - 4.0 mm needle was inserted into the vitreous cavity, posterior to corneal edge, and 2 mg of Aflibercept (0.05 mL) was slowly injected. After injection, the needle was withdrawn and sterile

cotton swabs were used to apply pressure to the injection site for 10 - 20 sec.

The intraocular pressure was checked and any discomfort or pain in the eye was observed. If the intraocular pressure was elevated, a small amount of aqueous humor was released along the corneal edge. Tobramycin and dexamethasone ointment were applied to the conjunctival sac, followed by dressing with a disposable bandage. On the second day, moxifloxacin hydrochloride eye drops (0.5 %) were introduced into the eye at a frequency of 4 - 6 times per day for 3 - 5 days. Thereafter, control group received the 3 + PRN injection regimen, which consisted of an initial intravitreal injection of Aflibercept (2 mg) three times, once a month for three months, followed by as-needed injections while study group received the 5 + PRN injection regimen, which consisted of an initial intravitreal injection of Aflibercept (2 mg) five times, once a month for five months, followed by as-needed injections. First, they received 5 regular injections, one every other month, and then during the subsequent treatment period, the need for further injections was assessed based on the patient's eye condition and disease exacerbation.

The criteria for as-needed injections were as follows: a decrease in BCVA by more than 5 letters, recurrence of DME, an increase in central macular thickness (CMT) by ≥ 100 μm, OCT indicating new retinal cystic changes or subretinal fluid, or as determined by the physician. The criteria for pausing injections were three consecutive follow-up visits without significant changes in BCVA. After the initial injection, all the patients underwent regular monthly follow-ups to collect data on blood glucose levels, BCVA, OCT, and slit-lamp examination results. The efficacy was evaluated based on the treatment outcome at the end of 12 months.

Evaluation of parameters/indices

Determination of best-corrected visual acuity (BCVA)

The BCVA of patients was assessed before treatment and at 1, 3, 6 and 12 months post-treatment. The BCVA letter scores at each time point were compared between the two groups. Additionally, the proportions of patients in each group who achieved an improvement of 10 and 15 letters in BCVA compared to baseline at the end of 12 months of treatment were calculated. In addition, the proportion of patients with unstable visual prognosis during the PRN period was also determined. Visual prognosis instability was defined as a decrease in BCVA by more than 5 letters compared to the previous month during the PRN period. However, this test was done only when the patient needed it, not on a fixed schedule or dose.

Central macular retinal thickness

Central macular retinal thickness (CMT) was measured using OCT before treatment and at 1, 3, 6 and 12 months of treatment. The measurements were compared between the two groups.

Injection frequency

The total number of injections and the number of injections during the PRN period were recorded for both groups.

Incidence of ocular adverse events

The occurrence of complications, including injection site hemorrhage, intraocular inflammation, conjunctival hemorrhage and intravitreal fluid accumulation during the follow-up period were recorded for both groups.

Statistical analysis

Data analysis was performed using Statistic Package for Social Science (SPSS) 24.0. Continuous data were expressed as mean ± standard deviation (SD). Independent samples *t*-test was used for between-group comparisons, and paired *t*-test was used for within-group comparisons. Categorical data were presented as n (%) and analyzed using the chi-square test for between-group comparisons. A $p < 0.05$ was considered statistically significant.

RESULTS

General data

Table 1 highlights the general information of patients in both groups. There were no statistically significant differences in gender, age, BCVA, and other general data of patients between the two groups ($p > 0.05$).

Best-corrected visual acuity score

At 3, 6 and 12 months after treatment, the BCVA of the two groups was significantly higher than that before treatment ($p < 0.05$), and there was no significant difference between the two groups at each time point ($p > 0.05$; Table 2).

Table 1: Comparison of the general data of patients in both groups

Group	Gender (male/ female)	Age (years)	Diabetes duration (years)	Fasting blood glucose (mmol/L)	Intraocular pressure (mmHg)	DME grade	
						Moderate	Severe
Control	21/18	53.48±7.82	8.97±1.26	6.15±1.64	13.61±1.52	23 (58.97)	16 (41.03)
Study	16/23	54.12±8.06	8.68±1.13	6.34±1.72	13.57±1.48	19 (50.00)	19 (50.00)
t/χ^2	1.285	0.356	1.070	0.499	0.118	0.625	
P-value	0.257	0.723	0.288	0.619	0.907	0.429	

There was also no significant difference in the proportion of BCVA improved by 10 and 15 letters after 12 months of treatment between the two groups ($p > 0.05$; Table 3). The incidence of unstable visual prognosis during PRN in study group was lower than that in control group ($p < 0.05$; Table 3).

