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RETINAL DISORDERS

Treatment compliance and adherence among patients with diabetic retinopathy and age-related macular degeneration treated by anti-vascular endothelial growth factor under universal health coverage

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Abstract

Purpose To analyze and compare loss to follow-up (LTFU) rates between patients with diabetic retinopathy (DR) and those with neovascular age-related macular degeneration (nAMD) in patients, receiving treatment with anti-vascular endothelial growth factor (VEGF), under universal health coverage.

Methods We retrospectively analyzed the relevant data of 1264 patients receiving anti-VEGF therapy, in this cohort study. The observation period ranged from September 01, 2015 to December 31, 2018. Intervals between each procedure and the subsequent follow-up examination were measured. Demographic data, visual acuity (VA), the type of transport for treatment access, and distance between the residence and clinic were evaluated as risk factors for LTFU.

Results We collected data for 841 patients with nAMD (age, 81.0 (± 8.1 years)) and 423 patients with DR (age, 67.7 (± 12.1 years)). The rate of LTFU, for at least 6 months, was 28.8% and 2.9% for patients with DR and nAMD, respectively ($p < 0.001$). In the DR group, 18.9% patients were lost to follow-up exceeding > 12 months. Multivariate regression analysis showed that advanced age, lack of mobility, and need for assisted transport, poor final VA despite treatment, and decrease in vision during the observational period were independent risk factors for LTFU exceeding 12 months ($p < 0.05$).

Conclusions We found a high long-term LTFU rate for patients with DR, despite treatment under universal health coverage. Considering the risk of disease progression, particularly in patients with chronic DR, strategies for better compliance and adherence to therapy should be considered for optimized patient care.

Keywords Loss to follow-up · Compliance · Risk factors · Diabetic retinopathy · Age-related macular degeneration · Anti-vascular endothelial growth factor · Universal health coverage

Introduction

Diabetic retinopathy (DR) has been identified as a major cause of vision impairment in patients with advanced diabetes mellitus (DM) [1]. The most common complications of DM are chronic kidney disease (27.8%), diabetic foot (22.9%), and DR (18.9%) [2]. From the patient's perspective, DR remains one of the most feared complications of DM. The preservation of vision by various therapies has led to screening programs, where patients with DR are staged and selected for therapy or close follow-up. Numerous appointments have a great impact on the quality of life and

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impose a social and, in several healthcare systems, financial burden on patients, leading to poor compliance.

According to recent literature, frequent intravitreal injections (IVIs) of anti-vascular endothelial growth factor (anti-VEGF) agents are necessary to achieve the best functional outcome in the treatment of DR and neovascular age-related macular degeneration (nAMD). However, real-life data have shown that fewer IVIs are administered in daily clinical practice [3]. Compliance seems to be an important factor for successful therapy. Recent studies by Obeid et al. [4, 5] documented that 25.4% patients who received IVI or panretinal photocoagulation (PRP) for proliferative DR (PDR) and 22.2% patients who received IVI for nAMD were lost to follow-up ≥ 12 months. Moreover, the assessment of potential risk factors revealed the possible impact of the type of procedure, age, race, and the regional average adjusted gross income on treatment compliance of patients with PDR or nAMD. A potential limitation of their studies was missing information regarding the patients' health insurance, which can greatly influence the loss to follow-up (LTFU) rate. In earlier studies, the lack of health insurance was hypothesized as a reason for underutilization of ophthalmological preventive care and treatment [6–10]. Therefore, the results of the studies by Obeid et al. [4, 5] may not be applicable to all healthcare systems. To the best of the authors' knowledge, there are no reports addressing LTFU rates during therapy for DR and nAMD in a universal healthcare system.

The aims of the present study were to determine and compare short- and long-term LTFU rates, as indicators of treatment compliance between patients with DR and patients with nAMD, receiving anti-VEGF therapy under universal health coverage. We also analyzed the potential risk factors for LTFU in these patients.

