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ORIGINAL RESEARCH

Factors Affecting Compliance to Anti-Vascular Endothelial Growth Factor Treatment of Diabetic Macular Edema in a Cohort of Jordanian Patients

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Purpose: To determine compliance rates and characteristics and to investigate factors affecting patients' adherence to treatment with anti-vascular endothelial growth factors (anti-VEGFs) for diabetic macular edema (DME) in a cohort of Jordanian patients.

Methods: A retrospective case series wherein the files of DME patients treated with anti-VEGFs were reviewed and analyzed for factors affecting treatment compliance was undertaken. Demographic, clinical and ocular characteristics were recorded. All patients were also interviewed by phone using a structured questionnaire. Univariate and multivariate analyses were performed to determine factors associated with compliance.

Results: A total of 117 patients (65 males 52 females) were included in this study with a mean age of 62.93 years (±9.75). Approximately, 85% of patients were compliant to their treatment and follow-up plan during the first year of management. Subjective perception of visual improvement after receiving three loading doses was the only independent variable with a unique statistically significant contribution to compliance. All other studied factors in this group of patients were not significantly associated with patient compliance.

Conclusion: VEGF suppression via the intravitreal route to treat DME is a long-term process that requires caregiver dedication but also proper patient compliance. Addressing real-life barriers in those patients may help guide future strategies to improve the treatment experience, lower the financial burden and contribute to better outcomes. Patients' perceptions of possible treatment outcomes at the short term may influence their long-term commitment to therapy.

Keywords: diabetic macular edema, anti-vascular endothelial growth factor, retinopathy, compliance

Introduction

According to the World Health Organization, more than 422 million people live with diabetes.[1] Diabetic macular edema (DME) is one of the many complications of the disease,[2] with an estimated 21 million people suffering from this complication.[3] DME is the leading cause of decreased vision in diabetic patients and has become one of the leading causes of blindness worldwide.[3–8] The management of DME has changed over the years. Laser photocoagulation therapy was the reference treatment and the most cost-effective option, but improvement in vision was not sustained over the long term.[9–12] Intravitreal injections of corticosteroids were the next choice,[13–18] but their side effects limit their benefits.[19,20]

Currently, first-line therapy for DME is intravitreal anti-vascular endothelial growth factor (anti-VEGF) medications which are proven to be effective and

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safe.[21–25] They were also proven to be efficient in the treatment of wet age-related macular degeneration (AMD) and macular edema secondary to central and branch retinal vein occlusions.[26–28] Despite these injections becoming the standard treatment for DME, adverse effects are still present. Intraocular pressure (IOP) elevations, subretinal hemorrhage, retinal detachment, uveitis and endophthalmitis are among the reported adverse effects.[29,30] Systemic adverse effects such as strokes, acute myocardial infarction, and thromboembolic events have also been reported.[31] Bilateral involvement in DME is very high due to the systemic nature of the disease.[32] For the convenience of the patients and to reduce the number of clinic visits, simultaneous bilateral intravitreal injections are being done more often.[33] Same-day injections for DME are safe and well-tolerated by patients.[34–36] No significant difference in the occurrence rate of adverse effects has been found between simultaneous bilateral injections and single injections.[37–39]

Among the most widely used anti-VEGF agents for the treatment of DME are ranibizumab (Lucentis®, Genentech), bevacizumab (Avastin®, Genentech) and aflibercept (Eylea®, Regeneron Pharmaceuticals).[22,39,40] Ranibizumab is FDA approved for ophthalmic use and is a recombinant humanized antibody (Fab) fragment that binds all active forms of VEGF-A.[41] It was the first anti-VEGF agent to show benefit in terms of visual acuity (VA).[42–44] Although improvement in VA varies, functional outcomes are similar.[45–48] Bevacizumab is used in an off-label manner to inhibit VEGF in the eye and is a humanized full-length monoclonal antibody that binds to and inhibits VEGF; it has also shown good results.[49–51] Aflibercept's mode of action incorporates the second binding domain of the VEGFR-1 receptor and the third domain of the VEGFR-2 receptor, preventing VEGF from binding to its original receptors, thereby "trapping" the molecule and reducing its activity due to its very high VEGF affinity.[52,53] When comparing the efficacy of the three types of injections, the relative effect depended on baseline VA. Mild initial visual loss showed no apparent differences, but at worse levels of initial VA, aflibercept was more effective at improving vision.[24]