Central macular thickness

After 1, 3, 6 and 12 months of treatment, the CMT of the two groups was significantly lower than that before treatment ($p < 0.05$). However, there was no significant difference between the two groups at each time point ($p > 0.05$). The results are presented in Table 4.

Injection times

There was no significant difference in the total number of injections between the two groups ($p > 0.05$). However, the number of injections during PRN in study group was significantly less than that in control group ($p < 0.05$; Table 5).

Incidence of ocular adverse events

During the follow-up period, both groups maintained stable blood glucose levels and there was no significant difference in the incidence of ocular adverse events between the two groups ($p > 0.05$). In control group, the incidence of subconjunctival hemorrhage or discomfort was 23.08 % (9/39), while in study group, it was 28.21 % (11/39). Symptomatic treatment led to improvement and there was no significant difference between the groups. The incidence of transient elevated intraocular pressure was 15.38 % (6/39) in control group and 10.25 % (4/39) in study group. Patients in both groups experienced self-relief after 2 days of study. The incidence of vitreous fluid accumulation was 5.13 % (2/39) in both groups and it resolved spontaneously without treatment. No serious ocular adverse events such as endophthalmitis, retinal detachment, or lens injury occurred in either group.

Table 2: Comparison of BCVA between groups (n = 39)

Group	Pre-treatment	Treatment for 1 month	Treatment for 3 months	Treatment for 6 months	Treatment for 12 months
Control	54.35±8.69	56.76±9.04	58.67±9.62[a]	60.29±9.74[a]	62.72±9.87[a]
Study	55.76±8.83	57.12±9.21	60.65±9.85[a]	62.97±9.82[a]	65.41±9.84[a]
t/χ^2	0.711	0.174	0.898	1.210	1.205
P-value	0.479	0.862	0.372	0.230	0.232

Compared with before treatment in the same group, [a]$p < 0.05$. Values are *n* (%)

Table 3: Comparison of BCVA increase and prognosis of visual acuity between groups (n = 39)

Group	BCVA increased the number of letters ≥ 10	BCVA increased the number of letters ≥ 15	The prognosis of visual acuity during PRN is unstable
Control	19 (48.72)	10 (25.64)	10 (25.64)
Study	21 (53.85)	12 (30.77)	3 (7.69)
t/χ^2	0.205	0.253	4.523
P-value	0.651	0.615	0.033

Compared with before treatment in the same group, [a]$p < 0.05$. Values are *n* (%)

Table 4: Comparison of CMT between groups

Group	Pre-treatment	Treatment for 1 month	Treatment for 3 months	Treatment for 6 months	Treatment for 12 months
Control	454.61±58.75	264.35±31.02[a]	248.37±25.62[a]	225.47±21.72[a]	202.45±19.17[a]
Study	455.76±59.23	254.97±27.68[a]	238.65±22.85[a]	218.43±20.67[a]	195.82±18.54[a]
T	0.086	1.409	1.768	1.466	1.553
P-value	0.932	0.163	0.081	0.147	0.125

Compared with before treatment in the same group, [a]$p < 0.05$

Table 5: Comparison of injection times between groups

Group	Total number of injections	Number of injections during PRN
Control	7.16±2.03	4.09±1.34
Study	7.23±2.11	2.42±0.76
T	0.149	6.770
P-value	0.882	0.000

DISCUSSION

Data from previous reports show that 7 % of patients with a history of diabetes have retinopathy, 25 % of patients with a diabetic history of 15 years have retinopathy and the incidence of retinopathy is as high as 60 - 84 % in patients with a diabetic history of 20 years [11]. Diabetic macular edema (DME) is the main manifestation of retinopathy, which is one of the four leading causes of blindness in China [6]. Therefore, the most important goal of DME treatment is to maximize the maintenance and protection of the patient's vision. Previous studies have shown that diabetes can lead to retinal ischemia and hypoxia in patients, promote the growth of vascular endothelial growth factor (VEGF) and then increase the permeability of the vascular wall, as well as induce neovascularization, thereby leading to the damage of the inner and outer retinal barrier, and the occurrence of DME [12].

Various anti-VEGF drugs reduce intraocular VEGF and vascular permeability, inhibit neovascularization and promote edema absorption, which has become a common treatment for DME [13]. However, as the anti-VEGF drug is metabolized in the eye, macular edema reappears when the intraocular concentration of the anti-VEGF drug is lower than the therapeutic concentration, so the anti-VEGF drug needs to be injected repeatedly. The anti-VEGF drug, 3 + PRN is widely recognized and used in clinical practice and its effectiveness and safety have been confirmed by several previous studies [14,15]. With the deepening of clinical research, the latest view is that early intensification of anti-VEGF drugs is more effective for edema resolution and visual protection. The 2020 Clinical Guidelines for Diabetes in the United States [8] recommends "early and intensive" treatment of DME with 4 - 6 times intensive treatment with anti-VEGF drugs, which can achieve the greatest improvement in vision, and only a small amount of additional injections are needed to obtain stable efficacy, which has both clinical and economic benefits.

