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RETINAL DISORDERS

# Treatment contentment and preference of patients undergoing intravitreal anti-VEGF therapy

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## Abstract

**Purpose** The aim of this study is to investigate patients´ treatment preference between the pro re nata (PRN) and treat and extend (T&E) regimens and their feelings and contentment undergoing intravitreal injections (IVI) with anti-vascular endothelial growth factor (anti-VEGF) agents.

**Methods** Six months after the switch of the treatment regimen from PRN to T&E, answers of a 16-item questionnaire of 105 patients under IVI therapy regarding age, sex and treatment preference (T&E or PRN regimen), as well as burden and anxiety resulting from therapy, were evaluated. Analysis of associations between answers of the questionnaire was executed using Pearson's $Chi^2$ test and Mann–Whitney $U$ test. $P$ values $\leq 0.05$ were considered statistically significant.

**Results** Nearly all patients (90.5%) felt well informed about disease and therapy. Comparing treatment regimen, 13.7% thought PRN was better and 23.3% felt T&E was better. The majority considered PRN and T&E to be equal (60.3%). No significant association between treatment regimen and age ($p = 0.15$), gender ($p = 0.35$) and duration of IVI therapy ($p = 0.42$) was seen. The examination results are associated with fear in the majority of patients (53.3%). Fear about the IVI was indicated by 47.6% of individuals and was significantly associated with pain during treatment ($p = 0.0003$), pain after treatment ($p = 0.004$) and fear about unfavourable examination results regarding disease activity ($p = 7.94 \times 10^{-7}$).

**Conclusions** Most patients are satisfied with the IVI therapy and the treatment regimen. Fear of the IVI and particularly of unfavourable examination results demonstrate the high treatment burden for patients undergoing anti-VEGF therapy. These aspects should be taken into account by healthcare professionals.

**Keywords** Anti-VEGF therapy · Patients · Regimen · Contentment · Preference

**Key messages**

What is known:

- Therapy with intravitreal injections (IVI) with anti-vascular endothelial growth factor agents implies a high treatment burden for patients with macular diseases.

New information in the paper:

- Treatment contentment and subjective benefit under IVI therapy with the treat and extend regimen is high.
- Fear of the IVI and particularly of unfavourable examination results are frequent and not related to the duration of treatment.

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## Introduction

Intravitreal injections (IVI) with anti-vascular endothelial growth factor (VEGF) agents have revolutionized the treatment of exudative macular diseases, especially neovascular

age-related macular degeneration (nAMD) and foveal macular oedema due to diabetic retinopathy or retinal vein occlusion [1–4]. To slow disease progression and to maintain visual acuity, in most cases repeated IVI have to be applied and frequent visits in ophthalmological centres are necessary. The treatment regimen usually begins with three to six monthly injections as a "loading phase", mostly followed by an individualized treatment regimen such as the Pro Re Nata (PRN) or the Treat and Extend (T&E) schedule. Recently, the T&E regimen was assessed to be able to optimize visual outcomes and to reduce burden on patients compared to the PRN regimen [5].

Retreatment depends on disease activity defined based on changes of best corrected visual acuity and lesions detectable in optical coherence tomography (OCT) images. Patients' compliance and adherence to therapy is crucial for success of treatment, but the unpredictable duration of frequent visits and IVIs imposes a considerable burden to the patient. An IVI can be stressful and can generate apprehension of pain and anxiety.

Most studies focus on morphological and functional outcome parameters and do not include the perception of patients on the treatment strategy so that evidence on this complex topic is limited. Less is known about patient's experience undergoing anti-VEGF therapy [6–9].

Patient experience is important for adherence to treatment [10] and long-term functional success.

To identify ways to improve comfort during therapy, we have analysed patient preference of treatment regimens and patients' contentment during IVI therapy with anti-VEGF agents.

## Materials and methods

### Data collection

Within the frame of regular quality assessment of medical care in a large outpatient ophthalmologic tertiary centre, patients with exudative macular diseases undergoing intravitreal anti-VEGF treatment were asked to anonymously respond to a 16-item questionnaire regarding age, gender, burden and anxiety associated with the therapeutic process. Treatment regime preference (T&E or PRN) was enquired, if IVI therapy was administered for at least 1 year so that the patient had comprehensive experience with both schedules. Prior to answering the questionnaire, patients were informed that their responses were analysed anonymously and with responding to the questionnaire they would agree to this data evaluation. The quality assessment was performed 6 months after a switch from PRN to T&E regime within a 2-week period. Data of 105 patients could be included in the study. The translated questionnaire is available in the supplementary material.