Materials and methods

Dataset

Data were retrieved from a structured electronic database for patients receiving anti-VEGF therapy for DR or nAMD at the Department of Ophthalmology, Medical University Innsbruck, Innsbruck, Austria. The observation period ranged from September 01, 2015 to December 31, 2018. The data included information about the patients' sex, eyes, lens status, best-corrected visual acuity (BCVA), visual impairment grade as defined by World Health Organization [11], central foveal thickness at baseline, and every subsequent follow-up visit. Data regarding the residential zip codes, type of transport for treatment access, hemoglobin A1c levels, type of diabetes, presence of PDR, presence of neovascularization in cases of PDR, history of PRP, and number of injections were also included. The time intervals between each procedure and subsequent follow-up examinations were noted. The collected BCVA measurements were expressed as Snellen visual acuity (VA) values and converted to logarithm of the minimum angle of resolution units for analysis. We used Google Maps (Google Inc., Mountain View, USA), to acquire and assess the distance of residence to the clinic.

Patients and clinical assessment

Data were retrieved for a total of 1264 consecutive patients. Ophthalmological examinations were performed by retina specialists, Optical coherence tomography (OCT, Spectralis® Heidelberg, Germany) was performed for every patient at the first and follow-up visits. Anti-VEGF agents included ranibizumab and aflibercept. After an initial loading dose of three injections every 4 weeks, injections were administered on a pro re nata basis. Follow-up appointments were routinely scheduled and recorded in the electronic health record at the end of every consultation. LTFU was defined as a one visit-free interval of > 6 months. LTFU for > 12 months (long-term LTFU), the duration of LTFU, and the interval between treatment indication and actual treatment were also noted. Patients who rescheduled their appointment beyond 6 months of follow-up were not considered LTFU.

The exclusion criteria were as follows: previous vitreoretinal surgery, posterior uveitis, history of retinal vein occlusion, complicated cataract surgery, and/or penetrating trauma. Patients who refused further control or therapy, moved residences, deceased during follow-up or changed their physician were not included in the analysis. In the state of Tyrol and the rest of Austria, anti-VEGF treatment is only covered by general health insurance in hospitals with an ophthalmology department. Thus, patients living at a shorter distance from other clinics offering IVIs were also excluded. To ensure a follow-up period of at least 6 months, we only included data if documentation had started before June 30, 2018.

The retrieved data were retrospectively audited using a standardized protocol. All data were anonymized prior to analysis. The study adhered to the tenets of the Declaration of Helsinki. Approval and informed consent procedures were waived by the institutional review board of the Medical University of Innsbruck.

Statistical analysis

All statistical analyses were performed using SPSS Statistics 24® (IBM, Armonk, NY, USA).

Demographic data and baseline findings were expressed as the number of patients and percentages, respectively. Continuously distributed data were reported as mean and standard deviation. The Kolmogorov–Smirnov

test, along with the visual inspection of histograms, was used to test all the variables for normal distribution. For the comparisons of continuous data, the unpaired *t* test was used for normally distributed variables, while the Mann–Whitney *U* test was used for data lacking normal distribution. Categorical data were compared using the chi-square and Fisher's exact tests. Demographic data, VA, the type of transport for treatment access, and distance between the residence and clinic were evaluated as risk factors for LTFU. Univariate and multivariable logistic regression analyses were conducted to determine odds ratios and 95% confidence intervals (CIs). All factors that were significantly associated with LTFU on univariate analysis were selected as independent variables, for the multivariable model. A p value of < 0.05 was considered statistically significant for all analyses.

Results

Of the 1264 patients, 841 were treated for nAMD and 423 for DR. In the DR group, 290 (68.6%) patients received monotherapy and 133 (31.4%) received IVI and PRP during the study period. The mean number of IVIs of anti-VEGF agents during the first year was 4.85 ± 1.9 in the nAMD group and 3.92 ± 2.2 in the DR group. Detailed characteristics of both groups are summarized in Table 1.

