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Exploring factors behind patient non-adherence to intravitreal anti-VEGF injections in macular diseases

Efrat Naaman¹, Noa Yanir-Prat², Diana Shair¹, Nitai Bar³, Beata Miller¹, Anna Fishman¹, Shiri Zayit-Soudry⁴

(1) Department of Ophthalmology, Rambam Health Care Campus, Haifa, Israel

(2) Ruth and Bruce Rappaport Faculty of Medicine, Technion Israel Institute of Technology, Haifa, Israel

(3) Department of Radiology, Rambam Health Care Campus, Haifa, Israel

(4) Department of Ophthalmology, Rabin Medical Center, Petah Tikva, Israel

Running title: Non-adherence to intravitreal injections

Correspondence to:

Efrat Naaman

Department of Ophthalmology

Rambam Health Care Campus

P.O.B 9602, Haifa, 31096, Israel

Tel: 972-4-777-2668

Fax: 972-4-777-2142

E-mail: E_NAAMAN@rambam.health.gov.il

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Abstract

Introduction: In recent years, intravitreal injections (IVT) of vascular endothelial growth factor (VEGF) inhibitors have become the standard of care for several macular disorders. Frequently, the therapeutic course requires numerous injections, posing a burden on patients. Non-adherence to treatment may result in reduced visual outcomes, therefore understanding and addressing the underlying causes is imperative.

Methods: A cross-sectional study of patients who missed their scheduled appointment for anti-VEGF IVT as part of the routine management of their macular disease at a single tertiary center between November 2020 and February 2021. A telephone survey was conducted and patient medical charts were reviewed for ophthalmological data.

Results: A total of 100/556 (18%) patients who failed to attend their scheduled anti-VEGF IVT appointments were documented. Among these subjects, the average age was 66 (SD \pm 14) years with a nearly equal gender distribution of 49:51 F:M ratio. Reported no-show reasons included concurrent illness (39%), administrative issues such as missing financial coverage forms or scheduling problems (28%), and lack of motivation (11%). Additionally, 73% of patients who missed appointments expressed a need for accompaniment, and 74% resided outside the hospital city.

Conclusions: Study results highlight modifiable factors contributing to no-shows to anti-VEGF IVT, such as poor transportation access, complicated administrative processes, and difficulty rescheduling missed appointments. Understanding potential obstacles to anti-VEGF IVT therapy, particularly those that are preventable, can enhance adherence and potentially improve the clinical outcome.

Keywords: Intravitreal injections, Treatment adherence, No-show, Macular diseases

Introduction

In recent years, intravitreal injections (IVT) of vascular endothelial growth factor (VEGF) inhibitors have become the standard of care for a variety of macular and retinal diseases. It is most commonly used to treat neovascular age-related macular degeneration (nAMD), diabetic macular edema (DME), retinal vein occlusion (RVO), and myopic choroidal neovascularization (mCNV).[1] The use of anti-VEGF for retinal disorders has shown a continuous rise since 2004 and is expected to escalate further in the future as a result of population growth and increasing lifespan.[2] Although several long-acting interventions for macular disease have become available or are in late-phase development [3,4], the need for frequent retreatments remains a significant burden on patients, and compliance to treatment continues to encounter considerable challenges.[5]

In the state of Israel, the healthcare system is public, with each citizen enrolled in one of several Health Maintenance Organization (HMO's) responsible for providing medical services. Funding of healthcare is allocated based on predefined criteria, and anti-VEGF IVT treatment for retinal care is covered under the public system as followings: For all indications, Bevacizumab (Avastin) is the first-line treatment. In the event that the response to Avastin treatment is insufficient, retinal specialists can submit a form to apply for second-line treatment. In the northern district of the state, where our hospital provides services, patients then present this printed form to their HMO, and it is their responsibility to obtain financial approval for the new treatment. For DME, exudative AMD, and RVO, the second-line anti-VEGF treatment consists of Ranibizumab (Lucentis), Aflibercept (Eylea), and Faricimab (Vabysmo), provided out of charge. In most public hospitals and specialized clinics, ophthalmology residents and specialists perform the injection procedures.