### Treatment regimes

Prior to April 2020, patients with active nAMD and foveal macular oedema due to diabetic retinopathy or retinal vein occlusion underwent IVI therapy with the PRN regimen. After making the diagnosis, three to six initial injections were followed by complete clinical ophthalmological examination including BCVA testing and OCT imaging. In case of persistence or increase of disease activity, another treatment cycle with three monthly injections was started. Eyes without disease activity received monthly controls. In order to reduce number of visits for the patients, the COVID-19 pandemic appeared to be the right time to switch to the T&E regimen. Newly diagnosed patients also received three to six monthly IV as the "loading phase". At the last IVI of the treatment cycle, the eye was examined with BCVA testing and OCT imaging. In case of disease activity, the next IVI was applied after 4 weeks. For eyes without disease activity, the interval for the next IVI was extended by 2 weeks up to 12 weeks during follow-up. In case of new disease activity during follow-up, the interval to the next IVI was reduced by 2 weeks with a minimum of 4 weeks.

### Statistical analysis

Statistical analysis was performed using SPSS software (version 25.0, IBM, Armonk, NY, USA). Analysis of associations between answers of the questionnaire was executed using Pearson's $Chi^2$ test for categorical variables and Mann–Whitney $U$ test for age as a continuous variable. $P$ values $\leq 0.05$ were considered statistically significant.

## Results

The characteristics of the study population and the patients' preference of the treatment regimen are outlined in Table 1. For analysis of treatment preference, 73 patients with more than 1 year of experience with IVI were included. There was no significant association between preferred treatment regimen and age ($p=0.15$), gender ($p=0.35$) and duration of IVI therapy ($p=0.42$). The huge majority of patients regarded the T&E regime as either very good (44.8%) or rather good (47.6%), whereas less than 5% defined the T&E schedule as rather bad (3.8%) or very bad (1.0%). In the subgroup of 73 patients who experienced each of the PRN and T&E treatment schedules for at least 6 months, 13.7% preferred PRN, whereas 23.3% preferred T&E. The majority considered PRN and T&E as equal (60.3%). In this subgroup, 90.5%

**Table 1** Characteristics of patients and treatment regime preference

| | **Patients** |
|---|---|
| Number of patients, n | 105 |
| Female n (%) | 60 (57.7%) |
| Age (years), mean ± SD | 76.10 ± 8.47 |
| Injected eye | |
| Right eye | 33 (31.4%) |
| Left eye | 32 (30.5%) |
| Both eyes | 39 (37.1%) |
| No response | 1 (1.0%) |
| IVI are given since | |
| < 6 months | 18 (17.1%) |
| 6–12 months | 12 (11.4%) |
| > 1–5 years | 54 (51.4%) |
| > 5 years | 19 (18.1%) |
| No response | 2 (1.9%) |
| The T&E regimen is | |
| Very good | 47 (44.8%) |
| Rather good | 50 (47.6%) |
| Rather bad | 4 (3.8%) |
| Very bad | 1 (1.0%) |
| No response | 3 (2.9%) |
| The T&E regimen is (subgroup: experience with IVI > 1 year, $n = 73$) | |
| Very good | 28 (38.4%) |
| Rather good | 38 (52.1%) |
| Rather bad | 4 (5.5%) |
| Very bad | 1 (1.4%) |
| No response | 2 (2.7%) |
| The PRN regimen was (subgroup: experience with IVI > 1 year, n = 73) | |
| Worse | 17 (23.3%) |
| Equal | 44 (60.3%) |
| Better | 10 (13.7%) |
| No response | 2 (2.7%) |

*IVI* intravitreal injections; *T&E* treat and extend; *PRN* Pro re nata

of patients regarded the T&E as very good or rather good (Table 1).

Subsequent to rescheduling from PRN to T&E as well as other measures for shortening of the time from arrival to leaving following IVI, nearly all but 4 patients confirmed the statement that they felt protected with regard to the current COVID-19 pandemic situation during their ophthalmological visits as either definitely true (62.9%) or mostly true (28.6%).

Detailed results about patients' feelings and contentment are summarized in Table 2. More than 90% confirmed that they felt well informed about their disease and therapy. Eighty percent reported that they benefited from therapy and even more patients (93.3%) confirmed that they would choose to receive the therapy again. Consequently, as patients accept the necessity of therapy, less than one-third of the patients felt the ophthalmic visits as arduous.