During the study period of 3.3 years, 122 (28.8%) patients in the DR group and 24 (2.9%) patients in the nAMD group were lost to follow-up for at least 6 months ($p < 0.001$; 95% CI, 7.53–18.54; binary logistic regression). Moreover, 18.9% patients with DR and 0.5% with nAMD were lost to follow-up for >12 months ($p < 0.001$; 95% CI, 14.18–111.12). Multivariate regression analysis revealed that the disease type was the only significant factor associated with LTFU for > 6 months, as well as LTFU for > 12 months. The time-lag between treatment selection and actual IVI was significantly longer in the DR group (20.1 ± 19.1 days) than that in the nAMD group (7.6 ± 12.0 days; $p < 0.001$, Mann–Whitney *U* test). Compliance-related characteristics are shown in detail in Table 2. The risk of LTFU for > 6 months and LTFU for > 12 months was 12 and 40 times higher, respectively, in the DR group than that in the nAMD group.

Long-term LTFU according to risk factors in patients with DR

In the DR group, 311 (73.5%) and 112 (26.5%) patients were diagnosed with non-proliferative DR and PDR, respectively. These two groups showed no differences in terms of LTFU for > 6 months and LTFU for > 12 months ($p = 0.33$ and $p = 0.68$, respectively). Long-term LTFU was significantly more common for patients aged ≥ 70 years ($p = 0.02$, chi-square test), compared with patients < 70 years (see Table 3). Patients who traveled independently showed a significantly lower long-

Table 1 Characteristics of patients with neovascular age-related macular degeneration or diabetic retinopathy treated by anti-vascular endothelial growth factor under universal health coverage

	AMD cohort *n* (% or IQR)	DR cohort *n* (% or IQR)
Sex (male/female)	308 (37)/533 (63)	275 (65) / 148 (35)
Age	81.0 (8.1)	67.7 (12.1)
Right/left	431 (51)/410 (49)	214 (50)/209 (49)
Distance to clinic (km)	17.3 (2.7–43.3)	18.5 (2.7–57.8)
BCVA	0.60 (0.40–1.0)	0.39 (0.20–0.69)
N of injections in first 12 m	5.0 (3.0–6.0)	4.0 (2.0–5.0)
Transport		
Independent arrival	386 (46)	293 (69)
Assisted transport	334 (40)	85 (20)
Arrival with ambulance	121 (14)	45 (11)
Visual impairment grade, *n* (%)[a]		
Mild	599 (71)	309 (73)
Moderate	209 (25)	81 (19)
High	26 (3)	32 (8)
Blindness	7 (1)	1 (0)

*Significant difference

[a] Visual impairment as defined by the WHO [11]

AMD age-related macular degeneration; *DR*, diabetic retinopathy; *n*, number; *IQR*, interquartile range; *BCVA*, best-corrected visual acuity; *m*, months; *km*, kilometers

Table 2 Comparison of treatment compliance-related characteristics between patients with neovascular age-related macular degeneration and those with diabetic retinopathy

	AMD cohort[a], *n* or median (% or IQR)	DR cohort[a], *n* or median (% or IQR)	Univariate model	Multivariable model[b]
			p value (unadjusted odds ratio, 95% CI)	*p* value (adjusted odds ratio, 95% CI)
LTFU ≥ 6 months	24 (3)	122 (29)	< 0.001* (9.6; 6.28–14.63)	< 0.001* (11.5; 7.53–18.54)
LTFU ≥ 12 months	4 (1)	79 (19)	< 0.001* (36.3; 13.38–98.59)	< 0.001* (40.0; 14.18–111.12)
Length of LTFU	9 (7–11)	17 (9–25)	< 0.001* (1.16; 1.06–1.29)	< 0.115 (1.14; 1.03–1.35)
Delay of first injection in days	0 (0–12)	16 (6–30)	< 0.001* (1.05; 1.04–1.06)	< 0.001* (1.05; 1.04–1.06)

*Significant difference

[a] Both groups were receiving anti-vascular endothelial growth factor treatment under universal health coverage

[b] Multivariable analysis performed for each characteristic independently, adjusted for age and sex