According to the World Health Organization, poor adherence to chronic disease treatment is an important global health issue.[6] In addition to worsening health-related outcomes, non-adherence to long-term therapies also increases healthcare costs.[6] In the context of macular diseases, such occurrences raise analogous concerns, as the failure to adhere to treatment regimens and lack of persistence in following medical recommendations over time can result in inferior visual outcomes.[7–9] Even with less intensive alternate dosing regimens, outcomes in the real-world practice rarely reach those seen in clinical trial settings in macular diseases, possibly due to lack of full adherence to follow-up and treatment.[10] Overall, nonadherence to anti-VEGF IVT treatment may result in undertreatment and can hence cause progressive

retinal damage, ultimately leading to irreversible vision loss. Thus, identifying and addressing factors contributing to non-adherence to intravitreal anti-VEGF treatment is crucial. The present study aims to identify reasons for non-adherence to intravitreal anti-VEGF injections among a broad population of patients with vision-threatening macular diseases in real world settings and to identify possible interventions to improve treatment adherence.

Methods

Study design

A cross-sectional study of patients who missed their scheduled appointment for anti-VEGF therapy as part of their routine macular disease management was performed. The study was conducted in the Department of Ophthalmology of the Rambam Health Care Campus (Rambam), a tertiary-level academic hospital in Haifa, Israel, between November 2020 and February 2021.

Ethics statement

The Rambam Institutional Ethics Committee approved the study protocol (0733-19-RMB), which was conducted according to the Declaration of Helsinki. All patients provided verbal informed consent that was documented in a form approved by the Rambam Institutional Ethics Committee, and anonymization of all patient data was ensured. Patients were further informed that their treating retina specialists would not be aware of their participation status.

Patients

Patients who did not attend their scheduled anti-VEGF IVT session were included in the study and defined as a “no-show”. Patients were contacted telephonically within 7 days of the missed appointment. To avoid bias related to patient adherence, only patients who missed their appointment were contacted. The survey was conducted by a resident or a medical student who were fluent in the patients’ primary language. The questions were read aloud from a pre-written questionnaire and responses to open-ended questions were transcribed word-by-word exactly as stated by the patients. The survey addressed the following issues: demographics of patients, reasons for no-shows, means of transportation to the hospital, the need for accompaniment, overall satisfaction with their ophthalmological treatment, self-perception of the treatment efficacy, fears and discomfort experienced during anti-VEGF IVT procedures, and suggestions for possible interventions to improve compliance. The survey included open questions, 1-5 scale questions and yes/no questions. Following completion of the survey for all patients, the responses to the open questions were categorized with unique answers categorized under “others”. For the answers to the 1-5 scale, rating of 1 or 2 were classified as low, and 4 or 5 as high. The medical charts were reviewed for underlying macular disease, anti-VEGF drug type intended for injection at the missed appointment, number of injections prior to the missing one and the objective response to treatment. Non-attendance due to a rescheduled appointment time or to continuation of treatment at another center was an exclusion criterion. Participants who did not agree to take part in the study were also excluded. Patients who missed more than one appointment they were not contacted or interviewed again, ensuring that each interview relates only to the first missed appointment during the study period.

Statistical analyses

Data was collected using Microsoft Excel software and entered into an electronic database. A continuous variable is expressed as a mean plus a standard deviation, and a categorical variable is expressed as a percentage (n). After verifying that conditions of validity were met, continuous variables were compared using a t-test or Mann–Whitney U test according to the sample size and distribution. For categorical and binary variables a chi-squared test was used when sample sizes in all categories were adequate, and a Fisher’s exact test used otherwise. A 2-sided p-value <0.05 was considered statistically significant. The statistical analysis was performed using R software, version 4.0.0 (R Core Team, Vienna, Austria).

Results

The overall missed appointment rate was 18% (100/556 patients). Of these, 49% were female (49 patients) and 51% were male (51 patients) with a mean age of 66 years (SD ±14). Most no-show patients lived outside of Haifa, the city in which the hospital is located (75%) and required an escort to attend their medical appointments (73%) (Table 1). The majority of the no-show patients received injections for diabetic retinopathy (including DME 50%, PDR 12%), while the remainder received injections for nAMD (26%) and

RVO (12%). The drug intended for use at the missed session was Avastin (Bevacizumab) in 59% of the cases and Eylea (Aflibercept) or Lucentis (Ranibizumab) in 41% (Table 2).

