Original Article

Factors affecting compliance to intravitreal anti-vascular endothelial growth factor therapy in Indian patients with retinal vein occlusion, age-related macular degeneration, and diabetic macular edema

Aditya Kelkar, Caroll Webers[1], Rohit Shetty[2], Jai Kelkar, Nikhil Labhsetwar, Abhishek Pandit, Madhulika Malode[3], Sayali Tidke

Purpose: To evaluate the rate of compliance and the reasons for loss to follow-up in Indian patients with diabetic macular edema (DME), age-related macular degeneration (AMD), and retinal vein occlusion (RVO) being treated with anti-vascular endothelial growth factor (VEGF) therapy. **Methods:** This was a retrospective single-center study. Patients with DME, AMD, or RVO were eligible if they initiated anti-VEGF therapy between January 2013 and December 2017. Patients' data were obtained from hospital electronic records, including the number of injections received, visits, details of follow-up, missed appointments, and reasons for loss to follow-up (>365 days). **Results:** A total of 648 patients were eligible for the study, of which 334 (51.54%) patients were lost to follow-up. Overall, 343 (64.96%) were males and the overall mean (SD) age was 66.40 (7.44) years. A total of 376 (58.0%) patients had a history of diabetes and 364 (56.2%) patients had a history of hypertension. Further, 127 (38.0), 112 (33.5), and 95 (28.4) had DME, AMD, and RVO, respectively and were lost to follow-up. The most commonly reported reason for loss to follow-up was "non-affordability" (n = 120; 41.1%) followed by "no improvement in vision" (n = 83; 28.4%). "No improvement in vision" (42.2%) and "non-affordability" (37.5%) were higher among patients with DME. No association was found in gender- and treatment-wise distribution of reasons for loss to follow-up. **Conclusion:** The results showed that around half of the patients with DME, AMD, and RVO were lost to follow-up to intravitreal anti-VEGF therapy, and the most common factors were "non-affordability" and "no improvement in vision."

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Retinal disorders including diabetic macular edema (DME), age-related macular degeneration (AMD), and retinal vein occlusion (RVO) are major causes of ophthalmic morbidity worldwide and have a significant burden on both patient and healthcare system.[1] Currently, anti-vascular endothelial growth factor (VEGF) therapy is an established treatment for various retinal diseases including DME, AMD, and RVO and has been used worldwide.[2-4]

Pegaptanib sodium was the first approved intravitreal anti-VEGF agent for the treatment of neovascular AMD; however, the most commonly used intravitreal anti-VEGF therapies are bevacizumab and ranibizumab.[5,6] These injections are recommended to be administered once a month and if monthly injections are not feasible, the pro re nata (PRN) protocol is used where the frequency depends on optical coherence tomography (OCT) findings. Recently, several studies have shown the usefulness of treat-and-extend where the patient receives a repeat intravitreal anti-VEGF at each visit; however, the next injection is extended if the lesion is stable or inactive based on OCT scan.[7-10]

Adherence to any treatment is of utmost importance to achieve expected health care benefits. Patients receiving intravitreal anti-VEGF are expected to be compliant and should follow-up regularly to receive their next scheduled dose; however, poor compliance has been observed. There is limited literature, particularly on RVO, on the factors that lead to non-compliance to anti-VEGF therapy.[11-14] This paper reports the results of a study that evaluated the rate of compliance and the reasons for loss to follow-up in Indian patients with RVO, AMD, and DME being treated with anti-VEGF. To the best of our knowledge, this is the first study from India.

Methods

This was a retrospective study that included patients with DME, AMD, or RVO who were receiving treatment at a tertiary

National Institute of Ophthalmology, Pune, India, [1]Department of Ophthalmology, Maastricht University Medical Center, Maastricht, The Netherlands, [2]Narayana Nethralaya, Bengaluru, Karnataka, [3]Sqarona Medical Communications LLP, Navi Mumbai, Maharashtra, India

Correspondence to: Dr. Aditya Kelkar, National Institute of Ophthalmology (NIO), Ghole Road, Near Mahatma Phule Museum, Shivajinagar, Pune, Maharashtra - 411 005, India. E-mail: adityapune4@gmail.com

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care eye hospital in western India. Patients were eligible if they initiated anti-VEGF (bevacizumab or ranibizumab) between January 2013 and December 2017. The study was approved by the institutional ethics committee. The study was conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki.

