The impact of compliance among patients with diabetic macular oedema treated with intravitreal aflibercept: a 48-month follow-up study

Reinhard Angermann, 1,2 Markus Hofer, 1 Anna Lena Huber, 1 Teresa Rauchegger, 1 Yvonne Nowosielski, 1 Marina Casazza, 1 Valeria Falanga 1 and Claus Zehetner 1

1 Department of Ophthalmology, Medical University Innsbruck, Innsbruck, Austria
2 Department of Ophthalmology, Paracelsus Medical University Salzburg, Salzburg, Austria

ABSTRACT.

Purpose: This study aimed to compare anatomical and functional outcomes between patients with non-proliferative diabetic retinopathy (NPDR) with diabetic macular oedema (DME) who adhered to intravitreal aflibercept therapy and patients lost to follow-up (LTFU).

Methods: We enrolled 200 patients and recorded the interval between each procedure and the subsequent follow-up visit. Moreover, visual acuity (VA) and anatomical outcomes were measured at each follow-up examination.

Results: Among the patients, 103 (51%) patients adhered to intravitreal aflibercept therapy and follow-up examination while 97 (49%) patients were LTFU. Forty-six (47%) patients LTFU who returned for further treatment showed a significant decrease in VA from 0.51 (±0.46) to 0.89 (±0.38) logarithm of the minimum angle of resolution (logMAR) after 48 months (p = 0.004). Compared with the adherent group, the return group showed a worse VA at 48 months (p = 0.036). Further, 1 (1%) patient in the adherent group and 8 (17%) patients in the return group developed a proliferative DR. Patients who were LTFU had a 13.0 times greater chance to develop a proliferative DR (p = 0.022).

Conclusions: Patients who did not adhere to intravitreal aflibercept therapy for DME showed significantly worse visual outcomes compared to patients with good therapy adherence. Moreover, patients with LTFU had a 13 times higher risk of developing a proliferative DR. Considering the potential disease progress, better strategies should be applied to optimize the functional outcome of patients at risk of reduced adherence.

Key words: adherence issues – diabetic macular oedema – long-term effect of compliance – lost to follow-up

Introduction

In 2012, there were approximately 21 million patients worldwide with diagnosed diabetic macular oedema (DME) (Yau et al. 2012). This number is likely to increase given the general sharp increase in the prevalence of diabetes and, specifically, the increasing diabetes mellitus (DM) prevalence among younger people (Dabelea et al. 2014). DME and proliferative diabetic retinopathy (PDR) are major contributors to vision impairment in patients with DM, and they are one of the most feared complications from a patient’s perspective (Antonetti et al. 2012).

Within the last decade, intravitreal anti-vascular endothelial growth factor (VEGF) has become the first-line therapy for DME management. Depending on the drug and approved regional labels, monthly to bimonthly injections are recommended during the first year of treatment (Nguyen et al. 2012; Korobelnik et al. 2014). However, real-life prospective studies have reported inconsistencies between the number of injections and results, and the outcome under idealized conditions (Egan et al. 2017). Among the key components for successful DME management is adherence to a rigorous treatment and examination regime. Compliance, which is mainly affected by numerous appointments in various medical specialities, comorbidities and polypharmacy, is a well-known issue in diabetes care. Moreover, it has been recently discussed with respect to ophthalmic care (Obeid et al., 2018a, 2018b; Weiss et al. 2018). However, data reporting the impact of compliance in the treatment of patients with NPDR and DME are scarce.

Thus, we aimed to evaluate and compare the long-term functional and anatomical outcomes of the eyes between patients with DME showing good adherence and patients being lost to follow-up (LTFU) to aflibercept therapy.
Materials and methods

Study population

Data were collected from a structured electronic database for patients receiving anti-VEGF therapy for DME and retrospectively audited using a standardized protocol. All data were anonymized before analysis. This study has been approved by the institutional review board of the Medical University Innsbruck (Innsbruck, Austria), which granted the waiver of informed consent given the fact that the analyses were performed retrospectively, and all the data extraction was performed without patient identifiers. The procedures of the study were in accordance with the Declaration of Helsinki. Data were collected from September 2015 to April 2020 at the University Clinic Innsbruck (Innsbruck, Austria).