Visual outcomes correlate with the number of injections given which makes compliance a key component to successful therapy.[45] Since DME causes progressive loss of vision and occurs in younger patients, it is important to address factors that prevent proper patient compliance. Cost-effectiveness of various interventions for DME has been scrutinized, and lack of therapy compliance was shown to lead to a worse outcome and therefore represents a huge economic burden.[54–57]

The purpose of this study is to determine patients' treatment compliance rates and investigate factors that may have a positive or negative effect on compliance with anti-VEGF treatment in a cohort of Jordanian patients with DME.

Materials and Methods

Study Design and Data Collection

After securing the Institutional Review Board approval to conduct this study and obtaining written informed consent from all participants, a retrospective analysis was performed on 117 consecutive patients diagnosed with DME and slated to receive anti-VEGF injections for treatment at Jordan University Hospital. Identified patients were subsequently contacted by phone and interviewed regarding their disease awareness, progression and adherence to their original treatment plan. All patients were prescribed three loading doses of an anti-VEFG agent to be given 4–6 weeks apart. This was followed by a clinical exam and an ocular coherence tomography (OCT) of the treated eye(s) with a PRN regimen of VEGF suppression according to clinical and tomographic findings. Patients were considered compliant if they received the three loading doses in a timely manner and maintained follow up for 12 months (including receiving all their prescribed injections during that period if indicated). Patients who failed those two conditions were considered noncompliant for the sake of this analysis.

Clinical records were extracted and reviewed to obtain data related to the dates of injections, clinical examinations (including VA and IOP) and OCT images from the day of diagnosis and up to 1 year follow-up for each patient.

The telephone questionnaire contained pre-determined questions divided into 2 sections; the first section included questions about age, marital status, educational level, employment status, place of residence, co-morbid systemic diseases, insurance, mode of transportation, number of companions (chaperones) and the duration of symptoms prior to diagnosis. The second section tackled the injection procedure itself: the average waiting time, attitude towards the injection process, complaints after the injection, whether the patient felt a subjective improvement in VA after receiving their injections and perceived challenges to adhere to the treatment plan and the follow-up visits.

Patients with incomplete medical records or who were unreachable by phone and patients who were deceased during the study period were excluded from the study.

Statistical Analysis

SPSS version 25.0 has been used in our analysis. Mean (± standard deviation) values have been used to describe continuous variables (i.e. age, symptoms, duration and VA). Count (frequency) has been used to describe other nominal variables (i.e. gender, laterality and others).

A p value of 0.05 has been adopted as a significant threshold.

Results

A total of 117 consecutive patients who met the inclusion criteria and visited the retina clinic at Jordan University Hospital between January 2017 and December 2017 were included in this study with a mean age of 62.93 years (±9.75). They were 65 (55.6%) men and 52 (44.4%) women. In terms of disease laterality, 3 (2.6%) had their right eyes treated, 5 (4.3%) their left eyes, and the remaining 109 (92.3%) had both eyes treated. The average number of injections per treated eye was 6 (range 3–10). Detailed patients' characteristics are presented in (Table 1).

Discussion

VEGF pharmacological suppression using intravitreal injections has emerged as the first line of treatment for DME and other ophthalmic pathologies like wet AMD and macular edema secondary to retinal vascular disease. The treatment strategy often entails loading the patient with three or more monthly injections, then following up the patient with a scheduled clinical exam and ancillary tests. The treatment burden in DME is enormous with multiple injections in the first year, often bilateral, and adherence to the treatment plan can face multiple hurdles.