Patients' data were obtained from hospital electronic records. The following data were obtained for this study: age, sex, disease, years with the disease (DME, AMD, and RVO), history of diabetes or hypertension, number of injections, details of follow-up, and missed appointments. Patients or relatives were called and the reason for noncompliance was noted using an oral questionnaire [Table 1]. Patients were allowed to choose only one reason. No follow-up between 14 days to 90 days was considered as missed appoint and no follow-up between 90 and 365 was considered as break-off and no follow-up visit for more than 365 days was considered as lost to follow-up. Reasons for break-off or loss to follow-up were captured, if available. If not, every effort was made to identify the reason by telephonic contact.

The statistical analysis was performed using SPSS for Windows version 23.0 (SPSS Inc., Chicago, IL, USA). The normality of data was analyzed using the Shapiro-Wilk test. The qualitative variables were comparatively analyzed using the Chi-square test. Quantitative variables were analyzed using a non-parametric test, Mann-Whitney U test (as data were not normally distributed and a number of groups were less than two). Statistical significance was considered if the *P* value was less than 0.05.

Table 1: Questionnaire

Reasons for lost to follow-up	Response
Non-affordability	
Treatment elsewhere	
Shift of residence	
No improvement in vision	
Transport issue	
Health issue	
Expired (death)	
Not willing	

Results

Out of a total of 648 patients included in the study, 434 (67.0%) were males and the overall mean (SD) age was 66.40 (7.44) years. A total of 234 (36.1%) patients had DME, 219 (33.8%) patients had AMD, and 195 (30.1%) patients were diagnosed with RVO. Of these, 293 (45.22%) patients were compliant, seven (1.08%) were missed appointments, 14 (2.16%) were break-offs, and 334 (51.54%) patients were lost to follow-up. Of the 334 patients who lost to follow-up, 42 patients were excluded from the analysis of reasons to loss to follow-up because the patients' number was changed, was a wrong number, or were not contactable [Table 2]. A total of 376 (58.0%) patients had a history of diabetes and 364 (56.2%) patients had a history of hypertension. A total of 363 (56.0) patients were receiving ranibizumab and 285 (44.0) patients were receiving bevacizumab [Table 2].

The most commonly reported reason for loss to follow-up was "non-affordability" (n = 120; 41.1%) followed by "no improvement in vision" (n = 83; 28.4%), "treatment elsewhere" (n = 27; 9.2%), and "shift of residence" (n = 24; 8.2%). A total of nine patients died [Figure 1]. Among patients who missed appointments, five patients reported "non-affordability" and two patients reported "health issues" as the reason; however, among patients with break-offs, five patients reported "non-affordability," and three patients each reported "no improvement in vision" and "treatment elsewhere."

Table 2: Demographic characteristics

Demographic characteristics	Compliant patients (*n*=293)	Patients who missed the appointments (14-90 days) (*n*=7)	Patients who missed the appointments (90-365 days) (*n*=14)	Patients who were lost to follow-up (>365 days) (*n*=334)	Total (*n*=648)	*P*[a]
Age (years), mean (SD)	66.72 (7.48)	65.43 (4.54)	65.79 (5.52)	66.15 (7.55)	66.40 (7.44)	0.145
Gender						0.268
Male	204 (69.6)	4 (57.1)	8 (57.1)	218 (65.3)	434 (67.0)	
Female	89 (30.4)	3 (42.9)	6 (42.9)	116 (34.7)	214 (33.0)	
Number of injections, median (range)	3 (0-19)	2 (1-3)	3 (1-12)	3 (1-16)	3 (1-19)	0.017
Number of visits, median (range)	10 (4-58)	7 (5-19)	7.5 (5-18)	8 (0-50)	10 (0-58)	0.005
Diabetes	176 (60.1)	3 (42.9)	5 (35.7)	192 (57.5)	376 (58.0)	0.255
Hypertension	170 (58.0)	4 (57.1)	7 (50.0)	183 (54.8)	364 (56.2)	0.421
Diagnosis						0.686
DME	102 (34.8)	2 (28.6)	3 (21.4)	127 (38.0)	234 (36.1)	
AMD	101 (34.5)	2 (28.6)	4 (28.6)	112 (33.5)	219 (33.8)	
RVO	90 (30.7)	3 (42.9)	7 (50.0)	95 (28.4)	195 (30.1)	
Injection						0.013
Ranibizumab	180 (61.4)	3 (42.9)	8 (57.1)	172 (51.5)	363 (56.0)	
Bevacizumab	113 (38.6)	4 (57.1)	6 (42.9)	162 (48.5)	285 (44.0)	