The inclusion criteria were as follows: (1) treatment-naive patients with type II diabetes with a clinically significant DME that were indicated for intravitreal treatment with aflibercept and (2) having a follow-up of at least 24 months. Patients were defined as treatment naïve if they had not received intravitreal anti-VEGF therapy, intravitreal or peribulbar corticosteroids within the previous 6 months prior to the defined observation period. Clinically significant DME was defined as retinal thickening at or within 500 µm to the fovea with associated vision loss.

The exclusion criteria were as follows: patients (1) with type 1 diabetes; (2) having a vision-reducing cataract; (3) having undergone vitreotinal surgery; (4) having a history of PDR, posterior uveitis, retinal vein occlusion, complicated cataract surgery and/or penetrating trauma; (5) having undergone follow-up examinations at another doctor and/or refused treatment at our clinic; (6) having changed their residential location; and (7) those diseased during follow-up. In Austria, anti-VEGF treatment is only covered by general health treatment; and (7) those diseased during observation period. Additionally, we noted between-procedure intervals and subsequent follow-up examinations to identify patients being LTFU. BCVA measurements were collected as Snellen visual acuity (VA) values, which were converted to the logarithm of the minimum angle of resolution (logMAR) units for statistical analysis. We determined the road distance between the residence and clinic using Google Maps (Google Inc., Mountain View, CA, USA).

The primary outcome measures were the functional and anatomical outcomes of patients with NPDR and DME being adherent and patients with reduced compliance to aflibercept therapy. Secondary outcome measures included the risk factors for reduced compliance. The patients’ compliance was assessed by analysing the occurrence of LTFU during the observation period. LTFU was defined by a visit-free interval of >6 months. Moreover, we recorded the frequency and duration of LTFU. Patients who were rescheduled or actively rescheduled their appointment beyond six follow-up months were not considered as LTFU. Patients who were LTFU were further subdivided into a group that did not return in the observation period and a group that returned for therapy or follow-up examinations during the study period. Furthermore, we recorded the number of injections and PRP, as well as the post-LTFU adherence duration for patients who returned to the department after being LTFU.

Clinical assessment & dataset

We retrieved data regarding 200 consecutive patients who were indicated for intravitreal aflibercept therapy. Retinal specialists performed ophthalmological examinations. Examinations using optical coherence tomography (OCT; Spectralis® Heidelberg, Germany) were performed at every visit. The included patients were exclusively treated using intravitreal aflibercept. After an initial loading dose of three injections for three consecutive months, further injections were administered bimonthly on a pro re nata basis. Follow-up appointments were routinely scheduled and noted in the electronic health record at the end of every consultation.

We collected the following data: demographic data, information regarding best-corrected visual acuity (BCVA) and central macular thickness (CMT) at baseline and at subsequent follow-up visits. The CMT was defined as the average thickness in the central 1 mm diameter through the fovea. Moreover, we recorded the residential zip codes, haemoglobin A1c levels, the number of aflibercept injections, the need of panretinal photocoagulation (PRP) and progress to PDR during the observation period. Additionally, we noted between-procedure intervals and subsequent follow-up examinations to identify patients being LTFU. BCVA measurements were collected as Snellen visual acuity (VA) values, which were converted to the logarithm of the minimum angle of resolution (logMAR) units for statistical analysis. We determined the road distance between the residence and clinic using Google Maps (Google Inc., Mountain View, CA, USA).