A study by Habib et al found that approximately 21% of DME patients were noncompliant to follow up and treatment with anti-VEGFs.[58] Main factors for noncompliance included cost of the drug being injected, whether the patient is covered by medical insurance or not, as well as the psychological burden and the degree of patients' satisfaction with having repeated intraocular injections. However, lack of formal education was not found to be a significant factor affecting compliance. Absence of funding/insurance, perceived susceptibility, perceived barriers, perceived benefits, and unilaterality of the injection are all factors that may affect patient compliance.[58] A quarter of DME patients were noncompliant in a similar study by Best et al.[45] Since diabetic patients must attend different medical consultations, sometimes with several specialists, this burden of repeated consultations may be a barrier to regular follow up. In another recent study by Weiss et al, only 35% of patients were compliant.[59] The number of break-offs and change of visual acuity was found to be significantly correlated. In 60% of break-off cases, visual acuity was worse than before break-off. The most common reason for abstaining in that study was having other co-morbidities, and many patients were found to have little disease insight.[59] The psychological burden including stress, discomfort, and fear from possible side effects has also been reported to affect patient compliance.[23,58,60]

In this study, we assessed compliance of DME patients to anti-VEGF treatment schedules over a period of 12 months. Approximately, 85% of patients were compliant with their treatment and follow-up plan during the first year of management, which mirrors results by previous investigators. In Egypt, Habib and coworkers followed patients for 1 year and noted the rate of dropped injections as a measure of compliance in 343 patients. They found that receiving bilateral injections at the same session correlated with the rate of adherence.[58] Our center previously reported a trend towards more bilateral simultaneous injections but this factor was not found to affect compliance in this study.[36]

It is noteworthy that in our cohort of DME patients, compliance rate was positively correlated with the improvement of VA as perceived by the patient receiving the treatment. Subjects who reported a subjective improvement in vision adhered more to the treatment plan. Interestingly, a study by Polat et al on AMD patients receiving anti-VEGF treatment found an inverse relationship with the initial best-corrected VA. Patients who lost more vision at diagnosis were more compliant down the line; their perceived drop of vision probably evoking fear of progression and spurring aggressive adherence.[61] Ehlken and colleagues found that higher age and poor baseline VA were associated with a higher risk for noncompliance in wet AMD but not in DME patients. They reported that DME subjects have the highest overall risk of patient-associated noncompliance, associated with a higher risk for significant visual loss. A possible explanation may be the presence of additional co-morbidities in patients with DME. This highlights that factors contributing to noncompliance may be different between diseases and communities.[62]

Table 1 Characteristics of Patients Included in This Study

		Mean	Standard Deviation	Count	Column N %
Age		62.93	9.75		
Sex	Male Female			65 52	55.6% 44.4%
Laterality	Right Left Both			3 5 109	2.6% 4.3% 92.3%
Insurance (types)	Ministry of health Medical exemption Official universities Military insurance Private			82 27 6 1 1	70.1% 23.1% 5.1% 0.9% 0.9%
Level of education	Higher education Basic education			38 79	32.5% 67.5%
Level of education (stages)	No education Elementary school High school Undergraduate Postgraduate			13 48 18 30 8	11.1% 41.0% 15.4% 25.6% 6.8%
Mode of travel	Private transportation Public transportation			55 62	47.0% 53.0%
Employment status (during disease management)	Employed Not employed			19 98	16.2% 83.8%
Place of residence	Inside Amman Amman suburbs Outside Amman			25 42 50	21.4% 35.9% 42.7%
Marital Status	Single Married Divorced Widowed			22 87 6 2	18.8% 74.4% 5.1% 1.7%
DME awareness level	Aware they have DME Limited awareness (not sure what DME is)			99 18	84.6% 15.4%
VA baseline	 <0.5 ≥0.5	0.30	0.23	 87 30	 74.4% 25.6%
Onset of symptoms until diagnosis	 Early (less than 3 months) Late (3 months or more)	13.94	30.34	 73 44	 62.4% 37.6%
Mobility	Patient wheel chair bound Not Impaired			26 91	22.2% 77.8%
Co-morbid systemic diseases	DM HTN IHD Kidney disease			117 85 38 12	100.0% 72.6% 32.5% 10.3%

(*Continued*)

Table 1 (Continued).