Data are shown as n (%) unless otherwise specified. [a]comparison of compliant patients versus patients who were lost to follow-up (>365 days). CME: Cystoid macular edema; CNVM: choroidal neovascular membranes; CSME: clinically significant macular edema

Among the three disease groups (DME, AMD, and RVO), a significant association between gender and loss to follow-up was observed ($P = 0.016$). History of diabetes and hypertension were also significantly associated with loss to follow-up to anti-VEGF therapy ($P < 0.001$). A significant association was also observed in lost to follow-up after 1, 2, or ≥3 injections.

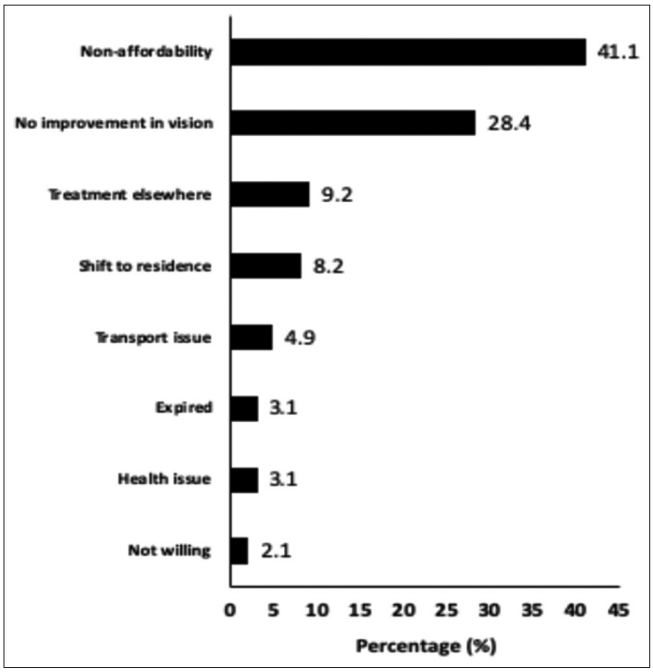

Figure 1: Overall reasons for patients who were lost to follow-up (>365 days) (n = 292). The total number of patients who were lost to follow-up (>365 days) was 334, out of which 42 patients were excluded from the reason's analysis

Among patients who were lost to follow-up after the first injection, 39.0% were from RVO group and 41.6% were from DME group; around 36.7% of patients from both RVO and AMD groups were lost to follow-up after the second injection; however, 38.0% and 39.4% of patients from AMD and DME groups were lost to follow-up after three or more injections. No improvement in vision was slightly higher among patients with DME (42.2%) than AMD (32.5%), and RVO (25.3%); however, "non-affordability" was slightly higher among patients with DME (37.5%). "Health issues" were higher in the RVO group (n = 5, 55.6%) leading to loss to follow-up for anti-VEGF therapy [Table 3].

A total of 218 (65.3%) males and 116 (34.7%) females were lost to follow-up [Table 3]. When the reasons for loss to follow-up were compared between males and females, all the reasons were proportionally higher in males, but there was no significant association in the gender-wise distribution of reasons [Table 4]. When the reasons for lost to follow-up were compared based on discontinuations after 1, 2, or > 3 injections, "non-affordability" and "no improvement in vision" were the most common reasons in all groups. Overall, 57.5% of all patients who responded "non-affordability" were lost to follow-up after three or more injections. Further, 44.4% of all patients who responded as "treatment elsewhere" were lost to follow-up after one injection [Table 5]. When the reasons were compared based on treatment (ranibizumab versus bevacizumab), "non-affordability," "death," and "health issues" were higher in patients receiving ranibizumab; "no improvement in vision," "treatment elsewhere," and "transport issues" were higher in patients receiving bevacizumab; however, "shift of residence" and "not willing" were equal in both the treatment groups [Table 6]. Overall, there was no significant association in reasons for loss to follow-up among the treatment groups.