AMD, age-related macular degeneration; *DR*, diabetic retinopathy; *n*, numbers; *IQR*, interquartile range; *LTFU*, loss to follow-up; *CI*, confidence interval

term LTFU rate, than those requiring assisted transport (28%; $p = 0.03$; chi-square test). These risk factors were used in the

Table 3 Findings of univariate and multivariate logistic regression analyses for determining the risk factors for loss to follow-up among patients with diabetic retinopathy

	Followed up, *n* (%, SD or IQR) (*n* = 344)	LTFU > 12 m, *n* (%, SD or IQR) (*n* = 79)	Univariate model	Multivariable model
			p value (unadjusted odds ratio, 95% CI)	*p* value (odds ratio, 95% CI)
Age			0.02*	
< 70a	175 (86)	29 (14)	(1.39; 1.01–1.89)	Reference
≥ 70a	169 (77)	50 (23)	(1.29; 1.05–1.57)	0.046* (1.68; 1.01–2.81)
Sex, *n* (%)			0.69	
Male	222 (81)	53 (19)	(1.03; 0.80–1.14)	
Female	122 (82)	26 (18)	(1.08; 0.76–1.52)	
Distance (km)	19.2 (2.7–57.8)	22.9 (2.7–68.9)	0.31 (1.00; 0.99–1.00)	
HbA1c	7.5 (1.3)	7.5 (1.5)	0.84 (1.02; 0.76–1.24)	
Type of diabetes, *n* (%)			0.87	
DM I	24 (83)	5 (17)	(1.08; 0.42–2.73)	
DM II	320 (81)	74 (19)	(1.01; 0.92–1.07)	
Procedure, *n* (%)			0.53	
IVI	236 (81)	54 (19)	(1.01; 0.86–1.19)	
IVI and PRP	108 (81)	25 (19)	(0.97; 0.64–1.46)	
BCVA	0.4 (0.2–0.7)	0.49 (0.3–0.9)	0.10	
Transport, *n* (%)			0.03*	
Independent arrival	246 (84)	47 (16)	Reference	Reference
Assisted transport	61 (72)	24 (28)	0.08 (2.15; 1.21–3.79)	0.014* (2.05; 1.15–3.63)
Arrival with ambulance	37 (82)	8 (18)	0.72 (1.16; 0.50–2.65)	0.90 (1.06; 0.40–2.23)
Visual impairment grade, *n* (%)[a]			0.37	
Mild	256 (83)	53 (17)	Reference	
Moderate	60 (74)	21 (26)	0.117 (1.59; 0.89–2.87)	
High	27 (84)	5 (16)	0.815 (1.13; 0.32–2.41)	
Blindness	1 (100)	0 (0)	n.a.	

*Significant difference

[a] Visual impairment as defined by the WHO [11]

LTFU, loss to follow-up; *n*, numbers; *SD*, standard deviation; *IQR*, interquartile range; *a*, age in years; *km*, kilometers; *DM*, diabetic mellitus; *IVI*, intravitreal injection; *PRP*, panretinal photocoagulation; *BCVA*, best-corrected visual acuity; *n.a.*, not applicable,

multivariate model to rule out confounders and confirm their role as key risk factors. Advanced age was significantly associated with LTFU for > 12 months ($p = 0.046$, binary logistic regression); the odds of LTFU for > 12 months were 1.68 times higher than those for younger patients. The odds of long-term LTFU for patients requiring assisted transport to the clinic were 2.05 times higher than those for patients traveling on their own ($p = 0.014$, binary logistic regression).

Long-term LTFU according to VA

Patients with moderate VA in the fellow eye, which did not receive any treatment, showed higher rates of LTFU for > 12 months, compared to patients with good VA in the fellow eye ($p = 0.011$, chi-square test). In multivariate analysis adjusted for age and type of transport, the odds of long-term LTFU were 2.5 times higher for patients with a worse visual outcome, than those with a good visual outcome ($p = 0.005$, binary logistic regression). Moreover, the long-term LTFU rate was higher for patients with vision loss, than those with vision gain during the follow-up period ($p = 0.025$). The odds were 2.3 times higher for the former group than for the latter group (see Table 4).