		Mean	Standard Deviation	Count	Column N %
	2 Diseases			45	38.5%
	3 or more diseases			50	42.7%
OCT done and explained to patient by physician	Done			110	94.0%
	Not done			1	0.9%
	Do not know			6	5.1%
Perception of the duration of the injection procedure		60.79	65.40		
	Quick (in and out in less than 1 hr)			90	76.9%
	Long (more than 1 hr)			27	23.1%
Perception of duration of the follow up visit		97.28	66.70		
	Quick (in and out in less than 1 hr)			59	50.4%
	Long (more than one hour)			58	49.6%
Same session bilateral	Yes			26	22.2%
	No			91	77.8%
Number of companions during visit		1.14	0.472		
	0			4	3.4%
	1			95	81.2%
	2			16	13.7%
	3			2	1.7%
Perceived complications Complications (types)	Positive			21	17.9%
	Bleeding in the eye			6	5.1%
	Increased IOP			1	0.9%
	Floaters			5	4.3%
	Swelling or redness or itching			6	5.1%
	Immediate drop of vision			2	1.7%
	Diplopia			1	0.9%
Objective compliance (per criteria)	Compliant			85	72.6%
Reasons for noncompliance	Financial			14	12.0%
	Social			2	1.7%
	Not satisfied with Patient care			7	6.0%
	Poor knowledge about disease			3	2.6%
Objective VA improvement	Improved 2 Snellen lines after 3 loading doses			36	30.8%
	Not improved			81	69.2%
Subjective VA improvement	Improved (patient asserts their vision is better after 3 loading doses)			59	50.4%
	Not improved			58	49.6%

Notes: A chi-square test of independence was performed to examine the relationship between objective compliance and other factors, and between subjective compliance and the same factors. Detailed results are presented in (Table 2).

Abbreviations: VA, Visual acuity; DME, Diabetic macular edema; DM, Diabetes mellitus; HTN, Hypertension; IHD, Ischemic heart disease.OCT, Optical coherence tomography; IOP, Intraocular pressure.

We looked into several patient factors for noncompliance including clinical parameters (e.g. co-morbidities, mobility) demographic and socioeconomic factors (e.g. education level, means of transport). However, no relevant correlation could be identified in this study. On the other hand, a French study by Boulanger-Scemama et al found

Table 2 Relation Between Compliance and Other Factors

Factor	Compliance	Pearson Chi-Square	df	Asymptotic Significance (2-Sided)
Same session bilateral	Objective	0.888	1	0.346
	Subjective	1.413	1	0.235
Sex	Objective	0.551	1	0.458
	Subjective	1.197	1	0.274
Insurance (types)	Objective	3.989	4	0.408
	Subjective	5.098	4	0.277
Insurance (yes or no)	Objective	0.632	1	0.427
	Subjective	1.114	1	0.291
Education Level	Objective	1.913	4	0.752
	Subjective	1.635	4	0.802
Level of education (high vs low)	Objective	0.381	1	0.537
	Subjective	0.045	1	0.833
Employment status	Objective	0.453	1	0.501
	Subjective	0.018		0.893
Mode of travel	Objective	0.000	1	0.986
	Subjective	0.120	1	0.729
Mobility impaired (Type)	Objective	0.164	2	0.921
	Subjective	3.285	2	0.193
HTN	Objective	0.337	1	0.562
	Subjective	0.003	1	0.956
IHD	Objective	0.381	1	0.537
	Subjective	1.347	1	0.246
Kidney disease	Objective	0.037	1	0.847
	Subjective	0.239	1	0.625
	Subjective	0.901	1	0.343
Disease laterality	Objective	2.828	2	0.243
	Subjective	4.527	2	0.104
VA at first visit	Objective	1.097	1	0.295
	Subjective	0.115	1	0.734
Symptoms duration (until diagnosis) early vs late	Objective	0.171	1	0.679
	Subjective	0.127	1	0.721
OCT performed	Objective	3.001	2	0.223
	Subjective	3.618	2	0.164
Complications types	Objective	6.584	6	0.361
	Subjective	5.577	6	0.472
Complications (with vs without)	Objective	0.161	1	0.688
	Subjective	0.149	1	0.699
Compliance subjective	Objective	70.987	1	0.000
	Subjective	70.987	1	0.000
Reasons for noncompliance	Objective	10.371	3	0.016
	Subjective	0.851	3	0.837
DME awareness level	Objective	1.222	1	0.269
	Subjective	1.519	1	0.218
Objective VA gain	Objective	0.688	1	0.407
	Subjective	0.232	2	0.630
Subjective VA gain	Objective	4.540	1	0.033
	Subjective	0.244	1	0.621