The telephone survey revealed that the most common reason for missing an appointment was concurrent illness (39%). However, data regarding hospitalization at outside institutions were not available. COVID-19 quarantine accounted for an additional 8% and was not included in the concurrent illness category. No statistically significant differences were found between the proportion of patients with DME and PDR who missed their appointment due to concurrent illness and those with AMD or RVO ($p=0.153$). Bureaucracy, including missing financial forms or administrative issues related to the appointment, accounted for 28% of no-shows. Of note, patients not showing up for scheduled Eylea or Lucentis injections have missed the appointment due to lack of financial obligations in 28% of cases compared to only 10% of the cases for Avastin ($p=0.02$). Lack of motivation was stated by 11% of the subjects as the reason for not attending their scheduled anti-VEGF IVT injection due to (Figure 1). Patients expressing lack of confidence in the treatment did not exhibit a higher rate of missed appointments attributed to lack of motivation ($p=0.853$). Nonetheless, patients stating low trust in the injecting ophthalmologists (ranks 1-2 on the 1-5 scale) did miss their appointments more often due to motivational deficits compared with patients expressing high levels of trust in the clinicians (4-5 on the 1-5 scale) ($p=0.026$). Of note, there was no difference in the number of previous injections or the rate of unilateral versus bilateral treatment between patients who missed their appointments due to lack of motivation and those who missed for other reasons ($p=0.053$), ($p=0.7$), correspondingly.

Patients reported high levels of fear from vision loss and expressed trust in the injecting clinicians. Approximately half of the patients reported moderate to severe anxiety during injections and 22% of the patients stated they perceived their treatment as ineffective (Figure 2).

In response to the yes-or-no questions, 61% of the patients who missed their appointment stated the treatment had met their expectations, with 53% experienced a subjective improvement in their vision, while only a minority thought that other treatments besides anti-VEGF could restore their vision (Figure 3). Additionally, 50% of patients indicated that no medical system changes could improve compliance, although one-third suggested that reducing waiting times and being treated by the same ophthalmologist for each visit would enhance adherence. Furthermore, patients suggested improving the physical access to the hospital and reducing the injection-related pain as helpful steps for addressing no-shows (Figure 4).

Discussion

This study explored primary reasons for missed appointments among patients scheduled for intravitreal injections of anti-VEGF therapy for retinal care. Its aim was to identify modifiable factors of non-adherence to this sight-saving treatment, for which compliance rates are suboptimal. The results highlight the potential for impactful interventions, such as improving transportation access and streamlining administrative processes. Additionally, offering alternative scheduling options for missed appointments may help reduce unnecessary treatment delays.

Non-adherence to medical treatment has been previously attributed to various factors, including condition-related, socioeconomic, patient-related, healthcare-related, and therapy-related factors.[6,11] The results of the current study, which focused on patient perspectives, both reinforce and refine previously reported evidence. Concurrent illness was the most common reason for non-adherence in this study, aligning with previous research highlighting similar condition-related variables, such as age and comorbidities, as crucial determinants of adherence to anti-VEGF IVT treatment. [12–16]

The prominent modifiable factors for non-adherence found in this study were healthcare-related administrative issues, previously reported important determinants.[14,17,18] Misunderstanding regarding appointment times and inaccuracies in financial form accuracy were the second most common causes of no-show. Moreover, patients struggled to reschedule missed appointments due to limited scheduling options or communication barriers, resulting in more skipped injections than delayed ones. Hence, clear communication of medical advice and future appointment times in the patients' native language, as well as providing prompt alternative appointment options for missed treatments could help reduce unnecessary delays.

The type of drug recommended for intravitreal anti-VEGF therapy was also shown to affect non-adherence. In Israel, second-line treatment requires health insurance approval, complicating the scheduling process. Indeed, patients scheduled to receive Eylea or Lucentis injection were more likely to miss appointments due

to inability to obtain financial forms. Newer VEGF inhibiting treatments with greater durability could potentially increase patient compliance[3], but obtaining financial forms for these drugs can be challenging. Implementing a direct approval system between retina specialists and healthcare providers, or allowing patients to upload financial forms in advance, could streamline the process and help prevent delays in treatment.

Socioeconomic factors such as travel time to the clinic and the burden of transportation on relatives or caregivers were previously identified as significant factors contributing to non-adherence.[19–22] Indeed, the majority of patients who missed their scheduled appointment were from outside the city and needed escorts to get to the clinic, posing logistical challenges. Improving access by offering affordable close parking and enhancing public transportation to the hospital may improve adherence to treatment. Previous evidence shows that patient-related factors play a significant role in nonadherence, with the perception of a treatment as ineffective being a strong risk factor.[17,21,23] Our data demonstrated that patients who expressed reduced trust in the injecting ophthalmologists missed appointments more frequently due to lack of motivation, implying an additional modifiable factor. To address this, it may be beneficial to supply educational materials in simple language explaining the importance of long-term treatment and alleviating patient anxiety, with an emphasis on trust-building between patients and physicians.