In contrast, and as could be expected, IVIs are also associated with anxiety and fear. The examination results are associated with fear in the majority of patients (53.3%), as they might indicate disease progression documenting visual loss, are resulting in more frequent IVI therapy or might indicate the therapy is no longer effective. In addition, fear about the IVI was significantly associated with fear about examination results regarding disease activity ($p = 7.94 \times 10^{-7}$), pain during treatment ($p = 0.0003$, Fig. 1) and pain after treatment ($p = 0.004$) and age ($p = 0.48$), gender ($p = 0.76$), duration of therapy ($p = 0.72$), preference of therapy regimen ($p = 0.17$) and burden of the number of visits ($p = 0.10$) were not associated with fear about IVI. Pain at IVI was associated with pain after IVI ($p = 5.65 \times 10^{-16}$). The long-term duration of IVI therapy had no influence on pain during ($p = 0.47$) or after treatment ($p = 0.61$).

**Table 2** Answers in the questionnaire about feelings and contentment

| Items | | | | | |
|---|---|---|---|---|---|
| N (%) | Definitely true | Mostly true | Mostly false | Definitely false | No response |
| I feel well informed about my disease and therapy | 59 (56.2%) | 36 (34.3%) | 8 (7.6%) | 0 (0.0%) | 2 (1.9%) |
| I am afraid of the treatment | 20 (19.0%) | 30 (28.6%) | 29 (27.6%) | 21 (20.0%) | 5 (4.8%) |
| I am afraid of examination results regarding disease activity | 23 (21.9%) | 33 (31.4%) | 32 (30.5%) | 9 (8.6%) | 8 (7.6%) |
| I feel pain during treatment | 10 (9.5%) | 23 (21.9%) | 49 (46.7%) | 16 (15.2%) | 7 (6.7%) |
| I regularly feel pain after treatment | 15 (14.3%) | 25 (23.8%) | 46 (43.8%) | 13 (12.4%) | 6 (5.7%) |
| The number of ophthalmological visits is arduous | 12 (11.4%) | 22 (21.0%) | 43 (41.0%) | 24 (22.9%) | 4 (3.8%) |
| I benefited from the treatment | 47 (44.8%) | 37 (35.2%) | 12 (11.4%) | 2 (1.9%) | 7 (6.7%) |
| I would choose the treatment again | 73 (69.5%) | 25 (23.8%) | 3 (2.9%) | 1 (1.0%) | 3 (2.9%) |
| I feel well protected with regard to the current Covid-19 pandemic situation at ophthalmological visits | 66 (62.9%) | 30 (28.6%) | 4 (3.8%) | 0 (0.0%) | 5 (4.8%) |

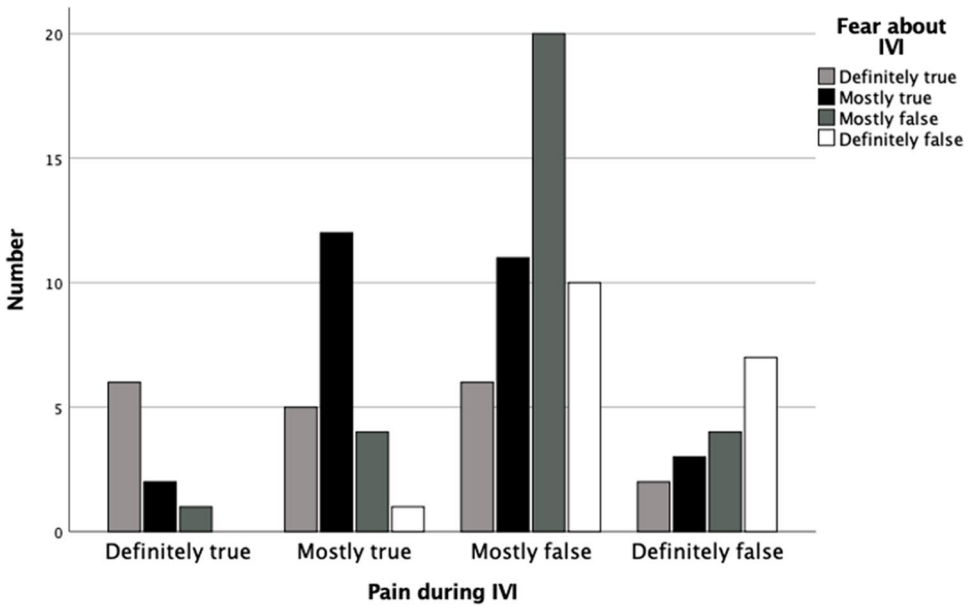


**Fig. 1** Answers of questions: "I am afraid of the treatment" and "I feel pain during treatment." IVI = intravitreal injection