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Statistical analysis

All statistical analyses were performed using SPSS Statistics 25® (IBM, Armonk, NY, USA). Demographic data and baseline findings were presented as the number of patients with percentages. The Kolmogorov–Smirnov test was used to determine the distribution of the variables. For continuous variables, normally and non-normally distributed variables were presented as mean ± standard and as the median and interquartile range, respectively. Within treatment group comparisons were performed using the paired sample t-test for normally distributed data. Among-group comparisons of normally and non-normally distributed data were performed using an analysis of variance and the Kruskal–Wallis test, respectively. For continuous data, group comparisons of normally and non-normally distributed data were performed using an unpaired t-test and the Mann–Whitney U-test, respectively. Categorical data were compared using the chi-square test and Fisher’s exact tests. Univariate logistic regression was used to determine odds ratio and 95% confidence intervals (CI). Baseline characteristics of the adherent and return groups were analysed using binary logistic regression and multinominal logistic regression to compare baseline characteristics between all groups. Linear regression models using all variables with a p-value <0.05 from the binary logistic regression analysis were used to determine the effect of LTFU episodes on CMT and BCVA at each visit. Within-group comparisons of BCVA and CMT were performed using the paired sample t-test. Statistical significance was set at a p-value of <0.05.

Results

This retrospective study included 200 patients (average age: 69 years, men proportion: 65%). Among them, 103 patients were adherent throughout the
observation period while 97 (49%) patients were LTFU for at least 6 months. In the latter group, 46 (47%) patients returned to the clinic for further examinations and treatment. Table 1 presents details regarding the characteristics of the groups. There was no different distance of residence to clinic between adherent group (10 [3–28] km) compared with LTFU group with return (40 [3–73] km, p = 0.092) and the LTFU group without return (25 [8–54] km, p = 0.173). Regarding intravitreal aflibercept injections in the first year, the adherent, return and LTFU without return groups received 5 (3–6), 3 (2–6) (p = 0.009) and 3 (3–5) (p = 0.004) injections, respectively. Before LTFU, the return group and the LTFU without return group adhered for 8.76 ± 6.69 and 11.65 ± 9.57 (p = 0.197) months, respectively. The return group showed up after 12.07 ± 7.07 months and remained adherent for 18.53 ± 10.95 months after returning. In the return group, 14 (30%) and 4 (9%) patients were LTFU for at least 6 months twice and thrice, respectively.

### Table 1. Characteristics of patients who adhered, patients who were LTFU with return and patients who were LTFU without return

| Characteristic                      | Adherent group (n = 103) | Return after LTFU (n = 46) | p-Value | LTFU with return (n = 51) | p-Value |
|-------------------------------------|-------------------------|-----------------------------|--------|---------------------------|--------|
| Age (years)                         | 69 (9)                  | 67 (10)                     | 0.810  | 70 (9)                    | 0.036  |
| Distance to clinic (km)             | 10 (3–28)               | 40 (3–73)                   | 0.065  | 48 (3–73)                 | 0.002  |
| HbA1c (mg/dl)                       | 7.0 (6.4–7.8)           | 7.2 (6.3–9.0)               | 0.403  | 7.8 (7.0–9.0)             | 0.086  |
| BCVA at baseline (logMAR)           | 0.52 (0.46)             | 0.51 (0.46)                 | 0.530  | 0.55 (0.44)               | 0.197  |
| Adherence until LTFU (m)            | 404 (120)               | 333 (75)                    | 0.009* | 381 (118)                 | 0.017* |
| Adherence until LTFU (µm)           | –                      | 323 (88)                    | –      | 347 (108)                 | 0.184  |
| BCVA at visit after LTFU (logMAR)   | –                      | 0.46 (0.36)                 | 0.06   | 0.6 (0.44)                | 0.119  |
| DME at visit after LTFU             | –                      | 24 (52)                     | –      | 21 (40)                   | 0.267  |
| DME at visit after LTFU             | –                      | 33 (72)                     | –      | –                         | –      |

*Statistical significance (p < 0.05). BCVA = best-corrected visual acuity; DME = diabetic macular oedema; km = kilometres; HbA1c = haemoglobin A1c; LTFU = loss to follow-up; m = month; N = number; PDR = proliferative diabetic retinopathy; PRP = panretinal photocoagulation.