Notes: Only one independent variable made a unique statistically significant contribution: the relationship between subjective VA improvement (as perceived by the patient after receiving three loading doses) and objective compliance (as set by aforementioned criteria) was statistically significant, X2 (1, N = 117) = 4.540, p =0.033, V =0.197.

Abbreviations: VA, Visual acuity; DME, Diabetic macular edema; DM, Diabetes mellitus; HTN, Hypertension; IHD, Ischemic heart disease; OCT, Optical coherence tomography; IOP, Intraocular pressure; Df, degrees of freedom.

that impaired mobility and lack of a chaperone were major causes for noncompliance for anti-VEGF regimens in wet AMD patients.[63]

Our study did not find a correlation between the patients' knowledge and the level of education with compliance. Psychosocial and socioeconomic factors we looked into did not reveal any meaningful correlation as well. Patients' profession and measured quality of life have been shown to affect patient adherence to treatment in previous studies nevertheless,[64–67] with vision loss due to DME producing a significant socioeconomic strain on communities.[68]

Stress, discomfort, and fear from possible side effects have been shown to have an effect on compliance.[23,58,60] In the study by Weiss et al, patients were followed for at

least 1 year (up to 30 months) and compliance was measured by missed appointments (lateness >14 days) or therapy beak-offs (lateness >100days).[59] The investigators showed that disease insight had a significant effect on compliance, but our study did not mirror a similar effect. Furthermore, our results demonstrated that the lack of formal education was not a significant factor affecting compliance. The cost of treatment had no significant impact on compliance in this cohort of Jordanian patients. Most patients are insured under the umbrella of the Ministry of Health and pay around 20% of the total cost of the injection procedure, which varies according to the cost of the medication injected. Still the financial burden of getting treatment was not a factor affecting compliance in this study.

The limitations of this study lie in its retrospective nature and the number of patients analyzed and the rather short follow-up period. We did not test the effect of the type of anti-VEGF medication on patients' compliance as many factors may confound the relationship.[39,69] In Jordan and many other developing countries, anti-VEGFs are used interchangeably and subject to availability, and the cost of treatment many times dictates the choice of the pharmacological agent. For example, patients who secure governmental medical exemption would often choose to be treated with either ranibizumab or aflibercept. Uninsured patients or those with medical insurance who have to co-pay will more likely choose bevacizumab due to its availability at a much lower cost. Moreover, we could not reliably investigate whether compliant patients were also stricter in their diabetic control, as concurrent HbA1c levels were not always readily available in patients' records with many subjects choosing to follow with an endocrinologist or a primary care practitioner elsewhere.

Conclusion

In this study on a group of Jordanian diabetics, DME patients receiving anti-VEGF intravitreal injections who appreciated a subjective improvement in their vision after three loading doses appeared to adhere better to their treatment plan. As the burden of DME treatment grows for both patients and health systems, compliance with therapy will continue to pose a challenge for treating doctors who strive to accomplish better visual outcomes. Patients' barriers and perceptions remain at the core of this ever-expanding approach to treat this common sight-threatening condition.

Data Sharing Statement

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

Ethics and Consent Statement

Institutional ethical approval was obtained from the IRB committee at Jordan University Hospital. All participants provided written informed consent. This research complies with the tenants of the Declaration of Helsinki.

Author Contributions

All authors contributed to data analysis, drafting or revising the article, gave final approval of the version to be published, and agree to be accountable for all aspects of the work.

Disclosure

The authors report no conflicts of interest in this work.

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