Table 3: Demographic characteristics of patients who were lost to follow-up (>365 days) across the study groups

Demographic characteristics	DME (n=127)	AMD (n=112)	RVO (n=95)	Total (n=334)	P
Gender					0.016
Male	95 (43.6)	66 (30.3)	57 (26.1)	218 (65.3)	
Female	32 (27.6)	46 (39.7)	38 (32.8)	116 (34.7)	
Injection name					0.422
Ranibizumab	64 (37.2)	63 (36.6)	45 (26.2)	172 (51.5)	
Bevacizumab	63 (38.9)	49 (30.2)	50 (30.9)	162 (48.5)	
Diabetes	127 (66.1)	35 (18.2)	30 (15.6)	192 (57.5)	<0.001
Hypertension	90 (49.2)	53 (29)	40 (21.9)	183 (54.8)	<0.001
Lost to follow-up after number of injections					0.05
1	32 (41.6)	15 (19.5)	30 (39.0)	77 (23.1)	
2	13 (26.5)	18 (36.7)	18 (36.7)	49 (14.7)	
≥3	82 (39.4)	79 (38.0)	47 (22.6)	208 (62.3)	
	DME (n=116)	AMD (n=87)	RVO (n=89)	Total (n=292)	P
Reasons					0.309
Non-affordability	45 (37.5)	36 (30)	39 (32.5)	120 (41.1)	
No improvement in vision	35 (42.2)	27 (32.5)	21 (25.3)	83 (28.4)	
Treatment elsewhere	10 (37)	6 (22.2)	11 (40.7)	27 (9.2)	
Shift to residence	10 (47.7)	8 (33.33)	6 (25)	24 (8.2)	
Transport issue	3 (21.4)	7 (50)	4 (28.6)	14 (4.9)	
Expired	7 (77.8)	0 (0)	2 (22.2)	9 (3.1)	
Health issue	3 (33.3)	1 (11.1)	5 (55.6)	9 (3.1)	
Not willing	3 (50)	2 (33.3)	1 (16.7)	6 (2.1)	

Data are shown as n (%). CME: Cystoid macular edema; CNVM: choroidal neovascular membranes; CSME: clinically significant macular edema

Discussion

Noncompliance or loss to follow-up during ophthalmic therapy is a major concern in India. This retrospective study evaluated the rate of compliance in Indian patients with DME, RVO, and AMD, and whether gender, type of disease, or cost have any impact on nonadherence to anti-VEGF therapy. Overall, the results found that around 45% of patients were compliant with anti-VEGF therapy and no major differences were found in the above mentioned parameters. In the present study, patients were considered lost to follow-up for more than 365 days which was reasonable considering the study parameters. This was consistent with a previous study published by Gao *et al*.[11]

A recent report from the United States, which included 2302 patients with proliferative diabetic retinopathy (PDR) and 9007 patients with nAMD, showed that around 22% and 28% of patients, respectively, were lost to follow-up.[12] Another study from Germany, which included 708 patients with nAMD, DME, and BRVO, reported that 32%, 44%, and 25% of patients, respectively, were noncompliant.[13] Similarly, a study from Germany showed that 46% of patients with DME and 22% of patients with AMD had at least one therapy break-off.[14] A study from Turkey, which evaluated 314 patients with nAMD, also reported around 40% noncompliance.[15] In contrast, the noncompliance or loss to follow-up was slightly higher (51.54%) in the present study compared with previous studies. This could be possibly due to cost issues and awareness that the treatment is needed on a regular basis.

In previous studies, "fear of intravitreal injection," and "disbelief in benefits of treatment," "financial limitations," and "continuation at another center" were the common reasons.[10] Another study reported, "other illness," "no explanation," "personal," and "problems with the clinic" as the most common reasons.[9] In the present study, the major factors that contributed to the loss to follow-up for therapy were "non-affordability" and "no improvement in vision." This could be attributed to the number of injections patients received since in our study around 30% of the patients discontinued the treatment after one or two injections (i.e. incomplete loading dose), which could have led to no improvement in vision and ultimately leading to discontinuation or seeking treatment with another doctor.

In the present study, the rate of loss to follow-up was slightly higher in females; however, AMD was higher among females and DME was higher among males. Among the reasons for loss to follow-up, the overall trend was similar between males and females. When compared between each reason, almost all reasons were comparatively higher in males than females, possibly due to the predominance of males in the study. A total of 120 patients reported "non-affordable" as the reason that accounted for around 41% of patients. The cost of bevacizumab in India ranges between 6,000 and 10,000 INR per

Table 4: Gender-wise distribution of reasons for patients who were lost to follow-up (>365 days)