**Anatomical outcomes**

At the last visit before being LTFU, 24 (52%) patients in the return group and 21 (40%; p = 0.267) patients in the LTFU group without return had a DME. At the first visit after being LTFU, 33 (72%) patients in the return group presented with a DME.

The adherent group showed a significant higher CMT (404 ± 120 µm) at baseline compared with the return group (333 ± 75 µm; p = 0.009). There were no between-group differences in CMT at the end of the observation period (see Fig. 1A). The CMT of the adherent group significantly decreased from baseline to the 6 months visit (360 ± 92 µm; p = 0.02) and stayed reduced until the end of the observation period after 48 months (349 ± 126; p = 0.012). Patients in the return group showed a significant increase in CMT from their last visit before LTFU (323 ± 88 µm) to their first visit after LTFU (387 ± 163 µm; p = 0.007; paired t-test). At the end of their individual study, 41 (40%) patients in the adherent group and 24 (52%) patients in the return group showed a DME (p = 0.379; binary logistic regression). At their 48-month visit, 12 (43%) patients in the adherent group and 4 (33%) patients in the return group showed a persistent DME (p = 0.810). Moreover, 6 (13%) patients in the return group and 2 (2%) patients in the adherent group required PRP (p = 0.020). In the return group, 4 (9%) patients and 1 (1%) in the adherent group experienced a vitreous haemorrhage during the study period (p = 0.999). While one (1%) patient developed a PDR in the adherent group, 8 (17%) patients developed a PDR in the return group until the end of the observation period (see Table 2). Patients who were LTFU during the study period had a 13.0 times higher risk to develop a PDR (p = 0.022; 95% CI, 1.44 – 125.0). None of these patients required surgical intervention.

**Visual outcome**

The adherent group showed an initial increase of BCVA (SD) from 0.52 ± 0.46 logMAR to 0.40 ± 0.33 logMAR (p < 0.001; 95% CI, 0.07 – 0.227; paired t-test) after 6 months, which remained significantly increased for 18 months (0.39 ± 0.32 logMAR; p = 0.038) and non-significantly increased at the end of the observation after 48 months (0.45 ± 0.32 logMAR; p = 0.58) (see Fig. 1B). In the return group, the baseline BCVA (0.51 ± 0.46 logMAR) did not significantly increase during the observation period. Rather, it significantly decreased to 0.89 ± 0.38 logMAR (p = 0.004) after 48 months. Patients in the return group experienced a significant reduction in BCVA from their last visit before LTFU (0.46 ± 0.36 log MAR) to their first visit after LTFU (0.61 ± 0.38 logMAR, p = 0.007). At the 36-month (0.41 ± 0.38, 0.73 ± 0.58 logMAR, respectively) and 48-month visit (0.45 ± 0.32, 0.89 ± 0.38 logMAR, respectively), the adherent group presented with a significantly better BCVA than the return group (p = 0.007 and p = 0.036, respectively) (see Fig. 1).

Logistic regression analysis adjusted for CMT at baseline, numbers of injection in the first year and episodes of LTFU during the follow-up period revealed that the occurrence of one LTFU episode during the observation period was the only variable with a significant impact on BCVA at the 36-
Fig. 1. A graph showing the change of central macular thickness (CMT) (A) and best-corrected visual acuity (BCVA) (B) in patients with non-proliferative diabetic retinopathy (NPDR) and diabetic macular oedema (DME) who adhered to anti-vascular growth factor therapy and those who were lost to follow-up (LTFU). Patients who were LTFU showed significant BCVA worsening over the observation period and had a significantly worse outcome compared with patients who adhered to the treatment regime. p-values on the line graphs represent statistical comparisons of CMT and BCVA at the given time points with the baseline. P-values below the designated time points represent statistical comparisons using linear logistic regression analysis, adjusted for CMT at baseline and numbers of injections in the first year, of CMT and BCVA between adherent patients and patients with LTFU at the given time points. logMAR = logarithm of the minimum angle of resolution; m = month.
month \((p = 0.954, p = 0.873\) and \(p = 0.007, \) respectively) and 48-month visit \((p = 0.801, p = 0.272\) and \(p = 0.036, \) respectively).