Discussion

The present study showed great disparity in the rate of LTFU between patients with nAMD and those with DR, during anti-VEGF therapy. During the follow-up period of > 3 years, 29% patients with DR and 3% patients with nAMD were lost to follow-up, for at least 6 months.

The LTFU rates were 5 to 10% over an observation period of 1 to 2 years in earlier randomized controlled trials for treatment of PDR [12, 13]. Moreover, recent studies from the tristate region of Pennsylvania, New Jersey, and Delaware showed that 25% patients with PDR and 22% patients with nAMD were lost to follow-up for ≥ 12 months over a 4-year observation period [4, 5]. When the regional average adjusted gross income was considered, the LTFU rate for patients with PDR and nAMD was as high as 34% and 26%, respectively. The authors considered their defined LTFU period of 12 months to be rather long and, consequently, a limitation of their studies. Therefore, those studies may not have demonstrated the actual clinical significance and magnitude of the problem.

As opposed to the USA, the healthcare system in Austria is universal, whereby almost all the residents of Austria and other European Union countries receive publicly funded care. Furthermore, anti-VEGF treatment is only covered by general health insurance in hospitals with an ophthalmology department, which allowed us to rule out

Table 4 Long-term loss to follow-up according to the visual acuity of the study eye and the fellow eye, final visual acuity, and change in the visual acuity among patients with diabetic retinopathy

	LTFU > 12 m, *n* (%)	Univariate model p value (unadjusted odds ratio, 95% CI)	Multivariable model[a] *p* value (odds ratio, 95% CI)
Study eye–VA at baseline		0.216	
≤ 0.4	43 (16)	Reference	
0.4–1.0	19 (25)	0.096 (1.68; 0.91–3.11)	
≥ 1.0	17 (21)	0.30 (1.38; 0.74–2.60)	
Fellow eye–VA at baseline		0.011*	
≤ 0.4	35 (14)	Reference	Reference
0.4–1.0	26 (29)	0.13 (2.10; 1.17–3.82)	0.308 (1.39; 0.38–1.36)
≥ 1.0	18 (20)	0.31 (1.30; 0.73–2.64)	0.224 (1.54; 0.77–3.09)
Study eye–last recorded VA before LTFU		0.009*	
≤ 0.4	26 (11)	Reference	Reference
0.4–1.0	9 (15)	0.20 (1.7; 1.38–4.00)	0.434 (1.39; 0.60–3.21)
≥ 1.0	25 (24)	0.003* (2.54; 1.38–4.67)	0.005* (2.42; 1.31–4.49)
Study eye–change in VA		0.043*	
≤ − 0.1	13 (11)	Reference	Reference
− 0.1 to 0.1	25 (13)	0.412 (1.35; 0.66–2.75)	0.41 (1.35; 0.66–2.77)
≥ 0.1	22 (22)	0.019* (2.43; 1.15–5.14)	0.025* (2.36; 1.11–5.00)

*Significant difference

[a] Multivariable analysis adjusted for age and mode of transport

LTFU, loss to follow-up; *n*, number; *VA*, visual acuity; *CI*, confidence interval

potential LTFU in patients receiving treatment from another ophthalmologist. In our patient cohort, the rates of LTFU for at least 6 months and LTFU for > 12 months were 29% and 19%, respectively, for patients with DR and 3% and 0.5%, respectively, for patients with nAMD. Most patients with DR, who were lost to follow-up, had no subsequent follow-up after 6 (74.6%) or 12 months (83.5%). In the studies conducted by Obeid et al. [4, 14], the insurance status of patients was not documented, and the expense of treatment and follow-up examinations may have greatly influenced the adherence to treatment.

Compliance and disease control have been major issues in diabetes management [15]. The complexity of noncompliance is reflected in a major review by Vermeire et al. [16], which showed that demographic variables, disease factors, the duration or frequency of treatment, and the presence of psychiatric disorders were consistently unrelated to compliance in different medical specialties. In the field of ophthalmology, various reasons have been proposed for decreased compliance with rigorous follow-up schedules, including the lack of insurance coverage, age, grade of visual impairment, and increased distance between the residence and clinic [4, 5, 8, 9].