Reasons	Male (*n*=195)	Female (*n*=97)	Total (*n*=292)	*P*
Non-affordability	82 (68.3)	38 (31.7)	120 (41.1)	0.989
No improvement in vision	53 (63.9)	30 (36.1)	83 (28.4)	
Treatment elsewhere	18 (66.7)	9 (33.3)	27 (9.2)	
Shift to residence	17 (70.8)	7 (29.2)	24 (8.2)	
Transport issue	10 (71.4)	4 (28.6)	14 (4.9)	
Expired	6 (66.7)	3 (33.3)	9 (3.1)	
Health issue	5 (55.6)	4 (44.4)	9 (3.1)	
Not willing	4 (66.7)	2 (33.3)	6 (2.1)	

Data shown as *n* (%)

Table 5: Number of injections-wise distribution of reasons among patients who were lost to follow-up (>365 days)

Reasons	One injection (*n*=69)	Two injections (*n*=41)	Three or more injections (*n*=182)	Total (*n*=292)	*P*
Non-affordability	27 (22.5)	24 (20)	69 (57.5)	120 (41.1)	0.027
No improvement in vision	15 (18.1)	9 (10.8)	59 (71.1)	83 (28.4)	
Treatment elsewhere	12 (44.4)	2 (7.4)	13 (48.1)	27 (9.2)	
Shift to residence	7 (29.2)	0 (0)	17 (70.8)	24 (8.2)	
Transport issue	5 (35.7)	2 (14.3)	7 (50)	14 (4.9)	
Expired	3 (33.3)	2 (22.2)	4 (44.4)	9 (3.1)	
Health issue	0 (0)	4 (22.2)	7 (77.8)	9 (3.1)	
Not willing	0 (0)	0 (0)	6 (100)	6 (2.1)	

Data shown as *n* (%)

Table 6: Treatment-wise distribution of reasons among patients who were lost to follow-up (>365 days)

Reasons	Ranibizumab (*n*=147)	Bevacizumab (*n*=145)	Total (*n*=292)	*P*
Non-affordability	68 (56.7)	52 (43.3)	120 (41.1)	0.509
No improvement in vision	34 (41)	49 (59)	83 (28.4)	
Treatment elsewhere	13 (48.1)	14 (51.9)	27 (9.2)	
Shift to residence	12 (50)	12 (50)	24 (8.2)	
Transport issue	6 (42.9)	8 (57.1)	14 (4.9)	
Expired	6 (66.7)	3 (33.3)	9 (3.1)	
Health issue	5 (55.6)	4 (44.4)	9 (3.1)	
Not willing	3 (50)	3 (50)	6 (2.1)	

Data shown as *n* (%)

injection and the cost of ranibizumab ranges between 21,000 and 26,000 INR. In the present study, a consistently higher number of patients receiving ranibizumab (56.7%) reported "non-affordability" as the reason for loss to follow-up than those receiving bevacizumab (43.3%).

In the present study, around 58% of patients had diabetes and 56% of patients had hypertension. Of the total patients with diabetes, more than half of the patients were from the DME group. Similarly, around half of the patients with hypertension also belonged to the DME group. It could be possible that the patients gave more preference to their other concomitant diseases like hypertension, diabetes, or any other chronic diseases and gave less importance to eye diseases. It is challenging but important to raise awareness among the patients and the general population about these diseases and their long-term outcomes. Frequent counseling sessions reiterating the importance of completing the treatment may help in reducing the number of dropouts.

The authors acknowledge the following limitations of the study. First, this was a retrospective study and may have inherited bias with no control on the treatment regimen, and patients may have also received other medications. Second, the reasons for loss to follow-up were not available for all patients and every effort was made to contact patients to find the reasons; however, for a few patients, whom the author was not able to contact, either the number was changed or the patients did not respond to the call, which may have impacted the results. Third, this was a single-center study, hence the author warrants the readers to carefully generalize these results. Fourth, we do not have data of patients who refused to receive even a single injection possibly due to higher cost. This could have impacted the overall results. Fifth, patients were allowed to choose only one option as the reason for discontinuation. Care must be taken while generalizing these results.

Conclusion

In conclusion, the results showed that around half of the patients with DME, AMD, and RVO were loss to follow-up to intravitreal anti-VEGF therapy, and the most common factors were "non-affordability" and "no improvement in vision." There is a significant need to raise awareness about compliance with therapy to avoid future complications.

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Conflicts of interest

Madhulika Malode is an employee of Sqarona Medical Communications LLP. All other authors have no conflict of interest to declare.

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