### Discussion

Our findings demonstrated that non-adherence to anti-VEGF therapy for NPDR with DME significantly affected functional and anatomical outcomes. Recent randomized clinical trials have reported that anti-VEGF therapy is an efficient treatment for DR (Brown et al., 2013; Korobelnik et al., 2014). The VISTA and VIVID studies reported an increase in the BCVA of at least 10 letters in 60% of participants with NPDR and DME who were treated with monthly and bimonthly intravitreal aflibercept for 25 months (Korobelnik et al., 2014). However, these outcomes are contingent on a rigid therapy regime and strict adherence to follow-up examinations. In our study, we observed a significant decline in vision in the LTFU cohort. This is expected since randomized clinical trials do not reflect real-life settings or report the outcomes of noncompliant patients. Previous studies have reported a 20–30% occurrence rate of LTFU for >6 months in patients being treated for DR (Obeid et al., 2018a, 2018b; Angermann et al. 2019). Despite these alarming compliance rates, the role of comorbidities in patients with DR should be considered. A recent study on compliance among patients with DME reported the presence of comorbidities as the most common reason for non-adherence (Weiss et al. 2018). Comorbidities and advanced age severely impede independent operation with patients often requiring assistance with activities of daily living (Wang et al. 2017). Such dependency can be devastating given the consistent appointments required to treat and screen various diseases. In our study, patients with LTFU lived farther from our tertiary based department. A lack of patients’ independence or assistance to adhere to appointments could be compounded by the greater distances and time effort.

These multifactorial reasons for reduced compliance contribute to a small rate of patient return for therapy after missing an appointment. There have been few reports regarding the impact of compliance in patients with DME undergoing anti-VEGF therapy. Weiss et al. (2018) reported a therapy break-off of at least 100 days in 46% of patients with DME undergoing anti-VEGF therapy. Patients with one break-off did not show a change in BCVA within a 24-month follow-up. On the other hand, patients with >1 break-off had a significant decline in BCVA; however, there was no significant difference in the number of intravitreal anti-VEGF applications. In contrast to the present study, this previous study employed three different drugs (aflibercept, ranibizumab, bevacizumab) for treatment. In our study, the return group received a significantly smaller number of aflibercept injections in the first year owing to compliance issues and showed a significant decline in visual acuity after a long-term follow-up period. Moreover, they had had a significantly lower BCVA than the adherent group after a 48-month follow-up. A recent study reported significantly better anatomical and functional outcomes in patients with DR receiving PRP who were LTFU compared with those receiving anti-VEGF therapy (Obeid et al., 2018a, 2018b). Generally, PRP has a more long-term effect and requires fewer appointments. Increased efficacy through prolonged durability of upcoming anti-VEGF drugs might relieve treatment burden by reducing the number of visits, and it might reduce the impact of short-term LTFU on visual and anatomical outcomes.

Given the lack of a between-group difference in CMT and DME prevalence at the end of our study, we assumed that patients with a longer period of therapy break-off experience a greater distortion and damage of the retinal layers secondary to macular oedema (see Fig. 2). In eyes with DR, steady neural cell loss and photoreceptor damage might be compounded by the effects of chronic macular oedema (Ciulla, Amador & Zinman 2003; Brown et al. 2013; Channa et al. 2014). Persistent DME may provoke a transition from acute inflammation and vascular dysfunction, which characterize early-stage DR, to chronic inflammation and damage observed in the later stages (Davis et al. 1998; Cunha-Vaz et al. 2014; Sadda et al. 2020). Consistent with this hypothesis, eight out of the nine patients who developed a PDR had a history of LTFU for at least 6 months; among them, four patients had persistent macular oedema at their last visit before being LTFU. However, the limited number of eyes with this outcome impedes us from making a definite conclusion.