## Discussion

In our study, we investigated patients' contentment about their IVI therapy and their estimation of the treatment regimens PRN and T&E. Nearly all patients (92.4%) have rated the introduced T&E regime as good, indicating high content about the therapy after the switch from PRN to T&E. The T&E regimen was preferred by one quarter of patients. Interestingly, with 60%, the majority of patients assessed both schedules as equal having no clear preference for a treatment regimen. On the one hand, many patients may have been satisfied with both modalities and therefore do not prefer the one or the other; on the other hand, patients may trust in the opinion of their ophthalmologist and do not value the treatment strategy. A recent study underlines high persistence to therapy of patients treated with the T&E regimen over two years with good functional results [11]. To our knowledge there is no data published about patient's preference comparing PRN and T&E after having been treated with both therapy regimes. Droege et al. found in their study that the majority of patients preferred the PRN regimen compared to fixed monthly IVI regimen and would prefer a lower number of ophthalmological visits [12]. Mueller et al. observed, that patients are willing to accept a high treatment burden for better functional outcome [13]. A Japanese study showed that comparing T&E, PRN and a fixed two monthly IVI regimen, the T&E dosing regimen was generally most preferred by patients [14].

In our cohort, the satisfaction of patients about information about disease and treatment and the benefit from therapy was very high. Over 93% would choose the treatment again. In addition to a huge number of studies, which have shown that IVIs with anti-VEGF agents defeat blindness [15–17], our results point out that patients ascertain their benefit from therapy by themselves.

Despite large overall contentment, 48% of the study group feels afraid of the treatment, but fear of unfavourable examination results is even higher. Thetford et al. documented that anxiety was mostly present at the beginning of the therapy [7], whereas in our study, fear was not associated with the time period since onset of treatment. Senra et al. showed similar results related to anxiety about anti-VEGF treatment [8]. In their report, concerns about treatment effectiveness were a main source of anxiety, comparable to our findings, that the majority of our patients are afraid of unfavourable results of the examination regarding disease activity. Mekala et al. reported similar results about fear, but a higher number of patients feeling pain during and after the IVI than in our study [9]. In line with our results, pain was not associated with the time period since onset of treatment.

Additionally, we could show that fear goes in line with pain during treatment, meaning that especially anxious patients experience the IVI as painful. Fear and pain are not associated with the time period since onset of treatment. Therefore, an IVI for a lot of individuals remains a stressful event even after many years of experience with this procedure.

Our study has the strength of a relatively high number of participants under real life conditions. Most of them had experience with IVI over a long time and could compare both treatment regimens. Limitations are that no validated questionnaires were used and that answers in our questionnaire are not objectifiable with measurements of physical parameters.

In conclusion, the T&E regimen is highly accepted by our patients. The patient's acceptance is of high importance

as visual outcome can only be as good as the patient is willing to follow a regimen over a long period of time. Patients are willing to endure a high treatment burden for maintenance or even increase of visual acuity, but fear and pain are attended by many of them. Healthcare professionals should keep in mind patients' possible anxiety. Comprehensive and empathic explanations about therapy, safe and structured processes and individual assistance to keep the appointments are crucial for good long-term adherence to anti-VEGF treatment. Additionally, an efficient organization of IVI visits with less waiting time might improve patient's contentment.

**Supplementary Information** The online version contains supplementary material available at https://doi.org/10.1007/s00417-021-05324-8.

**Author contribution** U Kellner, MS Bedar and T Schick contributed to the study conception and design. All authors contributed to data collection, and U Kellner and T Schick contributed to the analysis. The first draft of the manuscript was written by U Kellner and T Schick, and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

**Data availability** Not applicable.

**Code availability** Not applicable.

## Declarations

**Ethics approval** All procedures performed 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. The questioning was performed anonymously during the regular quality assessment of medical care in a large outpatient ophthalmologic tertiary centre. Anonymous data collection and analysis do not require ethical permission of the local ethical committee.

**Consent to participate** Prior to answering the questionnaire, patients were informed that their responses were analysed anonymously and with responding to the questionnaire they would agree to this data evaluation.

**Consent for publication** All authors have given their approval for this version to be published.

**Conflict of interest** T Schick has received speaker honoraria from Bayer and Novartis and has served on an advisory board for Allergan. The other authors declare no competing interests.

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