The study has several limitations. The data is related to a single missed appointment. As we included patients who had not come in for their scheduled injection during the study period, we could not exclude the possibility that the patients who did strictly follow their treatment regimen might also miss an appointment at a different time. Therefore, we were unable to establish a suitable control group. Additionally, the data is from Israel, which has a public healthcare system, thus individual financial barriers to treatment were not assessed. The study was conducted during the COVID-19 pandemic, which may have affected adherence rates. Further research with a larger sample size is needed in a non-pandemic situation.

Conclusions

The factors driving non-adherence to intravitreal anti-VEGF injections are multifaceted, spanning from health-related issues to socioeconomic and administrative challenges. Tailored interventions that address logistical and administrative obstacles are essential to improving patients adherence. With advancements in longer-lasting anti-VEGF therapies offering greater treatment durability, there is potential for reducing the treatment burden, although these may also exacerbate administrative challenges for some patients. Addressing modifiable factors of nonadherence holds promise for optimizing the clinical outcome of VEGF inhibition therapy, and ultimately, preserving vision.

Statement of Ethics:

This study protocol was reviewed and approved by Rambam Institutional Ethics Committee, approval number 0733-19-RMB. Verbal informed consent was obtained from the participants prior to the study. This consent procedure was reviewed and approved by the Rambam Ethics Committee, Rambam health care campus, Haifa, Israel, approval number 0733-19, decision date 25/02/2020.

Conflict of Interest Statement:

All authors declare that there are no known conflicts of interest associated with this publication.

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Author Contributions:

Efrat Naaman- conceptualization, data collection, analyzing data, writing manuscript.

Noa Yanir-Prat- conceptualization, data collection, analyzing data

Diana Shair- data collection, writing manuscript

Nitai Bar- statistical analysis, writing manuscript

Beata Miller- data collection

Anna Fishman- data collection

Shiri Zayit-Soudry- conceptualization, data collection, analyzing data, reviewing manuscript, Supervision

Data Availability Statement:

All data generated or analyzed during this study are included in this article. Further enquiries can be directed to the corresponding author.

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<https://www.tandfonline.com/doi/ful/10.1080/02713683.2018.1543708>

Figure Legends:

Figure 1.

Reasons for missing appointment. The distribution of reasons for no-show stated by the patients. An open question was used in the telephone survey and the answers were classified into six different reasons. Responses that were not suitable for any of the other categories were classified as "other".

Figure 2.

Survey of patient satisfaction using a 1-5 scale.

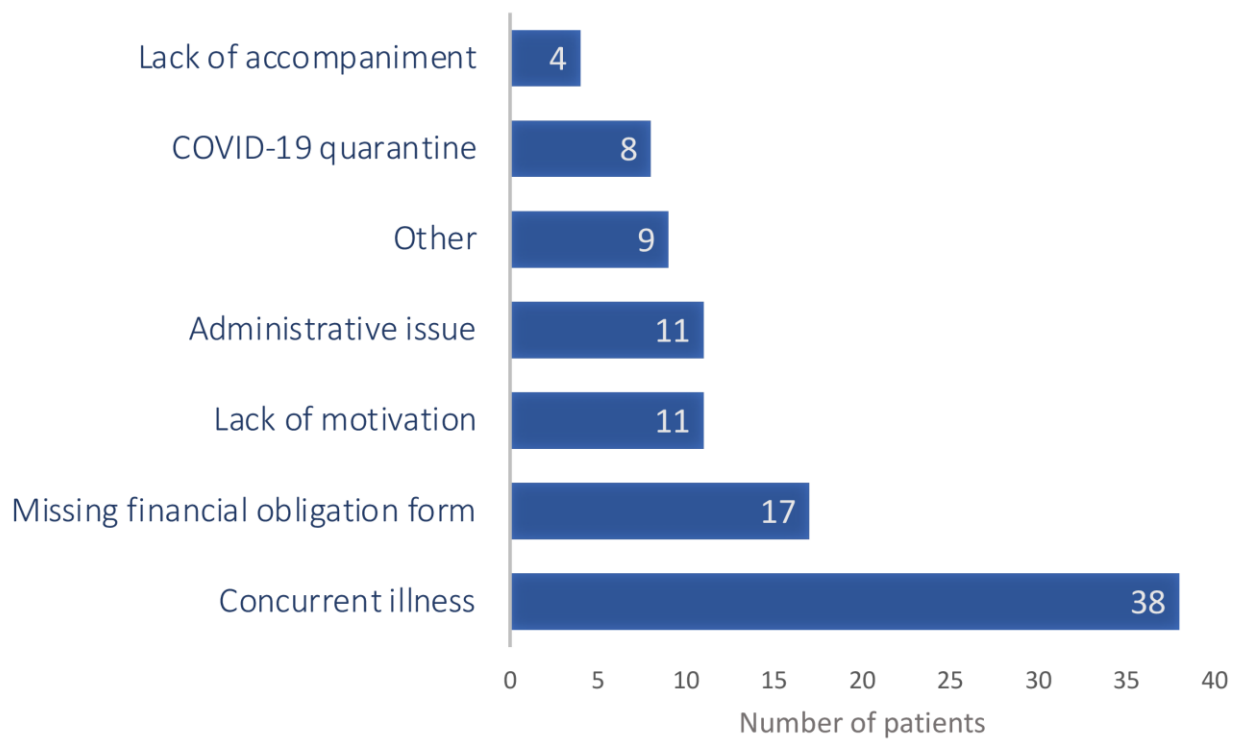
Figure 3.