There are some limitations to the study. First, the reasons for being LTFU were not determined; therefore, we could not analyse the patients’ special needs to improve their compliance. Second, due to limited knowledge among the patients regarding the onset of diabetic disease, as well as their compliance and disease course represented by haemoglobin A1c values, these factors could not be accounted for in the analysis. Third, the adherent group presented at baseline with a significantly higher CMT than the return group. The higher initial CMT in the adherent group might have led to a significant reduction in within-group analysis more easily in the adherent group than in the return group. Considering this potential bias, we used a multivariate analysis model adjusted to the different CMT at baseline to compare CMT and BCVA between both groups at each follow-up visit.

| Table 2. Prevalence of indication for panretinal photocoagulation (PRP) and clinical characteristics of patients who adhered and patients who were lost to follow-up (LTFU) and returned for intravitreal aflibercept therapy |
|----------------------------------|------------------|------------------|------------------|
| Indication for PRP (%) | Adherent group \((n = 103)\) | Return after LTFU \((n = 46)\) | \(p\)-Value* |
| Vitreous haemorrhage (%) | 2 (2) | 6 (13) | 0.020* |
| Progress to PDR (%) | 1 (1) | 4 (9) | 0.999 |
| DME at study end (%) | 41 (40) | 24 (52) | 0.379 |

*Statistical significance \((p < 0.05)\). **Binary logistic regression adjusted to CMT at baseline and number of injections in the first year. DME = diabetic macular oedema; \(N\) = number; PDR = proliferative diabetic retinopathy.
One strength of this study is the long-term follow-up period. Moreover, in Austria, anti-VEGF therapy is only covered by universal health insurance in public hospitals with ophthalmology departments. Therefore, private practices refer to patients with clinically significant DME to our department for further therapy. These unique requirements allowed us to limit the potential bias of patients receiving therapy from other ophthalmologists. Furthermore, it allowed analysis of the long-term effect of compliance issues on functional outcomes and disease progression. Taken together, our findings contribute to the understanding of the consequences of reduced compliance in patients with NPDR and DME. Improved management of patients at risk for a bad adherence to treatment and examination regimens is a viable target for the growing field of telemedicine (Olayiwola et al. 2011; Rho et al. 2014). Although there are upcoming novel anti-VEGF drugs with prolonged durability, teaching programmes and reminder software might efficiently reduce the number of patients with LTFU and promote long-term adherence to the rigid therapy programmes (Downer et al. 2005). However, this might prove difficult to apply to older patients and alternative routes should be explored in future investigations.

In conclusion, our findings revealed a long-term decline in visual acuity in patients with NPDR and DME with reduced adherence to the anti-VEGF treatment regime. Moreover, patients with LTFU needed PRP more often and had a 13 times higher risk of developing a proliferative DR. Further strategies are required to optimize therapy adherence and achieve better functional outcomes in patients requiring therapy for diabetic retinopathy.

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Fig. 2. A representative example of a spectral-domain optical coherence tomography (SD-OCT) image series of a patient who was lost to follow-up (LTFU) and returned for intravitreal aflibercept therapy. The patient showed no diabetic macular oedema (DME) at the study eye before being LTFU (A) and upon return after 14 months, presented with DME (B). At the 48-month visit, SD-OCT revealed a macula without DME that showed a severe thinning and distortion of the central retinal layers (C).
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Correspondence:
Claus Zehetner, MD
Department of Ophthalmology
Medical University Innsbruck
Anichstraße 35
6020 Innsbruck
Austria
Tel: +43 512 504 23720
Fax: +43 512 504 23722
Email: claus.zehetner@i-med.ac.at