It is the ultimate goal of ophthalmologists all over the world to develop a personalized treatment plan to maximize or maintain the vision of DME patients. Macular edema and thickening are the main causes of vision loss in diabetic patients. Zhang Shaohua *et al* showed that aflibercept, an anti-VEGF drug, significantly improved BCVA and CMT, reduced macular edema and improved visual acuity in patients with different types of DME [16]. In this study, at 3, 6 and 12 months after treatment, the BCVA values of the two groups were higher while the CMT values were lower than those before treatment, and there was no significant difference between the two groups at each time point. These results indicate that aflibercept is effective in the treatment of DME, improves visual acuity and reduces CMT. Compared with the 3 + PRN injection regimen, the 5 + PRN injection regimen had no obvious advantage in the treatment of DME. Aflibercept binds to VEGF-A and placental growth factor, thereby blocking the binding and activation of endogenous VEGF receptor with VEGF-A and placental growth factor, thus reducing macular neovascularization, repairing blood-retinal barrier, reducing CMT and improving visual acuity [11]. Therefore, aflibercept 3 + PRN injection and 5 + PRN injection effectively reduce macular edema and CMT values of DME patients and restore visual acuity.

In this study, after 12 months of treatment, the proportions of patients with an improvement in BCVA of ≥ 10 letters were 48.72 and 53.85 % in the control and study groups, respectively. The proportions of patients with an improvement in BCVA of ≥ 15 letters were 25.64 and 30.77 % in the control and study groups, respectively. There was no significant difference between the groups. During the PRN period, the occurrence rate of unstable visual prognosis was 7.69 % in study group, significantly lower than the 25.64 % in control group. These findings indicate that both the 3 + PRN and 5 + PRN injection regimens effectively improved visual acuity in patients with DME. However, the 5 + PRN regimen provided a more stable improvement in visual acuity with less fluctuation. The reason for this could be that after three months of core anti-VEGF treatment, most DME patients reach a plateau phase of visual recovery. However, with an increased frequency of core treatments, the affected eye can maintain a more stable therapeutic concentration, which is more beneficial for visual recovery and results in better visual prognosis stability.

Reducing the number of injections during the treatment while achieving effective therapy is an important indicator for evaluating both clinical

and economic benefits for patients [17]. In this study, there was no significant difference in the total number of injections between the two groups, but study group had a significantly lower number of injections during the PRN period compared to control group. This suggests that the 5 + PRN treatment regimen does not have any significant advantage over the 3 + PRN in reducing the total number of injections, but it does significantly reduce the number of injections during the PRN period. A previous study indicated that during the PRN period, the earlier the first injection was administered, the more likely the chances of edema recurring and the more frequent the injections [18]. The difference between this study and previous findings could be attributed to the relatively short follow-up period, where the 5 + PRN injection regimen requires five core treatments that may not have fully demonstrated its advantages. No serious complications such as endophthalmitis, retinal detachment, or lens injury occurred in either group throughout the follow-up treatment period. Subconjunctival hemorrhage resolved with symptomatic treatment and did not adversely affect the patients. Therefore, both the 3 + PRN and 5 + PRN injection regimens with Aflibercept demonstrated high safety.

Limitations of this study

However, this study has certain limitations, such as the small sample size and short follow-up period. Future prospective multicenter studies with a larger sample size are needed to further analyze the efficacy and differences between the two injection regimens for treating DME.

CONCLUSION

Both the Aflibercept 3 + PRN and 5 + PRN injection regimens significantly improve visual acuity and alleviate edema symptoms in patients with DME. The safety profiles of both regimens are high. The 5 + PRN regimen requires fewer additional injections during the PRN period and has a lower proportion of unstable visual prognosis. Future studies are needed to analyze the efficacy and differences between various injection regimens for treating DME.

DECLARATIONS

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Ethical approval

None provided.

Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Conflict of Interest

No conflict of interest associated with this work.

Contribution of Authors

The authors declare that this work was done by the authors named in this article and all liabilities pertaining to claims relating to the content of this article will be borne by them. Lan Liu and Xi Wang contributed equally to this work. We declare that this work was done by the authors named in this article and all liabilities pertaining to claims relating to the content of this article will be borne by the authors.

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