Survey of patient satisfaction using yes/no questions.

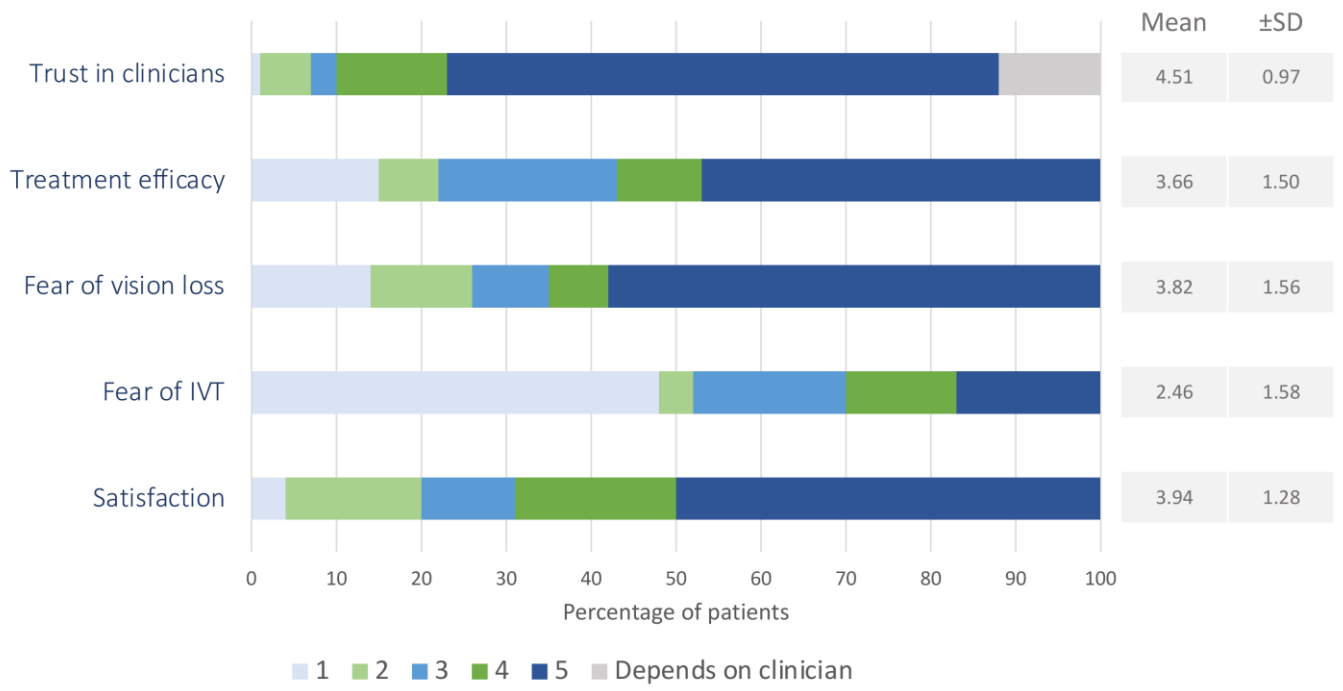
Figure 4.

Improving treatment adherence. Patient-suggested interventions to improve treatment adherence. In the telephone survey, an open question was used, and the answers were classified into five categories.