In contrast to the results of Obeid et al. [5], our results revealed that the long-term LTFU rate increased with age.

Obeid et al. reported that patients aged > 65 years can use Medicare as health insurance, which could be the reason for better treatment adherence among older patients. In fact, comorbid conditions also increase with age [17], and patients with DR and AMD reportedly have at least one comorbidity, with five or more comorbidities in the majority of cases [18]. Another study [19] reported that the presence of other illnesses was the most common cause for the lack of treatment of patients with AMD or DME. Comorbidities can severely limit the patient's ability to operate independently. Patients aged > 70 years are more likely to require assistance with activities of daily living [20]. Such dependency can be detrimental to compliance with numerous appointments for the treatment of various diseases. In our study, the lack of mobility was a key risk factor for long-term LTFU, and the proportion of patients with LTFU was significantly larger in the group that required assisted transport to the clinic, compared with the group that did not require assistance for traveling. This finding highlights the impact of the ability to operate independently on compliance with treatment and follow-up. Interestingly, the increased distance between the residence and the clinic did not influence the LTFU rate in our study.

The negative relationship between VA and LTFU, with an increase in the LTFU rate for patients with poor VA at their individual study endpoints, was a notable finding of this study. Moreover, improved or stable VA after treatment was associated with a lower long-term LTFU rate, while patients who experienced vision loss during the follow-up period were more susceptible to LTFU. However, visual impairment has not been sufficiently studied as a risk factor for noncompliance, and results from earlier studies have been controversial [21–23].

Earlier studies demonstrated progression from nonproliferative DR to PDR in 6% to 11% cases over a period of 5 to 7 years [24, 25]. Early detection and effective management of DR, along with glycemic control, are imperative for the prevention of chronic DR. Given the risk and progressive nature of DR and the potential vision-threatening adverse outcomes associated with poor treatment compliance, patients with DR need stringent monitoring protocols, in order to ensure adherence and adequate follow-up. In an earlier study, text message reminders resulted in a significant decrease in the number of missed appointments [26]. Advanced software similar to that used in the emerging field of telemedicine could power potential strategies to minimize LTFU and selectively target patients at risk.

This study has some limitations. Considering its retrospective design, the patients were not randomized. Moreover, the reasons for absence during appointments remained unknown for some patients. Thus, we could not analyze the patients' special needs to improve compliance.

The strength of this study was that it was conducted in a setting of universal health coverage, whereby patients must be treated in a hospital with an ophthalmology department, in order to receive insurance coverage. Thus, private practices refer patients with various disease stages to our department for further treatment. These unique requirements allowed us to focus on intrinsic reasons that lead to LTFU and to discard the potential influence of insurance status and treatment by other ophthalmologists. In summary, our findings could help ophthalmologists and physicians to thoroughly understand the risk of LTFU in patients with DR and the need for appropriate management of these patients. Interestingly, patients with nAMD, although markedly older than patients with DR, showed a much lower LTFU rate in this study. Lack of awareness of DR in patients with DM has been repeatedly considered an important risk factor for lack of attendance to screening programs designed for the purpose of disease management [27–29].

Further studies are needed to address the consequences and risks of reduced compliance in terms of vision loss and disease progression and to establish strategies for improving treatment adherence rates.

In conclusion, our findings revealed a high LTFU rate for patients with DR receiving IVIs of anti-VEGF agents, even though their treatment was under universal health coverage. Key risk factors for long-term LTFU included advanced age, the lack of mobility, poor VA despite therapy, and the lack of vision improvement. Considering the risk of disease progression, particularly in patients with chronic DR, strategies for better compliance and adherence to therapy should be considered for optimized patient care.

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Compliance with ethical standards

Ethical approval The approval for retrospective studies is waived by the institutional review board of the Medical University Innsbruck, Innsbruck, Austria. All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed consent Informed consent was obtained from all individual participants included in the study.

Conflict of interest The authors declare that they have no conflict of interest.

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