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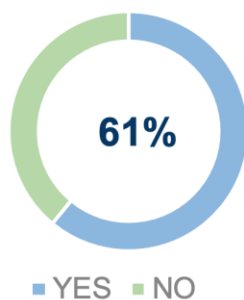


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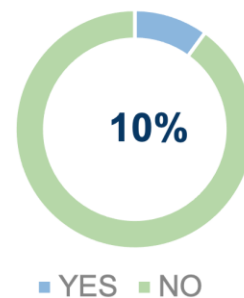
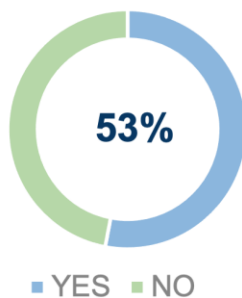
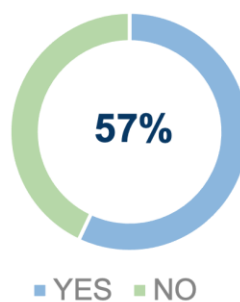


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Treatment fulfill your expectation?



Difficulties coming to the clinic?

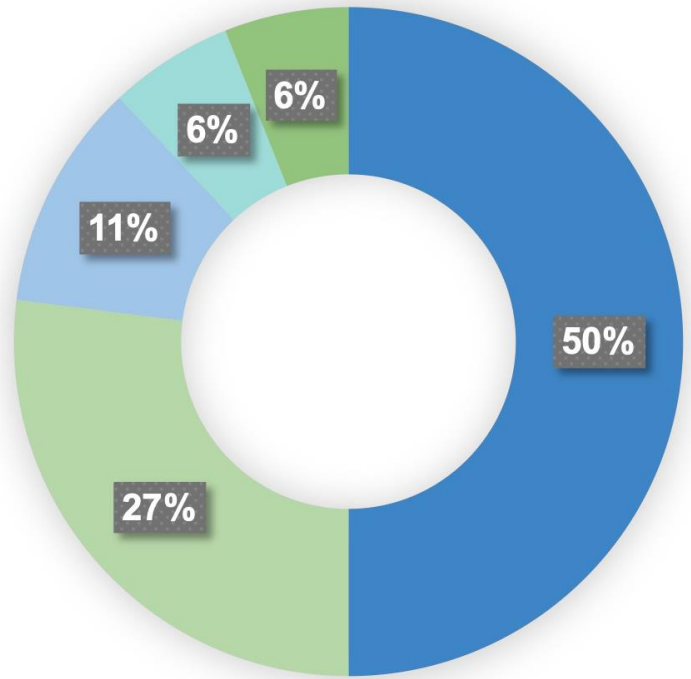


Subjective improvement in vision?

Other treatment can help?

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- Nothing
- Shorten waiting times
- Same clinician for all IVT appointments
- Better access to hospital
- Decrease pain



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Table 1.

Gender (N=100)	
Female	49 (49%)
Male	51 (51%)
Age (N=100)	
	66 (SD ±14)
HMO (N=95)	
Leumit	25 (26%)
Clalit	44 (46%)
Maccabi	16 (17%)
Meuhedet	10 (19%)
Country of birth (N=96)	
Israel	65 (68%)
Not Israel	31 (32%)
Native language (N=92)	
Arabic	32 (35%)
Hebrew	41 (44%)
Russian	11 (12%)
Other	8 (9%)
Familial status (N=83)	
With partner	65 (68%)
Without partner	31 (32%)
Need for an escort (N=88)	
yes	64 (73%)
No	24 (27%)
Region of residency (N=97)	
Haifa	25 (26%)
Outside Haifa	72 (74%)
Education (N=78)	
Less than 12 Y	28 (36%)
High School	28 (36%)
Academic	22 (28%)
Mode of transport (N=88)	
Privat car	52 (58%)
Public transportation	22 (25%)
Taxi	14 (16%)

Patients' demographics

Diagnosis N=95	
<i>DME</i>	48 (50%)
<i>PDR</i>	11 (12%)
<i>AMD</i>	25 (26%)
<i>RVO</i>	11 (12%)
Previous injections	26 (SD ±25)
Treatment N=95	
<i>Bevacizumab (Avastin)</i>	56 (59%)
<i>Aflibercept (Eylea)</i>	35 (37%)
<i>Ranibizumab (Lucentis)</i>	4 (4%)
<i>Dexamethasone implant (Ozurdex)</i>	0 (0%)

Table 2.
Patient's treatment

DME: Diabetic Macular Edema; PDR: Proliferative Diabetic Retinopathy; AMD: Age related Macular Degeneration; RVO: Retinal Vein Occlusion.